

REVIEW

Functional magnetic resonance: biomarkers of response in breast cancer

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Abstract

Functional magnetic resonance (MR) encompasses a spectrum of techniques that depict physiological and molecular processes before morphological changes are visible on conventional imaging. As understanding of the pathophysiological and biomolecular processes involved in breast malignancies evolves, newer functional MR techniques can be employed that define early predictive and surrogate biomarkers for monitoring response to chemotherapy. Neoadjuvant chemotherapy is increasingly used in women with primary breast malignancies to down-stage the tumour and enable successful breast conservation surgery. It also plays a role in the treatment of undetected micrometastases. Cardinal physiological features of tumours that occur as a result of interactions between cancer cells, stromal cells and secreted factors and cytokines and how they change with treatment provide the opportunity to detect changes in the tumour microenvironment prior to any morphological change. Through sequential imaging, tumour response can be assessed and non-responders can be identified early to enable alternative therapies to be considered. This review summarises the functional magnetic resonance biomarkers of response in patients with breast cancer that are currently available and under development. We describe the current state of each biomarker and explore their potential clinical uses and limitations in assessing treatment response. With the aid of selected interesting cases, biomarkers related to dynamic contrast-enhanced MRI, diffusion-weighted MRI, T2*/BOLD and MR spectroscopy are described and illustrated. The potential of newer approaches, such as MR elastography, are also reviewed.

Introduction

Magnetic resonance imaging (MRI) of the breast has an established role in assessing response to neoadjuvant chemotherapy and provides better monitoring of the chemotherapeutic effect than clinical breast examination, mammography and ultrasound, especially in non-mass lesions and tumours that have fragmented into many foci [1]. As the overall response rate offered by neoadjuvant chemotherapy ranges from 60% to 80%, with complete pathological response rates being around 10% to 20% [2], identification of early response is important in planning subsequent management. More complex functional MRI techniques offer to quantify changes in tumour microvasculature, cell density, hypoxia, metabolism and stiffness and so provide early predictive and surrogate biological biomarkers for monitoring response to chemotherapy.

As breast tumours respond to chemotherapy, changes occur within the tumour and its microenvironment. Angiogenesis, the fundamental physiological process associated with tumour development, is interrupted. The composition of the extracellular matrix and stroma is altered, and secreted factors and cytokines, which can affect the transport of molecules to and from tumour cells, change the physiology and chemical composition of the tumour. For example, tumour cells become hypoxic and fragment, leaving fibrotic and collagenous tissue that may be quantified using functional magnetic resonance (MR) techniques.

This article reviews the functional MR biomarkers of response currently routinely available and under development for assessing treatment response. Specifically, dynamic contrast-enhanced (DCE)-MRI, diffusion-weighted (DW)-MRI, intrinsic susceptibility-weighted MRI, MR spectroscopy (MRS) and MR elastography are described with a focus on the current state of each technique and its limitations as a response biomarker.

Dynamic contrast enhanced MRI

DCE-MRI of the breast involves an intravenous injection of a low molecular weight T1-shortening paramagnetic compound (a gadolinium chelate) at doses between 0.1 and 0.2 mmol/kg. Agents currently licensed for use

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include gadopentetate dimeglumine (Magnevist), gadodiamide (Omniscan), gadobenate dimeglumine (Multi-hance), gadoteriodol (ProHance), gadofosveset trisodium (Vasovist), gadoxetic acid (Eovist) and gadoversetamide (OptiMARK). Once injected, gadolinium circulates in the blood stream before passing into the extravascular extracellular or interstitial space. The concentration of gadolinium equilibrates between the intravascular and extravascular compartments over time and is eventually excreted by the kidneys. Post contrast images provide additional information to the unenhanced sequences by exploiting differences in temporal enhancement characteristics between malignant and normal or benign tissues. The differential uptake and washout of gadolinium in each of these tissues results in an increased signal on T₁-weighted (T₁W) images. Along with morphological assessment from the unenhanced T₁W and T₂W sequences, the use of gadolinium to depict enhancement characteristics of the tissues can improve the sensitivity of MRI for cancer detection to between 89% and 100% [3].

Along with its high sensitivity, the specificity of breast DCE-MRI, although initially reported to be low, has more recently been shown to equal that of mammography with significantly higher values than ultrasound [4]. The blooming sign seen in 63% of malignant compared to 14.7% of benign lesions describes a brisk enhancement with sharply shaped borders at 1 minute after a bolus contrast injection that become progressively unsharp [5]. Further potential adjunctive morphological indicators of malignancy include unifocal oedema (91% of malignant lesions and 45% of benign lesions), centripetal enhancement with a rapidly enhancing outer ring that fills in (52% malignant lesions [6]), and the hook sign, a hook-like connection to the underlying pectoral muscle (33% of malignant lesions and 5% of benign lesions [7]). The presence of an adjacent vessel on subtraction images is also a promising sign for malignancy (85.9% of malignant and *in situ* lesions compared to 19.6% of benign lesions [8]). Finally, the addition of morphologic signs from unenhanced T₂W sequences, such as spiculated margins, homogeneous intermediate signal intensity or stellate appearance, have been described to further improve the specificity of breast MRI [8].

The rate of contrast uptake into breast lesions is non-linear and differs between malignant and benign lesions (Figure 1) so that enhancement curve characteristics can be used in conjunction with morphologic features to aid differential diagnosis. Malignant lesions exhibit stronger and faster enhancement than benign changes or normal tissues. In benign lesions, a slow onset (type I) curve that plateaus after 3 to 5 minutes is described in 83% of cases. In malignant lesions, a rapid onset with plateau (type II) or rapid onset with washout (type III) curve can be found in 91% of cases (57% for type III and 34% for type II) [9].

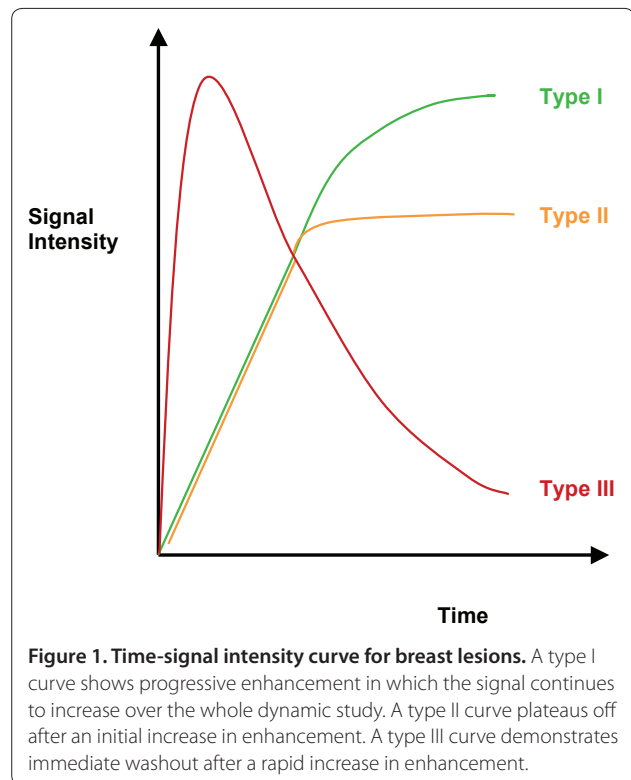
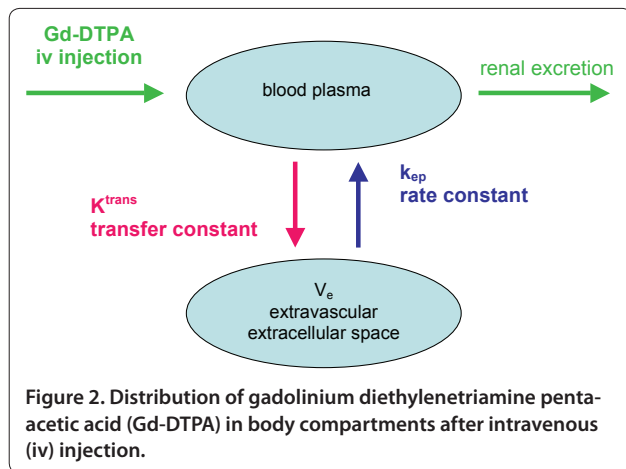


Figure 1. Time-signal intensity curve for breast lesions. A type I curve shows progressive enhancement in which the signal continues to increase over the whole dynamic study. A type II curve plateaus off after an initial increase in enhancement. A type III curve demonstrates immediate washout after a rapid increase in enhancement.

Semi-quantitative parameters can be calculated from these enhancement curves, including the onset time (from injection to the appearance of contrast in the tissues), maximum signal intensity, gradient or rate of contrast uptake and washout, and initial area under the time signal curve (IAUC).

Quantitative analysis involves pharmacokinetic modelling and requires more complex analysis methods of estimating changes in tissue contrast agent concentration following intravenous injection. Between 12% and 45% contrast leaks into the extravascular extracellular space (v_e) during the first pass and results in measurable T₁ shortening of tissues. The transfer constant, K^{trans} , describes the transendothelial transport of contrast medium by diffusion from the vascular space to the tumour interstitium and provides a measure of vascular permeability. Over time, gadolinium diffuses back into the vasculature, which can be measured by the rate constant, k_{ep} . These parameters are related by the equation $k_{ep} = K^{trans}/v_e$ [10] (Figure 2).

Magnetic field inhomogeneities induced by gadolinium on a T₂W image can also be exploited to derive relative measures of blood flow and volume (rBF and rBV) as well as mean transit time (MTT). These variables are related by the central volume theorem equation ($BF = BV/MTT$). The signal loss on a T₂W sequence caused by dephasing of spins is related to the concentration of gadolinium and thus to vessel size and density [11].



There is good evidence for use of such quantitative measures in breast cancer. K^{trans} is generally high in tumours, as is k_{ep} (Fig. 3), and a significant reduction of up to a third has been shown in both parameters in patients with locally advanced breast cancer responding early in their course of neoadjuvant chemotherapy [12]. In addition, an increase in v_e of nearly a third has been shown in non-responders [13]. rBV and rBF obtained from T_2^*W dynamic susceptibility sequences have also shown reductions of around two-thirds in patients responding to treatment [12]; however, T_2^*W functional imaging, while commonly used in MRI of the brain, is almost never used in breast MRI. Alterations in these parameters are likely to relate to changes in microvessel density and function of the microvasculature due to antiangiogenic effects of chemotherapy. The evidence from phase I and II studies strongly suggests that K^{trans} can be used as a predictive biomarker to determine response to antiangiogenic drugs or vascular disruptive agents, with a change in K^{trans} of greater than 40% considered by many investigators as the threshold required to represent definitive disease response [14]. There is some discrepancy in the published data, however, with several other studies demonstrating little or no decrease in K^{trans} or k_{ep} following neoadjuvant chemotherapy [15,16]; in fact, one small study of 29 patients scanned very early after one cycle of chemotherapy showed that early tumour size change is a better response predictor than either K^{trans} or k_{ep} [17].

The explanation for these variations in reported data are multifactorial: patient numbers, tumour type, chemotherapeutic agent and time-point of scanning after commencing therapy have all varied. The classification of responders was also not consistent, varying from a 65% reduction in the largest tumour volume [13] to the accepted Response Evaluation Criteria in Solid Tumours (RECIST) or International Union Against Cancer criteria [18] of 30% or more reduction in one-dimensional

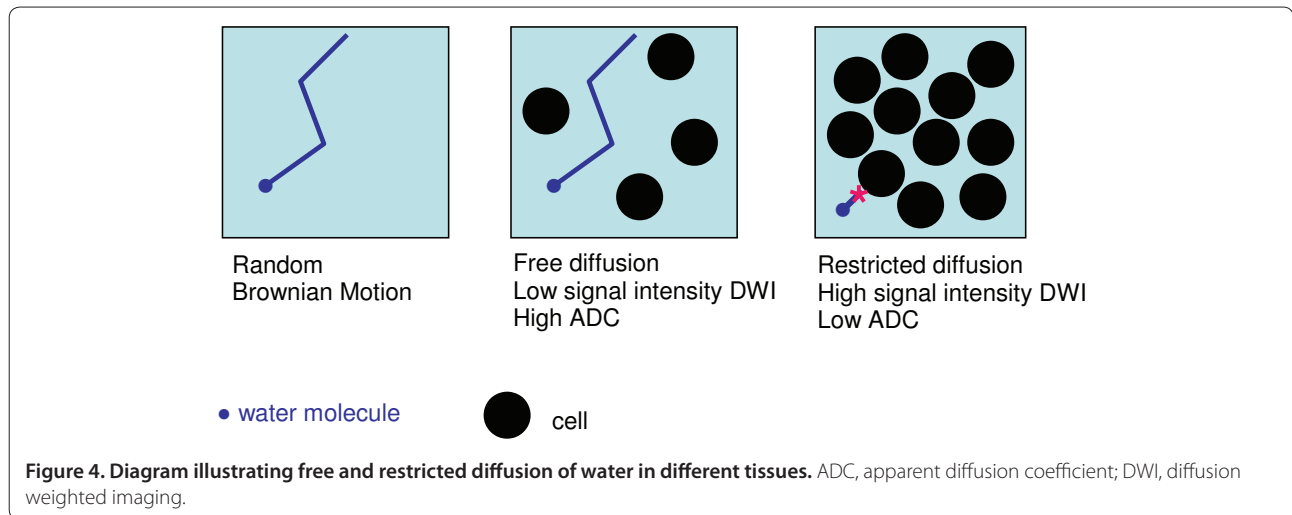
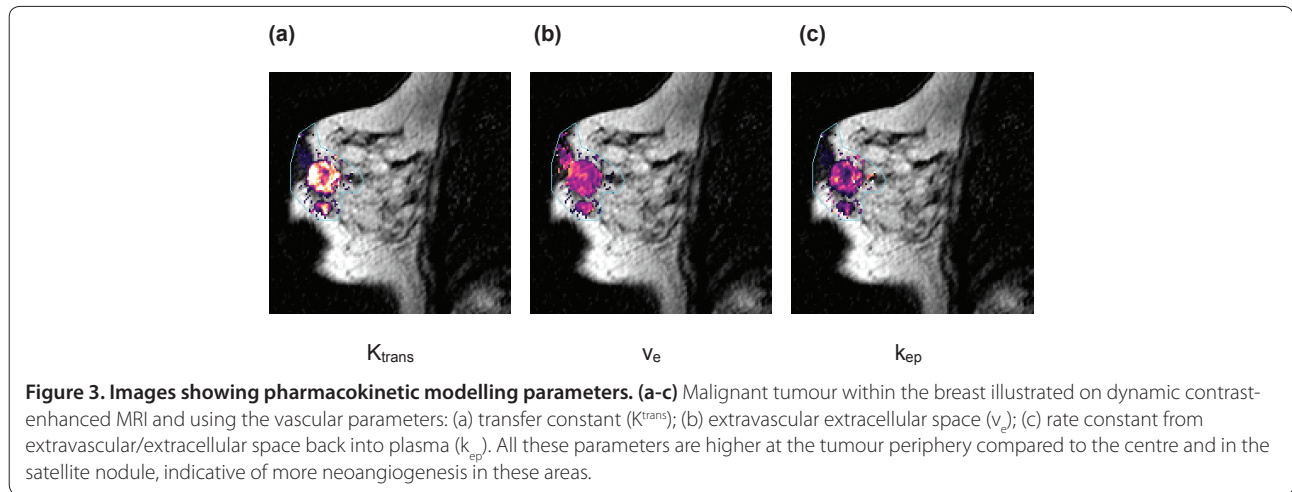
tumour size or a 50% or more reduction in the product of the tumour diameter (assuming a spherical tumour model), respectively [12,15,16]. The group who demonstrated change in tumour size to be a better predictor of response compared to K^{trans} or k_{ep} chose an arbitrary reduction of 15% in one-dimensional size [17].

There was also a significant difference in data analysis methodology; most studies used manual regions-of-interest (ROI) on enhanced subtracted images, although one group used semi-automated ROI generation, and in addition analysed a 3×3 pixel ROI hot spot [13]. Furthermore, the median or mean of each pharmacokinetic parameter for analysis has not been consistent. An increasing awareness of the heterogeneity of breast tumours makes the median a more appropriate parameter, with the change in the skewness of the distribution of these parameters likely to be as significant as changes in the median value.

Another source of variation is the range of mathematical models used for pharmacokinetic analysis and the choice of arterial input function measurement, which also impacts on the overall results of tumour vascular heterogeneity. Traditionally, use of a nearby blood vessel for arterial contrast was deemed the ideal arterial input function [19], but population-based arterial input functions are more robust [20]. Alternatively, tumour enhancement relative to that in neighbouring muscle tissue can be evaluated [21], and avoids error from flow effects in blood vessels. With the introduction of standardised scanning protocols, automated analysis software and the publication of reproducibility studies, derivation of pharmacokinetic parameters could become more standardised and robust and be usefully adopted as functional imaging markers in breast cancer.

Diffusion-weighted MRI

DW-MRI develops intrinsic contrast within tissues based on the microscopic motion of water molecules by applying magnetic field gradients during the MRI pulse sequence that sensitize the readout signal to losses from this motion. DW-MRI contrast provides different, and complementary, information to DCE-MRI, being sensitive to factors that affect this microscopic water motion, such as cell density, membrane integrity and tissue microstructure. Changes in signal intensity on DW-MRI reflect the movement of water diffusion over distances of 0 to 30 μm over time periods of 50 to 100 ms [22]. As with other tumours, breast cancers demonstrate restricted diffusion because water molecules cannot move as freely in tissues with a high cell density where extracellular space is limited (Figure 4); this results in reduced signal loss from Brownian motion and is seen as a high signal intensity lesion on the DW-MRI image (Figure 5).



Magnetic field gradients used to provide diffusion weighting can be varied in their amplitude, duration and spacing, which are jointly reflected by a 'b' value. Acquisition of DW-MRI data using at least two b values allows calculation of an apparent diffusion coefficient (ADC), a derived logarithmic parameter of signal change with b value. At very low b values ($<100 \text{ s/mm}^2$), the ADC predominantly reflects larger distances of water movement likely to represent movement within microvessels. This phenomenon is known as intravoxel incoherent motion [23]. By eliminating these low b values, this 'perfusion' effect in vascular rich areas can be suppressed and the ADC value can more accurately represent the shorter distances travelled by water protons in the extracellular space, or true diffusion [24].

The role of DW-MRI in tumour diagnosis is gradually being explored and it is increasingly shown to aid decision-making [25]. Differentiation between malignant and benign breast lesions using DW-MRI has been well reported [26-28], with the mean ADC value of malignant

lesions being significantly lower than that of benign lesions or normal breast tissue. This degree of overlap requires incorporation of an ADC threshold methodology for analysis; a $1.6 \times 10^{-3} \text{ mm}^2/\text{s}$ cutoff gives up to 96% sensitivity and 55% specificity for tumour identification [27]. More recently, one group has normalised ADC values to the surrounding glandular tissue and demonstrated a reduction in overlap between benign and malignant lesions. Using this method, normalised ADC values for tumour and benign lesions are $0.55 \times 10^{-3} \text{ mm}^2/\text{s}$ and $1.1 \times 10^{-3} \text{ mm}^2/\text{s}$, respectively) [29], with the optimal threshold of $1.6 \times 10^{-3} \text{ mm}^2/\text{s}$ normalising to $0.7 \times 10^{-3} \text{ mm}^2/\text{s}$.

The visibility of lesions on DW-MRI is better in older women compared to younger women, likely related to the density of the glandular parenchyma. Also, due to the lower spatial resolution offered by DW-MRI compared to DCE-MRI, the diagnostic performance of DW-MRI is less helpful for non-mass-like lesions such as invasive lobular carcinomas and lesions $<1 \text{ cm}$ in size [30]. The

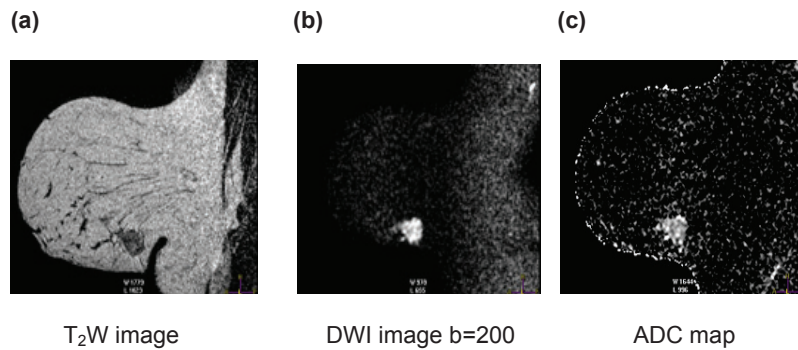


Figure 5. Diffusion weighted images of a breast tumour. (a) Sagittal T₂W image through the breast shows a well-defined lobulated mass inferiorly. (b) This appears as a bright area of restricted diffusion on the corresponding diffusion weighted MRI (DW-MRI) image (b = 200). (c) The calculated apparent diffusion coefficient (ADC) map shows the heterogeneity of diffusion coefficient values within the tumour.

major false-positive lesions reported are intraductal papillomas and fibrocystic disease, which can also result in overestimation of cancer extension [27]. Mucinous carcinomas interestingly demonstrate a significantly higher ADC compared to other types of breast cancer, leading to false-negative reports [31].

DW-MRI also shows promise as an early surrogate biomarker for detecting response to neoadjuvant chemotherapy. Induction of successful apoptosis results in loss of membrane integrity, alteration of membrane barriers to water diffusion and cell shrinkage, increasing extracellular space. This translates to a rise in the ADC value of up to 35% and precedes any decrease in tumour size in locally advanced tumours [32-34]. Transient early decreases in ADC have also been demonstrated before this increase, and are thought to be related to cell swelling, reduction in blood flow or changes in composition of the extracellular space [16].

The optimal b values for diffusion-weighted MRI in the breast have not been established; nor indeed have the optimal scanning protocol, imaging parameters and methods of analysis, which all have a bearing on the ADC value. Published data indicate that b values from 0, 600 to 850, and up to 1,000 may be optimal [27,28,30], with at least three values required to ensure robustness of reproducibility of the measurement. The ability to obtain these data without the use of extrinsic contrast agents, in a short scanning time, independent of magnetic field strength and operator interpretation is hugely advantageous. Reproducibility studies and quality assurance of methodology crucially need to be established.

T₂*/blood oxygen level-dependent MRI

Blood oxygen level-dependent (BOLD) or intrinsic susceptibility-weighted MRI relies on the paramagnetic property of deoxyhaemoglobin, which creates susceptibility variations in the magnetic field (or microscopic field gradients), which in turn decrease the transverse

relaxation rate R_2^* ($= 1/T_2^*$) of water in blood and the tissue surrounding blood vessels. An increase in the deoxyhaemoglobin concentration (that is, hypoxia) leads to a decrease in the signal intensity on the T₂* image and a faster R_2^* [35] (Figure 6). An improvement in oxygenation has the converse effect. Deoxyhaemoglobin therefore acts as an intrinsic BOLD contrast agent for imaging tissue hypoxia. Specific gradient-recalled echo (GRE) sequences are required to detect changes in R_2^* . Variations in R_2^* have largely been evaluated in xenograft and human models using inhaled carbogen (95% oxygen (O₂), 5% carbon dioxide (CO₂)) to intensify the otherwise small changes in signal intensity: the CO₂ induces vasodilation and the O₂ tension is high with 95% O₂ so that subtracted images with and without carbogen reveal regions of hypoxia where signal change is greatest. Unfortunately, the hyperventilation induced by breathing carbogen in humans is poorly tolerated so reliance has been largely on R_2^* measurements during air, or alternatively 100% oxygen, breathing.

A recent study in breast cancer patients has shown R_2^* values to be significantly lower in tumour than normal breast parenchyma prior to the commencement of chemotherapy [36], suggesting that breast tumours are less hypoxic than normal breast tissue, possibly because of their high vascularity. This contrasts with other recently published data in prostate cancer [37], where R_2^* is increased, indicating increased hypoxia in these tumours. The increased R_2^* in normal breast tissue has also been related to the fibrocollagenous ligaments of Cooper, which maintain normal breast structural integrity and contribute to higher R_2^* values. In responders following treatment, the R_2^* value has been shown to increase, likely as a result of decreased blood flow; however, in this one published study this parameter was not as efficacious as changes in other DCE-MRI parameters, such as K^{trans} , rBV, and rBF, or even morphological parameters such as tumour size, in indicating response [36]. The complexity

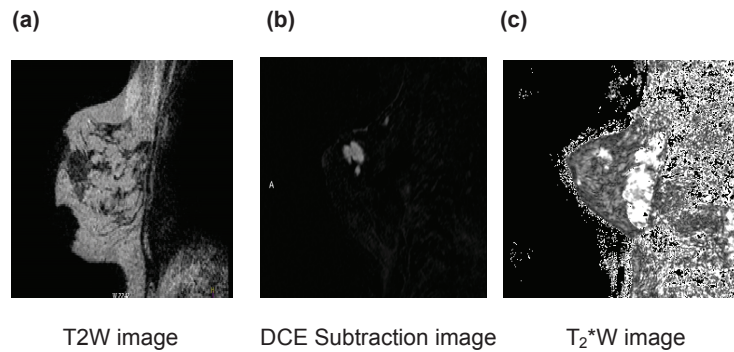


Figure 6. T₂*W images of a breast tumour. (a-c) Sagittal T2W (a), dynamic contrast-enhanced (DCE) subtracted image at time point 2.44 minutes (b), and T₂*W image (c) in a patient with a palpable breast lump in the upper outer quadrant. The tumour seen in (a) and highlighted in (b) shows heterogeneity of T₂* with faster signal decay in the inferior part of the tumour, indicating a greater deoxyhaemoglobin content here.

and heterogeneity of the microvasculature in different tumour types thus need to be understood prior to using such measurements for evaluating changes in tumour oxygenation in response to chemotherapy.

MR spectroscopy

MRS exploits the nuclear spin properties of hydrogen (¹H) as well as of other atoms with unpaired protons, such as ³¹P, ²³Na and ¹⁹F, in a magnetic field to absorb and emit radiofrequency. The acquired frequency spectrum of a range of metabolites provides information about the altered metabolism of cancer cells. With ¹H MRS, efficient water suppression is mandatory to document proton resonances within molecules known to be increased in cancer, such as choline and lipids; protons within these molecules resonate at slightly different frequencies when placed in a magnetic field because of their immediate molecular environment. In breast cancer, as with other tumours, high levels of choline-containing metabolites involved in phospholipid metabolism, and thus cellular membranes in proliferation, result in a triplet at 3.22 ppm of free choline, phosphocholine and glycerophosphocholine. Choline is virtually undetectable in normal breast tissue and a peak at 3.25 ppm indicates benign tissue [38].

Several groups have shown that total choline concentration [Cho] can be used as a marker of malignancy, and when combined with DCE-MRI, increases the specificity of breast MR up to 88% (and to 100% after the inclusion of a single slice T₂* perfusion measurement) [39]. *In vivo* ¹H-MRS has also been shown to be useful in monitoring metabolic response to chemotherapy, with increased [Cho] and water/fat ratios in malignant tumours indicative of residual disease [40]. Small patient studies to date show promising results, with reduction of the choline signal following two cycles of neoadjuvant chemotherapy being more sensitive than changes in tumour size at predicting pathological response [41]. Also, by imaging

after one cycle of chemotherapy, the same group demonstrated that a reduction in the choline signal may be more sensitive than DW-MRI in demonstrating pathological response [41,42].

In vivo ¹H MRS is a single, large voxel technique, and overall variations in the fat and water composition, particularly in heterogeneous tumours such as invasive lobular cancers and ductal carcinoma *in situ*, reduces sensitivity of [Cho] quantification. Partial volume effects in a large voxel also cause problems in the quantification of [Cho], which pose a significant problem after neoadjuvant chemotherapy [43].

Two dimensional localised correlated spectroscopy (L-COSY MRS) incorporates a second spectral dimension that is indirectly detected through the acquisition of multiple one-dimensional MRS with incrementally longer times to echo (TEs). Cross-correlation of peaks enables identification of lipid species by reducing contamination from overlapping metabolite resonances. Early reports have shown identification of invasive ductal carcinoma within these spectra versus normal fatty breast tissue with 92.4% sensitivity and 92.7% specificity [44]. However, the technique is time consuming (20 minutes for a 3 cm voxel) and requires specialist analysis software, so its clinical utility is limited.

Sodium (²³Na) MRI has also been shown to be a very sensitive indicator of cellular integrity and cellular energy metabolism [45], with an elevated tissue sodium concentration in neoplastic tissue. ²³Na images can be accurately determined by co-registering high-resolution ¹H images acquired during the same scan. Its potential as a surrogate biomarker of response has been reported with a significantly reduced tissue sodium concentration in responders after one cycle of chemotherapy [46].

MR elastography

MR elastography, an imaging correlate to palpation, is another novel technique that can be easily implemented

in the clinic. It assesses the viscoelastic shear properties of lesions by direct MRI visualisation of acoustic waves and quantifies the decreased elasticity of malignant tumours. Quantification of the differential 'stiffness' between a breast lesion and the background adipose and fibroglandular tissues is achieved by assessing the propagation of mechanical waves, generated by an electromechanical driver, through the breast using a gradient echo phase contrast sequence [47]. The tissue stiffness map (or elastogram) is based on a linear scale, calibrated into kilopascals and represented as a colour map.

MR elastography can be performed as an extension to conventional breast MRI and could potentially be incorporated into a standard MRI breast examination. It is already being used clinically for the assessment of patients with chronic liver disease. There have been very few studies of breast MR elastography; early published data on a small population group suggests that MR elastography in combination with DCE-MRI could increase the diagnostic performance of breast MRI and increase its specificity from 75% with a persistently high sensitivity of 90% [48]. Further investigations of larger cohorts and smaller lesions will be necessary to validate these results.

Discussion

In patients with breast cancer, traditional anatomical imaging using size and morphological criteria for assessing response to neoadjuvant chemotherapy does not provide information on functional changes within tumours. The current challenge is to move beyond these anatomical boundaries to develop a more personalised, individual assessment of functional changes within a tumour for response evaluation. For those with the poorest prognosis and most advanced disease, early identification of non-responders allows alternative management options to be considered. MRI has the versatility to contribute to the functional assessment of breast tumours and improve diagnostic confidence, as well as provide early surrogate markers of disease response.

Functional MRI biomarkers of response described need careful validation, ideally against clinical outcome measures, before they can be adopted as established surrogate end points of response. However, currently an insufficient number of clinical studies have been reported with this kind of data for this to happen; reported changes are summarised in Table 1. Multicentre validation against histopathological markers, such as for microvessel density, apoptosis, hypoxia and vascularity, would further qualify the use of these functional biomarkers and support their translation into clinical practice. However, histological validation lacks true 'functional' input, so the limitation of this kind of validation needs to

be recognised: it may well be that MRI on its own may more accurately reflect *in vivo* tumour physiology.

In an attempt to tackle the issues of validation, two phase II multicentre national trials are underway - Neo-COMICE in the United Kingdom and I-SPY 2 in the US, both of which are examining the effectiveness of MRI in the early prediction of response to neoadjuvant chemotherapy and the development of surrogate imaging biomarkers. Neo-COMICE, currently in its pilot stage, also aims to evaluate the optimal scanning protocols that determine parameters of greatest predictive value of treatment response and establish parity of MRI examinations between centres. Currently, there is no consensus on a standardized MR imaging examination or on the role of MRI for assessing response in patients receiving neoadjuvant chemotherapy. The adaptive design of the I-SPY 2 trial will allow early data from one set of patients to guide decisions about which treatments may be more useful in the trial in order to eliminate ineffective treatments and offer patients the best chance of successful therapy [49].

The increased availability of higher-field MRI scanners allows higher signal-to-noise ratio and so better spatial resolution to increase the visibility of small cancers. Early reports suggest that the sensitivity and specificity of DCE-MRI at 3T for malignant breast lesions increase to 95% and 91%, respectively, from 91% and 85% [50]. Going up in field strength from the commonly available 1.5T to 3.0T is not without challenges, however, as the non-uniformity of the magnetic induction field (B_1) results in non-homogeneity of fat suppression, which in turn leads to poor enhancement in areas with a very low magnetic induction field and errors in quantifying enhancement ratios. Reports have shown that the B_1 field in one breast can be reduced by as much as 40%, which is sufficient to reduce the conspicuity of a malignant lesion and reduce the sensitivity to cancer detection [51]. Quantitative functional MRI at 3T requires improved radiofrequency excitation methods and improved analysis to ensure B_1 inhomogeneity is accounted for when calculating DCE metrics.

Future potential in the search for biomarkers of efficacy for certain therapeutic treatments may lie in correlating baseline gene expression with MRI response using several of the above techniques. Gene arrays and immunohistochemistry analysis of vascular endothelial growth factor pathways could indicate which pattern of gene expression relates to specific changes in vascular volume and permeability assessed by MRI, and this is a promising area of research [52].

Ongoing research and recent technical advances indicate that the prospects for substantial improvements in monitoring of therapeutic response as well as for improved early detection and accurate diagnosis of breast

Table 1. Reported changes quantified on functional magnetic resonance following neoadjuvant chemotherapy for breast cancer

Functional technique and study	Responders	Non-responders	Time point imaged after NAC
DCE-MRI (percentage change in parameters)			
Ah-See <i>et al.</i> [12]	K^{trans} ↓39.8%	K^{trans} ↑18.1%	2 cycles
	k_{ep} ↓33.3%	k_{ep} ↑7.4%	2 cycles
	rBV ↓59.3%	rBV ↑73.4%	2 cycles
	rBF ↓56.4% (n = 19)	rBF ↑70.6% (n = 19)	2 cycles
Pickles <i>et al.</i> [13]	K^{trans} ↓19.7%	K^{trans} ↓19.6%	'At early time point'
	k_{ep} ↓19.9%	k_{ep} ↓36.2%	
	v_e ↑4.36% (n = 48)	v_e ↑27.6% (n = 20)	
Padhani <i>et al.</i> [15]	K^{trans} ↓22% (n = 9)	K^{trans} ↓6.5% (n = 6)	1 cycle
	K^{trans} ↓62% (n = 7)	K^{trans} ↓25% (n = 6)	2 cycles
DW-MRI (percentage change in ADC)			
Pickles <i>et al.</i> [32]	↑16% (n = 10)	NA	1 cycle
	↑27% (n = 10)	NA	2 cycles
Sharma <i>et al.</i> [33]	↑15% (n = 14)	NA	1 cycle
	↑27% (n = 24)	NA	2 cycles
	↑35% (n = 29)	NA	3 cycles
Nilsen <i>et al.</i> [34]	↑25% (n = 25)	NA	4 cycles
R₂* (change in s⁻¹)			
Li <i>et al.</i> [36]	↑10% (n = 27)	NA	2 cycles
MRS (percentage change in Cho SNR)			
Jacobs <i>et al.</i> [46]	↓35% (n = 15)	↓11% (n = 3)	1 cycle
²³Na MRI (percentage change in total sodium concentration)			
Jacobs <i>et al.</i> [46]	↓27% (n = 15)	↓21% (n = 3)	1 cycle

ADC, apparent diffusion coefficient; Cho, choline; DCE, dynamic contrast-enhanced; DW, diffusion-weighted; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NA, sodium; NAC, neoadjuvant chemotherapy; rBF, relative blood flow; rBV, relative blood volume; SNR, signal-to-noise ratio.

cancer with functional MRI are promising, with the rate of development indicating early translation to routine clinical care. A key factor in their success will depend on rigorous quality control and assurance to ensure that the quantitative measurements are robust and reproducible.

Abbreviations

ADC, apparent diffusion coefficient; BOLD, blood oxygen level dependent; DCE, dynamic contrast-enhanced; DW, diffusion-weighted; MR, magnetic resonance; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; rBF, relative blood flow; rBV, relative blood volume; ROI, region of interest.

Competing interests

The authors declare that they have no competing interests.

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