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REVIEW ARTICLE

The potential of multiparametric MRI of the breast

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ABSTRACT

MRI is an essential tool in breast imaging, with multiple established indications. Dynamic contrast-enhanced MRI (DCE-MRI) is the backbone of any breast MRI protocol and has an excellent sensitivity and good specificity for breast cancer diagnosis. DCE-MRI provides high-resolution morphological information, as well as some functional information about neoangiogenesis as a tumour-specific feature. To overcome limitations in specificity, several other functional MRI parameters have been investigated and the application of these combined parameters is defined as multiparametric MRI (mpMRI) of the breast. MpMRI of the breast can be performed at different field strengths (1.5–7 T) and includes both established (diffusion-weighted imaging, MR spectroscopic imaging) and novel MRI parameters (sodium imaging, chemical exchange saturation transfer imaging, blood oxygen level-dependent MRI), as well as hybrid imaging with positron emission tomography (PET)/MRI and different radiotracers. Available data suggest that multiparametric imaging using different functional MRI and PET parameters can provide detailed information about the underlying oncogenic processes of cancer development and progression and can provide additional specificity. This article will review the current and emerging functional parameters for mpMRI of the breast for improved diagnostic accuracy in breast cancer.

INTRODUCTION

MRI of the breast is an essential tool in breast imaging, with multiple indications such as pre-operative staging, therapy monitoring, detection of recurrence, assessment of breast implants, screening of females at high risk, in patients with cancers of unknown primary syndrome and as a problem-solving tool for equivocal findings on mammography and sonography.^{1,2} Dynamic contrast-enhanced MRI (DCE-MRI) is the backbone of any given MRI protocol and the most sensitive method for the detection of breast cancer, with a negative-predictive value ranging between 89 and 99%, but variable specificities ranging from 47 to 97%.^{1,3–7} DCE-MRI provides high-resolution morphological information, as well as some functional information about neoangiogenesis as a tumour-specific feature. To overcome limitations in specificity, several functional MRI parameters have been investigated and the application of these combined parameters is defined as multiparametric MRI (mpMRI) of the breast. In its development, cancer acquires several functional capabilities that are defined as the hallmarks of cancer: resistance to growth inhibitory factors; proliferation in the absence of exogenous growth factors;

evasion of apoptosis; limitless replication potential *via* the reactivation of telomerase; abnormal angiogenesis; evasion of destruction by the immune system; invasion; and metastasis.^{8,9} There is evidence that mpMRI, using different functional parameters, can provide detailed information about the hallmarks of cancer^{8,9} and can also provide additional specificity.^{5,10–16}

MpMRI of the breast aims to quantify and visualize biological, physiological and pathological processes at the cellular and molecular levels to further elucidate the development and progression of breast cancer and the response to treatment. MpMRI of the breast can be performed at different field strengths (1.5–7 T) and includes several functional MRI parameters, as well as hybrid imaging techniques such as positron emission tomography (PET)/MRI. This article will review the current and emerging functional parameters for mpMRI to improve diagnostic accuracy. We will discuss established MRI parameters [DCE-MRI with kinetic analysis, diffusion-weighted imaging (DWI) and proton MR spectroscopy (¹H-MRSI)], high-field and ultrahigh-field MRI at 3.0 T and abbreviated MRI. In addition, we will explain novel

MRI parameters, such as sodium imaging (^{23}Na -MRI), phosphorus MRSI (^{31}P -MRSI), chemical exchange saturation transfer (CEST) imaging, blood oxygen level-dependent (BOLD) and hyperpolarized MRI (HP MRI), and briefly review the emerging application of hybrid imaging with PET/MRI.

DYNAMIC CONTRAST-ENHANCED MRI

A hallmark of cancer development and metastatic potential is tumour angiogenesis, *i.e.* the development of a dedicated vasculature with abnormal vessel permeability that supports the high metabolic demand for oxygen and nutrients, especially in aggressive tumours.⁸ Specific peptide hormones released by cancer cells promote tumour angiogenesis as soon as they exceed 2 mm in size.¹⁷ DCE-MRI is able to depict and characterize this abnormal vasculature and permeability as a tumour-specific feature through the assessment of breast kinetic enhancement features, after the *i.v.* application of gadolinium chelates.^{18,19}

High-resolution, high-field and ultrahigh-field dynamic contrast-enhanced MRI

Both assessment of tumour morphology and enhancement kinetics are necessary for the optimal diagnosis of breast lesions.⁷ Parallel imaging techniques and the utilization of higher field strengths ($\geq 3\text{ T}$) allow both high-resolution spatial and temporal MRI with increases in sensitivity and specificity and thus, breast MRI is steadily moving to 3.0 T.^{3,4,7,20,21} Currently, ultrahigh-field MR scanners operating at a field strength of 7.0 T have become available. Ultrahigh-field MRI at 7.0 T offers a further significant increase in intrinsic signal-to-noise ratio, which can be translated into even higher temporal and spatial resolution imaging or functional and metabolic imaging.^{12,22,23} Initial studies have demonstrated the feasibility of this technique and highlighted the limitations of breast MRI at 7.0 T such as longer T_1 relaxation times, shorter T_2^* decay time, greater radiofrequency specific absorption rate and reduced transmit field (B_1^+) homogeneity, all of which can limit the 7.0-T image quality in practice.²⁴ However, since then, several studies investigating unilateral DCE-MRI of the breast at 7.0 T, in healthy volunteers and a few patients, have demonstrated that these challenges can be overcome.^{25–28} In the first clinical study, Pinker et al evaluated the application of bilateral contrast-enhanced MRI (CE-MRI) at 7.0 T in patients with breast tumours.¹² The authors concluded that bilateral, high-resolution CE-MRI of the breast at 7.0 T is clinically applicable and enables a breast cancer diagnosis with a high diagnostic accuracy (96.6%) and excellent interrater agreement and image quality (Figure 1). Gruber et al²² performed an intraindividual comparison of the image quality, the contrast enhancement behaviour and the diagnostic value of bilateral high-spatial resolution and high-temporal resolution CE-MRI at 7.0 T and at 3.0 T in patients with breast tumours. When using optimized T_1 weighted (T1W) three-dimensional (3D) sequences at 3.0 and 7.0 T, with a high temporal (both 14 s) and spatial resolution [$1.1 \times 1.1 \times 1.1\text{ mm}^3$ (3.0 T), $0.7 \times 0.7 \times 0.7\text{ mm}^3$ (7.0 T)], 7.0-T CE-MRI provided simultaneous high temporal and spatial resolution, which was a significant improvement over lower field strengths, with an excellent sensitivity (100%) and specificity (91.67%) for breast cancer diagnosis. To circumvent the limitations in T_2 weighted imaging due to the greater specific absorption rate at 7.0 T,

Bogner et al developed a DWI protocol which simultaneously yields high-quality apparent diffusion coefficient (ADC) maps and high-spatial resolution T_2 weighted MR images that can be used to assess tumour and breast morphology²⁹.

Abbreviated MRI

Recently, abbreviated as well as ultrafast dynamic imaging protocols have been evaluated for both breast cancer diagnosis and screening. Several studies investigated whether an abbreviated protocol, consisting of either a pre-contrast T1W image and a single early post-contrast T1W image^{30–34} or high-resolution ultrafast dynamic imaging,³⁵ was suitable to detect breast carcinoma (Figure 2). All authors concluded that the abbreviated MRI protocol for breast MRI screening allows detection of breast lesions and classification with high accuracy. These results indicate that a substantial shortening of scan protocols is possible and support the possibility of refining breast MRI screening protocols.

Quantitative contrast-enhanced MRI

Kinetic enhancement analysis of breast tumours is routinely performed semi-quantitatively by time–intensity curves, using a modest temporal resolution with at least 2–3 post-contrast T1W acquisitions and with k -space centred at approximately 90–120 s after contrast injection for the first post-contrast images.^{1,6,7,15} However, high-temporal resolution MRI techniques enable a quantitative kinetic enhancement analysis through pharmacokinetic modelling. Pharmacokinetic models quantify the contrast agent exchange between the intravascular and the interstitial space, providing measures of tumour blood flow, microvasculature and capillary permeability. The Tofts two-compartment model is the most commonly used approach and measures the exchange between the breast tissue plasma and the plasma space.^{36,37} Contrast agent concentrations for each compartment vary with time after bolus injection, and quantitative metrics can be derived using the following relationship: $K_{ep} = K_{trans}/V_e$. K_{trans} (min^{-1}) is the volume transfer constant, which describes the rate of transfer of contrast agent from the plasma to the tissue. K_{ep} (min^{-1}) is the transfer rate constant, which describes the reflux of contrast agent from the extravascular extracellular space to the plasma compartment. V_e (%) is the leakage of fractional volume from the extravascular extracellular space into the plasma compartment (Figure 3). Pharmacokinetic parameters such as K_{trans} and K_{ep} can potentially improve the differentiation of benign and malignant breast tumours and distinguish different breast cancer subtypes.¹⁵ Huang et al investigated pharmacokinetic parameters in suspicious lesions on standard clinical breast MRI and the results indicate that the application of a cut-off for K_{trans} values could be used to obviate unnecessary biopsies in lesions.³⁸ Li et al assessed morphological and quantitative DCE-MRI for breast cancer diagnosis and as an imaging biomarker for the differentiation of subtypes. K_{trans} and K_{ep} values were significantly higher in invasive ductal carcinoma and ductal carcinoma *in situ* than in the borderline and benign lesions or healthy breast tissue.³⁹

Another application for quantitative DCE MRI is the response assessment to neoadjuvant chemotherapy (NAC) in patients with breast cancer. In a recent meta-analysis, Marinovich et al⁴¹ showed that the measurement of alterations in tumour perfusion in response to pre-operative

Figure 1. MRI of the breast at 7.0 T: invasive ductal carcinoma grade 3 in the left breast in a 62-year-old female—high-resolution dynamic contrast-enhanced MRI (DCE-MRI) at 7.0 T is showing an irregular shaped and marginated mass lesion retromammillary right [(a) pre-contrast media, (b) initial and (c) delayed enhancement] with fast/washout enhancement kinetics (d). The non-enhancing cysts on the right breast (curved arrows) can be noted. High-resolution DCE-MRI at 7.0 T has accurately classified the lesion as malignant, breast imaging-reporting and data system 5 (highly suggestive of malignancy). ROI, region of interest.

therapy, using K_{trans} , is a powerful predictor of response to NAC and outperforms standard measures, such as tumour size.⁴⁰

Nevertheless, quantitative DCE-MRI with pharmacokinetic modelling remains challenging, as several parameters, such as the pre-contrast T_1 relaxation times of the tumour/tissue and the

Figure 2. MSKCC abbreviated MRI: invasive ductal carcinoma in the left breast in a 59-year-old female—abbreviated dynamic contrast-enhanced-MRI at 3.0 T is showing an irregular shaped and marginated enhancing mass in the lower quadrant of the left breast [(a) first post-contrast sequence, (b) first post-contrast subtraction sequence and (c) subtraction maximum intensity projection sequence].

arterial input function, *i.e.* the concentration of contrast agent as it changes over time within the arterial blood, must be known. The measurement of both parameters comes with unique challenges and introduces the potential for error. To overcome these limitations, different strategies have been developed, and it seems that quantitative DCE-MRI benefits from the high-resolution MRI techniques now available.^{38,39,41–43} However, owing to different modelling algorithms, several challenges and various potential solutions, there are significant differences in quantitative measurements and thus, the results of individual studies cannot be readily generalized. Thus, further data—derived using standardized techniques—are warranted to fully explore the true potential of quantitative DCE-MRI.

DIFFUSION-WEIGHTED IMAGING

DWI measures the random movement of water molecules, *i.e.* Brownian movement, and depicts the diffusivity of the examined tissues. DWI is a strong surrogate marker for tissue microstructure, membrane integrity and cell density and can be quantified by calculating the ADC. Changes in tissue water diffusion properties can be used to detect and characterize pathological processes in any given body part.⁴⁴ Developments in imaging techniques (*e.g.* parallel imaging) and hardware (stronger gradient systems and multichannel coils) have overcome previous limitations (susceptibility and respiratory motion artefacts) and DWI is now an integral part of oncologic imaging, including breast imaging.^{45,46} In short, malignant tumours tend to have a more restricted diffusion and lower ADC values than normal tissue or benign tumours owing to the high cellular density and abundance of intracellular and intercellular membranes.

DWI for breast cancer diagnosis has been evaluated with encouraging results by numerous studies using different ADC thresholds and *b*-values.⁴⁷ Optimal ADC determination and DWI quality was found with a combined *b*-value protocol of 50 and 850 s mm⁻², yielding a diagnostic accuracy of 96%

(Figure 4).⁴⁸ In a recent meta-analysis that included 26 studies, Dorrius et al confirmed that ADC values of breast lesions are influenced by the choice of *b*-values⁴⁶. For the most accurate differentiation of benign and malignant lesions, the combination of *b* = 0 and 1000 s mm⁻² was recommended. Nevertheless, there is a consensus that DWI yields a higher specificity (75–84%) than DCE-MRI (67–72%) and is a promising imaging biomarker that provides additional functional information to DCE-MRI.^{13,49} In addition to breast cancer detection, DWI can potentially be used as a non-invasive biomarker for the identification of different tumour subtypes, invasive vs non-invasive disease, tumour receptor status and tumour grading.^{50,51} Moreover, DWI shows promise for the monitoring of treatment response in breast cancer. Changes in ADC values occur earlier than lesion size changes or vascularity, as measured with DCE-MRI, and therefore, DWI can provide a valuable early indication of treatment efficacy.^{52,53}

Several advanced modelling approaches for DWI to provide further insights into tumour biology are currently under investigation.

Intravoxel incoherent motion

DWI is also sensitive to perfusion because the flow of blood in randomly oriented capillaries mimics a diffusion process through the intravoxel incoherent motion effect.⁵⁴ Several studies have investigated intravoxel incoherent motion in breast tumours and preliminary data suggest that it can provide valuable information about both tissue microstructure and the microvasculature for improved breast cancer diagnosis,^{55–57} as well as differentiation of different breast cancer subtypes and molecular prognostic factors (Figure 5).^{56,58}

Diffusion-weighted kurtosis

In living tissues, DWI is affected by Brownian incoherent motion and microperfusion or blood flow that demonstrates non-Gaussian phenomena. Diffusion-weighted kurtosis quantifies

Figure 3. MRI of the breast at 3.0 T: invasive ductal carcinoma grade 1 medially in the right breast in a 59-year-old female: short tau inversion-recovery images are showing an isointense to hyperintense irregular mass (a) with a restricted diffusivity (d) and decreased apparent diffusion coefficient values ($0.98 \times 10^{-3} \text{ mm}^2 \text{ s}$) (e). The irregular shaped and marginated mass (b) is showing fast/washout enhancement (c) and is having a mean plasma flow of $71.3 \text{ ml}/100 \text{ ml min}^{-1}$ (f), a mean volume distribution of $74.6 \text{ ml}/100 \text{ ml}$ (g) and a mean transit time of 63.6 s (h).

the deviation of tissue diffusion from a Gaussian pattern.⁵⁹ Diffusion-weighted kurtosis has demonstrated a substantially higher sensitivity and specificity in cancer detection than ADCs and thus could provide valuable information about the diffusion properties related to the tumour microenvironment and increase diagnostic confidence for breast tumours.^{60–62}

Diffusion tensor imaging

Diffusion tensor imaging (DTI) is an extension of DWI, which provides information about water motion in six or more directions and thereby characterizes the motion of water in more detail.⁶³ DTI measures the two parameters, mean diffusivity and fractional anisotropy (FA). Mean diffusivity reflects the average anisotropy, whereas FA describes the degree of anisotropy.^{64,65} Partidge et al investigated whether DTI measures of anisotropy in breast tumours are different from those in normal breast

tissue and could improve the discrimination between benign and malignant lesions.⁶⁵ Diffusion anisotropy is significantly lower in breast cancers than that in normal tissues, which may reflect alterations in tissue organization, but cannot reliably differentiate between benign and malignant lesions. Baltzer et al proved that DTI can visualize microanatomical differences between benign and malignant breast tumours and breast parenchyma⁶⁶, but FA did not have an incremental value compared with ADC.^{64,65} In addition, a recent study showed that DTI parameters are influenced by background parenchymal enhancement within the normal breast tissue and should be considered in DTI evaluation.⁶⁷

PROTON MR SPECTROSCOPIC IMAGING

MRSI reflects the chemical composition of a given tissue by demonstrating spatially localized signal spectra, which provide

Figure 4. MRI of the breast at 3.0 T: invasive ductal carcinoma grade 3 in the left breast in a 48-year-old female—high-resolution dynamic contrast-enhanced MRI [(a) pre-contrast media, (b) initial and (c) delayed enhancement] and T_2 weighted imaging (d) at 3.0 T are showing an 8-mm irregular shaped and marginated mass lesion medially in the left breast with fast/washout enhancement kinetics (g). Diffusion-weighted imaging is showing a restricted diffusivity (e) and low apparent diffusion coefficient values ($0.89 \times 10^{-3} \text{ mm}^2 \text{ s}$) (f), indicating high cellularity which is indicative of tumour malignancy. ROI, region of interest.

information about the varying levels of detectable metabolites. In breast imaging, the additional value of ^1H -MRSI is largely based on the detection of choline (Cho), a biomarker of increased cellular turnover, which is typically increased in malignant tumours and thus aids in the characterization of breast tumours.^{68–70} ^1H -MRSI can be performed as single-voxel or multivoxel MRSI. For a detailed review of acquisition techniques and analysis of breast MRSI, a recent review article by Bolan et al⁷¹

can be referred to. Gruber et al⁷² developed a high-spatial resolution 3D ^1H -MRSI protocol at 3.0 T, designed to cover a large fraction of the breast in a clinically acceptable measurement time of 12–15 min. Results indicated that 3D ^1H -MRSI at 3.0 T yields excellent data quality and allows a differentiation of benign and malignant breast lesions with an excellent sensitivity (97%) and good specificity (84%). In a recent meta-analysis, which included 19 studies, Baltzer et al evaluated

Figure 5. Invasive ductal carcinoma in the left breast in a 42-year-old female: the mass is visible on dynamic contrast-enhanced MRI (a) and intravoxel incoherent motion (IVIM) images (b, c) at $b = 0 \text{ s mm}^{-2}$ and $b = 500 \text{ s mm}^{-2}$. IVIM protocol b -values = 0, 10, 192 and 500 s mm^{-2} ; d, e and f are showing the IVIM parameter maps for f , D and D^* , respectively. Histogram analysis has gave median values of $f = 22\%$, $D = 147 \times 10^{-6} \text{ mm}^2 \text{ s}$ and $D^* = 7773 \times 10^{-6} \text{ mm}^2 \text{ s}$.

the diagnostic performance and feasibility of ^1H -MRSI for differentiating malignant and benign breast lesions.⁷³ The pooled sensitivity and specificity of ^1H -MRSI was 73% and 88%, respectively. There was a substantial heterogeneity of sensitivity in the studies (42–100%), with little variation in specificity. This meta-analysis did not show any significant performance advantages of 3.0 T over 1.5 T field strength, for multivoxel over single-voxel techniques or for qualitative over quantitative tCho assessments. ^1H -MRSI seems to be limited in the diagnosis of early breast cancer and small breast tumours, as well as in non-mass-enhancing lesions.

Available data show that ^1H -MRSI might also be a valuable tool in the assessment of response to NAC.^{74,75} Breast tumour tCho levels and the changes in these levels during treatment are reflective of treatment-induced alterations in cell proliferation prior to any changes in tumour size. Therefore, ^1H -MRSI can provide an early predictive imaging biomarker of response to treatment. In addition, tCho seems to be indicative of not only an increased proliferation, but also an imminent malignant transformation.^{76,77} Ramadan et al demonstrated that in BRCA-1 and BRCA-2 carriers, the healthy breast tissue is likely to differ from patient to patient, as well as from non-mutation carriers

Figure 6. MRI of the breast at 3.0 T: invasive ductal carcinoma in the right breast in a 60-year-old female—the extensive lesion occupying almost the whole right breast is demonstrating an irregular shape and margins [(a) pre-contrast media, (b) initial and (c) delayed enhancement], fast/washout enhancement (e), a restricted diffusivity (f) and decreased apparent diffusion coefficient (ADC) values ($881 \times 10^{-3} \text{ mm}^2/\text{s}$) (g). In baseline MRI before neoadjuvant cytotoxic chemotherapy, an additional enhancing lesion has been detected in the left breast lateral. The 7-mm non-mass enhancement (arrows) is demonstrating an irregular shape and margins [(a) pre-contrast media, (b) initial and (c) delayed enhancement], fast/plateau enhancement (d), restricted diffusivity (f) and decreased ADC values ($1004 \times 10^{-3} \text{ mm}^2/\text{s}$) (g) and has been confirmed to be high-grade ductal carcinoma *in situ*. ROI, region of interest.

with regard to levels of triglycerides, unsaturated fatty acids and cholesterol, in the absence of any other imaging findings.⁷⁸ Further studies are warranted, but if these findings are confirmed, there might be relevant clinical implications for the screening of high-risk females.

MULTIPARAMETRIC MRI

To overcome limitations in the specificity of DCE, several functional MRI parameters have been investigated, and the application of these combined parameters is defined as mpMRI of the breast. There is evidence that mpMRI using different functional parameters can provide detailed information about the hallmarks of cancer^{8,9} and provide additional specificity.^{5,10–16} MpMRI with DCE-MRI and DWI has been investigated for breast cancer diagnosis in multiple studies and results indicated that MpMRI with DCE-MRI and DWI increases diagnostic accuracy in breast cancer diagnosis.^{10,11,79} To solve the dilemma of how to combine the unique information from DCE-MRI and DWI, and how to implement mpMRI in the clinical routine, several different approaches have been introduced. Pinker et al developed a reading scheme that adapted ADC thresholds to the

assigned breast imaging-reporting and data system (BI-RADS) classification.⁸⁰ In that study, the sensitivity of the BI-RADS-adapted reading was not significantly different from the high sensitivity of DCE-MRI ($p = 0.4$), whereas the BI-RADS-adapted reading maximized specificity to 89.4%, which was significantly higher compared with DCE-MRI ($p < 0.001$). The authors concluded that BI-RADS-adapted reading, which combines DCE-MRI and DWI, improves diagnostic accuracy and is fast and easy to use in routine clinical practice (Figures 6 and 7).¹¹ Baltzer et al investigated improvements in the specificity of breast MRI by integrating ADC values with DCE-MRI using a simple sum score.¹⁶ The additional integration of ADC scores achieved an improved specificity (92.4%) compared with DCE-MRI-only reading (specificity of 81.8%), with no false-negative results. In a very recent study, Dijkstra et al investigated whether the specificity in the work-up of BI-RADS 3 and 4 breast tumours can be increased when a semi-automated breast lesion analysis of quantitative DWI is implemented after DCE-MRI. When quantitative DWI was added to DCE-MRI, the combined specificity improved significantly.⁸¹ Recently, the concept of mpMRI using DCE-MRI and DWI has been translated to

Figure 7. MRI of the breast at 3.0T: fibroadenoma in a 42-year-old female at 2 o'clock in the right breast—the round and partly irregularly marginated mass [(a) pre-contrast media, (b) initial and (c) delayed enhancement] is demonstrating a homogeneous fast/washout contrast enhancement (d) and has been classified as breast imaging-reporting and data system (BI-RADS) 4 on dynamic contrast-enhanced MRI. On diffusion-weighted imaging (e), the apparent diffusion coefficient values ($1.596 \times 10^{-3} \text{ mm}^2/\text{s}$) (f) were well above the threshold for malignancy, thus allowing an accurate classification as a benign finding (BI-RADS 3—probably benign) with the BI-RADS-adapted reading. ROI, region of interest.

ultrahigh field strengths (7.0 T).¹⁰ MpMRI, which combines high-resolution DCE-MRI and DWI at 7.0 T, yielded a sensitivity and specificity of 100% and 88.2%, respectively, with an area under the curve (AUC) of 0.941, which was significantly greater than that of DCE-MRI ($p = 0.003$). In that study, mpMRI of the breast at 7.0 T accurately detected all cancers, reduced false positives from eight with DCE-MRI to two and thus could have obviated unnecessary breast biopsies ($p = 0.031$) (Figures 8 and 9).

To further increase specificity, Pinker et al compared the diagnostic accuracy of DCE-MRI as a single parameter with mpMRI with two (DCE-MRI and DWI) and three (DCE-MRI, DWI and ¹H-MRSI) parameters in breast cancer diagnosis (Figure 10).⁸² MpMRI with three parameters yielded significantly higher AUCs (0.936) than DCE-MRI alone (0.814) ($p < 0.001$). MpMRI at 3.0 T with only two parameters did not yield higher AUCs (0.808) than DCE-MRI alone (0.814). MpMRI with three parameters eliminated all false-negative lesions and significantly reduced false positives ($p = 0.002$). Because MpMRI with three parameters increased the diagnostic accuracy of breast cancer, compared with DCE-MRI alone and mpMRI with two parameters, mpMRI should be considered for future implementation in breast cancer care. The concept of mpMRI with three parameters has been recently extended to 7.0 T. Schmitz et al investigated mpMRI with three parameters,

i.e. DCE-MRI, DWI and phosphorus MRSI (³¹P-MRSI), at 7.0 T for the characterization of breast cancer.⁸³ Results indicate that mpMRI of the breast at 7.0 T with three parameters is feasible in the clinical setting and shows an association between ADC and tumour grade and between ³¹P-MRSI and mitotic count.

EMERGING MRI PARAMETERS

In addition to already established functional MRI parameters, novel MRI parameters are rapidly being developed and translated into clinical imaging.

Sodium imaging

Sodium MRI (²³Na-MRI) is an emerging MRI technique for the detection and therapy monitoring of breast cancer. ²³Na-MRI provides information about the physiological and biochemical state of tissues, and sodium concentration is a sensitive indicator of cellular metabolic integrity and ion homeostasis.⁸⁴ ²³Na-MRI depicts increased sodium levels secondary to failure of the Na⁺/K⁺-ATPase pump due to the breakdown of cell membranes as a marker for malignancy. Ouwerkerk et al investigated the potential of ²³Na-MRI for the differentiation of benign and malignant breast tumours at 1.5 T^{84,85} and found that an increased total sodium concentration in breast tumours is a sensitive cellular level indicator of malignancy. In addition, ²³Na-MRI is a sensitive imaging biomarker for response assessment in

Figure 8. MRI of the breast at 7.0 T: invasive ductal carcinoma grade 3 and associated high-grade ductal carcinoma *in situ* in the right breast in a 36-year-old female—high-resolution dynamic contrast-enhanced MRI at 7.0 T is showing an irregular shaped, partly spiculated mass lesion retromammillary right (a) with fast/washout enhancement kinetics (b). Diffusion-weighted imaging is showing a restricted diffusivity (c) and low apparent diffusion coefficient values ($0.68 \times 10^{-3} \text{ mm}^2 \text{ s}$) (d), indicating high cellularity, which is indicative of tumour malignancy (breast imaging-reporting and data system 5—highly suggestive of malignancy). ROI, region of interest.

Figure 9. MRI of the breast at 7.0 T: fibroadenoma in a 32-year-old female in the right breast retromammillary—the round and partly irregularly marginated mass [(a) pre-contrast media, (b) initial and (c) delayed enhancement] is demonstrating a homogeneous medium/persistent contrast enhancement (d) and has been classified as breast imaging-reporting and data system (BI-RADS) 4 in dynamic contrast-enhanced MRI. On diffusion-weighted imaging (e), the apparent diffusion coefficient values ($1.473 \times 10^{-3} \text{ mm}^2/\text{s}$) (f) are well above the threshold for malignancy, thus allowing an accurate classification as a benign finding (BI-RADS 3—probably benign) with BI-RADS-adapted reading.

patients receiving NAC. Initial results at 1.5 T indicated that responders to NAC demonstrated significant changes in multiparametric imaging biomarkers with CE-MR, ¹H-MRSI and ²³Na-MRI parameters, even after the first cycle of NAC, and thus, mpMRI of the breast can provide new surrogate imaging biomarkers to predict response.^{90,91} However, at field strengths of 1.5 and 3.0 T, ²³Na-MRI is limited. Zaric et al investigated quantitative ²³Na-MRI at 7.0 T compared with DWI and proved that quantitative ²³Na-MRI of the breast at 7.0 T is feasible, with good resolution and image quality, in clinically acceptable measurement times. Similar to DWI ($p = 0.002$), ²³Na-MRI enabled differentiation of benign and malignant breast tumours ($p = 0.002$). ²³Na-MRI adds complementary information about pathophysiologic changes in tumours and thus has the potential to improve the detection, characterization and treatment monitoring of breast lesions.⁸⁶

Phosphorus spectroscopic imaging

Phosphorus spectroscopic imaging (³¹P-MRSI) measures the bioenergetics of tissue and membrane phospholipid metabolism, and the signals of phospholipid precursors and catabolites can be used as imaging biomarkers for tumour progression and response to therapy.^{87,88} However, at field strengths of 1.5 and 3.0 T,

the clinical application of ³¹P-MRSI is limited. Recently, the feasibility of ³¹P-MRSI at 7.0 T has been demonstrated in healthy volunteers and in patients with breast cancer. ³¹P-MRS provides endogenous biomarkers for phospholipid/phosphate energy metabolism and intracellular pH and allows *in vivo* monitoring of tumour metabolism during NAC. ³¹P-MRSI is expected to be used as a targeted imaging tool for breast cancer diagnosis, tumour staging and monitoring response to therapy.^{87,88}

Chemical exchange saturation transfer imaging

CEST is an MRI parameter that enables visualization of chemical exchange processes between protons bound to solutes and surrounding bulk water molecules.^{89–91} Endogenous CEST can discriminate tumour from healthy breast tissue, based on the information about protons associated with mobile proteins, through the amide proton transfer (APT) effect and has been implicated as a prognosticator of response to therapy. Initial feasibility studies hint at a significant potential for APT CEST-MRI in breast imaging.^{90,92} Recently, animal studies have investigated CEST contrasts other than APT, exploiting the entire CEST spectrum. Desmond et al found that imaging of the amide, amine and aliphatic signal allows non-invasive differentiation of areas of apoptosis and/or necrosis from actively progressing tumour.⁹³ Analogous to

Figure 10. MRI of the breast at 3.0 T: invasive lobular carcinoma grade 3 laterally in the right breast in a 44-year-old female at 3 T—the lesion (arrow) is presenting as a segmental heterogeneous non-mass enhancement [(a) pre-contrast media, (b) initial and (c) delayed enhancement] with a fast/plateau contrast enhancement (d). On diffusion-weighted imaging, there is a restricted diffusivity (e) with decreased ADC values ($0.89 \times 10^{-3} \text{ mm}^2/\text{s}$) (f). On proton MR spectroscopic imaging, there is a choline peak at 3.2 ppm (dashed arrow) (g). Multiparametric MRI has accurately classified the lesion as malignant, BI-RADS 5 (highly suggestive of malignancy).

fluorine-18 fludeoxyglucose (^{18}F FDG) PET, dynamic CEST imaging after the administration of glucose enables the non-invasive evaluation of the kinetics of glycolysis and thus, CEST imaging after the administration of glucose might serve as a potential substitute for PET/CT or PET/MRI without the need for radiolabelled isotopes.⁹⁴ Nevertheless, further studies will be necessary to explore the true potential of CEST imaging in breast cancer.

Blood oxygen level-dependent MRI

BOLD MRI, or intrinsic susceptibility-weighted imaging, is a non-invasive method for the indirect measurement of tumour perfusion and hypoxia. Hypoxia is a feature of most solid tumours, including breast cancer, and is associated with tumour progression, treatment resistance, local recurrence and metastasis. Initial results indicate that BOLD MRI is a simple and non-invasive technique with which to obtain information about hypoxia in breast cancer.^{95,96} Hypoxia imaging with BOLD MRI might, therefore, have the potential to serve as an imaging biomarker for breast cancer diagnosis and prognosis, as well as treatment response.⁹⁷

Hyperpolarized MRI

HP MRI is one of the most recent advances in molecular imaging. HP MRI allows a rapid, radiation-free, non-invasive

investigation of tumour metabolism by exploiting exogenous contrast agents that have been “hyperpolarized”, resulting in an extensive increase in signal intensity.^{98,99} Recently, ^{13}C -labelled substrates have been polarized to obtain enhancements of the ^{13}C nuclear MR signals, *e.g.* >50,000-fold at 3.0 T in the substrate, and the subsequent metabolic products. The HP ^{13}C probes can be injected into living organisms and their metabolism can be observed in real time by chemical shift imaging. Currently, (^{13}C) pyruvate is the most widely used probe for HP MR studies, since it polarizes well, has a long T_1 relaxation time and is rapidly taken up by the cell and metabolized at the juncture of glycolysis, tricarboxylic acid, amino acid biosynthesis and other critical pathways. Several animal studies have confirmed that the real-time measurement of the relative transformation of pyruvate into lactate and alanine with HP MRI enables the differentiation of benign and malignant tumours, as well as cancer progression.^{99–101} Other novel probes for redox (^{13}C dehydroascorbate), necrosis (^{13}C fumarate) and glutamine metabolism (^{13}C glutamine) have been developed to interrogate other metabolic pathways, and initial results are promising.¹⁰² To date, there is no specific clinical application for HP MRI in breast cancer, but pre-clinical results indicate that this technique may be applicable, in the future, for the detection of breast cancer and assessment of treatment response.¹⁰³

HYBRID IMAGING WITH POSITRON EMISSION TOMOGRAPHY/MRI

In recent years, mpMRI and PET of the breast have emerged as promising imaging tools^{5,104,105} that provide morphologic and functional data and are of complementary value.^{106,107} To overcome the individual limitations of morphologic and functional imaging techniques, hybrid imaging systems have been developed and introduced into the clinical routine. Initial studies investigating fused [¹⁸F]FDG PET and DCE-MRI for breast cancer diagnosis demonstrated that fused [¹⁸F]FDG PET/MRI provides accurate morphological and functional data.¹⁰⁸ Pinker et al investigated mpPET/MRI using DCE-MRI, DWI, ¹H-MRSI and [¹⁸F]FDG for the assessment of breast tumours at 3.0 T.¹⁰⁹ Multiparametric [¹⁸F]FDG PET/MRI provided an improved differentiation of benign and malignant breast tumours when several MRI and PET parameters were combined (Figure 10). In addition, the authors concluded that multiparametric [¹⁸F]FDG PET/MRI may lead to an up to 50% reduction of unnecessary breast biopsies. In a recent feasibility study, Pinker et al investigated combined PET/MRI of breast tumours with DCE-MRI, DWI, the radiotracer [¹⁸F]FDG and the hypoxia tracer [¹⁸F]fluoromisonidazole at 3.0 T, in eight patients, and correlated MRI and PET parameters with pathological features, grading, proliferation rate (ki67), immunohistochemistry and the clinical end-point metastasis and death.¹¹⁰ Preliminary results showed several moderate-to-excellent correlations between quantitative imaging markers, grading, receptor status and proliferation rate. Multiparametric criteria provided independent information. DCE-MRI, [¹⁸F]FDG and [¹⁸F]FMISO avidity strongly correlated with the presence of metastasis [$r = 0.75$ ($p < 0.01$), 0.63 ($p = 0.212$) and 0.58 ($p = 0.093$)] and death [$r = 0.60$ ($p = 0.09$), 0.62 ($p = 0.08$) and 0.56 ($p = 0.11$)].

These results demonstrate that multiparametric [¹⁸F]FDG/¹⁸F]FMISO PET/MRI can provide quantitative prognostic information in patients with breast cancer and thus might have the potential to enable tailored therapy through improved risk stratification.

CONCLUSION

Within the past few years, mpMRI has been established in the field of breast imaging. MpMRI of the breast comprises different established MRI parameters (DCE-MRI, DWI and ¹H-MRSI), as well as hybrid imaging with PET/MRI. Novel MRI parameters, such as ²³Na-MRI, ³¹P-MRSI, CEST, BOLD and HP MRI, are being rapidly developed and translated into clinical imaging. A paradigm shift, from morphologic to functional imaging in cancer imaging, is imminent. MpMRI of the breast has the potential to significantly enhance our understanding of tumour biology, and it can be expected that mpMRI will play a pivotal role in the genomic era of cancer care, enabling personalized medicine in patients with breast cancer.

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