D17168: The Prone to Supine Breast MRI Trial

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CairnSurgical, Inc.
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HISTORY OF CHANGES

Ver. 05.07.19	Addition of patient-reported outcome questionnaire comparing experience of supine to prone MRI. Minor editorial corrections. See pages 5, 7 & 11.
Ver. 08.27.18	Changes to this protocol have been driven by a change in the funding source from in-house NCCC funds to CairnSurgical, Inc. In addition to adding the funding source to the protocol (cover page and referenced on page 4), the protocol has been revised to allow de-identified data to be sent to CairnSurgical for use in the development of the Breast Cancer Locator. The consent form has been revised to reflects these changes. A Table of Contents has been added to the Protocol along with other minor editorial corrections.
Ver. 5.23.18	1. Method of providing consent prior to surgery changed from email and mail to "mail or email." 2. The MRI Technician-Investigator has been changed from Kim Krueger to Misty Fox on the front page and her title corrected. 3. Reference #1 was updated with complete publication information. 4. Language in sections 9-12 related to multiple sites was removed as study is being conducted only at NCCC-Lebanon. 5. Who can arrange for MRI scheduling has been modified as a result of team conversations with Comprehensive Breast Program schedulers.

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ABBREVIATIONS

3D	three-dimensional
BCL	Breast Cancer Locator
CBP	Comprehensive Breast Program
CCRC	Clinical Cancer Review Committee at the Norris Cotton Cancer Center
CPHS	The Committee for the Protection of Human Subjects at Dartmouth College
DCIS	ductal carcinoma in situ
DHMC	Dartmouth-Hitchcock Medical Center
DSMAC	Data Safety Monitoring and Accrual Committee at the Norris Cotton Cancer Center
FDA	U.S. Food and Drug Administration
Gd	gadolinium
IRB	institutional review board
MRI	magnetic resonance imaging
NCCC	Norris Cotton Cancer Center
NCI	National Cancer Institute (U.S.)
OR	operating room
SAE(s)	serious adverse event(s)
UADE(s)	unanticipated adverse device effect(s)
US	ultrasound

Section 1. INTRODUCTION

We have recently developed a device called the Breast Cancer Locator (BCL). The BCL (manufactured by CairnSurgical, Inc.) is a 3-D printed, bra-like form which transfers information about the location of a breast cancer derived from a supine MRI image to surgeons in the operating room. We have utilized BCLs in 19 breast cancer patients and have demonstrated that they are safe, easy to use and accurately transfer information about breast cancer location to the surgeon (1).

The Clinical Problem

A potential limitation to the widespread adoption of BCLs to aid surgeons to more accurately remove breast cancers is the current requirement that a patient have a supine MRI. The current diagnostic standard is a prone MRI. It is inconvenient and costly for patients to have a second (supine) MRI at a separate time after the diagnostic prone MRI is completed. The purpose of this study is to determine whether one could obtain a supine MRI immediately after a prone MRI exam, without a second injection of gadolinium (Gd) contrast material. The supine MRI would have to be of sufficient quality to allow the Radiologist to define the tumor edges (“segment” the tumor) so that a 3-D image of the tumor can be generated to form the BCL.

In many cases the tumor is identified by the differential uptake of Gd contrast material in the tumor compared to non-cancerous breast tissue. In a standard diagnostic prone MRI images are completed by 10 minutes after contrast injection. We have searched the literature and there is a paucity of information regarding whether the differential uptake observed during the 10 minutes after Gd injection is maintained for an additional 10 minutes required to flip the patient from a prone to a supine position and obtain additional MRI images. One paper demonstrated that use of a special sequence (3D spectral-spatial excitation magnetization transfer) did allow delayed tumor delineation (2). We plan to evaluate whether the same standard MRI sequences used for the 10 minute images provide the needed discrimination for up to 20 minutes.

Preliminary Data

In the course of obtaining supine MRIs on 8 patients with invasive cancer in another study (D0928), we obtained delayed images 5-10 minutes after the standard post-contrast images were obtained (15-20 minutes after contrast had been injected). We created unique files which contained the images obtained in the first 10 minutes and the images obtained 15-20 minutes after contrast injection. These files were then provided to 2 study Radiologists in random sequence and the Radiologists were asked to segment the tumor. Both Radiologist 1 and 2 were able to segment the 10 minute images in all patients. Radiologist 1 and 2 were both able to also segment the 15-20 minute images in 100% of the cases.

We quantitated the amount of enhancement (mean signal intensity) at the tumor site and at a site of benign fibrous breast tissue in these 8 patients from the images obtained 10 and 15-20 minutes after contrast injection. As shown in Table 1, there was very little diminution of the contrast in the tumor at 20 minutes compared to 10 minutes (no decrease in 5 patients, average decrease 5%). There was a slight increase in enhancement in benign breast tissue in 5 of the 8 patients (average increase 10%). The mean difference between the enhancement in the tumor vs benign breast at 10 minutes was 34, and at 20 minutes was 25. In all 7 patients who had a differential enhancement of the tumor compared to benign tissue at 10 minutes, the differential enhancement persisted at 20 minutes.

Table 1. Contrast enhancement over time in tumor and benign breast tissue

Patient	**Contrast in Tumor**			**Contrast in Benign Breast**		
.	10’	20’	% change	10’	20’	% change
1	61	60	-2	42	48	+14
2	85	85	0	32	42	+31
3	55	54	-2	55	53	-4
4	67	67	0	50	56	+12
5	72	68	-6	40	38	-5
6	72	77	+7	35	47	+34
7	83	70	-16	62	55	-11
8	162	130	-25	71	80	+13

This limited analysis of data from 8 patients is promising and justifies study of a larger number of patients.

Section 2. OBJECTIVES

The purpose of this study is to determine whether a supine MRI obtained immediately after a standard diagnostic prone MRI exam, without a second injection of gadolinium (Gd) contrast material, would be of sufficient quality to allow the Radiologist to define the tumor edges ("segment" the tumor) so that a 3-D image of the tumor can be generated to form a BCL.

The primary objective is to determine what percentage of cases that can be successfully segmented from 10 minute post-contrast prone MRI images can also be segmented using 20 minute post contrast supine MRI images.

Our secondary objectives are to:

1. Quantitate the amount of enhancement at the tumor site and in benign breast tissue at 10 minutes and 20 minutes after contrast injection.
2. Calculate the difference between tumor and benign breast tissue enhancement at 10 minutes and 20 minutes after contrast injection.
3. Calculate the additional time needed to obtain supine MRI images.
4. Quantify the perceived comfort level of the prone and supine MRI as reported by participants.

Section 3. ELIGIBILITY CRITERIA

1. Age $\geq$ 18 years.
2. Female gender.
3. Histologic diagnosis of invasive breast cancer or ductal carcinoma in situ.
4. Tumor size at least 1 cm in diameter as visualized on mammogram or US.
5. A diagnostic breast MRI is considered to be clinically indicated.
6. Ability to voluntarily provide informed consent to participate prior to any study-related assessments/procedures being conducted.

Exclusion Criteria

1. Absolute contraindication to MRI, including presence of implanted electrical device. (pacemaker or neurostimulator), aneurysm clip, or metallic foreign body in or near eyes.
2. Severe claustrophobia.
3. Contraindication to use of gadolinium-based intravenous contrast, including life-threatening allergy or compromised renal function (eGFR < 30 ml/min/1.73m^2).
4. History of median sternotomy.
5. Pregnancy. Patient attestation that they are not pregnant will be acceptable.
6. Patients who have received neoadjuvant chemotherapy.

An eligibility worksheet will be completed for each patient prior to enrollment and will be signed and dated by a study investigator.

Section 4. TREATMENT PLAN

Patients with a percutaneous core biopsy demonstrating invasive carcinoma or ductal carcinoma in situ who are being scheduled for a diagnostic bilateral prone breast MRI based on the standard criteria utilized by the Comprehensive Breast Program (CBP) of the NCCC (surgical provider preference) will be invited to participate in the study. This invitation to participate will be done by the study MRI technician-investigator after the patient is informed by the CBP that the diagnostic prone MRI is clinically indicated. If a patient indicates they are willing to participate, they will be informed that they will receive a consent form by mail or email for them to review prior to the date of the MRI. At this time the MRI technician-investigator will complete the eligibility worksheet and contact the study coordinator.

Upon receipt of the eligibility worksheet, the MRI Technologist or Study Coordinator will: 1) contact the CBP to ensure the Radiology MRI include extra time for the supine MRI, and 2) send the patient the consent form by mail or email.

When the patient comes to DH for the MRI, prior to the MRI being performed, the study MRI technician/investigator will sign and collect the consent form signed by the patient. If the patient has additional questions about the study when they come for the MRI, the study MRI

technician/investigator will answer the questions. The original signed consent form will be given to the study coordinator and a copy will be given to the patient. The study coordinator will be contacted and will enroll the patient on the study, prior to the supine MRI being performed.

Prior to starting the prone MRI, the study MRI technician/investigator will explain to the patient and practice with the patient the steps needed to transition from the prone to the supine MRI, so as to facilitate a timely transition. The supine breast MRI consists of 2 key sequences:

1) T1 pre-Gd, large field-of-view, without fat saturation: for skin surface rendering.
2) T1 dynamic pre- & post-Gd, with fat saturation: to visualize the tumor and co-register to the surface rendering.

The patient will be placed in the prone position and undergo a standard Gd contrast-enhanced bilateral breast MRI. The time from injection of Gd to completion of the prone MRI sequences will be noted. Immediately after the prone MRI is completed, the patient will be repositioned for the supine MRI. T1, dynamic (post-Gd) sequences will then be performed (with the time post-injection noted), followed by a fat saturated sagittal sequence, and finally by T1 large field of view sequences without fat saturation.

Following the completion of both MRIs, participants will be asked to rate their comfort with each method on a scale from 0-5 using a single-page questionnaire.

Section 5. POTENTIAL TOXICITY

Supine MRIs are administered according to standard-of-care practice for prone breast MRI and represent no more additional risk than would be experienced by women receiving these exams as part of their (non-research) breast care. The risk of contrast enhanced MRI is very low, reflecting the minute risk of life-threatening allergy and development of nephrogenic sclerosis related to gadolinium-based intravenous contrast. Patients deemed to be at higher risk for gadolinium-induced nephrogenic sclerosis because of compromised renal function will not be eligible for participation.

5.1 Reporting Requirements for Adverse Events and Unanticipated Adverse Device Effects (UADEs)

Adverse events and unanticipated problems will be reported to the Principle Investigator, Dr. Timothy Rooney as soon as possible. The Sponsor-Investigator complies with all DHHS and FDA regulations pertaining to AE and UADE reporting, as well as the Dartmouth Committee for the Protection of Human Subjects (CPHS) reporting policies. These policies are found at http://www.dartmouth.edu/~cphs/docs/aedsmmemo.pdf using their *CPHS – UPIRSO, SAE, UADE Reporting Form* found at http://www.dartmouth.edu/~cphs/tosubmit/forms/.

Unanticipated adverse device effect (UADE) is defined as any serious adverse effect on health or safety, or any life-threatening problem or death, caused by or associated with an investigational device. Unanticipated adverse device effects (UADEs) must be reported as soon as possible but no later than 10 working days after the local investigator learns of the effect.

Adverse effects to be reported to the Sponsor-Investigator are: any adverse experience, defined as any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research), that is considered:

- Serious: Death; a life-threatening adverse drug experience; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant disability or incapacity; or a congenital anomaly or birth defect; and
- Unexpected: Any adverse experience, the specificity or severity of which is not consistent with the current investigator brochure or consent form; and
- Possibly related: There is a reasonable possibility that the incident, experience, or outcome may have been associated with the procedures involved in the research.

The following definitions will be used to assess causality:

- No: The clinical adverse event is definitely unrelated to study procedures (e.g., does not follow a reasonable temporal sequence from study procedure, present prior to procedure, etc.)
- Unlikely: The study procedures do not have any reasonable association with the observed experience; however, relationship cannot be definitely excluded.
- Possibly: The connection with study procedures appears feasible, but cannot be

excluded with certainty (e.g., follows a reasonable temporal sequence from procedure, but may also be related to other known factors).

- Probably: The clinical experience appears related to the study procedures with a high degree of certainty (e.g., follows a reasonable temporal sequence from procedure and abates upon termination of the procedure, cannot be reasonably explained by known characteristics of the patient's clinical state or other modes of therapy administered to the patient, etc.)

An unanticipated problem involving risks to subjects or others is defined as any incident, experience, or outcome that meets each of the following criteria:

- Unanticipated in terms of nature, severity, or frequency given: (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and consent document; and (b) the characteristics of the subject population being studied; and
- Possibly related to participation in the research means there is a reasonable possibility that the incident, experience, or outcome may have been associated with research participation; and
- The problem suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, emotional, economic, legal, or social harms) than was previously known or recognized.

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

The Dartmouth Lead Investigator will report information on participants to the Data Safety Monitoring and Accrual Committee (DSMAC) of the Norris Cotton Cancer Center.

Section 6. DEVICE FORMULATION AND PREPARATION

Supine MRI images will be obtained on 1.5T or 3T MRI scanners at DH using manufacturer approved body coils and sequences that are designed to obtain both breast surface contour (T1 pre-Gd, large field-of-view, without fat saturation) and breast tumor (T1

dynamic, with fat saturation) signatures. These coils will be positioned over the patient using a plastic support structure that minimizes breast compression.

Section 7. ENDPOINTS AND STATISTICAL ANALYSIS

The purpose of this study is to determine whether a supine MRI obtained immediately after a standard diagnostic prone MRI exam, without a second injection of gadolinium (Gd) contrast material, will be of sufficient quality to allow a Radiologist to define the tumor edges ("segment" the tumor) so that a 3-D image of the tumor can be generated to form a BCL.

The specific primary objective is to determine what percentage of cases can be successfully segmented from 20-minute post-contrast supine MRI images. Two study Radiologists will independently attempt to segment the supine MRI images on all patients. They will have access to mammogram, US and prone MRI images from each patient to facilitate segmentation. A segmentation will be defined as successful if the Radiologist, using their clinical judgement and the images provided, can confidently identify the location of the tumor and delineate its edges on the supine MRI. The results for each patient will be binary: either a segmentation can or cannot be performed. Our main outcome measure will be the percentage of cases that can be successfully segmented from the supine MRI images by **both** study Radiologists.

We hypothesize that 80% of the supine MRI images obtained at 20 minutes after contrast will be successfully segmented by both Radiologists. For this descriptive study of a dichotomous variable, a sample size of 62 patients will allow us to say with 95% confidence that the true percentage of supine MRIs that can be segmented is 80% +/- 10%.

Our secondary objectives are to determine:

1. A) The amount of enhancement at the tumor site and in benign breast tissue at 10 minutes and 20 minutes after contrast injection. B) The difference between tumor and benign breast tissue enhancement at 10 minutes and 20 minutes after contrast injection. (This is quantitative data that underlies the Radiologists' clinical judgement and allows them to segment the tumors.)
2. The time needed to acquire the supine MRI images.

3. The percentage of cases that can be successfully segmented by both Radiologists using the prone MRI images, in conjunction with mammogram and US images. (If a tumor cannot be segmented based on the *supine* MRI images, there are many possible causes. One of these causes is that the tumors intrinsically do not enhance with gadolinium contrast, even at the optimal time (10 minutes after contrast injection). Based on previous experience, we expect that less than 10% of neoplasms will not enhance at 10 minutes and will not be able to be segmented. Knowing this exact percentage in this study will help us understand how frequently this may contribute to a potential inability to segment tumors at 20 minutes.)
4. If overall patient comfort drastically changes in prone vs. supine MR breast imaging. Clinical MRI breast imaging is obtained with patients lying in the prone position (on their belly). This position has the potential to cause difficulty breathing, pain along the rib-cage, and increased claustrophobia (face down). By asking each participant to rate both positions using a scale form 0-5, we can assess their overall comfort, and help determine if supine MR breast imaging is indeed the preferred position for our participants.

These secondary data will be tabulated and summarized using descriptive statistics.

Approximately 300 patients are diagnosed with breast cancer and 100 are diagnosed with DCIS annually at DH. Diagnostic prone MRI is clinically indicated in 75% of these patients. Therefore, approximately 300 diagnostic prone MRIs are performed annually at DH. Assuming that 25% of these patients will not meet the eligibility requirements, 225 patients would be eligible annually. Assuming that half of the eligible patients will be accrued, we should complete accrual of 62 patients in 6 months.

Relevant data will be saved in Velos electronic case report forms.

Section 8. SAFETY AND DATA MONITORING

This study will be monitored by the Data Safety Monitoring and Accrual Committee (DSMAC) of the Norris Cotton Cancer Center. The Committee meets quarterly to review accrual rates and information for studies that have accrued participants. The Clinical Cancer

Review Committee (CCRC) determines the frequency of DSMAC review. The DSMAC has the authority to suspend or to recommend termination to the CCRC of all research activities that fall within its jurisdiction. In the event that a study is suspended or terminated, that information will be forwarded to the CPHS (Dartmouth IRB) office.

Section 9. PROTOCOL COMPLIANCE MONITORING

Clinical research monitoring for regulatory compliance and data integrity will be conducted according to the NCI-approved NCCC *Data and Safety Monitoring Plan*. Monitoring is conducted by appropriately trained staff of the NCCC Office of Clinical Research and Dartmouth-Hitchcock Medical Center's Clinical Trials Office (CTO) who are not involved in the study. This monitoring will include periodic assessment of the regulatory compliance, data quality, and study integrity. The investigator will ensure the capability for inspections of applicable study-related facilities (e.g., diagnostic laboratory). Study records will be reviewed and directly compared to source documents and the conduct of the study will be discussed with the investigator. Monitors may request access to all regulatory documents, source documents, CRFs, and other study documentation for on-site inspection. Direct access to these documents is guaranteed by the investigator, who must provide support at all times for these activities.

Data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

Section 10. DATA TRANSFER

De-identified study data will be shared with the funding organization, CairnSurgical, Inc. (Cairn), under a data use agreement. Cairn will use the data to inform commercial development of optimal imaging strategies and requirements for the creation of the BCL device. In addition, the supine MRI data set will also help Cairn to develop efficient image processing techniques and algorithms to extract anatomical and disease features required for the construction of the BCL device. Published results from this study and other findings derived

from the study data may be submitted to the FDA to support regulatory submission(s) for the BCL device.

Cairn will store and maintain the data indefinitely in a secure password-protected database.

Data from participants who signed a consent which does not name CairnSurgical, Inc. in the privacy section will not be shared with Cairn.

Section 11. RECORD RETENTION

Following closure of the study, the investigator will maintain all site study records in a safe and secure location. The records are maintained to allow easy and timely retrieval when needed (e.g., for audit or inspection) and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Upon completion of study analysis, research information is stored in Dartmouth College Records Management off-site storage located at 6218 Etna Road, Hanover, NH. Documents are shredded on-site after 50 years of storage.

Electronic case report forms, participant, and study information will be kept in the password-protected Velos Clinical Trials Management System (or equivalent) indefinitely.

Section 12. HUMAN SUBJECTS

All patients will sign an informed consent, which describes the treatment to be performed and discusses the risks and benefits of participation in the study.

Patients must give a statement of informed consent. The informed consent must meet the requirements of the FDA (21 CFR 50.25 Elements of Informed Consent) and the Committee for the Protection of Human Subjects at Dartmouth College, the Dartmouth-Hitchcock Medical Center's IRB. The team members obtaining consent will have the appropriate education, expertise, and background to understand and relay the concepts in the study and answer questions. They will have documented protocol-specific training. Each subject must sign and date an informed consent prior to the subject entering the study (i.e., before initiation of non-routine tests). This form must be counter-signed by the person who conducted the consent discussion. The final consent form must be agreed to by the institution's IRB (CPHS) and must contain all elements required by federal regulation in language readily understandable by

subjects. Each subject's original consent form will be retained by the investigator. A copy of the informed consent will be given to the subject.

Risk/Benefit analysis:

Risks associated with this study include the risks additional time in the MRI machine and potential confidentiality risks.

The risk of additional time in the MRI machine is negligible.

Risk of breach of confidentiality of the medical records of participants will be minimized. Subject identity is numerically coded and is not available to research investigators or otherwise stored on the databases maintained by the researchers to archive the clinical encounters accrued as part of the studies conducted under this protocol. In this regard, all conventional clinical image data is de-identified prior to its use for analysis. Databases which are used to store subject-sensitive information, even though completely de-identified as stored, are password-protected and encrypted during file/data transfers from viewing terminals. As further safe-guard, the Data Safety Monitoring and Accrual Committee of the Norris Cotton Cancer Center will oversee the conduct of the trial.

The importance of the knowledge to be gained and the ultimate potential for benefit for future patients if this new technology is effective far outweighs the nominal risks experienced by the women who participate in this clinical study.

Pregnant women will be excluded due to the potential risk of gadolinium to the fetus.

Women with child-bearing potential are eligible for enrollment into the study. The risks of participating in the imaging sessions for these women are no greater than for any other participant. Risks associated with breast surgery vis-à-vis child-bearing potential are outlined as part of standard of care. Thus, any woman of child-bearing years enrolled in this protocol would already understand (and have accepted) the surgical risks to her fertility.

Only women will be enrolled in the study because breast cancer is predominantly a female disease. The imaging apparatus is design to accommodate the size and shape variations associated with the adult female breast. While a very small proportion of breast cancer appears in males, the imaging systems are not designed to image the male breast. All racial and ethnic categories will be recruited commensurate with the racial/ethnic composition of the DHMC patient catchment area.

Patients will be considered “on study” and will be monitored for adverse events by the Principle Investigator from the time of registration until 2 weeks after imaging.

Section 13. OBLIGATIONS OF INVESTIGATORS

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the *Code of Federal Regulations* and/or the *Declaration of Helsinki*. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his final signature to verify the accuracy of the data.

Section 14. REFERENCES

1. Barth R**,** Krishnaswamy V, Paulsen K, Rooney T, Wells W, Rizzo E, Angeles C, Marotti J, Zuurbier R, Black C. A patient specific 3D printed form accurately transfers supine MRI-derived tumor localization information to guide breast conserving surgery. *Ann Surg Onc* 2017; 10:2950-56.
2. Leong C, Daniel B, Herfkens R, et al. Characterization of breast lesion morphology with delayed 3DSSMT: an adjunct to dynamic breast MRI. *JMRI* 2000; 11:87-96.