Beyond T2 and 3T: New MRI techniques for clinicians

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ABSTRACT

Technological advances in Magnetic Resonance Imaging (MRI) in terms of field strength and hybrid MR systems have led to improvements in tumor imaging in terms of anatomy and functionality. This review paper discusses the applications of such advances in the field of radiation oncology with regards to treatment planning, therapy guidance and monitoring tumor response and predicting outcome.

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1. Introduction

Magnetic Resonance Imaging (MRI) is an established and valuable tool in radiation oncology for providing information regarding treatment planning and measuring treatment response. The main strengths of MRI are for visualizing soft tissue, as well as providing biological and functional information such as tissue perfusion and diffusion without the need for ionizing radiation.

Despite the incorporation of these MRI-based techniques, there are still many cancers for which there is a very poor clinical outcome for the patient. Continuing technological advances, however provide the opportunity for MRI to play a greater role in cancer treatment, as new techniques emerge that have the potential to further inform the clinician in the treatment process or aid therapy.

A significant and continuing trend is the availability of MRI scanners with even higher field strength than 3T. As MRI scanners increase in field strength, the enhanced sensitivity and emergent contrast mechanisms imply that improved imaging biomarkers for treatment response become clinically feasible. Furthermore, with the advent of hybrid MRI-linac systems in the clinical setting, MRI can be utilized to directly guide treatment through novel sequence development and reconstruction. Thus, new opportunities arise for therapy planning and monitoring. However, the use of these systems in the radiotherapy setting requires a thorough validation. Compared to clinical MR scanners, at higher fields strengths changes in the $T_1$, $T_2$ and $T_2$ times of tissue affects image contrast, and the larger off-resonance effects increase image distortions, which may affect accuracy in tumor delineation. On hybrid MR-linac systems, issues regarding therapy guidance arise from the rate at which it is possible to acquire MR images, thus accurately capturing motion with minimal latency.

In this paper, new potential clinical tools that have become relevant through new MRI hardware and their challenges and applications in radiation oncology will be reviewed.

2. Ultrahigh field MRI in radiation oncology

Ultrahigh field (UHF) MRI is considered to be at static magnetic field strengths of 7T or higher. Until recently, UHF imaging has been an interesting research tool; however, the first 7T MRI scanner with CE [1] and FDA [2] approval has been released, allowing for the possibility of UHF MRI to enter clinical routine. UHF-MRI has advantages and disadvantages, which are discussed in detail here [3]. One of the clear benefits of UHF MRI is the increased sensitivity, quantified as signal-to-noise ratio (SNR), which has an approximately linear relationship with the main magnetic field strength, which, at field strengths above approximately 3T, the increase in SNR is greater than linear [4]. The increase in SNR can be used to increase spatial resolution $\Delta x^3 \propto (1/{SNR})$, allowing for sharper images and increased visibility of finer structures. One field in which the increased sensitivity of UHF MRI is particularly valuable is in non-1H imaging. As the human body is mostly composed of water, $\text{H}_2\text{O}$, $^1\text{H}$ or proton imaging of water provides the
largest MR signal; however, in theory imaging with any nucleus with a nuclear spin > 0 is possible. The MR applications of non-\(^1\)H, isotopes, which are termed the X-nuclei, are reviewed in detail in Section 2.2. For magnetic resonance spectroscopy (MRS), utilizing either \(^1\)H or X-nuclei, the higher field strength not only provides higher sensitivity, but also increases spectral resolution and allows for the detection of more metabolites [5].

One of the disadvantages of UHF \(^1\)H imaging, is that the wavelength of the applied excitation field is short enough that the electromagnetic wave effects can no longer be ignored, meaning that uniform radiofrequency (RF) excitation at UHF strengths becomes increasingly difficult. This issue most commonly manifests as areas of large signal heterogeneity within the FOV. As the FOV increases, the RF heterogeneity becomes more pronounced and consequently, progress in whole-body imaging at UHF has been slower than neurological applications [6]. A further disadvantage of UHF MRI is that the RF energy is absorbed into tissue at a higher rate than at lower field strengths. The regulatory limits imposed on this rate of energy absorption, the Specific Absorption Rate (SAR), given in W/kg, are the same for all field strengths, but at higher fields these limits are reached at comparatively lower excitation flip angles, so that significant adjustments to some imaging sequences are necessary. Additionally, due to the shorter RF wavelength and more complex RF interactions at UHF, localized heating can occur and must be numerically simulated [7] in order to apply appropriate safety limits.

The issues around RF heterogeneity and SAR can be alleviated by application of multichannel RF systems, a technique known as parallel transmission. In such systems, multiple RF pulses are applied simultaneously though a dedicated multichannel transmit coil. Many different techniques have been proposed, in which the phases, and amplitudes can be adjusted on each channel in order to produce a more uniform RF excitation, such as B1+ shimming [8,9], SPOKES [10], k-T points [11] and SPIral Non Selective (SPINS) RF Pulses [12]. There are also additional methods requiring no user interaction such as universal pulses [13] and Time Interleaved Acquisition of MOdes (TIAMO) [14].

2.2. Measuring treatment response at UHF

Currently, clinical measures to treatment response rely on anatomical changes in the tumor, such as the RECIST (Response Evaluation Criteria In Solid Tumors) criteria [32]; however, this approach cannot detect or describe early cellular alterations in response to therapy, which can take up to months after therapy, to manifest morphologically [33].

Many MR-based surrogate biomarkers have been linked with treatment outcome, such as dynamic contrast-enhanced (DCE) MRI [34] and diffusion-weighted imaging (DWI) [35]. The limitation of contrast enhanced MRI is that it only visualizes disruptions in the Blood Brain Barrier, and so does not provide information in areas of non-enhancing tumor [36,37].

The apparent diffusion coefficient (ADC) is the most common DWI-derived imaging biomarker with broad clinical applications. The majority of studies show an inverse correlation between the ADC and tumor cellularity [38–41]. With regards to therapy response assessment, changes in the ADC have been shown to be associated with treatment response in glioma patients early after radiation therapy, with these changes being hypothesized to be linked to cellular structure reflecting apoptosis or necrosis [35,42,43].

Advances in UHF MRI open up the potential to investigate additional biomarkers. In clinical MRI, \(^1\)H is the nucleus that is predominately measured, as \(^1\)H is associated with imaging water. As water is the main component of the human body, it is from water that the largest MR signal is generated. However, other sources of signal apart from water are achievable with MRI. In the case of MR imaging of nuclei other than standard water protons (\(^1\)H), termed the X-nuclei, new insights into cellular function and metabolism may be accessible. Unlike \(^1\)H imaging, the X-nuclei allow for a more direct imaging of physiological processes, including biomarkers for treatment response that may provide information complementary to that obtainable by PET. X-nuclei can in principle be imaged on any MRI system; however, they have a relatively low abundance and therefore an SNR of several orders of magnitude lower than \(^1\)H [44]. UHF MRI and the development of SNR-optimized, ultra-short echo time (UTE) sequences [45–50] have allowed research involving the X-nuclei to advance to a level where the clinical impact can be realistically assessed. In addition, spectroscopic techniques that facilitate the imaging of \(^1\)H nuclei bonded to other molecules, other than water also benefit from higher sensitivity at UHF. Techniques such as Chemical Exchange Saturation Transfer (CEST) enable imaging of a subset of these molecules and also it can be recovered by the employment of \(T_2\) preparation at the start of the sequence [20].

Recent studies have investigated the role of UHF in radiotherapy planning, in particular the role of FLAIR [21], where images from glioblastoma patients at 7T and 3T were compared as shown in Fig. 1. Results suggested that the higher spatial resolution improves visualization of the white matter tracts, which are known infiltration routes of glioblastoma [28].

The technical feasibility of integrating 7T MR images into the treatment planning of brain tumor patients was explored in [29] using healthy volunteers, in which images were assessed on a qualitative basis, as well as for geometric distortions. Geometric distortions were further assessed in [30], in which the geometric accuracy of images at 3T and 7T were compared. Distortions were found to be higher at 7T compared to 3T, but were still considered to be within acceptable limits for therapy planning. A similar conclusion was also reached in [31], in which 7T images were assessed for geometrical distortions with regards to image guidance in neurosurgery.
benefit strongly from the increased spectral resolution associated with UHF MRI.

In the following sections, several X-nuclei and CEST applications in the context of radiation therapy are described.

2.2.1. Sodium-23 imaging
Sodium (23Na) has an important role in cell physiology [51]. With normal cell function, a large concentration gradient exists between the intra- and extracellular spaces, with the extracellular concentration being a factor of 10 higher than the intracellular concentration. This gradient is maintained by an energy dependent sodium-potassium pump (Na+/K+-ATPase), so that any disturbances in the cell metabolism or membrane manifest as an increase in the intracellular 23Na concentration.

In oncology, a change in the intracellular 23Na concentration is a biomarker for tumor malignancy [52–56], and cellular viability [57], and has shown promise as an indicator of treatment response. This has been demonstrated in animal models [58,59], and more recently in glioblastoma patients measured at 3T [60] and 7T [61].

2.2.2. Oxygen-17 imaging
The Warburg effect [62] is a phenomenon in which cancer cells are observed to metabolize glucose via the less efficient glycolysis pathway, producing lactate, in contrast to oxidative phosphorylation, in which glucose is metabolized with oxygen [63]. This change in metabolic pathway occurs even in the presence of sufficient oxygen.

Using PET with the glucose analog 18F-fluorodeoxyglucose (FDG) has become the clinical standard for imaging many malignant tumors [64]. FDG PET has found applications in tumor detection and staging [65], as well as in characterizing response to chemotherapy and radiotherapy [66–68].

A drawback to using FDG PET for measuring Cerebral Metabolic Rate of Oxygen consumption (CMRO2), and tumor characterization in general, is that FDG is not a specific tracer. Glucose is metabolized in all cells, and although in most cases cancer cells have a higher metabolic activity, this is not always the case, for example in prostate cancers. As a result, FDG PET is challenged by low specificity [69].

As an alternative to FDG PET, 15O-labeled water (H152O) can be used as the PET tracer, allowing for a direct measurement of CRMO2 [70,71] that is more specific to the Warburg effect. Although, 15O PET is considered the gold standard for imaging CRMO2, it is costly to apply in the clinical setting, as 15O has a short half-life (t1/2 = 123 s) and requires an on-site cyclotron for generation [71]. Despite technical and financial challenges, 15O PET has been used to show reduced levels of CRMO in tumors [72–76], which is particularly pronounced in high grade tumors [77].

MRI can also be used to image the same effect, through the use of the only stable isotope of oxygen, 17O, that produces an MR signal. 17O is a stable, non-radioactive isotope, but when compared to 1H (proton) MRI, 17O has a low natural abundance (0.037%) and a low gyromagnetic ratio, leading to a sensitivity of 2.9% compared to 1H [78], for an overall in vivo signal sensitivity approximately 20,000 times smaller than 1H. At this low sensitivity, 17O imaging benefits from UHF MRI, and additional higher concentrations of 17O are typically inhaled to increase SNR, although research on imaging naturally abundant 17O has been performed [79].

The first reported usage of 17O was as an agent to shorten the T2 of 1H [80], followed closely by MRS detection [81]. Usage of 17O was reported in a preclinical experiment [82], and in natural abundance imaging [83]. It was not until the introduction of UHF MRI however, that significant human in vivo studies occurred [84,85]. The first clinical demonstration of CRMO2 determination was in a glioblastoma patient [86], shown in Fig. 2, using an efficient, MR-compatible breathing system [87]. Inhaled 17O gas is not visible in the MR images until mitochondrial conversion to water, providing a direct, quantitative measure of CRMO2. Reproducibility of CRMO2 measurements has been investigated in healthy subjects [88], and the same method was applied in two glioma patients [89].

2.2.3. Phosphorous-31 spectroscopy
Phosphorous (31P) plays a role in detecting all metabolites involved in energy metabolism, as well as being able to indirectly measure tissue pH, using the Henderson-Hasselbalch equation [44], in which pH is related to the chemical shift of the inorganic phosphate peak compared to other peaks. The acidity of the cellular environment is a known influence on the response of a tumor to treatment [90]. The NMR spectrum of 31P has multiple peaks,
making the detection of $^{31}$P most suitable for spectroscopy, or spectroscopic imaging, although direct imaging is possible [91,92].

An advantage of, $^{31}$P MRS is that $^{31}$P has a high natural abundance in vivo and relatively high MR sensitivity (7% of the $^1$H signal based on gyromagnetic ratio [44]), making the detection of this nucleus feasible even at lower, clinical field strengths. Nevertheless, $^{31}$P detection has shown improvements at higher field strengths. Due to the increased SNR, 3D spectroscopic imaging can be acquired in clinically feasible scan time [93], and at higher field strengths, $^{31}$P spectroscopy benefits from increased spectral resolution, allowing for the detection of finer structures in the $^{31}$P spectra [94].

UHF field strengths have brought a significant improvement to $^{31}$P spectroscopy in the prostate [95] for the detection of metabolites in prostate cancer [96]. On observation of the $^{31}$P spectra, differences in the phosphomonoester (PME) to phosphocholine (PCr) ratio, PME to $\beta$-ATP ratio and the PCr to $\beta$-ATP ratio have been linked to the distinction between healthy and cancerous tissue [97-98]. Using the improved spectral resolution at 7T, the split NMR peaks of phosphocholine (PC) and phosphoethanolamine (PE) as well as their glycerol derivatives (GPC and GPE respectively) can be detected. These compounds are related to phosphohydration, and the distinction of which has been linked to tumor malignancy [99]. To date, several studies have demonstrated $^{31}$P spectroscopic imaging at 7T with custom-made transceive coils [100-104], and were successfully able to detect the phosphohydration peaks in the prostate.

2.2.4. Carbon-13 and deuterium spectroscopy

As almost all compounds involved in metabolism contain carbon, which allows for the detection of metabolites such as glucose, pyruvate and lactate with MRS [44]. The challenge of carbon detection under MRS is that the only stable isotope of carbon, carbon-13 ($^{13}$C), has a very low natural abundance of 1.1% and therefore a very low in vivo sensitivity. Nevertheless, MRS can be performed using the natural abundance of $^{13}$C, albeit with long acquisition times for a number of applications, such as glycolic measurements [105]. More common however, is to administer a $^{13}$C-labeled substrate such as [1-$^{13}$C]glucose and observe the metabolic pathways by detection of the resulting metabolites [106]. In oncology, the administration of [1-$^{13}$C]glucose can be used to detect lactate tumors directly on account of the altered glucose metabolism [107,108], an underlying characteristic of the Warburg effect.

To overcome limitations of low $^{13}$C sensitivity, nuclear hyperpolarization is a technique that has the potential to increase of the signal of nuclei such as $^{13}$C by several orders of magnitude. The most prominent $^{13}$C hyperpolarization techniques for $^{13}$C are dissociation Dynamic Nuclear Polarization (dDNP) [109], or parahydrogen synthesis (PASADENA) [110]. The metabolic pathways of hyperpolarized [1-$^{13}$C]pyruvate have been applied to glioma in a mouse model [111], and prostate cancer in a human study [112].

Hyperpolarized $^{13}$C MRS has been used as a biomarker for treatment response. [1-$^{13}$C]pyruvate is promising for the detection of early change in lymphoma cells after chemotherapy in mouse models, [113], as well as changes due to anti-VEGF treatments [114]. Furthermore, hyperpolarized [1-$^{13}$C]pyruvate MRS has been demonstrated as a surrogate for measuring reactive oxygen species [115], which has potential for real-time assessment of tissue response to ionizing radiation.

An alternative to $^{13}$C MRS is to label the metabolite with Deuterium ($^2$H), which was recently presented as a novel approach for imaging metabolism and the Warburg effect. First theorized in 1935 [116], experimental validation has required UHF MRI in order to overcome the inherently low sensitivity of this technique. To date, $^2$H-MRS has been performed [117] as well as $^2$H spectroscopic imaging [118], allowing for absolute maps of glucose, pooled glutamate and glutamine (Glx) as well as lactate to be acquired.

2.2.5. CEST

Chemical Exchange Saturation Transfer (CEST) is an imaging technique in which protons bound to metabolites such as proteins, amino acids and lipids are amplified. These metabolites resonate at a different frequency compared to that of $^1$H nuclei in water, but are nevertheless detectable with $^1$H MRI. The application of a saturation RF pulse targeted at the appropriate resonant frequency, or frequency range, can reduce the MR signal of $^1$H bound to a certain chemical species. These bound protons are in constant exchange with free water protons; the saturated $^1$H protons exchange with the free water $^1$H nuclei, and therefore become detectable by $^1$H MRI as a signal loss in the $^1$H water images. Furthermore, as this exchange is ongoing, the number of saturated protons becoming water protons increases with the duration of the applied saturation RF pulse, amplifying the detectable MR signal by a factor on the order of 100–1000 if the $T_1$ relaxation times are suitably long [119].

Of particular relevance with regard to tumor imaging is the detection of two metabolite signals known to have links to protein content: Amide Proton Transfer (APT) [120], and the delayed Nuclear Overhauser Effect (rNOE) [121]. Both of these have been shown to be correlated with brain tumor grade [122–127]. Additionally, APT mediated CEST MRI has been shown to be associated with the isocitrate dehydrogenase (IDH)-mutation status in newly-diagnosed gliomas [128,127]. Further studies have investigated the use of CEST imaging as an indicator of treatment response in glioma patients, and indicate that CEST could play an important role as an early measurement of treatment response [129–135], as shown in Fig. 3 with recent studies reporting the use of CEST to distinguish between therapy responders and non-responders during [131] or directly after [132] therapy. Recently, an association between CEST and long-term outcome by means of patient
overall survival and progression-free survival could be shown [136].

Besides imaging of endogenous metabolites, chemical exchange sensitive MR techniques also have the potential to detect exogenously administered substances containing exchangeable protons. A promising substance for such a new type of contrast agent is natural D-glucose, since it can be detected through chemical exchange saturation transfer (CEST) [137–139] or chemical exchange sensitive spin-lock (CESL) [140–142]. The feasibility of dynamic glucose-enhanced (DGE)-MRI in humans has recently been demonstrated in independent studies employing both CEST and CESL-based techniques [141–144]. The signal origin of DGE MRI seems to be dominated by tissue perfusion but still needs further investigation.

3. MR-guided radiotherapy

Intrafractional motion causes the radiation delivery to the target volume to be blurred over the path of motion and is a serious issue for the treatment of all thoracic and abdominal tumors, in particular, lung tumors [145]. Radiation treatment of central lung carcinoma poses a risk of toxicity [146], making localized irradiation in the lungs crucial. Liver metastasis treatment benefits from high dose [147], which makes guidance important to prevent side-effects. Tumor motion occurs mainly in the superior-inferior direction, but also components of left-right and anterior-posterior motion can occur [145].

Several methods are currently available to compensate for intrafractional motion. Breathing control methods include

![Fig. 3. rNOE-CEST as a measure of treatment response in glioma patients [132].](image)
breath-holding, in which dose delivery occurs while the patient consciously halts respiration for a short period of time, or techniques such as forced shallow breathing using abdominal compression \[148\]. A second common method is to use respiratory gating, in which dose is delivered during a certain portion of the breathing cycle. This method requires measurement of respiration, which can be achieved using internal fiducial markers under X-ray guidance \[149\], external markers on the skin surface or image-based tracking from video \[150\]. Breathing control and gating both have disadvantages. Breath-holding may not be reproducible, and patients can be non-compliant. With gating methods, patients can require some coaching to breathe effectively, and in addition, therapy duration increases as the dose is only delivered during certain time periods. Furthermore, when surrogates are used for motion measurement, there is the potential that the surrogate does not accurately represent the motion of the tumor \[151–153\]. The most desirable method of motion compensation is to directly track the tumor position and concurrently update the linac multi-leaf collimator (MLC) in real-time. To achieve this, tumors have been imaged under X-ray fluoroscopy \[154\]; however, tumor delineation is limited using this imaging modality. Alternative to directly imaging the tumor under fluoroscopy, it is possible to track internal fiducial markers \[155\] for real-time MLC updates. The theoretical benefits of real-time tumor tracking would be to reduce or eliminate the need for a safety margin for motion during planning, while simultaneously applying the X-ray beam at 100% duty cycle.

Recent advances in MR technology not only provide new opportunities for therapy planning and monitoring, they also open up new paths for direct, MR-guided radiotherapy. In particular is the availability of hybrid MR-linac systems which combine magnetic resonance imaging with a linear accelerator, are expected to have a large impact on radiotherapy treatment planning and intra-/inter-fractional tumor tracking.

Commercial MR-linac systems are now available: MRIdian (ViewRay, OH, USA) \[156,157\] and Elekta Unity (Elekta AB, Stockholm, Sweden) \[16,158–160\], as well as research systems in Edmonton, Canada (MagnetTx) \[161,162\] and Sydney, Australia \[163,164\]. Techniques in real-time MRI can be applied to monitor tumor position and compensate for intrafractional motion with the high soft-tissue contrast associated with MRI. These techniques are reviewed in the following sections.

### 3.1. Real-time techniques in MR imaging

In the ideal case, MRI can be used to acquire a 3D volume that encapsulates the entire tumor, that allows for full 3D characterization of tumor position and shape. However, as MRI is a relatively slow imaging modality, 3D real-time MRI is still limited in capability. Echo-planar imaging (EPI) is one technique that has been applied to 3D imaging. Echo volumar imaging (EVI) \[165\] is a single-shot EPI technique that can acquire a 3D volume in approximately 100 ms. In more recent implementations, variants of EVI have been applied in image navigation \[166\] and 3D fMRI \[167\], using segmented readouts or multi-slab fMRI \[168\] in which the image acquisition is distributed over a number of repetition times, leading to acquisition times of approximately 0.5–1 s. EPI acquisition has a number of disadvantages. The long read-out duration of these sequences introduces a large dependence on $T_2$ and non-uniformity in the main magnetic field, which can cause large geometric distortions in the images. Consequently image resolution is necessarily low to minimize the read-out duration. Furthermore, as magnetic field variations are more pronounced in the thorax and abdomen than in the brain, EPI is very limited in whole-body applications.

Typically, real-time acquisition is acquired in 2D, as is used in cardiac imaging of irregular heart motion \[169\], interventional MRI \[170\], joint kinetics \[171\] and speech analysis \[172\]. In the case of tumor tracking, balanced steady-state free precession (bSSFP) \[173\] acquisition techniques are commonly employed, due to good soft tissue contrast and high SNR, which is especially advantageous for MR-linacs, where the main magnetic field is often 1.5T or lower.

For tumor imaging, a single slice is typically acquired at a rate of 3–5 Hz \[174–176\]. Multiple 2D slices can be interleaved to determine motion in 3D \[177–179\] at a reduced acquisition rate of approximately 2–3 Hz. Imaging in 1D has also been studied using pencil-beam navigators in order to resolve the main component of motion in the superior-inferior direction \[180,181\] at a acquisition rate of 30–50 Hz. Full 3D imaging has been implemented as well \[182\], in which a volume was acquired every 7 s.

Due to the extent to which image acquisition can be accelerated and an inherent robustness against motion artifacts, radial acquisition techniques are often applied in real-time MRI imaging rather than the conventional Cartesian techniques generally applied in diagnostic imaging. Read-out lines can be skipped in radial imaging with a lower impact on image quality \[183\]. Imaging in 2D at up to 50 Hz has been achieved with a radial encoding scheme \[184\]. Using a golden angle increment between two adjacent radial profiles enables flexible adaption of the temporal resolution \[185\]. As with conventional Cartesian imaging, the bSSFP sequence is particularly advantageous for real-time tumor tracking and can be easily combined with fast radial imaging \[186\].

### 3.2. Acceleration and image reconstruction

MR imaging is a compromise between temporal and spatial resolution. Nyquist theory imposes limits on the minimum amount of data required to reconstruct an image at a certain spatial resolution. However, many techniques exist that overcome the Nyquist limit in order to accelerate image acquisition by undersampling the required amount of data but maintain a higher spatial resolution. For real-time imaging, this is highly desirable but is not always feasible in implementation, as the consequences of these acceleration techniques are prolonged, often iterative, image reconstruction algorithms. Some acceleration techniques can be employed for real-time imaging with a minimal cost to reconstruction times. These methods acquire undersampled images, but during reconstruction incorporate data from previous frames into the reconstruction of the current frame. View-sharing techniques such as Keyhole \[187,188\], 3D Time Resolved Imaging of Contrast Kinetics (TRICKS) \[189\] and Time Resolved Echo-shared Angiography Technique (TREAT) \[190\], have a long-established application in angiography, but have also been applied for 3D imaging of lung tumors at approximately 1 Hz \[191,192\]. Radial imaging is particularly suited to such view-sharing methods. Using golden angle acquisition methods \[185\], the reconstruction of a frame can be performed using an arbitrary number of radial profiles, which may have applications in sequences that adapt temporal resolution to the current motion situation \[193\].

Developments in computer hardware and algorithms, in particular in the area of parallel computing. Accelerated image reconstruction allows additional acquisition techniques to become feasible for real-time imaging. Reconstruction times of Sensitivity Encoding [SENSE] \[194\] and the related variants for dynamic imaging k-T SENSE \[195\] and TSENSE \[196\] have been decreased by a factor of 10–150 by parallelizing sections of the reconstruction on a Graphics Processing Unit (GPU) \[197,198\], with reconstruction times of approximately 10 ms per 2D image. Similar performance improvements have been observed for radial imaging with GPU implementations of Non-Cartesian SENSE \[198\], Radial GRAPPA \[200\] and regularized nonlinear inverse reconstruction \[201\], shown in Fig. 4.
3.3. Tracking and motion modeling

In addition to MR imaging and reconstruction, a real-time measure of tumor position is required in order to update the MLC, or to gate the dose delivery. The most straightforward approach is to derive the position information directly from the MR image. Often used in this case is autocontouring, in which the tumor or organ is automatically delineated [202–210]. Alternative methods include template matching, in which a template shape, for example of an organ or tumor, is located on the dynamic MR images [175,177,211,212], artificial neural networks [175,178] and non-rigid image registration [157]. Although this approach to tumor position determination is robust [213], the limitation of these approaches is that motion can only be derived in-plane.

More advanced tumor tracking methods aim to model the tumor or organ motion to predict 3D motion or to account for system latency that would delay updates to the MLC. A motion model may be constructed from 4D MR or CT images, which can be acquired before therapy and the image data binned according to a measurement of the breathing cycle. As model input, 2D real-time images can be used to estimate 3D motion [214–219], to overcome slow MR image acquisitions [220] or system latencies using filters [221,222] or system latencies using filters [221,222] or artificial neural networks [223,224].

4. Future role of MRI in radiation oncology

Radiotherapy has been a part of cancer treatment for the last 100 years, and has constantly evolved as new technologies and scientific understanding have emerged. The introduction of linear accelerators in the 1950s [225] allowed for higher energies and better collimation compared to the previously used radium and cobalt sources. With the introduction of computed tomography (CT) in the 1970s 3D treatment planning became possible and therefore the possibility to perform 3D dose delivery. The introduction of PET and MRI in the 1980s allowed for additional anatomical and functional information to be incorporated into treatment planning as well as valuable information on tumor response to be collected for updating the treatment regimen.

In recent years, improvements in MRI technology and computing hardware have impacted the radiotherapy workflow and provided new capabilities for refining patient care. As MRI moves toward higher field strengths, imaging of tumor microenvironment and metabolism comes closer to being a clinical reality; additionally, the increased spatial resolution allows for visualization of finer anatomical structures. Initial studies investigating the applications of UHF MRI for radiation treatment planning and measuring treatment response have been conducted with promising results. As another important step, MRI is now being incorporated directly into radiotherapy treatment, enabling hybrid MR-Linac systems that can simultaneously track and irradiate tumors. These developments have the potential to dramatically change how tumors in the thorax and abdomen are treated.

The role of MRI promises to increase over the coming years. If the clinical efficacy of these new techniques is proven, such approaches can be translated into the clinical routine, with the potential to strongly impact the outcome of radiotherapy treatments.

Conflict of interest

The authors declared that there is no conflict of interest.

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