UTSouthwestern
Harold C. Simmons
Comprehensive Cancer Center

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PROTOCOL NUMBER

Performance of contrast-enhanced spectral mammography to assess neoadjuvant chemotherapy response

[Phase III, Prospective, Single-Arm, Single-Center, Contrast-Enhanced Spectral Mammography, Breast Cancer]

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Amendment/Version #_V4.0_____

PROTOCOL NUMBER

Performance of contrast-enhanced spectral mammography to assess neoadjuvant chemotherapy response

[Exploratory, Prospective, Single Arm, Single Center, Contrast-Enhanced Spectral Mammography, Breast Cancer]

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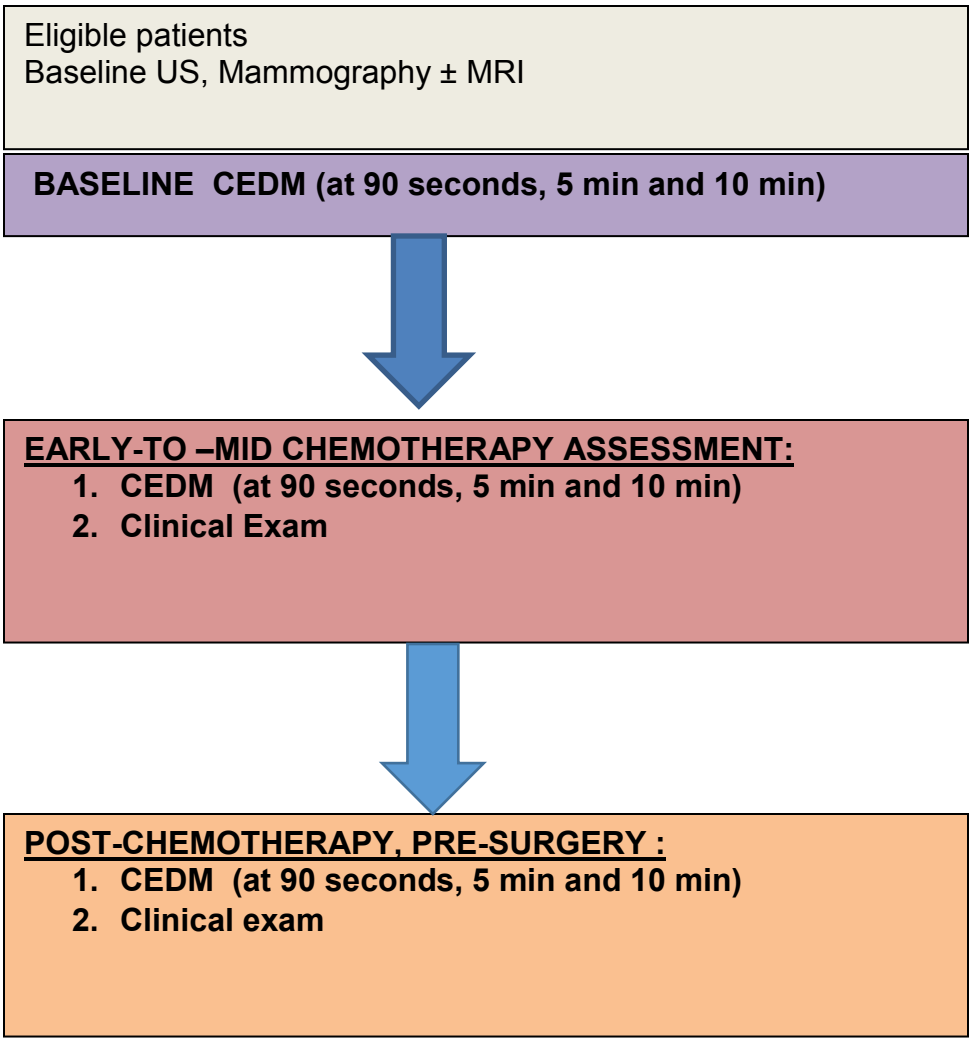
LIST OF ABBREVIATIONS (EXAMPLES)

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CEDM	Contrast enhanced digital mammography
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DOT	Disease Oriented Team
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
H&P	History & Physical Exam
HRPP	Human Research Protections Program
IDE	Investigational Device Exemption
IHC	Immunohistochemistry
IND	Investigational New Drug
IV (or iv)	Intravenously
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
pCR	Pathologic Complete Response
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
p.o.	peros/by mouth/orally
PR	Partial Response
RCB	Residual Cancer Burden
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SCCC	Simmons Comprehensive Cancer Center
SD	Stable Disease

SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
WBC	White Blood Cells

STUDY SCHEMA



STUDY SUMMARY

Title	Performance of contrast-enhanced spectral mammography to assess neoadjuvant therapy response
Short Title	Contrast-enhanced mammography Assessment of Breast Cancer Neoadjuvant Therapy response
Protocol Number	The standard protocol number used to identify this study
Phase	III
Methodology	Prospective, Single Arm, Unblinded
Study Duration	24 months
Study Center(s)	Single-Center, UTSW Breast Center & Parkland Moody Center for Breast Health
Objectives	Primary Objectives 1. To investigate the diagnostic accuracy of Contrast Enhanced Spectral Mammography (CEDM) in predicting early neoadjuvant therapy response and pCR compared to mammography. 2. To investigate the correlation accuracy of CEDM pre-operative lesion size and final pathological size,compared to mammography.
Number of Subjects	100
Diagnosis and Main Inclusion Criteria	1. 18 years and older male or female patients 2. Ipsilateral intact biopsy-proven breast cancer clinical T1-T4 (by imaging) 3. Available mammography and ultrasound imaging of the existing index cancer, with orthogonal measurements 4. Prior history of ipsilateral or contralateral breast cancer, presenting with a new primary or recurrent disease. 5. Patients who were determined to be candidates for either neoadjuvant chemotherapy or neoadjuvant endocrine therapy by the treating physician. 6. Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for days following completion of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.
Study Product(s), Dose, Route, Regimen	Contrast-Enhanced Digital Mammography
Duration of administration	N/A
Reference therapy	
Statistical Methodology	Descriptive Statistics will be produced. Spearman rank correlation will be used to measure the agreement between final pathologic and imaging tumor size data. ROC analysis will be used to assess the diagnostic performance of CEDM.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

The use of neoadjuvant systemic therapy in the treatment of breast cancer patients is increasing beyond the scope of locally advanced disease. Imaging provides important information in assessing response to therapy as a complement to conventional tumor measurements via physical examination. Tumor response to neoadjuvant therapy can also provide prognostic information. The attainment of pathologic complete response (pCR) after completion of neoadjuvant therapy and surgical resection is associated with improved disease-free survival (1-3). This correlation is especially strong for Triple-receptor negative (ER, PR negative and HER-2 non amplified), and HER-2 positive breast cancer. Studies of neoadjuvant therapy have used a variety of methods for assessing tumor response. Currently, there are no established clinical practice guidelines for how best to assess tumor response to neoadjuvant therapy. Typically, patients undergo conventional breast imaging (mammography and ultrasonography [US]) and physical examination, and dynamic contrast-enhanced breast MRI (DCR-MRI) in selected cases.

1.2 Study Agent(s)/Therapy(ies) Background and Associated Known Toxicities

Studies of neoadjuvant therapy have used a variety of methods for assessing breast cancer response to neoadjuvant therapy. Physical measurement of tumor size with calipers is typically performed prior to each chemotherapy cycle or monthly if neoadjuvant endocrine therapy is used (4). The accuracy of clinical breast examination for determining pCR in patients with locally advanced breast cancer after neoadjuvant hormonal or chemotherapy is 57%, which is inferior to mammography (74%) and US (79%) (5,6).Mammography has been shown to be more sensitive than physical examination for detecting presence of residual tumor after therapy but is less specific and may underestimate the degree of treatment response (7,8). The mammographic lesion type, such as architectural distortion, and margin impact its accuracy for size measurement, with decreased accuracy when margins are indistinct or spiculated and due to masking from adjacent normal tissue (9). Additional challenges with mammography include the presence of microcalcifications, which do not correlate with presence of viable tumor (10-12). US has been shown to be a better predictor for pathologic tumor size than mammography after treatment with neoadjuvant therapy (13-15). The sensitivity and specificity of mammography in predicting pathologic complete response were 54.2% and 86.3%, respectively. The sensitivity and specificity of breast ultrasound in predicting pathologic complete response were 45.8% and 93.8%, respectively. The best method for predicting complete pathologic response (pCR) appears to be the combination of mammography with US (80% likelihood when findings of both modalities are negative) (14,16). **Standard imaging methods used to monitor response to neoadjuvant therapy are summarized in Table 1.**

Table 1. Standard imaging methods used to monitor response to neoadjuvant therapy

Table 1

Current Breast Imaging Utilized Prior to Neoadjuvant Therapy

Variable	Mammography*	Breast US†	Breast MR Imaging‡
Ipsilateral breast	Extent of disease evaluation: full-field craniocaudal, full-field mediolateral oblique, full-field mediolateral/ lateromedial plus spot compression craniocaudal, spot compression mediolateral/ lateromedial	Extent of disease evaluation targeted to index lesion	Extent of disease evaluation: pectoralis/chest wall invasion
Contralateral breast	Screening: full-field craniocaudal, full-field mediolateral oblique	Not typically performed	Screening
Lymph nodes§	Lymphadenopathy evaluation: axillary (incomplete)	Lymphadenopathy evaluation: axillary	Lymphadenopathy evaluation: axillary, internal mammary

* Digital breast tomosynthesis may be utilized as part of the diagnostic evaluation. Substitute spot compression views with magnification craniocaudal and mediolateral/lateromedial views if associated microcalcifications.

† Whole-breast US may be performed for patients unable to undergo magnetic resonance (MR) imaging, particular for patients with mammographically dense breasts. However, the relatively high rate of false-positive findings limits recommendation of this approach.

‡ Utilization of breast MR imaging may vary with clinical practices due to surgeon and/or oncologist preferences.

§ Fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) imaging may be helpful for evaluating regional nodal sites of disease (axilla, internal mammary, and supraclavicular) for locally advanced breast cancer, especially in patients presenting with more advanced axillary disease.

Table 2. Meta-analyses depicting MRI sensitivity in achieving pCR (from Fowler et al Radiology 2017 Nov)

Table 2

Meta-Analyses of Breast MR imaging for Evaluation of Neoadjuvant Therapy Response

Meta-Analysis	No. of Studies	No. of Patients	Pooled Sensitivity (%)	Pooled Specificity (%)	Likelihood Ratio Positive	Likelihood Ratio Negative	Diagnostic Odds Ratio
Yuan et al 2010 (34)	25	1212	63 (56–70)*	91 (89–92)*	Not reported	Not reported	17.05 (10.59–27.19)
Wu et al 2012 (35)	30	1496	68 (57–77)*	91 (87–94)*	7.48 (5.29–10.57)	0.36 (0.27–0.48)	20.98 (13.24–33.24)
Marinovich et al 2013 (36)	44	2050	83–87†	54–83†	Not reported	Not reported	Not reported
Sheikbahaei et al 2016 (37)	10	492	88 (76–95)	55 (41–68)	Not reported	Not reported	Not reported

Note.—Data in parentheses are the range.

* Sensitivity defined as ability to correctly identify patients achieving pCR after preoperative therapy. Specificity defined as ability to correctly identify nonpCR after preoperative therapy.

† Sensitivity defined as ability to correctly identify presence of residual tumor after preoperative therapy in patients with nonpCR. Specificity defined as ability to correctly identify absence of residual tumor after preoperative therapy in patients with pCR.

DCE-breast MRI sensitivity and specificity in predicting pCR ranges from 63-88% and 55-91%, heavily depending on the imaging cut off criteria used to define imaging complete response on MRI interpretation. As demonstrated by a recent meta-analysis (Table 2) MRI can significantly underestimate residual disease. This is likely due in part because initial tumor enhancement and visibility on MRI peaks at 2 minutes, however with chemotherapy contrast delivery to the tumor may be significantly delayed due to the disruption of neovasculature.

1.3 Other Agents

Contrast Enhanced Digital Mammography (CEDM) is a novel imaging technique, which allows digital mammography to be used with contrast enhancement to depict cancers that would otherwise be occult on standard unenhanced mammography. CEDM is performed with and without i.v. iodine contrast, using the dual energy subtraction technique (20-25). Compared with mammography and US, CEDM improves the sensitivity for breast cancer detection without decreasing specificity (20,21). CEDM digital detector has higher spatial resolution than MRI (i.e. typically pixel sizes 100 µm and 1 mm, respectively), revealing

details that are approximately 10 times better. In contrast to the rapid washout in MRI, enhancement on CEDM in fact persists for at least 10 min after contrast agent infusion. Today CEDM is available commercially for clinical use. It is estimated that over 200,000 CEDM examinations have been performed to date in both research and clinical settings. CEDM costs significantly less compared to MRI. (26). Furthermore, longer time delays between contrast injection and CEDM exposure could result in stronger enhancement and hence better visibility compared to MRI, especially given the much higher spatial resolution of digital mammography. It is unknown whether CEDM can improve the sensitivity of mammography in the early assessment of neoadjuvant therapy response. We hypothesize that CEDM is superior to mammography and ultrasound in assessing early response, and pre-surgical residual cancer after neoadjuvant therapy, and when performed, non-inferior to MRI in assessing the residual disease using the metrics of pCR and RCB.

1.4 Rationale

The use of neoadjuvant systemic therapy in the treatment of breast cancer patients is increasing beyond the scope of locally advanced disease. Imaging provides important information in assessing response to therapy as a complement to conventional tumor measurements via physical examination. Tumor response to neoadjuvant therapy can also provide prognostic information. The attainment of pathologic complete response (pCR) after completion of neoadjuvant therapy and surgical resection is associated with improved disease-free survival (1-3). This correlation is especially strong for Triple-receptor negative (ER, PR negative and HER-2 non amplified), and HER-2 positive breast cancer. Studies of neoadjuvant therapy have used a variety of methods for assessing tumor response. Currently, there are no established clinical practice guidelines for how best to assess tumor response to neoadjuvant therapy. Typically, patients undergo conventional breast imaging (mammography and ultrasonography [US]) and physical examination, and dynamic contrast-enhanced breast MRI (DCR-MRI) in selected cases.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 To investigate the diagnostic accuracy of Contrast Enhanced Spectral Mammography (CEDM) in predicting early neoadjuvant therapy response and pCR.

2.2 Secondary Objectives

2.2.1 To investigate the correlation of CEDM pre-operative lesion size and final pathological size.

2.3.1

2.2.2 To determine additional sites of disease in the ipsilateral or contralateral breast identified by CEDM.

2.3 Exploratory Objectives

To determine the optimal post neoadjuvant therapy CEDM timing which helps demonstrate the residual disease extent.

2.3.2. To identify any patient preference differences between CEDM and breast MRI

2.4 Endpoints

2.4.1 Primary: Diagnostic performance (sensitivity and specificity) measured as area under the curve (AUC) in the response assessment by varying metrics including pCR and RCB classification.

2.4.2 Secondary: Correlative statistic for CEDM lesion sizing vs pathologic lesions sizing, frequency of finding additional sites of disease in ipsilateral or contralateral breasts by CEDM and number of such new lesions.

2.4.3 Exploratory: AUC of CEDM using varying time points for CEDM, survey scores for patient experience with CEDM

3.0 Subject ELIGIBILITY

3.1 Inclusion Criteria

18 years and older male or female patients

Ipsilateral intact biopsy-proven invasive breast cancer clinical T1-T4 (by imaging)

3.1.1 Available mammography and ultrasound imaging of the existing index cancer, with orthogonal measurements

3.1.2 Prior history of ipsilateral or contralateral breast cancer, presenting with a new primary or recurrent disease

3.1.3 Patients who were determined to be candidates for either neoadjuvant chemotherapy or neoadjuvant endocrine therapy by the treating physician

3.1.4

3.1.5

3.2 Exclusion Criteria

3.2.1 History of ipsilateral mastectomy.

3.2.2

3.2.3 Women who already started neoadjuvant chemotherapy or endocrine therapy.

3.2.4 Woman who may be pregnant.

3.2.5 Prior history of anaphylactic or anaphylactoid reaction to any contrast.

Prior allergy to iodine or iodinated contrast.

Imaging Services will practice safe contrast administration through the evaluation of the patients' history via the electronic medical record and/or patient questionnaire. Individualized, patient centric protocol planning, medication review, and contrast dosage will be utilized to reduce adverse events. Renal function testing is not routinely required for every patient receiving contrast. Creatinine and Estimated Glomerular Filtration Rate (eGFR) testing will be performed on patients at risk for contrast induced nephrotoxicity (CIN). Patients with reduced eGFR may be given intravenous (IV) iodinated contrast safely in many circumstances. Clinically significant nephrotoxicity after iodinated contrast media administration is highly unusual in patients with normal or mildly reduced renal function **GFR is tested in patients with a risk factor for decreased renal function.** Patients with one or more of the following conditions are considered to be at high risk for contrast induced nephropathy (CIN). These patients will be required to have renal function testing (eGFR) within 30 days before receiving intravenous iodinated contrast.

i) Kidney problems

ii) Kidney surgery
iii) Gout
iv) Hypertension
v) Diabetes mellitus
vi) Age > 60

Patients with known distant metastasis.

4.0 CEDM RESPONSE ASSESSMENT PLAN

Patients diagnosed with invasive breast cancer with available mammography and ultrasound imaging are eligible for the study.

3.2.6

Eligible patients will be imaged at baseline (before initiation of neoadjuvant chemotherapy or endocrine therapy), early (2-4 cycles of neoadjuvant therapy) and late (after completion of neoadjuvant chemotherapy or endocrine therapy) timepoints with mammography.CEDM will be done within 2 weeks of the specified timepoint. Three dimensional orthogonal measurements will be obtained in all timepoints. Additional sites of disease in the ipsilateral or contralateral breast identified by CEDM will be recorded and reported. ACR BI-RADS MRI lexicon will be used for reporting.

4.1 CEDM

To perform a CEDM examination, an IV is placed in the forearm or antecubital vein and a low osmolar iodinated contrast agent is administered at approximately 3ml/s using a power injector. Contrast agents with iodine concentration between 300 mg/ml and 370 mg/ml are typically used. The volume of contrast is similar to that used for a CT scan, approximately 1.5 ml/kg body weight, typically around 90-150 ml. After a delay of at least 90 seconds from the end of the injection, the patient is positioned for 2 standard mammography views (craniocaudal and mediolateral oblique) of each breast. Rather than a standard single energy mammogram, however, the CEDM device acquires dual-energy image pairs in each projection. Since there is less than 1 second between the low-energy and high energy images, the imaging time is the same as that needed for a standard mammogram. Additional projections may be obtained since optimally enhanced images can typically be obtained up to 7-10 minutes following injection. Following image acquisition, contrast-enhanced subtraction images are produced using a weighted logarithmic subtraction of the low energy image from the high energy image. Because the difference in iodine absorption between the images is larger than the difference in tissue absorption, this dual energy subtraction technique has the effect of increasing the visibility of the iodine while almost completely eliminating the visibility of background tissue. The resulting images will be sent to a review workstation or PACS for interpretation by the radiologist. The low energy images, which are identical to standard unenhanced mammograms, will also be used in the interpretation.

4.1.1

The risks of CEDM include the risks of contrast administration including allergic reactions and renal function abnormalities. Just as with CT, patients will be screened for allergy history and possible renal function abnormalities. Allergic or physiologic reaction are reported to occur in less than 1% of patients when using low osmolar contrast agents although this increases in patients with prior reactions (11,12). Severe acute reactions occur in 4/10,000 (0.04%) of patients (13). Any contrast reaction will be handled in accordance with the Radiology Department's Contrast-Reaction Guidelines https://hs.swmed.edu/communities_collaboration/radpoint/clinicaloperations/Practice%20Guidelines%20%20Procedures/Contrast%20Reactions%20-

%20Pocket%20Guide.pdf#search=contrast%20reaction)Concomitant Medications/Treatments

4.2 Other Modalities or Procedures

Every effort will be made to perform any additional imaging such as ultrasound and contrast-enhanced breast MRI at the same timepoint with CEDM, however patients will not be excluded based on inability to perform these imaging.

4.3 Duration of Follow Up

Adverse reactions to contrast will be monitored according to institutional guidelines. Patients will be observed for at least 30 minutes after contrast administration for any immediate side effects of contrast. Only contrast-specific side effects will be recorded, including moderate to severe allergic reactions to contrast, laryngospasm, angioedema, hypotension, bradycardia, diffuse hives.
Overall study duration is expected to be approximately 4-6 months from initiation of neoadjuvant therapy until final surgery in which negative margins are achieved.

4.4 Removal of Subjects from Protocol Therapy

Subjects will be removed from therapy when any of the criteria listed in Section 5.5 apply. Notify the Principal Investigator and document the reason for treatment discontinuation and the date of discontinuation. The subject should be followed-up per protocol.

4.5 Subject Replacement

Loss of any subjects before second timepoint CEDM occurs will result in subject replacement.

5.0 STUDY PROCEDURES

5.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

5.1.1 All screening procedures must be performed within 30 days prior to registration unless otherwise stated. The screening procedures include:

5.1.2

Medical history, and reviewing subject eligibility criteria previous and concomitant medications

Informed Consent

5.2 Procedures During CEDM

CEDM will be performed using UTSW Imaging Protocol (**attached, Appendix A**), including monitoring for immediate contrast reactions.

Discussion of additional findings: All breast imaging findings are routinely discussed with the patient by the radiologist immediately after imaging in our clinical practice. Additional findings identified on CEDM will be addressed similar to additional disease noted on ultrasound or breast MRI per standard of care.

Survey of patient experience with CEDM and other pre-operative imaging such as MRI will be collected after CEDM is performed, optimally at pre-operative time point (**Appendix B**).

5.3 Follow-up Procedures

Patients' medical records will be followed 30 days after completion of definitive surgery to collect final pathology outcomes, or if they develop progressive disease.

5.4 Time and Events Table

	Baseline	Mid chemotherapy	Pre-Operative
Informed Consent	x		
History and allergies	X	X	X
CEDM	X	X	X
QUESTIONNAIRE			X

5.5 Removal of Subjects from Study

Subjects can be taken off the study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

5.5.1 Subject voluntarily withdraws from treatment (follow-up permitted);

5.5.2 Subject withdraws consent (termination of treatment and follow-up);

5.5.6 Treating physician judges continuation on the study would not be in the subject's best interest;

5.5.7 Subject becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);

5.5.9 Patient develops moderate to severe reaction to contrast (as defined by the Department's guidelines for iodinated contrast) over the course of neoadjuvant therapy follow-up. Mild reactions will be considered for pre-medication and decided on a case by case basis.

6.0 Measurement of Effect

Response assessments will be performed in early and late (post chemotherapy and pre-surgery) timepoints. Every effort will be made to obtain CEDM during within 2 weeks of .

6.1.1

Response to therapy will be assessed for each patient as follows:

6.1 Response Evaluation Criteria

Response evaluation criteria in solid tumors (RECIST) 1.1 criteria, considering the sum of the largest dimension of malignancies at baseline and its variation at subsequent measurements . Clinical response is classified as follows: complete response (CR, disappearance of all lesions); partial response (PR, ≥ 30% dimensional reduction), stable disease (SD, < 30% dimensional reduction/< 20%

dimensional increase) and progressive disease (PD, ≥ 20% dimensional increase).

For pathologic response, RCB index is assessed routinely per standard of care, where a complete pathologic response has an RCB of zero, and residual disease is classified into three categories (RCB-I, RCB-II, and RCB-III)
http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3

6.1.2 This is not a treatment study. Patients will be treated either as per standard of care neoadjuvant protocol or as part of ongoing treatment trials in the UT Southwestern Medical Center.

Percent change in tumor volume using the following formula for ellipsoidal/spherical volume derived from mid-dynamic sequence subtraction series: V (cm3) = (4/3 π) x length/2 x width/2 x height/2

6.1.3

- Pre-surgery lesion size on CEDM, on 90 to120 second, 5 minute and 10 minute time points will be assessed using three maximal dimensions.
- On pre-surgery CEDM, association of any residual calcifications with enhancement will be recorded
- The largest single focus of enhancement will be recorded, as well as an overall residual tumor volume (single maximal dimension)
- The association of post biopsy clip with the enhancement will be recorded.

6.2 Safety/tolerability

Analyses will be performed for all patients having undergone at least one baseline and one mid or post therapy CEDM. We will perform standard of care pre and post CEDM monitoring in the immediate post CEDM phase, record and grade any reactions.

We will also ask patients to fill out a survey regarding their comfort level with **CEDM (APPENDIX B)** before their surgery.

6.3 Pathology

Final histopathology for correlation will include the size of residual tumor (ypT), tumor cellularity (%) and amount of DCIS (%).Per AJCC8th edition [Amin MB, Edge SB, Greene FL, et al, eds.AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017] (ypT) is based on the largest continuous focus of residual invasive cancer, if present. Treatment-related fibrosis adjacent to residual invasive carcinoma or between foci of residual cancer is not included in the ypT maximum dimension. When multiple foci of residual tumor are present, the (m) modifier is included.
In addition, we will record ki67 index pre and post therapy and its potential correlation with the degree of tumor response seen on CEDM.

The agreement between pre-operative CEDM measurements and mammography in categorizing tumor response RCB0-I/ RCBII/RCBIII will be assessed using weighed kappa.

7.0 ADVERSE EVENTS

7.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of subject safety and care.

All subjects experiencing an adverse event, regardless of its relationship to study therapy, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline or is stable in the opinion of the investigator;
- there is a satisfactory explanation other than the study therapy for the changes observed; or
- death.

Definitions

7.1.1 An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam, imaging finding or clinically significant laboratory finding), symptom, clinical event, or disease, temporarily associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

Acute Adverse Events

Iodine contrast is known to only have immediate side effects within the first 30 minutes of contrast injection. All subjects experiencing an adverse event will be monitored in Breast Imaging center for the first 30 minutes:

- Type and severity of contrast reaction or extravasation will be recorded.
- We will monitor the patient until the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;

- Extravasation will be managed according to the Department of Radiology Standard operating procedures.

Severity

Adverse events will be graded by a numerical score according to the defined NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0. Adverse events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined below.

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe or medically significant but not immediately life threatening
- Grade 4: Life threatening consequences
- Grade 5: Death related to the adverse event

Serious Adverse Events

ICH Guideline E2A and the UTSW IRB define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- Results in death
- Immediately life-threatening
- Results in inpatient hospitalization[1,2] or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: A "Serious adverse event" is by definition an event that meets ***any*** of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring ≥24 hour inpatient admission to the hospital would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death which occurs during the protocol-specified period of monitoring for adverse and serious adverse events would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study.

[1]Pre-planned hospitalizations or elective surgeries are not considered SAEs. Note: If events occur during a pre-planned hospitalization or surgery, that prolong the existing hospitalization, those events should be evaluated and/or reported as SAEs.

[2] NCI defines hospitalization for expedited AE reporting purposes as an inpatient hospital stay. Hospitalization is used as an indicator of the seriousness of the adverse event and should only be used for situations where the AE truly fits this definition and NOT for hospitalizations associated with less serious events. For example: a hospital visit where a patient is admitted for observation or minor treatment (e.g. hydration) and released in less than 24 hours. Furthermore, hospitalization for pharmacokinetic sampling is not an AE and therefore is not to be reported either as a routine AE or in an expedited report.

7.1.2

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs):

The phrase "unanticipated problems involving risks to subjects or others" is found, but not defined in the HHS regulations at 45 CFR 46, and the FDA regulations at 21 CFR 56.108(b)(1) and 21 CFR 312.66. For device studies, part 812 uses the term unanticipated adverse device effect, which is defined in 21 CFR 812.3(s). Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets ALL three (3) of the following criteria:

- Unexpected in terms of nature, severity or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

AND

- Related or possibly related to participation in the research (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);

AND

- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

Follow-up

All adverse events will be followed up according to good medical practices.

7.2 Steps to Determine If a Serious Adverse Event Requires Expedited Reporting to the SCCC DSMC and/or HRPP

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v5).

Step 2: Grade the adverse event using the NCI CTCAE v5.

Step 3: Determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows:

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

Note: This includes all events that occur within 30 minutes of the last dose of protocol treatment. Any event that occurs more than 30 minutes after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported as indicated in the sections below.

Step 4: Determine the prior experience of the adverse event. Expected events are those that have been previously identified as resulting from administration of the treatment. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol (if applicable);
- the drug package insert (if applicable);
- the current Investigator's Brochure (if applicable)
- the Study Agent(s)/Therapy(ies) Background and Associated Known Toxicities section of this protocol

7.2.1 Reporting SAEs and UPIRSOs to the Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC)

All SAE/UPIRSOs at all sites, which occur in research subjects on protocols for which the SCCC is the DSMC of record require reporting to the DSMC regardless of whether IRB reporting is required. All SAEs/UPIRSOs occurring during the protocol-specified monitoring period should be submitted to the SCCC DSMC within 5 business days of the PI or delegated study team members awareness of the event(s). In addition, for

participating centers other than UTSW, local IRB guidance should be followed for local reporting of serious adverse events.

The UTSW study team is responsible for submitting SAEs/UPIRSOs to the SCCC DSMC Coordinator. Hardcopies or electronic versions of the eIRB Reportable Event report; FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be submitted to the DSMC Coordinator. The DSMC Coordinator forwards the information onto the DSMC Chairman who determines if immediate action is required. Follow-up eIRB reports, and all subsequent SAE/UPIRSO documentation that is available are also submitted to the DSMC Chair who determines if further action is required. ***(See Appendix III of the SCCC DSMC Plan for a template Serious Adverse Event Form which may be utilized when a sponsor form is unavailable and SAE submission to the eIRB is not required).***

Reporting Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) to the UTSW HRPP/IRB

UTSW reportable event guidance applies to all research conducted by or on behalf of UT Southwestern, its affiliates, and investigators, sites, or institutions relying on the UT Southwestern IRB. Additional reporting requirements apply for research relying on a non-UT Southwestern IRB.

According to UTSW HRPP/IRB policy, UPIRSOs are incidents, experiences, outcomes, etc. that meet **ALL three (3)** of the following criteria:

1. Unexpected in nature, frequency, or severity (i.e., generally not expected in a subject's underlying condition or not expected as a risk of the study; therefore, not included in the investigator's brochure, protocol, or informed consent document),AND
2. Probably or definitely related to participation in the research, AND
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

For purposes of this policy, UPIRSOs include unanticipated adverse device effects (UADEs) and death or serious injury related to a humanitarian use device (HUD).

UPIRSOs must be promptly reported to the UTSW IRB within 5 working days of PI awareness.

Events NOT meeting UPIRSO criteria:

Events that do NOT meet UPIRSO criteria should be tracked, evaluated, summarized, and submitted to the UTSW HRPP/IRB at continuing review.

For more information on UTSW HRPP/IRB reportable event policy, see https://www.utsouthwestern.edu/research/research-administration/irb/assets/policies-combined.pdf.

7.3 Unblinding Procedures

N/A. There is no blinding in this study.

8.0 STATISTICAL CONSIDERATIONS

8.1 Study Design/Study Endpoints

The primary endpoint of this study is diagnostic performance (sensitivity and specificity) measured as area under the curve (AUC) in the response assessment. Key secondary and exploratory endpoints include correlation between pre-operative CEDM lesion size and final pathology and assessment of timing of CEDM for best performance in predicting pathologic response.

8.2 Sample Size and Accrual

Due to the exploratory nature of the study and lack of reliable prior information, a formal sample size calculation was not done. We are proposing to accrue 100 patients for enhanced certainty of our descriptive statistics. We assume 40% prevalence of pCR. A sample of 100 patients will provide 95% confidence intervals of at most (maximum) ± 0.17 (for sensitivities), ± 0.14 (for specificities) and ± 0.12 (for AUC). Simple asymptotic with continuity correction and normal approximation was used for calculation for sensitivity and specificity. Binormal approximation was used for the calculation for AUC. Assuming one lesion per patient, 100 patients will provide 95% confidence interval of spearman rank correlation of lesion size with a width no larger than 0.39. Fisher's transformation followed by a normal approximation was used for calculation. Results from this study would help us design a multi-institutional study allowing comparison to other imaging modalities with a larger patient cohort.

8.3 Data Analyses

Descriptive statistics will be produced for all patients; frequencies and percentages for categorical measures and means, medians, standard deviations, and ranges for continuous measures. The number of cancer foci identified by each imaging modality will be compared. Tumors will be categorized according to immunohistochemical approximated molecular profiles (Luminal A, Luminal B, Triple-negative and HER-2 amplified). Additional exploratory analyses will be performed as needed.

1. Sensitivity of CEDM versus mammography

Histopathological assessment will be used as the reference standard.
For categorical measurements of tumor response (CR/PR/SD/PD or RCB0-I /RCB II /RCB III):

1. Sensitivities and specificities in predicting pCR (or RCB0) will be calculated for CEDM and mammography respectively.
2. The agreement between CEDM and mammography in categorizing tumor response (CR/PR/SD/PD or RCB0-I/ RCBII/RCBIII) will be assessed using weighed kappa.

2. For continuous measurements of tumor response (RECIST, percent change in tumor volume and pre-surgery lesion size):

1. ROC analysis will be used to assess the diagnostic performance of CEDM and mammography. The Area under the ROC curve (AUC) will be compared. A leave-one-out cross validation algorithm will be used to reduce bias from overfitting.
2. The agreement between CEDM and mammography in RECIST, percent change in volume and pre-surgery lesion size will be assessed using intraclass correlation (ICC).

3. Spearman's rank correlation will be used to measure the association between final pathologic and imaging tumor size.

9.0 STUDY MANAGEMENT

9.1 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 the UTSW COI Committee and IRB according to UTSW Policy on Conflicts of Interest. All investigators will follow the University conflict of interest policy.

9.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB must approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

9.3 Registration/Randomization Procedures

All subjects must be registered with the Radiology Clinical Trials Office before enrollment to study. Prior to registration, eligibility criteria must be confirmed with the Radiology Clinical Trials Office Study Coordinator. To register a subject, call 214-645-1568 Monday through Friday, 9:00AM-5:00PM.

New subjects will receive a number beginning with 001 upon study consent such that the first subject consented is numbered 001, the second subject consented receives the number 002, etc.

Each newly consented subject should be numbered using the schema provided above. Upon registration, the registrar will assign the additional registration/randomization code according to the numbering schema outlined above, which should then be entered as the patient study id in Velos upon updating the status to enrolled.

The numbering schema should clearly identify the site number; the sequential number of the subject enrolled as well as the status of the subjects enrolled so that the number of subjects consented versus the number of subjects actually enrolled may be easily identified.

9.4 Data Management and Monitoring/Auditing

REDCap is the UTSW SCCC institutional choice for the electronic data capture of case report forms for SCCC Investigator Initiated Trials. REDCap will be used for electronic case report forms in accordance with Simmons Comprehensive Cancer Center requirements, as appropriate for the project
Trial monitoring will be conducted no less than annually and refers to a regular interval review of trial related activity and documentation performed by the DOT. This review includes but is not limited to accuracy of case report forms, protocol compliance, timeless and accuracy of Velos entries and AE/SAE management and reporting. Documentation of trial monitoring will be maintained along with other protocol related documents and will be reviewed during internal audit.

For further information, refer to the UTSW SCCC IIT Management Manual.

The UTSW Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UTSW SCCC clinical trials. As part of that responsibility, the DSMC reviews all local serious adverse events and UPIRSOs in real time as they are reported and reviews adverse events on a quarterly basis. The quality assurance activity for the Clinical Research Office provides for periodic auditing of clinical research documents to ensure data integrity and regulatory compliance. A copy of the DSMC plan is available upon request.

The SCCC DSMC meets quarterly and conducts annual comprehensive reviews of ongoing clinical trials, for which it serves as the DSMC of record. The QAC works as part of the DSMC to conduct regular audits based on the level of risk. Audit findings are reviewed at the next available DSMC meeting. In this way, frequency of DSMC monitoring is dependent upon the level of risk. Risk level is determined by the DSMC Chairman and a number of factors such as the phase of the study; the type of investigational agent, device or intervention being studied; and monitoring required to ensure the safety of study subjects based on the associated risks of the study. Protocol-specific DSMC plans must be consistent with these principles.

9.5 Adherence to the Protocol

9.5.1 Except for an emergency situation, in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

Exceptions (also called single-subject exceptions or single-subject waivers): include any departure from IRB-approved research that is *not due to an emergency* and is:

- intentional on part of the investigator; or
- in the investigator's control; or
- not intended as a systemic change (e.g., single-subject exceptions to eligibility [inclusion/exclusion] criteria)

➢ **Reporting requirement**: Exceptions are non-emergency deviations that require ***prospective*** IRB approval before being implemented. Call the IRB if your request is urgent. If IRB approval is not obtained beforehand, this constitutes a major deviation.

Emergency Deviations: include any departure from IRB-approved research that is necessary to:

- **Avoid immediate apparent harm, or**
- **Protect the life or physical well-being of subjects or others**
  - **Reporting requirement**: Emergency deviations must be promptly reported to the IRB within 5 working days of occurrence.

9.5.2

Major Deviations (also called violations): include any departure from IRB-approved research that:

- Harmed or placed subject(s) or others at risk of harm (i.e., did or has the potential to negatively affect the safety, rights, or welfare of subjects or others), or

9.5.3

- Affect data quality (e.g., the completeness, accuracy, reliability, or validity of the data) or the science of the research (e.g., the primary outcome/endpoint of the study)
  - **Reporting requirement**: Major deviations must be promptly reported to the IRB within 5 working days of PI awareness.

Minor Deviations: include any departure from IRB-approved research that:

9.5.4

- Did not harm or place subject(s) or others at risk of harm (i.e., did not or did not have the potential to negatively affect the safety, rights, or welfare of subjects or others), or
- Did not affect data quality (e.g., the completeness, accuracy, reliability, or validity of the data) or the science of the research (e.g., the primary outcome/endpoint of the study)
  - **Reporting requirement**: Minor deviations should be tracked and summarized in the progress report at the next IRB continuing review.

9.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. A summary of changes document outlining proposed changes as well as rationale for changes, when appropriate, is highly recommended. When an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

9.7 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

9.8 Obligations of Investigators

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

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

10.0 REFERENCES

List all protocol references.

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11.0 APPENDICES

Please list all relevant appendices in alphabetical order, e.g., Appendix A, Appendix B, etc.

Forms, questionnaires, performance scales, inclusion/exclusion checklists may be included in an appendix.

APPENDIX A. CEDM IMAGING PROTOCOL

CONTRAST-ENHANCED DIGITAL MAMMOGRAPHY (CEDM)

1. Indications

- **Screening Mammogram (with Contrast):**
  - o High-risk screening in patients who have previously been screened with breast MRI.
  - o Supplemental screening for patients with known dense breast tissue
- **Diagnostic Mammogram (with Contrast):**
  - o Evaluation of extent of disease of a recently diagnosed breast cancer
  - o Assessment of response to neoadjuvant therapy
  - o Axillary metastasis from a mammographically and clinically occult breast primary
  - o Evaluation of a callback finding seen on screening mammography
  - o Evaluation of mammographically OR clinically evident areas of concern without an ultrasound correlate
  - o Unilateral pathological nipple discharge with no mammographic and ultrasound correlate

2. Pregnancy and Breastfeeding

- All women of childbearing age should complete the 'Pregnancy Status Consent Form.'
- The policy regarding imaging pregnant or potentially pregnant patients is **UHISAD 108.00**.
- There is no medical indication to stop breastfeeding after IV iodinated contrast administration. If a mother chooses, she can pump and discard breast milk for 12-24 hours before resuming normal breast feeding. Ultimately, an informed decision to temporarily stop breast feeding should be left up to the mother.

3. Kidney Function

- The mammography technologist will review the electronic medical records of all patients to determine whether there are renal function test results available for review. Estimated glomerular filtration rate (eGFR), in mL/min/1.73m2, is used as a marker for renal function.
- Patients with one or more of the following conditions are considered to be at high risk for contrast induced nephropathy (CIN). These patients will be required to have renal function testing (eGFR) within **30 days** before receiving intravenous iodinated contrast. o Age > 60
  - o Hypertension (High blood pressure)
  - o Diabetes mellitus
  - o Kidney problems
  - o Kidney surgery
  - o Gout
  - o Patients taking metformin-containing medications (see Item 4)

- For patients with eGFR > ~~60~~ 30, proceed with the procedure.
- For patients with eGFR ≤ ~~60~~ 30 mL/min/1.73m2, the procedure should be aborted. DO NOT PERFORM THE PROCEDURE. Alternative imaging techniques will be explored.

4. Metformin-containing medications

- Metformin-containing medications include, but are not limited to, the following:

Brand Name	Active ingredient(s)
Actoplus Met	metformin and pioglitazone
Actoplus Met XR	metformin extended release and pioglitazone

Avandamet	metformin and rosiglitazone
Fortamet	metformin extended release
Glucophage	metformin
Glucophage XR	metformin extended release
Glucovance	metformin and glyburide
Glumetza	metformin extended release
Invokamet	metformin and canagliflozin
Invokamet XR	metformin extended release and canagliflozin
Janumet	metformin and sitagliptin
Janumet XR	metformin extended release and sitagliptin
Jentadueto	metformin and linagliptin
Jentadueto XR	metformin extended release and linagliptin
Kazano	metformin and alogliptin
Kombiglyze XR	metformin extended release and saxagliptin
Prandimet	metformin and repaglinide
Riomet	metformin
Synjardy	metformin and empagliflozin
Synjardy XR	metformin extended release and empagliflozin
Xigduo XR	metformin extended release and dapagliflozin

APPENDIX B. CEDM PATIENT SURVEY/QUESTIONNAIRE

Comfort level and tolerance

A. Please rate your comfort level during Breast MRI (please leave blank if not performed)	Extremely Comfortable 5	Relatively Comfortable 4	Neither comfortable Nor Uncomfortable 3	Somewhat Uncomfortable 2	Extremely Uncomfortable 1
B. Please rate your comfort level during Contrast-enhanced Mammography	Extremely Comfortable 5	Relatively Comfortable 4	Neither comfortable Nor Uncomfortable 3	Somewhat Uncomfortable 2	Extremely Uncomfortable 1

Scan Time

C. Study time for Standard Breast MRI (please leave blank if not performed)	Extremely Short 5	Relatively Short 4	Neither short Nor Long 3	Long 2	Extremely Long 1
D. Study time for Contrast-Enhanced Mammmography	Extremely Short 5	Relatively Short 4	Neither short Nor Long 3	Long 2	Extremely Long 1

Overall Satisfaction

E. Overall satisfaction level with Standard Breast MRI (please leave blank if not performed)	Extremely Satisfied 5	Relatively Satisfied 4	Neither Satisfied Nor Dissatisfied 3	Somewhat Dissatisfied 2	Extremely Dissatisfied 1
F. Overall satisfaction level with Contrast enhanced mammography	Extremely Satisfied 5	Relatively Satisfied 4	Neither Satisfied Nor Dissatisfied 3	Somewhat Dissatisfied 2	Extremely Dissatisfied 1

Disease Monitoring Preference- Please only respond if you also underwent breast MRI

G. Assuming they are equally accurate, how likely are you to choose contrast enhanced mammography over breast MRI as test of choice to measure your response ?	Extremely Likely 5	Relatively Likely 4	Neither Likely Nor Unlikely 3	Somewhat Unlikely 2	Extremely Unlikely 1
H. How likely are you to choose contrast enhanced mammography over breast MRI for your annual routine screening in the future ?	Extremely Likely 5	Relatively Likely 4	Neither Likely Nor Unlikely 3	Somewhat Unlikely 2	Extremely Unlikely 1

Other Comments:

Appendix C. AJCC 8th edition pre- and post neoadjuvant therapy staging (see attached file).

associated with significantly improved disease-free and overall survival for individual patients. A recent meta-analysis confirmed the reproducible prognostic value of pCR.[50]

Post Neoadjuvant Therapy ypT Classification

Preoperative or neoadjuvant systemic therapy has been used for several decades for managing inflammatory and locally advanced breast cancer, and it is being used increasingly for managing earlier stages of the disease, as well.[43] Clinical (pretreatment) T (cT) is defined by clinical and radiographic findings; pathological (posttreatment) T (ypT) is determined by the pathological size and extent of disease – this can only be determined if the primary site is resected after completing neoadjuvant therapy. The ypT is determined by measuring the largest contiguous focus of residual invasive tumor, with the modifier "m" indicating multiple foci of residual tumor. The measurement of the largest tumor focus should not include areas of fibrosis within the tumor bed. The inclusion of additional information in the pathology report may further assist the clinician in estimating the extent of residual disease. The residual cancer burden method (www.mdanderson.org/breastcancer_RCB) can be recommended, with demonstrated prognostic relevance within each molecular subtype of breast cancer, and provision of quantitative information that is complimentary to yp classification.[51, 52] Other methods, currently without subtype-specific prognostic evidence, semi-quantitatively compare the histopathology before and after treatment, e.g. Miller-Payne, Chevallier, Sataloff, or others.[53–56] Otherwise, description of the distance over which tumor foci extend, the number of tumor foci present, or the number of slides/blocks in which tumor appears, might be offered in the report.

If a cancer was classified as inflammatory (cT4d) before neoadjuvant chemotherapy, the cancer is still classified as inflammatory breast cancer after therapy, even if complete resolution of the inflammatory findings is observed during treatment. The posttreatment pathological classification (ypT) should reflect the extent of identified residual disease, and the pathology report should note that the pretreatment classification was cT4d. For example, a patient with several foci of microscopically confirmed residual disease measuring 2–9 mm in greatest dimension identified within a 22-mm² area of tumor bed fibrosis is classified as ypT1b(m), and a patient with no residual disease identified is classified as ypT0. When the only residual cancer in the breast is intravascular or intralymphatic (LVI), the ypT0 category is assigned, but the case cannot be classified as a complete pathological response (pCR).

Post Neoadjuvant Therapy ypN Classification

Clinical pretreatment node status (cN) is defined by clinical and radiographic findings with or without FNA, core needle biopsy, or sentinel node biopsy of a suspicious node or excision of a palpable node; pathological posttreatment N (ypN) is determined similar to pN. The "sn" modifier is used only if a sentinel node evaluation was performed after treatment and no axillary dissection has been performed. If no sentinel node or axillary dissection is performed, the (ypNX) classification is used.

The ypN categories are the same as those used for pN. Only the largest contiguous focus of residual tumor in the node evaluation is used for classification; any treatment-associated fibrosis is not included. Inclusion of additional information in the pathology report—such as the distance over which tumor foci extend and the number of tumor foci present—may assist the clinician in estimating the extent of residual disease.

Post Neoadjuvant Therapy M Classification

The M category for patients treated with neoadjuvant therapy is the category assigned for pretreatment clinical stage, prior to initiation of neoadjuvant therapy. If a patient was designated to have detectable distant metastases (M1) before chemotherapy, the patient will be designated as M1 throughout. Identification of distant metastases after the start of therapy in cases where pretherapy evaluation showed no metastases is considered progression of disease.

Other Rules for Classification – Functional Imaging, Multiple Primaries

Historically, TNM classification has been based on tumor morphology with size as the major indicator of prognosis and treatment efficacy. Although size is still the prime determinant in classification, the use of molecular breast imaging, CT, PET and MR imaging with contrast enhancement brings up many more measurement possibilities other than anatomic size. This includes biologic functional imaging characteristics that may be more accurate than size alone to evaluate prognosis and treatment options. At the moment, validated data are insufficient to incorporate these findings into staging. When sufficient data are accumulated these factors may be introduced into the staging system.

For patients who receive neoadjuvant systemic or radiation therapy pretreatment, T is defined as clinical (cT). Pretreatment staging is clinical, and the clinical measurement defined from examination and imaging is recorded (cT).

Multiple Simultaneous Ipsilateral Primary Carcinomas

Multiple simultaneous ipsilateral primary carcinomas in the same breast, which are grossly or macroscopically distinct and measurable using available clinical and pathological techniques, are defined as invasive carcinomas. T category

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Appendix D. ACR Contrast Manual, 2018 (excerpt)

ADMINISTRATION OF CONTRAST MEDIA TO WOMEN WHO ARE BREASTFEEDING

Imaging studies requiring either iodinated or gadolinium-based contrast media are occasionally required in patients who are breast feeding. Both the patient and the patient's physician may have concerns regarding potential toxicity to the infant from contrast media that is excreted into the breast milk. The literature on the excretion into breast milk of iodinated and gadolinium-based contrast media and the gastrointestinal absorption of these agents from breast milk is very limited; however, several studies have shown that the expected dose of contrast medium absorbed by an infant from ingested breast milk is extremely low.

Iodinated X-ray Contrast Media (Ionic and Nonionic) Background

The plasma half-life of intravenously administered iodinated contrast medium is approximately 2 hours, with nearly 100% of the media cleared from the bloodstream in patients with normal renal function within 24 hours. Because of its low lipid solubility, less than 1% of the administered maternal dose of iodinated contrast medium is excreted into the breast milk in the first 24 hours [1,2]. In addition, less than 1% of the contrast medium ingested by the infant is absorbed from its gastrointestinal tract [3]. Therefore, the expected systemic dose absorbed by the infant from the breast milk is less than 0.01% of the intravascular dose given to the mother. This amount represents less than 1% of the recommended dose for an infant being prescribed iodinated contrast material related to an imaging study (usually 1.5 to 2 mL/kg).

The potential risks to the infant include direct toxicity and allergic sensitization or reaction, which are theoretical concerns but have not been reported. The likelihood of either direct toxic or allergic-like manifestations resulting from ingested iodinated contrast material in the infant is extremely low. As with other medications in milk, the taste of the milk may be altered if it contains contrast medium [1-4].

Recommendation
Because of the very small percentage of iodinated contrast medium that is excreted into the breast milk and absorbed by the infant's gut, we believe that the available data suggest that it is safe for the mother and infant to continue breast-feeding after receiving such an agent. Ultimately, an informed decision to temporarily stop breast-feeding should be left up to the mother after these facts are communicated. If the mother remains concerned about any potential ill effects to the infant, she may abstain from breast-feeding from the time of contrast administration for a period of 12 to 24 hours.

There is no value to stop breast feeding beyond 24 hours. The mother should be told to express and discard breast milk from both breasts during that period. In anticipation of this, she may wish to use a breast pump to obtain milk before the contrast-enhanced study to feed the infant during the 24-hour period following the examination.