Evaluation of background parenchymal enhancement on breast MRI: a systematic review

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Abstract:

Objectives: To perform a systematic review of the methods used for background parenchymal enhancement (BPE) evaluation on breast magnetic resonance imaging (MRI).

Methods: Studies dealing with BPE assessment on breast MRI were retrieved from major medical libraries independently by four reviewers up to 6 October 2015. The keywords used for database searching are “background parenchymal enhancement’, ‘parenchymal enhancement’, “MRI” and “breast”. The studies were included if a qualitative and/or quantitative methods for BPE assessment were described.

Results: Of the 420 studies identified, a total of 52 articles were included in the systematic review. N=28 studies performed only a qualitative assessment of BPE, N=13 studies performed only a quantitative assessment and N=11 studies performed both qualitative and quantitative assessment. A wide heterogeneity was found in the MRI sequences and in the quantitative methods used for BPE assessment.

Conclusions: Wide variability exists in quantitative evaluation of BPE on breast MRI. More studies focused on a reliable and comparable method for quantitative BPE assessment are needed.

Advances in knowledge: More studies focused on quantitative BPE assessment are needed.

Keywords

Background parenchymal enhancement; Breast; Magnetic resonance imaging; Review

Introduction

As stated by the research committee of the European Society of Radiology (ESR), the future of medicine lies in the so-called 'personalised medicine' (PM) [1,2]. The concept of PM could be reassumed in delivering the right treatment to the right patient at the right time. The concept of personalized medicine is strictly linked to the "precision medicine" that has been defined in 2011 by the National Research Council of the National Academies white paper entitled "Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a new Taxonomy of Disease" [3]. On the light of these new goals of modern medicine, biomedical imaging requires a correct and rational use of quantitative imaging biomarkers (QIBs) [4].

In addition, implementation of quantitative imaging on a large scale will be critical to meet the demands of PM [4]. Indeed, PM presents new challenges to the radiologists with the need of validation and assessment of QIBs for diagnosis and treatment response assessment [1-6]. One primary metrology area of interest in the assessment of performance of a quantitative imaging biomarker is the ability of the QIB to consistently reproduce equivalent results when conditions change, as would be expected in any clinical trial [6]. In this perspective, background parenchymal enhancement (BPE), the term used to describe the enhancement of the normal breast tissue, is emerging as imaging biomarker [7].

The 'degree' of BPE is linked to the risk of developing breast cancer, may affect reading breast MRI, the staging and the risk of cancer even long-term outcome, particularly in patients with certain subtypes at immunohistochemistry [8-15]. BPE can be visually assessed qualitatively using the BI-RADS scores or quantitatively using software [7,16]. However, radiologists' agreement for BPE qualitative evaluation is fair [17] and, to the best of our knowledge, there is a lack of uniformity on quantitative measurements of background parenchymal enhancement on breast MRI. Indeed, an absolute categorizing

method based on percentage is not supported by the American College of Radiology (ACR), suggesting the need of further research in this topic [16]. It is crucial that, in the era of PM, the methods used for evaluation of background parenchymal enhancement, as for others imaging biomarkers, are reliable and comparable among different imaging sites [5]. Therefore, the purpose of this study is to perform a systematic review of the methods currently adopted to assess BPE on breast MRI and to drive future research on this QIB.

Methods

We followed the guidelines defined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [18]. The protocol of this study was published on PROSPERO (International Prospective Register of Systematic Reviews; protocol number: CRD42015026904) on 8 October 2015 (http://www.crd.york.ac.uk/PROSPERO/).

Search strategy

We identified all relevant studies that assessed the evaluation of background parenchymal enhancement (BPE) on breast MRI. A literature search using PUBMED (http://www.pubmed.org), Embase (http://www.embase.com.proxy.medlib.iupui.edu/search), ISI Web of Science (http://apps.webofknowledge.com), SpringerLink, ScienceDirect and Cochrane library (http://www.thecochranelibrary.com) was performed independently by four reviewers (Blind, Blind, Blind, Blind) up to 6 October 2015. Manual revision of the reference lists was also performed to integrate the initial search with additional studies, if necessary. We did not contact directly authors for additional data.

The search strategy included the following terms related to studies on humans: 'background parenchymal enhancement' or 'parenchymal enhancement', in combination with 'magnetic resonance imaging', 'evaluation' or 'assessment', and 'breast'.

The detailed search strategy in PubMed is presented in **Supplemental Appendix S1**.

Inclusion criteria

Studies were included if they met all the following criteria:

1. Women older than 18 years who performed breast MRI
2. Background parenchymal enhancement assessed on MRI
3. The method used for background parenchymal enhancement assessment clearly stated: qualitative with BI-RADS, qualitative without BI-RADS, automated quantitative on 2D MRI slices, automated quantitative on 3D MRI volumes, semi-automated quantitative on 2D MRI slices, semi-automated quantitative on 3D MRI volumes.

4. Languages: only publications in English were included.

Exclusion criteria: (1) case reports or case series, review articles, letters, comments; (2) duplicate publication; (3) BPE not assessed; (4) MRI exams below 1.5T.

No publication date restriction was used.

Study selection

Two authors (Blind, Blind) independently and manually reviewed article titles and abstracts for study selection, based on the pre-defined criteria. Then, the same authors independently read the methods of the full text of those studies to confirm fulfilment of the inclusion criteria. Disagreements arising during each phase of the study selection were resolved in consensus. If consensus could not be reached, a clinical expert (Blind) was asked to resolve any disagreements.

Data extraction and analysis

Two authors (Blind, Blind) independently extracted the data from each eligible study. A duplicate data extraction was performed and discrepancies were resolved by consensus. The following data were extracted from each study: first author, journal and publication year, country of the study, study designation (retrospective or prospective), study population, magnetic field of MRI scanner (1.5 T or 3.0 T), menstrual period of patients undergoing MRI, the type of contrast media used (high relaxivity and not high relaxivity contrast media) the type of BPE assessment (qualitative method, quantitative method, including automated software), the sequences which BPE was qualitatively and quantitatively assessed and the method used for quantitative evaluation of BPE. In particular, we recorded studies assessing BPE quantitatively using region-of-interest (ROI), fibroglandular tissue segmentation, automatic method or other methods. To assess studies using ROI, we considered studies in which BPE was assessed by using a region of interest traced to include normal fibroglandular tissue, or the most enhancing part of the normal fibroglandular tissue, or the normal tissue extended from the tumour edge,

excluding breast lesion enhancement. To assess studies using fibroglandular tissue segmentation, we considered studies in which BPE was calculated by the enhancements of every pixels/voxel contained within a previously segmented fibroglandular tissue. To assess studies using an automatic method, we considered studies in which was specified the use of a fully automatic software that gives the value of BPE without the need of further control by a radiologist. We also recorded studies using other methods, different from the ROI, fibroglandular or automatic one.

Among studies assessing BPE qualitatively, we recorded each study with intra and interreader agreement assessment for all readings by using the kappa statistics. We recorded kappa values for both ordinal (minimal, mild, moderate or marked BPE) and dichotomized variables (low and high BPE), when assessed. Strength of kappa agreement was defined as follows: 0.00–0.20, slight; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.81, substantial; 0.81–1.00, almost perfect.

We divided articles in those published in 2015 and those published before 2015 to evaluate the increase interest on this topic in the last year. We performed a narrative synthesis of the qualitative and quantitative methods reported.

Risk of bias

The quality assessments of the eligible study were evaluated independently by two authors (Blind, Blind) using a modified Quality Assessment of Studies of Diagnostic Accuracy Studies (QUADAS-2) checklist, which comprised four domains: patient selection, index test and reference standard, and flow and timing. For the purpose of this study, the domains “index test” and “reference standard” were considered together: in addition to the standard questions of these domains, we included the quality of the description of BPE assessment and the quality of MR images where the BPE assessment was performed, when available. Each domain is assessed in terms of risk of bias and the first three in terms of concerns regarding applicability. The answers ‘yes’ (+), ‘no’ (-) or ‘unclear’ (?) to

the standard questions of each domain represent the judgment regarding bias and applicability: low risk of bias, high risk of bias and insufficient data to permit a judgement, respectively. The two authors then discussed the results of their quality assessments. Disagreements were resolved by consensus.

Results

The initial database searching identified 420 articles. A total of 63 full-text articles were assessed after removal of duplicates and reading abstracts because they did not meet selection criteria. From the 63 full-text articles, 11 studies were excluded because they did not meet screening criteria and a total of 52 articles were included in the systematic review (**Figure 1**). **Table 1** and **Table 2** show characteristics of the included studies that assessed BPE with a qualitative and quantitative method, respectively. Among these 52 studies, 28 studies (54%) performed only a qualitative assessment, 13 studies (25%) performed only a quantitative assessment and 11 studies (21%) performed both qualitative and quantitative assessment of BPE and were included in both tables. Among these 52 studies, 20 studies (38%) were published in 2015.

Qualitative BPE assessment

Among the 39 (28+11) studies that assessed BPE qualitatively [7,8,10-13,15,17,19-49], 38% (15/39) were published during 2015 (January-October) and 62% (24/39) were published during 2010-2014. Most of the studies were performed in the United States of America (17/39) and Republic of Korea (10/39) and Japan (6/39). Only one study [49] had a prospective study design. The patient population of the included studies ranged from 18 to 1275 numbers of patients. N=20 studies performed breast MRI using a 1.5 T scanner, nine studies performed breast MRI using a 3.0 T scanner and nine studies using both 1.5 T and 3.0 T scanners. In one studies [11] the MRI scanner was not clearly stated but it was above 1.5T. Most of the studies (59%; 23/39) used gadopentetate dimeglumine as contrast agent. Only three studies (8%; 3/39) used high-relaxivity contrast agent [7,34,47]. All the studies graded BPE on a four-point scale as minimal, mild, moderate, or marked in accordance with the Breast Imaging-Reporting and Data System (BI-RADS) categories [16]. Iacconi et al. [25] classified BPE according to BI-RADS lexicon but for statistical purpose clumped into two groups (low and high BPE). N=16 studies qualitatively assessed

BPE using a combination of unenhanced and contrast-enhanced fat-suppressed T1-weighted and subtracted images, and five studies added also maximum-intensity projection images; N=14 studies qualitatively assessed BPE using a combination of post-contrast fat-suppressed T1-weighted and/or subtraction images; one studies [27] used only maximum-intensity-projection images; in three studies the sequences used for qualitative BPE assessment were not clearly stated (**Table 1**).

A total of nine studies performed intra and/or interreader agreement of qualitative evaluation of BPE [7,8,17,22,31,36,37,39,48]. In particular, four studies [7,8,17,39] evaluated both intra and interreader agreement and the other five studies evaluated only interreader agreement. Kappa values for intrareader agreement were moderate to almost perfect, while more variability was found for kappa values for interreader agreement, that was demonstrated to be fair to almost perfect (**Table 3**).

In the majority of studies (7 of 9) the agreement was assessed for ordinal variables. In studies by King et al. [8] and by Melsaether et al. [17] authors assessed intra and interreader agreement for both ordinal and dichotomized variables, but the strength of kappa agreement was not changed (kappa values for intrareader agreement were substantial and for interreader agreement were moderate in both studies).

Quantitative BPE assessment

Among the 24 (13+11) studies that assessed BPE quantitatively [7,14,40-62], 33% (8/24) were published during 2015 (January-October) and 67% (16/24) were published during 2008-2014. Most of the studies were performed in the United States of America (9/24) and Republic of Korea (4/24) and Germany (4/24). A total of seven studies were prospective, and 17 studies were retrospective. The patient population of the included studies ranged from 16 to 651 numbers of patients. N=18 studies performed breast MRI using a 1.5 T scanner and five studies performed breast MRI using a 3.0 T scanner. Most of the studies (42%; 10/24) used gadopentetate dimeglumine (Magnevist) as contrast agent. Only two

studies (8%; 2/24) [7,47] used a high-relaxivity contrast agent (gadobenate dimeglumine, MultiHance). N=15 studies (62%) performed a quantitative evaluation of parenchymal enhancement from a ROI. Among these studies, BPE was described as a signal enhancement ratio in four studies [43,46,47,52]. The signal enhancement ratio was based on comparison of signal intensity in an early contrast-enhanced image with signal intensity in a delayed contrast-enhanced image relative to a pre-contrast image.

BPE was described as a percentage enhancement rates or relative percentage enhancement in eleven studies [41,42,44,45,48,49,53-55,58,59], with the use of both pre- and post-contrast images. There was a wide heterogeneity on time selection of images obtained after contrast agent injection for relative percentage enhancement or percentage enhancement rates calculation.

Three studies performed a quantitative evaluation of BPE using an automatic method [7,57,61]. Tagliafico et al. [7] assessed BPE using fully automated software that performed an objective and reproducible voxel-by-voxel analysis. This software used an algorithm based on the maximum entropy method and a threshold value [7]. Mazurowski et al. [57] used computer vision algorithms that extracted all the features automatically, including dynamic feature of the background parenchyma [57]. Wu et al. [61] used a validated fully automated method that allowed segmentation and quantitatively measure of fibroglandular tissue and BPE [61].

Qualitative and quantitative BPE assessment

Among the 11 studies that assessed BPE both in a qualitative and quantitative methods [7,40-49], 27% (3/11) were published during 2015 (January-October) and 73% (8/11) were published during 2010-2014. Most of the studies were performed in the United States of America (3/11) and Republic of Korea (3/11). The majority of the studies (10/11) were prospective. The patient population of the included studies ranged from 26 to 229 numbers of patients. Seven studies performed breast MRI using a 1.5 T scanner and four studies

performed breast MRI using a 3.0 T scanner. Most of the studies (45%; 5/11) used gadopentetate dimeglumine (Magnevist) as contrast agent. Among these 11 studies that assessed BPE both in a qualitative and quantitative methods, only the study of Kim MY et al. [46] found a statistical difference between qualitative and quantitative data.

Considering menstrual period of pre-menopausal patients that underwent MRI, in the majority of studies (30 of 52) the patient menstrual cycle was unknown or not available [8,10,12,13,15,20,21,23,25,27,28,30,32-35,38,39,45,46,47,50-54,57,59,60,62]. In five studies [11,17,19, 36,43], authors acknowledged that, due to the retrospective nature of the study, it was not possible to analyse the point of menstrual cycle, although, following Institutional protocol, screening breast MRI of pre-menopausal patients are performed during the second week of the menstrual cycle. In a total of 14 studies authors stated the menstrual period [7,22,24,26,31,37,40-42, 44,48,55,56,61]. In eight of these 14 studies, breast MRI were performed ideally in the second week of the menstrual cycle [7,22,24,37,41,42,56,61]. In three studies [29,49,58], the patients were post-menopausal women.

Risk of Bias

Assessment of the methodological quality of the included studies by the modified QUADAS-2 tool is depicted in **Table 4** and **Table 5**.

The domain of “patient selection” for the qualitative and quantitative BPE evaluation was unclear in the studies of DeMartini et al. [11], Choi et al. [21], Jansen et al. [43], Kajihara et al. [44], Kang et al. [55], Kim JY et al. [45], Park et al. [35]. The domain “index test and reference standard” was described in detailed in most of the studies that assessed BPE qualitatively and quantitatively. High risk of bias and concerns regarding applicability were judged in the paper of Chen et al. [50] and in the papers of Grimm et al. [23] and Myers et al. [34], specifically for low quality of MR imaging examinations where the BPE assessment was performed and a low detailed of the qualitative assessment of BPE,

respectively. The domain of ‘flow and timing’ was the only domain to potentially contribute a high risk of bias in the papers evaluated. However, we believe that this domain could be less relevant because we focused only on the methods of assessment of BPE that in most instances is performed with a retrospective review of a dataset of breast MRI.

Discussion

We performed a systematic review of the literature currently available about qualitative and quantitative assessment of BPE in breast MRI. We divided the 52 articles included in the systematic review in those that performed a qualitative evaluation of BPE and in those that performed a quantitative evaluation of BPE. Most of the studies found (28/52) performed only a qualitative evaluation of BPE, 13 studies performed only a quantitative evaluation and 11 studies both qualitative and quantitative evaluation of BPE. Therefore, a total of 24 studies performed a quantitative assessment of BPE. Among these 24 studies, one of the most difficult issues was the analysis of the quantitative method used, due to the lack of standardization of the BPE quantitative assessment. Indeed, the studies used different methods and software to evaluate BPE, although the majority of these studies performed a quantitative evaluation of parenchymal enhancement from a region-of-interest (ROI). However, the use of ROI usually needs radiologist involvement, and this issue should be faced in the perspective of a standardized quantitative imaging evaluation of BPE. In addition, only three studies used an automatic method, and in all these studies different software were used. We can state that in the “era” of PM and emerging QIBs, BPE quantitative assessment is still far to be standardized. The ACR distances itself from prescribing an absolute quantification method for BPE assessment [16], and this is probably the source of the heterogeneity that we found in our study. Indeed, our study found extensive heterogeneity in the methods used for BPE quantitative assessment and encourage further studies assessing comparable method for quantitative BPE evaluation. Among the 11 studies that performed a BPE assessment with both qualitative and quantitative methods, only one study [46] reported a statistical difference between the qualitative and quantitative methods used. Noteworthy, the study by Kim et al. [45] was able to associate high values of BPE around the tumours on the pre-operative MRI with an increased risk of ipsilateral breast tumour recurrence. Without using a quantitative

approach, this information would have been missed. Indeed, with a study design similar to that of Kim et al., [46] a huge number of breast MRI examinations were necessary to obtain the same information.

Our systematic review found that the majority of papers published had a retrospective design, and only few studies were prospective. A retrospective study design reduces the possibility of associating BPE with others factors relevant to tumour biology. In addition, in the majority of the studies the menstrual period of pre-menopausal women that underwent MRI was unknown or not available.

Regarding the contrast media used, we found that only few studies used high-relaxivity contrast media. The use of a high relaxivity contrast media such as gadobenate dimeglumine is reported to offer advantages for lesion conspicuity, detection rate, and sensitivity for malignant breast lesions [63]. Besides, a higher enhancement of benign lesions and breast parenchyma is possible with a high relaxivity contrast media [63]; therefore, we cannot confirm that the amount of BPE assessed with the same method, but different contrast media, is comparable.

Regarding the quality assessment, we used a modified QUADAS-2 checklist, since our systematic review did not focus on diagnostic accuracy studies; indeed, we merged the domain “index test” and “reference standard”. In addition to the standard questions of these domains [64], we also considered the quality of the description of BPE assessment and the quality of MR images where the BPE assessment was performed. In spite of the modified method for quality assessment, the domain of ‘flow and timing’ was the only domain to potentially contribute a high risk of bias in the included studies. However, this review focused on the methods used on BPE evaluation, and the majority of the studies performed the assessment with a retrospective review of the breast MRI dataset; therefore, we believe that this domain could be less relevant and the overall risk of bias in these studies could be considered low.

Considering qualitative evaluation, BPE was always graded on a four-point scale by the BI-RADS categories representing the main standardized area in BPE assessment, as recommended by the ACR BI-RADS fifth edition itself [16]. However, a huge variability in the MRI sequences adopted to assess BPE was noted, although the main principle was to find the sequences where the amount of BPE was most evident. It is clear that there is no consensus on what MRI sequences the BPE should be assessed even with the relatively simple suggested BI-RADS grading system. In addition, a wide variability was found among kappa values for the interreader agreement, from fair to almost perfect agreement. Considering intrareader agreement, kappa values were moderate to almost perfect. However only 9 of 39 studies assessed intra and/or interreader agreement for qualitative evaluation of BPE, and further studies could be useful on this topic.

Considering quantitative evaluation, we acknowledge that our study did not include a detailed descriptions of the methods used for quantitative assessment of BPE. However, we performed the division of these studies among four main different methods (ROI, fibroglandular tissue segmentation, automatic methods or other methods) to allow a more uniform analysis. Further systematic reviews that focus on this topic could be useful to provide future directions for a standardization of quantitative methods used to assess BPE.

Finally, the first study about BPE assessment was published in 2008 [52] and the 38% (20/52) of all the studies included were published during 2015, reflecting the growing interest in this topic. The relatively recent interest in the BPE assessment could be another possible explanation for the wide variability found in the sequences used for the qualitative assessment and in the methods used for the quantitative assessment.

In conclusion, since background parenchymal enhancement (BPE) is considered an emerging imaging biomarker, new methods to assess BPE quantitatively are being developed. However, a wide variability exists in the methods used to perform a

quantitative evaluation of BPE on breast MRI. In addition, no consensus exists on the sequences to be used to visually assess BPE. Therefore, more studies on quantitative BPE assessment are needed.

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Table 1: Characteristic of the 39 studies that assess BPE qualitatively included in the systematic review.

Study	Year	Journal	Country	Design	Study population	Magnetic field	Contrast media (commercial names)	Sequences used for qualitative assessment of BPE				
								Combination of unenhanced and contrast-enhanced fat-suppressed T1-weighted and subtracted images	Combination of the unenhanced, initial contrast-enhanced subtraction, and maximum-intensity-projection images	MIP	post-contrast series and/or subctracted images	not clear
Albert et al.	2015	Clin. Imaging	USA	R	475	3.0 T and 1.5 T	Magnevist	x °				
Amarosa et al. ◆	2013	Radiology	USA	R	58	3.0 T	Magnevist	x				
Baek et al.	2014	Eur J Radiol	Republic of Korea	R	322	3.0 T and 1.5 T	Magnevist		x ^			
Cho et al. ◆	2015	European Journal of Radiology	USA	R	77	3.0 T	Magnevist	x				
Choi et al.	2015	Acta Radiol	Republic of Korea	R	98	1.5 T	Magnevist	x °				
Cubuk et al. ◆	2010	Rad Med	Turkey	R	26	1.5 T	Magnevist				x	
DeMartini et al.	2012	AJR	USA	R	736	not clear	not clear		x			
DeLeo et al.	2015	AJR	USA	R	55	3.0 T and 1.5 T	not clear	x				
Dontchos et al.	2015	Radiology	USA	R	487	1.5 T	Omniscan		x			
Grimm et al.	2015	AJR	USA	R	222	3.0 T and 1.5 T	Magnevist					x
Hambly et al.	2011	AJR	USA	R	250	1.5 T	Magnevist	x				
Hansen et al.	2014	JMRI	Germany	R	468	1.5 T	Gadovist				x °	
Iacconi et al.	2014	EJR	USA	R	96	3.0 T and 1.5 T	Magnevist					x
Jansen et al. ◆	2011	Eur Radiol	USA	R	229	1.5 T	Omniscan				x	
Kajihara et al. ◆	2013	Magn Reson Med Sci	Japan	R	165	1.5 T	Magnevist				x	
Kawamura et al.	2015	Nagoya J Med Scie	Japan	R	160	3.0 T	Magnevist	x °				
Kim JY et al. ◆	2015	Magn Reson Imaging	Korea	R	81	3.0 T	Gadovist				x °	

Kim MY et al.	2015	Clin Radiol	South Korea	R	178	3.0 T	Dotarem				x			
Kim MY, et al. ◆	2013	Acta Radiol	Republic of Korea	R	133	1.5 T	Gadovist	x°						
Kim SA et al. ◆	2014	Radiology	Republic of Korea	R	215	1.5 T	Multihance	x°						
Kim YJ et al.	2014	Asian Pac j Cancer Prev	Korea	R	62	3.0 T	Gadovist					x°		
King et al.	2012	Radiology	USA	R	149	3.0 T and 1.5 T	Magnevist	x						
King et al.	2012	Breast J	USA	R	88	1.5 T	Magnevist	x						
King et al.	2012	Eur Radiol	USA	R	330	3.0 T and 1.5 T	Magnevist	x						
King et al.	2011	Radiology	USA	R	1275	1.5 T	Magnevist	x						
Kohara et al.	2015	Nagoya	Japan	R	91	3.0 T	Magnevist					x °		
Koo et al.	2013	Eur J Radiol	Republic of Korea	R	52	1.5 T	Gadovist	x °						
Melsaether et al.	2014	AJR	USA	R	119	3.0 T and 1.5 T	Magnevist	x °						
Myers KS et al.	2015	Clin Breast Cancer	USA	R	168	1.5 T	Multihance							x
Park et al.	2015	BrJ Radiol	Republic of Korea	R	314	3.0 T and 1.5 T	Magnevist			x				
Preibsh et al.	2015	Eur Radiol	Germany	R	73	1.5 T	Gadovist					x •		
Price et al.	2014	Eur Radiol	USA	R	18	1.5 T	Magnevist					x°		
Scaranelo et al. ◆	2013	Radiology	Canada	R	147	1.5 T	Gadovist					x °		
Schrading et al. ◆	2014	Radiology	Germany	P	40	1.5 T	Magnevist	x °						
Tagliafico et al. ◆	2015	BJR	Italy	R	48	3.0 T	Multihance					x °		
Uematsu et al.	2012	Breast Cancer	Japan	R	70	1.5 T	Magnevist					x°		
Uematsu et al.	2011	Eur Radiol	Japan	R	146	1.5 T	Magnevist					x°		
Uematsu et al.	2012	Eur J Radiol	Japan	R	146	1.5 T	Magnevist					x°		
Yoon et al.	2015	Eur Radiol	Republic of Korea	R	145	3.0 T	Magnevist			x				

◆Articles with both qualitative and quantitative assessment of BPE; °early post-contrast images were used; ^the unenhanced images were not used; •only subctracted images were used; R: retrospective study; P: prospective study.

Table 2: Characteristic of the 24 studies that assess BPE quantitatively included in the systematic review. In the last column there is the name of the software used, when retrievable.

Study	Year	Journal	Country	Design	Study population	Magnetic field	Contrast media	Method used for quantitative assessment of BPE			Software used
								ROI	Fibroglandular tissue segmentation	Other	
Amarosa et al. ◆	2013	Radiology	USA	R	58	3.0 T	Magnevist			x	Interactive Data Language (Exelis, Boulder, Colo)
Chen et al.	2015	Translational Oncology	USA	R	46	1.5 T	Omniscan		x		
Chen et al.	2013	Magn Reson Imaging	USA	R	45	1.5 T	Omniscan		x		
Cho et al. ◆	2015	Eur J Radiol	USA	R	77	3.0 T	Magnevist	x			Matlab,Mathworks, Natick, MA, USA
Cubuk et al. ◆	2010	Rad Med	Turkey	R	26	1.5 T	Magnevist	x			
Hattangadi et al.	2008	Am J Roentgenol	USA	P	42	1.5 T	Magnevist	x			
Hegenscheid et al.	2012	Eur Radiol	Germany	P	651	1.5 T	Gadovist	x			Syngo 2008A MultiModality Workplace (Siemens Medical Solutions, Erlangen, Germany)
Hegenscheid et al.	2013	Radiology	Germany	P	651	1.5 T	Gadovist	x			Syngo 2008A MultiModality Workplace (Siemens Medical Solutions, Erlangen, Germany)
Jansen et al. ◆	2011	Eur Radiol	USA	R	101	1.5 T	Omniscan	x			CADstream research version 5.0 (Confirma, CA, USA)
Kajihara et al. ◆	2013	Magn Reson Med Sci	Japan	R	165	1.5 T	Magnevist	x			Aquarius (TeraRecon INc., San Mateo, CA, USA)
Kang et al.	2014	J Magn Reson Imaging	Korea	P	272	3.0 T	Magnevist	x			Extended MR Work Space (Philips Medical Systems)
Kim JY et al. ◆	2015	Magn Reson Imaging	Korea	R	81	3.0 T	Gadovist	x			
Kim MY et al. ◆	2013	Acta Radiol	Korea	R	133	1.5 T	Gadovist	x			
Kim SA et al. ◆	2014	Radiology	Republic of Korea	R	215	1.5 T	Multihance	x			
Klifa et	2011	J Magn	USA	R	16	1.5 T	Magne		x		

al.		Reson Imaging					vist				
Mazurowski et al.	2014	Radiology	USA	R	48	1.5 T	not clear			x*	
Mousa et al.	2012	Menopause	Canada	P	14	1.5 T	Gadovist/ Omniscan	x			
Scaranelo et al. ◆	2013	Radiology	Canada	R	147	1.5 T	Gadovist	x			
Schrading et al. ◆	2014	Radiology	Germany	P	40	1.5 T	Magnevist	x			View Forum (Philips, Best, the Netherlands)
Schrading S et al.	2015	Radiology	Germany	P	62	1.5 T	Magnevist	x			DynaCAD software package, version 3.0 (Invivo, a Philips Healthcare Company, Best, the Netherlands)
Tagliafico et al. ◆	2015	BJR	Italy	R	48	3.0 T	Multihance			x*	MedDensity©
van der Velden et al.	2015	Radiology	Netherlands	R	531	1.5 T	Prohance		x		Insight Segmentation and Registration Toolkit and Visualization Toolkit (Kitware, Clifton Park, NY) and MeVisLab software (MeVis Medical Solutions, Bremen, Germany)
Wu et al.	2015	Breast Cancer Res	USA	R	55	1.5 T	Omniscan		x*		
Yang et al.	2015	Med Phys	China	R	115★	1.5 T	Magnevist			x	

◆Articles with both qualitative and quantitative assessment of BPE; MR images; R: retrospective study; P: prospective study.
*Automatic method.

Table 3: Intra- and interreader agreement for all readings for qualitative BPE evaluation among the nine studies that assessed agreement by using kappa statistics.
In two studies (King et al. and Melsaether et al.) authors assessed the agreement also for dichotomized variables (low or high BPE).

Study [Reference number]	Year	Journal	Number of readers	Agreement	
				Intra-reader (for dichotomized variables)	Inter-reader (for dichotomized variables)
DeLeo et al.[22]	2015	AJR	2	n.a.	0.49
King et al.[31]	2012	Eur Radiol	2	n.a.	0.95
King et al.[8]	2011	Radiology	2	0.62(0.69)	0.47(0.57)
Melsaether et al.^[17]	2014	AJR	4	0.79(0.80)	0.45(0.47)
Preibsh et al.⬥[36]	2015	Eur Radiol	2	n.a.	Right breast:0.73 Left breast:0.77
Price et al.[37]	2014	Eur Radiol	3	n.a.	0.3-0.6
Scaranelo et al.[48]	2013	Radiology	2	n.a.	0.37
Tagliafico et al.[7]	2015	BJR	2	0.69	0.70
Yoon et al.[39]	2015	Eur Radiol	2	0.82	0.85

^pooled over all four readers; values after training at the end of the third lecture.
⬥kappa values before neoadjuvant chemotherapy.
n.a.: not available.

Table 3: Risk of bias table demonstrating overall risk of bias for each of the domains of patient selection, index test and reference standard, flow and timing. Qualitative studies. +: low risk of bias; -: high risk of bias; ?: unclear.

	Patient Selection	Index Test and Reference Standard	Flow and Timing
Albert et al.	+	+	+
Amarosa et al. ◆	+	+	?
Baek et al.	+	+	+
Cho et al. ◆	+	+	+
Choi et al.	?	+	?
Cubuk R et al. ◆	+	?	?
DeMartini et al.	?	+	+
DeLeo et al.	+	+	+
Dontchos et al.	+	+	+
Grimm et al.	+	-	?
Hambly et al.	+	+	-
Hansen et al.	+	+	+
Iacconi et al.	+	+	?
Jansen et al. ◆	?	+	?
Kajihara et al. ◆	?	+	?
Kawamura et al.	+	+	+
Kim JY et al. ◆	?	+	+
Kim MY et al.	+	?	+
Kim MY ◆	+	+	+

Kim SA et al. ◆	+	+	+
Kim YJ et al.	+	?	-
King et al.	+	+	+
King et al.	+	+	+
King et al.	+	+	+
King et al.	+	+	+
Kohara et al.	+	+	?
Koo et al.	+	+	+
Melsaether et al.	+	+	+
Myers et al.	+	-	?
Park et al.	?	+	?
Preibsh et al.	+	+	?
Price et al.	+	+	+
Scaranelo et al. ◆	+	+	+
Schrading et al. ◆	+	+	+
Tagliafico et al. ◆	+	+	+
Uematsu et al.	+	+	?
Uematsu et al.	+	+	?
Uematsu et al.	+	+	?
Yoon et al.	+	+	?

◆Studies that assessed BPE with both qualitative and quantitative methods.

Table 4: Risk of bias table demonstrating overall risk of bias for each of the domains of patient selection, index test and reference standard, flow and timing. Quantitative studies. +: low risk of bias; -: high risk of bias; ?: unclear.

	Patient Selection	Index Test and Reference Standard	Flow and Timing
Amarosa et al. ◆	+	+	?
Chen et al.	+	-	?
Chen et al.	+	+	?
Cho et al. ◆	+	+	+
Cubuk R et al. ◆	+	?	-
Hattangadi et al.	+	?	?
Hegenscheid et al.	+	+	+
Hegenscheid et al.	+	+	+
Jansen et al.□◆	+	+	?
Kajihara et al.□◆	?	+	?
Kang et al.	?	+	+
Kim JY et al.□◆	?	+	+
Kim MY et al.◆	+	?	?
Kim SA et al.◆	+	+	+
Klifa et al.	+	+	+
Mazuroski et al.	+	?	?
Mousa et al.	+	+	-
Scaranelo et al. ◆	+	+	+
Schrading et al.◆	+	+	+
Schrading et al.	+	?	+
Tagliafico et al. ◆	+	+	+

Van der Velden et al.	+	+	+
Wu et al.	+	+	+
Yang et al.	+	+	?

◆Studies that assessed BPE with both qualitative and quantitative methods.

Figure Legends

Figure 1: Flowchart for selection of studies.

Figure

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