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- Protocol title: SUPINE MRI IN BREAST CANCER PATIENTS RECEIVING UPFRONT SURGERY OR NEOADJUVANT THERAPY
- NCT #: NCT02956473
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**TITLE: Supine MRI in Breast Cancer Patients Receiving Upfront Surgery or Neoadjuvant Therapy**

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**Study Exempt from IND Requirements per 21 CFR 312.2(b).**

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# STUDY SCHEMA

**Selection, Enrollment and Imaging:**

Newly diagnosed breast cancer (stage I, II, III non-inflammatory) planning upfront surgery or neoadjuvant therapy (NAT)

↓

Patient informed consent obtained
Eligibility confirmed
Patient registered

↓

Pre-surgery or Pre-NAT MRI performed in routine prone position and investigational supine position

↓

Extent of disease/ lesions seen on MRI compared with other standard imaging modalities including mammogram and ultrasound

↓

If additional suspicious findings seen only on MRI a second-look US and/or addition mammographic views with or without biopsy will be performed using prone and supine MRI sequences for guidance

↓

Radiologist completes brief survey regarding usefulness of supine MRI for second-look US +/- biopsy (if applicable)

**Patient proceeds with upfront surgery or NAT:**

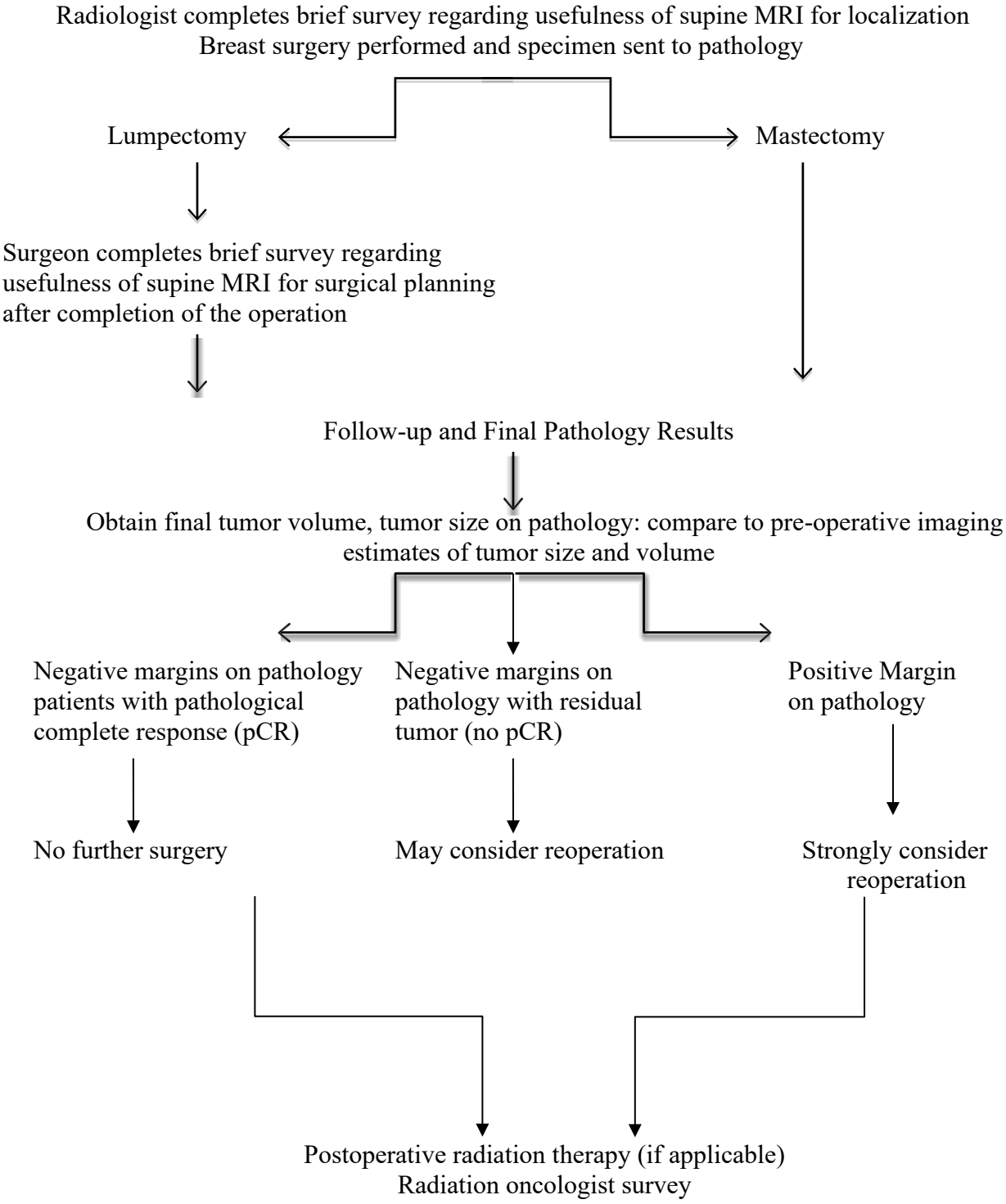
If receives NAT, post-NAT imaging obtained to include +/-mammogram, +/- US, + breast MRI prone+supine

↓

**Surgery:**

Per surgeon/radiologist preference, tumor localization (with wire or radio-seed) performed by radiologist prior to surgery

↓


Radiologist completes brief survey regarding usefulness of supine MRI for localization
Breast surgery performed and specimen sent to pathology
Lumpectomy
Mastectomy
Surgeon completes brief survey regarding usefulness of supine MRI for surgical planning after completion of the operation
Follow-up and Final Pathology Results
Obtain final tumor volume, tumor size on pathology: compare to pre-operative imaging estimates of tumor size and volume
Negative margins on pathology patients with pathological complete response (pCR)
Negative margins on pathology with residual tumor (no pCR)
Positive Margin on pathology
No further surgery
May consider reoperation
Strongly consider reoperation
Postoperative radiation therapy (if applicable)
Radiation oncologist survey

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# OBJECTIVES

## 1.1 Study Design and Hypotheses

This study is designed as a prospective Phase II trial aimed to determine the value of supine breast MRI for women newly diagnosed with stage I-III non-inflammatory breast cancer undergoing upfront surgery or neoadjuvant therapy (NAT).

We hypothesize that breast MRI with supine sequences will provide advanced image-based characteristics for (1) radiological procedures (2) surgical operations and (3) adjuvant radiation delivery, and further hypothesize that these images will allow for superior characterization and localization of breast lesions as compared to traditional imaging studies (mammography, ultrasound, prone MRI). This will be measured by a combination of qualitative (clinician surveys of supine MRI usefulness for radiologic and surgical procedures and for radiation treatment/delivery) and quantitative measures (correlation in residual tumor size estimation with the gold standard method, success rate of US-guided lesion identification and/or biopsy performed with supine MRI guidance, and rate of re-excisions for breast conserving surgical operations when supine MRI used for surgical planning).

More specifically, we hypothesize that:
(1) Supine breast MRI will provide an accurate assessment of residual breast tumor size
(2) Supine breast MRI will be superior to other imaging modalities in estimation of final tumor size as determined on post-operative pathology (gold standard).
(3) Supine MRI will help radiologists identify suspected satellite lesions and/or additional suspicious findings during the second look ultrasound procedure. Tissue sampling under sonographic-guidance is more cost effective and patient centric for the patient compared to biopsy under MRI-guidance; therefore, the correlation of MRI findings with ultrasound findings is an important patient-centered endpoint.
(4) Supine breast MRI will improve surgical planning efforts for breast conserving surgery by providing surgeons with more accurate information regarding the tumor's location within the breast in the supine position, which will translate into reduced re-excision rates associated with this procedure.
(5) Supine breast MRI will improve adjuvant radiation therapy planning efforts following breast surgery by providing radiation oncologists with more accurate imaging information of the patient in the supine position, allowing for potentially improved radiation delivery

A total of 74 patients will be recruited to participate in this study. Enrolled patients will under go upfront surgery or receive a NAT regimen at the discretion of the treatment team. All patients will have their breast tumor evaluated with standard imaging to include mammography, 2D and/or 3D, ultrasound, prone contrast-enhanced MRI and investigational supine contrast-enhanced MRI sequence pre-surgery. For patients planning for NAT, we will also attempt to obtain a prone contrast-enhanced MRI and investigational supine contrast-enhanced MRI sequence pre-NAT; however if a patient presents with an outside pre NAT MRI this will not be repeated. The tumor's position on all imaging modalities will be registered, and tumor location between supine and prone MRI sequences will be determined. Investigational supine MRI images will be provided to radiologists and surgeons for purposes of performing additional imaging interventions, if they are deemed necessary by the treatment team, and for surgical

planning. Estimates of tumor size pre-operatively as identified by each imaging modality will be compared to final pathology, allowing the correlation of each imaging modality for estimating residual tumor size with the gold standard method (pathology).

For patients undergoing BCT, the prone and supine MRI images will be registered in the image-processing software, 3D Slicer, and the segmented tumor models will be overlaid on the images. Screenshots showing the displacement of the tumor from the prone to the supine images will be provided to the surgeon to plan the tumor resection. Following completion of the operation a survey of the breast surgeon will be administered to determine their perceived usefulness of the supine imaging for surgical planning. Volume of excised tissue, rates of positive margins, and the need for reoperation, will be recorded, and these measures (using supine MRI imaging) will be compared to historical data to determine the impact of supine MRI imaging on surgical outcomes.

Patients requiring postoperative radiation therapy will be referred to radiation oncology post-operatively. Supine MRI images obtained prior to surgery will be provided to the radiation oncologists for breast treatment planning. A survey will then be administered to the attending treating radiation oncologist to assess the usefulness of supine MRI for treatment planning.

## 1.2 Primary Objectives

The primary objectives are:

1) Determine the Pearson correlation between pre-operative prone and supine MRI for estimating tumor size as compared to the gold standard of pathologic evaluation of the surgical specimen.
2) To compare the Pearson correlation between pre-surgical standard imaging (mammography, ultrasound, prone MRI) and the gold standard of pathologic evaluation of the surgical specimen and the Pearson correlation between pre-surgical supine MRI and gold standard of pathologic evaluation of the surgical specimen for the evaluation of tumor size.

3) To explore the potential changes occurring in tumor-associated properties/dimensions between the prone and supine imaging position and to determine the correlation of tumor location and geometry on pre-surgical supine MRI with prone MRI. Tumor location will be assessed in terms of distance from nipple, chest wall, and skin. Tumor geometry will be assessed on multiple properties including volume, surface area, diameter, spherocity, and compactness. Patients with both pre-NAT and pre-surgical MRI will also be evaluated for the pre-NAT prone/supine MRI and pre-surgical prone/supine MRI comparison.

## 1.3 Secondary Objectives

Secondary objectives for this trial are listed below.

1. To assess the value of supine MRI for radiologists performing second look US examinations/ biopsies following identification of new lesions on MRI, and performing preoperative lesion localization using supine MRI guidance. Value will be assessed by both qualitative (survey of

radiologists on perceived usefulness of supine MRI for imaging localization/procedures*) and quantitative measures (success rate of second-look ultrasound lesion localizations and procedures utilizing supine MRI guidance). Procedures include lesion biopsy and pre-surgical lesion localization performed by radiologist.
2. To explore the perceived benefit of pre-surgical supine MRI for surgical planning as measured by the collective results of a survey of surgeons performing BCS in our study patient population.
3. To explore the effect of supine MRI on influencing BCS outcomes by determining the percent of patients requiring re-excisions or having a pathologic positive margins when supine MR imaging is performed and available for surgical planning purposes.
4. To explore the perceived benefit of pre-surgical supine MRI for adjuvant radiation breast treatment planning as measured by the collective results of a survey of radiation oncologists treating patients in our study population post-operatively.

## 2. BACKGROUND

### 2.1 Study Disease and Rationale

Breast cancer affects millions of women worldwide and is the second most common cancer in the world [1]. Over 249,00 new cases of breast cancer are estimated to be diagnosed in 2016 in the United States alone, with breast-cancer specific morality rates predicted to exceed 40,000 [2]. Treatment for breast cancer has evolved in recent decades following an improved understanding of the biology of the disease, and contemporary breast cancer care now mandates a multidisciplinary, multimodal approach for optimal outcomes. Surgery, radiation, and systemic therapy (including endocrine, biologic, and chemotherapeutic agents) are key modalities utilized in the ongoing treatment algorithm for breast cancer patients. For early stage disease, breast conservation therapy or 'BCT' (consisting of lumpectomy or 'breast conserving surgery' (BCS) followed by post-operative radiation therapy) has become a mainstay of treatment following demonstration of its equivalence to mastectomy in terms of long term survival in at least six modern prospective randomized trials [3-8].

BCT has enabled less invasive surgical treatment for breast cancer without compromising survival, however it currently is limited in its application to well-selected candidates. Although size is not an absolute contraindication to BCT, a very large tumor size relative to breast volume is considered a relative contraindication [9]. MRI is routinely utilized to determine extent of disease at diagnosis and to determine candidacy for upfront surgery in patients who are desirous of BCT. For women with large and locally advanced breast cancers, breast conserving surgery only became a surgical option following the inclusion of neoadjuvant therapy (NAT) into contemporary cancer treatment algorithms. NAT has demonstrated efficacy in shrinking breast tumors preoperatively, enabling some patients to become BCT candidates who otherwise would not have qualified [10-14]. Numerous studies have established equivalence of BCT after NAT compared to BCT with post-surgical systemic adjuvant therapy with respect to both survival and local recurrence rates [13, 15-17]. By utilizing modern era therapy, over 50% of patients with certain breast cancer subtypes (including triple negative and HER2+) treated with NAT are expected to achieve a pathological complete response (pCR) following NAT administration, which is associated with improved long-term prognosis [18, 19].

In the upfront surgery setting, the use of Breast MRI has been shown to compliment traditional

imaging modalities (MMG/US) for determining extent of disease; however there remains a problem with over-estimation of lesion size. This combined with the frequency of identification of second lesions which require biopsy (and are often not visible on MMG/US) has been shown to correlate with increased use of mastectomy, with patients often deferring biopsy altogether. Whether or not supine MRI can improve upon correlation with tumor size in the upfront surgery setting and whether or not supine MRI can lead to improved identification of second lesions requiring biopsy has not been tested.

In the NAT setting, breast MRI has demonstrated higher accuracy over physical examination, mammography, and targeted breast ultrasound in the evaluation of tumor response to NAT and prediction of amount of residual disease. [12, 20-28]. The correlation of residual tumor size following NAT and histopathology in patients who underwent prone MRI before BCS has been reported to be approximately r=0.7 (Bhattacharyya et al (r=0.71), Rosen et al (r=0.75), Martincich et al (r=0.72), Segara et al (r=0.75)[12, 27-29]. For patients who require NAT for downstaging to BCT, repeating the MRI after NAT (pre-surgery) is standard for surgical treatment planning. In practice, it is uncommon to exclusively rely on a single imaging modality for breast cancer evaluation, and newly diagnosed breast cancer patients routinely have diagnostic mammography and ultrasound imaging as well. In patients undergoing NAT, these images are also repeated after NAT (pre-surgery) for surgical treatment planning.

One of the challenges inherent with the current breast MRI design is that the images are obtained with the patient in the prone position. Tumors are displayed to both radiologists and surgeons in relation to their position in the prone breast, however both ultrasound and surgery are performed on the supine breast. The changes in breast position- especially for patients with large or pliable breasts- can significantly displace breast tumors, making it difficult for radiologists to correlate MRI and sonographic findings, and for surgeons to localize tumors intraoperatively[33, 34].

Limitations of other modalities are numerous. For example, NAT can induce unpredictable fibrous changes that can reduce the reliability of clinical examination. Certain breast cancer subtypes, such as lobular carcinoma for example, are difficult to visualize mammographically and can increase in firmness after NAT, causing an initially occult lesion to become more clinically palpable with treatment[30]. Assessment of tumor size on exam and with mammography can be undermined by the infiltrative nature of locally advanced breast cancers, especially in the setting of dense breast tissue [25, 26, 31]. Suspicious microcalcifications initially noted on mammogram may persist, become coarser, or occasionally increase on mammograms after NAT. Peintinger et al demonstrated that a combination of mammogram and ultrasound could provide moderate agreement in predicting residual tumor size after NAT; however, the correlation and agreement with pathologic residual tumor size was underestimated for lobular carcinoma and overestimated for poorly differentiated tumors [32]. Yeh et al also demonstrated similar findings when comparing agreement regarding the rate of response between clinical examination, mammography, sonography, and MRI with pathology as the reference standard, with agreement rates of 19%, 26%, 35%, and 71%, respectively [26]. Although MRI was noted to be the superior modality in this study, it was not without its own limitations; MRI was felt to both underestimate and overestimate residual tumor measurements, leaving clinicians with an ongoing need for an improved way to monitor the response to and the disease remaining after NAT regimens.

Breast imaging, most commonly breast CT, is used post-operatively for patients requiring adjuvant radiation therapy, in order to identify radiation delivery regimens that will accurately and completely target the desired tissue while minimizing the effect on surrounding structures such as the heart and lungs. Treatment plans are designed on a patient-by-patient basis, and are influenced by a range of factors including breast density, lumpectomy cavity volume, and use of adjuvant chemotherapy, which can delay radiation treatment and contribute to cavity contraction making cavity identification more challenging [35, 36]. Multiple studies have demonstrated limitations in single-modality treatment planning with significant inter-observer variability in delineation of tumor cavities, and multi-modality imaging using a combination of MRI and CT has been suggested as a way of improving target volume definition in patients with difficult to visualize cavities [35, 37-39]. Jacobson et al, for example, found that acquisition of a non-contrast supine MRI during treatment planning sessions provided more detailed visual information than CT in the post-lumpectomy breast, and suggested that the combination of images could improve delineation of target cavities [35]. Nevertheless, debate remains about the ultimate utility of MRI for breast treatment radiation planning, and additional studies evaluating the potential benefits are warranted [39-42].

A secondary objective of a Phase I Clinical Trial we recently completed at our institution evaluating the feasibility of intraoperative breast MRI was to better characterize the positional change that occurs between the prone and supine imaged breast [30, 33, 34]. Our results, presented in 2015 at the Society of Breast Imaging Annual Meeting and at the New England Surgical Society Annual Meeting, showed that substantial tumor displacement occurs when the breast changes from the prone to the supine position, with an average tumor displacement of over 6cm [43, 44]. Additionally, we found substantial tumor deformation occurring between positions, with an average change in the measured volume of 23.8%, surface area of 6.5%, compactness of 16.2% and maximum 3D diameter of 7.1% (mean change from prone to supine imaging (as a percentage of the prone metrics) [34, 43]. This was unanticipated, as breast cancers have been shown to be more stiff than surrounding breast parenchyma (Krouskop et al showed stiffness of normal fat, normal glandular tissue, and invasive ductal carcinomas to be 20 kPa, 57 kPa, and 490 kPa, respectively) and thus deformation was suspected to be negligible [43, 45]. These deformations and displacements were visually represented on ‘composite’ MRI images, which simultaneously displayed a tumor’s location/shape using “3D tumor models” in both the prone and supine position (tumors were registered, and prone and supine MRI were overlaid), enabling surgeons and radiologists alike to visually identify each tumor’s location/size/shape in both orientations. Briefly, this was achieved by rigidly registering breast tumors on both post-contrast MRI series on thoracic cavities using the Mutual Information criterion, following initial alignment of the pulmonary veins [46-48]. 3D tumor models were then created in 3D Slicer by segmenting the tumors on the supine and prone MRIs using semi-automatic threshold-based algorithms on the subtracted images computed from the first post- and pre-contrast volumes, which were then further registered using Iterative Closest Point registration [48]. These tumor models, and their associated prone and MRI scans, were overlaid to generate the composite models presented to surgeons prior to surgery. Anecdotally, we found that these composite images were viewed as useful by both radiologists and surgeons alike, in assisting with tumor localization and with surgical planning. Based on these results, our institution adopted a policy

that allows for selective performance of supine MRI sequences in addition to prone MRI sequences for patients undergoing breast MRI earlier this year.

Contrast-enhanced breast MRI is a useful imaging tool however it is not indicated for all patients with breast cancer. Although it has high sensitivity and moderate specificity for detecting breast carcinoma, it is associated with false positive findings and prospective and retrospective studies have failed to show that routine prone preoperative MRI is beneficial in improving BCT outcomes in terms of re-excision, local recurrence, or overall survival rates yet its use persists.[49-55] Further although post NAT is associated with the highest correlation between residual tumor size and pathologic size; it's use in this setting has also not been demonstrated to improve BCT outcomes. This study will evaluate the role of obtaining supine breast MRI in addition to prone breast MRI in patients undergoing upfront surgery or receiving NAT. We hypothesize that having supine sequences in addition to prone sequences available for review by breast surgeons and radiologists that this will 1) improve surgical conceptualization of breast tumors in the supine position and thus improve surgical planning, 2) influence outcomes including positive margin/reoperation rates following breast conserving surgery, 3) aid radiologists in identifying tumors on targeted ultrasound, and 4) improve the direct comparison of tumors at MRI and ultrasound.

### 2.2 Correlative Studies Background

Not applicable

## 3. PARTICIPANT SELECTION

### 3.1 Inclusion Criteria

3.1.1 Participants must be female

3.1.2 Participants must have a pre-operative standard mammogram with or without ultrasound. These may be performed at outside institutions but must be reviewed at BWH/DFCI.

3.1.3 Participants must have biopsy confirmed and clinical stage I, stage II, or stage III non-inflammatory breast carcinoma. If biopsy was done at an outside hospital, pathology will be reviewed at (BWH, BWFH)

3.1.4 Patient must meet standard MRI guidelines and be able and willing to undergo MRI

3.1.5 Participants must be candidates for definitive local therapy with breast conserving therapy or deemed as potential candidates following NAT (this takes into account tumor to breast size ratio appropriate for BCT, and the ability to undergo standard radiation therapy post-operatively).

3.1.6 Study participants will be restricted to those aged ≥18.

3.1.7 Ability to understand and the willingness to sign a written informed consent document.

### 3.2 Exclusion Criteria

3.2.1 Participants with a known BRCA 1 or 2 mutation.
3.2.2 Participants with a known Li-Fraumeni or Cowden's Disease.
3.2.3 Participants with prior mantle radiation.
3.2.4 Participants with inflammatory breast cancer or multi-centric disease
3.2.5 Participants who are pregnant.
3.2.6 Participants who are already enrolled in a conflicting investigational trial
3.2.7 Participants with known active collagen vascular disease.
3.2.8 Participants with prior history of ipsilateral breast carcinoma treated with BCS and radiation therapy.
3.2.9 Patients who have biopsy confirmed multi-centric disease not eligible for BCS.
3.2.10 Participants who are unable to undergo MRI because of documented contra-indications for contrast-enhanced MRI, including but not limited to renal failure
3.2.11 Participants who exceed the weight limit for the operative surgical table, 350 lbs or who will not fit into the 60 cm diameter bore of the MRI scanner.

### 3.3 Inclusion of Women and Minorities

3.3.1 **Inclusion of Women and Minorities:** Only women are involved in this study. Men are not at likely as women to have breast cancer and are not likely candidates for breast conserving surgery, and are not eligible for this trial. Approximately 10% of the target enrollment is Hispanic or African American, which is reflective of the demographics of a patient population who present serially and are evaluated for breast cancer in our practice.

3.3.2 **Inclusion of Children:** Breast cancer is rare in children and children would not likely be candidates for neoadjuvant therapy and are excluded from this study.

## 4. REGISTRATION PROCEDURES

### 4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

### 4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol*

*Registration* (SOP #: REGIST-101) must be followed.

### 4.3 General Guidelines for Other Investigative Sites

Not applicable

### 4.4 Registration Process for Other Investigative Sites

Not applicable

## 5. TREATMENT AND IMAGING PLAN

### 5.1 Treatment Plan

Enrolled patients are those who have newly diagnosed Stage I, II, or III non-inflammatory breast cancer undergoing upfront surgery or NAT, with inclusion and exclusion criteria in Section 3. For this study, the treatment will include performance of an investigational supine MRI, in addition to standard prone MRI, mammography, and ultrasound, performed at one of our participating sites in the pre-surgical setting. Imaging will be performed on an outpatient basis, as is standard for breast cancer patient management. For patients receiving NAT, as is described in Section 5.2.1, pre NAT MRI will be attempted. If additional lesions/extent of disease is suggested on investigational MRI, additional imaging evaluation with mammography and/or ultrasound may be performed (refer to Section 5.2.1 below). In cases in which additional imaging evaluation with/without biopsy is required following MRI exams, attending breast radiologists will complete a short survey on their perceived usefulness of the supine MRI in lesion localization and/or lesion biopsy. Histopathology will be correlated to radiographic lesion findings in cases in which biopsy are performed.

Patients deemed candidates for BCS with upfront surgery will proceed to surgery using the supine and prone imaging studies for surgical planning. Patients who will be receiving NAT per their clinical treating team. Post NAT (pre-surgical) imaging will be obtained at the completion of NAT (refer to Section 5.2.2). These imaging studies will then be reviewed by the treating radiologist and surgeon, and will be utilized for surgical planning. Surgery will be either standard BCT or mastectomy (with appropriate nodal intervention including sentinel lymph node biopsy and/or axillary dissection), as deemed appropriate by the treating surgeon. No investigational or commercial agents, or devices will be used or administered during the operation with the intent to treat the participants' breast cancer. When BCT is performed, standard cavity shave margins will be taken (as per institutional guidelines). At the conclusion of the operation, the surgical specimen will be sent for histopathology. If the final pathology indicates that there are positive margins amendable to resection, the patient will be scheduled to undergo re-excision and/or mastectomy in the standard operating room. At the discretion of the treating surgeon, additional re-excisions may be performed for close margins not meeting the definition of a true positive margin. Following completion of each BCT operation, the attending surgeon will be asked to complete a brief survey to assess their perceived usefulness of the supine MRI data in surgical planning/lesion localization.

This protocol will include the standard imaging sequences to image the patient in the prone position and identify the extent of the disease. In addition, a single post-contrast MRI VIBE sequence of the breast with the patient in the supine position will be obtained. The prone and

supine MRI images will be registered in the image-processing software, 3D Slicer, and the segmented tumor models will be overlaid on the images. Screenshots showing the displacement of the tumor from the prone to the supine images will be provided to the surgeon to plan the tumor resection. The supine post-contrast sequences will be used to estimate the tumor position with respect to fixed landmarks such as the nipple, skin and chest wall. If there are additional findings seen initially on MRI, the supine sequence will help to localize the findings during second look ultrasound.

For patients who received NAT, post-NAT pre-operative breast MRI with supine sequence will be obtained. If tumor was visible pre-NAT on the other imaging modalities such as mammogram, 2D and/or 3D ultrasound they will also be performed at post-NAT. These images will be used to determine if preoperative lesion localization is necessary using either radioactive seed or wire placement; if required, these images will be utilized by the breast imaging service preoperatively for lesion localization procedure per standard practice and the radiologist will be surveyed post-localization regarding usefulness of supine MRI for lesion localization procedure. Supine MRI will be provided in addition to standard imaging modality images for patients ultimately eligible for breast conserving surgery for preoperative surgical planning and for intraoperative tumor resection.

Patients enrolled to participate in this study will receive standard of care with breast conserving therapy or mastectomy for local therapy. Detailed risks and benefits of participating in the study will be reviewed with patients prior to obtaining consent, and all questions will be answered. After general endotracheal anesthesia is induced, the standard operation will be performed by a breast surgical oncologist, including a lumpectomy or mastectomy, with or without sentinel node biopsy and/or possible axillary dissection. The surgical specimen will be sent for standard histopathology. Final specimens will include the original lumpectomy specimen, any nodal tissue (sentinel node(s) versus axillary dissection components if nodal procedure was performed), and shave margins/targeted re-excisions. These samples will be sent for analysis by pathology.

## 5.2 Description of Intervention/Intervention Regimen

### 5.2.1 Pre-Surgical Evaluation

Patients with biopsy-proven breast cancer deemed eligible for this study (refer to inclusion/exclusion criteria, Section 3) will be identified during surgical consultation at a participating institution. A signed, written consent form will be obtained before any study-specific assessments are initiated. Each participant will undergo a history and physical examination, and will be required to have a diagnostic mammogram with or without ultrasound reviewed at Brigham and Women's Hospital (BWH) or Dana Farber Cancer Institute (DFCI). Patients who are eligible and give written consent to participate will then be scheduled to receive a prone and supine contrast-enhanced MRI. Patients who have already had a breast MRI at an outside institution, for their present cancer, and who will receive NAT, will not be required to undergo an additional pre-NAT MRI. All patients (upfront surgery and NAT patients) will be required to have a pre-surgical prone and supine MRI. Prone MRI will consist of the standard imaging sequences as identified by institutional guidelines to image the patient's breast(s) in the prone position and identify the extent of the disease. An FDA-approved gadolinium-based MRI contrast agent, as per standard of care, will be administered in order to acquire images that will be used to identify the lesion. The dosage will be consistent with institutional safety guidelines. See Section 6 below for further information regarding MRI contrast agent.

In addition, a single post-contrast MRI VIBE (volumetric interpolated breath-hold examination) sequence of the breast with the patient in the supine position will be obtained. Prior to obtaining this MRI, a second dose of gadolinium MRI contrast agent may be given at the discretion of the radiologist, with dose calculated by the radiologist per institutional policy, to ensure adequacy of supine MRI images. The supine post-contrast sequences will be used to estimate the tumor position with respect to fixed landmarks such as the nipple, skin and chest wall. If MRI identifies additional disease not initially seen on other imaging exams, repeat ultrasound and/or mammogram with additional views will be performed ('second look' exams) to attempt to identify these lesions on an additional imaging modality. Biopsy of newly identified suspicious lesions will be executed with MRI, ultrasound, or stereotactic guidance at the discretion of the treatment team, and histopathologic-radiographic correlation will be performed.

### 5.2.2 Post-NAT Evaluation

For patients undergoing NAT, repeat evaluation with imaging studies will be performed at the conclusion of NAT treatment,. Imaging will include dedicated pre-surgical breast MRI in both prone and supine positions, as well as ultrasound and mammography as deemed necessary by the treatment team. Imaging protocols utilized for post-NAT evaluation will be per institutional standards and will be consistent with those utilized for pre-NAT evaluation.

These imaging studies will then be reviewed by the treating radiologist and surgeon, and determination will be made if a radiographic complete response (rCR) has occurred. Quality of the supine MRI sequence will be determined by the attending radiologists, and at this time if the quality is deemed unacceptable for interpretation, the image will not be utilized in residual tumor calculations. If rCR has not occurred, estimated sizes and volumes of the remnant tumor will be made using each imaging modality by the treating radiologist and recorded in standard format. If additional disease is uncovered at this time, it will also be recorded. Using the information obtained from the totality of imaging studies, the surgeon will determine whether or not the patient is eligible to proceed with BCT or mastectomy.

### 5.2.3 Surgery

Surgery will be either BCT or mastectomy (with appropriate nodal intervention including sentinel lymph node biopsy and/or axillary dissection), as deemed appropriate by the treating surgeon and according to current guidelines. Informed consent as per institutional standards will be obtained from the patient prior to surgery and all risks and benefits of surgical intervention and alternative options (no surgery) will be reviewed with the patient. When BCT is performed, standard cavity shave margins will be taken (as per institutional guidelines). At the conclusion of the operation, the surgical specimen will be sent for histopathology. Following completion of each BCT operation, the attending surgeon will be asked to complete a brief survey to assess their perceived usefulness of the supine MRI data in surgical planning/lesion localization.

### 5.2.4 Post-Surgery: Histopathogy Assessment

Lymph node specimens (if taken during surgery) will be evaluated by histopathological analysis along with the breast specimen (lumpectomy or mastectomy) at the conclusion of surgery. If the final pathology indicates that there are positive margins amendable to resection, the patient will be scheduled to undergo re-excision and/or mastectomy in the standard operating room. At the discretion of the treating surgeon, additional re-excisions may be performed for close margins not meeting the definition of a true positive margin.

## 5.3 Post-Surgery: Adjuvant Radiation Therapy

Patients who require adjuvant radiation therapy postoperatively will be referred to radiation oncologists at the DFCI. If the patient chooses to pursue their radiation treatment with DFCI clinicians (patients are offered a choice as to where to complete their radiation treatment), then the radiation oncologist will be provided with all imaging, including supine MRI images acquired pre-surgery for treatment planning purposes. These images will be utilized for planning of the radiation treatment plan. Following completion of the initial radiation treatment plan, the attending treating radiation oncologists will be asked to complete a brief survey to assess their perceived usefulness of the supine MRI data for treatment planning purposes.

## 5.4 Duration of Follow Up

All patients will have a post-surgical visit at their surgical institution (BWH or BWFH). Participants will be followed until their first post-surgical visit after the completion of surgical therapy.

## 5.5 Criteria for Taking a Participant Off-Study

If the patient is enrolled in the study, and they are unable to undergo supine MRI for any reason, or during the course of the supine MRI they are unable to complete the supine MRI series, they will discontinue participation in the study at that time. Those patients who, following enrollment in the trial, do not proceed to receive a pre-surgical MRI, or who do not receive surgery at one of our institutions, will be removed from the study.

Participants will also be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

For Centralized Subject Registrations, the research team submits a completed Off Treatment/Off Study form to ODQ when a participant comes off study. This form can be found on the ODQ website or obtained from the ODQ registration staff.

For Decentralized Subject Registrations, the research team updates the relevant Off Treatment/Off Study information in OnCore.

## 6. EXPECTED TOXICITIES, ADVERSE EVENTS, AND DOSING DELAYS/DOSE MODIFICATIONS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. There are no interventional agents (drugs or devices) being investigated as part of this protocol, and therefore there are no associated adverse events such as toxicities that would commonly be anticipated in these scenarios. There are also therefore are no protocol-specific dose delays or modifications unique to this study to report.

This protocol will utilize gadolinium contrast-enhanced MRI imaging, which is a standard FDA-approved imaging agent, and expected toxicities are therefore included and described here. The use of gadolinium contrast has been associated with relatively minimal risk compared to other contrast agents; however, some contrast-related reactions have been identified [56, 57]. IV-administered gadolinium contrast has been associated with renal failure and allergic reactions. Both of these events are identified as potential adverse events, and patients will be informed of the risk of such adverse events. Patients that have a known contrast allergy will be excluded from participating in this study. There is approximately 0.07% risk of an allergic reaction with IV contrast according to a retrospective review of 78,353 cases of IV-gadolinium injections published in 2007, with a more recent study reporting an overall adverse effect rate of 0.0404% among 158,439 administrations, within the 0.0003-1.2% range reported in other studies [56, 57]. If an allergic reaction does occur, the procedure will be aborted and supportive care, including maintaining airway and administration of steroids and epinephrine, will be initiated. This will be reported appropriately as an adverse event. Patients will be screened to ensure they are MRI-eligible and those who are not for any reason, including but not limited to renal failure, will be excluded from participating in this study.

In our protocol, two MRI sequences will be obtained. Of these two sequences, prone and supine, the prone sequence is standard and the supine MRI is investigational. Additional adverse events applicable to this study will therefore be related to performance of supine MRI sequences. All patients undergoing supine MRI will already be receiving a prone MRI. To perform supine MRI, patients will be subjected to physical maneuvering required to position them and their breast(s) in the supine position to obtain the imaging series. It is possible that an adverse event may occur during this maneuvering. These events would be unanticipated, and would be reported according to institution guidelines. An additional smaller dose of gadolinium-based contrast agent may be administered prior to supine MRI, which would result in patients receiving higher contrast doses

than routine breast MRI examination. The risk for nephrotoxicity and nephrogenic systemic fibrosis is infinitesimally small in patients with normal renal function, however, and the dose and concentration that each patient receives will be calculated such that FDA guidelines for contrast agents are met and such that there will be no significant increased risk of nephrotoxicity compared to that with routine breast MRI with contrast. The additional dose of contrast may, however, slightly increase the risk of gadolinium-based contrast retention. Recent studies have shown that gadolinium-based contrast may persist long after administration (primarily in the brains of patients who are subjected to four or more contrast-based MRI scans), even in patients with normal renal function. The significance of this retention, however, remains uncertain, as it is currently unknown if these gadolinium deposits are harmful or could lead to adverse health effects.

## 6.1 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

## 6.2 For Expedited Adverse Event Reporting

6.2.1 Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the intervention, or within 30 days of the intervention, on the local institutional SAE form.

6.2.2 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

## 6.3 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

### 6.4 Routine Adverse Event Reporting

Not Applicable

## 7. STUDY CALENDAR

| Assessment | Prior to upfront surgery or NAT treatment (within 3 months of registration) | Post-NAT Evaluation | Surgery | Post-operatively (within six weeks after surgery) |
|---|---|---|---|---|
| History and Breast Exam | X | X | | X |
| Vital Signs | X | | | X |
| Conventional Mammogram with or without US | X | X | | |
| Staging biopsy | X | | | |
| Informed Consent | X | | | |
| Prone MRI | X | X | | |
| Supine MRI | X | X | | |
| Second look Ultrasound / Mammography with/without biopsy* | X* | | | |
| Radiologist Surveys | X‡ | X‡ | X‡ | |
| Surgery | | | X | |
| Surgeon Survey s | | | | X |
| Pathology Review | | | | X |
| Radiation Oncologist Survey | | | | X† |

*Second look ultrasound and/or biopsy will only be performed if deemed necessary by the treating team in scenarios in cases in which additional lesions are newly identified during MRI evaluation (this is an 'optional' and not 'mandatory' portion of the study)

‡ Radiologist surveys will be completed after second-look US performance (pre/post NAT) and/or at time of breast biopsies (pre/post NAT) and/or at time of lesion localization (day of surgery) when supine MRI information is used.

†Only in cases of patients who are referred for postoperative radiation therapy and have a treatment plan made by DFCI radiation oncologists.

## 8. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event information and instructions for AE reporting can be found in Section 6 (Adverse Events: List and Reporting Requirements).

### 8.1 Data Reporting

8.1.1 Method

The trial is collecting limited data variables. The study team will collect, manage, and perform quality checks on the data for this study. The study will utilize a case report form collected after patients complete all study procedures and up to 30 days after their study completion. Surveys from providers will be collected at the completion of a patient's on study procedures. Data will be collected and shared with an outside collaborator for analysis. The data will not be identifiable.

8.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC are responsible for submitting data forms to the Overall PI within 30 days of a patient coming off study.

### 8.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

### 8.3 Multicenter Guidelines

Not applicable

### 8.4 Collaborative Agreements Language

Not applicable

## 9. STATISTICAL CONSIDERATIONS

This is a phase II study aimed at evaluating the ability of breast MRI (prone and supine) to accurately estimate breast tumor size (in term of correlation with gold standard size on post-operative pathology analysis). This study is also designed to compare correlation between supine

breast MRI with existing imaging modalities at estimating tumor size. Finally, this study is designed to characterize the changes occurring in breast tumor-associated properties/dimensions between the prone and supine imaging position and to determine the correlation of tumor location and geometry on pre-surgical supine MRI and prone MRI. A total of 80 patients will be recruited to participate in this study.

### 9.1 Study Design/Endpoints

The primary objective of the study is to determine the usefulness of pre-surgical prone and supine MRI for estimating tumor size (as compared to tumor size on post-operative pathology, which is the existing gold standard). This will be evaluated using correlation coefficients between estimated tumor size on prone MRI and estimated tumor size on post-operative pathology.

### 9.2 Sample Size, Accrual Rate and Study Duration

For the primary outcome, with 73 eligible patients we will have 90% power to detect a correlation coefficient between pre-surgical prone or supine MRI and tumor size of 0.85 from 0.70 with a two-sided one sample z-test at alpha=0.05 level.

With 73 eligible patients, we will also have more than 80% power to detect a difference in correlation from 0.85 between the supine MRI and the pathology tumor size and 0.70 between the standard imaging and the pathology tumor size with a two-sided two sample z-test at alpha=0.05 level, assuming the correlation between the supine MRI and the standard imaging is 0.70.

Assuming the dropout rate will be 10%, we will plan to accrue a total of 80 patients. With an anticipated enrollment of 5 patients per month, accrual should be completed in approximately 16 months.

The below table “Accrual Targets” reflects the accrual targets anticipated for this study. As noted in detail in Section 3.3, men are not likely candidates for breast conserving surgery, and are not eligible for this trial. Approximately 10% of the target enrollment will be Hispanic or African American.

| Accrual Targets | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Ethnic Category** | **Sex/Gender** | | | | | | | |
| | **Females** | | | **Males** | | | **Total** | |
| Hispanic or Latino | 8 | | + | 0 | | = | 8 | |
| Not Hispanic or Latino | 72 | | + | 0 | | = | 72 | |
| **Ethnic Category: Total of all subjects** | 80 | (A1) | + | 0 | (B1) | = | 80 | (C1) |
| **Racial Category** | | | | | | | | |
| American Indian or Alaskan Native | 1 | | + | 0 | | = | 1 | |
| Asian | 4 | | + | 0 | | = | 4 | |
| Black or African American | 12 | | + | 0 | | = | 12 | |
| Native Hawaiian or other Pacific Islander | 0 | | + | 0 | | = | | |
| White | 63 | | + | 0 | | = | 63 | |
| **Racial Category: Total of all subjects** | 80 | (A2) | + | 0 | (B2) | = | 80 | (C2) |
| | | (A1 = A2) | | | (B1 = B2) | | | (C1 = C2) |

### 9.3 Stratification Factors
Not applicable

### 9.4 Interim Monitoring Plan
Not applicable

### 9.5 Analysis of Primary Endpoints
There are three primary objectives of this study, each with unique endpoints.

The first is to evaluate the correlation between prone breast MRI and pathologic measurement in estimating tumor size, and the correlation between supine breast MRI and pathologic results. A 95% confidence interval will also be calculated for each correlation coefficient. One sample z-test will be conducted to compare whether these correlation coefficients are different from 0.6.

The second is to compare the correlation between supine breast MRI and pathologic measurement for estimation of tumor size, and the correlation between existing breast imaging modalities and pathologic tumor size. Similarly, correlation coefficient will be calculated between supine MRI and the pathologic results and between existing breast imaging modalities and the pathologic tumor size. Two-sample z-test for comparing correlated correlation coefficients will be conducted to compare whether these two correlation coefficients are equal.

The third is to characterize the changes occurring in breast tumor-associated properties/ dimensions between the prone and supine imaging position for all patients with pre-surgical MRIs. We will also determine the correlation of tumor location and geometry on pre-NAT and post-NAT (pre-surgical) supine MRI with prone MRI among the subgroup of patients with pre and post NAT imaging. As described in Section 2.1, in our prior work comparing prone to supine MRI, we utilized image processing software that enabled us to generate tumor models and specifically calculate differences in the metrics computed from the segmented tumor label maps on supine and prone MRI. As a first order statistics, we plan to examine differences in the shape

and size of the tumor on supine and prone MRI. Further, we hope to correlate these difference metrics with variables including but not limited to breast size (measured on the axial slice through the nipple) and location (inner/outer, upper/lower). Correlation coefficients will be calculated for parameters related to tumor shape and size between supine and prone MRI, and one sample t-test (or non- parametric Wilcoxon test) will be used to test whether the difference in shape and size parameters between these two measurements are significantly different from 0. A regression model will be used to check whether these differences are correlated to breast size and location, age and other clinical characteristics.

### 9.6 Analysis of Secondary Endpoints

There are four secondary objectives for this study. Descriptive statistics will be used for these objectives.

The first is to assess the value of supine MRI for radiologists performing second look US examinations/ biopsies following identification of new lesions on MRI, and performing preoperative lesion localization using supine MRI guidance. This value will be assessed by both qualitative (survey of radiologists on perceived usefulness of supine MRI for imaging localization/procedures*) and quantitative measures (success rate of second-look ultrasound lesion localizations and procedures utilizing supine MRI guidance). Procedures include lesion biopsy and pre-surgical lesion localization performed by radiologist.
A frequency table will be calculated for the survey questions and the success rate of second-look biopsies and/or localizations.

The second is to assess the perceived benefit of supine MRI for surgical planning as measured by the collective results of a survey of surgeons performing BCT in our study patient population. A frequency table will again be calculated for the survey responses.

The third is to explore the effect of supine MRI on influencing BCS outcomes by determining the percent of patients requiring re-excisions or having pathologic positive margins when supine MR imaging is performed and available for surgical planning purposes. This will be an exploratory endpoint.

The fourth and final secondary endpoint is to assess the perceived value of supine MRI for adjuvant radiation breast treatment planning as measured by the collective results of a survey of radiation oncologists treating patients in our study population post-operatively. Again, a frequency table will be calculated for the survey responses.

### 9.7 Reporting and Exclusions

1. Patients who are not evaluable for tumor evaluation by MRI as a result of MRI-related problems (ie degree of contrast washout for supine MRI prevents MRI interpretation as deemed by attending radiologist) will not be included in the primary analysis.

2. Patients who do not have surgical treatment at our institution will not be included in the primary analysis.

9.7.1 Evaluation of Toxicity
Not applicable

## 10. PUBLICATION PLAN

Results of this study should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in Section 9.2. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. We anticipate that a full report of the outcomes should be made public no later than three (3) years after the end of the study.

## REFERENCES

1. International Agency for Research on Cancer (IARC) and World Health Organization (WHO). GLOBOCAN 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx, 2014. .
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016; 66: 7-30.
3. Blichert-Toft M, Rose C, Andersen JA et al. Danish randomized trial comparing breast conservation therapy with mastectomy: six years of life-table analysis. Danish Breast Cancer Cooperative Group. J Natl Cancer Inst Monogr 1992; 19-25.
4. Arriagada R, Le MG, Rochard F, Contesso G. Conservative treatment versus mastectomy in early breast cancer: patterns of failure with 15 years of follow-up data. Institut Gustave-Roussy Breast Cancer Group. J Clin Oncol 1996; 14: 1558-1564.
5. van Dongen JA, Voogd AC, Fentiman IS et al. Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial. J Natl Cancer Inst 2000; 92: 1143-1150.
6. Fisher B, Anderson S, Bryant J et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002; 347: 1233-1241.
7. Veronesi U, Cascinelli N, Mariani L et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 2002; 347: 1227-1232.
8. Poggi MM, Danforth DN, Sciuto LC et al. Eighteen-year results in the treatment of early breast carcinoma with mastectomy versus breast conservation therapy: the National Cancer Institute Randomized Trial. Cancer 2003; 98: 697-702.
9. Surgeons ASoB. The American Society of Breast Surgeons Performance and Practice Guidelines for Breast Conserving Surgery/Partial Mastectomy, 2014 (Revised February 2015). Available at https://www.breastsurgeons.org/new_layout/about/statements/PDF_Statements/PerformancePracticeGuidelines_Breast-ConservingSurgery-PartialMastectomy.pdf. In.
10. Bonadonna G, Veronesi U, Brambilla C et al. Primary chemotherapy to avoid mastectomy in tumors with diameters of three centimeters or more. J Natl Cancer Inst 1990; 82: 1539-1545.
11. Fisher B, Brown A, Mamounas E et al. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. J Clin Oncol 1997; 15: 2483-2493.
12. Rosen EL, Blackwell KL, Baker JA et al. Accuracy of MRI in the detection of residual breast cancer after neoadjuvant chemotherapy. AJR Am J Roentgenol 2003; 181: 1275-1282.
13. van der Hage JA, van de Velde CJ, Julien JP et al. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. J Clin Oncol 2001; 19: 4224-4237.
14. Wolmark N, Wang J, Mamounas E et al. Preoperative chemotherapy in patients with operable breast cancer: nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. J Natl Cancer Inst Monogr 2001; 96-102.
15. Golshan M, Cirrincione CT, Sikov WM et al. Impact of neoadjuvant chemotherapy in

stage II-III triple negative breast cancer on eligibility for breast-conserving surgery and breast conservation rates: surgical results from CALGB 40603 (Alliance). Ann Surg 2015; 262: 434-439; discussion 438-439.
16. Mauri D, Pavlidis N, Ioannidis JP. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. J Natl Cancer Inst 2005; 97: 188-194.
17. Rastogi P, Anderson SJ, Bear HD et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. J Clin Oncol 2008; 26: 778-785.
18. Brown J, Smith RC, Lee CH. Incidental enhancing lesions found on MR imaging of the breast. AJR Am J Roentgenol 2001; 176: 1249-1254.
19. Ikeda DM, Hylton NM, Kinkel K et al. Development, standardization, and testing of a lexicon for reporting contrast-enhanced breast magnetic resonance imaging studies. J Magn Reson Imaging 2001; 13: 889-895.
20. Abraham DC, Jones RC, Jones SE et al. Evaluation of neoadjuvant chemotherapeutic response of locally advanced breast cancer by magnetic resonance imaging. Cancer 1996; 78: 91-100.
21. Gilles R, Guinebretiere JM, Toussaint C et al. Locally advanced breast cancer: contrast-enhanced subtraction MR imaging of response to preoperative chemotherapy. Radiology 1994; 191: 633-638.
22. Mumtaz H, Davidson T, Hall-Craggs MA et al. Comparison of magnetic resonance imaging and conventional triple assessment in locally recurrent breast cancer. Br J Surg 1997; 84: 1147-1151.
23. Partridge SC, Gibbs JE, Lu Y et al. MRI measurements of breast tumor volume predict response to neoadjuvant chemotherapy and recurrence-free survival. AJR Am J Roentgenol 2005; 184: 1774-1781.
24. Rieber A, Zeitler H, Rosenthal H et al. MRI of breast cancer: influence of chemotherapy on sensitivity. Br J Radiol 1997; 70: 452-458.
25. Shin HJ, Kim HH, Ahn JH et al. Comparison of mammography, sonography, MRI and clinical examination in patients with locally advanced or inflammatory breast cancer who underwent neoadjuvant chemotherapy. Br J Radiol 2011; 84: 612-620.
26. Yeh E, Slanetz P, Kopans DB et al. Prospective comparison of mammography, sonography, and MRI in patients undergoing neoadjuvant chemotherapy for palpable breast cancer. AJR Am J Roentgenol 2005; 184: 868-877.
27. Bhattacharyya M, Ryan D, Carpenter R et al. Using MRI to plan breast-conserving surgery following neoadjuvant chemotherapy for early breast cancer. Br J Cancer 2008; 98: 289-293.
28. Segara D, Krop IE, Garber JE et al. Does MRI predict pathologic tumor response in women with breast cancer undergoing preoperative chemotherapy? J Surg Oncol 2007; 96: 474-480.
29. Martincich L, Montemurro F, De Rosa G et al. Monitoring response to primary chemotherapy in breast cancer using dynamic contrast-enhanced magnetic resonance imaging. Breast Cancer Res Treat 2004; 83: 67-76.
30. Golshan M, Sagara Y, Wexelman B et al. Pilot study to evaluate feasibility of image-guided breast-conserving therapy in the advanced multimodal image-guided operating (AMIGO) suite. Ann Surg Oncol 2014; 21: 3356-3357.
31. Herrada J, Iyer RB, Atkinson EN et al. Relative value of physical examination,

mammography, and breast sonography in evaluating the size of the primary tumor and regional lymph node metastases in women receiving neoadjuvant chemotherapy for locally advanced breast carcinoma. Clin Cancer Res 1997; 3: 1565-1569.
32. Peintinger F, Kuerer HM, Anderson K et al. Accuracy of the combination of mammography and sonography in predicting tumor response in breast cancer patients after neoadjuvant chemotherapy. Ann Surg Oncol 2006; 13: 1443-1449.
33. Gombos E JJ, Richman DM, Caragacianu D, Mallory MA, Jolesz, Golshan M. Intraoperative Supine Breast MRI for Quantifying Tumor Deformation and Detection of Residual Breast Cancer. Radiology. Forthcoming 2016. .
34. Mallory MA SY, Aydogan F, Desantis S, Jagadeesan J, Caragacianu D, Gombos E, Vosburgh KG, Jolez F, Golshan M. Feasibility of Intraoperative Breast MRI and the Role of Prone Versus Supine Positioning in Surgical Planning for Breast Conserving Surgery.The Breast Journal. Forthcoming 2016
35. Jacobson G, Zamba G, Betts V et al. Image-Based Treatment Planning of the Post-Lumpectomy Breast Utilizing CT and 3TMRI. Int J Breast Cancer 2011; 2011: 246265.
36. Strauss JB, Gielda BT, Chen SS et al. Variation in Post-Surgical Lumpectomy Cavity Volume With Delay in Initiation of Breast Irradiation Because of Chemotherapy. International Journal of Radiation Oncology*Biology*Physics 2010; 77: 831-835.
37. Landis DM, Luo W, Song J et al. Variability Among Breast Radiation Oncologists in Delineation of the Postsurgical Lumpectomy Cavity. International Journal of Radiation Oncology*Biology*Physics 2007; 67: 1299-1308.
38. den Hartogh MD, Philippens ME, van Dam IE et al. MRI and CT imaging for preoperative target volume delineation in breast-conserving therapy. Radiat Oncol 2014; 9: 63.
39. Jolicoeur M, Racine ML, Trop I et al. Localization of the surgical bed using supine magnetic resonance and computed tomography scan fusion for planification of breast interstitial brachytherapy. Radiother Oncol 2011; 100: 480-484.
40. Mast M, Coerkamp E, Heijenbrok M et al. Target volume delineation in breast conserving radiotherapy: are co-registered CT and MR images of added value? Radiat Oncol 2014; 9: 65.
41. Giezen M, Kouwenhoven E, Scholten AN et al. Magnetic resonance imaging- versus computed tomography-based target volume delineation of the glandular breast tissue (clinical target volume breast) in breast-conserving therapy: an exploratory study. Int J Radiat Oncol Biol Phys 2011; 81: 804-811.
42. Vinod SK, Min M, Jameson MG, Holloway LC. A review of interventions to reduce inter-observer variability in volume delineation in radiation oncology. J Med Imaging Radiat Oncol 2016.
43. Jayender J. GM, Narayan V., Durgapal S., Mallory M.A., Jolesz F.A., Gombos E. . Clinical Impact and Quantification of Prone to Supine Position in Breast MRI. SBI/ACR Breast Imaging Symposium, 2015. Plenary Presentation.
44. Mallory MA; Sagara Y DS, Jagadeesan J, Caragacianu D, Aydogan F, Gombos E, Vosburgh KG, Jolesz FA, Golshan M. Final Results of the Phase I Trial Evaluating the Feasibility of Intraoperative MRI for Margin Assessment During Breast Conserving Surgery in the Advanced Multimodality Image Guided Operating (AMIGO) Suite." New England Surgical Society, 96th Annual Meeting, Newport, RI, September 2015. Plenary Presentation.
45. Krouskop TA, Wheeler TM, Kallel F et al. Elastic moduli of breast and prostate tissues under compression. Ultrason Imaging 1998; 20: 260-274.

46. Johnson H, Harris G, Williams K. BRAINSFit: mutual information rigid registrations of whole-brain 3D images, using the insight toolkit. Insight J 2007; 1-10.
47. Viola P, Wells III WM. Alignment by maximization of mutual information. International journal of computer vision 1997; 24: 137-154.
48. Fedorov A, Beichel R, Kalpathy-Cramer J et al. 3D Slicer as an image computing platform for the Quantitative Imaging Network. Magn Reson Imaging 2012; 30: 1323-1341.
49. Houssami N, Turner R, Macaskill P et al. An individual person data meta-analysis of preoperative magnetic resonance imaging and breast cancer recurrence. J Clin Oncol 2014; 32: 392-401.
50. Turnbull L, Brown S, Harvey I et al. Comparative effectiveness of MRI in breast cancer (COMICE) trial: a randomised controlled trial. Lancet 2010; 375: 563-571.
51. Houssami N, Turner R, Morrow M. Preoperative magnetic resonance imaging in breast cancer: meta-analysis of surgical outcomes. Ann Surg 2013; 257: 249-255.
52. Solin LJ, Orel SG, Hwang WT et al. Relationship of breast magnetic resonance imaging to outcome after breast-conservation treatment with radiation for women with early-stage invasive breast carcinoma or ductal carcinoma in situ. J Clin Oncol 2008; 26: 386-391.
53. Houssami N, Hayes DF. Review of preoperative magnetic resonance imaging (MRI) in breast cancer: should MRI be performed on all women with newly diagnosed, early stage breast cancer? CA Cancer J Clin 2009; 59: 290-302.
54. Bleicher RJ, Ciocca RM, Egleston BL et al. Association of routine pretreatment magnetic resonance imaging with time to surgery, mastectomy rate, and margin status. J Am Coll Surg 2009; 209: 180-187; quiz 294-185.
55. Houssami N, Ciatto S, Macaskill P et al. Accuracy and surgical impact of magnetic resonance imaging in breast cancer staging: systematic review and meta-analysis in detection of multifocal and multicentric cancer. J Clin Oncol 2008; 26: 3248-3258.
56. Dillman JR, Ellis JH, Cohan RH et al. Frequency and severity of acute allergic-like reactions to gadolinium-containing i.v. contrast media in children and adults. AJR Am J Roentgenol 2007; 189: 1533-1538.
57. Hunt CH, Hartman RP, Hesley GK. Frequency and severity of adverse effects of iodinated and gadolinium contrast materials: retrospective review of 456,930 doses. AJR Am J Roentgenol 2009; 193: 1124-1127.