PROTOCOL TITLE:

Added Value of Contrast Enhanced Mammography for Breast Cancer Staging in Patients Referred for A Second Opinion to A Tertiary Cancer Center

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4 (07/21/2021)

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
2		Responses to SRC questions	
3	2-2-2021	Responses to IRB	yes
4	7-21-2021	Remove the presence of breast implants as an exclusion criterion	No

Table of Contents

1.0 Study Summary

Study Title	Added value of contrast enhanced mammography for breast cancer staging in patients referred for a second opinion to a tertiary cancer center
Study Design	Prospective observational cross-sectional or correlational study
Study Specific Abbreviations/ Definitions	CEM: contrast enhanced mammography BC: breast cancer OSF: outside facility (medical institution or office outside of MD Anderson) FFDM: full field digital mammogram (2D mammogram) LE: low energy images (a part of CEM exam, FFDM equivalent) DBT: digital breast tomosynthesis (3D mammogram) US: ultrasound
Primary Objective	To compare the accuracy of CEM and LE images (equivalent of FFDM as the standard of care) for the detection of additional cancer sites in the affected breast and in the contralateral breast. For the purpose of the study, up to 4 additional biopsy sites will be included in the analysis.
Secondary Objective(s)	1. To evaluate the sensitivity, specificity, positive and negative predictive value of CEM compared to LE CEM images (FFDM equivalent), DBT and ultrasound for the detection of additional malignant lesions in the ipsilateral and contralateral breast. 2. To evaluate the difference of the index cancer size estimation among CEM, LE images, DBT, and ultrasound compared to pathology measurements as the ground truth. 3. To evaluate the incremental cancer detection rate provided by CEM, DBT, and US compared to the OSF diagnosis.
Exploratory Objective(s)	1. To evaluate the rate of referral to breast MRI in the study cohort. 2. To evaluate the performance of MRI for breast cancer diagnosis and compare it with other imaging modalities of CEM, LE images, DBT and ultrasound. 3. To evaluate the feasibility of CEM-guided biopsy of CEM- only detected lesions. The technical success of CEM guided biopsies will be determined by the

	fraction of biopsies that achieve adequate sampling of the target.
Research Intervention(s)/ Investigational Agent(s)	IV injection of iodinated contrast material
IND/IDE #	
Study Population	• Female patients with known invasive or in-situ breast cancer diagnosed at an outside facility and presenting to MD Anderson for staging with imaging. • Female patients referred from outside institutions with imaging findings categorized as highly suspicious (BI-RADS 5 or 4C) on outside imaging or on re-review by MD Anderson's radiologists, and referred for staging at MDACC.
Sample Size	83
Study Duration for individual participants	One diagnostic CEM imaging examination In addition, if indicated, one CEM-guided biopsy

2.0 Objectives*

2.1 Primary Objectives

- *To compare the accuracy of CEM and LE images (equivalent of FFDM as the standard of care) for the detection of additional cancer sites in the affected breast and in the contralateral breast.*

2.2 Secondary Objectives

- *To evaluate the sensitivity, specificity, positive and negative predictive value of CEM compared to LE CEM images (FFDM equivalent), DBT and ultrasound for the detection of additional malignant lesions in the ipsilateral and contralateral breast.*
- *To evaluate the difference of the index cancer size estimation among CEM, LE images, DBT, and ultrasound compared to pathology measurements as the ground truth.*
- *To evaluate the incremental cancer detection rate provided by CEM, DBT, and US compared to the OSF diagnosis.*

2.3 Exploratory Objectives

- *To evaluate the rate of referral to breast MRI in the study cohort.*
- *To evaluate the performance of MRI for breast cancer diagnosis and compare it with other imaging modalities of CEM, LE images, DBT and ultrasound.*
- *To evaluate the feasibility of CEM-guided biopsy of CEM-only detected lesions. The technical success of CEM guided biopsies will be determined by the fraction of biopsies that achieve adequate sampling of the target.*

2.4 Hypothesis

We hypothesize that CEM will improve the diagnostic accuracy of incremental breast cancer detection compared to standard 2D mammography and will improve the accuracy of the index cancer size estimation. The overarching goal is to determine whether CEM will reduce the need for breast MRI and decrease the overall time and cost of preoperative imaging evaluation of patients with breast cancer.

3.0 Background*

3.1 Current MDACC practice protocols

As a major tertiary cancer center, MD Anderson Cancer Center has a significant population of patients who present for staging of known breast

cancer (BC) which was already diagnosed at an outside facility (OSF), or who have OSF imaging findings that are assigned category 5 (highly suspicious with the probability of malignancy >95%) or 4C (suspicious with the probability of malignancy 50-95%) according to the American College of Radiology (ACR) Breast Imaging Reporting and Database System (BI-RADS) on OSF imaging [1]. Precise delineation of the extent of disease in the affected breast and evaluation of the contralateral breast are crucial for surgical treatment planning in BC patients [2]. Even in patients with no known BC, a second opinion at a specialized cancer center can make a significant impact on clinical management, changing the original interpretation in 36- 47% of lesions [3, 4]. In patients who present with known BC at MDACC, the rate of upstaging upon second opinion interpretation and possible re-imaging is 25%, which changes surgical management in 12% of patients [5]. At the same time, the re-operation rate after breast conservation surgery in BC patients is 19% [5]. This is suboptimal and may be due to underestimation of tumor size, but this rate is lower than the national rate, which reaches 30% [2].

The current protocol for staging of OSF BC cases consists of a second read of interpretable OSF mammograms or repeating technically suboptimal mammograms, followed by ultrasound, ultrasound-guided and/or stereotactic-guided biopsies, when indicated. Some patients also require breast MRI with second look ultrasound and ultrasound- or MRI-guided biopsies, which prolongs work-up and delays treatment.

At our institution, using ultrasound and MRI almost doubles the number of additional suspicious breast lesions found on mammography. 45% of these additional lesions are malignant. The sensitivities of mammography (MG), US, and MRI are 36, 71, and 85%, respectively, and their specificities are respectively 76, 68, and 39%, making MRI the most sensitive, and the MG the most specific modality. 18% of additional malignant lesions at MDA are found on MRI only [6]. Unfortunately, the need for breast MRI often delays treatment due to the limited availability of magnet time. MRI is also an expensive imaging test, further limiting access.

3.2 The role of functional imaging

Functional imaging modalities such as breast MRI and nuclear breast imaging (NBI) require IV contrast injections and provide information on abnormal vascular architecture and increased vessel wall permeability that is common in BC [7]. Breast MRI is the most extensively researched among the functional modalities and serves as the gold standard for evaluation of new imaging modalities. MRI shows the highest sensitivity in detecting additional malignant lesions in the affected breast and the contralateral breast [2, 8-10]. MRI is also the most accurate modality for the evaluation of the index cancer size, while the conventional imaging modalities used for the first line of cancer staging- mammography and ultrasound- only modestly correlate with the tumor size on pathology [2, 11]. These attributes of MRI contribute to improved outcomes of surgical

treatment of BC, in particular, to the decreased need for re-excision for positive margins [2, 12, 13]. At the same time, MRI has a high rate of false positive results that require additional biopsies and may delay cancer treatment [14, 15].

Additional limitations of MRI include high cost, long scanning time, and limited availability of equipment. There is also a significant patient acceptance factor [16]. In one large study, only 51.6% of patients who were offered MRI at no cost agreed and successfully completed the MRI study. The main reasons for patient refusal were claustrophobia and time constraints [17].

Dedicated nuclear breast imaging (NBI) is a group of functional imaging modalities that depict the distribution of radioactive tracers injected into the patient. This group includes breast specific gamma imaging (BSGI), molecular breast imaging (MBI), and positron emission mammography (PEM) [18]. The role of NBI is evolving. The positive predictive values (PPVs) of MBI and BSGI in cancer detection are reported at 35-60% and are not affected by breast density, but are affected by lesion size, detecting 71% of lesions less than 5 mm in size, as opposed to 84-99% of larger tumors.

The disadvantages of NBI are long scanning time, relatively low resolution, whole-body radiation, and limited visualization of the prepectoral tissues. Yet NBI may be a viable diagnostic option for eligible women who cannot tolerate MRI [18].

3.3 Contrast Enhanced Mammography

CEM is a relatively new imaging technique that is based on mammography (MG) but utilizes intravenous contrast that adds functional information to morphologic information. Each CEM study has two components. The first component is a set of low-energy (LE) images, which are equivalent to non-contrast MG and are interpreted as FFDM, providing all the benefits of conventional mammography. A set of high-energy images are also obtained, above the k-edge of iodine (i.e. > 33 kVp). Then processing is performed to subtract the low-energy from the high-energy images and thereby create the second component, subtracted contrast images (SCI), which reflect only areas of enhancement. Enhancement shows the functional state of the tissues, i.e. tissue vascularity and blood vessel permeability that is similar to MRI.

CEM improves the diagnostic accuracy of MG alone, and even performs better than MG combined with DBT or MG with US [19-22]. CEM has been shown to be similar in sensitivity, but higher in specificity, than MRI for detection of index BC [19, 23]. It also efficiently finds multicentric and multifocal BC, as well as cancer in the contralateral breast with similar sensitivity but higher specificity than MRI [19, 24]. The higher specificity may make CEM more desirable than MRI in pre-operative cancer staging, since the high false positive rate currently limits the use of MRI [25].

CEM is also significantly faster and significantly less costly than MRI [16]. It can be easily incorporated into the workflow without any added work-up time. In addition, CEM is preferred over MRI by patients [22].

The main concerns raised about CEM are the need for intravenous iodinated contrast administration and the associated risk of contrast-related complications, as well as increased radiation exposure. However, in a recent (2019) systematic literature review of CEM technique involving 14,012 patients, only 30 adverse reactions were reported, of which 26/30 were mild (pruritus, hives, etc, that resolved promptly without treatment); 3/30 cases were moderate (nausea, vomiting, urticaria etc, resolved after antihistamines or corticosteroids); and 1/30 cases was severe, non-fatal, requiring short-term intensive care [26].

As routinely performed, the radiation dose from CEM is approximately 2.3 mGy for a combination of 2 exposures. This is 1.5 times higher than a single exposure of FFDM, but is 25% lower than a combination mode mammography, which is the current standard of care at MDACC and consists of FFDM and DBT exposures. It is also significantly below the FDA allowed maximum glandular dose of 3 mGy per one exposure [27-29], [personal communication with GE Healthcare engineering team].

Until recently, no direct method of tissue sampling under direct CEM guidance existed, which made it impossible to biopsy CEM-only detected lesions, and often required performing breast MRI to search for a correlating lesion and for biopsy guidance [30]. This has changed with the introduction of the first commercially available CEM-guided biopsy device (GE Healthcare Pristina Serena Bright), which has obtained 510(k) clearance by the Food and Drug Administration in June 2020. This enables direct biopsy of CEM- only detected lesions without the need for MRI and MRI- guided biopsies that increase cost and delay patient care (Appendix A).

3.4 Multiparametric cohort

We are proposing to add comprehensive multiparametric data collection on the study cohort that could aid in patient stratification [ongoing MERIT study (PA17-0584)]. This would involve administering a questionnaire, collecting blood samples, and archiving raw mammographic images, for blood and imaging biomarkers discovery and validation. The analysis of the multiparametric data may provide additional predictive and prognostic information on BC patients, which could be helpful in the choice of therapy and follow-up.

3.5 INNOVATION

The use of CEM as a first line modality in the evaluation of breast cancers diagnosed at OSF has not been studied. Our proposed protocol may prove beneficial for improving the time and cost-efficiency of imaging work-up, as well as for the overall optimization of workflow for the benefit of the

unique population of patients referred from OSF to MD Anderson Cancer Center.

4.0 Study Endpoints*

4.1 Primary study endpoint:

Accuracy of CEM for incremental cancer detection in the ipsilateral and contralateral breasts. For the purpose of the study, up to 4 additional biopsy sites will be included in the analysis.

4.2 Secondary study endpoints:

- *Sensitivity, specificity, positive and negative predictive value of CEM, LE images, DBT, and ultrasound compared to pathology measurements as the ground truth.*
- *The difference of the largest measurement of the index cancer on LE, CEM, DBT and US compared to pathology.*
- *Incremental cancer detection rate provided by CEM, DBT and US.*

4.3 Exploratory Endpoints:

- *Rate of breast MRI utilization and the corresponding diagnosis in the study cohort.*
- *The fraction of CEM biopsies that achieve adequate sampling of the target.*

5.0 Procedures Involved*

5.1 PROCEDURE TO OBTAIN CONSENT

Eligible and interested subjects will be consented for study participation. A research staff member who is trained in the informed consent process will explain the study, invite the patients to enroll, and obtain the informed consent of women who wish to participate. Subjects may be enrolled using the approved MD Anderson procedures for remote consenting.

5.2 PATIENT WORKFLOW (Fig.1)

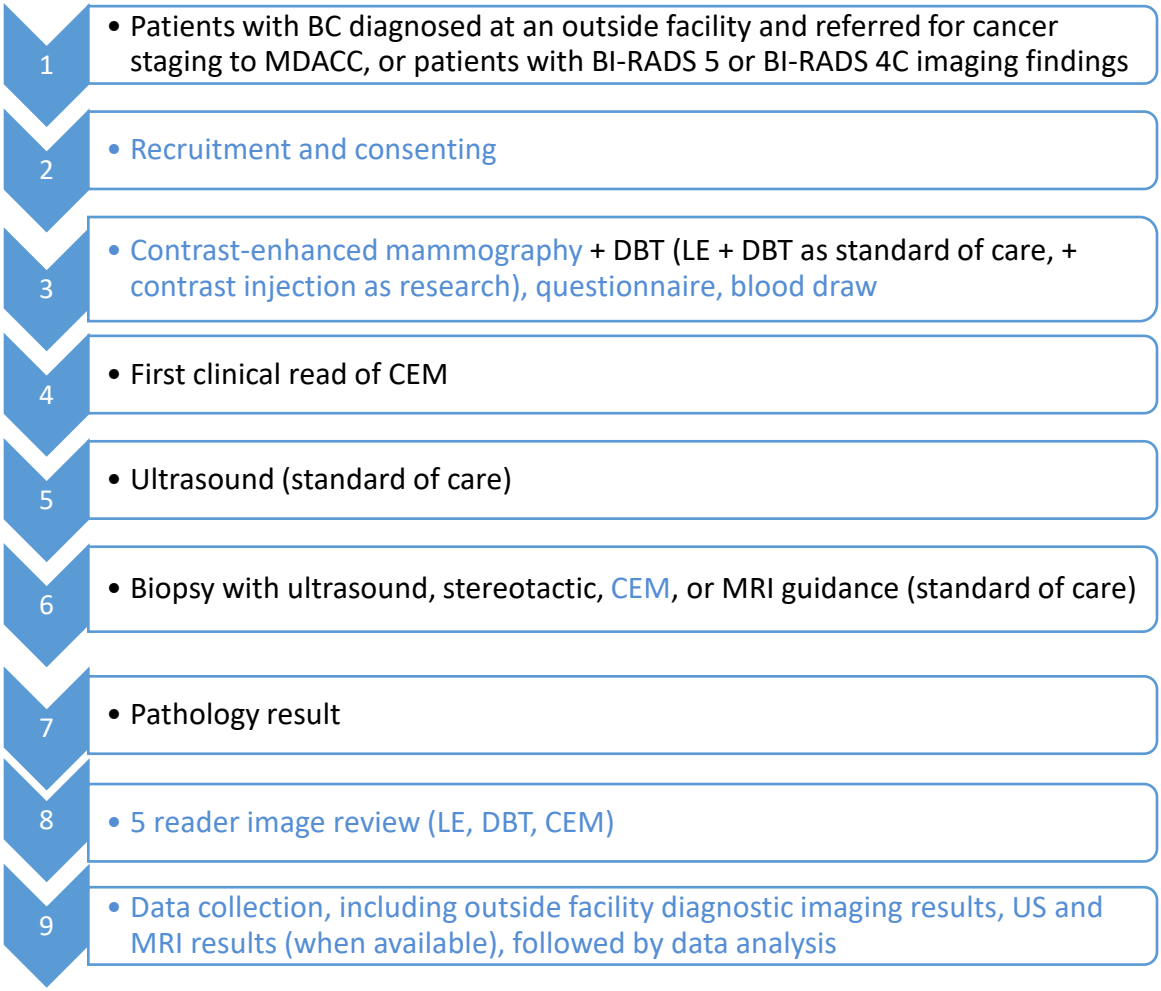


Fig. 1. Patient workflow. Research components are represented in blue, and standard of care components in black.

5.3 IMAGING WITH CEM

Safety checklist and IV injection:

The imaging technologist, the study personnel, and the radiologist will be responsible for ensuring the safe administration of IV contrast. IV contrast injections and eligibility screening will be performed in accordance with MDACC institutional policies. Contrast safety will be ensured by following the current UTMDACC DIVISION OF DIAGNOSTIC IMAGING POLICY # 3.30, amendment for CEM (Appendix B).

The imaging technologist and the study nurse or research coordinator will use a patient safety checklist for verifying that the patient has no contraindications for the study.

If a patient passes the safety checklist, an IV catheter will be placed in the patient's forearm or antecubital vein in the mammography suite

immediately before the procedure by a trained nurse, mammography technologist, or study coordinator. The patients will be sitting for the injection to minimize vaso-vagal reactions. Low-osmolality iodine-based intravenous contrast (Omnipaque 350 mg I/mL; GE Healthcare or equivalent) will be injected using a power injector, at a rate of 3 mL/s for a total dose of 1.5 mL/kg body weight, but not exceeding 150 ml, followed by a 30 mL saline flush [30-32].

Imaging technique:

CEM will be administered using FDA-approved equipment. The study will be conducted using a full-field digital mammography system capable of providing low- and high-energy exposures to the breast under the same compression, as well as producing subtracted contrast images, such as Senographe Pristina (GE Healthcare, Buc, FR) or an equivalent system.

1. The imaging will start with the affected breast 2 min after contrast injections and will consist of one high and one low energy exposure in succession. The affected breast will be imaged in craniocaudal (CC), mediolateral oblique (MLO), and lateromedial (LM) projections (Fig.1). CC and MLO images will also be obtained of the unaffected breast (Fig. 2).

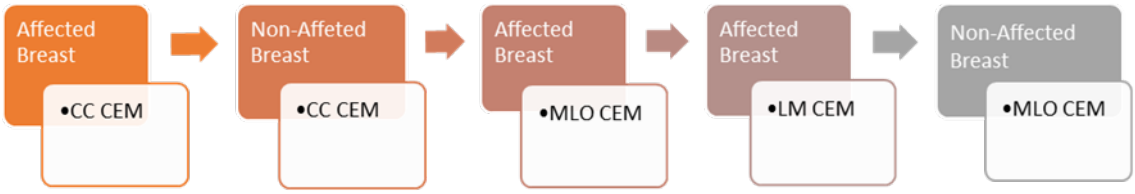


Fig. 2. CEM imaging sequence.

2. Additional views will be obtained, when needed (e.g. XCCL (exaggerated craniocaudal lateral) view), to include all breast tissue per clinical protocol.

3. For those women who have not undergone DBT as a part of their screening or diagnostic imaging within 3 month from the study, bilateral DBT study will be performed immediately following the CEM study. A complete bilateral DBT study will be obtained utilizing DBT projections and reconstructed synthetic 2D views. This will include CC, MLO, and LM projections of the affected breast, and CC and MLO projections of the non-affected breast.

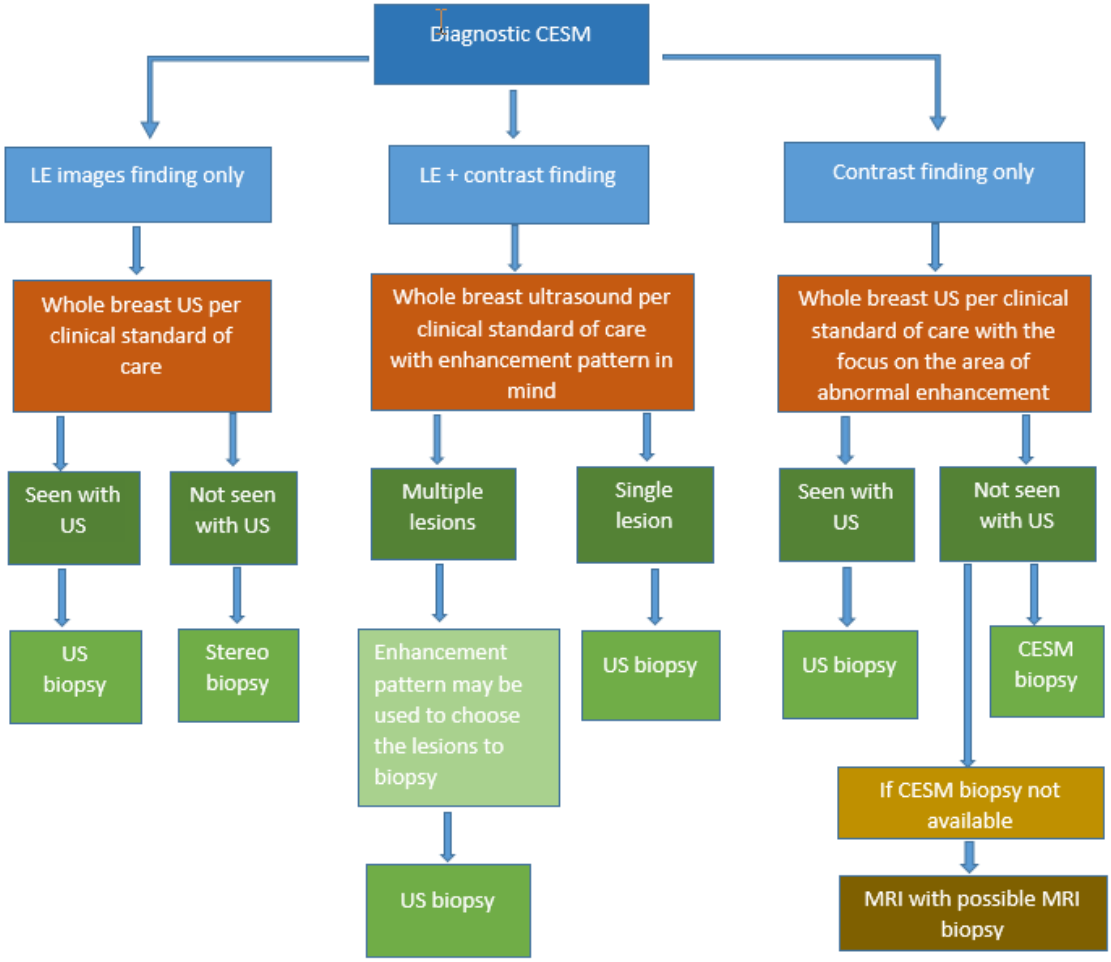
Patients will be observed for 30 minutes after the contrast injection to ensure the absence of symptoms of delayed reaction to iodine-based contrast as reported by patients. The patient will be encouraged to drink at least 500 ml of water after the procedure.

Imaging quality assurance:

The images will be immediately sent to the radiologist for quality assurance via PACS. Additional images (exaggerated or repeat views) may be obtained for technical issues, if necessary.

OTHER IMAGING STUDIES:

Decision making algorithm



Ultrasound

Due to a subjective nature of ultrasound, the ultrasound images will not be included in the reader study. However ultrasound images and reports will be obtained from the patients' medical records and analyzed to provide correlation per lesion with the FFDM, DBT, and CEM studies.

MRI

When available, MRI reports and MRI images will be obtained from the patients' medical records and analyzed to correlate with the FFDM, DBT, CEM, and ultrasound findings.

Image-guided biopsies

Ultrasound-guided FNA or core biopsies, as well as stereotactic, or MRI-guided core biopsies will be performed as a part of routine clinical care, when indicated. The biopsies may also be performed using a CEM-guided biopsy instrument (GE Healthcare Pristina Serena Bright).

The following data will be collected from the biopsy reports:

- *Number of core samples*
- *Needle gauge*
- *Adequacy of sampling, which for stereotactic biopsies will include the percent of microcalcifications removed, and the number of cores with microcalcifications*
- *Concordance with the pathology results.*

5.4 CEM-guided biopsies:

CEM- guided biopsy device uses a stereotactic technique to target areas of abnormal enhancement in the breast. The first commercially available CEM-guided biopsy device (GE Healthcare Serena Bright™ CEM biopsy system) has been U.S. Food & Drug Administration 510(k) cleared in May 2020. This system is capable of both conventional stereotactic and CEM-guided biopsies. For both methods the system uses angular mammographic acquisitions in the breast to calculate the target, but for stereotactic biopsies it uses the morphologic abnormality in the breast as the target, whereas for CEM-guided biopsies it uses the area of suspicious enhancement as the target. With the exception of targeting, the biopsy procedure and the biopsy needles used for the procedure are identical for both methods (Appendix A).

For those study patients who demonstrate abnormal CEM enhancement with no correlate on FFDM or US, GE Healthcare Serena Bright™ CEM biopsy system will be used to perform CEM- guided biopsies. CEM-guided biopsies may also be utilized for choosing the areas of most prominent CEM enhancement as biopsy targets for extensive mammographic abnormalities, where precise targeting is difficult. The presence of distinct abnormal enhancement within a target is expected to correlate with the most metabolically active areas of the lesion [31]. This may improve the accuracy of biopsy and decrease the rate of upgrade to malignancy at surgery.

5.5 Biopsy markers and post-procedure mammograms

For all biopsy methods a biopsy marker will be placed at the target as the standard of care [32]. As a part of the standard of care we will perform a post-procedure mammogram after tissue sampling and clip placement [32].

For those patients who undergo CEM-guided biopsies for pathologic enhancement, post-procedure CEM images of the biopsied breast will be obtained.

The technical success of CEM guided biopsies will be determined by the fraction of biopsies that achieve adequate sampling of the target.

5.6 Ground truth

Pathology results from image guided biopsies and surgical pathology results will be considered the ground truth. Breast tissue lesions will be categorized as positive if diagnosed as invasive BC or ductal carcinoma in situ (DCIS), and otherwise will be categorized as negative, including the lesions of uncertain malignant potential without subsequent surgical upgrade to invasive cancer or DCIS.

5.7 Pathology

As part of the standard of care, the biopsy will be evaluated by a breast pathology specialist as part of the routine diagnostic clinical service. After the case has been finalized, the slides will be reviewed by the breast pathology collaborator for this study in order to record the additional information listed below.

The following parameters will be recorded:

- *Pathologic diagnosis*
- *The maximal diameter of the dominant abnormality*
- *The maximal diameter of the abnormality with the highest level of suspicion (Invasive cancer, in-situ cancer, atypia)*

For invasive cancers/DCIS:

- *Histologic/nuclear grade*
- *Presence of tumor necrosis for invasive carcinoma and/or comedonecrosis for DCIS*
- *Architectural growth pattern for DCIS*
- *The Presence of lymphovascular invasion*
- *Biomarker status (ER, PR, Her-2/neu, Ki-67)*
- *Presence of calcifications*
- *Tumor infiltrating lymphocyte analysis*

5.8 Multiple reader study design

Low-energy images produced as a part of CEM are of sufficient quality for clinical interpretation (equivalent to directly acquired 2D mammographic images), and will be interpreted accordingly by radiologists.

The reader study will have 2 components:

1. The first interpretation of the entire CEM study, including all its components, will be done clinically by one radiologist after the exam is performed. Its results will be actionable and will affect the patient's management.

2. Multiple reader study. The results of this study will not be used for clinical care, and will not be reported to the patients or referring clinicians.

Each patient's study will contain LE images (FFDM equivalent), DBT images, and CEM subtraction images. All these components will be separated and presented to radiologists in different combinations for within-subject comparison. As a part of the multi-reader component, the study images for every patient will be reviewed in 4 sets by 5 radiologists each. Images for the same patients will be read by radiologists with an interval of at least 2 month to prevent case memorization.

1. LE (FFDM equivalent) images only

2. LE (FFDM equivalent) with DBT

3. LE followed by DBT followed by CEM subtraction images

4. LE followed by subtraction images (complete CEM study)

The study radiologists will be aware of the patients' inclusion criteria, but will be blinded to the clinical diagnostic reports, any and all comparison images of any modality outside of the assigned protocol, and the pathology report.

5.9 The sequence of the imaging studies and the parameters to be collected are presented below. The reporting will be done using ACR BI-RADS Fifth edition recommendations.

1. LE images:

- *Laterality*
- *Clock position*
- *3 dimensional measurements of the index mass (antero-posterior, craniocaudal, transverse), when possible*
- *View demonstrating the finding best (CC, MLO, LM)*
- *The number, laterality, and clock position of additional lesions*
- *Breast density (Bi-RADS A-D)*
- *BI-RADS assessment per lesion using the 7-point BI-RADS® scale (1, 2, 3, 4a, 4b, 4c, 5) (Fig.3). BI-RADS categories 1-3 will be considered negative, and BI-RADS categories 4-5 will be considered positive.*

2. DBT images:

- *Laterality*
- *Clock position*

- *3 dimensional measurements of the index mass in question (antero-posterior, craniocaudal, transverse), when possible*
- *View demonstrating the finding best (CC, MLO, LM)*
- *The number, laterality, and clock position of additional lesions*
- *BI-RADS assessment using the 7-point BI-RADS® scale (1, 2, 3, 4a, 4b, 4c, 5) (Fig.3). BI-RADS categories 1-3 will be considered negative, and BI-RADS categories 4-5 will be considered positive.*

3. CEM

- *Background enhancement*
- *The presence or absence of pathologic enhancement in the area of index mass, and the degree of enhancement above background.*
- *3 dimensional diameters of the pathologic enhancement (antero-posterior, craniocaudal, transverse), when available.*
- *The number, laterality, and clock position of additional lesions*
- *View demonstrating the finding best (CC, MLO, LM)*
- *BI-RADS assessment after adding CEM. BI-RADS categories 1- 3 will be considered negative, and BI-RADS categories 4-5 will be considered positive.*

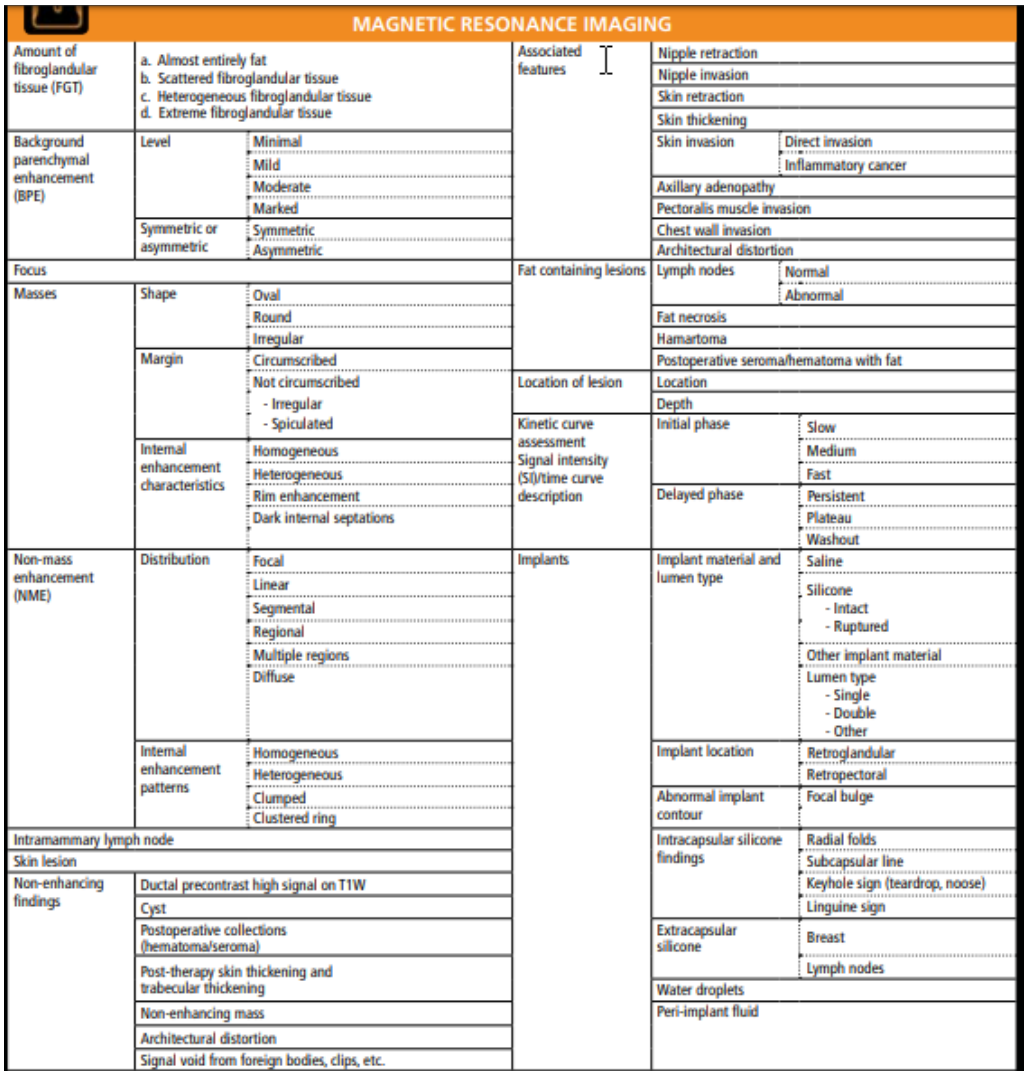
BI-RADS® ASSESSMENT CATEGORIES		
Category 0:	**Mammography:** Incomplete – Need Additional Imaging Evaluation and/or Prior Mammograms for Comparison **Ultrasound & MRI:** Incomplete – Need Additional Imaging Evaluation	
Category 1:	Negative	
Category 2:	Benign	
Category 3:	Probably Benign	
Category 4:	Suspicious	Mammography & Ultrasound: Category 4A: Low suspicion for malignancy Category 4B: Moderate suspicion for malignancy Category 4C: High suspicion for malignancy
Category 5:	Highly Suggestive of Malignancy	
Category 6:	Known Biopsy-Proven Malignancy	

Fig. 3 BI-RADS assessment categories [1]

A PACS-based MDACC-created and approved software will be utilized for data collection by the radiologists and directly transferred for statistical analysis.

Lexicon

There is currently no standard reporting language for contrast enhanced mammography. The most commonly used conventional approach to reporting will be utilized for the study: for the mammographic findings, the BI-RADS mammography lexicon will be utilized; for the enhancement patterns, the BI-RADS MRI lexicon will be applied (fig.4) [1, 33].



MAGNETIC RESONANCE IMAGING

Amount of fibroglandular tissue (FGT)	a. Almost entirely fat b. Scattered fibroglandular tissue c. Heterogeneous fibroglandular tissue d. Extreme fibroglandular tissue		Associated features	Nipple retraction	
				Nipple invasion	
				Skin retraction	
				Skin thickening	
Background parenchymal enhancement (BPE)	Level	Minimal		Skin invasion	Direct invasion
		Mild			Inflammatory cancer
		Moderate		Axillary adenopathy	
		Marked		Pectoralis muscle invasion	
	Symmetric or asymmetric	Symmetric		Chest wall invasion	
		Asymmetric		Architectural distortion	
Focus			Fat containing lesions	Lymph nodes	Normal
					Abnormal
Masses	Shape	Oval		Fat necrosis	
		Round		Hamartoma	
		Irregular		Postoperative seroma/hematoma with fat	
	Margin	Circumscribed			
		Not circumscribed - Irregular - Spiculated	Location of lesion	Location	
				Depth	
	Internal enhancement characteristics	Homogeneous	Kinetic curve assessment Signal intensity (SI)/time curve description	Initial phase	Slow
		Heterogeneous			Medium
		Rim enhancement			Fast
		Dark internal septations		Delayed phase	Persistent
					Plateau
					Washout
Non-mass enhancement (NME)	Distribution	Focal	Implants	Implant material and lumen type	Saline
		Linear			Silicone - Intact - Ruptured
		Segmental			Other implant material
		Regional			Lumen type - Single - Double - Other
		Multiple regions			
		Diffuse			
	Internal enhancement patterns	Homogeneous		Implant location	Retroglandular
		Heterogeneous			Retropectoral
		Clumped		Abnormal implant contour	Focal bulge
		Clustered ring			
Intramammary lymph node				Intracapsular silicone findings	Radial folds
Skin lesion					Subcapsular line
Non-enhancing findings	Ductal precontrast high signal on T1W				Keyhole sign (teardrop, noose)
	Cyst				Linguine sign
	Postoperative collections (hematoma/seroma)			Extracapsular silicone	Breast
	Post-therapy skin thickening and trabecular thickening				Lymph nodes
	Non-enhancing mass			Water droplets	
	Architectural distortion			Peri-implant fluid	
	Signal void from foreign bodies, clips, etc.				

Fig. 4 MRI descriptors of the BI-RADS lexicon [34]

Follow-up

We will follow up the study patients for at least 12 months. We will review the patients' medical records, including clinical notes, pathology, and radiology reports. This will be done to monitor for possible development of new BC or cancer recurrence. Results from biopsy and/or follow-up will serve as the ground truth and will be used to determine the true positive and true negative.

6.0 Data and Specimen Banking*

6.1 Registration

All subjects who have given informed consent and meet eligibility criteria must be registered through the MDACC CORe system.

6.2 Questionnaire

If not already enrolled in the MERIT study (PA17-0584), participants will be asked to complete a questionnaire that collects data on personal and family history of cancer, health status, breast cancer risk factors, diet, weight gain, and physical activity (Appendix C1, C2). The questionnaire or a link to the questionnaire may also be sent to the participants at a different time from their mammography appointment (before or after) via text or email, or through our electronic health record system. The questionnaire data may also be collected via telephone by research staff. Essential data elements will be collected from the patients' medical records.

6.3 Biospecimen Collection

A member of the research staff will collect blood at the time of the CEM examination but before contrast is injected. To collect blood specimens, a PIVO™ device (Velano Vascular) may be used by trained staff to perform the blood draw and the contrast injection through the same IV access to avoid multiple patient sticks (Appendix D).

The blood will be delivered to a facility within MD Anderson where it will be processed by trained personnel. Additional details regarding blood processing Standard Operating Procedures (SOPs) are described in Appendix E. The McCombs Institute will manage the biospecimens and will utilize portions of samples to evaluate candidate biomarkers.

Samples from each patient will be assigned a unique specimen identification number. This number will become a part of the repository and will be used to identify the subjects' data in the system. In this way, no personal identification information such as name or a social security number is necessary.

If the participant is also enrolled in any other McCombs Institute early detection study (for example, 2013-0609, PA17-0791), biospecimen collection is not required if the last collection was within 30 days.

7.0 Sharing of Results with Subjects*

7.1 The results of the first clinical read of CEM studies will be provided within the frame of the clinical workflow, will affect patient care, and will be reported to the patient and her referring physician.

7.2 The results of the multi-reader component will not be shared with the patient or her referring provider.

8.0 Study Timelines*

8.1 Describe:

- *The subject participation will consist of a one-time CEM study. The patients' pertinent clinical information, including imaging, pathology and clinical reports will be collected for 12 months.*
- *In those patients who need a CEM-guided biopsy, the participation in the study will also include IV contrast administration for the biopsy.*
- *The study enrollment process is expected to continue for 12 months.*
- *March 2022*

9.0 Inclusion and Exclusion Criteria*

9.1 INCLUSION CRITERIA

- *Female patients 18 years of age or older with known invasive or in-situ BC diagnosed at an outside facility and presenting to MD Anderson for staging with imaging.*
- *Female patients 18 years of age or older referred from outside institutions with imaging findings categorized as highly suspicious (BI-RADS 5 or 4C) on outside imaging or on re-review by MD Anderson's radiologists and referred for staging at MDACC.*
- *Willingness to participate in the study and ability to provide informed consent.*

9.2 EXCLUSION CRITERIA

-
- *Breast surgery within 6 months.*
- *Known allergy to iodine-containing contrast agents.*
- *History of anaphylactic reaction to any substance that required hospitalization or IV placement.*
- *Renal insufficiency; hyperthyroidism.*
- *Detection of non-breast primary or metastatic cancer in the breast.*

9.3 PROCEDURE TO OBTAIN CONSENT

Eligible and interested subjects will be consented for study participation. A research staff member who is trained in the informed consent process will explain the study, invite the patients to enroll, and obtain the informed consent of women who wish to participate. Subjects may be enrolled using the approved MD Anderson procedures for remote consenting.

10.0 Local Number of Subjects

10.1 83 subjects

11.0 Recruitment Methods

Research staff will identify potential subjects via the UT MDACC information system. The patients will be approached by either the Clinical Cancer Prevention or the Diagnostic Imaging faculty, or qualified research staff, for their consent prior to their procedure. This may be done before or on the day of their diagnostic mammography appointment at the MDACC Nellie B. Connally Breast Imaging Center, or via a telephone conversation or a teleconference with a study coordinator, an email, or text messaging via MD Anderson approved systems. MyMDAnderson website and flyers may be utilized to contact patients. The patients will not be compensated for their participation.

12.0 Withdrawal of Subjects*

12.1 The patients may refuse participation at any time for any reason.

12.2 The subjects will be withdrawn from the research without their consent in the following situations:

- *The patient has consented to the study but is determined to be ineligible before CEM is completed*
- *The patient does not complete CEM imaging*
- *The patient refuses a biopsy or chooses to have a biopsy at an outside institution*
- *In these cases, the patients' research files will be removed and any collected data will not be used for analysis.*

13.0 Risks to Subjects*

13.1 The study will require an IV contrast injection, which carries a small risk of contrast reaction, which will be minimized by the study personnel by patient pre-screening and following MDACC IV contrast injection protocols.

13.2 The extra imaging study carries small extra dose of ionizing radiation, approximately 30% more than a standard 2D mammogram, but less than a combination mode 3D mammogram.

13.3 CEM may detect abnormalities in the breasts which are not seen with mammography or ultrasound and may require CEM- guided biopsies.

14.0 Potential Benefits to Subjects*

14.1 CEM is known to have higher sensitivity for cancer detection than MG and US and may benefit the study patients by finding BC that were not previously seen on other imaging studies.

14.2 CEM may eliminate the need for breast MRI, which is a costly and time-consuming study that can delay treatment in BC patients.

14.3 The presence of a CEM-guided biopsy device can enable direct biopsy of CEM- only detected lesions without the need for breast MRI or breast MRI-guided biopsies.

15.0 Data Management* and Confidentiality

15.1 Statistical considerations

The primary objective of this study is to compare the accuracy of CEM and LE images (FFDM equivalent) for the detection of additional cancer sites in the affected breast and in the contralateral breast among patients with known BC diagnosed or highly suspicious at an outside facility and presenting to MD Anderson for staging imaging. The images of CEM/LE and DBT for each patient will be read/reviewed by 5 radiologists, and the majority agreement among 5 radiologists on the lexicon and BI-RADS assessment will be used for consensus. If all 5 radiologists disagree, then a consensus conference will be held. Pathology results will be considered the ground truth. Breast tissue lesions will be categorized as positive if determined as invasive cancer or DCIS, and otherwise will be categorized as negative that includes the lesions of uncertain malignant potential without subsequent surgical upgrade to invasive cancer or DCIS.

The primary outcome of this study is accuracy determined by comparing the CEM/LE results to that of the pathologic evaluations. Specifically, it is defined as the number of concordant cases between CEM/LE and pathologic evaluation divided by the total sample size. Secondary outcomes include sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV). Sensitivity (specificity) is defined as the number of correctly diagnosed positive (negative) cases divided by the total number of confirmed positive (negative) cases, NPV is defined as the number of true negative lesions obtained from CEM/LE divided by the corresponding total predicted number of negative lesions. The PPV is similarly defined for positive breast lesions. Cancer detection rate is defined as number of invasive malignancy or DCIS divided by the total sample size.

A successful CEM guided biopsy is defined as a biopsy which successfully sampled the abnormality in question. This procedure will be considered feasible if 95% patients or more have successful CEM guided biopsy among those who will undergo this procedure, which is similar to the success rate of the prone stereotactic vacuum assisted biopsies [41].

15.2 Sample size

In two recent studies, the authors reported the accuracies of 78.0% (versus 69.0% for MG) [35] and 79.8% (versus 65.3% for MG) [36], respectively. We utilize these clinical evidences for our sample size justifications. Using a two-sided extended McNemar test with a significance level of 0.05, a sample size of 83 patients provides 80% power to detect an accuracy difference of 12% between the two modalities of CEM and FFDM assuming the discordant of 20%. The method proposed by Wu (2018) was used to calculate the sample size, where the multiple lesions were adjusted via the average number of lesions and the variance that were assumed to be 1.4 and 1, respectively [37]. We further assumed the intracluster correlation of 0.4, and 0.2 for the intracluster correlation of the discordant pairs.

15.3 Statistical analysis plan

Descriptive statistics will be used to summarize clinical variables of interest. Specifically, categorical measures will be summarized using frequencies and percentages and continuous measures will be summarized using means, standard deviations, medians, and ranges. Outcome variables of cancer detection rate, accuracy, sensitivity, specificity, PPV, and NPV will be estimated along with 95% confidence intervals; and compared between the modalities using the McNemar test or the weighted generalized score statistic proposed by Kosinski [38], if deemed appropriate . To account for multiple lesions, outcome variables will be analyzed using generalized liner mix models or extended McNemar's test [39-41], and additional analyses may be further performed if deemed appropriate.

16.0 Provisions to Protect the Privacy Interests of Subjects

Identifiers (name, medical record number) will be collected but will be replaced by study numbers in the analytical file. Scan/report dates will also be collected as part of this study, in order to identify different scans from the same patient. The key linking these numbers will be retained in a restricted database by the investigator. All study personnel have completed training in methods for maintaining the confidentiality of health information. Electronic records will be stored on password protected institution computers behind the institution firewall. Only the PI and research staff involved in the study will have access to this data. Complete confidentiality will be maintained during this retrospective evaluation, manuscript preparation, and submission.

Study sponsors and/or supporters receive limited amounts of PHI. They may also view additional PHI in study records during the monitoring

process. MD Anderson's contracts require sponsors/supporters to protect this information and limit how they may use it

17.0 Compensation for Research-Related Injury

17.1 The research involves only minimal risk to subjects. The patients will not be compensated for their participation.

18.0 Economic Burden to Subjects

18.1 The patients are not expected to encounter out of pocket costs. The cost of the imaging and IV contrast for the study is expected to be covered by a combination of insurance, GEIK grant, and an internal DICRC grant. The costs of biospecimen collection, questionnaire administration, and data storage will be covered by the Little Green Book Foundation.

19.0 Resources Available

19.1 A full-field digital mammography system capable of providing low- and high-energy exposures to the breast under the same compression, as well as producing subtracted contrast images, such as Senographe Pristina (GE Healthcare, Buc, FR)

19.2 A CEM- guided biopsy device (GE Healthcare, Buc, FR) is planned to be installed in November 2020

19.3 %FTE is requested for a dedicated clinical mammography technologist and a clinical study coordinator

19.4 Approximately 5-8 patients per day are seen in the multidisciplinary clinic for staging of BC diagnosed at OSF. This results in a minimum of 1,305 potentially eligible patients. Recruiting 6% of the eligible pool, or 2 patients per week will allow completion of recruitment within 12 months.

20.0 Multi-Site Research*

N/A

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