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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 ± 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.

1. 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

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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.

2. 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 (4th edition) criteria.

2.1. 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 s 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 s 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.

2.2. 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.

2.3. Quantitative lesion enhancement analysis

CEbCT and bCT images were analyzed using the methods of Prionas et al. [9] 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.

2.4. 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 [12] 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).

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