### Title

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# Differentiation of Ductal Carcinoma In-Situ from Benign Micro-Calcifications by Dedicated Breast Computed Tomography

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## Abstract

**Purpose—**Compare conspicuity of ductal carcinoma in-situ (DCIS) to benign calcifications on unenhanced (bCT), contrast-enhanced dedicated breast CT (CEbCT) and mammography (DM).

**Methods and Materials—**The institutional review board approved this HIPAA-compliant study. 42 women with Breast Imaging Reporting and Data System 4 or 5 category micro-calcifications had breast CT before biopsy. Three subjects with invasive disease at surgery were excluded. Two breast radiologists independently compared lesion conspicuity scores (CS) for CEbCT, to bCT and DM. Enhancement was measured in Hounsfield units (HU). Mean CS ± standard deviations are shown. Receiver operating characteristic analysis (ROC) measured radiologists' discrimination performance by comparing CS to enhancement alone. Statistical measurements were made using ANOVA F-test, Wilcoxon rank-sum test and robust linear regression analyses.

**Results—**39 lesions (17 DCIS, 22 benign) were analyzed. DCIS (8.5±0.9, n=17) was more conspicuous than benign micro-calcifications (3.6±2.9, n=22; $p<0.0001$) on CEbCT. DCIS was equally conspicuous on CEbCT and DM (8.5±0.9, 8.7±0.8, n=17; $p=0.85$) and more conspicuous when compared to bCT (5.3±2.6, n=17; $p<0.001$). All DCIS enhanced; mean enhancement (90HU

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**Conflict of Interest**

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±53HU, n=17) was higher compared to benign lesions (33 ±30HU, n=22)(p<0.0001). ROC analysis of the radiologists' CS showed high discrimination performance (AUC=0.94) compared to enhancement alone (AUC=0.85) (p<0.026).

**Conclusion—**DCIS is more conspicuous than benign micro-calcifications on CEbCT. DCIS visualization on CEbCT is equal to mammography but improved compared to bCT. Radiologists' discrimination performance using CEBCT is significantly higher than enhancement values alone. CEbCT may have an advantage over mammography by reducing false positive examinations when calcifications are analyzed.

## Introduction

Distinguishing benign from malignant calcifications can be challenging due to overlap of imaging features. Core biopsy is often required to establish a definitive diagnosis. Although approximately 90% of ductal carcinoma in-situ (DCIS) is detected as micro-calcifications [1], mammographic features of micro-calcifications alone cannot predict presence of DCIS [2]. Nearly two-thirds of biopsies of micro-calcifications are benign [3]. False positive findings lower positive predictive values (PPV) of biopsy of micro-calcifications in cancer detection and come at a high cost both to the patient and the health care system[4, 5]. Although screening mammography remains the only modality demonstrated to reduce death from breast cancer, 70–80% of biopsies performed for suspicious mammographic findings (masses and calcifications) are benign [6, 7]. These shortcomings have led to studies of other imaging modalities with the goal of improving the current benchmarks of mammography.

Dedicated breast CT (bCT) has been proposed as a fully three-dimensional modality that could potentially improve detection of breast cancer and reduce the number of false positive imaging evaluations and biopsies. In an initial study, unenhanced dedicated breast CT was superior to mammography for visualization of breast masses due to the reduction in the masking effect from surrounding tissue[8]. Calcifications, both benign and malignant, however, were not as well seen on unenhanced bCT as on mammography, leading to questions about the ability of dedicated bCT to identify DCIS. A later study of contrast-enhanced dedicated bCT, in which the definition of conspicuity included the visibility of an area of enhancement, demonstrated significantly increased conspicuity of 22 malignant masses compared to mammography and equal conspicuity of 5 cases of malignant micro-calcifications on enhanced bCT and mammography[9].

The utility of dedicated breast CT is dependent on its ability to detect and diagnose both invasive and in situ breast cancers. With promising preliminary studies of DCIS detection by contrast-enhanced bCT, we undertook this study to compare benign and malignant micro-calcifications without other associated findings on contrast-enhanced dedicated breast CT. In this study, we hypothesize that CEbCT can accurately detect DCIS and distinguish it from benign causes of micro-calcifications when compared with non-contrast bCT and mammography.

## Materials and Methods

Women with micro-calcifications categorized as Breast Imaging Reporting and Data System (BI-RADS) 4 or 5 by mammography (1 screen-film, 41 digital) were recruited and prospectively enrolled in our Health Insurance Portability and Accountability Act-compliant study. Subject recruitment and studies were performed in accordance with protocols approved by our institutional review board. Written informed consent was obtained from all participants prior to the study. Patients with other findings such as architectural distortion or mass associated with the micro-calcifications on mammographic workup were not included in the final analysis. Subjects with contraindications to the use of intravenous contrast material were excluded from the study. All study participants had mammography, unenhanced and contrast enhanced dedicated breast CT. All subjects underwent image-guided core biopsy immediately following the breast CT scan. Only lesions with known final histopathology were included in the study. Of the 42 lesions analyzed, 5 cases of DCIS were previously reported in a pilot study comparing conspicuity of suspicious breast lesions on bCT, CEbCT and mammography[9]. Breast density was defined at mammography according to BI-RADS (4$^{th}$ edition) criteria.

### Image Acquisition

Subjects were imaged using a prototype dedicated breast CT system previously reported [10, 11]. Images were acquired using a tube voltage of 80 kV. The tube current was adjusted according to breast size and mammographic breast density while keeping the mean glandular radiation dose equivalent to that of two-view screening mammography. Each breast was scanned individually in the pendant position. The duration of each acquisition was 17 seconds during which the subject was instructed to hold her breath. Breast compression was not utilized. Participants were instructed to remain still upon completion of the non-contrast scan of the affected breast, while one hundred milliliters of intravenous iodixanol (Visipaque 320; GE Healthcare, Waukesha, WI) was administered at a rate of 4 mL/sec using a power injector. The affected breast was re-scanned approximately 90 seconds after the start of the injection. The unaffected breast was scanned subsequently as well. CEbCT images were acquired at an average of 110 s (range 70–272 s) following contrast injection.

### Lesion Conspicuity Analysis

To compare mammography, unenhanced and contrast enhanced bCT, a conspicuity score (CS) for each histologically proven lesion was assigned for each modality by 2 independent observers. Craniocaudal and mediolateral oblique mammographic views, bCT and CEbCT were independently reviewed by two dedicated breast imaging radiologists, each with at least 5 years of experience using dedicated breast CT. For the breast CT images, a custom-designed image viewer allowed viewing of three orthogonal planes simultaneously. A training set of mixed cases of benign and malignant lesions was used to familiarize the readers with the study protocol and standardize readings. Unenhanced breast CT images were reviewed first followed by review of CEbCT images and then mammograms. Readers were unaware of the biopsy results at the time of reading. The conspicuity of each lesion was scored on a continuous scale from 0 to 10, where 0 represents non-visualization and 10

refers to excellent conspicuity; this rating method was used for each imaging modality independently. Conspicuity scores of lesions on mammography and unenhanced bCT were based on the visibility of the micro-calcifications. For lesions seen on CEbCT, the conspicuity score represents visibility of the micro-calcifications as well as any enhancement of the lesion. As such, the conspicuity score of a lesion on CEbCT represents the visibility of abnormal lesion enhancement and may therefore be considered as a marker to determine probability of malignancy. This is the basis for receiver operating characteristic (ROC) analysis of the conspicuity scores from breast CT images.

### Quantitative Lesion Enhancement Analysis

CEbCT and bCT images were analyzed using the methods of Prionas et.al[12]. Lesions were identified and outlined manually on the pre and post contrast images, using a graphical user interface (MATLAB 7.8 with Image Processing Toolbox 4.2; Math-Works, Natick, Mass). Mean voxel intensity in Hounsfield units and standard deviations were measured for each outlined lesion. Window and level settings were held constant at 350 HU and 25 HU respectively. For each breast, background adipose enhancement was also measured using 4 square regions of interest throughout the breast volume. The mean adipose tissue intensity was used to normalize lesion intensity and account for any fluctuations between image acquisition and contrast delay times. Lesion enhancement was calculated as the difference between normalized lesion intensity in the pre- and post- contrast image: $\Delta HU = (HU_L^{Post} - HU_A^{Post}) - (HU_L^{Pre} - HU_A^{Pre})$ where L is the lesion intensity and A is the adipose intensity measured in the pre-contrast (Pre) and post-contrast (Post) image set. Using enhancement as a marker for probability of malignancy, ROC analysis was performed.

### Statistical Analysis

Univariate statistical summaries were performed with calculation of mean conspicuity scores of each lesion for each modality. Data are shown as mean conspicuity scores ± standard deviation. The two-sided paired *t*-test or Wilcoxon signed-rank test was used when appropriate, to compare conspicuity between two modalities. The repeated measures ANOVA *F*-test was used for comparison of conspicuity among the three modalities- CE-bCT, bCT and mammography. For each modality, robust linear regression[13] was used to study the relationship between the outcome variable (conspicuity score) and each of the explanatory variables (age, lesion size, and breast density). The Kruskal-Wallis test was used to study the association between lesion conspicuity and malignant tumor grade. All analyses were performed with SAS v9.2 (Cary, NC).

ROC analysis of radiologist's conspicuity scores used the proper binormal model with area under the curve (AUC) as the study endpoint. Statistical analysis was conducted using the OR-DBM MRMC software (Version 2.5) available from the University of Iowa [14–18]. Analysis was performed on the 39 cases (17 malignant and 22 benign) for which complete reader data was available for both radiologists. Readers were considered a fixed effect because of the limited number available for analysis. Thus our results generalize to the population of cases for the two readers considered in the study. A mixed effects ANOVA model (modalities and readers as fixed effects, cases as a random effect) was used to evaluate the significance of AUC for CE-bCT. As a check, we also conducted an analysis of

each reader separately using a non-parametric ROC model implemented in the iMRMC software [19].

Nonparametric ROC analysis was also used to compare the discrimination performance of enhancement alone to the average performance of radiologists using CEbCT images. For this comparison, 10,000 bootstrap resamples within malignant and benign cases were used to assess the significance of the difference between the average reader AUC and the AUC from measured enhancement in the images.

## Results

A total of 42 patients with BI-RADS 4 or 5 micro-calcifications were recruited. All patients were women with an average age of 55 years (age range 40–71 years).

Core biopsy of the 42 suspicious micro-calcifications yielded 18 DCIS, 21 benign and three atypical ductal hyperplasia (ADH) diagnoses. Two of the three ADH lesions were upgraded to DCIS and the third remained ADH (benign) at final surgical excision. Three of the 18 patients with DCIS on core biopsy had invasive disease on final histopathology and were subsequently excluded from the study leaving a final cohort of 39 patients including 17 with pure DCIS and 22 with benign diagnoses.

On mammography, 14 out of 17 (82%) participants with DCIS and 14 out of 22 (64%) with benign micro-calcifications had heterogeneously dense or dense breast parenchyma. All others had scattered fibroglandular tissue or fatty replaced breast parenchyma. Average lesion dimensions on mammography for DCIS and benign calcifications were 9 mm (2–26mm) and 8 mm (3–17mm) respectively. There were 8 high-grade, 8 intermediate grade and 1 low-grade DCIS lesions.

DCIS lesions (8.5 ±0.9, n=17) were more conspicuous than benign micro-calcifications (3.6 ±2.9, n=22) on CEbCT with high statistical significance ($p<0.0001$). For both mammography and unenhanced bCT, there was no significant difference in the conspicuity of benign and malignant micro-calcifications. Among the three modalities, benign micro-calcifications were significantly better seen on mammography (8.9 ±0.6 for DM, n=22) ($p<0.0001$) than on either unenhanced (2.7 ±2.8, n=22) or contrast-enhanced breast CT (3.6 ±2.9, n=22) (p=NS), both of which performed similarly (Table 1).

When comparing modalities, DCIS lesions were equally conspicuous on CEbCT (8.5 ±0.9, n=17) and mammography (8.7 ±0.8, n=17, $p=0.85$), both of which were superior to unenhanced bCT (5.3 ±2.6, n=17, $p<0.001$) (Figures 1 & 2). All DCIS enhanced on CEbCT. The mean enhancement value was 90 ±53 HU for malignant calcifications and 33 ±30 HU for benign calcifications ($p<0.0001$).

No correlation was found between patient age, lesion size or breast density and conspicuity of benign or malignant calcifications on any of the three imaging modalities. No significant correlation was found between DCIS tumor grade and lesion conspicuity on mammography, bCT or CEbCT, although the number of cases in each grade was small.

Results of the ROC analysis are shown in Figure 3. Fitting the PROPROC model to the reader conspicuity scores for the CEbCT images shows high discrimination performance (Figure 3A) for both readers (Reader 1: AUC = 0.98 ± 0.022; Reader 2: AUC = 0.92 ± 0.042). The reader average (AUC = 0.95 ± 0.026) is significantly different from chance performance ($H_0$: AUC = 0.5; $p < 0.0001$). The single-reader analysis using empirical ROC curves finds a significant difference from chance performance for both readers (AUC = 0.97 ± 0.018 and 0.92 ± 0.041; $p < 0.0001$ in both cases). Both results are considered significant when multiple comparisons are accounted for using a Bonferroni correction.

The empirical ROC curve using lesion enhancement measurements is significantly greater than chance (AUC = 0.85 ± 0.053). Comparison of the AUC from measured lesion enhancement to the average AUC of the two readers are shown in Figure 3B. Performance was significantly higher for the radiologists compared to the enhancement values alone (AUC of 0.94 compared to 0.85, $p < 0.026$).

## Discussion

### All DCIS enhanced on CEbCT

On average DCIS lesions enhanced nearly 60 HU more than the benign micro-calcifications. Previously, we reported a similar pattern of differential enhancement of benign and malignant lesions on CEbCT that included both masses and calcifications. With this study, we show that enhancement values of DCIS represented by malignant calcifications are significantly higher than those of benign micro-calcifications. Benign calcifications did not enhance or showed a significantly lower enhancement than DCIS lesions. DCIS lesions even as small as 2 millimeters in diameter were visualized equally on contrast-enhanced breast CT and mammography. Benign calcifications were significantly less conspicuous on CEbCT than on mammography. CEbCT may have an advantage over mammography by reducing false positive examinations when calcifications are analyzed, thus leading to a reduction in benign biopsies.

Micro-calcifications, whether benign or malignant, are indiscriminately visualized with mammographic technique. Elucidation of the morphology and distribution of micro-calcifications is necessary for appropriate categorization, often requiring biopsy to distinguish benign from malignant lesions due to the overlap of their features. The enhancement differential of DCIS and benign micro-calcifications on CEbCT suggests that biopsy may not always be necessary to distinguish the two categories if CEbCT is utilized. CEbCT may be a useful tool for diagnostic evaluation as an aid to decide whether a lesion should be biopsied based on its enhancement. Enhancing lesions on CEbCT would be recommended for biopsy thus potentially diminishing short-interval follow up for probably benign (BI-RADS category 3) lesions. Non-enhancing lesions could potentially undergo surveillance in place of biopsy, thus increasing biopsy PPV. A 50% reduction in false positives would increase the biopsy PPV by about 50%.

In this study, we compared contrast enhanced dedicated breast CT to unenhanced breast CT as well as conventional mammography, the gold standard for routine clinical evaluation of micro-calcifications. Newer imaging modalities utilizing contrast material such as contrast-

enhanced mammography (CEM) and magnetic resonance imaging (MRI) have been developed and also compared to standard mammography. Studies of DCIS with CEM have been limited to date. More recently, a retrospective study of BI-RADS 4 micro-calcifications has shown promising results supporting the utility of CEM in the evaluation of calcifications. In addition to allowing for mammographic evaluation of the calcifications, CEM also provides enhancement information[20]. While early studies have suggested that CEM may be useful in replacing MRI for certain indications, the role of CEM in the clinical setting is still unclear [21, 22]. Breast MRI is now an integral part of breast imaging for specific indications. In a recent study, MRI was reported to increase the PPV of BI-RADS category 4 lesions helping to avoid benign biopsies. However, MRI workup of mammographic micro-calcifications was associated with a 12% false-negative rate due to lack of enhancement of low-grade DCIS lesions[23]. In our study, 100% of DCIS lesions of all grades including low-grade, enhanced on CEbCT. In comparison to MR, breast CT has significantly higher spatial resolution. The voxel volumes at breast CT are on the order of 20–500 times smaller than those at breast MR imaging[12]. Moreover, breast images are obtained much faster with bCT than with MRI and bCT is likely to be much less expensive. Future comparison studies of CEbCT to other imaging modalities using contrast such as MRI are warranted.

An early study of non-contrast enhanced dedicated breast CT showed decreased conspicuity of micro-calcifications in comparison to mammography[8]. In our study, the ROC performance of CEbCT images suggests that contrast enhancement adds significant information for discriminating malignant and benign lesions for the radiologists who participated in the study. The radiologists performed significantly better than the enhancement values alone. This result reflects the radiologists' use of both enhancement as well as the morphology and distribution characteristics in their conspicuity scores.

Our study has limitations. It is based on a small number of subjects with matched modality comparisons. To keep radiation doses low, no dynamic information was collected to evaluate lesion kinetics on CEbCT. DCIS kinetic behavior has been extensively studied on other modalities such as dynamic contrast-enhanced breast MRI [1, 24] and has been shown to be quite variable. The average contrast delay time of approximately 100 seconds in our study coincides with the earliest post-contrast sequences typically obtained in MRI. One study suggests that time to peak enhancement of DCIS lesions is approximately 200 seconds[25]. While a majority of DCIS lesions are seen at these early time points, there is variability of the timing and rate of contrast-enhancement of DCIS [26]. While the overall trend of DCIS kinetic curves is likely similar for breast CT and MRI, there may be differences in optimal imaging timing post-contrast injection, given differences between iodine and gadolinium based contrast materials. Further investigation of optimum contrast timing for breast CT is underway.

Another limitation of our study is the subjective scoring of lesion conspicuity on the three modalities by the two readers. The readers were involved in patient recruitment, therefore there is potential for recall bias. Additionally, since abnormal findings on clinical mammography triggered subject recruitment, there is potential for bias favoring mammography when modalities are compared.

In summary, conspicuity of DCIS on CEbCT is similar to mammography. We have shown that malignant micro-calcifications due to DCIS show significantly greater enhancement and conspicuity than benign calcifications on CEbCT. CEbCT provides quantitative data that may be useful for differentiating DCIS from benign micro-calcifications. Although randomized, blinded, multi-centered trials with a larger number of participants are needed; the results of this investigation show a promising role for contrast-enhanced breast CT in the diagnosis of early stage breast cancer.

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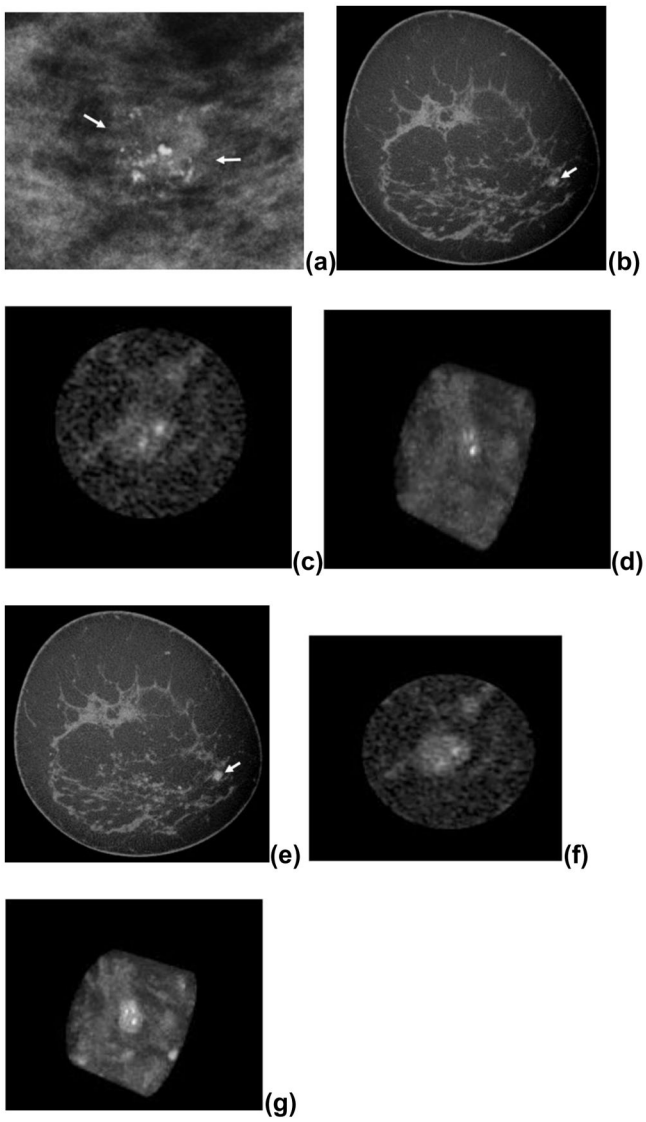
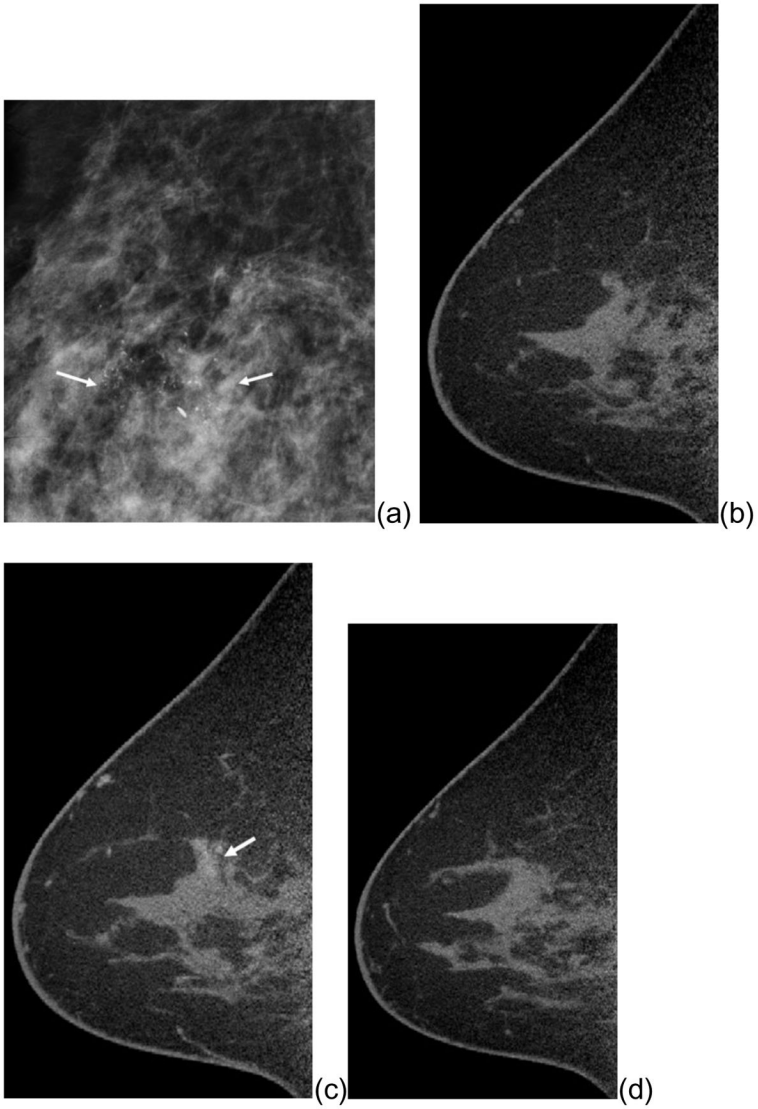



**Figure 1.**

Micro-calcifications shown to be a 5mm focus of high nuclear grade DCIS (arrows) are shown on a MLO magnification mammogram (a). The coronal unenhanced bCT (b) shows the calcifications (arrow), which were given a mean conspicuity score of 8; ROI-reconstruction in coronal view (c), cut out view of 3-D MIP of ROI (d). The corresponding enhanced coronal bCT (e) shows an enhancing 5mm lesion (arrow) at the site of the calcifications mean conspicuity score of 9.5; ROI-reconstruction in coronal view (f), cut out view of 3-D MIP of ROI (g).



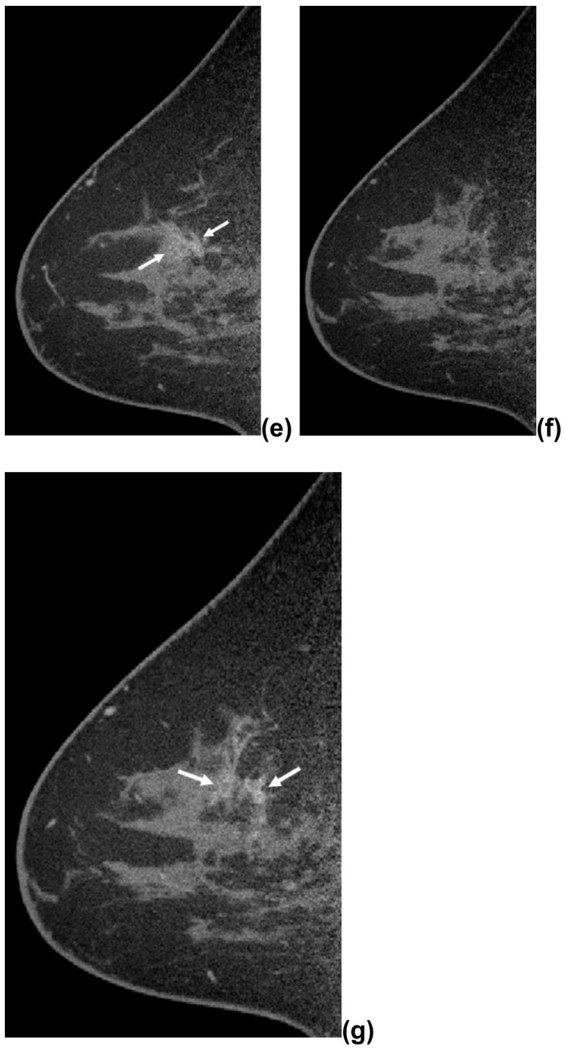



**Figure 2.**

Ductal Carcinoma in Situ, intermediate nuclear grade, is shown on a magnification MLO mammogram (a) as a 17mm area of pleomorphic micro-calcifications (arrows). The calcifications were not seen on unenhanced bCT sagittal reconstruction images (b,d,f). After contrast administration sagittal bCT images show an irregular 21 mm area of non-mass enhancement (arrows) in the upper outer quadrant of the right breast (c,e,g). The mean conspicuity score for the contrast-enhanced images was 9.0.

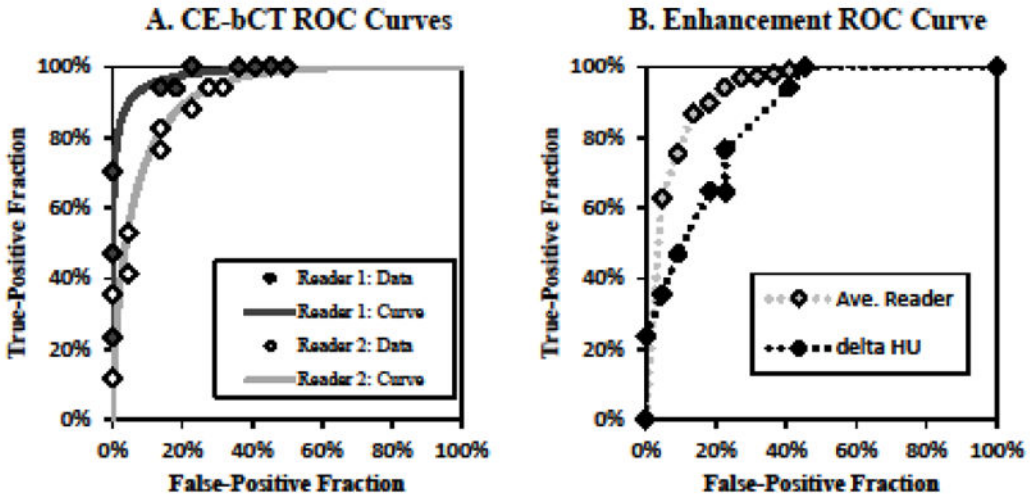



**Figure 3.**

ROC performance plots for CE-bCT (A) are shown for Reader 1 and Reader 2. The plots show both the points associated with the raw conspicuity data as well as the fitted proper binormal curves. Empirical ROC curves (B) averaged for the two readers are compared to the curve generated from the measured enhancement values (delta HU).

## Table 1
### Conspicuity of micro-calcification lesions by modality

Benign micro-calcification and DCIS lesions are equally visualized on mammography and non-contrast CT. On CEbCT, DCIS is significantly more conspicuous than benign micro-calcification lesions. DCIS conspicuity scores (CS) are not significantly different for CEbCT and mammography (DM) (p=0.85) both of which are higher than bCT (p<0.001). Benign micro-calcifications have higher CS on mammography than the other 2 modalities (p<0.0001). CS of benign calcifications are not different on bCT and CEbCT (p=0.11).

| | DCIS | Benign | p-value |
|---|---|---|---|
| **bCT CS±SD (n)** | 5.3 ± 2.6 (17) | 2.7 ± 2.8 (22) | 0.0052 |
| **DM CS±SD (n)** | 8.7 ± 0.8 (17) | 8.9 ± 0.6 (22) | 0.2335 |
| **CEbCT CS±SD (n)** | 8.5 ± 0.9 (17) | 3.6 ± 2.9 (22) | <0.0001 |