

REVIEW

Breast MR with special focus on DW-MRI and DCE-MRI

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Date accepted for publication 10 May 2011

Abstract

The use of magnetic resonance imaging (MRI) for the assessment of breast lesions was first described in the 1970s; however, its wide application in clinical routine is relatively recent. The basic principles for diagnosis of a breast lesion rely on the evaluation of signal intensity in T2-weighted sequences, on morphologic assessment and on the evaluation of contrast enhancement behaviour. The quantification of dynamic contrast behaviour by dynamic contrast-enhanced (DCE) MRI and evaluation of the diffusivity of water molecules by means of diffusion-weighted MRI (DW-MRI) have shown promise in the work-up of breast lesions. Therefore, breast MRI has gained a role for all indications that could benefit from its high sensitivity, such as detection of multifocal lesions, detection of contralateral carcinoma and in patients with familial disposition. Breast MRI has been shown to have a role in monitoring of neoadjuvant chemotherapy, for the evaluation of therapeutic results during the course of therapy. Breast MRI can improve the determination of the remaining tumour size at the end of therapy in patients with a minor response. DCE-MRI and DW-MRI have shown potential for improving the early assessment of tumour response to therapy and the assessment of residual tumour after the end of therapy. Breast MRI is important in the postoperative work-up of breast cancers. High sensitivity and specificity have been reported for the diagnosis of recurrence; however, pitfalls such as liponecrosis and changes after radiation therapy have to be carefully considered.

Keywords: Breast MRI; diffusion-weighted MRI; dynamic contrast-enhanced MRI; breast cancer; BI-RADS.

Background

Magnetic resonance imaging (MRI) can be a valuable addition to the diagnostic work-up of a patient with a breast abnormality or biopsy-proven cancer and it is recommended by the American College of Radiology (ACR) in selected cases for screening, assessing extent of disease and for additional evaluation of clinical and imaging findings^[1]. MRI is therefore increasingly used for breast imaging.

The standard breast MRI performed in clinical routine relies on both morphologic and dynamic contrast enhancement of lesions^[1]. Advanced imaging techniques have been proposed and increasingly used in the last few years. One such technique is diffusion-weighted (DW)-MRI, providing an evaluation of tissue cellularity and

integrity of cell membranes^[2,3]. Another technique is the pharmacokinetic analysis of contrast uptake, providing a quantitative assessment of the contrast agent exchange between the vascular and interstitial compartments.

However, there are limitations to breast MRI. The major limitation of breast MRI is the low to moderate specificity, which, in combination with high sensitivity, can lead to false positives, detecting abnormalities that are not evident clinically, mammographically, or sonographically and that could not be clinically significant. The ACR recommends caution in making treatment choices and changing management based on MRI findings alone without confirmation from biopsy. Due to the complex clinical interpretation and technical requirements in performing breast MRI, it is recommended that this

examination should be performed in specialist breast units. Another limitation is the lack of standardization in advanced imaging techniques, which has limited their widespread application in clinical routine.

The purpose of this paper is to provide the basic technical and clinical knowledge to perform and interpret breast MRI, and to provide a brief overview on advanced imaging techniques.

What does a breast MR examination look like?

MR scanners with a magnetic field ≥ 1 Tesla (T) equipped with bilateral dedicated multichannel coils are recommended. The standard requirements for breast MRI sequences in clinical routine are defined by the ACR and the European Society of Breast Cancer Specialists (EUSOMA)^[1,4].

T2-weighted MR imaging (T2W-MRI)

The standard requirements for this sequence include a bilateral morphological study using T2-weighted fast/turbo spin-echo with or without fat saturation, short-tau inversion recovery (STIR), or spectral pre-saturation with inversion recovery (SPAIR) sequences, with the scan plane chosen by the radiologist. No additional requirements have been specified for other sequence parameters.

In our institution the protocol for T2W-MRI of the breast includes STIR sequences with the following parameters: repetition time (TR)/echo time (TE)/inversion time (TI), 3510/72/170 ms; thickness, 3 mm; gap, 0.3 mm; matrix, 320 × 320; time of acquisition, 3 min 38 s.

Dynamic contrast-enhanced MRI (DCE-MRI)

The standard requirements for this sequence include bilateral two- or three-dimensional gradient-echo T1-weighted dynamic sequence, with or without fat saturation, slice thickness ≤ 3 mm, spatial in-plane resolution preferably ≤ 1 mm², temporal resolution ≤ 120 s and scan plane chosen by the radiologist. The use of two-compartment (vascular/interstitial) gadolinium chelates at the standard dose of 0.1 mmol/kg with an injection rate of 2–3 ml/s, followed by a saline flush (10–30 ml at the same flow rate) is recommended, preferably using an automatic injector.

In our institution, 6 dynamic sequences are performed: 1 basal pre-contrast acquisition followed by 5 continuous acquisitions after contrast agent administration (0.1 mmol/kg at a flow rate of 2 ml/s) injected via an automated injector, followed by a saline flush (20 ml at the same flow rate). Our dynamic sequences are gradient echo (GE) flash 3D with the following parameters: TR/TE, 7.4/4.7 ms; slice thickness, 1.3 mm with 0.25 mm gap; field of view (FOV), 320 × 320 mm; reconstructed

matrix, 384 × 384; voxel size, 0.9 × 0.9 × 1.3 mm; time of acquisition, 90 s each.

Image post-processing is performed on DCE-MR images, after they are acquired, to facilitate the detection of contrast-enhancing lesions.

Digital subtraction of the basal dynamic pre-contrast sequences from the dynamic post-contrast sequences should be performed for dynamic sequences without fat saturation. Digital subtraction removes all non-enhancing tissue, thus also removes the signal from fat tissue, and thereby only alterations that take up contrast medium are seen. Subtracted images should however be interpreted in conjunction with original unsubtracted images, as misregistration due to patient motion may result in false enhancement areas. Motion correction may therefore be helpful in reducing artefacts encountered with digital subtraction.

Maximum intensity projection (MIP) is another post-processing tool that can be utilized for better visualization of enhancing areas. MIP is obtained from the post-processing of subtracted images and is a ray tracing method that projects the brightest pixel value along each parallel ray projected through the volume of data, onto a bi-dimensional surface. MIP in some cases can rapidly show the site of a suspicious lesion in only one image and may show additional findings, such as the asymmetric increase in breast vascularity. The first or second set of subtracted images after contrast administration is generally the most suitable for evaluation of breast vascularity. There is preliminary evidence that a one-sided asymmetric increase in vascularity can be associated with ipsilateral cancer^[5].

Image analysis

Image analysis includes a combined analysis of both T2-weighted and dynamic contrast-enhanced images.

Signal intensity on T2W-MRI

Hyperintense lesions of the breast are mostly benign. This is the case with simple cysts and lymph nodes, which are hyperintense. Fibroadenomas often also show hyperintensity on T2W-MRI^[6]. However, the signal intensity alone cannot be considered sufficient as diagnostic criteria, as the necrotic part of a tumour as well as mucinous and medullary breast carcinomas may also show a hyperintense signal on T2W-MRI^[7]. Hypointense lesions of the breast are mostly malignant, probably due to collagen-rich fibrotic tissue with a low water and fat content^[8]. In a study of 641 cases, 74% of malignant lesions were hypointense on T2W-MRI, whereas only 37% of benign lesions were hypointense^[9]. However, even benign lesions such as haemorrhagic cysts (due to the susceptibility artefact of blood) and hamartomas (due to the predominant fibrous nature) may show signal hypointensity^[10].

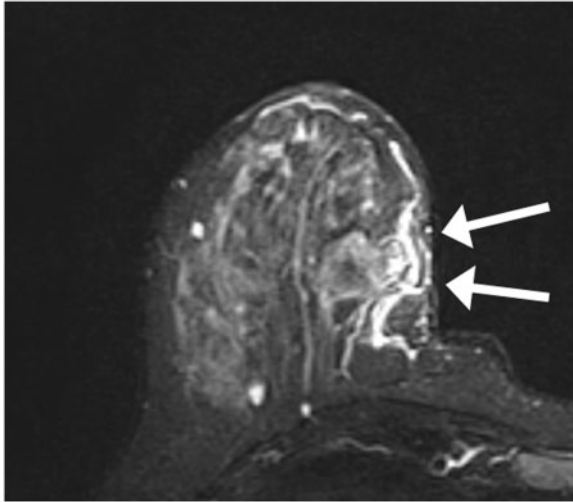


Figure 1 Axial T2-weighted STIR image of the left breast showing a breast carcinoma with peri-focal oedema (arrows).

Further signs of breast lesions can be evaluated on T2W-MRI. For example, in a study of 641 cases the presence of the hook sign (a hook-like spiculated dendrite coming from the lesion's centre, leading to the pectoral muscle), and of uni- and peri-focal oedema in the enhancing lesion (Fig. 1) were strong signs of malignancy, with a prevalence ratio in malignant compared with benign lesions of 6.6 and 3.4, respectively^[9].

Identification of contrast-enhancing lesions

Subtracted images or fat-suppressed dynamic images can be used. If there are no contrast-enhancing lesions, the likelihood of a negative breast MRI is much increased, with high negative predictive value. On the other hand, not all lesions that enhance are malignant tumours^[11] and when contrast-enhancing lesions are detected, it is necessary to evaluate their morphology and dynamic contrast behaviour, as suggested in the Breast Imaging Reporting and Data System Atlas (BI-RADS)^[11].

For morphologic assessment of enhancement, enhancing lesions are divided into three main groups: focus or foci, masses, and non-mass-like enhancements^[11].

- (1) *Focus and foci* are enhancements measuring less than 5 mm that cannot be otherwise specified. They are often unchanged on follow-up images and may be related to hormonal changes. They are mostly benign, especially when multiple and symmetric. However, they should be considered malignant when they are located in the same quadrant as an invasive breast cancer.
- (2) *Masses* are space-occupying lesions within the breast, described in terms of shape, margins, and internal enhancement characteristics.

- (a) *Shape*. A mass can be round, oval, lobulated, or irregular (Fig. 2a–d). Lobulated masses are characterized by an undulating contour (Fig. 2c), and irregular masses (Fig. 2d) show an uneven shape that cannot be characterized as round, oval, or lobulated. The shape analysis should be performed on the early post-contrast images to avoid washout and progressive enhancement of the surrounding breast tissue, which can impair lesion analysis.
- (b) *Margins* are described as smooth, irregular, or spiculated (Figs. 2b,d and 3). For adequate margin assessment, a high spatial resolution is required. For instance, irregular borders can appear relatively smooth when insufficient resolution is used or when the tumour is small. On the other hand, as time elapses after contrast agent administration, the periphery of the lesion may become more indistinct^[6].
- (c) *Internal enhancement characteristics* have been conventionally divided into 6 types:
 - (i) Homogeneous enhancement is uniform throughout the mass (Fig. 2b). It can also be suggestive of a benign process.
 - (ii) Heterogeneous enhancement is non-uniform and varies within the mass. It is more characteristic of malignant lesions^[6].
 - (iii) Rim enhancement is mainly concentrated at the periphery of the mass (Fig. 4). This finding is particularly suspicious for malignancy, being most frequently a feature of high-grade invasive ductal cancer^[12,13]. However, benign findings including fat necrosis and cysts with inflammation may show rim enhancement.
 - (iv) Non-enhanced internal septations within an enhanced lesion are characteristic of fibroadenomas, especially when the lesion has smooth or lobulated borders^[14]. However, they are only seen in a minority of cases; when present, masses can be considered benign with a high degree of certainty (>95%)^[15].
 - (v) Enhanced internal septations are usually a feature of malignant lesions, although these signs occur less commonly.
 - (vi) Central enhancement is an enhancing nidus within a mass that is usually more pronounced than the rest of the enhanced mass. Central enhancement has been associated with high-grade ductal cancer and vascular breast tumours^[12].
- (3) *Non-masslike enhancements* are areas of enhancement that do not belong to a space-occupying lesion and do not have distinct mass characteristics. Features of non-masslike enhancement are

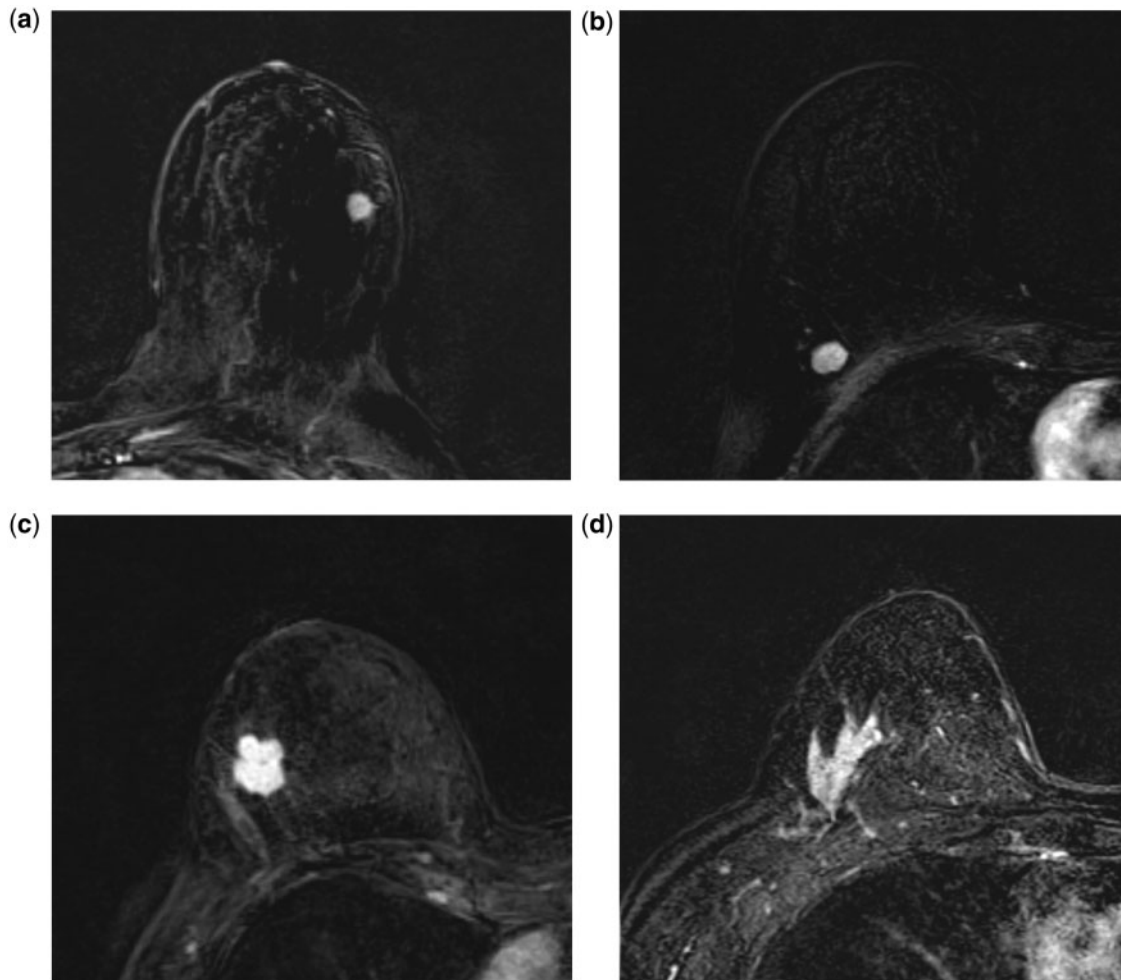


Figure 2 Axial subtracted image showing mass-enhancing lesions, with (a) round, (b) oval, (c) lobulated, and (d) irregular shape.

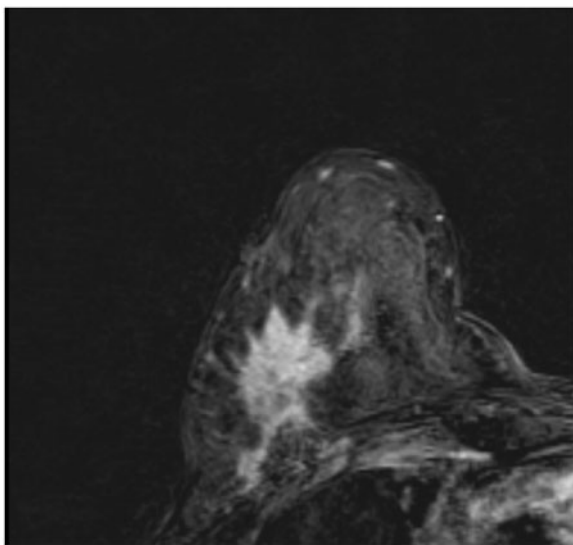


Figure 3 Axial subtracted image showing mass-enhancing lesion of the right breast with spiculated margins.

categorized by distribution, internal enhancement pattern, and symmetric or asymmetric enhancement:

- (a) **Distribution.** A focal area is described in the presence of an enhancement occupying less than 25% of a breast quadrant, showing fat or normal glandular tissue between abnormally enhanced components. This type of enhancement may present as clumped, irregular contrast enhancement. Linear enhancement is an enhancement that does not follow the shape of a ductal system. In contrast, ductal enhancement follows the shape of a ductal system, pointing towards the nipple. Segmental enhancement has a conical appearance and probably represents one or more ductal systems. Ductal and segmental distribution of enhancement may be associated with in situ ductal cancer (DCIS) or invasive ductal cancer, atypical ductal hyperplasia, papillary

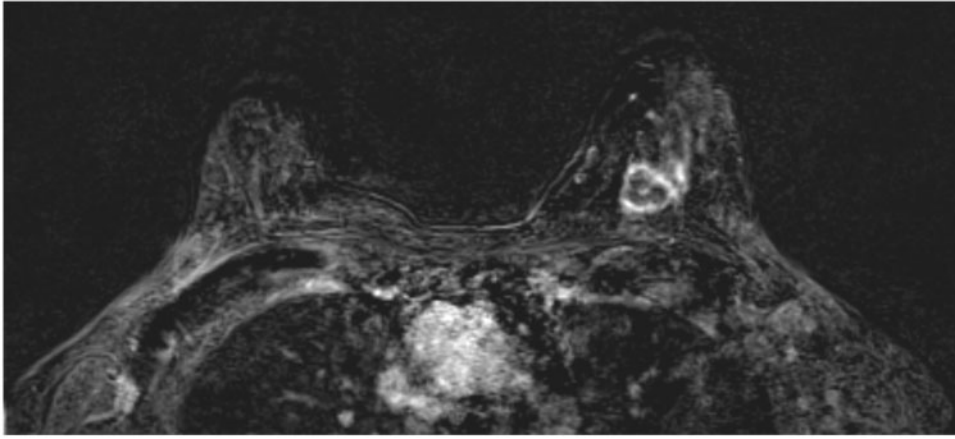


Figure 4 Axial subtracted image showing mass-enhancing lesion of the left breast with rim enhancement.

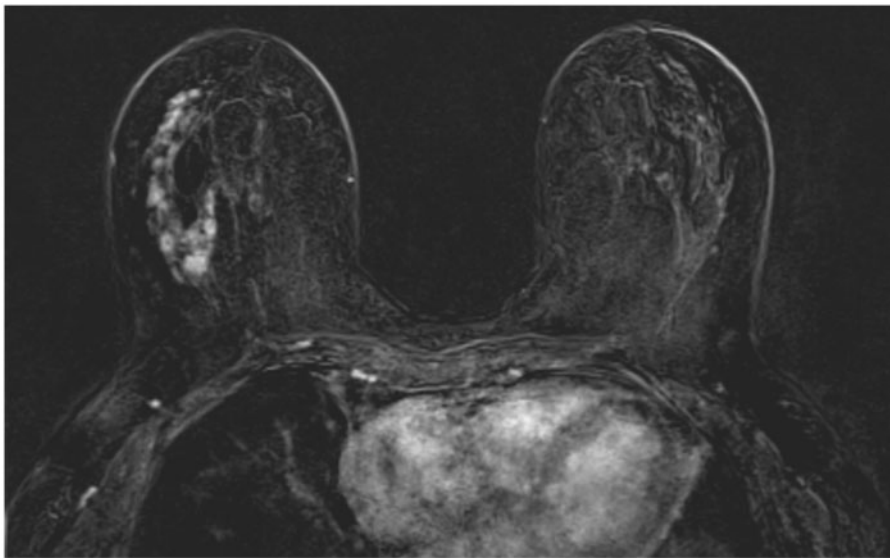


Figure 5 Axial subtracted image showing non-masslike lesion of the right breast with a clumped internal enhancement pattern referring to a cobblestonelike pattern with occasional confluent areas.

neoplasms, or sclerosing adenosis^[1]. Regional enhancement does not correspond to a single duct system, and may be within multiple ducts. Diffuse contrast enhancement is uniform enhancement of the entire parenchyma of the breast. Regional enhancement and diffuse enhancement are more characteristic of benign disease such as proliferative changes, although multicentric DCIS may have this appearance^[6].

- (b) Internal enhancement patterns are homogeneous, heterogeneous, clumped, stippled or punctate, and reticular or dendritic. Clumped refers to a cobblestonelike enhancement, with occasional confluent areas (Fig. 5). Punctate or stippled refers to multiple punctate foci

approximately 1–2 mm in size. They are often distributed in an area of the breast that does not usually conform to a duct. Punctate or stippled enhancement is more characteristic of benign normal variant parenchymal enhancement or fibrocystic changes. In the reticular or dendritic pattern, the normal fat–glandular tissue interface is lost; this finding is usually associated with inflammatory breast cancer or lymphatic involvement.

Kinetic curve assessment

The evaluation of contrast enhancement is performed by measuring the changes in signal intensity over time in a region of interest (ROI), in order to obtain an intensity–time curve describing the dynamic contrast behaviour

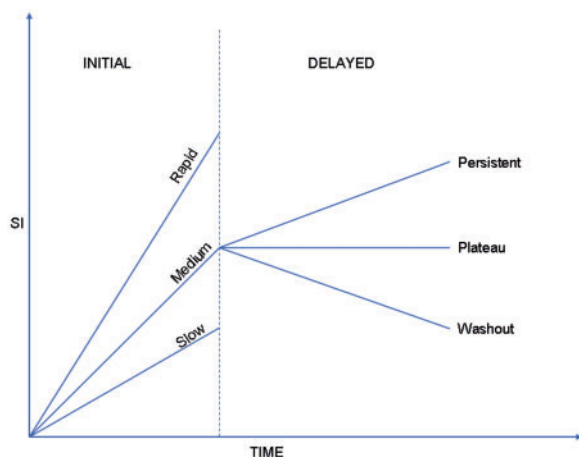


Figure 6 Signal intensity–time curve describing the dynamic contrast behaviour of the lesion of interest.

of the lesion of interest. The part of the lesion showing the strongest and fastest enhancement is chosen as the ROI and thus to describe the enhancement curve. The initial enhancement phase (enhancement within the first 2–3 min after contrast administration) is described as slow, medium, or rapid. The delayed phase is described as persistent, plateau, or washout (Fig. 6).

Lesions with rapid or medium initial enhancement followed by a delayed phase plateau or washout have a positive predictive value of 77% for malignancy^[16]. This behaviour is typically seen in invasive breast cancer, due to the presence of leaky capillaries in the tumour, which cause an increased and fast passage of contrast agent from the vascular to the interstitial compartment followed by a rapid return to the vascular compartment by passive diffusion due to the hyperpermeability of newly formed capillary vessels^[17].

The persistent increase in signal intensity in the delayed phase is typical of benign lesions in at least 80% of cases^[18].

Following image analysis, every breast lesion can be classified according to BI-RADS, ranging from groups I to VI^[1]. The Fischer–Göttingen scoring system^[19] may also be useful to identify the correct BI-RADS group for a breast lesion. According to BI-RADS, the technique used, the clinical indication, knowledge of previous breast ultrasound or mammography, observations and conclusions must be reported.

There can be pitfalls in image analysis of breast MRI. A common one could be the differential diagnosis between intramammary benign lymph nodes and suspicious enhancing lesions (Fig. 7a). Lymph nodes often show an intensity–time curve characterized by a rapid initial enhancement and by a plateau or washout in the delayed phase. However lymph nodes can be distinguished from enhancing nodules because they often show hyperintense signal in T2W-MRI (Fig. 7b). This can be confirmed by a second-look ultrasound (Fig. 7c).

Another pitfall could be the differential diagnosis between focal fibrocystic change and recurrent breast cancer, because they may present with similar contrast enhancement morphology^[20] (Fig. 8a,b).

Finally, fat necrosis next to the scar can be characterized by irregular contrast enhancement, mimicking recurrent disease. However, the presence of fat within the suspicious lesion, which then disappears in fat-suppressed MR sequences, may help clinicians to achieve a correct diagnosis (Fig. 9a,b).

Advanced imaging

The term advanced imaging refers to innovative techniques one step beyond morphology, able to provide a better insight into tumour biology. These techniques are increasingly investigated in clinical trials, but are not yet used in clinical routine for breast MRI. In our opinion, the two techniques that seem to be closest to clinical application, due to their feasibility and the promising results, are the pharmacokinetic analysis of DCE-MRI and DW-MRI. A brief description of the basic technical requirements and fundamental knowledge required for the execution and analysis of these examinations is provided in the following sections.

Pharmacokinetic analysis of DCE-MRI

There are a number of published papers reporting the utility of this approach in the oncologic research setting for breast cancer. However, there are limitations to its widespread utilization in routine practice.

First, the kinetic models used for pharmacokinetic analysis often require very high temporal resolution sequences, thus interfering with the acquisition of image matrices that would allow a state-of-the-art analysis of morphologic features of lesions. Another limitation is related to the lack of standardization in imaging technique and data analysis in multicentre applications.

Imaging technique and analysis

Dynamic images are usually performed with T1 sequences. Preliminary T1 mapping is strongly suggested for adequate T1 assessment of the volume of interest. Contrast administration ideally requires a bolus at high flow rate (more than 3 ml/s), followed by saline (at least 20 ml at the same flow rate). Acquisition of dynamic sequences is targeted on tumour volume; the balance has to be weighed between time resolution (less than 10 s is suggested) and tumour volume coverage (in ideal cases the entire tumour is covered). GE 3D is preferred for consistent acquisition over time.

In our institution we perform pharmacokinetic analysis of DCE-MRI only in breast cancer patients undergoing neoadjuvant chemotherapy, when the tumour is bigger than 2 cm, thus reducing artefacts resulting from partial volume and movement. The following protocol is used.

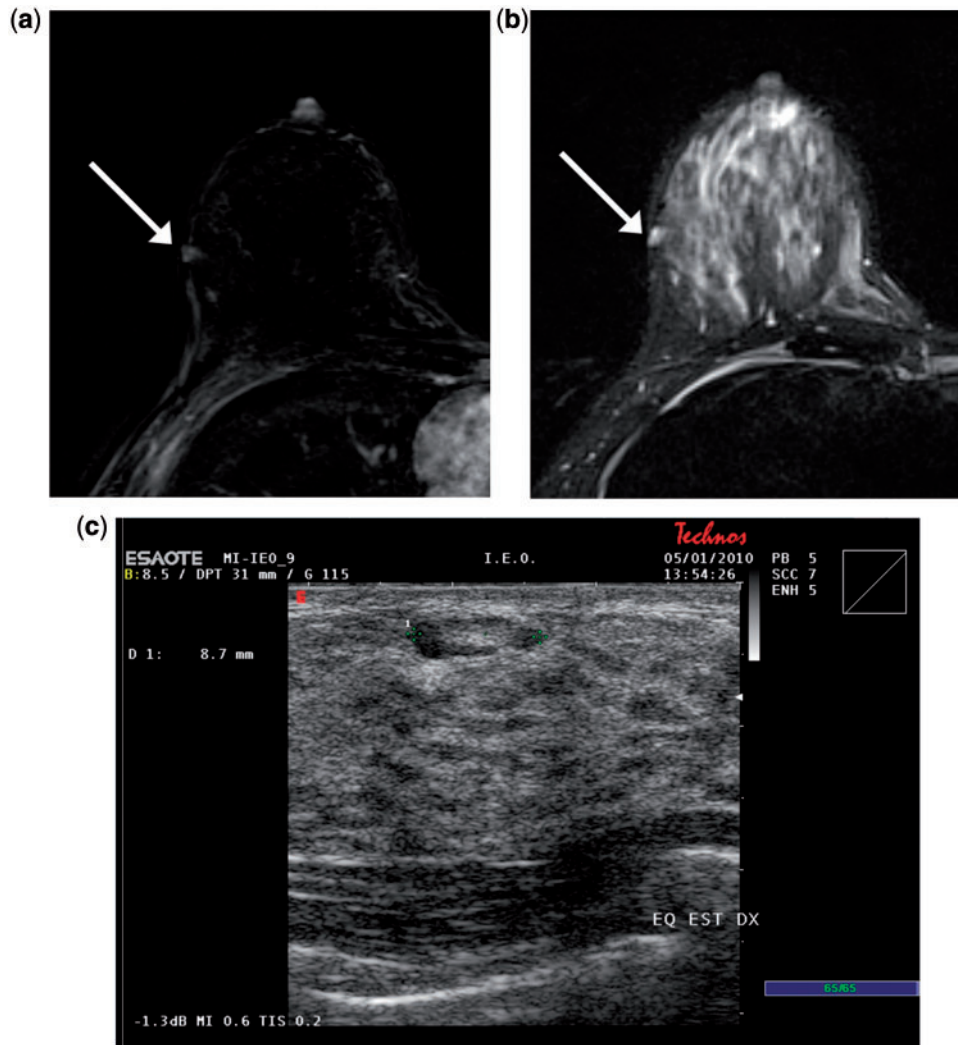


Figure 7 Potential pitfalls: (a) axial subtracted image of the right breast showing an 8-mm mass-enhancing lesion, with oval shape, well-defined margins and slightly heterogeneous contrast enhancement. (b) Axial T2-weighted STIR image shows an 8.7-mm hyperintense lesion of the left breast (arrowhead) with oval shape. (c) A second-look ultrasound examination showed the presence of an oval-shaped lymph node with well-defined margins and a hyperechoic central hilar structure, typical of benign lymph nodes.

Preliminary T2 STIR and DW (b -values of 0, 250, 500 and 1000 s/mm^2) sequences are performed to localize the breast cancer. Our dynamic sequences have a volume coverage of 6 cm (12 slices of 5 mm, gap 0). Dynamic sequences include pre-contrast axial T1 GE 3D sequences with different flip angles for T1 mapping (TR 5 ms; matrix 128×128 ; FOV 320×320 ; voxel size of $2 \times 2 \times 5 \text{ mm}$) and 80 post-contrast measurements performed with axial GE 3D sequences with a time resolution of 5.4 s each (TR/TE, 5/2 ms; matrix 128×128 ; FOV 320×320 ; voxel size of $2 \times 2 \times 5 \text{ mm}$).

For pharmacokinetic analysis, commercially available software (Tissue4D, Siemens Medical, Erlangen, Germany) is used in our institution, which is based on Tofts model (see Appendix 1). Within this software, ROIs can be manually drawn over the tumour volume on subtracted images and then copied on pixel-by-pixel

colour maps, representing on a colour scale each pixel value for the following pharmacokinetic parameters (Fig. 10a,b):

- K^{trans} measures the leakage of contrast agent into the extravascular–extracellular space
- K^{ep} measures the back flux of contrast agent from extravascular–extracellular space into the vascular space
- V^e measures the fraction of volume where contrast agent can leak into the extravascular–extracellular space
- $i\text{AUC}^{60}$ measures the integral of the area under the concentration–time curve up to 60 s

The values of the pharmacokinetic parameters for the selected ROI can be expressed in summary statistics (mean, median and standard deviation) or in histograms.

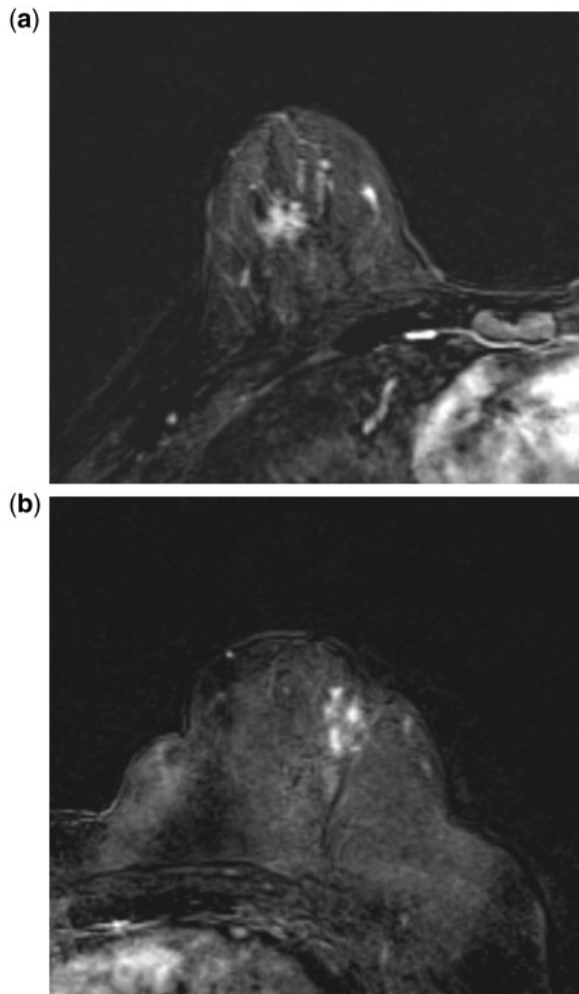


Figure 8 Potential pitfalls: (a) axial subtracted image of the right breast showing a 13-mm mass-enhancing lesion with irregular shape and margins. Similar contrast enhancement morphology is seen in another lesion in a different patient (b). Based on the morphologic characteristics of contrast enhancement, the most likely diagnosis would be malignancy. However, in this case the signal intensity–time curve showed rapid initial enhancement, and a mild continuous increase in the delayed phase for the lesion in (a), but rapid initial enhancement and wash-out in the delayed phase for the lesion in (b), indicating focal fibrocystic change and disease recurrence, respectively.

Clinical applications

The pharmacokinetic parameters might serve as a surrogate biomarker of angiogenesis, as demonstrated in two articles on 118 and 39 patients, in which a correlation between contrast enhancement pattern of breast cancer and microvessel density (MVD) was observed^[21,22]. Therefore, these parameters should have different values in tumours due to the process of neoplastic angiogenesis, when compared with normal tissues.

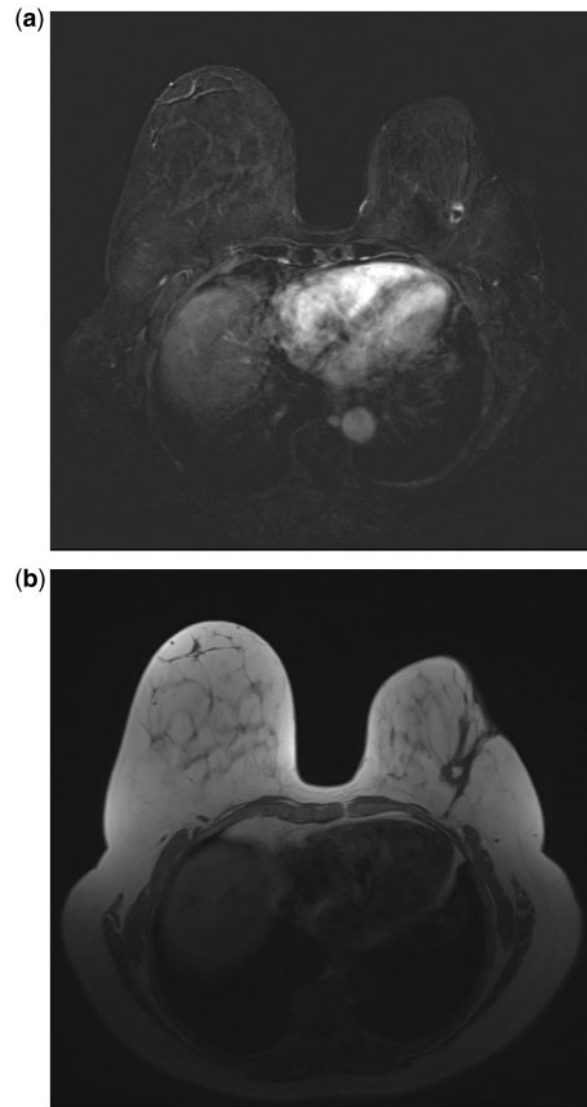


Figure 9 (a) Axial subtracted image in a patient previously surgically treated for breast cancer, showing irregular contrast enhancement in the proximity of the surgical scar making the differential diagnosis between recurrent disease and fat necrosis difficult. (b) Axial T1-weighted MR image of the same breast, showing the predominantly fat content of the suspected lesion pointing towards the diagnosis of fat necrosis.

In particular, K^{trans} values are expected to be higher in breast cancer than in benign lesions and in normal breast tissue due to the higher presence of leaky capillaries in breast cancer due to the process of angiogenesis, as seen in a study of 39 patients using a 1.5-T scanner in patients with breast cancer^[23]. Similarly K^{ep} is also expected to be higher in breast cancer, because it is another measure of capillary leakiness. iAUC^{60} is also expected to be higher in breast cancer than in normal breast tissue due to the greater contrast uptake in breast cancer. In contrast, V^{e} is expected to be lower in tumours, due to a

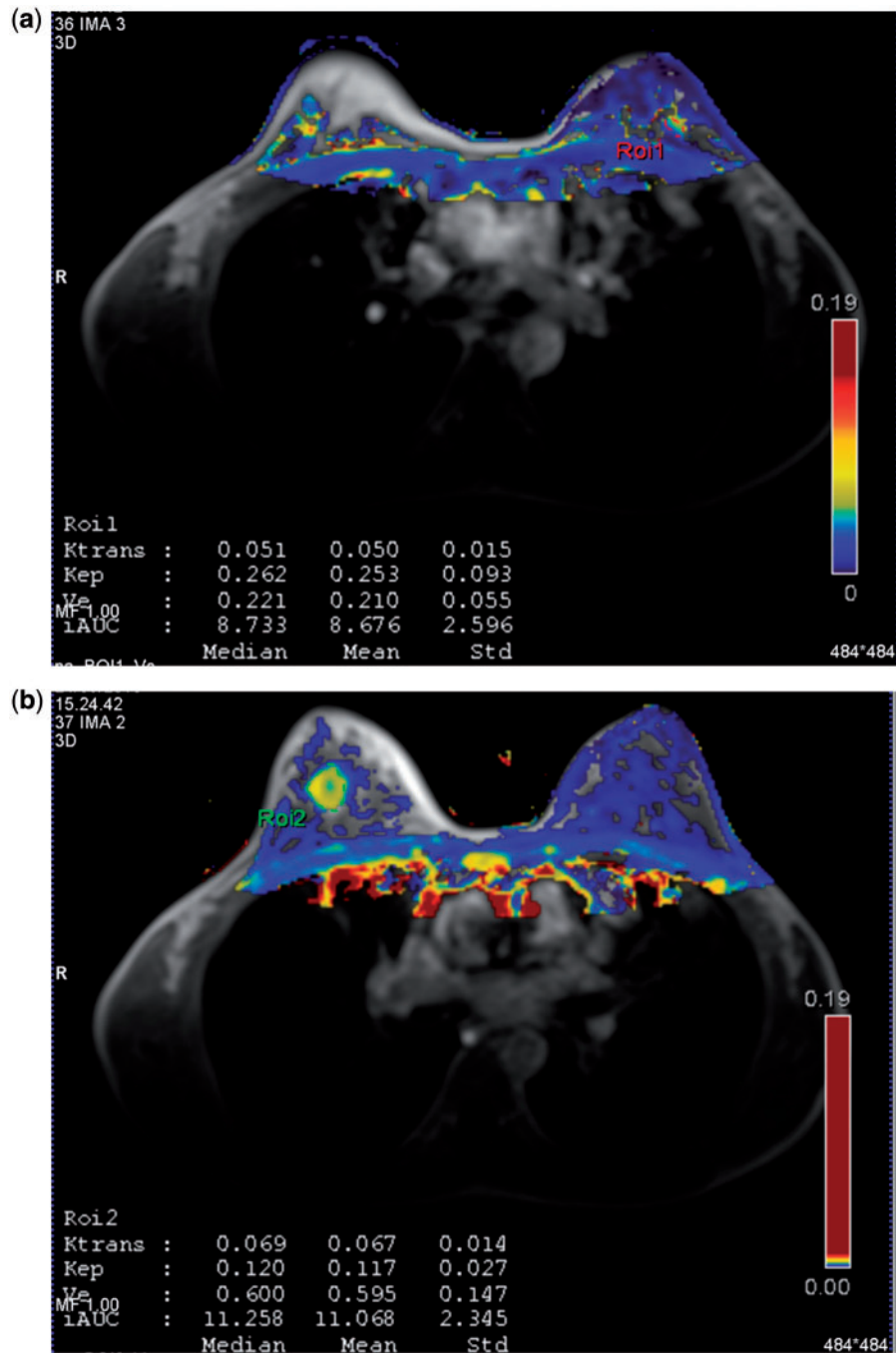


Figure 10 Pixel-by-pixel colour maps with each pixel representing values for K^{trans} (other maps can be generated for K^{ep} , V^{e} , iAUC^{60}). The tabulated values are derived from the ROIs drawn on subtracted images and copied to the colour maps for each parameter. In this example, ROI 1 is for breast cancer (a) and ROI 2 is for fibroadenoma (b).

smaller extravascular–extracellular space, as a result of higher cellularity and vascularity in tumours.

The pharmacokinetic analysis of DCE-MRI can be useful in monitoring and predicting response to therapy. After the administration of antiangiogenic drugs, the changes in tumour vascularization in responder patients precede changes in tumour size and may better describe tumour response to therapy. In particular, an early reduction in K^{trans} , K^{ep} and iAUC might be expected, due to

the loss of immature and hyperpermeable vessels, associated with an early vasoconstriction induced by therapy, leading to a reduction of the total contrast agent uptake after therapy. Changes in V^{e} might also be expected, as this parameter may reflect changes in the extracellular–extravascular space due to the shrinkage of neoangiogenic vessels after antiangiogenic therapy. These findings were observed in two studies on 19 and 21 patients, reporting that K^{trans} , K^{ep} , V^{e} and iAUC at

180 s significantly decreased after the first cycle of bevacizumab^[24,25].

After the administration of cytotoxic chemotherapy, the expected changes in pharmacokinetic parameters are similar in responder patients. Cytotoxic drugs are firstly directed to kill tumour cells; however, after cell death, with the consequent loss of pro-angiogenic factors produced by tumour cells, they also induce a significant reduction in pharmacokinetic parameters. In a study of 21 patients who underwent neoadjuvant chemotherapy with epirubicin and paclitaxel, a significant reduction of K^{cp} ($p < 0.002$) was observed in responder patients already after the first cycle, whereas a change in tumour size was only observed after the third cycle ($p < 0.008$)^[26]. In another study of 28 breast cancer patients who underwent neoadjuvant chemotherapy with FEC (5-fluorouracil, epirubicin, and cyclophosphamide), K^{trans} and K^{cp} decreased after two cycles of therapy (-39.8% and -33.3% , respectively) in responders, whereas they increased in non-responders (18.1% and 7.4% , respectively)^[27]. These findings suggest that DCE-MRI may predict response to therapy as early as after one or two cycles of neoadjuvant chemotherapy, thus potentially selecting non-responder patients for an alternative treatment.

Pre-therapy DCE-MRI may predict response to therapy, as demonstrated in a study of 15 patients with higher pre-therapy K^{trans} in responder patients^[28], and should in theory have a prognostic value in breast cancer, because MVD has shown prognostic value in terms of progression-free survival (PFS) or overall survival^[29]; however, larger studies are required to validate these preliminary observations, although they have already been demonstrated in other tumours^[30].

DW-MRI

Imaging technique and analysis

DW-MRI measures the microscopic mobility of water molecules (Brownian motion) in biological tissues. After the application of two equal-sized gradients, separated by a 180-degree radiofrequency (RF) pulse, the water molecules lose their coherence according to their movement. Stationary water molecules therefore generate a hyperintense DW image, whereas non-stationary water molecules generate a hypointense DW image. The signal loss after the second gradient is also dependent on the strength of the gradient applied (b -value), which is expressed in s/mm^2 (see Appendix 2).

Two to 3 different b -values (ranging from 0 to $1000 s/mm^2$) are generally applied in a DW-MRI sequence for breast imaging, so that 2–3 images of the same volume with different signal intensity of tissues are obtained. If the logarithm of signal intensity for each b -value is plotted, a line through the points can be calculated. The slope of this line defines the apparent diffusion coefficient (ADC) of water molecules (expressed in mm^2/s) (see

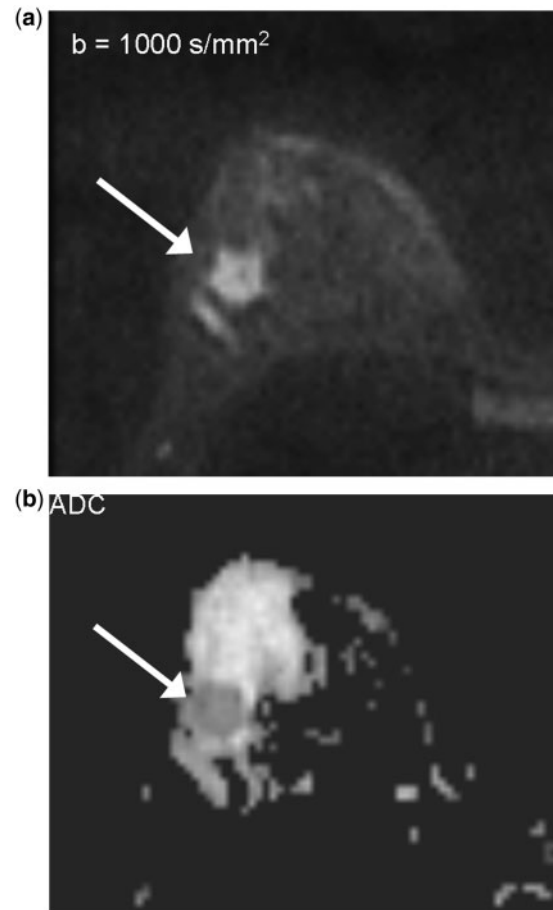


Figure 11 A 16-mm mass lesion of the right breast, which is hyperintense in (a), the axial high b -value ($1000 s/mm^2$) DW-MR image, and dark on (b), ADC maps representing low ADC values (impeded diffusion), characteristic of breast cancer.

Appendix 2). The ADC is often displayed on pixel-by-pixel maps (ADC maps), which are automatically generated from the commercial workstations of the MRI scanners and commonly displayed in grey scale: tissues with higher ADC values (increased diffusion) appear bright and tissues with lower ADC values (impeded diffusion) appear dark.

At our institution, we perform DW sequences with the following parameters: TR/TE, 4800/71 ms; thickness, 5 mm; gap, 1 mm; matrix, 150×90 ; acquisition time, 5 min 4 s; 4 b -values (0, 250, 500, $1000 s/mm^2$); and suppression of the fat signal using SPAIR.

The analysis of DW-MRI can be performed qualitatively or quantitatively.

Qualitative analysis of DW-MRI is performed by a combined visual assessment of the high b -value DW-MR images and the corresponding ADC maps. Breast cancer is usually characterized by hyperintensity on the high b -value DW-MR images and a dark colour on ADC maps (Fig. 11a,b), indicative of impeded diffusion of water molecules; however, proteinaceous cysts might

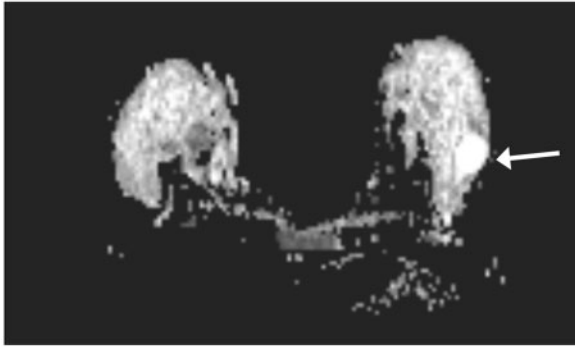


Figure 12 Cyst showing bright colour on the ADC map indicating high ADC values (free diffusion).

also have a viscous environment, which generates impeded diffusion of water molecules, with similar appearance. A simple cyst (or the necrotic/cystic component of a breast cancer) is usually characterized by hypointensity on the high b -value DW-MR images and a bright colour on ADC maps, indicative of apparently free diffusion of water molecules (Fig. 12).

Quantitative analysis of DW-MRI is performed by calculating the ADC values of tissues. An ROI is manually drawn along the margins of the suspicious lesion on high b -value DW-MR images, in each section where it is present. The ROI is then copied on ADC maps to extract the ADC value. The ADC value of the ROI is usually displayed in summary statistics (mean, median and standard deviation), which is the simplest and most frequently used method.

Clinical applications

The detection of a breast cancer by qualitative analysis of DW-MRI alone is possible in theory, as reported in a study of 70 patients^[31]. However, its utility in clinical routine is limited because conventional contrast-enhanced MRI already has very high sensitivity for the detection of breast cancer.

The ADC value can be used to characterize breast lesions; the sensitivity and specificity are influenced by the ADC cut-off values selected. For example, in a study of 78 patients, the mean ADC value for the 35 malignant lesions included was $(1.298 \pm 0.129) \times 10^{-3} \text{ mm}^2/\text{s}$, with reported sensitivity and specificity rates of 88.6% and 95.3% for a cut-off value of $1.48 \times 10^{-3} \text{ mm}^2/\text{s}$, and sensitivity and specificity rates of 100% and 86% for a cut-off value of $1.53 \times 10^{-3} \text{ mm}^2/\text{s}$ ^[32]. The mean ADC values reported in the largest published series of breast cancer patients who underwent DW-MRI at 1.5 T using b -values of 1000–1074 s/mm² range from $(0.89 \pm 0.17) \times 10^{-3} \text{ mm}^2/\text{s}$ to $(1.17 \pm 0.18) \times 10^{-3} \text{ mm}^2/\text{s}$ for breast cancer and from $(1.35 \pm 0.10) \times 10^{-3} \text{ mm}^2/\text{s}$ to $(1.90 \pm 0.20) \times 10^{-3} \text{ mm}^2/\text{s}$ for normal breast tissue or benign lesions^[3,33–39]. This means that it is still difficult to identify a reliable cut-off for malignancy that

can be used in clinical routine across different institutions, mainly due to the lack of standardization in DW-MRI protocols.

The ADC value of breast cancer is expected to increase after therapy, due to cell death and consequent decrease of cellularity and integrity of cell membranes (Fig. 13). It has been demonstrated in several studies^[40–42] that the changes in ADC values usually precede changes in tumour size detected by conventional breast MRI. Larger studies are encouraged to validate these promising preliminary observations.

DW-MRI may also have a role in the identification of residual tumour (Fig. 14a–d) after neoadjuvant chemotherapy, when it can be difficult to correctly evaluate tumour size with conventional breast MRI. In a study of 69 breast cancer patients who underwent neoadjuvant chemotherapy^[43], DW-MRI showed higher accuracy than conventional contrast-enhanced MRI (96% versus 89%) for the detection of residual tumour.

Tumours with high ADC values at baseline have been correlated with higher grades of necrosis and thus poor response to therapy^[2], due to poor drug delivery. In a study of 21 patients with breast cancer undergoing neoadjuvant chemotherapy^[44], the mean ADC value before therapy for non-responder patients was $(1.46 \pm 0.33) \times 10^{-3} \text{ mm}^2/\text{s}$, compared with $(0.99 \pm 0.27) \times 10^{-3} \text{ mm}^2/\text{s}$ for responders. Similar observations were reported in a study of 53 patients, where the pretreatment mean ADC of non-responders $((1.299 \pm 0.079) \times 10^{-3} \text{ mm}^2/\text{s})$ was significantly higher ($p = 0.004$) than that of responders $((1.036 \pm 0.015) \times 10^{-3} \text{ mm}^2/\text{s})$. The authors also identified a pretreatment ADC cut-off of $1.17 \times 10^{-3} \text{ mm}^2/\text{s}$, which provided a sensitivity of 94% (95% confidence interval [CI] 81%, 99%) and a specificity of 71% (95% CI 44%, 90%) for predicting response groups^[45].

Clinical indications

As a general recommendation, good indications are all those that use the high sensitivity of breast MRI for diagnosis and we stress the point that breast MRI is not a problem-solving modality for mammography or ultrasonography in a diagnostic setting.

There are many clinical indications for which breast MRI is believed to add value to the conventional clinical and diagnostic work-up, which are clearly defined and explained in detail by the ACR^[1]. The main indications are summarised as follows:

- (1) Screening (high-risk patients; contralateral breasts in patients with a new breast malignancy; patients with breast augmentation).
- (2) To evaluate the extent of invasive carcinoma and DCIS; in patients with invasion deep to the fascia; in post-lumpectomy patients with positive margins; in patients on neoadjuvant chemotherapy.

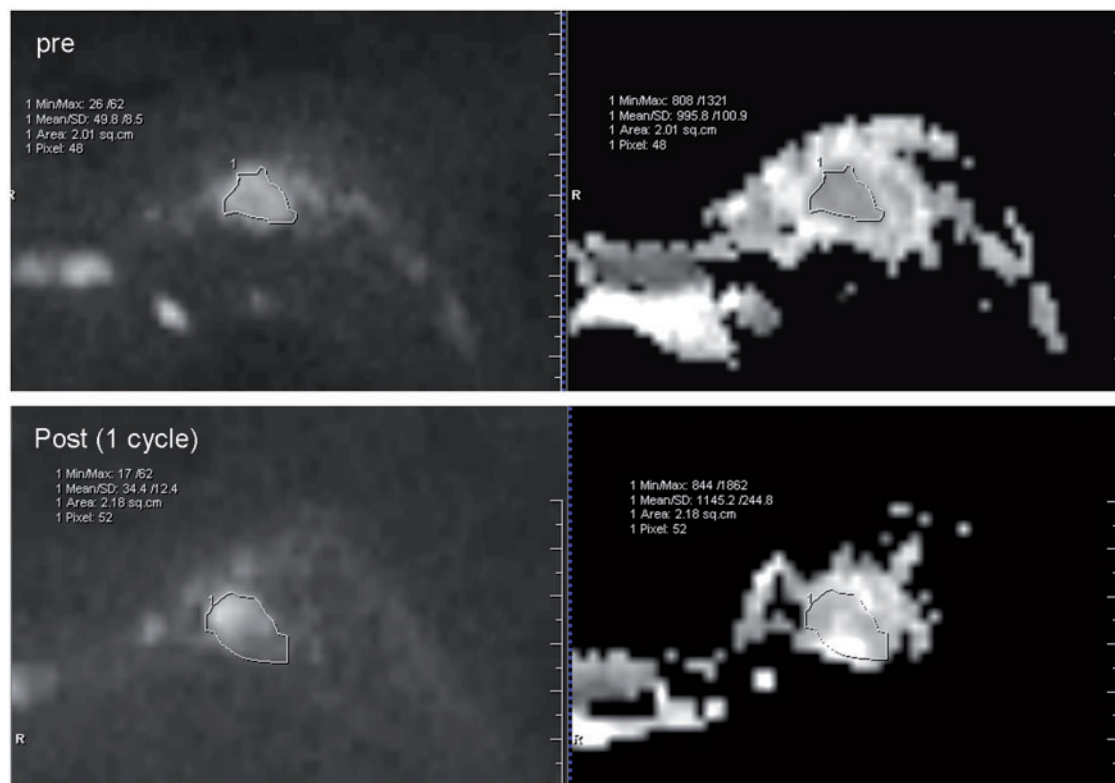


Figure 13 Top two images showing axial high b -value (1000 s/mm^2) DW-MR image (top left) with corresponding ADC map (top right): an ROI has been drawn on the DW-MR image ($b = 1000 \text{ s/mm}^2$) and copied on the corresponding ADC maps for delineating a breast carcinoma of the left breast. The bottom two images showing axial high b -value ($b = 1000 \text{ s/mm}^2$) DW-MR image (bottom left) with corresponding ADC map (bottom right) of the same tumour after one cycle of neoadjuvant chemotherapy showing an increase in mean ADC values (circled values) from $995 \times 10^{-6} \text{ mm}^2/\text{s}$ to $1145 \times 10^{-6} \text{ mm}^2/\text{s}$.

- (3) For additional evaluation of clinical or imaging findings (recurrence of breast cancer; in metastatic cancer, when primary cancer in unknown and breast origin is suspected; for lesion characterization when biopsy is not possible; in postoperative tissue reconstruction; for MRI-guided biopsy).

Conclusions

As a result of the major efforts conducted in the recent years to standardize breast MRI technique and interpretation, as well as to clearly define its clinical indication, breast MRI is increasingly applied worldwide. This article has provided the basic technical and clinical skills to perform and interpret breast MRI, to facilitate the approach to breast MRI. The brief overview on advanced imaging techniques introduces the readers to these techniques, which will be increasingly performed in the coming years.

Appendix 1: diffusion

Water molecules that are in close proximity at one instant in time will become more and more widely distributed as

time passes due to thermal motion. For spins in the water have been excited in MRI, the transverse magnetization will precess at a frequency related to the local magnetic field strength. Thus, an excited spin that moves away from its position at the start of a bipolar gradient (a pair of equally strong but oppositely directed gradients) will accrue a phase shift relative to one that stayed at its point of origin throughout the bipolar gradient. The resulting dispersion of phases of spins in a voxel reduces signal intensity in image data collected after the bipolar gradient.

In pure water, the signal decays exponentially ($S = e^{-bD}$) with the rate of diffusion (D) and a scaling factor (the b -value) that combines the time over which diffusion took place, the strength of the gradient applied and the gyromagnetic ratio of the spins. Higher rates of diffusion and/or higher b -values lead to greater reduction in signal^[46]. In vivo, molecular and cellular structures impede the motion of water molecules, leading to lower effective rates of diffusion (D_{slow}) than are seen in pure water. It has also been noted that microvascular flow causes a dispersion of positions similar to a high effective rate of diffusion (D_{fast}). The values of D_{slow} and D_{fast} can be determined by fitting a bi-exponential equation to the

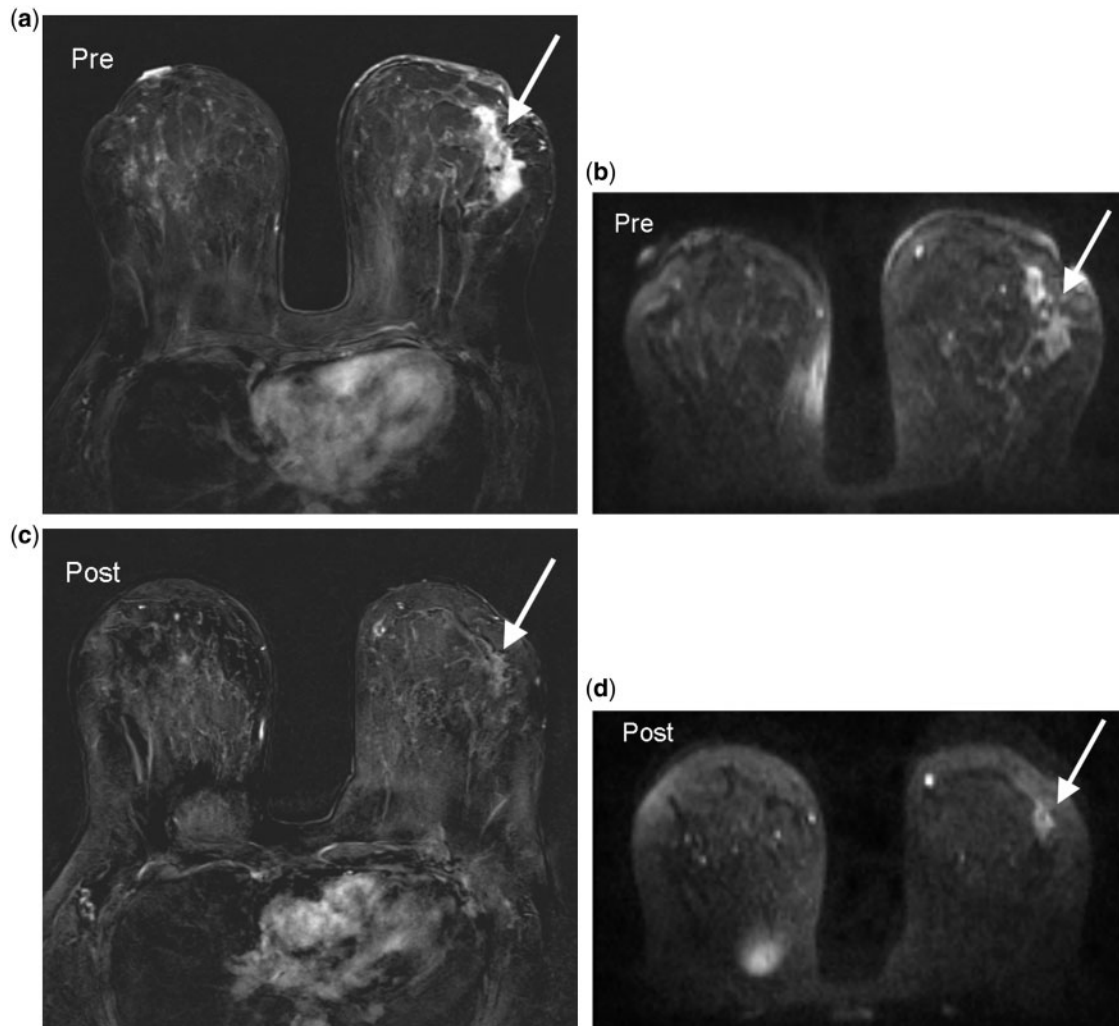


Figure 14 (a) Axial subtracted image at baseline shows a mass-enhancing lesion of the left breast (arrow) with irregular shape and margins, characterized by heterogeneous contrast enhancement. (b) Axial high b -value ($b = 1000 \text{ s/mm}^2$) DW-MR image of the same lesion (arrow), appearing hyperintense, characteristic of breast cancer. (c) The axial subtracted image after completion of neoadjuvant chemotherapy does not clearly allow exact identification of the extent of residual tumour (arrow), if any, due to the mild contrast enhancement. (d) The axial high b -value ($b = 1000 \text{ s/mm}^2$) DW-MR image of the same lesion (arrow) shows a discrete hyperintense lesion, more clearly distinguishable from the surrounding breast tissue, accounting for residual disease, which was then confirmed after surgery.

signal intensities obtained at a large number of b -values^[46], but most clinical DWI examinations are performed with a small number of b -values (often just 2 or 3) and are more appropriately fit using a mono-exponential fitting that yields a so-called ADC. The resulting ADC values have, however, been found to depend strongly on the b -values used, and so care must be taken in comparing measurements obtained with different combination of b -values.

Appendix 2: pharmacodynamic analysis with Tofts' model

The arrival of an injected T1-shortening contrast agent first affects only the signal from the blood plasma. In

most tissues, a concentration gradient will cause some of the contrast agent to pass out of the blood and into the extravascular–extracellular (interstitial) space causing enhancement of the MR signal from this space. Unlike computed tomography, the relationship between contrast agent concentration and signal enhancement is non-linear, and so one must estimate the baseline T1 and convert the signal intensities at each time point into concentration values prior to applying pharmacokinetic models.

The two-compartment Tofts' model^[47] is one of several mathematical approaches to describing the contrast enhancement in terms of pharmacokinetic parameters. Mechanisms that drive the contrast agent along the concentration gradient from the blood to the extravascular

extracellular space during the first arrival of the bolus are encapsulated in the parameter K^{trans} . As the concentration in the blood plasma subsides, the concentration gradient reverses pushing contrast agent from extravascular–extracellular space to the blood in an exponential way determined by the parameter K^{ep} . The volume of extravascular space (as a fraction V^{e} of the voxel size) is also estimated by the model. As the driver of the model, the concentration of contrast agent in the feeding artery (the arterial input function, AIF) is needed. Obtaining an AIF for an individual patient is often difficult due to vessel motion, pulsation of the blood and partial volume effects, and so population-based AIFs are often used in analysis.

The temporal resolution of scans used for pharmacokinetic modelling are also suitable for calculating the cumulative enhancement (area under the curve), an indicator of the combined blood and extravascular extracellular volumes. Limiting the duration of integration for the calculation of the area under the curve to 60 s is a widely accepted approach (iAUC⁶⁰) to standardizing this measurement but other rules (e.g. injection to end of first pass, and the first 30 s after injection) have been used.

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