Protocol Narrative

DEVELOPMENT AND TESTING OF AN ACCURATE, RAPID AND INEXPENSIVE MRI PROTOCOL FOR BREAST CANCER SCREENING--A PILOT STUDY

Principal Investigator: Hiro Abe, MD, Dept. of Radiology

Co-Investigators: Gregory Karczmar, PhD, Dept. of Radiology
Kirti Kulkarni, MD, Dept. of Radiology
Deepa Sheth, MD, Dept. of Radiology
Olufunmilayo Olopade, MD, Dept. of Medicine
Gillian Newstead, MD, Dept. of Radiology
Milica Medved, PhD, Dept. of Radiology

Address: University of Chicago
Dept. of Radiology
5841 S Maryland, MC 2026
Chicago, IL 60637
Telephone: (773) 702-2781

1. BACKGROUND

X-ray mammography has significantly reduced breast cancer mortality. However, even with mammography, many breast cancers are not detected until they are advanced, and illness and death due to breast cancer is a major problem. The best way to control breast cancer is to detect it at an early stage when it is relatively easy to treat. MRI has potential to significantly improve sensitivity to cancer, and detect many cancers years earlier than mammography, especially in women with dense breasts. Given the great sensitivity of MRI, it is likely that properly designed MRI screening would detect almost all invasive cancers and many pre-invasive cancers at an early stage, resulting in tremendously decreased mortality and illness. Effective MRI-screening would have an exceptional impact in the region surrounding the University of Chicago Medical Center, where rates of breast cancer are unusually high, with an especially high prevalence of aggressive breast cancer. If MRI screening can identify cancers several years earlier than conventional methods – with very few 'false positives' - this would have tremendous benefits for patients.

Mammography is not very effective in women with dense breasts and these women currently do not have good options for screening. Even in women with normal breast density – mammography often does not detect cancers until they are fairly large. It would be much better to detect cancer early when it is easier to cure. This is especially important for women who are at high risk for aggressive breast cancer. MRI has very high sensitivity, and has potential to detect cancer earlier than conventional mammography [1]. Sensitivity of MRI is not affected by breast density [1]. However,

there are concerns that MRI lacks the specificity required for screening large numbers of women, and will generate an unacceptable number of false positives, producing unnecessary stress, inconvenience, and expense. In addition, there are concerns that even if the accuracy of MRI can be significantly improved, MRI is too expensive for screening in the general population.

Routine screening for breast cancer with X-ray mammography has significantly reduced morbidity and mortality [1], and clearly demonstrated the benefits of early detection. While X-ray mammography is effective for many women – there is concern that it does not provide adequate screening for large groups of women. In women with dense breasts, the sensitivity of mammography to early cancers is reduced by 30-50% [5, 6]. This is particularly problematic because women with dense breasts are at higher risk for aggressive breast cancers [7]. In fact, there is concern that for all women at increased risk for aggressive breast cancer, e.g. triple negative breast cancer, X-ray mammography does not always detect cancer early enough [1]. Much earlier detection is likely to substantially decrease morbidity and mortality.

2. PURPOSE/HYPOTHESIS

We propose to test an innovative MRI breast cancer screening protocol in women with mammographically dense breasts as well as other women with moderately increased cancer risk. MRI, combined with other methods of risk assessment, has potential to significantly improve sensitivity to cancer in dense breasts and detect cancer in all cases at a much earlier stage, with far fewer interval cancers than mammography [8, 9]. Previous tests of MRI sensitivity show that this screening could significantly increase the likelihood of detecting invasive cancers resulting in decreased mortality from breast cancer [1]. Effective MRI-screening would have an exceptional impact in the region surrounding the UC Medical Center, where rates of breast cancer are unusually high, and where the prevalence of aggressive breast cancer is also very high. If MRI screening can identify breast cancers, particularly the most aggressive subtype of breast cancer, several years earlier than conventional methods, this would have tremendous benefits for patients.

We propose to develop fast, accurate, quantitative, and inexpensive MRI screening methods that can easily be implemented in routine clinical practice. This research will build on innovative work from this team that has significantly advanced breast MRI, including dynamic contrast enhanced MRI of the breasts. This is an opportunity for the University to have a significant impact, initially in our immediate neighborhood, and eventually nationally and internationally. This is an area where the University should lead because of the devastating effect of breast cancer in south Chicago.

The specific purpose of the study is as follows:

1. Develop an efficient, quantitative MRI-screening protocol, less than 15 minutes in duration. Evaluate signal-to-noise ratio and reproducibility in 10 volunteers with dense breasts.

2. Scan approximately 50 women with mammographic or sonographic findings that require biopsy using the short MRI protocol (15 minutes), to establish reasonable cutoffs for MRI parameters derived from the short protocol, that are likely to identify benign and malignant lesions with high sensitivity.

3. In partnership with the Cancer Risk Clinic and the Breast Center, we will identify and recruit 150 women with dense breasts and/or intermediate risk of breast cancer who will also undergo the short MRI protocol.

4. Perform a reader study to evaluate false positive rate, based on the cutoffs established in women with biopsy proven benign and malignant lesions.

5. Perform quantitative analysis to determine standard DCEMRI protocols including Ktrans (the rate constant for contrast media uptake; [2-4]). In addition, we will test novel parameters that can be extracted from ultrafast datasets; initial time of enhancement in parenchyma and suspicious lesions, new approaches to calculating Ktrans and the arterial input function based on early enhancement, and number and size of arteries feeding suspicious lesions and rate of enhancement of those blood vessels. These markers can be accurately calculated from ultrafast imaging but **cannot** be accurately measured with conventional methods. Determine the rate of false positives based on the cutoffs for each of these parameters determined from the study of women with confirmed breast cancer ('2' above).

6. Suspicious lesions will be defined by the clinical interpretation of the breast MRI images performed by the attending breast radiologist. Based on the radiologist determination that the MRI findings are suspicious (these findings include masses, non-mass enhancement and foci), suspicious lesions will be assigned a Bi-Rads code specifying whether additional work up or biopsy is necessary. These are BiRads codes 0, 4 and 5. False positive diagnosis should be minimized as all attending physicians reading breast MRI at this institution are fellowship trained in breast imaging.

3. RECRUITMENT PLAN

We plan to enroll approximately 200 subjects in total.

1. We will scan approximately 200 women who meet the entry requirements described below. This number may vary slightly because we will scan women with suspicious findings on mammography until we find 30 cancers, verified by the subsequent biopsy. Therefore it is not possible to report the exact number of women who will be in this group.
2. We will scan 150 healthy women with dense breasts and/or women who have risk of breast cancer that is average of higher.

Dense breasts are defined as categories C and D, defined in the American College of Radiology (ACR) BiRads manual. We will also follow ACR guidelines for risk categories. The ACR defines intermediate risk as those patients with a lifetime risk for breast cancer of 15%-20%. This includes women with a personal history of breast cancer, history of proven lobular neoplasia, atypical ductal hyperplasia or other women with 15%-20% risk based on risk models.

4. ELIGIBILITY

Inclusion criteria:

- Women who have a mammographically and/or sonographically identified finding that will require image guided biopsy.
- OR
- For the 'screening group' we will recruit women between ages of 30 –70 who have above10% lifetime risk of breast cancer or who have dense breasts (based on BIRADS score) but who currently do not have any diagnosis of breast cancer.
- We will select women for the screening group and the group of women with suspicious mammographic findings so that the two groups are well-matched. Our target is to match the percentage of parous and non-parous women, and premenopausal and post-menopausal women. In addition we will match the age distribution in the two groups.

Exclusion criteria:

- Women with a history of adverse reactions to contrast media.
- Women who are pregnant.
- Patients who are demonstrated to be at risk for an allergic reaction or nephrogenic systemic fibrosis (NSF) will be excluded from the study. Details as to how patients are evaluated for these risks are provided below (see 'Potential Risks').

5. STUDY DESIGN

Enrollment:

1. Approximately 50 women with suspicious findings on mammography who are scheduled for biopsy will be recruited. We expect this will result in 30 cancers and 20 benign lesions. **When possible**, we will perform MRI scans before the biopsy so that biopsy will not affect MRI results. Lesions will be classified as benign and malignant based on the subsequent biopsy. We will continue scanning until we have scanned 30 women with biopsy-confirmed malignancy. We estimate that

this will require a total of 50 scans, but the total number may turn out to be slightly higher or slightly lower.

2. We will also recruit 150 women with dense breasts and/or women who have intermediate risk of breast cancer for this study.

MRI scans:

Women will receive a mammogram and an MRI-screening exam. The MRI screening exam will consist of calibration scans, bilateral T2-weighted scans, and a DCEMRI scan. The duration of the entire protocol will be less than 15 minutes.

Ground truth assignment:

Assignment for the group who will have biopsy based on mammogram and/or ultrasound:

a. Surgical pathology will be the gold standard for these patients for the lesions previously identified on mammogram or ultrasound.
b. Any additional lesions detected on MRI will follow the assignment as below for the screening group.

Assignment for the dense breast/intermediate risk group:

a. Women who have no cancer found on MRI will be classified as having no cancer.
b. If additional lesions are deemed suspicious on MRI and these lesions are biopsied, they will be classified as benign or malignant based on biopsy surgical pathology results.
c. If additional lesions are found on MRI but physicians elect not to biopsy based on the findings, these lesions will be assumed to be benign for the purposes of this study. In some cases, women may be referred for follow-up exams, e.g. in 6 months. In these cases, lesions that are still not biopsied after 6 month follow-up will be assumed to be benign for the purposes of this study.

Reader Study:

The T2-weighted scans and high resolution post contrast T1-weighted scans will be evaluated by Radiologists using conventional diagnostic procedures. Radiologists will also evaluate ultrafast scans to identify regions with anomalously rapid enhancement, or abnormally enhancing blood vessels in ultrafast images. Based on this evaluation they will assign a probability of malignancy, on a scale from 1 – 10. Three independent readers will evaluate images and assign a probability of malignancy. We will calculate ROC curves for each of the 3 readers to assess 1) variability of Reader's 'probability of malignancy' scores 2) AUCs for Radiologists compared to the quantitative parameters described above. The Reader study is an exploratory aim and the study is not powered to perform this analysis with reasonable statistical confidence. The goal is simply to obtain

a preliminary assessment that can provide a basis for future studies with a larger number of patients and readers.

Statistical Power:

Thirty women with biopsy-confirmed breast cancer and between sixty and seventy controls (women with dense breasts and/or moderate breast cancer risk, frequency-matched by parity, age, and menopausal status; control group also includes some women with biopsy-proven benign lesions) will be scanned using the short MRI protocol. Receiver Operating Characteristic (ROC) curves and statistics will be constructed for several MRI parameters of interest: Ktrans, initial time of enhancement in parenchyma and suspicious lesions, new approaches to calculating Ktrans and the arterial input function based on early enhancement, and number and size of arteries feeding suspicious lesions and rate of enhancement of those blood vessels. The primary endpoints of this study are Ktrans and 'initial time of enhancement'. Optimal diagnostic thresholds will be determined for each parameter, where the optimal threshold for a given parameter is defined as the parameter value which has highest sum of specificity and sensitivity over all possible thresholds with specificity > 80%. We will also test whether the area under the curve (AUC) for each parameter exceeds 60%. 95% confidence intervals will be constructed for the AUC for each curve and the sensitivity and specificity of each optimal threshold. For our two primary endpoints (Ktrans and initial time of enhancement), our sample of 200 subjects (30 cases + 170 controls) is large enough to detect AUCs of 74% (i.e., a difference of 14%) at the 5% significance level.

Thresholds determined in this pilot study will later be validated in a larger cohort – this is the subject of an RO1 proposal to be submitted soon. In the future cohort, we will construct covariate-adjusted ROC curves that will be used to calculate thresholds, specificities, and sensitivities for patients with different breast cancer risk factors (Gail scores, family history, etc.).

We will also produce ROC curves for each reader in the 'reader study' to obtain a preliminary estimate of how standard evaluation of abbreviated MRI datasets compare with the quantitative analysis described above. However, this is an exploratory aim of the study and the study is not powered to evaluate the statistical confidence of these measurements.

6. PROCEDURES TO WHICH HUMANS WILL BE SUBJECTED:

Patients with lesions detected on mammography or ultrasound:

Patients with scheduled biopsy will undergo the research MRI prior to their biopsy. At the time that the biopsy is recommended, the radiologist will identify the patient as one who will be having a biopsy and could qualify for research MRI. The breast care treatment teams (high risk clinic, surgery clinic) will contact the Radiology Research Coordinator if they have a patient that they believe could be eligible for the study. Once identified, the patient's name and MRN will be given to the research coordinator. She will be contacted by phone regarding the research study by the research coordinator. The

study will be explained to her, and she will be asked about her interest in participating. Questions, if any, will be answered. If interested, she will be scheduled in an MRI time slot. Biopsy patients will be scheduled for their MRI in the same visit unless they prefer otherwise. Prior to the MRI, they will be asked to read and sign the informed consent document by the research coordinator.

Data will be collected from the subjects regarding their race and ethnicity, age, weight, height, menopausal status, last menstrual cycle date.

All routine precautions will be taken prior to the MRI scans (screening for metallic or electronic (e.g., pace-maker) implants, removal of all metallic objects, etc.).

Patients with dense breasts and those referred for intermediate risk:

Women age 30-60 with dense breasts presenting for screening mammography are one of the target populations. The radiologist will identify scheduled mammography screening patients who are known to have mammographically dense breasts based on prior screening mammograms. Once identified, the patient's name and MRN will be given to the research coordinator. In cases identified by the Breast Center or Cancer Risk Clinic as intermediate risk, the research coordinator will be contacted about the patient.

The patient group who has dense breasts will be recruited by the Radiology Research Coordinator. Recruitment will be based upon the fact that the patient, who is scheduled for a screening mammogram, is known to have dense breasts on a previous years screening mammogram. Based on her known breast density, she will be eligible for recruitment into the study. Once a patient with dense breasts or intermediate risk is identified, she will be contacted by phone or in person during a clinic visit regarding the research study by the research coordinator. The study will be explained to her, and she will be asked about her interest in participating. Questions, if any, will be answered. If interested, she will be scheduled in an MRI time slot. Mammography patients will be scheduled for their MRI in the same visit unless they prefer otherwise. Prior to the MRI, they will be asked to read and sign the informed consent document by the research coordinator.

Data will be collected from the subjects regarding their race and ethnicity, age, weight, height, menopausal status, last menstrual cycle date.

1) Patients undergoing a screening or routine diagnostic mammogram will also undergo an MRI exam on the same day. The mammography exams will be part of standard clinical care, and not acquired specifically for the purpose of this study. The MRI exams will be research-only exams.
2) Blood test of kidney function (standard screening procedure) for breast MRI w/contrast is only required if: over 60 years old, have hypertension or diabetes.

All routine precautions will be taken prior to the MRI scans (screening for metallic or electronic (e.g., pace-maker) implants, removal of all metallic objects, etc.).

7. BENEFIT/PAYMENT

It is possible that participation in an innovative MRI breast cancer screening study may help to improve early detection in women with dense breasts and/or women who have moderate risk of breast cancer. Also, the additional MR images may provide information, which may influence treatment. For example, abnormal tissue, which was not detected by mammography, may be detected by MRI. It is possible that participation may lead to the detection of an early breast cancer that was not visible on mammography.

Subjects will be paid $75 for participation in this study. In addition they will receive a coupon for lunch and a parking pass.

8. COSTS

The cost of the research MRI scans will be covered by the study. If clinically significant findings are noted on the MRI, they will be reviewed/processed as standard of care and if the patient selects to do follow-up studies and/or treatment, the patient and/or the patient's insurance will be responsible for those costs.

9. POTENTIAL RISKS

A) **The detection of abnormalities not visible using conventional x-ray mammography.** The experimental scans do not carry any risks to the patients beyond those posed by the clinical MRI exam. The primary risk of clinical MRI is that some of the lesions detected by MRI are likely to be benign. If suspicious lesions are detected by MRI they may be biopsied and in some cases the lesion will prove to be benign and the biopsy will have been unnecessary. In this case the patient will have unnecessary discomfort, anxiety, and expense. However, in the cohort of women at an elevated risk for breast cancer, the risk of false-positive is considered to be justified by the benefits of finding cancers at an early stage when they can be easily treated.

B) **Allergic reactions to the contrast media:** Most study subjects will be injected with the standard dose of a magnetic resonance contrast agent. Nationally, MRI contrast agents are used in tens of thousands of patients each year. Current research findings suggest that there are fewer than four serious allergic reactions per year. A small percentage of patients (1% - 5% of those injected) suffer an allergic reaction to this agent. These reactions are usually mild (e.g., headache, nausea, vomiting, hypotension) and resolve spontaneously after a few minutes or hours. However, in very rare cases the reactions can be severe and require hospitalization. Several deaths have been reported which may have been associated with the use of gadolinium contrast agents. This is difficult to verify because the patients involved were very ill before receiving contrast injections. MRI contrast agents may also cause mild and transient elevations in the levels of certain chemicals in the blood (e.g., iron and bilirubin). Study subjects will be questioned regarding their history of allergic

reactions before undergoing MRI exams. When contrast agent is administered, the patients are monitored by the MRI technician over a video and audio connection. The patients are also given a 'panic button' that they can activate at any time to alert the technician. If there is a reaction to the contrast agent, the on-site radiologist will examine the patient and direct further treatment. If necessary, emergency staff will come to the site to administer first aid. This is standard procedure that is followed for clinical and research subjects alike. The catheter that is used to inject the contrast medium will be inserted intravenously by an experienced physician, nurse, or technologist. Insertion may cause some bruising and or bleeding which may result in some discomfort.

C) **Nephrogenic systemic fibrosis (NSF):** NSF is a very rare but very serious condition that can lead to disability or even death. It has been associated with the use of non-ionic gadolinium-based MRI contrast agents, and is thought to be the result of gadolinium toxicity due to slow clearance by the kidneys. NSF has only been documented in patients with severe renal impairment. After 2007, routine screening protocols have been implemented to identify such patients prior to their MRI, which resulted in a steep drop in the number of reported cases. At our hospital, this protocol is implemented via a questionnaire that is designed to identify patients at risk for compromised kidney function. For patients identified as such, the medical record will be searched for a recent kidney function test, or a new test will be ordered that day. If a recent test is not available, or if a glomerular filtration rate (GFR) value lower than 60 is measured, the patient will not be recruited for the study.

D) **Pregnancy:** Although we are unaware of any such injuries caused by the contrast agents used in the present study, the remote possibility of fetal injury or even fetal death does exist. Therefore, pregnant women will be excluded from this study. Prospective study participants of childbearing age will be told about the potential risks to a fetus.

E) **Breastfeeding:** The contrast agent used in the study may transfer to the breast milk, exposing a nursing child to a small but unnecessary risk. Prospective patients, who are breast feeding, will not be asked to participate in a contrast-enhanced exam.

F) **Sickle cell anemia, hepatic disease or other hemolytic illness, any type of seizure disorder or a predisposition toward seizures:** For persons with each of these conditions, the contrast agent used in the study may slightly increase their risk of complications from their condition. Subjects with the above-mentioned conditions will not be asked to participate.

G) **The presence of devices, implants, or other objects containing metal:** Metal objects pose a serious risk to all patients undergoing MRI exams. This includes internally implanted objects such as surgical clips, bio-support devices (e.g., pacemakers), and in some cases artificial joints which contain metal. Patients are questioned carefully before MRI imaging to insure that they do not have metal

implants. Prospective study participants who have such implants that are not MRI safe will be excluded from the study. Patients who have worked in or near machine shops and electronics shops are also excluded from the study. In these work environments metal slivers may become trapped in the eyes, posing a potential hazard if exposed to a strong magnetic field. In addition, metal objects such as heavy key chains that are carried into the scan room can cause serious accidents. Patients will be cautioned to remove all metal objects before entering the scan room. Access to the scan room is carefully controlled to insure that no ferrous metal is inadvertently brought in.

H) Exposure to magnetic fields: Apart from its effects on metal objects and implants, there are no known negative effects associated with the magnetic fields used to produce MRI images. Despite the exposure of millions of people to high-intensity magnetic fields in MRI scanners over the last 15 years, and to those generated near cyclotrons during the last 50 years, there are no confirmed reports of adverse health effects. The radio-frequency (RF) energy that is used to excite the MRI signal may in extraordinary circumstances cause heating and burning of tissue. In addition, rapid switching of the gradients may cause transient discomfort. In addition, there is a remote likelihood of tissue damage when rapidly changing magnetic fields are used. As a further protection, even if a higher energy pulse programming protocol were to be used in error, the commercial MRI machine that will be used for this study (Philips 3T) is equipped with both software and hardware power limiters that prevent the execution of pulse sequences in excess of FDA limits. The statistical evidence suggests that exposure to excessive RF energy caused by this equipment is, for all practical purposes, impossible -- there have been no reports of significant RF injury in over one hundred thousand clinical MRI exams.

I) Claustrophobia. Some patients may experience claustrophobia during the MRI exam due to the limited space available inside the bore of the magnet. Prospective participants will be counseled about this possibility before the exam. The magnet is equipped with an intercom system enabling study subjects to communicate with the operators at any time during the exam. If they report any discomfort during the MRI examination they will be removed from the magnet immediately.

J) Blood draw. Some patients may experience mild pain, discomfort, irritation, swelling, bruising, and/or redness at the site of the needle stick, or the patient may get a light-headed feeling. Rarely, an infection can occur. It is uncommon, but the patient may feel faint from the procedure. Care will be taken to avoid these complications.

K) Risk of false positive findings:
Sometimes MRI finds additional areas that need more testing (such as mammograms, ultrasound or MRI) in order to determine their cause. In some cases, that further testing turns out to be benign (not cancer). If lesions are detected by MRI they may even need to be biopsied to determine whether they are benign and the biopsy will have been unnecessary. In these cases there will have been unnecessary discomfort, anxiety, and

expense. However, the risk of false-positive is considered to be low and justified by the converse benefits of potentially finding cancers at an early stage when they can be easily treated. All of the standard MR images we obtain during this study will be examined carefully by an experienced radiologist. If there is anything suspicious, the radiologist or the nurse will contact you and/or your physician and discuss further imaging.

10. ALTERNATIVE PROCEDURES AVAILABLE TO SUBJECTS

Patients can choose not to volunteer for this study. The proposed study is ***experimental*** and is in no way a necessary part of standard or specialty patient care. The enrollment in the study does not affect the patient's ongoing clinical care.

11. REPORTING OF SERIOUS AND UNEXPECTED ADVERSE CIRCUMSTANCES

Serious and unexpected adverse experiences will be immediately reported by telephone to the University of Chicago IRB. A written report will follow the initial telephone call within three working days to the IRB.

12. CONFIDENTIALITY

As with all research studies involving the use of clinical data, there is a minimal risk of breach of confidentiality. This risk is minimized by the coding/de-identifying of clinical data with limited study personnel having access to the code key. Only the PI and research staff will have access to study patient information. Names or other unique identifiers will not be utilized in any abstracts or manuscripts generated from the data obtained in this study. If data is shared with collaborators outside of this study, only de-identified data will be shared. All research files and computer databases will be stored in secure locations, with access limited to members of the research team. These data files will be maintained for at least six years after the study is completed and destroyed and/or erased when no longer needed.

1. **Saslow, D., et al., American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin, 2007. 57(2): p. 75-89.**
2. **Leach, M.O., et al., The assessment of antiangiogenic and antivascular therapies in early-stage clinical trials using magnetic resonance imaging: issues and recommendations. Br J Cancer, 2005. 92(9): p. 1599-610.**
3. **Tofts, P.S., Modeling tracer kinetics in dynamic Gd-DTPA MR imaging. J Magn Reson Imaging, 1997. 7(1): p. 91-101.**
4. **Tofts, P.S., et al., Estimating kinetic parameters from dynamic contrast-enhanced T(1)-weighted MRI of a diffusable tracer: standardized quantities and symbols. J Magn Reson Imaging, 1999. 10(3): p. 223-32.**

5. Kolb, T.M., J. Lichy, and J.H. Newhouse, Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27,825 patient evaluations. Radiology, 2002. 225(1): p. 165-75.

6. Wang, A.T., et al., Breast density and breast cancer risk: a practical review. Mayo Clin Proc, 2014. 89(4): p. 548-57.

7. Yaghjyan, L., et al., Mammographic breast density and subsequent risk of breast cancer in postmenopausal women according to tumor characteristics. J Natl Cancer Inst, 2011. 103(15): p. 1179-89.

8. Pinsky, R.W. and M.A. Helvie, Mammographic breast density: effect on imaging and breast cancer risk. J Natl Compr Canc Netw, 2010. 8(10): p. 1157-64; quiz 1165.

9. Warner, E., The role of magnetic resonance imaging in screening women at high risk of breast cancer. Top Magn Reson Imaging, 2008. 19(3): p. 163-9.

10. Kuhl, C., et al., Prospective multicenter cohort study to refine management recommendations for women at elevated familial risk of breast cancer: the EVA trial. J Clin Oncol, 2010. 28(9): p. 1450-7.

11. Fan, X., et al., Use of a reference tissue and blood vessel to measure the arterial input function in DCEMRI. Magn Reson Med, 2010. 64(6): p. 1821-6.

12. Fan, X. and G.S. Karczmar, A new approach to analysis of the impulse response function (IRF) in dynamic contrast-enhanced MRI (DCEMRI): a simulation study. Magn Reson Med, 2009. 62(1): p. 229-39.

13. Medved, M., et al., Semiquantitative analysis of dynamic contrast enhanced MRI in cancer patients: Variability and changes in tumor tissue over time. J Magn Reson Imaging, 2004. 20(1): p. 122-8.