Breast MRI at reduced gadolinium dose

By Dr. A Melsaether

This review is a synopsis of previously reported work on reduced-dose contrast-enhanced breast MRI, originally published in the Journal of Clinical Imaging in FEB/MARCH 2020 [1] and includes a brief summary of work by other authors who have also investigated reduced-dose MRI.

BREAST CANCER SCREENING AND MRI

Breast cancer is widely prevalent, affecting one in eight women over their lifetimes, and is second only to lung cancer in causing cancer-related deaths in women [2]. Although imaging screening for breast cancer, specifically mammography, has been shown to improve survival [3,4], there has been pushback recently, with many bodies recommending reduced mammographic screening or eventually even no mammographic screening at all, such as is the case in Switzerland, in deference to the potential harms of mammography, such as the stress caused by the need for additional imaging and biopsies that turn out to be benign [5,6]. The improved survival in patients who are screened is in part because imaging-detected cancers are smaller in size and are less likely to have metastasized to the axilla or systemically than cancers that are detected by palpation or physical exam. These smaller node-negative cancers have higher long-term disease- free survival rates and also necessitate less invasive treatments than their larger counterparts [1,7]. However, mammographic sensitivity is relatively low, especially in dense breasts, being consistently reported at around 40% [8,9]. This low sensitivity may be a reason for some discontent with mammography, as many women who are routinely screened by mammography end up later by having interval cancers detected.

Breast imaging technologies have improved since mammography was widely tested as a screening tool. Dynamic contrast enhanced (DCE) breast magnetic resonance imaging (MRI) specifically has been shown to double the cancer detection rates compared to mammography and ultrasound combined in elevated risk women [8,9] DCE-MRI has demonstrated incremental cancer detection rates of up to 22.6 per 1000 MRIs in normal risk women, with cancer yields among all four breast densities, even fatty breasts [10]. The sensitivity of screening MRI routinely approaches 100% and interval cancers in such screened populations are rare [10,11]. Further, MRI detects cancers of average smaller sizes and lower rates of nodal metastases than cancers detected on physical exam, mammography, or ultrasound [8-10].

DCE breast MRI screening was initially reserved for breast cancer screening in women with a 20% or greater lifetime risk of breast cancer. Thankfully, recommendations have recently expanded, with the ACR now recommending MRI for many more women, including those with a personal history of early-onset breast cancer (before 50) and those with a personal history of breast cancer and dense breasts [12-15]. A trial in dense breast women recently reported significantly fewer interval cancers in MRI-screened women [11]. Eventually, MRI may be able to replace more conventional screening tools, much as cross-sectional imaging has replaced conventional x-rays in searching for lung cancers.

GADOLINIUM-BASED CONTRAST AGENTS

At least for now, gadolinium-based contrast agents (GBCA)s are integral to screening with DCE-MRI, but they present an obstacle to widespread screening since GBCAs have been shown to deposit gadolinium in the bodies of imaged patients [16,17] and to persist in the environment (e.g. streams, tap water) in areas with robust advanced imaging [18,19]. Other obstacles such as the time and cost of MRI are being addressed by several groups, who show that DCE-MRI protocols including a single pre- and post-contrast T1-weighted sequence have sensitivity nearly equivalent to the current ACR protocol [20-22].

Whether deposited GBCAs could be harmful is an open question. In its free form, gadolinium is toxic because it interferes with calcium channels and protein binding sites [23,24]. Gadolinium ions are therefore chelated to a conjugate base into linear or macrocylic GBCAs, which can be renally excreted. Recent studies have demonstrated, however, that clearance in many patients is incomplete, and that gadolinium accumulates in the brain and bone [16,17]. These accumulations have been shown with repeated administrations,

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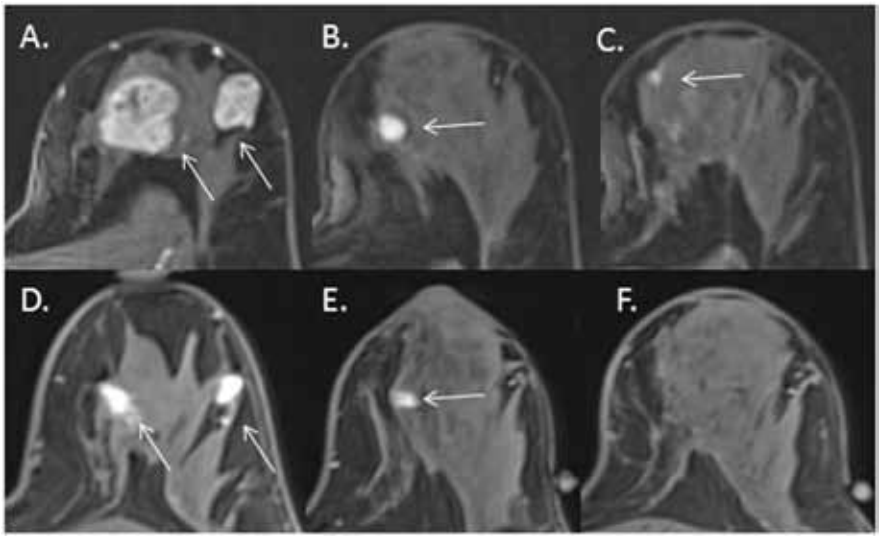


A 43 year old BRCA1+ woman with a family history of breast cancer presented with a palpable mass in her left breast. She had a negative mammogram and ultrasound six months prior. She subsequently underwent core biopsy of the largest mass of three masses seen on initial ultrasound, which yielded high grade IDC. A second mass underwent find needle aspiration biopsy and yielded adenocarcinoma. Pre-chemotherapy half-dose DCE MRI demonstrates A) two heterogeneously enhancing masses (arrows) consistent with the biopsy proven cancers and B) an additional 1.1 cm mass (arrow) and C) and a 0.4 cm focus (arrow) that, on subsequent full-dose DCE-MRI, E) decreased (arrow) F) or disappeared D) in tandem with decrease in size in response to therapy of the biopsy-proven cancers (arrows). Image reproduced from Melsaether *et al.* [1], with permission of Clin Imaging.

such as would be necessary in a gadolinium-based screening program. Although accumulation appears to be related to the chelate, for example, linear agents demonstrate greater deposition than macrocyclic contrast agents (25,26), with repeated administration, macrocyclic agents have also demonstrated some Gd accumulation in the brain (27,28). As of yet, no toxic effects have been demonstrated. However, the United States Food and Drug Administration (USFDA) comments, "health care professionals should limit GBCA use to circumstances in which additional information provided by the contrast agent is necessary and assess the necessity of repetitive MRIs with GBCAs."

In Europe, linear GBCAs have been withdrawn from the market.

Further, GBCAs have been shown to cause minor allergic and even rare anaphylactic reactions [29,30]. In patients with renal failure (likely to be rare in a screening population), gadolinium administration may lead to nephrogenic systemic fibrosis [31]. Finally, and importantly, increasing concentrations of excreted gadolinium have been documented in environmental water including tap water, with highest concentrations in places with high volume advanced medical imaging [18,19].

STUDY RATIONALE

Regardless of whether gadolinium eventually proves to have negative effects, it makes sense to titrate down to a minimal effective dose, rather than using a maximum tolerable dose. As in many things, an "as low as reasonably achievable (ALARA)" approach is a good model,

This was the motivation behind our study that imaged breast cancers with a half dose of Gadobutrol [1]. This idea has been approached by a few research groups who work with lower GBCA doses in MRI exams of the brain [32], prostate [33], and heart [34] and have yielded promising results. In the breast, two older studies looked at GBCA dose: one investigated multiple doses of linear GBCAs [35] of variable relaxivities and another compared our now standard 0.1mmol GBCA dose with a higher dose [36], but both were performed without the object of finding a minimal effective dose.

More recently, our study and one by Pineda *et al* at the University of Chicago investigated the ability of breast MRI to detect lesions with reduced GBCA doses. The Pineda study showed improved visualization of nine benign-appearing lesions at a 15% GBCA dose [37] and our study showed visualization of breast cancers as small as 3mm with a 50% GBCA dose.

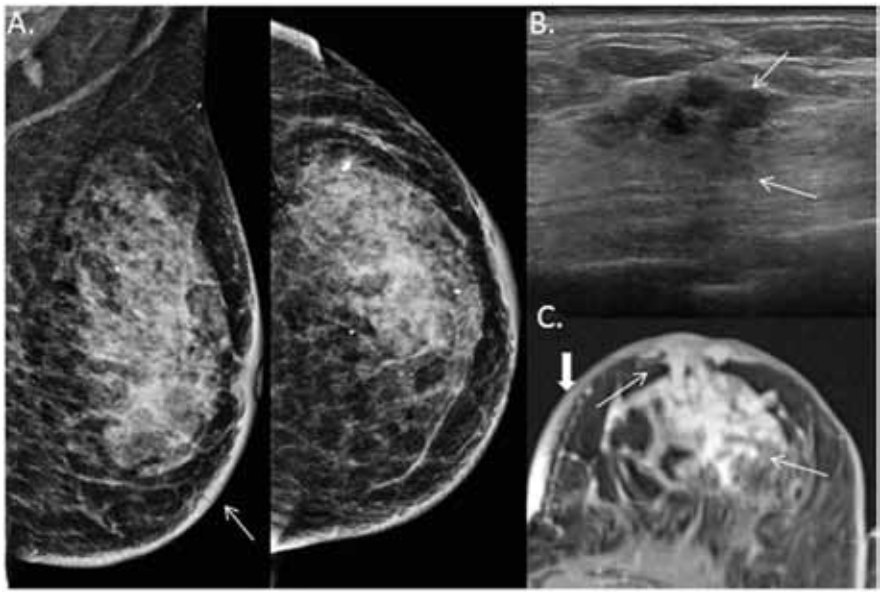
STUDY DESIGN

We didn't have strong referral support for the ideal study design, which would be women with known untreated, biopsy-proven breast cancers who were undergoing PET/MRI of the breast and whole body. These women received a 0.05mM (half-dose) of Gadovist for the breast portion of their exam and a second half-dose for the later, whole body portion of their exam and formed our patient population.

INCLUSION AND EXCLUSION CRITERIA

The inclusion criteria for the PET/MRI study in which these women took part, were that a patient needed to have a core biopsy-proven untreated breast cancer that measured at least 2cm, was multi-focal or multi-centric, had metastasized to the axilla, or involved the skin. For a cancer to be included in our study, it had to be biopsy-proven, either by core biopsy, by fine needle aspiration biopsy if in the same breast as the index cancer. Alternatively the lesion had to demonstrate suspicious imaging characteristics on the initial breast MRI and been shown on MRI to decrease in size in tandem with the index lesion following chemotherapy if in the same quadrant as the index cancer. These broader criteria allowed us to include cancers smaller than the 2cm size which was the most commonly met requirement for study inclusion. Exclusion criteria were exam failure, for clear reasons, and gadolinium injection within 24 hours of the study to avoid residual enhancement.

Because in most cases we couldn't directly compare the breast cancer



A 74 year old woman with a remote history of right breast cancer presented with skin thickening and a palpable area of concern in her left breast. Skin involvement was demonstrated by punch biopsy. A) Mammogram shows skin thickening (arrow) best on the MLO view, without a discernable mass, B ultrasound shows a 3.2 cm irregularly shaped mass with indistinct margins, and C half-dose MRI demonstrates 8.2 cm of clumped and segmental nonmass enhancement (arrows) extending to and involving the nipple. Image reproduced from Melsaether *et al.* [1], with permission of Clin Imaging

sizes or conspicuities between a low dose and standard dose exam, we instead had two radiologists to read the exams. One radiologist had minimal experience and one had a decade of experience,. Each radiologist recorded, on a 4-point scale, whether the cancers could be seen and measured the cancer sizes. The radiologist also characterized the cancer as a mass, nonmass enhancement (NME) or a focus, as masses could be easier to discern than NME and documenting inclusion of NME could strengthen the implications of the work.

DATA ANALYSIS

We assessed inter-reader agreement with the idea that if both radiologists could see the cancers confidently and measured them similarly, this would suggest the MRI was clearly depicting the abnormality. We also correlated size on half-dose MRI with size on mammography (available in nearly all cases), ultrasound (available in all cases), standard-dose MRI (available in about a quarter of cases), and with the gold-standard size at surgical pathology (available in about a quarter of cases). For comparison, we correlated size on mammogram and ultrasound with gold-standard size on surgical pathology as well.

RESULTS

Cancer characteristics and detection

Cancers ranged in size from 0.4-9.2cm with 5 cancers 1cm or less and 13 cancers 2cm or less. There were 35 masses, 13 areas of NME, and 1 focus. All 49 cancers were seen by both readers, with average conspicuity scores of 2.9 on a scale of 0-3. No cancers were rated as 0 not seen or 1 questionably seen by either reader. Readers measured cancers similarly, with a concordance of 1.0, i.e. nearly perfect.

"... the cancer size on half-dose MRI correlated with size at surgical pathology while the cancer size determined on mammogram and ultrasound did not..."

Comparison with mammography, ultrasound images and pathology

For the subsets of these cancers imaged with mammogram and ultrasound, but not from size at surgical pathology or standard-dose MRI, the cancer size on half-dose MRI correlated with size at surgical pathology while the cancer size determined on mammogram and ultrasound did not.

IMPLICATIONS

Our results indicate that breast cancers as small as 4mm and of all morphologies (mass, NME, focus) can be well seen on breast DCE-MRI with a half dose of GBCA by both experienced and relatively inexperienced breast radiologists. Further, our study suggests that the cancer borders are clear at this reduced dose, as there was near perfect concordance in size measurements between the two radiologists. That there was also significant correlation between size on the half-dose MRI and size at pathology corroborates that half-dose MRI accurately depicts tumor margins. As significant correlations were not seen between size on mammogram or ultrasound and size on pathology, it appears half-dose MRI outperforms mammogram and ultrasound, even in this group of larger cancers. A similar recent study, published the same month as our study, provides similar results in benign lesions at an even lower contrast dose. The authors looked at 10 lesions with imaging features compatible with fibroadenomas- first at a 0.015 mmol GBCA dose and, 10 minutes later, at a 0.085 mmol GBCA dose [37]. This study showed that 9 of the 10 lesions were seen on both image sets and that lesion conspicuity and enhancement rate were higher on the lower dose images. This study is exciting since it suggests that these benign lesions may preferentially recruit contrast, so that at lower doses, more contrast agent would go to the lesion and at higher doses, there may be more contrast angiogenesis. Thus it is likely that preferential contrast recruitment by malignant lesions would be even greater than that seen by benign lesions in this study. This suggests this low dose, or even a lower contrast dose, may be sufficient. Another recent study looked at inter- and intra-observer agreement in assessment of tumor volumes prior to neoadjuvant radiation therapy and found similar agreement in half- and full-dose groups [38]. As a result, this team changed to half-dose

exams for the remainder of their trial. Other authors have demonstrated that lower doses of GBCA provide similar results in other organ systems. He *et al*. showed that a 0.015mM dose of gadobentate demonstrated similar sensitivity (50%) and conspicuity score as a near complete dose (0.085mmol/kg) for known prostate cancers [33]. Studies of the myocardium [34] and pituitary gland [39] have also suggested a half dose of gadolinium may be sufficient.

FUTURE DIRECTIONS

We hope that the preliminary study summarized here, together with similar early work from additional authors, will provide evidence for wider investigations looking specifically at the feasibility of low- and eventually ultra-low dose screening DCE-MRI.

"... we hope to see continued focus on "minimal necessary" rather than "maximal tolerated" doses..."

With continuous advances in artificial intelligence (AI), another hope is that small changes in signal intensity could be detected and augmented artificially, potentiating even smaller contrast doses. Eventually, non-contrast MRI may become useful for breast cancer screening. Until that happens, though, we hope to see continued focus on "minimal necessary" rather than "maximal tolerated" doses.

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