Diffusion-Weighted MRI: Influence of b-value and lesion characteristics on conspicuity of mammographically-occult invasive breast cancer in women with dense breasts

Purpose:

Women with increased breast density are at elevated risk for breast cancer, independent of other risk factors. While dynamic contrast-enhanced (DCE) MRI is the gold standard for identification of cancer in dense breasts, high costs and safety concerns associated with gadolinium contrast preclude its use for routine screening. As such, there is a critical need for a safe, effective, low cost screening method in this population. Diffusion weighted imaging (DWI), a rapid non-contrast MRI technique, has shown promise for the detection and characterization of breast cancer. We sought to evaluate DWI conspicuity of invasive breast cancers in women with dense breasts and to determine whether b-value and lesion characteristics affect visibility.

Materials and Methods:

After IRB approval, we retrospectively evaluated all mammographically-occult invasive malignancies detected on MRI between January 2014 and August 2015 in women with dense breasts, defined as at least heterogeneously dense on mammogram. Breast MR examinations included multi-b value (0, 100, 600, 800 and 1000 sec/mm²) DWI and DCE sequences. As a quantitative measure of lesion conspicuity, contrast-to-noise ratio (CNR) between lesion and normal fibroglandular tissue signal on DWI was measured at each b-value. CNR was compared between b-values by Wilcoxon signed rank test, and between lesion groups (based on histology, morphology, and size) by Wilcoxon rank sum test.

Results:

Over the study period, 25 mammographically-occult invasive cancers (22 ductal; 3 lobular) were detected on MRI in 23 women with dense breasts (median age=58). Lesion sizes ranged from 4 to 83mm (median=12mm). On DWI, 24/25 lesions exhibited higher signal intensity than normal tissue (CNR>0) at b≥600 sec/mm². No significant differences in lesion CNR were observed based on histology (ductal versus lobular), morphology (mass versus NME) or size (<1cm versus ≥1cm), p>0.05. CNR increased significantly with increasing b-value (p<0.05), reaching the highest levels at b=1000 sec/mm² (median CNR, 2.5; range, 0-5.5).

Conclusion:

Mammographically-occult invasive cancers exhibited higher signal intensity on DWI than normal fibroglandular tissue in women with dense breasts (CNR>0). Lesion contrast on DWI was not significantly...
affected by lesion characteristics (histology, morphology or size), but progressively increased with b-value over the range 0-1000 sec/mm².

Clinical Relevance Statement:

Our study shows that non contrast enhanced DWI can distinguish mammographically-occult cancers in women with dense breasts, with improved lesion conspicuity at a higher b-value of 1000 sec/mm².

Authors
Corresponding: Savannah Partridge (University of Washington)

Tamara Carroll (University of Wash), Averi Kitsch (University of Washington), Habib Rahbar (University of Washington), Savannah Partridge (University of Washington)

Role of Diffusion Weighted Imaging in Predicting Pathologic Response to Neoadjuvant Chemotherapy in Breast Cancer Subtypes

Purpose: It is controversial if baseline MRI diffusion weighted imaging (DWI) is predictive of pathologic complete response (pCR) to neoadjuvant chemotherapy (NAC) in breast cancer patients. There are very few studies evaluating the use of normalized apparent diffusion coefficient (ADC) in this scenario. We investigated DWI performance with normalized ADC values in predicting pCR in different breast cancer subtypes.

Materials and Methods: We retrospectively studied 88 patients who had breast MRI with DWI prior to NAC followed by breast surgery. Regions of interest were drawn on ADC maps and normalized ADCs were calculated as tumor ADC divided by normal glandular tissue ADC. The pathologic response was classified into either pCR or no pCR. The relationship between both absolute and normalized ADCs and pathologic response to NAC was evaluated for overall population and within each tumor subtype and area under the curve (AUC) statistics were calculated.

Results: The tumor subtypes were luminal (n=57; 65%), human epidermal growth factor receptor 2 (HER2)-enriched (n=15; 17%), and triple-negative (n=16; 18%). Twenty four patients (27%) had pCR. pCR was significantly higher in HER2-enriched (6/15; 40%) and triple-negative (9/16; 56%) subtypes than luminal subtype (9/57; 16%) (p=0.003). No statistically significant difference was observed between the mean of absolute or normalized ADCs in patients with pCR versus no pCR in overall population (p=0.2 and p=0.07 for absolute and normalized ADCs, respectively). After stratifying the patients by subtype, we detected significant difference between the mean of normalized ADCs in patients with pCR versus no pCR within the triple-negative subtype (0.52 versus 0.78; p=0.01, AUC=0.78) and HER2-enriched subtype (0.44 versus 0.58; p=0.04 AUC=0.69), but no significant difference between normalized ADCs of pCR and no pCR within the luminal subtype (0.58 versus 0.56; p=0.42). Although the absolute ADCs in the triple-
negative and HER2-enriched subtypes showed similar trend of lower values for pCR versus no pCR, the differences were not statistically significant (p>0.05).

Conclusion: Pretreatment DWI may be predictive of pathologic response to NAC in triple-negative and HER2-enriched subtypes of breast cancer, but not in luminal subtype. Normalizing ADC values enhances this predictive value of DWI.

Clinical Relevance Statement: Maximizing the benefits of baseline DWI by normalizing ADC values may help predict response to NAC in triple-negative and HER2-enriched subtypes of breast cancer. In the future, this may improve the ability to individualize therapies in breast cancer patients, avoiding unnecessary chemotherapy.

Authors
Corresponding: Maryam Etesami (Case Western Reserve University, University Hospitals Case Medical Center)

Maryam Etesami (Case Western Reserve University, University Hospitals Case Medical Center), Cheryl Thompson (Case Western Reserve University, University Hospitals Case Medical Center), Christina Dubchuk (Case Western Reserve University, University Hospitals Case Medical Center), Anastasia Dines (John Carroll University), Donna Plecha (Case Western Reserve Univerisy, University Hospitals Case Medical Center)

Quantitative MR Imaging Biomarkers to Evaluate Response of Breast Cancer to Neoadjuvant Chemotherapy

Purpose: Objective is to assess breast tumor response to neoadjuvant chemotherapy (NACT) using imaging biomarkers that quantify tumor heterogeneity on MRI and further correlate these metrics with pathological response (pR) and 5-year disease free survival (DFS).

Materials and Methods: 82 biopsy proven breast cancers were evaluated from baseline and post-NACT MRI and compared with the pR (complete or significant pathological response [pCR] = tumor loss > 90% vs partial or no response [non-pCR]) and DFS. A breast-imaging radiologist segmented the cancer on pre- and first post-contrast images of baseline and post-NACT MR in the 3D Slicer software. 57 metrics that quantify the shape, morphology, distribution statistics, geometry and texture were obtained for each cancer using the HeterogeneityCAD module in 3D Slicer. Statistical correlation of the pR was performed with the % change in metrics evaluated from baseline and post-NACT MRI on pre- and post-contrast MRI using the Mann-Whitney test. Statistical analysis was performed for subgroups according to the receptor
status. The metrics were also correlated to DFS. A Support Vector Machine (SVM) algorithm was trained (80% of the samples) and tested (20% of samples) to predict the pR.

Results: Percentage change in 44/57 metrics on pre-contrast and 43/57 metrics on post-contrast MRI showed significant difference between the pCR and non-pCR groups (p<0.05), as shown in the box plot (red: pCR and blue: non-pCR). In the molecular subgroups, % change in metrics that correlated with pR were: ER-, HER2+ group: max 3D diameter; luminal, HER2-: none; luminal, HER2+: 9/57 metrics; triple - : 43/57 metrics. LRE (a metric that quantifies distribution of long-run lengths and coarse textural structures) showed 91.0% mean change in the disease free group and 27.2% in the group with recurrence, and a strong correlation with DFS (p<0.05). The SVM predicted pR with an accuracy of 81%.

Conclusion: We found correlation with multiple MR heterogeneity metrics to pathological response and strong correlation of LRE with 5-year disease-free survival. Imaging biomarkers could be useful to predict NACT outcome in breast cancer patients.

Acknowledgements: P41EB015898 and P41RR019703

Clinical statement: Patients who achieve pathological complete response after NACT have better prognosis compared to patients who show incomplete response. It is critical to evaluate the treatment response of tumors at an early stage. Quantitative imaging biomarkers could potentially be utilized to identify and predict pathological response of breast tumors to NACT.

Authors
Corresponding: Jagadeesan Jayender (Brigham and Women's Hospital, Harvard Medical School)

Ruth Morais Bonini (Hospital de Cancer de Barretos), Eva Gombos (Brigham and Women's Hospital, Harvard Medical School), Clara Meinzer (Semmelweis Universität), Judy Garber (Dana Farber Cancer Institute, Harvard Medical School), Jagadeesan Jayender (Brigham and Women's Hospital, Harvard Medical School)

Prognostic Significance of transverse relaxation rate (R2*) in Blood Oxygenation Level-Dependent Magnetic Resonance Imaging in Patients with Invasive Breast Cancer

Clinical relevance: As tumor hypoxia is an important biological characteristic, hypoxia imaging may provide prognostic indicators for cancer therapy. BOLD-MRI is a leading candidate for an optimal imaging modality of hypoxia. However, pathophysiologic–imaging correlates and prognostic value of BOLD-MRI have not been well established in human invasive breast cancers.
Purpose: To examine the relationship between magnetic resonance transverse relaxation rate ($R2^*$) and well-established clinicopathological prognostic factors.

Materials and Methods: A total of 159 women with invasive ductal carcinomas (IDCs) underwent breast magnetic resonance imaging (MRI) including blood oxygenation level-dependent (BOLD) sequence at 3T. The distribution of the measured $R2^*$ values were analyzed, and the correlation between $R2^*$ and various prognostic factors (age, tumor size, histologic grade, lymphovascular invasion, and axillary lymph node status, as well as expression of estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2, p53, and Ki-67) were retrospectively assessed using patient medical records.

Results: The baseline $R2^*$ values of the IDCs were very heterogeneous. The mean $R2^*$ value was $(32.8 \pm 14.0)$ Hz with a median of 29.3 Hz (range 13.5–109.4 Hz). In multivariate analysis, only older age was associated with decreased $R2^*$ value ($P = 0.011$). Other prognostic factors were not significantly correlated with $R2^*$ value.

Conclusion: In this study, $R2^*$ values were not significantly correlated with most prognostic factors except for age. Further studies are necessary to determine the prognostic value of BOLD-MRI.

Authors
Corresponding: Seung Hee Choi (Gyeongsang National University Hospital)

Seung Hee Choi (Gyeongsang National University Hospital), Eun Sook Ko (Sungkyunkwan University School of Medicine), Hye Young Choi (Gyeongsang National University Hospital)

Background Parenchymal Enhancement Levels on MRI Reflect Metabolic Activity in Breast Tissue as Measured by 18F-FDG PET

Purpose

Recent research has shown that the amount of enhancement of the normal fibroglandular tissue (FGT) on breast MRI, known as background parenchymal enhancement (BPE), may be a marker of breast cancer risk and treatment outcomes. However, the biological basis of these emerging correlations of BPE levels with breast cancer is unclear. It has been hypothesized that breast tissue that exhibits higher levels of BPE may reflect a tissue microenvironment that is more metabolically active, possibly due to chronic inflammation. Thus, we aimed to investigate whether BPE levels correlate with metabolic activity by comparing standardized uptake values (SUV) on 18F-fluorodeoxyglucose (FDG) PET imaging with qualitative BPE categories.
Materials and Methods

In this IRB-approved prospective study, 34 women with locally advanced breast cancer (median age 43 yrs; range 31-66 yrs) underwent serial breast MR and FDG PET imaging during neoadjuvant chemotherapy treatment. Imaging characteristics of normal FGT in the contralateral breast were assessed at baseline and mid therapy: BPE was categorized according to BIRADS, mean SUV was calculated from FDG PET, Breast density was obtained from prior mammograms. Associations of BPE with SUV, and mammographic density were assessed by linear regression modeling and with tumor molecular markers (ER, PR, HER2, Ki67) and pathologic response by Wilcoxon rank sum test.

Results

At baseline, BPE levels were minimal in 26%, mild in 32%, moderate in 21%, and marked in 21%, normal FGT SUV values ranged from 0.101 to 1.863 (median, 0.924), and BPE levels were positively associated with SUV (Fig1, p<0.01). BPE was significantly lower in postmenopausal vs. premenopausal women (p<0.01), but was not significantly associated with breast density. Mid-therapy, the change in BPE with treatment was significantly correlated with change in SUV. Neither BPE nor SUV of normal FGT were significantly correlated with tumor molecular markers or pathological response (p>0.05).

Conclusion

Correlations between BPE and SUV levels in normal tissue suggest that BPE reflects increased metabolic activity in normal tissue that is associated with cancer risk. This study warrants further investigation of the biological properties that may create an environment susceptible to tumorigenesis and how these are reflected on imaging.

Clinical Relevance Statement

BPE is reflective of metabolic activity in normal breast tissue, which may provide valuable information for predicting cancer risk and response to therapy.

Acknowledgements

This study was funded in part by NIH/NCI grants P50 CA138293 and R01CA151326, an ISMRM 2013-2014 Seed Grant, and a gift from the Safeway Foundation.

Authors

Corresponding: Averi Kitsch (University of Washin)

Averi Kitsch (University of Washin), Habib Rahbar (University of Washington), Lanell Peterson (University of Washington), Larissa Korde (University of Washington), Jennifer Specht (University of Washington), Savannah Partridge (University of Washington)
Radiation Exposure to the Contralateral Breast Across Mammographic Modalities

Purpose:

The purpose of this study was to measure the amount of scatter radiation received by the contralateral breast during routine screening and diagnostic mammographic examinations.

Materials and Methods:

A single-use radiation dosimeter was used to measure ionizing radiation (InLight® nanoDotTM). Initial phantom data measured radiation from 0cm, the epicenter of the radiation field, up to 40cm (increased incrementally by 10cm). Cranio-caudal and medial-lateral oblique, with and without magnification views, were evaluated.

Patient data was obtained by placing a dosimeter on the medial and lateral aspect of the contralateral breast at the level of the nipple approximately half way between the nipple and the chest wall while patient was in the standing position during mammographic procedures.

Results:

Phantom data demonstrated between 5-7% and 2-3% of scatter radiation at 10 cm and 20cm from the epicenter of the radiation field, respectively. Negligible radiation was noted beyond 20cm.

During screening mammograms, patients with larger breast sizes (D cup and larger) received more scatter radiation to the medial aspect of the contralateral breast than patients with smaller breast sizes (A through C cup).

Conclusion:

There are currently no data that directly links low-dose ionizing radiation with a risk of future cancer. However, use of radiation should be conservative. The linear no-threshold (LNT) model suggests that ionizing radiation can cause cancer at any dose no matter how low. Our study demonstrates that scatter radiation received to the contralateral breast during screening mammograms is small but still present. Future studies will need to evaluate radiation exposure across multiple diagnostic evaluations and tomosynthesis. Subsequently, we plan to evaluate methods to reduce scatter radiation to the contralateral breast using modified breast shielding.

Authors
Corresponding: sergio dromi (University of Maryland)

sergio dromi (University of Maryland), Jessica Galandak (University of Maryland), Hannah Nien (University of Maryland), Gabrielle Messina (University of Maryland)
Radiologists' assessment of synthesized digital images as compared to FFDM in a screening practice

Purpose

Although synthesized 2D digital mammographic images (sDM) with 3D tomosynthesis as approved by the FDA decreases patient radiation compared to acquired 2D digital images (FFDM) and tomosynthesis, the lack of radiologists’ experience and outcomes reporting hinders its acceptance into clinical practice. Our study prospectively compares sDM and FFDM in a screening population.

Materials & Methods

This prospective IRB approved study includes 695 patients who underwent screening with FFDM and tomosynthesis (TM) on a Hologic Selenia Dimensions unit (C-View™ software) from 6/4/2015 – 9/8/2015. 46 were excluded due to incomplete imaging or assessments, leaving 649 studies. During mammographic interpretation, breast imagers prospectively assessed how sDM images compared to FFDM using a five-point Likert scale: sDM superior to FFDM; sDM better than FFDM; sDM equal to FFDM; FFDM better than sDM; and FFDM superior to sDM. For cases with specific findings, up to two findings of mass, calcifications, architectural distortion (AD) and/or asymmetry (AS) were scored using a similar Likert scale. The order images were viewed first alternated by odd/even calendar days. BI-RADS®0 outcomes were recorded.

Results

Of the 649 screening studies, there were 392(60.4%) BI-RADS®1; 203(31.3%) BI-RADS®2 and 54(8.3%) BI-RADS®0. Ten biopsies were performed and three were malignant (2 DCIS, 1 invasive). One false negative exam was identified.

Of the 392 BI-RADS®1 cases, sDM was equivalent to FFDM in 339(86.5%), better than FFDM in 10(2.6%) and worse than FFDM in 43(10.9%). For the 49 BI-RADS®2 and 0 cases with no specific findings, sDM was equivalent in 37(75.5%), better in 3(6.1%), and worse in 9(18.4%). In 208 cases with 285 findings, sDM was equivalent to FFDM in 130(45.6%) - 62(21.8%) masses, 42(14.7%) calcifications, 5(1.8%) AD, and 21(7.4%) AS. FFDM was better than sDM for 92(32.3%) findings, in particular, 40(14.0%) masses and 38(13.3%) calcifications, while sDM was better for 63(22.1%) findings, specifically 46(16.1%) calcifications. “Pseudo-lesions” on sDM (not on FFDM or TM) were seen in 4 cases (1.4%).

Conclusion

Prospectively, radiologists assessed sDM to be equivalent to FFDM in the majority of BI-RADS®1, 2 and 0 cases. In studies with specific findings, sDM performed comparably to FFDM and breast imagers should consider adapting sDM with tomosynthesis into clinical practice.

Clinical Relevance
As synthesized digital images were assessed to be equivalent to FFDM in a majority of cases, increased adoption of this technology into clinical practice seems warranted thereby minimizing patient radiation exposure and maximizing the benefits of screening with tomosynthesis.

**Authors**
Corresponding: Valerie Fein-Zachary (Beth Israel Deaconess Medical Center)

Valerie Fein-Zachary (Beth Israel Deaconess Medical Center), Ferris Hall (Beth Israel Deaconess Medical Center), Priscilla J. Slanetz (Beth Israel Deaconess Medical Center), Vandana Dialani (Beth Israel Deaconess Medical Center), Jordana Phillips (Beth Israel Deaconess Medical Center), Shambhavi Venkataraman (Beth Israel Deaconess Medical Center), M Julie Armada (Beth Israel Deaconess Medical Center), Peter Gross (Beth Israel Deaconess Medical Center), Phoebe Olhava (Beth Israel Deaconess Medical Center), Tejas S. Mehta (Beth Israel Deaconess Medical Center)