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RESEARCH ARTICLE

CATEGORIZATION OF BACKGROUND PARENCHYMAL ENHANCEMENT: REPEATABILITY AND REPRODUCIBILITY

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ABSTRACT

Background: Background parenchymal enhancement (BPE) on breast Magnetic Resonance Imaging (MRI) is the amount of enhancing fibroglandular tissue, BPE influences both MRI interpretation and possibly risk of breast cancer. If increased BPE proves to be an important risk factor, then it has the potential to serve as a bio-marker of breast cancer risk. Before BPE can be introduced into clinical practice, data confirming the repeatability and reproducibility of its measurement is required.

PURPOSE The aim of this study is to assess repeatability and reproducibility of BPE measurements by expert and non expert breast radiologists.

Material and Method: BPE measurements were made retrospectively on a consecutive series of 51 clinically indicated MRI's performed. All examinations were independently assessed for BPE by two expert readers and an inexperienced reader and assigned a category 1-4 in accordance with the proposed BIRADS MRI categorisation.

Results: The inter-reader agreement between expert readers obtained was substantial ($k=0.75$ $p<0,01$). Agreement between expert and non expert readers was moderate ($k=0,494$ $p<0,01$ and $k=0,55$ $p<0,01$). The intra-reader agreement between the three readers was strong (ICC 0.94). The intra-reader agreement for the expert readers was substantial ($k=0.78$ $k=0.68$ $p<0,01$).

Conclusion: Our results show a high intra and inter-reader reproducibility, between expert readers. Lower reproducibility for non-expert radiologists suggests the presence of a learning curve and training requirements for categorization of BPE.

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INTRODUCTION

Background parenchymal enhancement (BPE) on breast Magnetic Resonance Imaging (MRI) is the amount of enhancing fibroglandular tissue, or non fatty, non cystic breast parenchyma (King), seen on the first contrast-enhanced series in a standard DCE MRI examination. BPE reflects the vascularity of the fibroglandular tissue and has been shown to vary with hormonal changes, being highest during weeks 1 and 4 and lowest during week 2 (muller, Kuhl radiology 1997) (Hussain, Kuhl, King radiology 2012 MousaOksa, Engwok, King V 2012 breast jourm, pfeiderer, harevey, delille, graham, hussainmelasether AJR 2014). The amount of BPE refers qualitatively to the volume and intensity of the enhancement of

normal breast tissue after intravenous contrast administration (morrisradiolclinnort am 2007). Evidence suggests that BPE correlates negatively with subject age and increases with greater hormonal activity (muller, pfeiderer, kuhl radiology 1997, delille). One study suggested that BPE does not correlate with mammographic density, although the results clearly showed that both of these parameters were reduced in postmenopausal women as compared with premenopausal women (Cubuk). Although BPE has been shown not to directly correlate with breast density (Cubuk), BPE is similar to breast density in that it should be considered a physiological variable which affects both interpretation and risk of breast cancer. (Melsaether 2014). Four recent studies suggest increased BPE may also affect both reading accuracy (De martini, Hambly) and risk (King radiology 2011, Dontchos). However this is an emerging topic and some studies have not shown these correlations (AJR 2014 Melsaether). If increased BPE proves to be an important risk factor, then it has the

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potential to serve as an additional tool for risk stratification, especially in high-risk women undergoing breast MR imaging screening, and has possibly for monitoring chemoprevention (King radiology 2011).

However, there is very little data available in the literature on BPE, especially regarding the repeatability of categorisation of BPE, so before BPE measurements can be implemented into routine clinical practice, it is crucial to measure the repeatability of BPE measurements. The aim of this study is to assess repeatability (intra) and reproducibility (inter-reader agreement) of BPE measurements between expert and non expert breast radiologists, using a retrospective evaluation of a consecutive series of breast MRI performed for a variety of clinical indications. If BPE measurement is proved to be reproducible then it could be used for risk stratification in the future.

MATERIALS AND METHODS

Categorisation reproducibility

To assess inter-and intra-reader repeatability, BPE measurements were made retrospectively on a consecutive series of 51 MRI scans (mean age 51 years, range 28-78 years), performed for local staging or as a baseline prior to neoadjuvant chemotherapy (NAC) (n=48 (94%)) or for screening (n=3 (6%)) at our institution (Diagnostic Senology Unit AOU Careggi Florence) between July 2014 and October 2014. All premenopausal women were studied during the second week (8-14) of their menstrual cycle. Exceptions were rare; however we do not have specific data to determine the percentage of women who underwent an MRI examination outside this window. This retrospective study was approved by our institutional review board. Women undergoing MRI for implant assessment or interim or final assessment of NACT were excluded. The latter group was excluded to ensure the absence of post treatment effects. BPE assessment was made of the contralateral breast to avoid the influence of tumour neo-vascularity. If the patient had a personal history of breast conservation therapy less than 5 years earlier the evaluation was made on the contralateral breast. 10 patients were excluded, 5 were having neoadjuvant chemotherapy, one had a contralateral tumor and 4 underwent MRI for implant assessment.

All breast MRI examinations were independently assessed for BPE by each of two expert readers and an inexperienced reader. Each radiologist was blinded to the other readers' assessments and to the assessment included in the original report. At each assessment the order of examinations was varied by random computer sorting and each reader was blinded to his prior interpretation. Expert readers repeated the analysis after a minimum interval of 2 weeks to further reduce bias. For each MRI examination BPE was retrospectively recorded and assigned a category 1-4 in accordance with the proposed BIRADS MRI categories (De Martini, Morris rad clin 2007); where 1 indicates minimal enhancement (<= 25% enhancement of glandular tissue); 2 mild enhancement (25-50% enhancement of glandular tissue); 3 moderate enhancement (51-75% enhancement of glandular tissue); 4 severe enhancement (\geq 75% enhancement of glandular tissue). (Figure 1).

A combination of unenhanced, initial contrast-enhanced, subtraction and maximum-intensity-projection images was typically used to determine BPE according to the literature (King, De Martini, Hambly, Melsaether)

MRI acquisition/technique

MRI images were performed at 1.5 Tesla (MagnetomAera Siemens Healthcare) with the patient placed in a head-first prone position with a dedicated breast coil (4 channels). The standard imaging protocol includes localizing sequences followed by:

- Axial T1 weighted sequence Conventional GRE FID imaging (Flash) 3D with fat suppression Dixon 2 point (TR 6.84 ms / TE 2.39 - 4.77 ms) slice thickness 2.5 mm; FoV 330 mm; Flip Angle 20 degrees;
- Axial T2 weighted Rapid Acquisition SE with fat suppression adiabatic RF pulse SPAIR (TR 3300ms / 114.0 ms) slice thickness 3.5 mm; FoV 320 mm; Flip angle 150 degrees
- Axial Rapid Acquisition GRE FID imaging 3D (T1 weighted sequence Flash 3D) fat saturated (TR 4.67 ms / 1.91 ms) slice thickness 1.5 mm FoV 320 mm; Flip Angle 35 degrees

After localizer images, T1w Rapid acquisition GRE FID imaging with fat saturation DIXON 2 point and Rapid Acquisition SE T2w with fat suppression adiabatic RF pulse SPAIR without use of contrast medium were performed. The third and last sequence, Rapid acquisition GRE FID imaging 3D Dyn VIBE is used as dynamic study of the intravenous administration of contrast, with a time resolution of 1:30 minutes. The contrast agent is administered 0.2 mmol per kilogram of body weight (Multihance, Bracco). The sequence Dyn VIBE is composed of 5 measures of 1:30 minutes each one, which fill k-space with sequential encoding and the whole study volume is acquired 5 times. The first is acquired without contrast and the next 4 acquisitions post contrast injection to allow subtraction. Image acquisition begins after the administration of contrast material and a saline bolus, which is injected at the beginning of the second volume acquisition at 1:30 minutes. Therefore, the first contrast-enhanced sequence was obtained approximately 90 to 180 seconds and the last one at 6 to 7:30 minutes.

Image analysis

Image analysis was performed using a high-resolution PACS workstation. The images were anonymized and randomly presented to readers to minimize bias. All image analysis was performed by two experienced breast radiologist (5 years reporting breast MRI) and an inexperienced breast sonographer with no experience on reading breast MRI.

Statistical analysis

Simple kappa coefficients were used to assess inter and intra-reader agreement. Kappa was interpreted as an indication that agreement was slight when 0-0.2, fair when 0.2-0.4, moderate when 0.4 to 0.6, substantial when 0.6 to 0.8 and near perfect when greater than 0.8 in accordance with Landis and Koch (Landis). BPE agreement between the three readers was

assessed with intra-class correlation coefficients (ICC) and scatterplots, (Bland altman and international, 1994). For all analyses, the results were considered to indicate a statistically significant difference if associated with a p-value of less than 0.05.

RESULTS

The number of breast MRI examinations assessed as BPE category by each of the three readers at each time are showed in Table 1.

Table 1. Number of breast MRI examination assessed as BPE category by each of three readers at each time are showed

Readers	Minimal (1)	Mild (2)	Moderate (3)	Severe (4)	Tot
Reader 1- First Reading	30	7	7	7	51
Reader 1-Second Reading	28	11	5	7	51
Reader 2- First Reading	29	10	6	6	51
Reader 2- Second Reading	29	7	6	9	51
Reader 3- First Reading	22	15	8	6	51

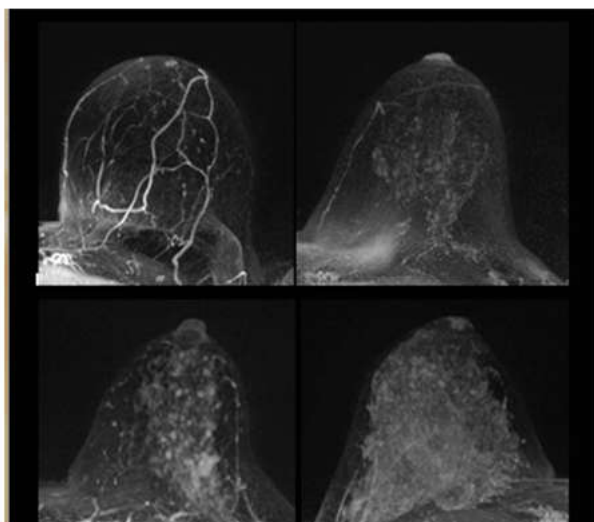


Figure 1. Examples of varying amounts of BPE, as prospectively assessed qualitatively. Axial postcontrast maximum intensity projection MR images show (a) minimal, (b) mild, (c) moderate, and (d) marked BPE

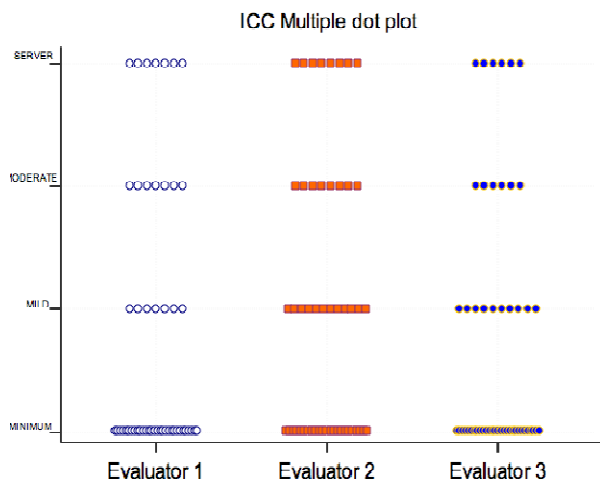


Figure 2. ICC Multiple dot plot for intra reader agreement between three readers

Both expert readers did two evaluations, in order to study also their intra-reader agreement. Having 4 total readings we tried all the combinations and got a medium value of the 4 results. The inter-reader agreement obtained was substantial ($k=0.75$ $p < 0, 01$). To evaluate the intra-reader agreement between the three readers ICC was used and we got as a medium value between the 4 combinations an ICC of 0.94 (Figure 2). K coefficient was also used to evaluate the inter-reader agreement between the first reading of expert readers and non expert readers, all got moderate agreement, particularly between reader expert 1 and the inexperienced reader was $k=0,494$

$p < 0,01$ while between reader expert 2 and the inexperienced reader $k=0,55$ $p < 0,01$. The intra-reader agreement was evaluated only for the expert readers and both had substantial results ($k=0.78$ $k=0.68$ $p < 0, 01$).

DISCUSSION

BPE appears to influence the rate of abnormal MRI interpretation and may correlate with breast cancer risk, but currently there is very little data regarding this field. Accurate and standard assessment of BPE has important clinical implications in terms of examinations outcome and risk stratification (melsaether), but before BPE measurements can be implemented into routine clinical practice, it is crucial to assess the reproducibility of BPE measurements. Our results show a high intra and inter-reader agreement, especially between expert readers. The intra-reader agreement is substantial for both expert readers; the inter-reader agreement is better between expert readers than between expert and non expert readers; This lower reproducibility for non-expert radiologists suggests the presence of a learning curve and the presence of training requirements for categorization of BPE.

In a recent study of Melsaether () repeated assessment at three time point, before and 1 and 3 weeks after training and they found that with training inter-reader agreement increased from fair ($k=0.36$) to moderate ($k=0.48$). Improvement was sustained at 3 weeks after training ($k=0.45$) for ordinal BPE categories and collapsed BPE categories ($k=0.36-0.50$ sustained at 0.47) analysis. BPE assessment were collapsed into low (BPE categories minimal and mild) and high (BPE categories moderate and severe). They conclude that inter-reader agreement was fair among breast radiologist but achieved sustained improvement with training, showing that training changed the way readers evaluated BPE highlighting the importance of education and inclusion of standardized BPE categories in a reference atlas. Regarding intra-reader agreement, it improved for three of four readers to moderate, near perfect, and near perfect ($k=0.65,0.98$ and 0.95) between time 2 and 3 compared with fair, moderate and near perfect ($k =0.45,0.58$ and 0.84) between time 1 and 2. In their study a

change in intra-reader agreement occurred in all but one reader. This change was greater in the less experienced readers indicating that these readers were the most receptive to training. Inexperienced readers showed the most improvement with training, reflecting the importance of dedicating training. In another study King *et al* () report inter-reader agreement for BPE and reported an inter-reader agreement (k) for BPE level between two readers of 0.47 for ordinal BPE and 0.57 for collapsed BPE. The same study reported intra-reader agreement (k) for one reader of 0.62 for ordinal BPE and 0.69 for collapsed BPE.

Several studies have investigated inter reader agreement for mammographic density and Melsaether *et al* () reviewed 4 studies (Redondo, Berg, Bernardi, Ciatto) and found moderate to substantial inter-reader agreement (K=0.43-0.73) and intra-reader agreement (k=0.58 -0.71). Considering that the evaluation of breast density could be comparable to evaluation of BPE we can consider our results acceptable and reproducible. Similarly to breast density at mammography, the amount of fibro glandular tissue (FGT) seen on MRI images and the level of background parenchymal enhancement (BPE) at MR imaging after contrast material administration are features of normal breast tissue (King radiology 2011). Breast density and BPE are not clearly linked, many have wondered whether the tissue characteristic of BPE may have a similar important effect on the diagnostic accuracy of breast MRI. (De Martini) BPE could cause false negatives obscuring malignancies or could result in false positives mimicking the appearance of breast cancers (De Martini).

Some recent studies suggest that increased BPE may also affect both reading (DeMartini, Hambly) and risk of developing a breast cancer (King radiology, Dontchos). This is an emerging topic that has been reported variably (AJR 2014 Melsaether). Hambly *et al* () and DeMartini *et al* () did not find an increased incidence of cancer with increased BPE, but King *et al* and Dontchos *et al* have suggested a relationship between BPE and breast cancer risk. Hambly *et al* () evaluated the effect of BPE in short-term follow up and cancer detection rates in 250 baseline high-risk screening MRI. They found that mild, moderate and marked BPE are associated with a significantly higher rate of short term follow-up than minimal BPE. There is no significant difference in biopsy rate or positive predictive value of biopsies.

De Martini *et al* () analyzed 736 MRI examinations and found that BPE was influenced by age and that increased BPE was associated with higher abnormal interpretation for MRI, in keeping with the results of Hambly *et al* () Moderate or marked BPE resulted in more assessment leading to additional imaging or biopsy but that these initial finding did not impact performance outcome when compared with women with minimal or mild BPE (De Martini). King *et al* analyzed () 1275 MRI's and found that increased BPE at breast MRI is associated with greatly increased odds of breast cancer, greater than MR imaging FGT. These odds may be as great as those associated with mammographic density. Dontchos *et al* found that women at high risk of developing breast cancer undergoing screening breast MR imaging who have mild, moderate, or marked background parenchymal enhancement were nine times more likely to develop breast cancer within a mean follow-up interval of 5.6 years 6 1.3 [standard deviation]

than were those with minimal BPE in their cohort (odds ratio = 9.0; 95% confidence interval: 1.1, 71.0). This study has some limitations. The firstly is its retrospective nature, we had small number of patients and readers, and we did not analyzed the role of a training to improve the agreement. We used qualitative measures, according to our clinical practice, because no reliable quantitative measure is available. We were not able to evaluate the relationship between BPE and other variables such as mammographic breast density, menopausal status or timing relative to the menstrual cycle in premenopausal women.

Conclusion

Further studies to elucidate the relationship between the role of BPE are needed especially to evaluate relationship between BPE and breast cancer risk, as BPE is a promising imaging bio- marker of breast cancer risk and could refine clinical risk assessment models to aid individualization of screening strategies. Our study shows good reproducibility of BPE categorisation, particularly between expert readers. Specific training, and an atlas of BPE categories could improve BPE reproducibility, and facilitate the introduction of BPE categorization in routine clinical practice. The scientific guarantor of this publication is Dr Jacopo Nori. None of the authors of this manuscript disclose any conflicts of interest. We would like to thank Dr Stefano Chiti and Dr Simona Covizzoli AOU Careggi for technical support.

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