Abstract

Magnetic Resonance Imaging (MRI) of the breast is a powerful imaging tool for the characterization, diagnosis, staging, and treatment monitoring of breast cancer. Applications at clinical magnetic field strengths (≤ 3T) have been extensively described. At 7T*, substantial improvements in image quality could be provided, if technical challenges can be overcome. In this article, the authors discuss the technical considerations and challenges, and present preliminary imaging examples obtained in patients on a 7T MAGNETOM MR scanner using dynamic contrast-enhanced MRI, diffusion-weighted MRI, and sodium MRI.

Introduction

While only a few ultra-high field MR (7T) systems were installed ten years ago, between fifty and sixty 7T whole-body MR systems are currently available worldwide. The majority of these systems are dedicated primarily to method development (sequence and hardware design). Only recently clinical studies have become possible. Body MRI, in particular, has been challenging at 7T.

At 7T, the increased signal-to-noise ratio (SNR) may provide images with higher spatial resolution and dynamic imaging with higher temporal resolution. Significant improvements have already been described in morphological MRI, diffusion-weighted imaging (DWI) and MR Spectroscopy (MRS) of the brain and in musculoskeletal imaging [1-4]. If technical challenges can be overcome, 7T has the potential to substantially improve multiparametric breast MRI. This would allow better detection of small and non-mass lesions that are challenging to identify with other existing clinical breast imaging modalities.

To give an overview this article provides initial clinical results of breast MRI performed at 7T, with special focus on dynamic contrast-enhanced (DCE) MRI, DWI, and sodium imaging. Results and images published in this article were acquired at the MRCE in Vienna, Austria.

Dynamic contrast-enhanced imaging

Dynamic contrast-enhanced (DCE) MRI of the breast is an important clinical imaging tool for detection and characterization of breast lesions. By DCE-MRI, differentiation between benign and malignant contrast-enhanced breast cancer lesions is possible with an excellent diagnostic sensitivity close to 100% [5-10]. In early reports of clinical DCE-MRI performed at 1.5 or 3T a wide range of specificities were reported that ranged from 29% to 100% [8-10].

An example of bilateral DCE MRI obtained with 0.7 × 0.7 × 0.7 mm³ isotropic resolution at 7T of a 45-year-old breast cancer patient with malignant grade 2 invasive ductal carcinoma (arrow) with ring enhancement.
DCE-MRI provides both, morphologic assessment and enhancement characteristics of the lesions. On the one hand, using high spatial resolution enables the analysis of the morphological features of the lesions after contrast agent application and increases the sensitivity and specificity for detection of single and multiple breast lesions. On the other hand, high temporal resolution is advantageous for the analysis of contrast behavior during contrast agent uptake and wash-out phase [13]. Most malignant lesions show a strong contrast increase in the wash-in phase, followed by wash-out.

Due to limited SNR per time at field strengths ≤ 3T, a trade-off between spatial and temporal resolution is necessary [14]. Kuhl et al. compared different temporal resolutions, suggesting that a higher spatial resolution is preferable, even at the expense of temporal resolution [14]. Other studies have demonstrated that an accurate assessment of both lesion morphology and enhancement kinetics is crucial for optimal diagnosis [11, 15-19]. Pinker and co-workers used a block design at 3T to acquire high spatial (pre- and post-contrast) and high temporal resolution (wash-in and post-contrast) to achieve high diagnostic accuracy [13].

Higher magnetic fields (i.e., ≥ 3T) offer increased SNR that can be translated into higher spatial resolution [20]. Recently, several studies explored the increased SNR at 7T compared to 1.5T or 3T promising increased spatial and/or temporal resolution. In a preliminary study, Stehouwer et al. measured one patient with a mammographically suspicious breast mass (BI-RADS 5) at 3T and 7T using DCE-MRI with a unilateral breast coil [21]. They found a contrast-enhancement-to-noise ratio of 4.6 at 7T and 2.8 at 3T. Umutlu et al. reported high spatial resolution data from ten healthy subjects and five patients using a single-loop surface coil at 7T [22].

A direct comparison of contrast-enhanced breast MRI between 3T and 7T showed excellent diagnostic accuracy at both field strengths in the same patients (n=24), and comparable SNR when using a 3.2-fold higher spatial resolution at 7T, compared to 3T [25]. At 7T the authors used an isotropic spatial resolution of 0.7 × 0.7 × 0.7 mm³ combined with a temporal resolution of 14 s resulting in images without significant artifacts and satisfactory fat suppression (Fig. 1). This resulted in a sensitivity of 100% and a specificity of 92% demonstrating the high potential of breast-MRI at 7T [26].

Figure 2 shows a DCE MRI at 3T with lower resolution (1.4 × 1.4 × 1.4 mm³) but similar SNR than in 7T with the resolution of 0.7 × 0.7 × 0.7 mm³ in the same patient with grade 3 invasive ductal carcinoma (IDC).

There are still several technical challenges of breast-MRI at 7T. The majority of authors found that the B₁ field decreases toward the chest wall, which was observed and confirmed in their studies when performing (DCE-) breast MRI at 7T [27, 28]. Gruber et al. observed an SNR drop toward the chest at 7T of about 50% from the center of the breast. Measurements in the breast of healthy female subjects revealed that B₁ increased by 21% in the pre-pectoral region and 33% in the lateral region compared to the central region at 7T [27]. This may hamper the overall image quality, influence curve kinetics and hinder the diagnostic use of 7T MRI in those regions.

The use of T2-weighted sequences for breast MRI at 7T was not reported, because T2-weighted sequences based on turbo spin echo have significant B₁ problems due to the use of multiple refocusing pulses. In addition, the use of multiple refocusing pulses and inversion recovery increases the specific absorption rate (SAR) requirements substantially and fat suppression in complicated. This was already a problem even at 3T. 3D T1-weighted sequences at 7T are limited to the use of low flip angles to minimize B₁ inhomogeneities and SAR.

Promising results for DCE-MRI of the breast at 7T were shown by several groups, indicating that high spatial and temporal resolution are possible and result in high diagnostic accuracy. As soon as B₁ inhomogeneities and

Comparison of DCE-MRI of a 63-year-old breast cancer patient. The pictures represent a malignant grade 3 invasive ductal carcinoma measured at 3T (2A) with spatial resolution of 1.4 × 1.4 × 1.4 mm³ isotropic and at 7T (2B) with spatial resolution of 0.7 × 0.7 × 0.7 mm³.
excessive local SAR are mitigated by improved coil design (pTX technology and B1+ shimming) and sequence techniques the potential of breast MRI at 7T can be fully explored. This will allow to measure breast lesions that are more difficult to diagnose at lower field strengths (e.g., small lesions, non-mass-like enhancing lesions, ductal carcinoma in situ).

**Diffusion-weighted imaging**

Diffusion-weighted imaging (DWI) is the most promising adjunct MRI method to improve the diagnostic specificity of the established DCE-MRI examinations of the breast [29, 30].

By assessing the apparent diffusion coefficient (ADC) of water molecules, DWI probes tissue microstructure on a cellular level. Low ADC values in breast tissue reflect the higher cellular density that is present in malignant lesions [30]. Therefore, DWI has a high potential for characterizing breast tumors and monitoring/predicting treatment response [31].

However, DWI suffers from lower spatial resolution than DCE-MRI. For adequate morphologic assessment of breast lesions, the EUSOMA working group recommends to use spatial resolutions not below 1 x 1 x 2.5 mm³ for CE-MRI [32]. If this degree of anatomical detail can be also reached by DWI sequences, it may allow, both, the detection of smaller lesions and the morphological evaluation of breast DWI beyond simple ADC measures. This prospect of combining molecular and morphologic information has driven the urge to improve imaging techniques, hardware, and measure at higher static magnetic field strength.

While there is some initial clinical experience published on DCE-MRI of the breast at 7T [26, 27, 33], reported experience on breast DWI at 7T is scarce. Promising, but preliminary unilateral breast DWI results of three patients [34] and a volunteer [35] have so far been shown at 7T, but larger patients studies have not been reported. Yet, an up to 5.7-fold SNR increase compared to 3T indicates the available potential, but the spatial resolution and image quality were hampered by the use of single-shot echo planar imaging (ss-EPI), fat suppression failure, and motion artifacts [34].

Routine breast DWI at ≤ 3T is based on ss-EPI, but ss-EPI is known to be prone to image artifacts (i.e., geometric distortions, T2* image blurring, ghosting artifacts, and insufficient fat suppression) and these artifacts become stronger at 7T [36-39]. Strong T2* image blurring, in particular, prevents the anticipated increase in spatial resolution at 7T.

Recent sequence developments for DWI of the brain at 7T, have conclusively illustrated that most of these artifacts can be effectively overcome even at ultra-high magnetic field strength, when using a novel 2D-navigator-corrected readout-segmented EPI sequence known as RESOLVE (REadout Segmentation Of Long Variable Echo trains) in combination with GRAPPA (GeneRalized Autocalibrating Partially Parallel Acquisitions) [40]. Our initial experiences show that this sequence can also significantly improve the image quality of breast DWI at 7T (Fig. 3). A combination of RESOLVE and GRAPPA may overcome former restrictions in spatial resolution by providing high-quality DWI with sub-millimeter in-plane resolution (FOV 320 x 160 mm³, matrix 340 x 170, 0.9 x 0.9 x 5 mm³) for characterization of breast lesions in only 3:35 min. Our data show that this combination allows for clinical breast DWI protocols that reduce the amount of artifacts by a factor of 7 and significantly improve the apparent spatial resolution compared to regular ss-EPI sequences (Fig. 4).

A DWI example of a 36-year-old breast cancer patient with grade 3 invasive ductal carcinoma. The first image depicts the lesion on the contrast-enhanced T1-weighted image (3A). Following are the DWI images: (3B) b = 0 s/mm², (3C) b = 850 s/mm² and (3D) the ADC map.
One additional aspect that we observed in our data, is the fact that acquired RESOLVE images without diffusion weighting (i.e., b=0 s/mm²) had already very similar spatial resolution and contrast as regular STIR. This raises the question whether such RESOLVE-based T2-weighted images could not possibly replace additionally acquired STIR images soon. This would make the additional acquisition of STIR obsolete and save valuable measurement time.

With spatial resolutions of DWI reaching those recommended for DCE-MRI of the breast [41, 42], future DWI evaluation may not anymore be limited to ADC quantification alone, but could allow the additional assessment of morphologic features, which is a cornerstone of current DCE-MRI evaluation. This new aspect of DWI could further improve the specificity of breast MRI and should be the subject of future investigations.

Our preliminary data are still far from what could be possible at 7T. Currently, our image quality improvements were predominantly achieved via sequence improvements. However, our hardware was limited. We used a dual tuned four-¹H-channel receive breast coil (Stark, Erlangen, Germany) that provided reasonably good B₁ homogeneity, but can be easily outperformed with respect to SNR by modern multi-array coil design with ≥ 16 channels, and which would in combination with multi transmit technology, mitigate B₁ errors to reduce sensitivity dropouts e.g. near the axilla. Stronger diffusion gradients than used for our preliminary study (max gradient strength, 45 mT/m; slew rate, 150 T/m/s) will further shorten TE and substantially improve the SNR of DWI, in particular since T2 decay in breast parenchyma is twice as fast as in brain tissue [43]. Partial Fourier reconstruction could further shorten the TE or scan time of RESOLVE [44]. Further improvements in hardware and software may, therefore, double or even triple the SNR obtained in our preliminary study, paving the way for further improvements in spatial resolution.

**Sodium imaging**

Proliferating cells have an abnormally high sodium content, because the normally very low intracellular sodium concentration of about 10–15 mmol/l is elevated several fold as a result of altered Na⁺/H⁺ transport kinetics and pH [45]. Outside the cells continuous perfusion of living tissue will ensure a constant sodium concentration of ~140 mmol/l. Thus, an increase in the extracellular volume fraction through the increased vascularization (angiogenesis) and the increased interstitial space in tumors will also lead to an increase in tissue sodium concentration (TSC) in tumors. While the total

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Sample DWI images with b=0 s/mm² of a 23-year-old female volunteer were obtained for (4A) rsEPI with GRAPPA factor 2; (4B) ssEPI with GRAPPA factor 2; (4C) ssEPI without parallel imaging, compared to a T1-weighted reference image obtained with 0.7 × 0.7 × 0.7 mm isotropic resolution (4D). Although all DWI sequences were adjusted to the same spatial resolution (i.e., 0.9 × 0.9 mm in-plane), rsEPI with GRAPPA showed significantly less T2* blurring (4A) than both versions of ssEPI (4A, B), as well as lower distortion. (Reproduced with permission from Bogner, Radiology, 2014)
TSC (extracellular and intracellular) is known to be a good measure of altered cell metabolism [46-49], it is expected that the quantification of only intracellular sodium concentration (IC-TSC) is an even more specific marker of pathology, since changes in IC-TSC are more pronounced than changes in total TSC [50].

The unique sensitivity of $^{23}$Na-MRI to both extra-cellular volume and intracellular changes related to cell proliferation can provide information that is supplemental to high resolution CE-MRI.

While $^{23}$Na-MRI is interesting for characterization, it is expected that it could play a much bigger role in treatment prediction/monitoring. Lack of substrate and oxygen can cause very significant changes in TSC. As soon as the energy dependent Na/$^+K$/-ATPase stops pumping sodium out of the cell, passive sodium influx from the extracellular environment will rapidly raise the intracellular levels of sodium several fold. This effect is exacerbated if a stress on the cells increases the permeability of the cell wall for sodium ions. It was also shown recently that Na/$^+K$/-ATPase is a critical factor in multi drug resistance of cancer cells [51, 52]. Na/$^+K$/-ATPase is thus an important target in drug development for cancer treatment. Also in treatment monitoring the discrimination of IC-TSC and EC-TSC may potentially improve the possibility to observe even small changes in IC-TSC.

The acute effect of a therapy that causes cell death on an appreciable scale should therefore be easy to monitor with $^{23}$Na-MRI. Several animal studies found significantly increased TSC a few days after therapy [48, 49]. Only one treatment response study extracted information on both IC-TSC and EC-TSC one day after treatment [50]. Long-term effects of such therapies remain to be investigated. In a limited number of breast cancer patients that underwent pre-operative adjuvant therapy the effect of the therapy in responders showed an increase in the tumor TSC along with a decline in lesion size as reported recently [53].

While $^{23}$Na with reasonably good spatial resolution was not possible at ≤ 3T, we can show that at 7T breast $^{23}$Na MRI can reach spatial resolutions that are already similar to that of DWI at lower field strengths. With a bilateral dual tuned $^1$H/$^{23}$Na phased array breast coil (i.e., $^{16}$Na receive-channels) in combination with a highly sensitive ultra-short echo-time sequence, AWSOS (Acquisition Weighted Stack Of Spirals) [54] were able to acquire high resolution $^{23}$Na images in both healthy volunteers and patients with high in-plane spatial resolution of 1.5 × 1.5 mm$^2$ (FOV 320 × 320 mm$^2$, matrix 208 × 208, 1.5 × 1.5 × 5 mm$^3$) in a reasonable scan time of 16:19 min.

Our preliminary results show that even the low $^{23}$Na content in healthy glandular breast tissue can be well imaged using advanced imaging techniques/hardware at 7T (Fig. 5). Due to the low gyromagnetic ratio of $^{23}$Na compared to $^1$H nuclei, there are no significant problems related to expected B$^1$ inhomogeneities, however the very short relaxation times are challenging for the design of sensitive MR sequences. It can be expected that the significantly higher $^{23}$Na content in malignant breast lesions can be imaged with further improved spatial resolution. Satisfactory image resolution, SNR and reasonable imaging time, enable this technique to be potentially implemented in routine MRI protocols. However, future sequence development will have to target a more specific quantification of IC-TSC concentration [55]. With such IC-TSC sensitive methods in hand, $^{23}$Na could be become a powerful imaging tool for characterization of breast tumors and particularly assessment of treatment status,
since changes in IC-TSC are known to appear even far before they can be depicted by other modern MRI techniques such as DCE-MRI, DWI, MR spectroscopy. In combination with other 1H MRI techniques 23Na imaging may, thus, become an attractive tool for the investigations of breast tumors with a particular focus on the early treatment prediction and monitoring.

Conclusion
Although in the near future, MRI of the breast at 7T will remain technically challenging, our recent patient results show already significant image quality improvements with a high potential for clinical application.

With the additional use of the most recent hardware (stronger gradients, parallel transmit technology, improved coil design) and further improved MR sequences, we will soon be able to fully exploit the imaging potential of 7T MRI even for the assessment of breast cancer. 7T MRI of the breast will simultaneously provide high temporal and spatial resolution DCE-MRI, allow increased spatial resolution of DWI that can compete with that of CE-MRI at lower field strength, and even make additional imaging contrasts such as 23Na imaging available that were impossible to perform in the past. While this will likely not change routine breast cancer diagnosis, it remains to be shown, what impact multi-parametric MRI of the breast at 7T can have in the fine-tuning of expensive, but life-saving neoadjuvant treatments.

References


