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Research article

Breast MRI background parenchymal enhancement as an imaging bridge to molecular cancer sub-type

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ABSTRACT

Purpose: To evaluate the distribution of MRI breast parenchymal enhancement (BPE) among different breast cancer subtypes searching for any significant difference in terms of immunohistochemical and receptorial patterns (Estrogen Receptor -ER, Progesterone Receptor - PR, Human Epidermal Growth Factor Receptor 2 - HER2).
Methods: 82 consecutive patients affected by breast cancer underwent breast DCE-MRI. Two radiologists retrospectively evaluated all subtracted MR enhanced images for classifying BPE. ER, PR and HER2 expression was assessed by immunohistochemical analysis. ER and PR status was evaluated using Allred score (positive values: score ≥ 3). The intensity of the cerbB-2 staining was scored as 0, 1+, 2+, or 3+ (positive values: $\geq$ 3+; negative:0 and 1+; 2+ value assessed with silver in-situ hybridization). Patients were classified into five categories based on cancer subtypes: Luminal A, Luminal B HER2 negative, Luminal B HER2 positive, HER2 positive non luminal, triple negative. The $\chi 2$ test was used for evaluating the significance of BPE type distribution into the five groups of tumor subtypes and the distribution of the five breast cancer subtypes among every single BPE type. The correlation of BPE with factors such as age, menopausal status and lesion diameter was investigated using multivariate regression analysis and logistic regression. Cohen's kappa statistics was used in order to assess inter-observer agreement for classifying BPE.
Results: 6/82 cases were Luminal A-like (7.3%), 42/82 Luminal B-like (HER2-) (51.2%), 12/82 Luminal B-like (HER2+) (14.6%), 4/82 Non Luminal (HER+) (4.9%), 18/82 Triple Negative (ductal) (22%). 16/82 cases showed minimal BPE, 28/82 mild BPE, 22/82 moderate BPE, 16/82 marked BPE. Mild BPE pattern was significantly more prevalent ($p = 0.0001$) than other BPE types only in the luminal B (HER-) tumors. Moderate and marked BPE prevailed over minimal and mild, in triple negatives. Among all patients with mild BPE, luminal B (HER2-) tumors were significantly higher ($p = 0.0001$). Among all patients with marked BPE, triple negative subtypes were significantly higher ($p = 0.0074$). No significant confounder to BPE qualitative evaluation was found ($p = 0.39$). The inter-rater agreement in evaluating BPE patterns on MRI was almost perfect with Cohen's $k = 0.83$.
Conclusions: BPE could play a crucial role as an imaging bridge to molecular breast cancer subtype allowing an additional risk stratification in the field of breast MRI and targeted screening tests. Luminal B (HER2-) tumors could prevail in case of mild BPE on CE-MRI examinations and TN tumors in patients with marked BPE. Further studies on larger series are needed to confirm this hypothesis.

1. Introduction

Both normal and abnormal breast tissue enhances after contrast material intravenous injection at magnetic resonance imaging (MRI), but the morphology and the dynamic enhancement features represent the basis for breast cancer detection.

Background Parenchymal Enhancement (BPE) is defined as the enhancement of normal breast tissue at contrast enhanced MRI dynamic studies [1–10].

Several authors found no correlation between BPE and mammographic density [11–14], but other studies reported that increased BPE was associated with greatly increased risk of breast cancer in high risk

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patients [7,13,15] and with lower recurrence-free survival in breast cancer patients treated with neoadjuvant chemotherapy [16–18]. In fact, King et al. [15] and Dontchos et al. [7] reported that greater BPE was strongly predictive of breast cancer odds and was associated with a higher probability of developing breast cancer in women at high risk. On the other side, Bennani Baiti et al. [19] found that neither BPE nor fibroglandular tissue independently correlated with breast cancer risk in non-high-risk patients at MRI and Van der Velden et al. [17] showed that BPE in the contralateral breast of patients with invasive unilateral breast cancer was significantly associated with long-term outcome.

Breast cancer has been classified during last years into several subtypes by using genetic array testing or approximations to this method using immunohistochemistry [20,21] and guidelines have been established for evaluating estrogen and progesterone receptor expression [22] and for detecting Human Epidermal Growth Factor Receptor 2 (HER2) over-expression [23]. In fact, the receptorial expression pattern, combined with Ki-67 labeling index, allows to identify different breast cancer subtypes, with different risk factors, natural history and response to therapies [24–33].

Few authors tried to correlate BPE patterns with molecular breast cancer subtypes [18,20]. Ha et al. [34] reported that patients with high BPE may be at increased risk for breast cancer but not necessarily for molecular subtypes with poor prognosis. Similarly, Wu et al. [35] found that higher volume of BPE conferred a higher risk for Luminal B cancers.

However, no general consensus exists in the medical literature in this field.

The aim of our study is to retrospectively evaluate the distribution of MRI BPE among different breast cancer subtypes searching for any significant difference in terms of immunohistochemical and receptorial panels (Estrogen Receptor -ER, Progesterone Receptor - PR, HER2).

2. Materials and methods

2.1. Patients

Between January 2017 and June 2017 a total of 137 consecutive female patients (mean age 57, range 39–71, 49 premenopausal, 86 postmenopausal) underwent breast MR examination. Indications to MR examination were represented by family history of breast cancer and dense glandular structure (n = 61), suspected breast lesions on mammography or ultrasonography (n = 46), and preoperative evaluation in breast cancer (n = 30).

Written informed consent was obtained from all patients according to the Declaration of Helsinki principles. MR examinations were performed in the second week of menstrual cycle in case of premenopausal women.

Definitive lesion characterization was obtained by the histological examination and surgical specimen in patient with breast cancer, by histological examination in suspected breast lesions on mammography or ultrasonography and by 12 months follow-up evaluation in negative MR exams. Twelve month follow-up evaluation consisted of clinical, mammographic and ultrasound examinations.

As result, we finally selected a total of 82 breast cancer affected patients (34 premenopausal, 48 postmenopausal).

Inclusion criteria for the molecular cancer subtype evaluation were:

- Unilateral lesion detected at DCE-MRI;
- Absence of BRCA1/2 gene mutation;
- Histologically proven cancer.

2.2. Receptor expression analysis

In order to classify cancer subtypes, ER, PR, HER2 and Ki67 expression was assessed by immuno-histochemical analysis performed on formalin-fixed, paraffine-embedded tissue sections [36–38].

As already reported by M.Y. Kim et al. [18], the ER and PR status was evaluated using Allred score, and considered positive when the total score (sum of proportion and the immune-intensity score) was ≥ 3. The intensity of the c-erbB-2 staining was scored as 0, 1+, 2+, or 3+, and considered as positive for values of ≥ 3+, negative for 0 and 1+; when the score was 2 + we used silver in-situ hybridization, and considered positive if the ratio of HER2 gene copies to chromosome 17 signals was > 2.

According to Cheang et al., a Ki67 threshold value of 14% was selected [38].

2.3. MR protocol

MR examinations were performed on a 1.5 TMR device (Achieva, Philips Medical Systems, Best, The Netherlands) by using a four channel breast coil. The protocol consisted of:

- Transverse short TI inversion recovery (STIR) turbo-spin-echo (TSE) sequence (TR/TE/TI = 3.800/60/165 ms, field of view (FOV) = 250 × 450 mm (AP × RL), matrix 168 × 300, 50 slices with 3-mm slice thickness and without gaps, 3 averages, turbo factor 23, resulting in a voxel size of 1.5 × 1.5 × 3.0 mm3);
- Transverse T2-weighted TSE (TR/TE = 6.300/130 ms, FOV = 250 × 450 mm (AP × RL), matrix 336 × 600, 50 slices with 3-mm slice thickness and without gaps, 3 averages, turbo factor 59, SENSE factor 1.7, resulting in a voxel size of 0.75 × 0.75 × 3.0 mm3);
- Three-dimensional (3D) dynamic, contrast-enhanced (CE) T1-weighted high resolution isotropic volume (THRIVE) sequences (TR/TE = 4.4/2.0 ms, FOV = 250 × 450 × 150 mm (AP × RL × FH), matrix 168 × 300, 100 slices with 1.5-mmslice thickness, turbo factor 50, SENSE factor 1.6, 6 dynamic acquisitions, resulting in 1.5-mm3 isotropic voxels, a dynamic data acquisition time of 1 min 30 s, and a total sequence duration of 9 min). Gadobutrol (Gadovist, Bayer Shering, Berlin, Germany) was intravenously injected at a dose of 0.1 mmol/kg of body weight and flow rate of 1.5 ml/s followed by 20 ml of saline solution.

After the dynamic series, image subtraction sequences were created in order to suppress the signal from fat tissue and enhancing lesions were identified on the subtracted images.

2.4. Image analysis

All MRI data were transferred to and analyzed on a diagnostic workstation equipped with dedicated software for MRI (ViewForumR5.1 V1L1 2006). Two radiologists with more than 5 years of experience in the field of breast MRI retrospectively evaluated all subtracted enhanced images for classifying BPE. In order to standardize the image interpretation, the third dynamic sequence (about after 180 s from the intravenous injection of contrast material) was used for this purpose. BPE was classified into 4 categories: minimal (< 25% of glandular tissue enhancement), mild (25%–50% enhancement), moderate (50%–75% enhancement) and marked (75–100% enhancement). In case of suspected MR lesions, BPE was evaluated on the contralateral breast in order to avoid any increased vascularization caused by breast cancer. The post-processing mean duration time was of about 10 min for MR post-contrast imaging.

2.5. Statistical analysis

Patients were classified into 5 groups of cancer subtypes according to St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013 [36]: Luminal A, Luminal B HER2 negative, Luminal B HER2 positive, HER2 positive non luminal, triple negative.

The $\chi 2$ test was used in order to evaluate the significance of BPE type distribution among the five groups of tumor subtypes. The $\chi 2$ test

was also performed for investigating the distribution of the five breast cancer subtypes among every single BPE type.

A multivariate regression analysis including patient age, menopausal status and tumor diameter was used searching for any confounding effect to BPE measurement and distribution among the different groups of lesions. A dichotomized approach on BPE with logistic regression was also performed.

Cohen's kappa statistics was used in order to assess inter-observer agreement for classifying BPE. A k value of m6re than 0.81 was considered to represent almost perfect agreement and values of 0.61–0.80 and 0.41–0.60 to represent substantial and moderate agreement, respectively.

All calculations were performed using NCSS2007® statistical software.

3. Results

Six out of 82 cases were Luminal A-like (7.3%), 42/82 cases were Luminal B-like (HER2-) (51.2%), 12/82 cases were Luminal B-like (HER2+) (14.6%), 4/82 cases were Non Luminal (HER+) (4.9%), 18/82 cases were Triple Negative (ductal) (22%).

Sixteen of 82 cases showed minimal BPE, 28/82 cases mild BPE, 22/82 cases moderate BPE, 16/82 marked BPE cases.

3.1. BPE distribution among tumor subtypes

Mild BPE pattern was significantly more prevalent (p = 0.0001) than other BPE types only in the luminal B (HER-) tumors (Fig. 1). No other significant distribution difference was found in other breast cancer subtypes. In fact, BPE had casual distribution into the remaining four groups, with mild and moderate types being respectively the first and second most common patterns, and marked BPE the rarest one in almost all categories. The only exception was represented by triple negative group, in which an inversion of this trend occurred, with moderate and marked BPE prevailing on minimal and mild (Table 1; Fig. 2).

3.2. Breast cancer subtype distribution among BPE types

Among all patients with mild BPE, luminal B (HER2-) tumors were significantly higher (p = 0.0001).

Among all patients with marked BPE, triple negative subtypes were significantly higher (p = 0.0074).

None of the five tumor subtypes had significant higher rates in minimal and moderate BPE groups (p = 0.06 and p = 0.09, respectively) (Table 1; Fig. 3).

3.3. Multivariate regression analysis

A mean age of 53.4 (range 39–71; 95% confidence intervals (CIs) 48.6–58.2) was found for minimal BPE group of patients; 53.3 (range 39–71; 95% CIs 49.7–56.8) for mild BPE; 53.9 (range 39–71; 95% CIs 49.9–57.8) for moderate and 49.9 (range 39–62; 95% CIs 46.3–53.5) for marked BPE. Premenopausal rates of 25%, 38%, 45% and 50% were found respectively among minimal, mild, moderate and marked BPE patients. A mean lesion diameter of 11.3 mm (range 8–17) was found for minimal BPE group of patients; 11.2 mm (range 7–17) for mild BPE; 10.6 mm (range 7–17) for moderate and 11.9 mm (range 7–17) for marked BPE.

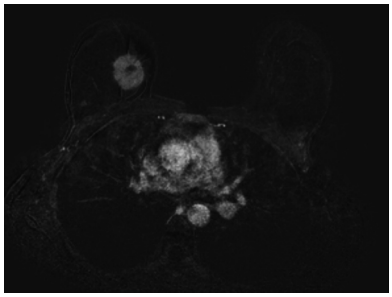

Fig. 1. Subtracted THRIVE contrast enhanced MR image showing a Luminal B HER2- breast cancer of the right breast in a 54-year-old woman with mild BPE evaluated in the contralateral breast.

Table 1
Data distribution by comparing BPE patterns with molecular breast cancer subtypes.

BPE	LUMINAL A	LUMINAL B HER2-	LUMINAL B HER2+	NON LUMINAL	TRIPLE NEGATIVE
MINIMAL	0	12	4	0	0
MILD	2	18	2	4	2
MODERATE	2	10	4	0	6
MARKED	2	2	2	0	10

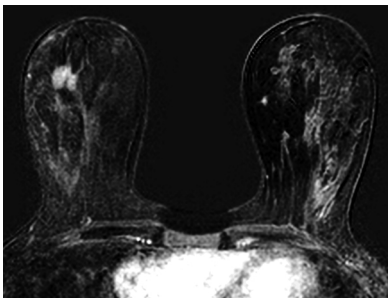

Fig. 2. Subtracted THRIVE contrast enhanced MR image showing a triple negative breast cancer of the right breast in a 49-year-old woman with marked BPE evaluated in the contralateral breast.

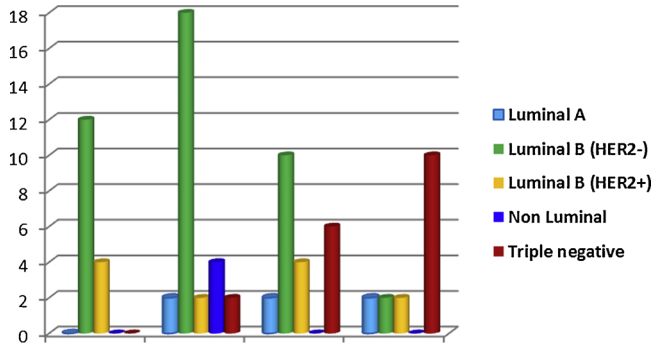

Fig. 3. Breast cancer subtype distribution among different BPE patterns. Groups: 1 = Minimal; 2 = Mild; 3 = Moderate; 4 = Marked.

Multivariate regression analysis found no statistical significant effect of age, menopausal status and lesion diameter on BPE distribution (p = 0.39; coefficient of determination R^2 = 0.03; multiple correlation coefficient = 0.19). The following values were obtained for the single independent variables: age (p = 0.26; coefficient = -0.01); menopausal status (p = 0.16; coefficient = 0.3); lesion diameter (p = 0.98; coefficient = -0.0006).

3.4. Logistic regression

A dichotomized approach on BPE with logistic regression was performed in order to verify the obtained data and the study sample was divided into two groups: group 1 (BPE 0; n = 44; 53.6%); group 2 (BPE1; n = 38; 46.3%). Logistic regression found no statistical significant value (p = 0.49). The following values were obtained for the single variables: age (p = 0.43; coefficient = -0.02); menopausal status

(p = 0.37; coefficient = 0.4); lesion diameter (p = 0.72; coefficient = -0.03).

3.5. Inter-rater agreement

The inter-rater agreement in evaluating BPE patterns on MRI was almost perfect with Cohen's k = 0.83.

4. Discussion

The introduction of MRI in the field of breast imaging has increased the sensitivity and specificity for detecting breast cancer respectively to 95%–99% and 80%. MRI also provides crucial information concerning the normal breast tissue features, including BPE, defined as the enhancement of the normal breast tissue after contrast material injection. BPE can be classified as minimal (< 25% of glandular tissue demonstrating enhancement), mild (25%–50% enhancement), moderate (50%–75% enhancement), or marked (> 75% enhancement). Typically BPE is minimal or mild and shows diffuse, bilateral and symmetric distribution. In a minor percentage of patients, it could be moderate or marked, and could have asymmetric or not diffuse pattern, affecting breast cancer detection [1–4].

BPE is influenced by the anatomy of the breast's arterial and venous systems, and by endogenous hormones levels during the menstrual cycle; therefore, it is recommended to perform breast MR in the first half of the menstrual cycle, in order to minimize the enhancement of the normal breast tissue. A negative BPE correlation with menopausal status has been reported [1,5–9]. Also hormone therapies can reduce BPE, like selective estrogen receptor modulators (SERMs) or aromatase inhibitors [10]. Verardi et al. [39] reported an association between asymmetric increased breast vascularity and ipsilateral cancer, particularly for invasive cancers of more than 2 cm in diameter or with high pathologic grade. This data suggests to perform any evaluation of BPE on the contralateral breast. In fact, BPE was evaluated in the contralateral breast in all patients enrolled in our study.

Several studies investigated the effect of BPE on breast cancer detection and its association with different tumor types. Some authors found no correlation between BPE and mammographic density [11–14], but many studies demonstrated that increased BPE at breast MRI was associated with greatly increased risk of breast cancer in high risk patients [7,13,15] and with lower recurrence-free survival in breast cancer patients treated with neoadjuvant chemotherapy [16].

Particularly, Dontchos et al. and King et al. found a positive BPE correlation with breast cancer risk in high risk patients while Bennani-Baiti et al. found no correlation with breast cancer risk in non high risk patients [7,15,19]. Van der Velden et al. also stated that BPE in the contralateral breast of patients with invasive unilateral breast cancer was significantly associated with long-term outcome particularly in case of estrogen receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer [17].

In fact, most relevant studies about breast cancer during last decades involve its molecular characterization, using genetic array testing (or approximations to this method with immunohistochemistry) to detect the expression of hormonal and epidermal growth factor 2 receptors in the tumor cells. This data, associated with Ki67 labeling index, allows to classify several cancer subtypes, which differ for etiology, natural history and response to treatment [21].

The 12th, 13th and 14th (2011, 2013 and 2015) St Gallen International Breast Cancer Conference Expert Panel adopted a new approach to the classification of patients for therapeutic purposes based on the recognition of intrinsic biological subtypes within the breast cancer spectrum (Luminal A, Luminal B HER2 -, Luminal B HER 2 +, HER 2 + not Luminal, Triple negative) [36–38].

The aim of our study was to retrospectively evaluate the distribution of MRI BPE among different breast cancer subtypes searching for any significant difference in terms of immunohistochemical and receptorial panels.

We found that mild BPE pattern was significantly more prevalent than other BPE types only in the luminal B (HER-) tumors; no other significant distribution difference was found among other breast cancer subtypes. The only exception was represented by triple negative group, in which an inversion of this trend, where moderate and marked BPE prevailed over minimal and mild types. Among all patients with mild BPE, luminal B (HER2-) tumors were significantly higher while among all patients with marked BPE, triple negative subtypes were significantly more prevalent. None of the five tumor subtypes had significant higher rates in minimal and moderate BPE groups in our series.

Our results differ from what Kim already observed, with no statistical evidence of correlation between BPE grade and the receptorial cancer subtype, and are confident with *J*. Wang's, who stated that the heterogeneity of BPE characterized by texture on DCE-MRI was associated with triple negative cancers [18,20].

In fact, this study shows a significant distribution of mild BPE pattern within Luminal B (HER2-) tumor subtypes, with higher rates of mild BPE among all Luminal B (HER2-) tumors and Luminal B (HER2-) subtypes among all mild BPE patients. These results are slightly different from the ones obtained by Ha et al. [34] and Wu et al. [35] who found that patients with high BPE may be at increased risk for breast cancer but not necessarily for molecular subtypes with poor prognosis with a higher risk for Luminal B cancers.

Another important data emerging from our study reveals an increasing trend for BPE in triple negative tumors, respectively with no patient with minimal BPE, 2 patients with mild BPE, 6 patients with moderate BPE, and finally 10 patients with marked BPE. This distribution does not show a statistical significance, probably because of the small number of triple negative patients in our sample, that represents one of the study limitations.

On the other side, among all patients with marked BPE, triple negative tumors showed significant higher rates than other subtypes.

These results strongly suggest a potential role of BPE as a predictive tool for Luminal B (HER2-) and triple negative tumor diagnosis; however, more studies in this field are required to confirm this hypothesis on larger series.

Our study only indicates a potential role of breast MRI for a prognostic stratification; in fact, minimal, mild and moderate BPE patterns are poorly distributed among triple negative tumors and could indicate a more favorable prognosis.

On the other side, an additional risk stratification for triple negative tumors could be proposed with dedicated screening programs and shortened intervals for MRI surveillance in case of marked BPE.

With regard to the BPE qualitative evaluation in our study and the possible effect of any confounding factor, the multivariate regression analysis and the dichotomized approach on BPE with logistic regression found no statistical significant effect of age, menopausal status and lesion diameter on BPE distribution; these results could be due to the small number of the enrolled patients and to the fact that only patients affected by breast cancer, and not at high risk of breast cancer, were enrolled.

Our study has some important limitations. First of all, the small number of the enrolled patients with an unequal distribution of molecular subtypes, with few triple negative cancer affected patients, although they usually represent the 10–20% of all breast cancers, as in our series.

The second limitation concerns the qualitative and potentially subjective BPE evaluation, but this bias is reduced by the almost perfect inter-rater agreement observed in our study. A quantitative or automated BPE measurement could be useful to standardize and compare data among different experiences.

Furthermore, we did not evaluate the symmetrical or asymmetrical distribution of BPE on the contralateral breast.

Of course, the retrospective design of the study is also an important limitation, especially regarding the possibility of demonstrating a cause-effect association between BPE grade and tumor subtype development.

A prospective study, including also a control group of healthy patients, is necessary to investigate the effect of BPE on the risk of single breast cancer subtypes.

5. Conclusions

BPE could play a crucial role as an imaging bridge to molecular breast cancer subtype allowing an additional risk stratification in the field of breast MRI and targeted screening tests. Luminal B (HER2-) tumors could prevail in case of mild BPE on CE-MRI examinations and TN tumors in patients with marked BPE. Further studies on larger series are needed to confirm this hypothesis.

Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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