

Magnetic Resonance Imaging of the Breast

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1. Introduction

Magnetic resonance imaging (MRI) of the breast was first performed in the late 1980s. At first, differentiation between benign and malignant breast lesions was primarily based on their differences in T1 and T2 relaxation times (Rausch et al., 2006). Due to the large overlap in T1 and T2 relaxation times in benign and malignant breast lesions, it became apparent that contrast administration was mandatory for reliable breast MRI. Heywang et al. demonstrated that breast carcinomas showed significant enhancement within 5 minutes after contrast administration (Heywang et al., 1989).

Since then, increasing field strengths, dedicated breast coil designs, and improvements in sequence protocols have led to a large improvement in diagnostic accuracy of breast MRI. Currently, the sensitivity of contrast-enhanced MRI for detecting breast cancer reaches 88%, with a specificity of 68%. The positive predictive value is reported to be 72%, with a negative predictive value of 85% (Bluemke et al., 2004). The reported sensitivity and specificity may vary in different publications due to differences in study populations, and technical and diagnostic criteria used. Reported sensitivities therefore vary from 83-100%, with reported specificities varying from 29-100% (Rausch et al., 2006).

These numbers are superior to mammography and ultrasound, and are independent of factors such as tumor histology, breast density, and hormonal therapy use. They also show that breast MRI is highly accurate for detecting breast cancer. However, due to the rather limited specificity, false-positive results are frequently observed, requiring additional imaging or (MR guided) biopsy, in turn causing patient anxiety and discomfort.

In this chapter, the technical aspects and proper indications of breast MRI are discussed. In addition, a systematic approach to the image interpretation of breast MRI is proposed.

2. Performing magnetic resonance imaging of the breast

2.1 Patient handling

Before performing breast MRI, it is important to instruct the patient thoroughly. It is important to inform the patient that lying comfortably and motionless is important for successful imaging of the breast. They should be instructed that administration of the contrast agent can result in various physical sensations, which may cause patient anxiety (and motion) when not properly instructed.

A dedicated breast coil should be used for breast MRI. These coils usually consist of a multichannel coil (nowadays up to 32-channel) with two loops in which the breasts are placed while the patient is lying in prone position. The breasts should be placed as deep as possible in the coil loops, with the nipples pointing downward if possible. To further reduce motion artefacts, the breasts can be gently fixated using cushions. Excessive compression should be avoided, as this might influence breast perfusion, and thus contrast enhancement pharmacokinetics.

In premenopausal women, the enhancement of the fibroglandular tissue after contrast administration is dependent of the menstrual cycle. MR imaging of the breast in the wrong phase of the menstrual cycle can result in strong glandular enhancement, complicating the interpretation of the images. Elective breast MRI is ideally performed in the first phase of the menstrual cycle, i.e. days 3-14, with day 1 being the first day of menstruation (Delille et al., 2005). In patients with proven breast cancer who undergo breast MRI as part of their preoperative staging, MRI should be performed at the earliest opportunity. In these cases, rapid presurgical patient work-up is preferred over optimal MR image quality.

2.2 Technical aspects

2.2.1 Field strengths

Increasing field strengths are associated with increased signal-to-noise (SNR) ratios. In order to acquire sufficient spatial resolution for accurate assessment of lesion morphology, it is generally accepted that field strengths of more than 1.5 Tesla are recommended for breast MRI (Weinstein et al., 2010). Theoretically, a higher field strength (e.g. 3 Tesla) increases the SNR for breast MRI. At a similar temporal resolution, this increased SNR might be used to increase spatial resolution, and thus improve lesion morphology evaluation and diagnostic accuracy.

In a proof-of-concept study, Kuhl et al. compared the accuracy of both 1.5 and 3.0 Tesla breast MRI in the same patients. Although the study population was small (n=37, total of 53 breast lesions, both malignant and benign), they demonstrated that the overall image quality scores for the dynamic contrast-enhanced series were higher (p<0.01). They also demonstrated that at 3.0 Tesla, the differential diagnosis of enhancing lesions was possible with a higher diagnostic confidence, as reflected by a larger area under the ROC-curve (Kuhl et al., 2006).

In another proof-of-concept study by Pinker et al., contrast-enhanced breast MRI was performed on a 3 Tesla MRI scanner in 34 patients (having 55 breast lesions). Their imaging protocol enabled accurate detection and assessment of breast lesions, with a sensitivity of 100% (95% confidence interval 90.6-100.0%). The specificity was 72.2%, with a 95% confidence interval of 49.1-87.5% (Pinker et al., 2009). Although these preliminary results are promising, there is no strong evidence to date of the superiority of 3.0 over 1.5 Tesla breast MR imaging.

2.2.2 Imaging planes

In the past, breast MR imaging was usually performed in a sagittal plane. The advantage of this imaging plane was that a relatively small field-of-view could be selected to cover the

breast, resulting in an improved spatial resolution. However, simultaneous contralateral breast cancer can be detected in 3% of the cases (Lehman et al., 2007), indicating that bilateral breast imaging is strongly recommended. Bilateral sagittal imaging of the breast can lead to decrease of SNR and spatial resolution (Kuhl, 2007). Therefore, current bilateral imaging protocols use the transverse or coronal plane. Coronal imaging of the breast tends to give more respiratory motion artifacts. Also, nipple and chest wall involvement is more difficult to detect on coronal images. Therefore, the transverse imaging plane is preferred when bilateral breast imaging is performed (Kuhl, 2007).

2.2.3 Spatial and temporal resolution

Breast MRI needs to be performed with adequate spatial resolution in order to assess lesion morphology accurately. It is widely adopted that an optimal breast MRI should have a minimum size threshold for detection of lesions of 5 mm. Therefore, a voxel size of at least 2.5 mm in any direction should be used (Mann et al., 2008). However, higher in-plane spatial resolution results in more accurate lesion morphology assessment. Therefore, the minimal in-plane spatial resolution as recommended by the American College of Radiology is ≤ 1 mm (Weinstein et al., 2010).

2.2.4 Temporal resolution and contrast-enhanced dynamic T1 weighted imaging sequences

Gadolinium (Gd, atom number 64) is a chemical that belongs to the element category of the lanthanides. Due to its paramagnetic properties, it is often used as an intravenous contrast agent in MRI. However, free Gd-atoms are highly toxic and as a result, gadolinium-based contrast agents consist of a chelated Gd-complex to render it non-toxic. Gd-based contrast agents lower T1, T2, and T2* relaxation times. Since the decrease is highest for T1 relaxation times, contrast-enhanced MR imaging sequences are mostly T1-weighted.

The contrast agent is administered intravenously with an automated injector to ensure a continuous inflow of contrast. Although the optimal dose is unknown, a dose of 0.1-0.2 mmol per kilogram of body weight and a flow rate of 3 mL/second is generally accepted (Kuhl, 2007, Rausch et al., 2006). The administration is followed by a saline flush to ensure complete administration of the dose.

After intravenous administration, the contrast agent leaks through immature ('leaky') microvessels that were formed by tumor angiogenesis (Carmeliet et al., 2000, Hashizume et al., 2000, Jansen et al., 2009). As a result, breast lesions tend to demonstrate a peak enhancement between 90-120 seconds. In order to assess the pharmacokinetic enhancement curves (see paragraph 4 on 'Image interpretation'), a minimum of three different time points should be included: first, a non-enhanced scan; second, a scan which captures the peak enhancement of the lesion, and third, a scan which shows the delayed enhancement characteristics of the lesion. In order to capture the peak enhancement of the lesion, temporal resolution of the acquisitions performed should be in the order of 60-120 seconds, but they should not compromise the in-plane spatial resolution (which must be used for lesion morphology). In order to acquire a reliable measurement of the delayed enhancement characteristics, it is recommended to continue imaging until approximately 8 minutes after contrast administration (Weinstein et al., 2010).

2.2.5 T2-weighted imaging sequences

This sequence is often used as ‘problem solver’ sequence, since it provides additional relevant information on different breast lesions, narrowing down the differential diagnostic considerations.

For example, breast cysts (when inflamed) can show rim enhancement after administration of contrast agent. In these cases, signal intensity of the cyst is often slightly increased on the non-enhanced T1-weighted image due to the proteinaceous content of the cyst. Due to the high water content and, consequently, the longer T2 relaxation times, cysts show a very high signal intensity on T2-weighted images, and can thus be distinguished (in combination with their sharp margins) from malignant breast lesions (Figure 1).

In 1999, Kuhl et al. demonstrated the additional value of T2-weighted imaging in breast MRI by examining 205 benign and malignant tumors. By means of visual assessment of the lesion appearance on T2-weighted fast spin echo images, they were able to distinguish between fibroadenomas and breast cancers, with a respective (age-dependent) sensitivity, specificity, positive predictive value, and negative predictive value for patients over 50 years of age of 89%, 62%, 85%, and 68% (Kuhl et al., 1999a).

In another recent study, Baltzer et al. evaluated 316 patients, of which 65 showed nonmass like enhancement on breast MRI. BI-RADS predictors could not discriminate between benign and malignant lesions with respect to nonmass like enhancement. However, the signal intensity of T2-weighted images and the presence of cysts improved the diagnostic accuracy, with a sensitivity of 91% and a specificity of 65% (Baltzer et al., 2011).

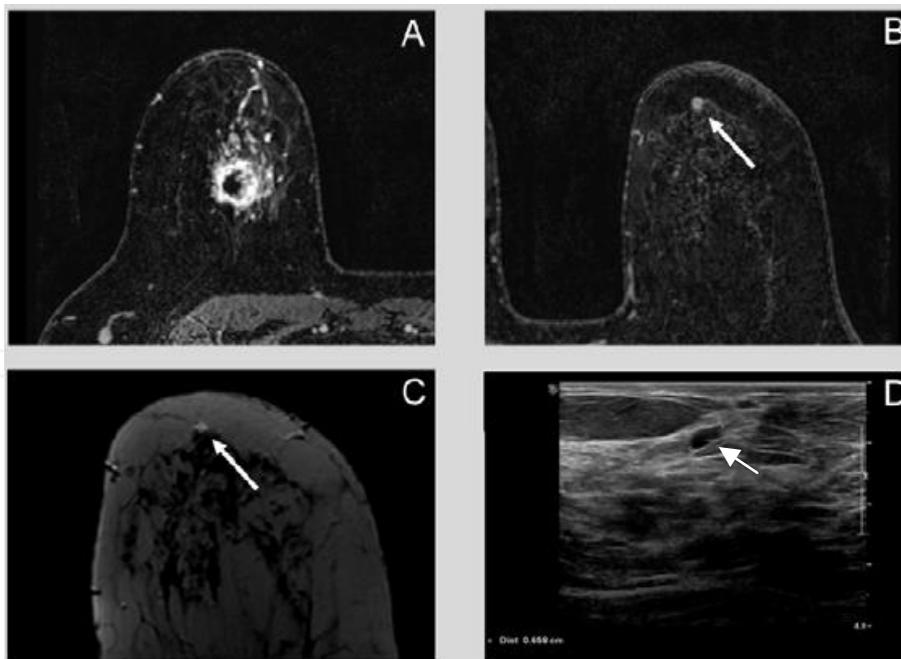


Fig. 1. Example of the added value of T2-weighted breast imaging. (A) shows the primary metaplastic tumor in the right breast. At MRI, a suspicious lesion was observed in the contralateral breast (B), with a corresponding high signal intensity on T2-weighted imaging (C). Second look ultrasound demonstrated a small simple cyst at this site, which was subsequently aspirated (D).

However, both benign and malignant breast lesions may show increased signal intensity on T2-weighted images. In a review of the histopathologic findings in such a group of lesions, Santamaria et al. stated that MR signal hyperintensity is most likely to be associated with the following conditions: extensive necrosis, (micro)cysts, fatty or sebaceous components, mucinous stroma, loose myxoid stroma, edema or hemorrhage (Santamaria et al., 2010). But also other benign entities, such as myxoid fibroadenomas, oil cysts, and intramammary lymph nodes are known to show an increased signal intensity on these sequences (Kuhl, 2007). In addition, some malignant lesions might also demonstrate an increased signal intensity on T2-weighted images, especially mucinous carcinomas due to their mucinous content (Santamaria et al., 2010).

3. Indications for breast MRI

Breast MRI can be used for a variety of diagnostic problems. Proper indications for performing breast MRI (as supported by the European Society of Breast Cancer Specialists and the European Society of Breast Imaging) are: inconclusive findings in conventional imaging, preoperative staging, unknown primary cancer, evaluation of therapy response in neoadjuvant chemotherapy, imaging of the breast after conservative therapy, screening of the high risk patient, breast implant imaging, and MR-guided interventions, such as biopsy and lesion localization (Mann et al., 2008, Sardanelli et al., 2010, Yeh, 2010).

3.1 Inconclusive findings in conventional imaging

In a study by Berg et al., 177 malignant lesions in 121 breast were evaluated with mammography, ultrasound, and MRI. They showed that the sensitivity for detecting tumors decreased from 100% in fatty breasts, to only 45% in extremely dense breasts. The sensitivity of mammography was highest for invasive ductal carcinoma (89%), versus 55% for ductal carcinoma in situ, and only 34% for invasive lobular carcinoma. Ultrasound demonstrated a higher sensitivity for both invasive ductal (94%) and invasive lobular carcinoma (86%). Sensitivity for detecting ductal carcinoma in situ was worse for ultrasound (47%), presumably owing to the fine microcalcifications associated with ductal carcinoma in situ, which are much better visualized on mammography. However, MRI was superior to all other modalities and for all tumor types: it detected 95% of the cases of invasive ductal carcinoma, 96% of the cases of invasive lobular carcinoma, and 89% of the cases of ductal carcinoma in situ (Berg et al., 2004). Due to this superior ability to detect breast cancer, MRI can be used as a problem-solving modality, when inconclusive findings in conventional imaging are encountered. For example, patients can be referred from the mammography screening program with abnormalities owing to a presumable superposition of fibroglandular tissue. These patients can undergo a single breast MRI to exclude possible underlying malignancies. Also, if there are discrepancies between clinical examination, mammography, and/or ultrasound, MRI can serve as a powerful problem-solving entity.

This was demonstrated by Moy et al., who retrospectively reviewed all MRI examinations (n=115) of the breast that were performed for inconclusive findings at mammography. They found no suspicious correlate on MRI in 87% of the cases. In the remaining 15 cases (13%), 6 malignancies were found. However, 18 incidental lesions were also observed on these examinations (Moy et al., 2009). Similar results were observed by Yau et al., who reviewed

3001 MRI exams and found 204 MRI exams that were performed for 'problem solving'. Of these 204 exams, 42 were graded as BI-RADS category 4 or 5 (see also paragraph 4.4). Malignant lesions were found in 14 cases, whereas benign findings or follow-up imaging encompassed the remaining 28 cases. 162 exams were graded as BI-RADS category 0, 1, 2, or 3. In this group, biopsy was performed in 28 cases, revealing 1 malignant lesions. In the remaining 134 cases, no biopsy was performed within the following 12 months (Yau et al., 2011). Both studies concluded that MRI is a valuable tool for evaluation of inconclusive mammography findings, but patient selection criteria should be strict because of the high incidence of incidental lesions seen on MRI.

3.2 Preoperative staging

The assessment of tumor size and additional tumor foci is essential for establishing the proper surgical and post-surgical treatment of each individual patient.

Recently, Uetmatsu et al. compared the ability to assess breast cancer extension for mammography, ultrasound, breast MRI, and even multidetector row computed tomography (MDCT). In this study of 210 breast tumors, they showed that the accuracy for establish the tumor extent (compared to histopathological results) was highest for breast MRI: 76%. The accuracy of establishing the tumor extent was lower for the other modalities: MDCT 71%, ultrasound 56%, and mammography 52%. However, they showed that MRI and ultrasound had a substantial risk of overestimating the tumor size. With respect to ductal carcinoma in situ extent, their study showed that the accuracy of breast MRI was also highest: 89% (followed by MDCT (72%), ultrasound (61%), and mammography (22%)). They concluded that breast MRI had the highest accuracy for assessing the true breast cancer extent, but emphasize that there is a risk of overestimation, which should be considered in pre-surgical planning (Uematsu et al. 2008). In line with these results, the superiority of assessing the proper breast tumor extension was also demonstrated by several other studies (Mann et al., 2008, 2008b).

Also, MRI can be helpful for detecting additional tumor foci (Figure 2). In a study of 969 patients by Lehman et al., simultaneous contralateral breast cancer was detected by breast MRI in 3% of the cases (Lehman et al., 2007).

Tumor multifocality or multicentricity can also be accurately assessed by MRI (Figure 3). For instance, this was demonstrated by Drew et al. in their study of 334 women, with 178 confirmed cancer cases. With preoperative breast MRI, multifocal or multicentric breast cancers was suggested in 38% of the cases. In this particular group, histology eventually demonstrated multifocality or multicentricity in 74% of the cases. Unifocal breast cancer was found in 22% of the cases, benign breast disease in 4%. Their observations resulted in a sensitivity of breast MRI for detecting multifocal/multicentric cancer of 100%, with corresponding specificity, positive predictive value, and negative predictive value of 86%, 73%, and 100%, respectively (Drew et al., 1999).

Although these results seem promising, the effectiveness of performing pre-operative breast MRI was not evaluated until recently. In 2010, the COMICE trial, by Turnbull et al., randomly assigned a total of 1623 patients to undergo either pre-operative breast MRI (n=816) or no breast MRI (n=807). They demonstrated that next to the conventional triple

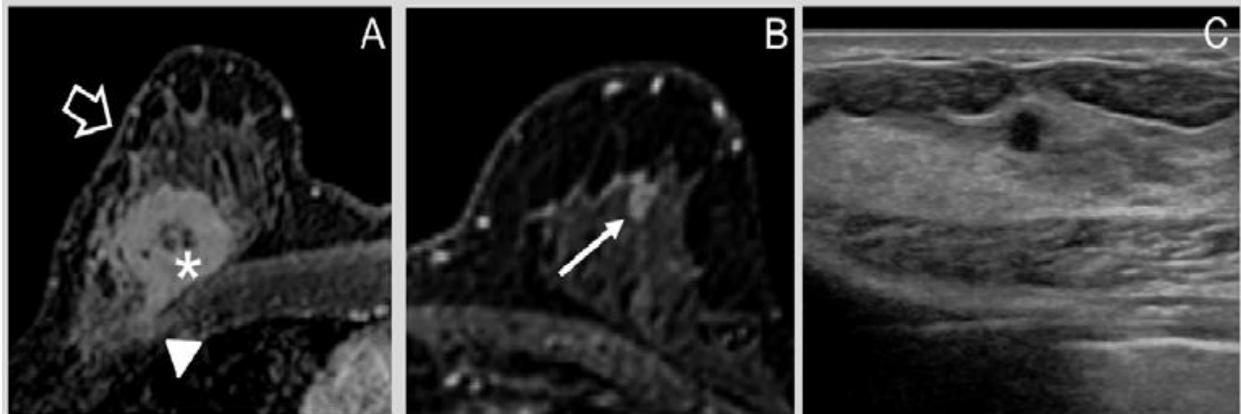


Fig. 2. Detection of contralateral breast cancer by breast MRI. (A) shows the primary index tumor in the right breast, presenting as an irregular mass with rim enhancement. The tumor shows a surrounding area of nonmass-like enhancement, with skin enhancement (open arrow) and pectoral muscle ingrowth (arrow head). (B) shows an additional small enhancing mass in the left breast (arrow), which corresponded with a small hypoechoic mass on second look targeted ultrasound (C). Histologic biopsy of this small mass revealed invasive ductal carcinoma, similar to the primary mass in the right breast.

assessment performed in breast cancer, addition of a pre-operative breast MRI did not result in a significantly reduced re-operation rate (odds ratio 0.96, 95% confidence interval 0.75-1.24, $p=0.77$, Turnbull et al., 2010).

In another (randomized controlled) trial of 418 patients (the MONET trial), Peters et al. allocated 207 patients to preoperative staging with MRI, and 21 patients to the control group (no preoperative MRI). They found that the number of re-excisions performed because of positive resection margins after primary breast conserving therapy was increased in the MRI group: 34% in the MRI group versus 12% in the control group ($p=0.008$). The number of conversions to mastectomy were similar (Peters et al., 2011).

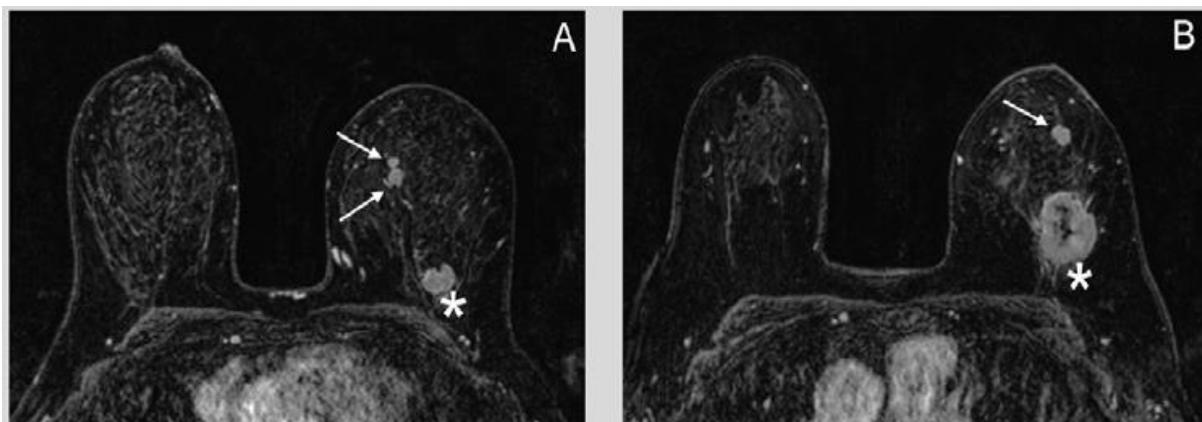


Fig. 3. Detection of tumor multifocality and/or multicentricity by breast MRI. (A) shows the index tumor in the lateral side of the left breast (*), with additional tumor deposits in the medial part of the breast (arrows), resulting in a multifocal, multicentric malignancy. (B) shows the index tumor in the lateral side of the left breast (*), with an additional tumor deposit in the same quadrant (arrow), resulting in a multifocal malignancy. Both cancers proved to be invasive ductal carcinomas at biopsy.

However, both studies have some limitations. For example, the COMICE trial recruited patients from 45 centres, resulting in a large variation of radiologic experience when evaluating the breast MRI exams. The MONET trial only evaluated non-palpable breast tumors and a subanalysis of their results showed that the volume of the lumpectomy specimen was significantly larger in the control group than in the group which was assigned to preoperative breast MRI.

3.3 Unknown primary cancer

This indication refers to the group of patients who are diagnosed with metastases, but in who a primary tumor cannot be identified. Schorn et al. demonstrated that MRI was helpful in patients with an unknown primary cancer and a negative mammography and ultrasound of the breasts. Breast cancer was detected by MRI in almost 50% of the cases. However, it should be mentioned that this study only consisted of 14 patients (Schorn et al. 1999). When looking only at axillary lymph node metastasis, Orel et al. demonstrated in a study of 38 patients that breast MRI could detect the previously unknown breast cancer in even 86% of the cases (Orel et al. 1999). Therefore, in patients diagnosed with metastasis and negative mammography and ultrasound, breast MRI should be strongly considered.

3.4 Evaluation of therapy respons in neoadjuvant chemotherapy

In a study by Yeh et al., 31 women who underwent neoadjuvant therapy for palpable breast cancer were included. Agreements with the therapy respons rate as measured by clinical examination, mammography, ultrasound, and breast MRI (as compared with pathology results) were 19%, 26%, 35%, and 71%, respectively. Of these four modalities, MRI agreed with the pathology results significantly more often: $p < 0.002$ for all three comparisons with MRI (Yeh et al., 2005).

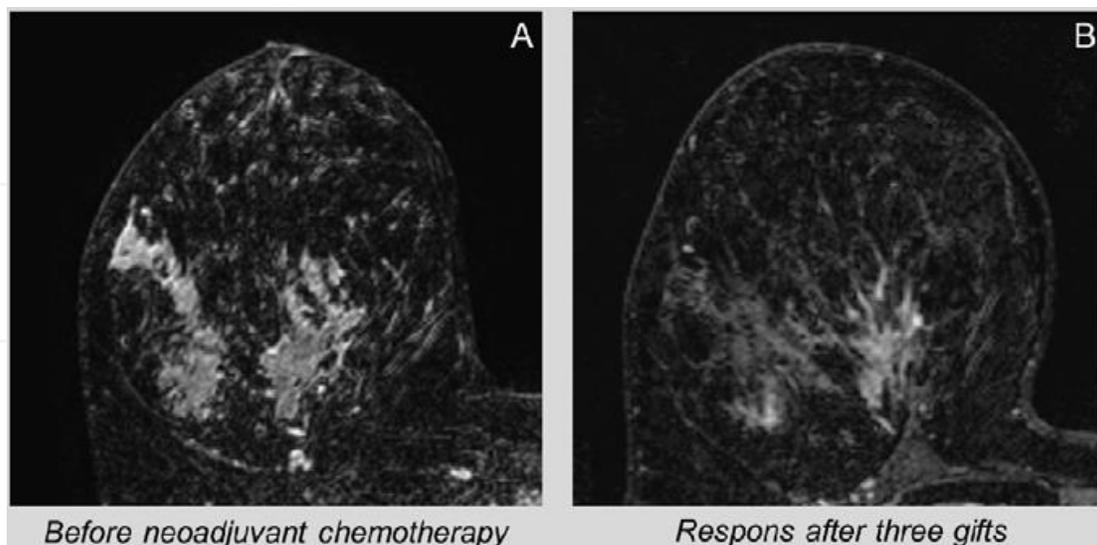


Fig. 4. Evaluation of tumor respons after neoadjuvant chemotherapy. (A) shows the initial (large) tumor (invasive lobular carcinoma at biopsy) in the right breast, presenting as a large area of regional nonmass like enhancement. (B) shows significant reduction in tumor size and enhancing volume after three gifts of chemotherapy. Thus, adequate chemotherapy respons was proven and continued in this patient.

In another study, Shin et al. prospectively included 43 patients with locally advanced or inflammatory breast cancer who underwent neoadjuvant therapy. The assessment of therapy response was evaluated for clinical examination, mammography, ultrasound, and breast MRI. The intraclass correlation coefficients between predicted tumor size (as assessed by the different modalities) and the pathologically determined tumor size were calculated. The values were highest for breast MRI (0.97), followed by ultrasound (0.78), mammography (0.69), and clinical examination (0.65). Agreement between the prediction of final therapy response and the response assessed by pathology were expressed as the Kappa-value and were highest for MRI (0.82), followed by ultrasound (0.50), mammography (0.44), and clinical examination (0.43, Shin et al., 2010).

These results show that breast MRI is the most suitable imaging modality to assess chemotherapy response (Figure 4). In addition, it is significantly more accurate in assessing the response than non-imaging techniques, such as clinical examination.

3.5 Imaging of the breast after conservative therapy

There are three important reasons to perform breast MRI after breast conserving therapy: 1) an evaluation tool for detecting residual disease after positive tumor margins, 2) evaluation when recurrence is suspected, and 3) screening for patients that underwent breast conservative therapy in the past (Mann et al., 2008).

Due to the strong enhancement of the breast tissue immediately after surgery (which can last for more than a year), the interpretation of breast MR images for residual disease is hampered (Orel et al., 1997). Lee et al. concluded that the evaluation of MRI for residual disease in patients with close or positive margins is limited due to overlap in the appearances of benign and malignant lesions (Lee et al., 2004). Image interpretation can also be hampered by post-radiation enhancement of the breast, which is known to occur up to three months after the last irradiation of the breast. Nonetheless, Morakkabati et al. demonstrated that the detection and characterization of breast lesions can be performed with comparable diagnostic accuracies in irradiated breasts (when compared with non-irradiated breasts, Morakkabati et al., 2003).

Finally, the risk of local recurrence is dependent on the age of the patient at the time of the diagnosis (Mann et al., 2008). Even with additional booster radiation therapy, these patients still have a life-time risk of developing breast cancer of probably more than 20%, which is equal to the life-time risk for breast MRI screening for the high risk patient, as discussed in paragraph 3.6. Therefore, annual MRI screening can be considered for patients that underwent breast conservative surgery for primary breast cancer, but large trials are needed to confirm this assumption.

3.6 Screening of the high risk patient

The first non-randomised studies to determine the additional value of breast MRI to conventional mammography in women who were BRCA1 or -2 gene mutation carriers, or who had a lifetime risk of at least 20-25% for developing breast cancer were published in the 1990s. Based on these studies initiated in the Netherlands, the United Kingdom, the United States, Canada, Italy, and Germany, the American Cancer Society (ACS) and European Society of Breast Imaging (EUSOBI) recommended annual MR evaluation of the breasts for

all women with a lifetime risk for breast cancer of more than 20-25% (Saslow et al., 2007, Mann et al., 2008). These women include known BRCA gene mutation carriers, first-degree untested relatives of a BRCA gene mutation carrier, women with radiation to the chest wall between ages 10 and 30 years, Li-Fraumeni syndrome and first degree relatives, and Cowden syndrome with first degree relatives (Boetes, 2010).

3.7 Breast implant imaging

Past publications have shown that breast MRI can be an excellent modality to assess breast implant integrity. The sensitivity of MRI for detecting implant rupture can be as high as 80 to 90%, with a specificity of over 90% (Brown et al., 2000, Cher et al., 2001, Hölmich et al., 2005). However, specific sequences have to be used to optimize the visualisation of silicone and to provide concurrent suppression of water signal. Depending on the reason the study was requested, these prosthesis-specific sequences can replace, or can be added to the previously discussed dynamic, contrast-enhanced breast MR imaging protocol. It is the authors' opinion, however, that a more elaborate description on the technical aspects and interpretation of images in breast implant imaging is beyond the scope of this chapter. An instructive pictorial essay on breast implant rupture was recently published by Colombo et al. (Colombo et al., 2011).

3.8 MR guided interventions

Despite the high sensitivity of breast MRI, its specificity is relatively low. In practice, this leads to many false-positive findings, which require additional tissue sampling to exclude malignancy. In 2009, an interdisciplinary European committee established a consensus on the uses and technique of MR-guided vacuum-assisted breast biopsies (Heywang-Köbrunner et al., 2009). Although an elaborate discussion on the indications and techniques of MR guided breast interventions is beyond the scope of this chapter, the authors wish to emphasize some essential recommendations of this consensus meeting

Before performing any kind of MR guided breast intervention, a full imaging work-up should be completed. It must be absolutely certain that the culprit lesion can only be visualized by breast MRI. Patients should not have any kind of contra-indication for MRI or contrast administration. Relative contra-indications are lesions close to the chest wall who are estimated to be unfeasible or unsafe, patients with coagulation disorders, and patients with breast implants. When these criteria are met, MR guided biopsy of a breast lesion should be performed using a vacuum-assisted breast biopsy system (core needle biopsies are not recommended). Minimum probe size should be 11 Gauge, and the average number of cores taken should be 24 or more (or an equivalent volume if a larger probe is used). The intervention does not stop with acquiring the samples: proper correlation between histopathologic results and MR findings should be performed, preferably in a multidisciplinary setting. If the correlation is uncertain, re-biopsy or short-term follow-up should be considered (Heywang-Köbrunner et al., 2009).

4. Image interpretation

According to the Breast Imaging Reporting and Data System (BI-RADS), the interpretation of breast MR images should start with the analysis of the type of enhancement observed.

Three categories of enhancement can be observed: focal, mass-, and nonmass-like enhancement (Figure 5, Molleran et al., 2010).

Subsequently, shapes and margins of the lesions should be assessed in the case of masslike enhancement. In the case of nonmass-like enhancement, it should be assessed whether this enhancement pattern is linear, ductal, regional, or segmental. In addition, the reader should assess if the nonmass-like enhancement is clumped, in other words beaded or cobblestonelike.

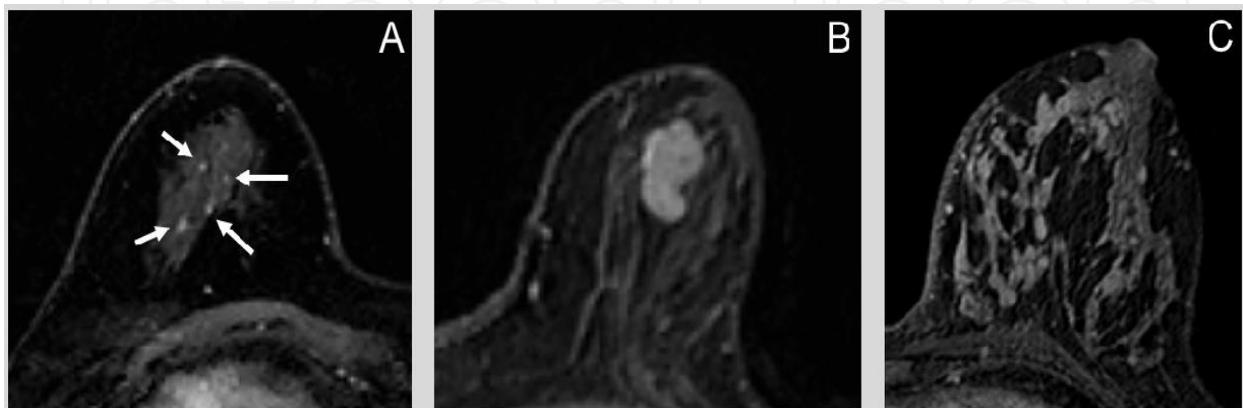


Fig. 5. Examples of focus (A), mass (B), and segmental (clumped) nonmass-like enhancement (C).

Finally, the enhancement characteristics of the lesion should be assessed by looking at both the internal enhancement characteristics and the signal intensity time curves. Internal enhancement characteristics can be described as homogeneous, heterogeneous, rim enhancement, or dark internal septations (American College of Radiology, 2003). Lesions can demonstrate slow, intermediate, or rapid contrast enhancement in the initial enhancement phase. In general, this initial enhancement phase can be followed by three different types of enhancement curves in the delayed phase: persistent enhancement, plateau phase, or wash-out. The enhancement characteristics of lesions can be indicative for their benign or malignant character.

By combining the findings of these different analyses, the radiologist estimates the likelihood of a lesion being benign or malignant. This estimation can be expressed in the final conclusion of the report as the BI-RADS classification, and should be the basis for management recommendations (i.e. biopsy or follow-up).

4.1 Focal, mass-, and nonmass-like enhancement

Focal enhancement can be described as small (less than 5 mm) area of enhancement that cannot be specified otherwise. A mass is a lesion that is visible in three dimensions and which occupies a space. Masses can be round, oval, lobulated, or irregular, and may have smooth, irregular, or spiculated margins. Nonmass-like enhancement is an area of enhancement that does not belong to a three dimensional mass or that has no distinct mass characteristics (American College of Radiology, 2003, Erguvan-Dogan et al., 2006). Nonmass-like enhancement patterns can be divided in linear, ductal, segmental, and regional enhancement (Figures 5 and 6).

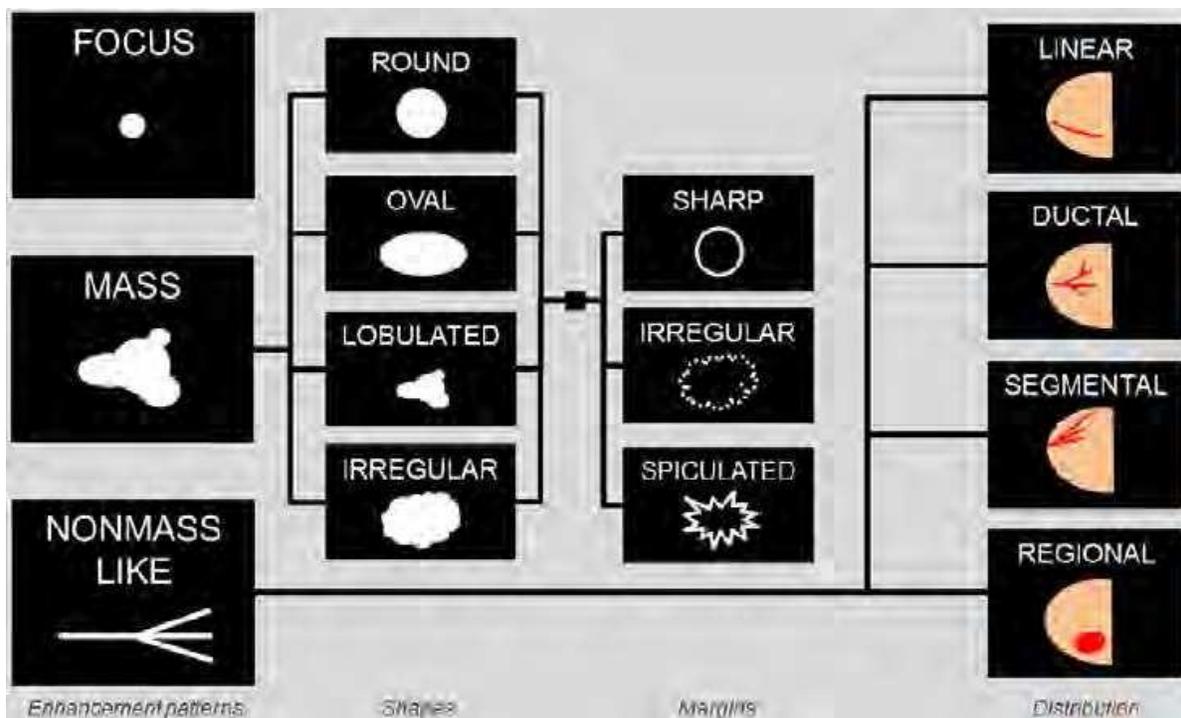


Fig. 6. Proper terminology (according to the BI-RADS lexicon) for enhancement patterns, shapes, margins, and nonmass-like enhancement distributions.

Linear nonmass-like enhancement is defined according to the BI-RADS lexicon of the American College of Radiology as 'enhancement in a line that is not definitely in a duct'. Ductal enhancement can be defined as 'enhancement in a line that points towards the nipple, and may have branching, conforming to a duct'. Segmental enhancement can be defined as 'a triangular region or cone of enhancement, with the apex pointing towards the nipple'. Finally, regional enhancement can be defined as 'enhancement in a large volume of tissue not conforming to a ductal distribution' (American College of Radiology, 2003).

Jansen et al. recently investigated the pathology and kinetics of mass, nonmass, and focal enhancement in a retrospective study using dynamic contrast-enhanced breast MRI. They analyzed a total of 852 breast lesions (histologically proven) in 697 patients. Of the lesions demonstrating mass-like enhancement (n=552), 71.7% proved to be malignant. Of the lesions demonstrating nonmass-like enhancement (n=261), 81.2% proved to be malignant. The remaining lesions demonstrated focal enhancement (n=30), which were usually benign (76.9%). Malignant mass- and nonmass-like enhancing lesions differed significantly in their pathology ($p < 0.0001$), with mass-like enhancing lesions usually consisting of invasive ductal carcinoma and nonmass-like enhancement usually consisting of ductal carcinoma in situ. Similarly, benign mass- and nonmass-like enhancing lesions differed significantly in their pathology ($p < 0.002$), with the former usually consisting of fibroadenomas and the latter usually presenting fibrocystic changes. Finally, the predominant pathology of focal enhancing lesions was fibrocystic changes (Jansen et al., 2011).

4.2 Morphologic descriptors in masslike- and nonmass-like enhancement

Margins of masses can be described as smooth (or sharp), irregular, or spiculated. Similar to mammography, some morphologic features of a lesion are more associated with

malignancy than others (Lieberman et al., 1998). Past studies showed that spiculated margins, irregular shapes, and linear/ductal nonmass-like enhancement had the highest positive predictive values for malignancy (Nunes et al., 1997, 2001). However, these studies included patients with mammographic or palpable findings, creating a potential bias in the study population.

Therefore, Lieberman et al. performed a retrospective review of 100 consecutive solitary MR imaging-detected lesions. For mass-like enhancement, margins and shape were evaluated. With respect to lesion margins, spiculated margins had the highest positive predictive value for malignancy (80%), much higher than irregular (22%) and smooth (17%) margins. With respect to lesion shapes, irregular shapes had the highest positive predictive value for malignancy (32%), lobular shapes had a positive predictive value for malignancy of only 13% (Lieberman et al., 2002).

In the same study, the pattern of nonmass-like enhancement was evaluated. With respect to linear or ductal enhancement, clumped enhancement (or beadlike enhancement) had a positive predictive value for malignancy of 31%. Smooth linear enhancement was not observed in malignant lesions. Clumped regional enhancement had a positive predictive value of 67%, whereas clumped segmental enhancement had a positive predictive value of 67% too (Lieberman et al., 2002).

In addition, Siegmann et al. looked at lesion size as an additional descriptor for the assessment of malignancy. They showed in a study of 51 lesions (in 45 patients) that lesions with a diameter of more than 10 mm have a higher positive predictive value (45.5%) than lesions smaller than 10 mm (27.6%, Siegmann et al., 2002).

To summarize, features that have the highest positive predictive value for malignancy are spiculated (ill-defined) margins and irregular shapes (based on morphology alone and in the case of masslike enhancement). For nonmass-like enhancement, features that have the highest positive predictive value are clumped linear, segmental or regional enhancement. Lesions larger than 10 mm have a higher positive predictive value for being malignant than lesions ≤ 10 mm (Tse et al., 2007).

4.3 Kinetic analysis of the signal intensity time curves

Lesion enhancement is described as homogeneous, heterogeneous, rim enhancement, or enhancement with dark internal septations (American College of Radiology, 2003, Figure 7).

In a landmark paper by Kuhl et al., the value of signal intensity time curves was evaluated with respect to the differential diagnosis of enhancing breast lesions. A total of 266 breast lesions (101 malignant, 165 benign) were examined using a dynamic contrast-enhanced breast imaging protocol. The relative enhancement of breast lesions was assessed by drawing a region-of-interest in the lesion itself. The enhancement was then calculated according to the following formula:

$$\text{Relative signal enhancement (\%)} = (SI_{\text{post}} - SI_{\text{pre}}) / SI_{\text{pre}} \times 100$$

In this formula, SI_{pre} and SI_{post} represent pre-contrast and post-contrast signal intensities, respectively. By calculating the signal intensity time curves, it was demonstrated that enhancement patterns can be divided into two phases: early enhancement (from contrast

administration to approximately two minutes post-contrast, or when the curve starts to change), followed by the delayed enhancement.

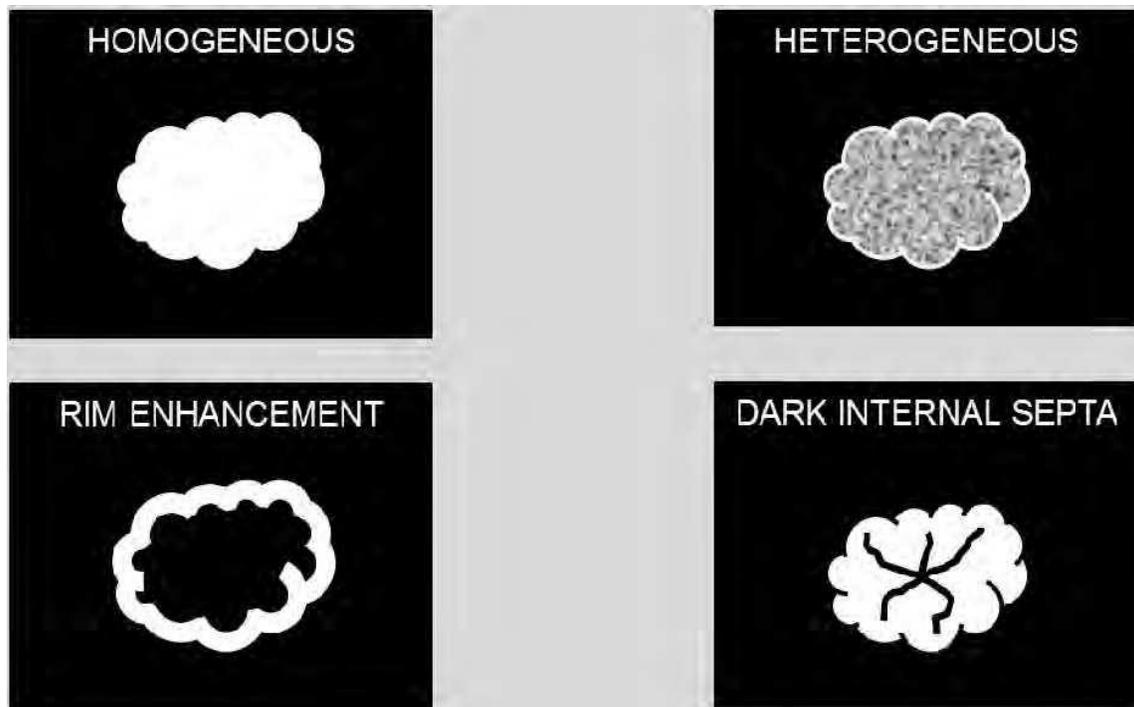


Fig. 7. Proper terminology (according to the BI-RADS lexicon for lesions enhancement patterns) homogeneous, heterogeneous, rim enhancement, and enhancement with dark internal septa.

For the early enhancement phase, it was assumed that benign lesions had a (slow) enhancement of 60% or less. Indeterminate lesions were assumed to have an (intermediate) enhancement of more than 60%, but less than 80%. Finally, malignant lesions were assumed to have a (strong) enhancement of more than 80%. For these assumptions, the diagnostic accuracies in this study were: sensitivity 91%, specificity 37%, positive predictive value 47%, negative predictive value 87%, diagnostic accuracy 58%. Mean peak enhancement was significantly higher for malignant lesions than for benign lesions: mean enhancement 104% versus 72%, $p < 0.001$ (Kuhl et al., 1999b).

For the delayed phase, three different type of signal intensity curves were defined. A type I curve was characterized by a persistent increase in signal intensity over time. A type II curve was characterized by a plateau in signal intensity values over time. Finally, a type III curve was characterized by a so-called washout, i.e. the signal intensity decreases in time after the initial upslope in the early enhancement phase (Figure 8).

For benign lesions, a type I curve was observed in 83.0% of the cases. A type II curve was observed in 11.5% of the cases, whereas a type III curve was hardly seen in benign lesions: 5.5% of the cases. For malignant lesions, a type III curve was most frequently observed: 57.4% of the cases. A type II curve was observed in 33.6% of the cases, whereas a type I curve was infrequently seen in these cases: 8.9%. The assessment of the signal intensity timecurves had an excellent interreader agreement with a Kappa-value of 0.849, $p < 0.001$ (Kuhl et al., 1999b).

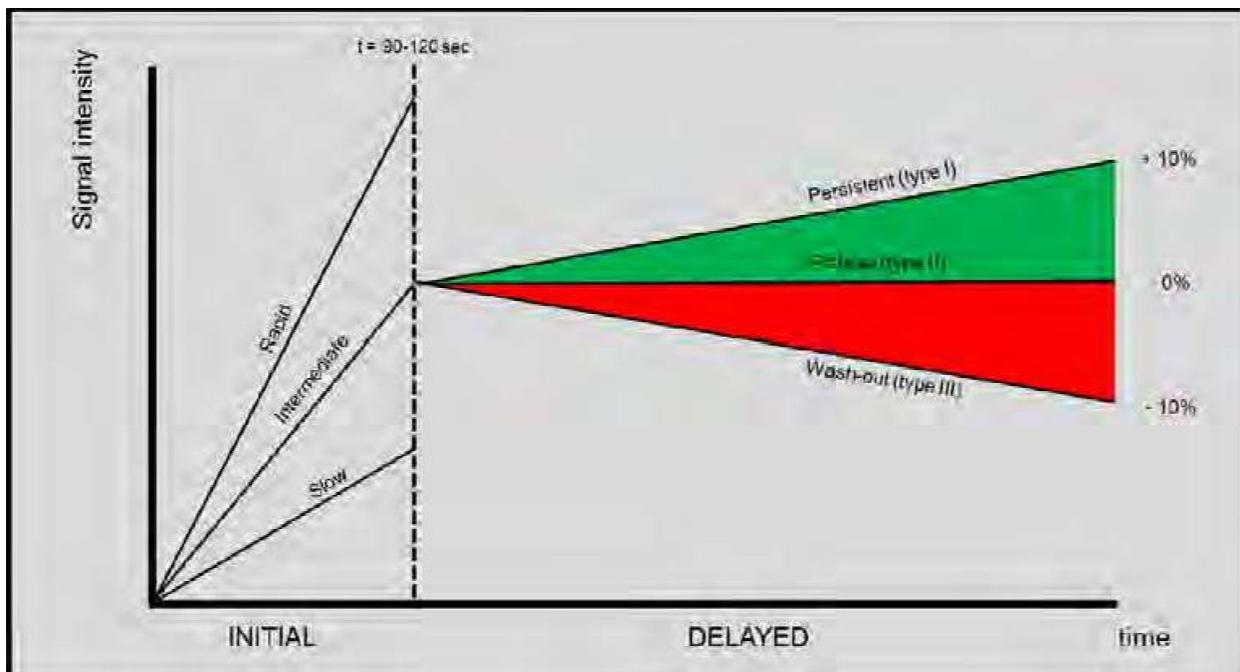


Fig. 8. Possible enhancement characteristics that can be observed in dynamic contrast-enhanced breast MRI.

In the past, Jansen et al. demonstrated that analysis of the signal intensity time curve can help distinguish between benign and malignant mass lesions effectively, but the analysis is not that useful in discriminating between benign and malignant nonmass-like lesions. Although their pilot study only consisted of a total of 108 breast lesions with 70 observed masses, 44 of which were malignant and 26 benign. There were 38 nonmass-like lesions observed, of which 31 were malignant and 7 benign. Despite these relatively small numbers, they showed that analysis of the signal intensity time curve was helpful in distinguishing between benign and malignant masses on MRI. However, it could not be used to accurately distinguish between benign and malignant nonmass-like lesions. Therefore, they suggested that analysis of the signal intensity time curves of nonmass-like enhancement is not very useful and that morphology analysis should be favored (Jansen et al., 2008).

In summary, it is advised by the BI-RADS MRI lexicon that the signal intensity curve of a lesion should be described qualitatively. A proper region-of-interest should at least contain 3 pixels and if this enhancement of the lesion is heterogeneous, the most suspicious enhancement curve should be mentioned in the final report. Initial enhancement can be slow, moderate, or rapid, while the delayed enhancement can show a persistent, plateau, or wash-out curve (American College of Radiology, 2003). A strong early enhancement is suggestive of malignancy, whereas a slow signal intensity increase is suggestive of a benignity. More importantly, type I signal intensity curves are suggestive of benign breast lesions, whereas type III curves are suggestive of malignancy. The indeterminate type II curve can be observed in both benign and malignant breast lesions, albeit slightly more suggestive of malignancy (in a ratio of 2:3, Kuhl et al., 1999b).

It should be emphasized that kinetic analysis of contrast enhancement is no substitute for morphology analysis. It should be used as an aid in further narrowing the differential diagnosis. With this respect, several recommendations can be made:

First, it is recommended to perform the kinetic analysis after morphologic analysis of a lesion. When the morphology is highly suggestive of malignancy, kinetic analysis should be skipped, and the lesion should be biopsied. Kinetic analysis should be performed in lesions with indeterminate or benign morphologies.

Second, lesions with a type III enhancement curve should always be biopsied, even if morphology is suggestive of a benign lesion. In contrast, the absence of a clear wash-out phase in the signal intensity time curve cannot rule out malignancy.

Third, when lesion morphology is indeterminate and a type I curve is observed, follow-up of the lesion might be considered to reduce false-positive biopsy findings.

4.4 What the clinicians need to know: report organization

The pre-surgical planning and post-surgical treatment is dependent not only on tumor type, but also on its corresponding TNM-classification. The most recent TNM-classification, edition 7, was recently published in 2010. (Edge et al., 2010). For a proper TNM- classification, several issues need to be addressed in the final report of any breast MRI.

For a proper T-classification of breast cancer, the maximum diameter of the culprit mass should be mentioned in the report, including any suspicious nonmass-like enhancement that can be associated with an extensive intraductal component. In addition, the relationship of the tumor to the skin, pectoral muscle and thoracic wall must be accurately described. Enhancement of the pectoral muscle or skin is one of the most reliable signs for the assessment of tumor invasion in these structures. Although inflammatory breast cancer is clinical diagnosis, it can be suggested in MRI when strong enhancement of the breast is observed, together with diffuse skin thickening and enhancement.

Many authors have tried to develop accurate criteria for the assessment of axillary lymph node status on MRI. In a study of 65 patients, Kvistad et al. demonstrated a significant correlation between flow kinetics and axillary lymph node status (Kvistad et al., 2000). Murray et al. demonstrated a correlation between nodal enhancement and nodal area and axillary lymph node status in a study encompassing 47 patients (Murray et al., 2002). More recently, Mortellaro et al. stated in their study of 56 patients that the presence of any axillary lymph node without a fatty hilum and the number of nodes without a fatty hilum correlated significantly with axillary lymph node positivity for metastases (Mortellaro et al., 2009). In summary, study results on MRI of axillary lymph node status vary in study design, study population, and outcome. Until now, there are no reliable criteria for the evaluation of axillary lymph node positivity. However, it is the authors' opinion that analysis of the axillae is an important part of the total breast MRI evaluation. Patients with suspicious axillary lymph nodes on MRI should be considered for (re)evaluation with (second look) ultrasound.

With respect to a proper M-classification, it should be emphasized that other imaging modalities, such as (PET-)CT, need to be performed. However, extramammary findings on breast MRI should be noted and reported. In a retrospective review of 1535 breast MRI examinations, Rinaldi et al. observed 285 patients with extramammary (incidental) findings. Most incidental findings occurred in the liver (51.9%). Other sites were lung (11.2%), bone (7%), and mediastinum (4.2%). Pleural or pericardial effusions were observed in 15.4% of

the cases. Of all these incidental findings, 20.4% proved to be malignant (Rinaldi et al. 2011). Therefore, the occurrence of extramammary findings is a non-negligible phenomenon.

Finally, the radiologist should construct a comprehensible report of all findings observed on breast MRI. By analyzing morphology, enhancement, and signal intensity time curves, the probability of malignancy should be estimated. The maximum diameter of suspicious lesions should be provided, together with their location within the breast and their relationship with the skin, pectoral muscle, or thoracic wall. Together with an assessment of the axillary lymph node morphology and incidental extra-mammary findings, the radiologist should finish the report with the appropriate BI-RADS classification and possible management recommendations (American College of Radiology, 2003):

- BI-RADS 1: Additional imaging is needed (i.e. failure of equipment, severe artefacts)
- BI-RADS 1: Normal, there is nothing to comment on
- BI-RADS 2: Benign findings
- BI-RADS 3: Probably benign findings; the probability of malignancy is less than 2%. Short-term follow-up is recommended
- BI-RADS 4: Suspicious findings; the probability of malignancy is 2-95%. Biopsy should be considered
- BI-RADS 5: Highly suggestive of malignancy; the probability of malignancy is higher than 95%. Appropriate action should be taken
- BI-RADS 6: Proven malignancy (through histopathologic results)

In conclusion, dynamic, contrast-enhanced breast MRI can be a powerful adjuvant imaging modality for the detection of breast cancer. It can be of help when inconclusive findings are encountered on conventional imaging or in the case of an unknown primary cancer. The evaluation of neoadjuvant chemotherapy response can be evaluated with breast MRI, and it can aid in the assessment of the postoperative breast. Breast MRI is advised in screening certain populations with high risk of developing breast cancer, breast implants can be accurately analyzed with MRI, and it can aid in MR guided breast interventions. One of the most important indications of breast MRI is preoperative planning, and its superiority compared to other breast imaging modalities to evaluate disease extent, multifocality or multicentricity, and the presence of (occult) contralateral malignancy. However, due to its limited specificity, false-positive findings are frequently observed. Therefore, patient selection should be performed with care and the proper indications for breast MRI should be observed.

This chapter is dedicated to professor Carla Boetes (1949-2011).

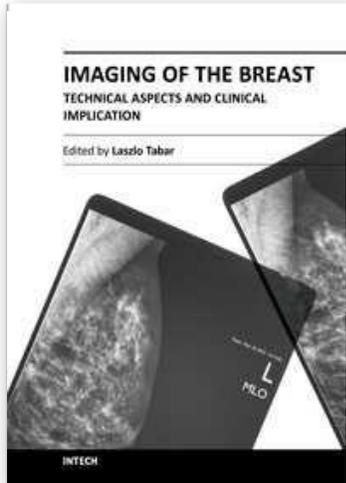
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