NCT03750240

Metabolic Sodium MRI to Assess Early Response of Breast Cancer to Neoadjuvant Chemotherapy

Primary Investigators: **Guillaume Madelin, PhD -** *Radiology*
NYU School of Medicine / Langone Medical Center
Department of Radiology
660 1st Avenue, 4th Floor
New York, NY 10016
(212) 263-3343

Regulatory Sponsor: NYU Langone Medical Center
Department of Radiology
660 1st Avenue
New York, NY 10016

Funding Sponsor: National Institute of Health

Protocol Number: **s17-00269**

Initial version: 08.03.2017
Amended: **08.01.2018**
Amended: **03.06.2019**
Amended: **08.06.2019**
Amended: **11.14.2019**
Amended: **01.27.2020**
Amended: **04.06.2020**
Amended: **06.4.2020**
Amended: **07.21.2020**
Amended: **09.21.2020**
Amended: **11.02.2020**

Table of Contents

List of Abbreviations

^{1}H	Proton
^{23}Na	Sodium
3-CM	Three-compartment model
α_2	Extracellular volume fraction
AC-T	Adriamycin+Cyclophosphamide and Taxol
ADC	Apparent Diffusion Coefficient
aISC	apparent Intracellular Sodium Concentration
aTSC	apparent Total Sodium Concentration
ATP	Adenosine Triphosphate
B0	Constant magnetic field
B1	RF magnetic field
BC	Breast Cancer
C_1	Intracellular Sodium Concentration
C_2	Extracellular Sodium Concentration
CCD	Charge Coupled Device
CV	Coefficient of Variation
DCE	Dynamic Contrast-Enhanced
DFS	Disease-Free Survival
DWI	Diffusion Weighted Imaging
FDA	Food and Drug Administration
ER	Estrogen Receptor status
FISH	Fluorescence In Situ Hybridization
FLORET	Fermat Looped Orthogonally Encoded Trajectories
GBCA	Gadolinium-based MRI contrast agent
Gd	Gadolinium
GFR	Glomerular Filtration Rate
GRE	Gradient Echo
HER2	Human Epidermal growth factor Receptor 2
HIV	Human Immunodeficiency Virus
HR	Hormone Receptor status
ICC	Intra-Class Correlation
IEC	International Electrotechnical Commission
IR	Inversion Recovery
IRB	Institutional Review Board
MRI	Magnetic Resonance Imaging
MRF	Magnetic Resonance Fingerprinting
Na^+	Sodium ions
NACT	Neoadjuvant Chemotherapy
NSD	Nephrogenic Fibrosing Dermopathy
NSF	Nephrogenic Systemic Fibrosis
OS	Overall Survival
pCR	Pathologic Complete Response
PD	Proton Density
PR	Progesterone Receptor status
RF	Radiofrequency
ROI	Region Of Interest
Rx	Receive
SAE	Safety and Adverse Events
SAR	Specific Absorption Rate

SNR	Signal-to-Noise Ratio
SPAIR	SPectrally selective Adiabatic Inversion Recovery
T1	Longitudinal relaxation time
T2	Transverse relaxation time
TA	Acquisition Time
TE	Echo Time
TNBC	Triple Negative Breast Cancer
TR	Repetition Time
TSC	Total Sodium Concentration
Tx	Transmit
UHF	Ultra-high field
UTE	Ultrashort Echo Time
V_1	Intracellular volume
V_2	Extracellular volume
V_s	Solid volume
V_t	Total volume
w	Water fraction

Study Summary

Title	Metabolic Sodium MRI to Assess Early Response of Breast Cancer to Neoadjuvant Chemotherapy
Short Title	Sodium MRI to assess breast cancer NACT
Protocol Number	s17-00269
Methodology	1. Methodology study: Radiofrequency (RF) coil and MRI protocol development on healthy subjects, including patients with benign tumors. 2. Prospective longitudinal pilot study: 20 patients with any breast cancer, some of them undergoing chemotherapy (scanned up to 4 times maximum)
Study Duration	3 years (07/01/2017-08/31/2020)
Study Center(s)	Multiple centers: 1. Center for Biomedical Imaging (CBI), Department of Radiology - *MRI* 2. NYU Cancer Center - *Patient recruitment* 3. Center for Women's Imaging 4. NYU Winthrop
Objectives	To develop a sodium MRI method to quantify changes in intracellular sodium concentration (C_1) and extracellular volume fraction (α_2) in vivo (imaging biomarkers of loss of homeostasis), in order to assess the efficacy of neoadjuvant, or any other, chemotherapy in breast cancer as early as possible, before tumor size reduction can be detected with standard dynamic contrast-enhanced (DCE) MRI. 1. *Methodological development of metabolic sodium MRI in breast*: new RF coil, MRI protocol and data processing algorithm for C_1 and α_2 quantification 2. *Application of sodium MRI to assess response of breast cancer to chemotherapy as proof-of-concept*: assessment of chemotherapy at up to 4 time points with sodium MRI, compared with standard DCE MRI for tumor size measurement.
Number of Subjects	42 Subjects: 24 Healthy Subjects & 18 Women with breast cancer who are planning to undergo chemotherapy
Diagnosis and Main Inclusion Criteria	Women (age ≥ 18 years) with no sign of breast cancer as controls, and women newly diagnosed with breast cancer and planned to undergo chemotherapy.
Study Product and Planned Use	- Dual-tuned $^{1}H/^{23}Na$ radiofrequency (RF) breast coil for conjoint proton and sodium MRI. This coil will be built in-house (aim 1). - Whole body Siemens scanner at 7 Tesla (research only scanner). - Gadolinium (Gd) based MRI contrast agent for DCE MRI (intravenous injection)
Reference therapy	Chemotherapy

Statistical Methodology	- All statistical tests will be conducted at the two-sided 5% significance. - Paired sample t tests will assess the change in each measure in tumor and healthy tissue from pre- to each post-onset time point and compare tumor to healthy tissue in terms of these changes. - Pearson and Spearman rank correlations will assess the association of intra-tumor changes in C_1 and α_2 with changes in tumor size. - SAS 9.3 software

1 Introduction

This document is a protocol for a human research study. This study is to be conducted in accordance with US government research regulations, and applicable international standards of Good Clinical Practice, and institutional research policies and procedures.

1.1 Background

Neoadjuvant chemotherapy (NACT) is administered to treat invasive breast cancer before surgery[1-4]. NACT was originally limited to patients with inoperable locally advanced breast cancer (for whom even mastectomy was not an option), in order to shrink the tumor and allow surgery. It is now also frequently applied to operable breast cancer in early stage to enable breast-conserving surgery. Patients with small tumors may also be offered NACT if their cancer subtype has a high likelihood of response.As the treatment for breast cancer has advanced, the latest AJCC Staging for Breast Cancer for breast cancer includes genomic assays as well as management based on tumor subtype. NACT does not improve disease-free survival (DFS) or overall survival (OS) compared with adjuvant (post-surgery) therapy[5,6], but it **offers the opportunity to evaluate tumor response to treatment in aggressive disease, and guide additional therapies for patients with inadequate response**[7]. Pathologic complete response (pCR) is defined as the absence of residual invasive and in situ cancer on the resected breast specimen and all sampled regional lymph nodes following completion of NACT[8,9], and is a significant predictor of long-term survival. Therefore, a reliable and early assessment of tumor response to NACT can help identify patients for novel treatments to increase their chance of pCR, and thus improve DFS or OS after NACT compared with adjuvant therapy. In the past few years, one of the major benefits of NAC is achieving pCR has been widened to include patients with luminal A and luminal B tumors.

Currently, dynamic contrast-enhanced magnetic resonance imaging (**DCE MRI**)[10-13] is the standard technique to evaluate tumor shrinkage and residual cancer after NACT. However, DCE MRI often overestimates the extent of residual cancer, does not correlate well with histopathological results, and cannot distinguish between scar, necrosis, fibrosis and viable residual cancer. It is thus difficult to accurately assess the effect of NACT in responder patients with this technique. Diffusion weighted imaging (**DWI**)[13-16] is also currently investigated to determine therapy response. The apparent diffusion coefficient (ADC) calculated from DWI provides a quantitative measure of intra-tumoral water diffusivity, which can be related to the tumor cellularity and cell membrane integrity. However, these two MRI techniques can detect only structural changes (such as size and cellularity) in breast cancer, which generally take weeks or even months to yield measurable changes on MR images[17]. There is therefore a need to non-invasively quantify the **metabolic changes** in breast cancer within the first weeks (or even days) of therapy, before structural changes occur or can be detected. Assessing this early metabolic response to therapy in vivo would be of great importance to guide greater life-saving treatment options for the patients, to help the development of new drug treatments for different subtypes of cancer, and ultimately to allow tailored breast cancer therapy for each patient. For this purpose, **we propose to develop metabolic breast sodium (^{23}Na) MRI[18,19] which is based on the direct detection of endogenous sodium ions (Na^+) from salt in tissues**, instead of water protons (^{1}H) as in standard MRI. Sodium MRI does not require intravenous contrast agents, and allows a quantitative assessment of important biochemical information such as **ion homeostasis** (steady-state maintenance of asymmetric ion concentrations inside and outside cells) that is vital for normal cell and also cancer cell viability[19-33].

1.2 Hypothesis and Goal

Hypothesis. Cell damage induced by NACT can be characterized by loss of ion homeostasis in the abnormal cells forming the malignant tumor, through changes in pH, membrane depolarization and dysregulation of trans- membrane ion transporters (Na^+/K^+ pump, Na^+/H^+ and Na^+/Ca^{2+} exchangers), leading ultimately to cancer cell death[26,27,32,34-36] and subsequent tumor shrinkage. As a consequence, large variations of Na^+ concentrations inside the cells are induced, which can be quantified with ^{23}Na MRI *in vivo*. **Measuring variations of both intracellular sodium concentration C_1 (due to cell damage/loss of ion homeostasis) and extracellular volume fraction α_2 (due to cell death, but also maybe inflammation) with ^{23}Na MRI will give new metabolic information on the early effects of NACT on breast cancer, before tumor size reduction is detected with standard MRI[19,22,37-43]. See Fig 1.**

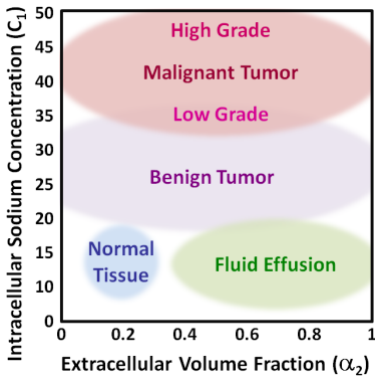


Figure 1. C_1-α_2 diagram. This diagram represents the working hypothesis for baseline measurements of C_1 and α_2 in healthy breast tissue and in tumors. Both C_1 and α_2 will vary during NACT.

Goal. We will develop a ^{23}Na MRI method to quantify C_1 and α_2 *in vivo* as two new metabolic imaging biomarkers of loss of homeostasis, in order to assess the efficacy of NACT in breast cancer as early as possible. The long-term benefit for the patient would be the possibility of tailored breast cancer therapy.

Goal for preliminary data: Although the original goal of this study is to assess NACT with ^{23}Na MRI, we plan to test the MRI protocol first on patients with any breast cancer (and before any treatment) as proof-of-concept (1 scan only for each subject), and also on patients with any breast cancer undergoing any chemotherapy regime, at multiple time-points: baseline, 2-3 weeks, 2-3 months, after treatment (about 5 months). This data is expected to be used for a R01 application which will be focusing on more specific breast cancer types and therapy regimes (such as the initial goal of this project: triple-negative breast cancer patients undergoing NACT).

1.3 Sodium MRI

Sodium nuclear magnetic resonance (NMR). The nucleus of $^{23}Na^+$ has a spin 3/2. It possesses a quadrupolar moment that interacts with surrounding electric field gradients, which leads to complex relaxation processes in biological tissues and results in short T1 and bi-exponential T2 relaxation times (T1 ~ 20-40 ms, $T2_{short}$ ~ 0.5-4 ms, $T2_{long}$ ~ 10-25 ms)[18]. ^{23}Na NMR sensitivity is 9.2% of the ^{1}H sensitivity. In healthy breast tissue, the average total ^{23}Na concentration is ~35 mM[44], which is approximately 1,500 times lower than the water ^{1}H concentration in breast tissue (~55 M, water fraction ~0.5). As a result, the ^{23}Na NMR signal is ~16,000 times lower than the ^{1}H signal in breast. High fields ≥3 T are therefore recommended to increase the ^{23}Na signal-to-noise ration (SNR). Since the sodium nuclei exhibit short bi-exponential T2 relaxation, 3D MRI sequences with ultrashort echo time (UTE) such as Fermat Looped Orthogonally Encoded Trajectories (FLORET)[45] must be implemented with TE ≤ 0.5 ms in order to maximize the signal strength. Due to the low ^{23}Na signal, and traditionally crude coil and acquisition methods, ^{23}Na images are acquired with coarse resolution (~3-5 mm isotropic) at 3 T and below.

Fluid/extracellular sodium suppression. Inversion recovery (IR) can be used to suppress (or minimize the effect of) of fluid signals to increase the sensitivity of ^{23}Na MRI to intracellular sodium in brain[46], and looks promising for future applications to brain tumors[19,39,47]. The IR method exploits the T1 difference between fluid and motion-restricted compartments (T1 ~ 40-50 ms in fluids outside the cells, T1 ~ 20-25 ms inside the cells). Our group has recently developed a ^{23}Na MRI method based on IR and a

multicompartment model of brain tissue to estimate C_1 and α_2 in vivo[48,49]. We will adapt and improve this method to quantify C_1 and α_2 in breast at 7 T. IR will be applied either using an adiabatic inversion pulse[50] (less sensitive to B0 and B1 inhomogeneities), or a single hard pulse with short duration and large bandwidth. Both types of pulse will be compared to optimize uniform fluid suppression while minimizing loss of signal from intracellular ^{23}Na.

1.4 DCE MRI

Dynamic contrast-enhanced MRI is a standard clinical imaging tool for evaluating the breast and breast cancer. DCE-MRI can be used to measure tumor size before and after treatment.

1.5 Investigational Device

1.5.1 MRI scanner at 7 T

All images will be acquired on a whole body 7 T system (Siemens, Erlangen, Germany) with multichannel (32 channels) and multinuclear (proton and sodium) capabilities, located on the 1st floor of the Center of Biomedical Imaging, Department of Radiology, 660 First Avenue, New York, NY 10016. MRI scanners are Class II (moderate risk) medical devices, meaning that an MRI manufacturer is required to submit a Premarket Notification 510(k) prior to marketing their MRI System. This device belongs to category B. All MRI equipment up to 3 Tesla has received FDA approval and has been in widespread clinical use for many years. However, the 7 Tesla MRI system and its hardware equipment are not FDA-approved for routine clinical use, although they have been developed and operate according to strict FDA guidelines and standards for research purposes only. All new technologies used in this investigation meet or surpass the safety standards of the FDA and are considered nonsignificant risk as defined in the “Guidance for Industry and FDA Staff–Criteria for Significant Risk Investigations of Magnetic Resonance Diagnostic Devices” issued July 14, 2003 (Magnetic resonance devices operating within FDA guidelines up to 8 T are considered non-significant risk).

The 7 T scanner in question is not intended as an implant. It is not purported or represented to be for use supporting or sustaining human life, and does not present a potential for serious risks to the health, safety, or welfare of a subject. The 7T scanner is a research device and is not for use of substantial importance in diagnosing, curing, mitigating, or treating disease or otherwise preventing impairment of human health. It is therefore not a significant risk device.

1.5.2 Radiofrequency (RF) coil

We built a dual-tuned multichannel RF coil (with 4 ^{23}Na-channels and 1 ^{1}H-Helmholtz-channel per breast) for bilateral breast ^{1}H/^{23}Na MRI at 7 T. The RF coil will be tested for imaging performance and validated for patient safety using a phantom. Coil Committee approval will be sought once the phantom testing is completed. The IRB will be provided with the Coil committee approval. No human testing will be conducted with investigational coils prior to IRB review and approval of this modification. This device belongs to category B. Coil performance is a primary determinant of breast MRI quality. A coil that allows concurrent ^{23}Na and ^{1}H breast imaging is not yet commercially available and presents technical challenges: complex coupling between the ^{1}H and ^{23}Na channels can degrade SNR, coverage, and uniformity. In our previous work for cartilage and head imaging, high performance was achieved on both channels by implementing new design strategies that alleviated inter-channel coupling and wideband matching that allowed the ^{23}Na array to substantially outperform traditional single channel designs. No adverse events have been seen. Our Coil Safety Committee will confirm safe operation of the coil such that RF power limits are restricted to a level consistent with International Electrotechnical Commission guidelines (IEC).

The RF coil in question is not intended as an implant. It is not purported or represented to be for use supporting or sustaining human life, and does not present a potential for serious risks to the health, safety, or welfare of a subject. The coil is not for use of substantial importance in diagnosing, curing, mitigating, or treating disease or otherwise preventing impairment of human health. It is therefore not a significant risk device.

1.6 Preclinical Data (Preliminary Data)

Preliminary ^{23}Na data was acquired at 7 T in breast cancer (without therapy) with a unilateral 4-channel prototype RF coil as proof-of-feasibility (**Fig. 2**). We generated C_1 and α_2 maps of breast with 3.75 mm isotropic resolution in 21 min for a total of 2 ^{23}Na acquisitions necessary to quantify C_1 and α_2. For this purpose, we built a unilateral ^{1}H/^{23}Na coil that consists of a ^{23}Na transmit solenoid, 4-channel ^{23}Na receive array, and ^{1}H transmit/receive solenoid (**Fig. 3**). Two healthy volunteers and one patient with breast cancer were scanned with the prototype coil at 7 T using the following MRI protocols:

^{1}H MRI. T1-weighted (T1w) 3D gradient echo with SPAIR (spectrally selective adiabatic inversion recovery) fat suppression, resolution = 0.9×0.9×1 mm^3, acquisition time TA = 3:33 min. 3D Gradient Echo (GRE) Dixon scans for automatic glandular tissue masking (TE = 2, 2.3, 2.6, resolution = 0.9×0.9×3.8 mm^3, TA = 6 min).

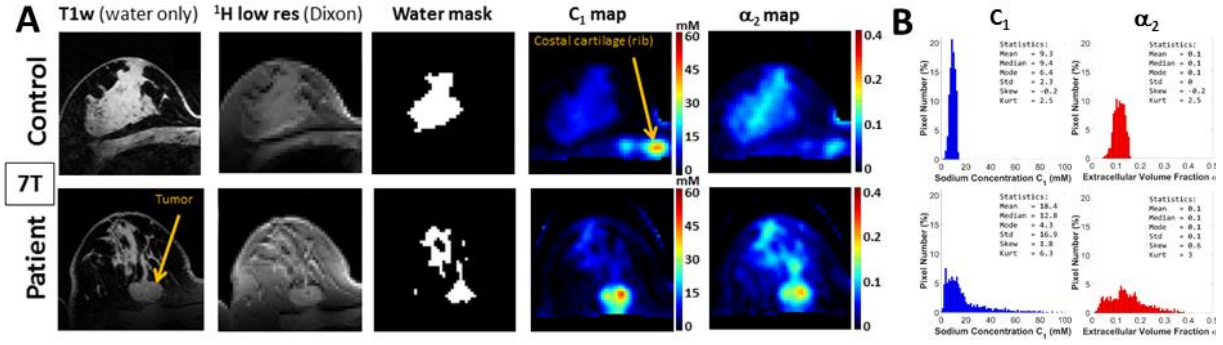


Figure 2 (**A**) Preliminary data from a healthy volunteer and a patient with a breast tumor at 7 T with the new prototype RF coil. A 3 cm invasive adenocarcinoma was detected in the right breast of the patient after T1-weighted ^{1}H MRI during her clinical scan. Notice the local large increase of C_1 and α_2 in the tumor. (**B**) Histograms of C_1 and α_2 in healthy tissue and in tumor. These histograms represent the distributions of C_1 and α_2 measured for bulk tissue analysis, using the 3D water mask (from ^{1}H Dixon MRI) applied to the ^{23}Na data. We can notice a large variation in the shape of the distributions (mainly skewness and kurtosis) when a lesion is present.

^{23}Na MRI. FLORET[45] sequence with: repetition time TR = 100 ms, echo time TE = 0.2 ms, 3 hub of 260 interleaves, 3.75 mm base resolution, inversion time TI = 27 ms for IR, TA = 7:50 (no IR) and 13:10 (IR). The C_1 and α_2 maps were calculated from linear regression of the reference phantom signals (see **Fig. 3B** and **3C**) and a 3-compartment model (**Fig. 4**), after correction of the ^{23}Na RF coil sensitivities from the scan of a uniform phantom with both acquisitions (with and without IR).

Results. Our prototype coil and data processing pipeline demonstrate feasibility of metabolic breast ^{23}Na MRI (**Fig. 2A**). For healthy volunteers, mean C_1 = 13±2 mM and mean α_2 = 0.13±0.02 in glandular tissue, which are in the previously reported range[19,21,42,49]. A healthy subject was scanned twice for repeatability testing: both measurements of mean C_1 and α_2 over 4 slices in parenchyma were within the range of 1 standard deviation (C_1 = 12±2 mM and 14±2 mM, α_2 = 0.13±0.02 and 0.15±0.02, respectively). In tumor, we measured C_1 = 62±10mM and α_2 = 0.33±0.04. These elevated values correspond to malignant tumors in our baseline hypothesis (**Fig. 1**) and are clearly differentiable from normal glandular and adipose tissues. See **Fig. 2B** for bulk distributions of C_1 and α_2 values measured with the water mask calculated from the Dixon acquisition.

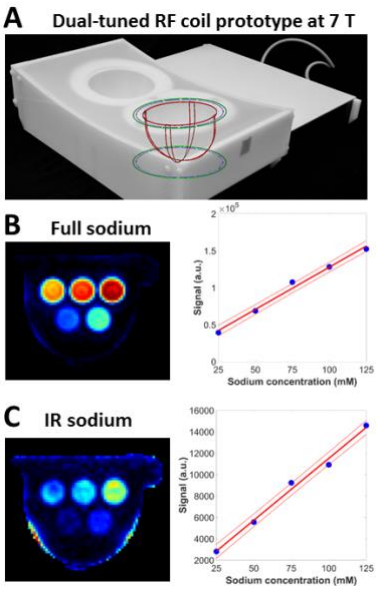


Figure 3. RF coil prototype and linear regression. (A) New prototype ^{1}H/^{23}Na breast coil at 7 T. Overlay of the position of the solenoid coil for ^{1}H transmit-receive (blue), of the solenoid for ^{23}Na transmit (green), and of the ^{23}Na 4 receive loops (red). **(B)** Transverse ^{23}Na image of reference phantoms (3% agar with 25, 50, 75, 100, 125 mM of [Na^+]) without IR (left), and linear regression of the phantom signals (right). **(C)** ^{23}Na image with IR (left), and linear regression of the phantom signals (right).

1.7 Clinical Data to Date

Although ^{23}Na MRI is under active development around the world due to its ability to detect new biochemical information in vivo, its application to breast cancer has not yet been sufficiently explored. All previous studies on breast tumors either quantified the total sodium concentration (TSC) or reported only relative variations of total sodium signal without quantification of the TSC. TSC is the average of both intracellular and extracellular sodium content, and does not allow discrimination between cell damage and loss of homeostasis (through C_1) and cell death and/or inflammation (through α_2). Prior studies on tumor samples showed significant differences in ^{23}Na content between normal tissues (C_1 ~ 15 mM, TSC ~ 35-45 mM), benign (+50% in C_1) and malignant tumors (+100-200% in C_1)[19,22,35,39,44]. Moreover, tumor resistance to certain therapies was correlated with tissue sodium content in animal studies[51]. The first application of ^{23}Na MRI in vivo to patients with breast tumors (at 1.5T) was published in 2004 by Jacobs et al.[52]. They found an increase of around 67% in TSC in tumors compared to glandular tissue. Their subsequent work differentiated TSC in benign (26±5 mM) and malignant tumors (53±16 mM), but detected a small difference between benign tumor and glandular tissue (34±13 mM).72 Importantly, the same team found that ^{23}Na MRI was able to distinguish TSC variations in NACT responders (-20 to -30%) and non-responders (+5-10%)[38,53].

Though these works showed encouraging results, their impact was hampered by the following important limitations:

1. C_1 and α_2, which are more useful and sensitive biomarkers of early effect of chemotherapy on tumors, were not differentiated from TSC, and variations of TSC are difficult to interpret;

2. Spatial resolution was limited to 6 mm isotropic due in part to the single-channel volume coil operating at low-field (1.5T), resulting in significant partial volume effects;
3. New efficient sampling and reconstruction schemes were not applied.

We will remedy these drawbacks by measuring C_1 and α_2 using a combination of highly sensitive techniques, such as efficient sampling and reconstruction with FLORET and compressed sensing, 13-channel bilateral receive array with wideband matching, at ultra-high field (7 T).

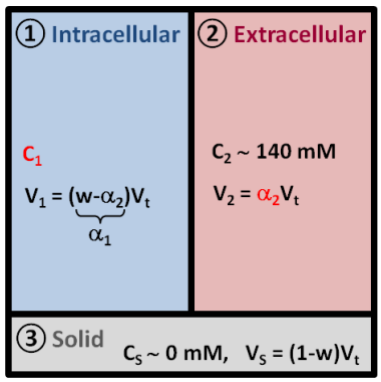


Figure 4. Three-compartment model (3-CM): Compartment 1 = intracellular volume V_1 (in L) of sodium concentration C_1 (mM). Compartment 2 = extracellular volume V_2 of sodium concentration C_2. Sodium ions are only present in the 'water' volume of the tissue (V_1+V_2). Compartment 3 = volume V_S with all the 'solid' components within the voxel (cell membranes and nuclei, proteins, and other metabolites), where sodium content is negligible. The total volume is V_t = V_1+V_2+V_S. Unknown values of interest are C1 and the extracellular volume fraction α_2 (in red). In this simple model, we assume that C_2 is constant ~140 mM, and that the water volume fraction w is also constant and known ~0.65 in breast (but planned to be measured with ^{1}H MRI in the future).

1.8 Research Risks & Benefits

1.8.1 Risk of Investigational Device

All MRI equipment up to 3 T has received FDA approval and has been in widespread clinical use for many years. However, the 7 T MRI system and its hardware equipment are not FDA-approved for routine clinical use, although they have been developed and operate according to strict FDA guidelines and standards for research purposes only. All new technologies used in this investigation meet or surpass the safety standards of the FDA and are considered non-significant risk as defined in the "Guidance for Industry and FDA Staff–Criteria for Significant Risk Investigations of Magnetic Resonance Diagnostic Devices" issued July 14, 2003 (Magnetic resonance devices operating within FDA guidelines up to 8 T are considered non-significant risk). We can however notice that despite the fact that ultra-high field (UHF) MRI (>7 T) is not yet approved for clinical practice, recent improvements in safety and image quality have shown superior results for neuroimaging, musculoskeletal and breast imaging applications. As a consequence, Siemens is now waiting for FDA approval for a new 7 T clinical scanner (Magnetom Terra scanner), which could extend the use of UHF MRI to clinical practice in the near future.

There are 4 categories of risk associated with this study:

1. **Risks associated with MRI in general:** MRI uses a strong magnetic field to create images of the body but there are no known risks or adverse effects resulting directly from exposure to MRI. Because of the strong magnetic field, the greatest risk is that a metal object could be pulled into the scanner and hit subjects. To reduce this risk, everyone near the magnet will remove all metal from their clothing or pockets when in the scanning environment. The door to the scan room will remain closed during the exam for subject safety. All subjects will be asked to fill out a standard MRI safety checklist to make sure that subjects with metal implants or any other routine contraindication to MRI will not be scanned. Subjects who have a pacemaker or metal objects in their body such as shrapnel or metal in the eye should not have the scan performed. If subjects have any question about metal implants or metal fragments in the body, they should inform the technologist or investigators before entering the magnet room. During the MRI examination subjects will be periodically monitored through an intercom and visually using a CCD camera, and if any problems arise, the study will be immediately terminated. Subjects are given a squeeze ball to communicate with the technologist. Instructions will be given prior to and during the MRI scan. No sedation will be administered. Since 2007, many volunteers and

162 patients were scanned on the 7T magnet. We have no documented adverse effects secondary to being imaged on a 7T scanner.

2. **Risks associated with an experimental MRI pulse sequence at 7 T:** All MRI equipment up to 3 T has received FDA approval and has been in widespread clinical use for many years. However, the 7 T MRI system and its hardware equipment are not FDA-approved for routine clinical use, although they have been developed and operate according to strict FDA guidelines and standards for research purposes only. All new technologies used in this investigation meet or surpass the safety standards of the FDA and are considered nonsignificant risk as defined in the "Guidance for Industry and FDA Staff– Criteria for Significant Risk Investigations of Magnetic Resonance Diagnostic Devices" issued July 14, 2003 (Magnetic resonance devices operating within FDA guidelines up to 8 T are considered non-significant risk). The RF power deposition (tissue heating) can be higher at 7 T when compared to clinical systems (0.5-3T). However, we will not exceed the RF power deposition mandated by FDA. Further safeguard is built into the scanner software, such that during the MRI experiments, the scanner monitors the RF power. If it detects that RF power has exceeded the allowed limits, it automatically stops the scan. This eliminates the risk associated with any inadvertent errors during the scan.

3. **Risks associated with Gadolinium-based MRI contrast agent (GBCA) injection for DCE MRI**: The risks and discomforts from the I.V. needle include the possibility of pain or bruising at the site here the needle is inserted. Occasionally, people experience feelings of lightheadedness. In rare instances there may be an infection at the site where the needle is inserted. There is also a risk of an allergic reaction to the contrast agent. The FDA approves the imaging agent gadolinium for use in MRI. Some subjects, (less than 3%) may experience minor discomforts that include nausea and/or headache after injection. These side effects usually pass quickly without medical treatment.

   Risk of NSF: Nephrogenic systemic fibrosis (NSF) is a rare disorder that occurs in some individuals with reduced kidney function, who have been exposed to an intravenous contrast material that contains gadolinium. NSF is also known as nephrogenic fibrosing dermopathy or nephrogenic systemic fibrosis/nephrogenic fibrosing dermopathy (NSF/NFD). A contrast material is a dye that is sometimes used during magnetic resonance imaging (MRI). **Gadobutrol** (**Gadavist**; Bayer Healthcare, Whippany, NJ), the MRI contrast material used in this study, has a very low rate of adverse reactions and is designated as a low risk contrast agent by the European Committee for Medicinal Products for Human Use. Gadavist has been used in more than 29 million patients. As of December 2015, there were a total of 12 reports of NSF or NSF-like symptoms in patients who reportedly were administered gadobutrol. Fewer than 1% of patients develop nausea, vomiting, or headaches.

   Subjects with any kidney disease or other kidney problems, will be asked not to participate in this study.

   Fairly recently (in 2014) evidence indicated that individuals who receive multiple doses of GBCA may have traces of gadolinium deposited into their brains for an indeterminate amount of time. To date, there is a lack of data indicating whether or not this could be harmful.

4. **Risks associated with the development of a new RF coil:** Our Coil Safety Committee has confirmed safe operation of the coil; infrared, direct, and fiber optic thermometry were carried out to assign RF power limits such that tissue heating and the specific absorption rate (SAR) are restricted to a level consistent with International Electrotechnical Commission guidelines (IEC)[55]. Given the high level of habitus variability and its potential impact on SAR, we implemented a 5 W/kg limit to provide a two-fold buffer over the 10 W/kg limit established by the IEC.

1.8.2 Other Risks of Study Participation

Because the risks of participating in this research study are identical to those arising from the performance of clinical MRI, all subjects will undergo the same rigorous screening procedures that are used for clinical MR examinations. All subjects will be screened for biomedical implants and devices by questioning at the time of recruitment into the study as well as on the day of the examination. Those with potentially MR incompatible devices or other hazards such as orbital foreign bodies, will be excluded. If pregnancy is a possibility, female subjects will undergo a urine test on the day of the MR examination. If the test is positive, then the subject will be excluded from the study. During the MRI experiments, MRI scanner monitors the RF power deposition. If it detects any sequence parameters that exceed the allowed RF power limits, it automatically stops the sequence and a message is displayed indicating that the sequence cannot be run as it exceeds the power deposition limits. This eliminates the risk associated with inadvertent errors during scanning time.

For breast cancer patients who would not undergo clinical MRI examination before neoadjuvant therapy, additional information gained from this research MRI may lead to detection of abnormalities and possibly to the need for additional biopsies and clip placements if breast conserving therapy is planned. For healthy volunteers the research MRI could detect abnormalities in the breast including false positives which could result in additional diagnostic workup and biopsies.

1.8.3 Potential benefits

As this is a preliminary study, no direct benefit is expected for participants. No treatment change in patients will be recommended based on the preliminary results of this study. A possible benefit to the subjects is the unlikely event in which an unsuspected but treatable disorder is incidentally noted on the MR images. The benefit to society of establishing a non-invasive and quantitative metabolic imaging technique for the early assessment of breast cancer response to chemotherapy is considerable as it will help develop reliable monitoring of cancer treatment. This could ultimately result in developing tailored therapy for individual patients and increase their chances of disease-free survival.

2 Study Objectives

2.1 Primary Objective

We will develop a new robust, quantitative and non-invasive ^{23}Na MRI method to assess new metabolic information (C_1 and α_2) in breast cancer in vivo. The proposed method will allow us to quantify the efficacy of NACT in breast cancer as early as possible, before tumor size reduction can be detected by standard MRI. For this purpose, we will design and build a 13-channel-receive ^{23}Na array per breast, optimize the ^{1}H/^{23}Na MRI protocol and data processing (image reconstruction, data quantification, mechanistic model) at 7 T. The long-term benefit for the patient would be the possibility of tailored breast cancer therapy.

2.2 Secondary Objective(s)

2.2.1 Methodological development of metabolic ^{23}Na MRI in breast

1. **Radiofrequency (RF) coil**: We will build a dual-tuned multichannel ^{1}H/^{23}Na RF coil (with 13 ^{23}Na-channels and 1 ^{1}H-Helmholtz-channel per breast) that will allow bilateral breast ^{1}H/^{23}Na MRI at 7 T.
2. **MRI protocol**: We will optimize data acquisition (FLORET) and reconstruction (compressed sensing[57]) to generate ^{23}Na images of the breasts with 2.5-3 mm isotropic resolution in ~7 min/acquisition. We will perform DCE MRI afterwards to prevent influence of the contrast agent on ^{23}Na data.

3. **Data processing:** We will develop a software to quantify C_1 and α_2 based on two ^{23}Na data acquisitions (with and without extracellular fluid suppression)[49] and a multicompartment model of cancer cells in breast. A mechanistic model of loss of ion homeostasis due to chemotherapy will also be developed in order to interpret the results. Reproducibility and repeatability[48,58] of C_1 and α_2 quantification will be assessed on 8 healthy subjects.

2.2.2 Application of ^{23}Na MRI to assess response of breast cancer to chemotherapy

1. **Patient scanning**: We will scan 20 patients with any breast cancer diagnosis
    a. 10 women will only be scanned at baseline (before any therapeutic intervention) to obtain preliminary images of cancerous breast tissue with the new optimized MRI protocol.
    b. 10 women who plan to undergo any chemotherapy will participate to up to 4 scans: (1) baseline; (2) after 2-3 weeks of treatment; (3) after 2-3 months of treatment; (4) after treatment (about 5 months).
2. **Assessment of** chemotherapy **response**: We will compare C_1, α_2 and tumor size at all time-points acquired. Using statistical analysis and the mechanistic model, we will assess which measurements are best predictors of the outcome at the end of treatment.

3 Study Design

3.1 General Design

We will design a ^{1}H/^{23}Na RF coil. The investigational coil will first be tested on a phantom before human subjects' involvement. Once phantom testing is complete, all appropriate materials will be submitted to the Coil Committee for review and approval. Once Coil Committee approval is obtained, the study modification will be submitted to the IRB. No human subjects in Aims 1 or 2 will be enrolled until after approval is obtained by both the Coil Committee and the IRB.

We will then optimize a ^{23}Na breast MRI protocol for quantification of C_1 and α_2 in vivo at 7 T. 16 healthy subjects will be used to design and test the new 1H/23Na RF coil and optimize the final ^{1}H and ^{23}Na MRI protocol (Aim 1) that will be applied later to patients in Aim 2 of the project. As shown in Figure 6 in the Protocol document, healthy subjects will be scanned for (1) coil testing, (2) fluid suppression optimization, (3) relaxation times measurements, and (4) assessment of repeatability and reproducibility of the proposed ^{23}Na MRI method to quantify intracellular sodium concentration and extracellular volume fraction in vivo in healthy tissue (8 subjects will be scanned twice for this part of the study) We will scan 9 patients with any breast cancer (before any treatment) to demonstrate the efficacy of sodium imaging in cancerous tissue. We will also scan 9 breast cancer patients who undergo chemotherapy. All patients will be scanned up to 4 times over the duration of chemotherapy (~5 months): (**1**) at baseline (pre-treatment); (**2**) after 2-3 weeks of treatment; (**3**) after 2-3 months of treatment); (4) after complete treatment (4-5 months). Each scan session will consist of ^{23}Na MRI and ^{1}H MRI.

3.2 Primary Study Endpoints

Milestones are shown in **Fig. 5**:

1. **Month 9 of year 1**: The RF coil will be constructed, tested, and validated for breast imaging on a 7 T scanner. The ^{23}Na MRI protocol will be ready and scanning of patients with breast cancer can begin.
2. **End year 1**: The ^{23}Na data processing, including C_1 and α_2 quantification and mechanistic model of NACT effect on tumors, will be optimized and ready to be tested on patients for early assessment of NACT.
3. **End year 2**: We will have scanned and compared 12 patients during NACT (4 scans each) with ^{23}Na MRI and DCE MRI. A co-authored manuscript on the results of the study will be submitted to a peer-reviewed journal.

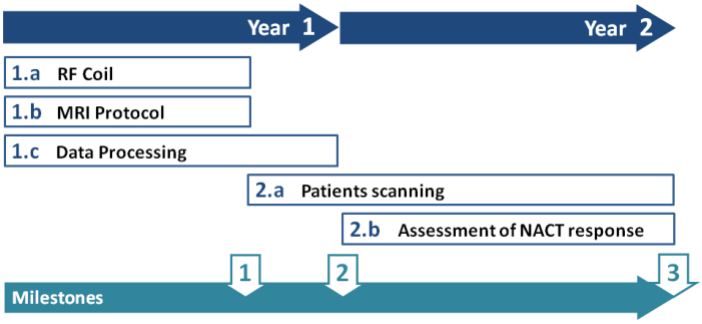


Figure 5. Timeline with milestones.

3.3 Secondary Study Endpoints

Sodium data quantification in 3 steps

1. **Linear regression:** Five reference gel phantoms (Agar 3%) were built with known sodium concentrations (25, 50, 75, 100, 125 mM) and pre-measured T1 and T2* relaxation times at 7 T. The phantoms were scanned separately to provide a reference to allow ^{23}Na data quantification (see **Fig. 3A-B**) under same in vivo conditions (coil filling, shimming, reference voltage). A full density operator simulation for spin 3/2 dynamics[61,62], implemented in Matlab (Mathworks, Natick, MA, USA), will be used to estimate phantom signal loss due to relaxation during RF pulses and delays in the acquisition sequence. From this simulation, phantom signal from sequences 1 (FLORET) and 2 (FLORET+IR) will be corrected prior to performing linear regression of their signal magnitudes. Linear regression will be considered valid only when the coefficient of determination R^2>0.99, to ensure robustness against noise corruption.
2. **The apparent total and intracellular sodium concentration (aTSC, aISC) maps**, corresponding to sequences 1 and 2 respectively, will be calculated using the parameters from linear regression of the phantom signals. These two maps will also be corrected from simulation of the sequence-specific ^{23}Na spin dynamics with relaxation times measured in breast tissue on 4 healthy subjects.
3. **Intracellular sodium concentration (C_1) and extracellular volume fraction (α_2) quantification** is based on the combination of a 3-compartment model (**Fig. 4**) with the aTSC and aISC maps. We assume that all extracellular fluid sodium signal (milk ducts, interstitial sodium, plasma) is either suppressed by inversion recovery or within noise level of the image. The values of each voxel of the aTSC and aISC maps are: $aTSC = (C_1V_1+C_2V_2)/V_t$, and $aISC = C_1V_1/V_t$. Using equations in **Fig. 4**, we calculate: $\alpha_2 = (aTSC-aISC)/C_2$, and $C_1 = aISC \times C_2/(w \times C_2 - aTSC - aISC)$ for each voxel.

Biophysical model

We will develop a biophysical model[63-66] of ion homeostasis in breast tumors in order to simulate the possible effects of chemotherapy on cancer cells[67-69]. This model will be composed of an extracellular compartment, an intracellular compartment, and inter-compartment membranes. We will simulate ionic currents of Na^+, K^+, Ca^{2+}, Cl^-, H^+, HCO^{3-} and glutamate (Glu^-) between all compartments through their trans-

membrane ion channels and active transporters (ATPases, co-transporters and exchangers)[24,27,32,34,70]. Variable pH, membrane depolarization, ATP depletion and impaired energetic metabolism in cancer cells induced by chemotherapy will be inputted to the model to simulate changes in all intracellular ionic concentrations and cell volume[20,23,25,26,31,71-74]. This simulation will be used to interpret and predict the biophysical effects of chemotherapy over time on C_1 and α_2 values measured with ^{23}Na MRI.

Reproducibility and repeatability

Reproducibility and repeatability of C_1 and α_2 quantification will be assessed as described in Ref.[48,58] on 8 healthy volunteers, with all sodium data processed twice (by 2 independent operators). Each subject will be scanned 4 times on 2 separate days, without contrast. In one paid scan session of 1 h on each day, the same ^{23}Na MRI protocol (FLORET with and without IR) will be performed twice with subject repositioning during an intermission period. Data will therefore be: C_1 and α_2 from 1 region of interest (ROI) in each breast, from 4 scans, collected and processed by 2 operators. Restricted maximum likelihood for a mixed effects model will estimate the inter-subject variance and the intra-session, inter-session and inter-operator (intra-scan) components of intra-subject variance. The estimates will be used to compute the intra-class correlation (ICC) and coefficient of variation (CV) for the inter-session and intra-session variation as measures of repeatability, and for inter-reader variation as measures of reproducibility.

Spatial analysis

1. **Local lesion analysis.** Lesions will be manually segmented in ^{1}H T1w images by Co-Investigator Dr Linda Moy (breast radiologist with 15+ years experience) and size will be defined as the longest linear dimension of the lesion. The ROIs will be transferred to co-registered ^{23}Na images to measure intracellular sodium concentration C_1 and extracellular volume fraction α_2 in lesion.
2. **Bulk tissue analysis.** We will acquire multi-echo ^{1}H datasets that cover the entire breast volume to automatically segment the glandular tissue using the Dixon chemical species separation algorithm[75,76], which is a masking technique used in our previous work[77]. The water mask identified in ^{1}H images will be transferred to co-registered ^{23}Na images. Finally, C_1 and α_2 in water mask pixels will be displayed in a histogram, which is expected to have a variable distribution shape between normal subjects and patients with tumors.

Assessment of chemotherapy response

We will compare C_1 and α_2, and tumor size at all 4 stages of treatment. Using statistical analysis and the mechanistic model, we will assess which measurements are best predictors of the outcome at the end of AC treatment, and at the end of NACT. The mechanistic model will be used to: (**1**) interpret the results from all imaging modalities from a biophysical point-of-view; (**2**) simulate and predict the effect of chemotherapy on C_1 and α_2 (metabolic change) first, and the subsequent effect on tumor size (structural change).

3.4 Primary Safety Endpoints

N/A

4 Subject Selection and Withdrawal

4.1 Patient with breast cancer

4.1.1 Inclusion Criteria

- Histologically confirmed invasive cancer of the breast.

- Planned chemotherapy for a subset of patients with breast cancer
- Age ≥ 18 years.
- Non-pregnant and non-lactating.
- Ability to understand and willingness to sign a written consent.

4.1.2 Exclusion Criteria

- Previous therapy with chemotherapy or targeted therapy for the current breast cancer. Prior endocrine therapy for a prior invasive cancer or risk reduction as well as estrogen/progesterone replacement therapy is allowed if >6 months prior to study entry. Prior chemotherapy for other cancers is allowed if >2 years prior to study entry.
- Contra-indications to MRI (i.e., ferromagnetic prostheses, metallic surgical implants that are not compatible with an MRI machine, claustrophobia etc.)
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Pregnant or lactating women, women using hormonal treatment in the 6 months prior to the study
- Women with history of breast disease, previous ipsilateral breast surgery, or breast implants.
- Psychiatric illness or other conditions and circumstances which could prevent the patient from being compliant with the protocol.
- Women with any kidney disease or other kidney problems, who are at risk for developing NSF/NSD (Nephrogenic Systemic Fibrosis, or Nephrogenic Fibrosing Dermopathy) due to gadoliunium injection.
- Subjects with Glomerular Filtration Rate (GFR) < 15 ml/min/1.73m^2 or who are on dialysis.

4.2 Healthy subjects

4.2.1 Inclusion criteria

- Women with no sign of breast cancer as controls
- Age ≥ 18 years
- Non-pregnant and non-lactating
- Ability to understand and willingness to sign a written consent
- Patients with benign tumors (e.g., hyperplasia, cysts, intraductal papillomas, etc.) will be included per PI discretion

4.2.2 Exclusion criteria

- Contra-indications to MRI (i.e., ferromagnetic prostheses, metallic surgical implants that are not compatible with an MRI machine, claustrophobia etc.)
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Pregnant or lactating women, women using hormonal treatment in the 6 months prior to the study.
- Women with history of breast disease, previous breast surgery, or breast implants.
- Patients with a currently active second malignancy other than non-melanoma skin cancers. Patients are not considered to have a currently active malignancy if they have completed therapy and are free of disease for 3 years.
- Psychiatric illness or other conditions and circumstances which could prevent the patient from being compliant with the protocol.

- If injection of contrast agent: Women with any kidney disease or other kidney problems, who are at risk for developing NSF/NSD (Nephrogenic Systemic Fibrosis, or Nephrogenic Fibrosing Dermopathy) due to gadoliunium injection.
- If injection of contrast agent: Subjects with GFR < 15 ml/min/1.73m^2 or who are on dialysis

4.3 Subject Recruitment and Screening

Potential participants for this study will be solicited from a broad base of individuals who meet the conditions outlined for the study. This may incidentally include NYU Langone Health employees and/or students, whose participation is entirely voluntary. Participation in research is not a requirement for employment, and neither the participant's academic status or grades, nor their employment will be affected by their decision to participate in this study. Record of the participation cannot be linked to an academic or employment record. To reduce the possibility of the appearance of coercion: 1) NYU staff and students will be made aware that their participation will not affect employment or academic status and 2) NYU staff and students that directly work on this project will not be allowed to participate.

4.3.1 Healthy Subjects

Healthy subjects will be recruited through advertising across NYU Medical Center facilities. Thus, we will have brochures for participants to take, placed at the front desks of the Center for Biomedical Imaging and at the Laura and Isaac Perlmutter Cancer Center (see brochure in attachments).

We will also utilize Craigslist, an online classified advertisements website, to advertise the study to healthy volunteers.

All advertisements will be approved by the IRB.

Participation to the study will not be limited by race or ethnicity, and patients of all ethnic backgrounds will be encouraged to participate. The study will be limited to female subjects only.

Most of the controls (healthy subjects) will be scanned without contrast agent injection for coil and sodium MRI protocol optimization. Once enough data has been obtained to optimize the MRI protocol (at the end of year 1), we will then expect to scan approximately 4 controls with contrast agent injection to test and optimize the DCE MRI sequence timing and resolution. We will ensure that these healthy controls have no contraindication to gadolinium contrast agent and they will sign the consent form dedicated to "controls with contrasts". As for patients with breast cancer, they will be screened prior to the scan by the research coordinator and MR technicians at the CBI.

Only once the complete $^{1}H+^{23}Na$ MRI protocol is ready and tested on controls, we will start to scan patients with breast cancer to assess treatment response (year 2).

Prospective subjects will receive detailed information regarding this study; its investigational nature, required study procedures, alternative treatments, risks and potential benefits of the study. They will also receive the informed consent document to read. All questions are answered by the PI and qualified research personnel.

Subjects with benign lesions/masses will also be included as healthy subjects, since benign (non-cancerous) breast conditions are very common, and most women have them.

Incidental Findings:

In some cases, a scan of a volunteer will reveal an incidental abnormality with (or without) a clinical significance. Every scan performed in this study is saved and handled under the standard PHI confidentiality

restrictions and regulations employed for subjects' information. Each scan is additionally reviewed by a radiologist, who might then detect an abnormality. If clinically useful information is uncovered, either the Principal Investigator or another clinician on the study will ask to speak to the subject's physician to communicate these results. It will be the subject's responsibility to follow-up with his/her physician outside of the study.

As this is a pilot study, findings from the research project itself will not be communicated directly to individual patients. As written in section 7 in all the consent forms, there will be no direct benefit for the subjects to participate in the study. However, the new research images are important for future MRI studies and clinical uses. The imaging knowledge gained will be of benefit to others in the future.

4.3.2 Breast cancer patients

Participation to the study will not be limited by race or ethnicity, and patients of all ethnic backgrounds will be encouraged to participate. The study will be limited to female patients only, as this is the predominant population with breast cancer.

Breast cancer patients will be recruited from the NYU Cancer Institute and NYU Winthrop by our co-investigators. Linda Moy, MD, will identify potential patients who present to the Breast Imaging Center with a known diagnosis of breast cancer. Patients who undergo imaging tests (mammography, breast ultrasound and/or breast MRI) and are diagnosed with breast cancer will be identified and screened. Similarly, Sylvia Adams, MD, an oncologist specializing in breast cancer, and Freya Schnabel, MD and Shubhada Dhage, MD, breast surgeons, will also screen patients seen in their offices who meet the inclusion criteria.

Patients recruited from Winthrop may opt to use the car service, Communicar, free of charge, to be transported from their homes to the Center for Biomedical Imaging and back for their appointments.

Subjects who have been diagnosed with breast cancer and meet inclusion criteria as outlined above will be recruited from oncology with an initial discussion of the study. If subjects are interested in participating, the PI/co-investigators or study coordinator will meet with each of the subjects at the Cancer Center in a room that gives privacy to discuss the study. A copy of the consent will be given to the subjects to read and retain and the original signed consent will be retained by the study team, which will document the consent process. The subject will be given an opportunity to ask questions and will be encouraged to ask questions. We will ask the subjects to verbally describe what they have consented to do so that we know that they understand the scope of the research study. When all concerns about the study have been addressed, they will be asked to sign the consent form. Subjects must fully understand the potential risks and benefits involved in participating in the study. Participation in the research is voluntary and withdrawal from participation will not affect an individual's care in any way.

Two types of patients with breast cancer will be recruited: (1) patients with any type of breast cancer will be recruited for testing and optimizing the MRI procotol (1 scan); (2) patients with any breast cancer who are scheduled to receive chemotherapy will be recruited for the longitudinal part of the study (4 scans: at baseline, 2-3 weeks, 2-3 months, post-treatment).

Although we expect to scan all patients with breast cancer with contrast agent injection (gadolinium) for DCE MRI, at baseline and at 3 follow-ups (2-3 weeks, 2-3 months, post-treatment), we will prepare an informed consent form without contrast agent injection for these patients in case some of them cannot be scanned with injection for personal or medical reason at any time-point of the study.

The Principal Investigator or IRB approved sub-investigator will be responsible for documentation in the medical record that consent has been obtained from all participants. A signed copy of the consent form will be given to each participant. Original consent forms and informed consent checklists will be stored in a study binder that is kept in a locked file cabinet inside of a locked office. If there are any amendments made

to the protocol after initial IRB approval, all subjects will be re-consented; that newly signed consent form will also be stored in the study binder.

4.3.3 Consent forms

The major emphasis in approaching a subject is that:

1. They fully understand the potential risks involved;
2. That participation in the research is purely voluntary.

Informed consent will be obtained from all participants prior to their participation in this research study. Informed consent will be obtained in accordance with the FDA regulation 21CFR, Part 50. A copy of the approved Subject Informed Consent Form, along with a copy of each subject's signed and dated consent form, will be maintained by the study coordinator in a designated study binder. This file will be locked in a file cabinet that is located in a locked room. In the absence of informed consent no research will be performed. A copy of the signed informed consent will also be given to the subject. If amendments to the protocol are made after initial IRB approval which involve a change to study procedures or alter the risks and benefits to study participants, all subjects will be re-consented. The original re-consented forms will be locked away in the administrative file with the original forms.

Four sets of informed consent forms will be available:

1. Informed consent form without contrast agent injection (for healthy subjects).
2. Informed consent form with contrast agent injection (for healthy subjects).
3. Informed consent form without contrast agent injection (for patients with breast cancer).
4. Informed consent form with contrast agent injection (for patients with breast cancer).

The Principal Investigator will:

1. Obtain signed and dated informed consent from the potential subject before any study specific procedures are performed.
2. Determine patient eligibility See Sections 4.1.1, 4.1.2, 4.2.1 and 4.2.2
3. Submit registration to NYU Langone Perlmutter Cancer Center CTO
4. Receive registration confirmation from the Research Coordinator at NYU Perlmutter Cancer Center CTO, including a unique study identification number assigned to the patient by the research coordinator, which will be distributed to the study team upon registration of the patient.

The informed consent process and documentation follows the established procedures of the NYULMC IRB.

The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with it for IRB approval.

If applicable

For non-English speaking patients, institutional translation services will be utilized. For these patients the consent letter and all other information will be administered orally and a witness, not related to the research project, will be present while the oral presentation is given. A short form will be utilized for the subject to sign in his/her name and the translator and/or witness must sign the short form. The translator will also sign the main consent form.

Due to COVID-19 and to keep the safety of both our research team and research subjects, we will be collecting consent via telephone during the COVID-19 crisis. A trained Research Assistant will schedule a time with eligible interested participants to go over the written consent via telephone. Research Assistants will email or mail a copy of the consent to participants in preparation for the telephone consent. After going

over the written consent via telephone, research assistants will also send the consent via a RedCap link where the participant has the opportunity to read a copy of the written consent and sign electronically, confirming that they read and understood the consent. Research Assistants will also document on RedCap the time and date of the telephone consent and note that the consent process was done via telephone due to COVID-19.

An IRB-approved phone script will be used to contact patients during the COVID-19 crisis. The phone script will be used as an initial determination of a subject's eligibility. The PI and the research coordinator will have access to this collected eligibility data. We will keep this information until the end of the study to avoid screening the same ineligible subject more than once. Subjects who do not meet eligibility criteria will have their information discarded after the end of the study.

4.4 Registration Procedures

4.4.1 General Guidelines

Each patient must sign and date an informed consent form before undergoing any study specific procedure unless a procedure is being performed as part of the patient's standard of care.

Enrollment in the study requires that all inclusion and exclusion criteria have been met. Enrollment occurs upon confirmation of registration from the NYULMC PCC Clinical Trials Office. The following materials must be submitted to the Research Coordinator for subject registration:

1. Complete signed and dated informed consent form
2. Complete signed and dated informed consent checklist
3. Complete signed and dated eligibility checklist
4. All supporting documentation verifying each criterion has been met

Registration will occur within 48 hours of research coordinator receipt of all of the above documents. A written confirmation of enrollment including a unique study identification number assigned by the research coordinator will be disbursed to the study team upon registration.

Once eligibility is verified, a unique patient study number will be issued within 24 hours of receiving all required registration material. This is the point, at which, the patient is considered on study. Subjects must not start any protocol study specific procedures, unless part of standard of care prior to registration.

4.5 Early Withdrawal of Subjects

4.5.1 When and How to Withdraw Subjects

A subject will be withdrawn from the study if, after signing informed consent, he or she is found to have any contraindication for MRI, fails to adhere to the protocol requirements, or if the PI has any safety concerns. Inadequate imaging quality due to lack of subject collaboration (ability to remain still) will be considered as a cause of withdrawal from the study. Additionally, participation is entirely voluntary, and a subject may withdraw from the study at any time. If a subject wishes to withdraw from the study, the following sequence of events will occur:

- PI and research coordinator will be alerted immediately by the interviewer,
- PI and research coordinator will meet with the participant to address any concerns,
- PI or research coordinator will provide participant with the telephone number for the NYULMC Radiology IRB, should the subject wish to discuss any issues with a representative of the Board.

If a subject does not wish to participate in a study procedure, or wishes to discontinue the procedure prior to its completion, the procedure would be stopped immediately. If there are any safety concerns regarding

an individual's participation in the study, per our exclusion criteria, or a problem that occurs during the study, the study will be stopped per standard radiology clinical practice.

4.5.2 Data Collection and Follow-up for Withdrawn Subjects

Patients that will be participating in our study will be under the care of an oncologist and are expected to have close clinical follow-up. The participation in the research study is voluntary and withdrawal from participation will not affect care in any way. Healthy controls will be aware that participation in this study is voluntary and they may revoke or withdraw consent at any time. Data from early withdrawn subjects may or may not be included in the analyses. In the event that a subject is withdrawn or revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. No follow-up data is required.

5 Study Devices and Imaging Procedures

5.1 Description

1. **MRI scanner at 7 T**: All proton and sodium images will be acquired on a whole body 7 T system (Siemens, Erlangen, Germany) with multichannel (32 channels) and multinuclear capabilities.
2. **Radiofrequency (RF) coil**: We will build a dual-tuned multichannel RF coil (with 13 ^{23}Na-channels and 1 ^{1}H-Helmholtz-channel per breast) that will allow bilateral breast ^{1}H/^{23}Na MRI at 7 T.

5.2 Treatment Regimen

Patients who are scheduled to receive neoadjuvant (preoperative) chemotherapy (NACT) will be considered for participation in this study. The type and length of chemotherapy will be determined by the treating physician in breast medical oncology, according to institutional guidelines.

5.3 Description of the ^{1}H/^{23}Na RF Coil

5.3.1 Rationale

We built 8-channel-^{23}Na/2-channel-^{1}H coil for bilateral breast imaging at 7 T (**Fig. 7**) in our fully equipped RF laboratory. The array provides the following innovations:

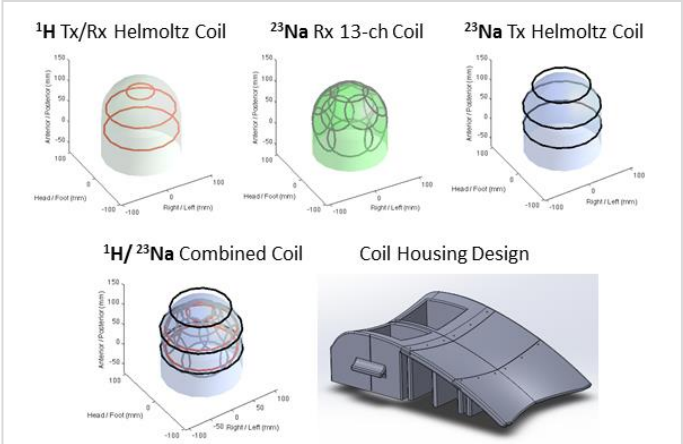


Figure 7. RF coil design. Tx = transmit, Rx = receive.

1. Well-known raw SNR advantage over volume coils, with expected +50% gain in the breast center and +100% in the periphery;
2. Iterative image reconstruction technique will benefit from improved noise properties and domain sparsity associated with dense receive arrays to allow 2.5-3 mm isotropic resolution in ^{23}Na images.

5.3.2 Methods

Coil performance is a primary determinant of breast MRI quality. A coil that allows concurrent ^{23}Na and ^{1}H breast imaging is not yet commercially available and presents technical challenges: complex coupling between the ^{1}H and ^{23}Na channels can degrade SNR, coverage, and uniformity. In our previous work for cartilage and head imaging, high performance was achieved on both channels by implementing new design

strategies that alleviated inter-channel coupling and wideband matching that allowed the ^{23}Na array to substantially outperform traditional single channel designs[78,79].

Based on previous experience on dual-tuned and breast coil design[77,79,80], the coil consists of 3 modules mounted on concentric dome-shaped layers (**Fig. 7**):

1. The inner layer houses the ^{1}H transmit/receive (Tx/Rx) Helmholtz coil, which provides excellent coverage and uniformity to enable standard ^{1}H MRI;
2. The middle layer houses the 8-element ^{23}Na Rx module , which provides a +50% SNR advantage in the center of the breast over a mono-nuclear volume coil;
3. The outer layer houses the ^{23}Na Tx Helmholtz coil, which will provide high excitation uniformity.

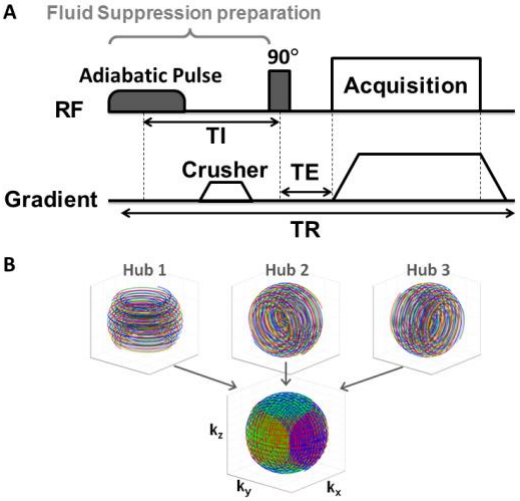


Figure 8. RF pulse sequence. **(A)** chronogram of the RF sequence, with RF: radiofrequency, TI: inversion time, TE: echo time, TR: repetition time. **(B)** k-space trajectory of the FLORET sequence.

5.3.3 Testing and validation

1. We have built a multi-layer dielectric phantom with breast and muscle tissue properties (electrical permittivity and conductivity) to replicate human loading conditions[81].
2. Coil performance was tested at various construction stages in order to measure SNR gain. Transmit field uniformity was assessed in flip angle maps[82] and SNR will be assessed in gradient- echo images.
3. Our Coil Safety Committee confirmed safe operation of the coil and approved the RF power limits that restrict tissue heating and the specific absorption rate (SAR) to a level consistent with International Electrotechnical Commission guidelines (IEC)[55]. Given the high level of habitus variability and its potential impact on SAR, we will implement a 5 W/kg limit to provide a 2-fold buffer over the 10 W/kg IEC limit.

5.4 Description of the MRI Procedures

5.4.1 ^{23}Na MRI

Sodium scans: Two ^{23}Na data will be acquired: (**1**) FLORET without IR, and (**2**) FLORET with IR (**Fig. 8**). We will optimize the acquisition parameters (number of hubs and interleaves, repetition time, averages) in order to minimize TE (<0.5 ms) and acquisition time (<7 min) while maximizing SNR (>20) and isotropic resolution (2.5-3 mm). The sodium scan is performed without any injection of contrast agent.

Fluid suppression: Fluids present in breast tissue (in extracellular volume, milk ducts, blood, plasma) are assumed to have similar properties as other body fluids ([Na^+] = 140 mM, T1 = 30-50 ms, T2 = 20-40 ms)[19,83,84]. The inversion pulse power, shape and duration, and inversion time, will be optimized from simulation, then on phosphate buffer saline (PBS), and on 2 healthy volunteers.

Relaxation times: We will measure ^{23}Na T1 and T2* relaxation times in breast tissue on 4 healthy volunteers. These parameters will be used for correcting breast signal during the data processing for C_1 and α_2 quantification. T1 will be measured with FLORET acquisition with different TRs, and T2* with FLORET and different TEs.

5.4.2 ^{1}H MRI

Pre- and post-contrast T1 weighted DCE MRI will be performed at each time-point of the study with the same ^{1}H/^{23}Na RF coil at 7 T and used to measure tumor size. DCE MRI will be acquired subsequent to ^{23}Na MRI to prevent influence of the contrast agent on ^{23}Na data. DCE MRI will be performed with a fat-suppressed T1-weighted 3D SPAIR sequence with 1 mm isotropic resolution in 2-3 min, that was optimized for 7 T breast MRI. A gadolinium contrast agent (Gadavist) will be delivered in the antecubital vein at 0.1 mmol/kg. Magnetic Resonance Fingerprinting (MRF) for T1, T2 and proton density (PD) quantification will also be included if time permits prior to DCE MRI.

The contrast Gadavist is lawfully marketed in the United States. The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug. In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug. The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2(b)(1)(iii)). The use of contrast on healthy subjects does not significantly impact the risk/benefit ratio associated with use of the contrast. The FDA recommended dosage will be used on healthy controls and the data acquired from contrast MRI scans will be used to optimize the resolution of the images.

5.5 Pathologic assessment of response

5.5.1 Criteria for evaluation of pathologic complete response (pCR)

Pathologic complete response in breast and ipsilateral axillary lymph nodes as well as non-axillary sentinel nodes (pCR breast and nodes) is defined as no histologic evidence of invasive tumor cells in the surgical breast specimen, axillary nodes, or sentinel nodes identified after neoadjuvant chemotherapy. In situ carcinoma is allowed.

5.5.2 Determination of pCR

The determination of pCR (definition see above) will be performed by the local pathologist following examination of tissue (breast and nodes) removed at the time of surgery. Both, pathology evaluation and surgery are being performed as standard of care for the patient. No tissue will be stored and/or used for this research.

5.6 Subject Compliance Monitoring

Because subjects enrolled in the study have breast cancer, they will be closely monitored and are expected to have regular visits with their oncologist.

5.7 Prior and Concomitant Therapy

This is not a treatment trial, the treating physician will determine subject's treatment as clinically appropriate.

6 Study Procedures

6.1 Visit 1: Baseline

1. The potential study subject will be given ample time to review and sign the informed consent if willing to participate in the research study. They will also complete an MRI safety sheet prior to any study related procedures taking place. No information will be retained or collected prior to the patient signing consent.

2. **Sodium MRI protocol**: 2 or more acquisitions (if necessary) with and without fluid suppression. Time: 30 min maximum.
3. **Proton MRI protocol**: Localizer, T2-weighted MRI, T1 weighted MRI pre- and post-contrast (DCE MRI). MRF for T1, T2 and PD quantification will also be included if time permits. Time: 30 min maximum.

   Note: We will allow a delay of at least 48 hours between the clinical DCE MRI (performed as part of the standard clinical procedure for breast cancer diagnosis, at 1.5 T or 3 T) and the first research DCE MRI scan at 7 T (baseline data in our study).

6.2 Visit 2: 2-3-week follow-up

1. **Sodium MRI protocol**: 2 or more acquisitions (if necessary) with and without fluid suppression. Time: 30 min maximum.
2. **Proton MRI protocol**: Localizer, T2-weighted MRI, T1 weighted MRI pre- and post-contrast (DCE MRI). MRF for T1, T2 and PD quantification will also be included if time permits. Time: 30 min maximum.

6.3 Visit 3: 2-3-month follow-up

1. **Sodium MRI protocol**: 2 or more acquisitions (if necessary) with and without fluid suppression. Time: 30 min maximum.
2. **Proton MRI protocol**: Localizer, T2-weighted MRI, T1 weighted MRI pre- and post-contrast (DCE MRI). MRF for T1, T2 and PD quantification will also be included if time permits. Time: 30 min maximum.

6.4 Visit 4: End of treatment

1. **Sodium MRI protocol**: 2 or more acquisitions (if necessary) with and without fluid suppression. Time: 30 min maximum.
2. **Proton MRI protocol**: Localizer, T2-weighted MRI, T1 weighted MRI pre- and post-contrast (DCE MRI). MRF for T1, T2 and PD quantification will also be included if time permits. Time: 30 min maximum.

7 Statistical Plan

7.1 Sample Size Determination

As described in Fig. 6, 16 healthy controls will be necessary for RF coil development and optimization of the $^{1}H/^{23}Na$ MRI protocol (including repeatability/reproducibility study) prior to application of the proposed method to patients with breast cancer. A greater amount of healthy controls to patients is used in this study to help generate an MRI protocol for repeatability and reproducibility. Once the technique is optimized, the data necessary to prove the objective can be obtained through 20 patients. From the literature[19,22,35,38,39,85], we can expect changes in C_1 and α_2 of 30-50% between time points, and a CV ≤ 20% for each measure in patient with breast cancer undergoing neoadjuvant chemotherapy. To detect a 30% change for a CV of 20%, data is needed from at least 9 patients to achieve 80% power. The study will accrue 20 women to allow for 50% attrition.

7.2 Statistical Methods

All statistical tests will be conducted at the two-sided 5% significance. Data from 1 scan before and 3 scans after NACT onset for 12 women will be tumor size, C_1 and α_2 of tumor and of healthy tissue in both the affected and contralateral breasts. Local lesions will be manually segmented in DCE images by co-investigator Dr. Moy; lesion size will be defined by its longest linear dimension. ROIs will be transferred to co-registered sodium images to determine the C_1 and α_2 in the lesion. Paired sample t tests will assess the change in each measure in tumor and healthy tissue from pre- to each post-onset time point and compare tumor to healthy tissue in terms of these changes. Healthy tissue will be automatically segmented using 3D proton multi-echo data processed using the Dixon chemical species separation algorithm. Tissue with > 50% water content, excluding the local lesion, will be defined as normal glandular tissue. Pearson and Spearman rank correlations will assess the association of intra-tumor changes in C_1 and α_2 with changes in tumor size. Focus will be on the correlation of short-term (2 weeks, 2 months) changes in C_1 and α_2 with both short-term and long-term (5 months)

7.3 Subject Population(s) for Analysis

Protocol-compliant population: Any subject who received an imaging procedure.

8 Safety and Adverse Events (SAE)

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research).). This will be limited to SAEs associated with the reseach MRI, SAEs related to neoadjuvant chemotherapy or surgery WILL NOT be reported for this non-therapeutic study.
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Unanticipated Adverse Device Effect

An Unanticipated Device Effect is any serious adverse effect on health or safety, or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Serious injury

Any injury or illness that is any one of the following:

- life-threatening
- results in permanent impairment of a body function or permanent damage to body structure
- necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse device effect
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

8.2 Recording of Adverse Device Effects

At each contact with the subject, the investigator must seek information on adverse device effects by specific questioning and, as appropriate, by examination. Information on all adverse device effects should be recorded immediately in the source document, and also in the appropriate adverse effect module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse device effects occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse device effects that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse device effects that occur after the study period should be recorded and reported promptly (see section 8.3 below).

The minimum initial information to be captured in the subject's source document concerning the adverse device effect includes:

- Study identifier
- Study Center
- Subject number
- Device model and serial number
- A description of the event
- Date of onset
- Investigator assessment of the association between the event and study treatment
- Current status
- Whether study treatment was discontinued
- Whether the event is serious and reason for classification as serious

8.3 Reporting of Adverse Device Effects and Unanticipated Problems

8.3.1 Investigator reporting: notifying the NYULMC IRB.

The following describes events that must be reported to the CTO in an expedited fashion.

Initial Report: within 24 hours:

The following events must be reported to the CTO via email within 24 hours of awareness of the event:

- Unanticipated problems related to study participation,
- Serious adverse events, regardless of whether they are unexpected.

Email: NYUPCCsafetyreports@nyumc.org

Tel: 212-263-4427

Follow-up report: within 48 hours:

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated device event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist in the understanding of the event. All report forms must be signed and dated by the Principal Investigator. If the Principal Investigator is not available at the time of the initial report, then the form can be submitted by a Co-Investigator. This form should be reviewed by the Principal Investigator, whom sign/date initial report upon return.

Other Reportable events: Deviations from the study protocol

Deviations from the protocol must receive the investigator's IRB approval before they are initiated. Any protocol deviations initiated without the investigator's IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be reported to the investigator's IRB as soon as a possible, but ***no later than 5 working days*** of the protocol deviation.

8.3.2 Investigator reporting: Notifying the IRB

Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to subjects or others. The following describes the NYULMC IRB reporting requirements, though Investigators at participating sites are responsible for meeting the specific requirements of their IRB of record. The NYU IRB address is:

NYU School of Medicine IRB
1 Park Avenue, 6th Floor
New York, NY 10016

Report Promptly, but no later than 5 working days:

Researchers are required to submit reports of the following problems promptly but no later than 10 working days from the time the investigator becomes aware of the event:

- ***Unanticipated problems including adverse events*** **that are unexpected and related**
  - *Unexpected: An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.*
  - *Related to the research procedures: An event is related to the research procedures if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.*
  - *Harmful: either caused harm to subjects or others, or placed them at increased risk*
- ***Unanticipated adverse device effect***: Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Other Reportable events:

The following events also require prompt reporting to the IRB, though no later than10 working days:

- ***Complaint of a research subject*** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- ***Protocol deviations or violations*** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  - *one or more participants were placed at increased risk of harm*
  - *the event has the potential to occur again*
  - *the deviation was necessary to protect a subject from immediate harm*

- ***Breach of confidentiality***
- ***Incarceration of a participant*** when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- ***New Information indicating a change to the risks or potential benefits*** of the research, in terms of severity or frequency. (e.g. analysis indicates lower-than-expected response rate or a more severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market)

Reporting Process

The reportable events noted above will be reported to the IRB using the "Reportable New Information" submission or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

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

At the time of each annual review any protocol deviations stated above must be reported to the IRB.

8.3.3 Stopping Rules

During the MRI examination subjects will be periodically monitored through an intercom and visually using a CCD camera, and if any problems arise, the study will be immediately terminated. Instructions will be given prior to and during the MRI scan.

8.4 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan detailed below. Medical monitoring will include a regular assessment of the number and type of adverse device events. The principal investigator in conjugation with the research team will evaluate any adverse device events regularly.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Records Retention

Records pertaining to conducted research must be retained for at least three years after completion of the research. IRB records not associated with research or for protocols cancelled without participant enrollment will be retained at the facility for at least three years after closure.

Physical records associated with closed or terminated studies shall, after the three year retention period expires, be electronically scanned and thereafter shredded or otherwise destroyed in accordance with institutional policy. Electronic records must be retained for at least 3 years on the IRB's current production systems.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

This study will be monitored according to the monitoring plan discussed in this section. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

Although this research is not a clinical trial, it will be in compliance with the NYU Institutional Review Board.

The review of AEs and trial conduct for this trial occurs at several levels:

(1) Principal Investigator: Adverse events are evaluated monthly by the principal investigator in conjunction with the research team.

(2) Institutional Review Board (IRB): An annual report to the IRB is submitted by the trial PI for continuation of the protocol. It includes a summary of all AEs, total enrollment with demographics, protocol violations, and current status of subjects as well as available research data.

(3) In addition, the quality assurance unit will provide quarterly interim monitoring visits, to verify adherence to the protocol; the completeness, accuracy and consistency of the data; and adherence to ICH Good Clinical Practice guidelines.

The PIs will be responsible for gathering and monitoring the data regarding the recruitment rate and regarding unanticipated adverse events. This will be limited to SAEs associated with the research MRI, SAEs related to neoadjuvant chemotherapy or surgery WILL NOT be reported for this non-therapeutic study. This data will be reviewed with the research team every month. Any adverse events will be immediately reported in the subject's file and to the IRB from onset to resolution. We will stop this study if a significant adverse event related to the imaging procedure occurs.

(1) Types of Data or Events:

- Captured data will include recruitment rate and unanticipated adverse events. In general, subject outcomes will depend on the standard of care imaging or other exams subjects undergo as part of their routine case. However, in cases where experimental data provides potentially treatment changing information not seen on conventional imaging, referring physicians will be notified. No change to the protocol will result from these possible incidents.
- Adverse events will be graded in severity as follows:
    - 0 - No adverse event or within normal limits
    - 1 - Mild adverse event
    - 2 - Moderate adverse event
    - 3 - Severe adverse event resulting in hospitalization or the prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect
    - 4 - Life-threatening or disabling adverse event
    - 5 - Fatal adverse event
- Adverse events > level 3 will be reported to the IRB within 24 hours. Other adverse events will be reported to the IRB within 5 working days, using the following predefined causal relationships:
    - i. Definite: Adverse event(s) will clearly be related to investigational agent(s) or other intervention
    - ii. Probable: Adverse event(s) will likely be related to investigational agent(s)
    - iii. Possible: Adverse event(s) may be related to investigational agent(s)
    - iv. Unlikely: Adverse event(s) will doubtfully be related to investigational agent(s)
- Adverse events will be collected at each study visit by the imaging technologist performing the procedure.

(2) Responsibilities and roles for gathering, evaluating and monitoring the data:

- PIs will gather data regarding recruitment rate. This will be reviewed with the research team every month and with the study monitor bi-monthly.
- PI and co-investigators overseeing the procedures will gather data regarding unanticipated adverse events. The PI and co-investigators will report any adverse event immediately to the NYU IRB (3) Information about the monitoring entity:
- The Individual Data Monitor will be the PI: Guillaume Madelin, PhD., NYU Langone Medical Center, Department Radiology, 660 First Avenue, 4th floor, NY, NY 10016.

- The PIs will follow the policies and procedures of the IRB for monitoring this study for safety concerns, with ongoing updates from the Co-investigators on a continuous basis. co-PI Ryan Brown, PhD, and co-investigator Linda Moy, MD will assist the PI in monitoring the data, assuring protocol compliance, and conducting the safety reviews.

(4) Reporting adverse events and unanticipated problems to the monitoring entity:

- Any adverse events will be immediately reported by the investigator overseeing the procedure to the PI. The PI will ensure that adverse events are reported in the subject's file and to the IRB from onset to resolution.
- A bi-annual report of the data safety monitoring reviews will be prepared and submitted to the sponsor and IRB by the study monitor.

(5) Assessments:

- Linda Moy, MD, will review safety data after every major study related visit and at research team meetings, which will be conducted at a minimum of every 6 months, and will suspend or modify the study (with IRB approval), if indicated. The IRB will be informed if any reasons warrant "holding" the study. A review of the study will be submitted to the IRB annually, including when re-approval of the protocol is sought.
- The PIs and co-investigators will assess the risk to benefit ratio and determine whether the level of risk and patient safety were accurately outlined and accounted for in study application, protocol and consent.

(6) Criteria for action:

- The PIs will ensure that adverse events, whether considered related or not to the imaging procedure are reported in the subject's file and to the IRB from onset to resolution. If no follow up is performed, the PIs will provide justification. Significant adverse events will be reported to the IRB according to institution guidelines.
- We will stop this study if a significant adverse event related to the imaging procedure occurs. The imaging hardware will then be evaluated the vendor. Only after rigorous QA analysis by the vendor will the protocol resume.

(7) Procedures for Communicating – dissemination of safety information

As appropriate:

- Any significant deviation will be reported immediately via email to the IRB (irb-full-board@nyumc.org) using the IRB Reportable Event form.

New information that would affect the safety of the subject or their decision to participate in the study will be provided by the PI or his co-investigators.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

In addition, describe who will obtain consent and how the process of informed consent will be structured to be conducive to rational and thoughtful decision making by the subject/subject's legally authorized representative. If children and/ or cognitively impaired adults will be subjects, include a specific plan to assess comprehension during assent or the subject's agreement Individuals who are authorized to obtain consent must be listed on the protocol (or FDA form 1572) and consent form document. If necessary to use 'Auditor/Witness' and/or translator, these roles would be described in this section. Include a plan for assessing subject capacity in cognitively impaired subjects. Describe the anticipated degree of impairment relative to their ability to consent and the anticipated direct benefits to the subjects.

12 Study Finances

12.1 Funding Source

National Institute of Health

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYU investigators will follow the applicable University conflict of interest policy(ies).

12.3 Subject Stipends or Payments

All subjects (healthy volunteers and patients with breast cancer) will be compensated $50 for each study visit. If the subject completes all four visits, she will receive a total of $200. This amount aligns closely with other current NYU SoM clinical research protocols.

13 Publication Plan

Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

14 References

1. Gralow JR, Burstein HJ, Wood W, et al. Preoperative therapy in invasive breast cancer: pathologic assessment and systemic therapy issues in operable disease. *Journal of Clinical Oncology.* 2008;26(5):814-819.
2. Holmes D, Colfry A, Czerniecki B, et al. Performance and Practice Guideline for the Use of Neoadjuvant Systemic Therapy in the Management of Breast Cancer. *Annals of Surgical Oncology.* 2015;22(10):3184-3190.
3. Sikov WM, Wolff AC. Neoadjuvant therapy for breast cancer: Rationale, pretreatment evaluation, and therapeutic options. *UpToDate.* 2015.
4. Thompson AM, Moulder-Thompson SL. Neoadjuvant treatment of breast cancer. *Annals of Oncology.* 2012;23(suppl 10):x231-x236.
5. Carey LA, Winer EP. Defining success in neoadjuvant breast cancer trials. *The Lancet.* 2014;384(9938):115-116.
6. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *The Lancet.* 2014;384(9938):164-172.
7. Schott AF, Hayes DF. Defining the benefits of neoadjuvant chemotherapy for breast cancer. *Journal of Clinical Oncology.* 2012;30(15):1747-1749.
8. Food US, Administration D. Guidance for industry: Pathologic complete response in neoadjuvant treatment of high-risk early-stage breast cancer: Use as an endpoint to support accelerated approval. *UCM305501.* 2012.
9. von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *Journal of Clinical Oncology.* 2012;30(15):1796-1804.
10. Drisis S, Metens T, Ignatiadis M, Stathopoulos K, Chao SL, Lemort M. Quantitative DCE-MRI for prediction of pathological complete response following neoadjuvant treatment for locally advanced breast cancer: the impact of breast cancer subtypes on the diagnostic accuracy. *European Radiology.* 2015:1-11.
11. Gruber S, Pinker K, Zaric O, et al. Dynamic contrast-enhanced magnetic resonance imaging of breast tumors at 3 and 7 T: a comparison. *Investigative Radiology.* 2014;49(5):354-362.
12. Li X, Arlinghaus LR, Ayers GD, et al. DCE-MRI analysis methods for predicting the response of breast cancer to neoadjuvant chemotherapy: Pilot study findings. *Magnetic Resonance in Medicine.* 2014;71(4):1592-1602.
13. Yankeelov TE, Lepage M, Chakravarthy A, et al. Integration of quantitative DCE-MRI and ADC mapping to monitor treatment response in human breast cancer: initial results. *Magnetic Resonance Imaging.* 2007;25(1):1-13.
14. Hahn SY, Ko EY, Han BK, Shin JH, Ko ES. Role of diffusion-weighted imaging as an adjunct to contrast-enhanced breast MRI in evaluating residual breast cancer following neoadjuvant chemotherapy. *European Journal of Radiology.* 2014;83(2):283-288.
15. Richard R, Thomassin I, Chapellier M, et al. Diffusion-weighted MRI in pretreatment prediction of response to neoadjuvant chemotherapy in patients with breast cancer. *European Radiology.* 2013;23(9):2420-2431.
16. Thomassin-Naggara I, De Bazelaire C, Chopier J, Bazot M, Marsault C, Trop I. Diffusion-weighted MR imaging of the breast: advantages and pitfalls. *European Journal of Radiology.* 2013;82(3):435-443.

17. Brindle K. New approaches for imaging tumour responses to treatment. *Nature Reviews Cancer.* 2008;8(2):94-107.
18. Madelin G, Lee JS, Regatte RR, Jerschow A. Sodium MRI: Methods and applications. *Progress in NMR Spectroscopy.* 2014;79:14-47.
19. Madelin G, Regatte RR. Biomedical applications of sodium MRI in vivo. *Journal of Magnetic Resonance Imaging.* 2013;38:511-529.
20. Becchetti A. Ion channels and transporters in cancer. 1. Ion channels and cell proliferation in cancer. *American Journal of Physiology-Cell Physiology.* 2011;301(2):C255-C265.
21. Boada FE, LaVerde G, Jungreis C, Nemoto E, Tanase C, Hancu I. Loss of cell ion homeostasis and cell viability in the brain: what sodium MRI can tell us. *Current Topics in Developmental Biology.* 2005;70:77-101.
22. Cameron IL, Smith NKR, Pool TB, Sparks RL. Intracellular concentration of sodium and other elements as related to mitogenesis and oncogenesis in vivo. *Cancer Research.* 1980;40(5):1493-1500.
23. Cuddapah VA, Sontheimer H. Ion channels and tranporters in cancer. 2. Ion channels and the control of cancer cell migration. *American Journal of Physiology-Cell Physiology.* 2011;301(3):C541-C549.
24. Leanza L, Biasutto L, Manago A, Gulbins E, Zoratti M, Szabo I. Intracellular ion channels and cancer. *Frontiers in Physiology.* 2013;4(227):1-7.
25. Litan A, Langhans SA. Cancer as a channelopathy: ion channels and pumps in tumor development and progression. *Frontiers in Cellular Neuroscience.* 2015;9(86):1-11.
26. Pedersen SF, Stock C. Ion channels and transporters in cancer: pathophysiology, regulation, and clinical potential. *Cancer Research.* 2013;73(6):1658-1661.
27. Prevarskaya N, Skryma R, Shuba Y. Ion channels and the hallmarks of cancer. *Trends in Molecular Medicine.* 2010;16(3):107-121.
28. Repke KRH. *The role of the Na+/K+ pump in normal and cancer cell proliferation*: Springer; 1988.
29. Reshkin SJ, Cardone RA, Harguindey S. Na+-H+ exchanger, pH regulation and cancer. *Recent Patents on Anti-Cancer Drug Discovery.* 2013;8(1):85-99.
30. Schwab A, Fabian A, Hanley PJ, Stock C. Role of ion channels and transporters in cell migration. *Physiological Reviews.* 2012;92(4):1865-1913.
31. Yang M, Brackenbury WJ. Membrane potential and cancer progression. *Frontiers in Physiology.* 2013;4(185):1-10.
32. Yu SP, Canzoniero LMT, Choi DW. Ion homeostasis and apoptosis. *Current Opinion in Cell Biology.* 2001;13(4):405-411.
33. Yu SP, Choi DW. Ions, cell volume, and apoptosis. *PNAS.* 2000;97(17):9360-9362.
34. Kunzelmann K. Ion channels and cancer. *Journal of Membrane Biology.* 2005;205(3):159-173.
35. Li L, Li P, Fang J, et al. Simultaneous Quantitation of Na+ and K+ in Single Normal and Cancer Cells Using a New Near-infrared Fluorescent Probe. *Analytical Chemistry.* 2015;87:6057-6063.
36. Li M, Xiong ZG. Ion channels as targets for cancer therapy. *International Journal of Physiology, Pathophysiology and Pharmacology.* 2011;3(2):156.
37. Babsky AM, Hekmatyar SK, Zhang H, Solomon JL, Bansal N. Application of 23 Na MRI to monitor chemotherapeutic response in RIF-1 tumors. *Neoplasia.* 2005;7(7):658-666.
38. Jacobs MA, Ouwerkerk R, Wolff AC, et al. Monitoring of neoadjuvant chemotherapy using multiparametric, 23Na sodium MR, and multimodality (PET/CT/MRI) imaging in locally advanced breast cancer. *Breast Cancer Research and Treatment.* 2011;128(1):119-126.
39. Kline RP, Wu EX, Petrylak DP, et al. Rapid in vivo monitoring of chemotherapeutic response using weighted sodium magnetic resonance imaging. *Clinical Cancer Research.* 2000;6(6):2146-2156.
40. Schepkin VD, Chenevert TL, Kuszpit K, et al. Sodium and proton diffusion MRI as biomarkers for early therapeutic response in subcutaneous tumors. *Magnetic Resonance Imaging.* 2006;24(3):273-278.

41. Schepkin VD, Lee KC, Kuszpit K, et al. Proton and sodium MRI assessment of emerging tumor chemotherapeutic resistance. *NMR in Biomedicine.* 2006;19(8):1035-1042.
42. Sykov\'a E, Mazel T, Vargov\'a L, Vo\vr ivel, Prokopov\'a KaS. Extracellular space diffusion and pathological states. *Progress in Brain Research.* 2000;125:155-178.
43. Winter PM, Poptani H, Bansal N. Effects of chemotherapy by 1, 3-bis (2-chloroethyl)-1-nitrosourea on single-quantum-and triple-quantum-filtered 23Na and 31P nuclear magnetic resonance of the subcutaneously implanted 9L glioma. *Cancer Research.* 2001;61(5):2002-2007.
44. Ouwerkerk R, Jacobs MA, Macura KJ, et al. Elevated tissue sodium concentration in malignant breast lesions detected with non-invasive 23Na MRI. *Breast Cancer Research and Treatment.* 2007;106(2):151-160.
45. Pipe JG, Zwart NR, Aboussouan EA, Robison RK, Devaraj A, Johnson KO. A new design and rationale for 3D orthogonally oversampled k-space trajectories. *Magnetic Resonance in Medicine.* 2011;66(5):1303-1311.
46. Stobbe R, Beaulieu C. In vivo sodium magnetic resonance imaging of the human brain using soft inversion recovery fluid attenuation. *Magnetic Resonance in Medicine.* 2005;54(5):1305-1310.
47. Nagel AM, Bock M, Hartmann C, et al. The potential of relaxation-weighted sodium magnetic resonance imaging as demonstrated on brain tumors. *Investigative Radiology.* 2011;46(9):539-547.
48. Madelin G, Babb JS, Xia D, Regatte RR. Repeatability of Quantitative Sodium Magnetic Resonance Imaging for Estimating Pseudo-Intracellular Sodium Concentration and Pseudo-Extracellular Volume Fraction in Brain at 3 T. *PloS ONE.* 2015;10(3):e0118692.
49. Madelin G, Kline R, Walvick R, Regatte RR. A method for estimating intracellular sodium concentration and extracellular volume fraction in brain in vivo using sodium magnetic resonance imaging. *Scientific Reports.* 2014;4:4763.
50. Garwood M, DelaBarre L. The return of the frequency sweep: designing adiabatic pulses for contemporary NMR. *Journal of Magnetic Resonance.* 2001;153(2):155-177.
51. Schepkin VD, Bejarano FC, Morgan T, Gower-Winter S, Ozambela M, Levenson CW. In vivo magnetic resonance imaging of sodium and diffusion in rat glioma at 21.1 T. *Magnetic Resonance in Medicine.* 2012;67(4):1159-1166.
52. Jacobs MA, Ouwerkerk R, Wolff AC, et al. Multiparametric and multinuclear magnetic resonance imaging of human breast cancer: current applications. *Technology in Cancer Research \& Treatment.* 2004;3(6):543-550.
53. Jacobs MA, Stearns V, Wolff AC, et al. Multiparametric magnetic resonance imaging, spectroscopy and multinuclear (23 Na) imaging monitoring of preoperative chemotherapy for locally advanced breast cancer. *Academic Radiology.* 2010;17(12):1477-1485.
54. Rieke V, Butts Pauly K. MR thermometry. *Journal of Magnetic Resonance Imaging.* 2008;27(2):376-390.
55. Commission IE. Medical electrical equipment. Part 2-33: particular requirements for the basic safety and essential performance of magnetic resonance equipment for medical diagnosis. *International Standard IEC.* 2010:60601-60602.
56. Christ A, Kainz W, Hahn EG, et al. The Virtual Family--development of surface-based anatomical models of two adults and two children for dosimetric simulations. *Physics in Medicine and Biology.* 2009;55(2):N23.
57. Lustig M, Donoho DL, Santos JM, Pauly JM. Compressed sensing MRI. *IEEE Signal Processing Magazine.* 2008;25(2):72-82.
58. Madelin G, Babb JS, Xia D, Chang G, Jerschow A, Regatte RR. Reproducibility and repeatability of quantitative sodium magnetic resonance imaging in vivo in articular cartilage at 3 T and 7 T. *Magnetic Resonance in Medicine.* 2012;68(3):841-849.

59. Boyle P. Triple-negative breast cancer: epidemiological considerations and recommendations. *Annals of Oncology.* 2012;23(suppl 6):vi7-vi12.
60. Joensuu H, Gligorov J. Adjuvant treatments for triple-negative breast cancers. *Annals of Oncology.* 2012;23(suppl 6):vi40-vi45.
61. Jerschow A. From nuclear structure to the quadrupolar NMR interaction and high-resolution spectroscopy. *Progress in NMR Spectroscopy.* 2005;46(1):63-78.
62. Lee JS, Regatte RR, Jerschow A. Optimal excitation of Na nuclear spins in the presence of residual quadrupolar coupling and quadrupolar relaxation. *Journal of Chemical Physics.* 2009;131:174501.
63. Blaustein MP, Kao JPY, Matteson DR. *Cellular Physiology and Neurophysiology: Mosby Physiology Monograph Series*: Elsevier Health Sciences; 2011.
64. Fall CP, Marland ES, Wagner JM, Tyson JJ. Computational Cell Biology. *Interdisciplinary Applied Mathematics.* 2002.
65. Hoppensteadt FC, Peskin C. *Modeling and simulation in medicine and the life sciences.* Vol 10: Springer Science \& Business Media; 2012.
66. Liu W. *Introduction to Modeling Biological Cellular Control Systems.* Vol 6: Springer Science \& Business Media; 2012.
67. Cooper GM, Hausman RE. *The cell: a molecular approach*: ASM Press; 2009.
68. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell.* 2011;144(5):646-674.
69. Weinberg R. *The biology of cancer*: Garland Science; 2013.
70. Lang F, Lepple-Wienhues A, Paulmichl M, Szabo I, Siemen D, Gulbins E. Ion channels, cell volume, and apoptotic cell death. *Cellular Physiology and Biochemistry.* 1998;8(6):285-292.
71. Lehen'kyi V, Shapovalov G, Skryma R, Prevarskaya N. Ion channnels and transporters in cancer. 5. Ion channels in control of cancer and cell apoptosis. *American Journal of Physiology-Cell Physiology.* 2011;301(6):C1281-C1289.
72. Mijatovic T, Jungwirth U, Heffeter P, et al. The Na+/K+-ATPase is the Achilles Heel of multi-drug-resistant cancer cells. *Cancer Letters.* 2009;282(1):30-34.
73. Orlov SN, Platonova AA, Hamet P, Grygorczyk R. Cell volume and monovalent ion transporters: their role in cell death machinery triggering and progression. *American Journal of Physiology-Cell Physiology.* 2013;305(4):C361-C372.
74. Pla AF, Avanzato D, Munaron L, Ambudkar IS. Ion channels and transporters in cancer. 6. Vascularizing the tumor: TRP channels as molecular targets. *American Journal of Physiology-Cell Physiology.* 2012;302(1):C9-C15.
75. Glover GH, Schneider E. Three-point dixon technique for true water/fat decomposition with B0 inhomogeneity correction. *Magnetic Resonance in Medicine.* 1991;18(2):371-383.
76. Reeder SB, Wen Z, Yu H, et al. Multicoil Dixon chemical species separation with an iterative least-squares estimation method. *Magnetic Resonance in Medicine.* 2004;51(1):35-45.
77. Brown R, Storey P, Geppert C, et al. Breast MRI at 7 Tesla with a bilateral coil and T1-weighted acquisition with robust fat suppression: image evaluation and comparison with 3 Tesla. *European Radiology.* 2013;23(11):2969-2978.
78. Brown R, Lakshmanan K, Madelin G, et al. A flexible nested sodium and proton coil array with wideband matching for knee cartilage MRI at 3T. *Magnetic Resonance in Medicine.* 2015.
79. Brown R, Madelin G, Lattanzi R, et al. Design of a nested eight-channel sodium and four-channel proton coil for 7T knee imaging. *Magnetic Resonance in Medicine.* 2013;70(1):259-268.
80. Brown R, Storey P, Geppert C, et al. Breast MRI at 7 Tesla with a bilateral coil and robust fat suppression. *Journal of Magnetic Resonance Imaging.* 2014;39(3):540-549.
81. Duan Q, Duyn JH, Gudino N, et al. Characterization of a dielectric phantom for high-field magnetic resonance imaging applications. *Medical Physics.* 2014;41(10):102303.

82. Yarnykh VL. Actual flip-angle imaging in the pulsed steady state: A method for rapid three-dimensional mapping of the transmitted radiofrequency field. *Magnetic Resonance in Medicine.* 2007;57(1):192-200.
83. Constantinides CD, Gillen JS, Boada FE, Pomper MG, Bottomley PA. Human Skeletal Muscle: Sodium MR Imaging and Quantification. Potential Applications in Exercise and Disease. *Radiology.* 2000;216(2):559-568.
84. Ouwerkerk R. Sodium MRI. *Magnetic Resonance Neuroimaging*: Springer; 2011:175-201.
85. Schepkin VD. Sodium MRI of glioma in animal models at ultrahigh magnetic fields. *NMR in Biomedicine.* 2015.

15 Attachments

- x
- Brochure for recruitment of healthy subjects

Help Us Improve Breast Imaging!

Study Goal

In this pilot study, we want to develop a new Magnetic Resonance Imaging (MRI) technique based on the detection of sodium (salt) in breast tissues, that will allow us to detect tumors and assess the early metabolic response of breast cancer to chemotherapy. The long-term goal of this study is to help develop personalized treatment of breast cancer.

What We Ask of You

We are looking for women older than 21 years of age who do not have breast cancer and are willing to have an MRI of their chest to help us to optimize the new MRI technique before scanning patients. with breast cancer.

NYU Langone MEDICAL CENTER

Still Have Questions?
Wish to Participate?

Contact our research coordinator for more information:

Nadia Maknoun
(212) 731- 5318
Nadia.Maknoun@nyumc.org

Laura and Isaac Perlmutter Cancer Center
160 East 34th Street, 2nd Floor
Room 234, New York, NY 10016

NYU School of Medicine
NYU LANGONE MEDICAL CENTER

A New MRI Technique for Breast Cancer Imaging

Participate in Research as a Healthy Volunteer!

Center for Biomedical Imaging
NYU Department of Radiology

NIH National Cancer Institute

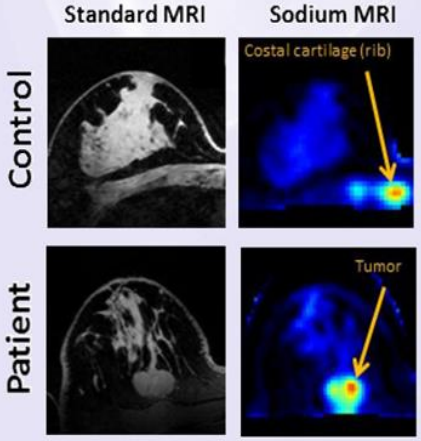
Scanner

The scan will be performed on a unique 7 Tesla MRI research scanner, that is located at:

Center for Biomedical Imaging (CBI)
Department of Radiology
660 First Avenue, New York, NY, 10016 (corner with 38th street).

Example

Below is an example of breast images acquired on the 7 Tesla scanner with standard MRI (without contrast agent) and with sodium MRI, on a healthy volunteer (control) and on a patient with breast cancer.



Frequently Asked Questions

What will I have to do?

You will undergo a breast MRI. The exam takes approximately 45 minutes to 1 hour (maximum). During the scan, you may receive an intravenous contrast agent for the MRI scan, which has been FDA-approved for diagnostic imaging and is generally included in routine clinical breast MRI.

Who will pay for the MRI?

There is no cost to you. You will be compensated $50 for your time and participation in this study.

What are the risks?

The risks are extremely low and same as that of any routine MRI exam, with or without intravenous contrast agent. All participants will be asked to fill out a standard MRI safety checklist to make sure that subjects with metal implants or any other contraindications to MRI will not be scanned.

What happen to the images?

All images will be reviewed by a breast radiologist. We will notify participants with any suspicious lesions or other potential clinical findings.

Safety

All new technologies used in this investigation meet or surpass the safety standards of the US Food and Drug Administration (FDA) and are considered non-significant risk as defined in the "Guidance for Industry and FDA Staff–Criteria for Significant Risk Investigations of Magnetic Resonance Diagnostic Devices" issued July 14, 2003.

Our team of investigators

Guillaume Madelin, PhD
Ryan Brown, PhD
Linda Moy, MD
Freya Schnabel, MD
Sylvia Adams, MD
Farbod Darvishian, PhD
James Babb, PhD