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Quantitative MRI on MR-Linacs: Towards Biological Image-Guided Adaptive Radiotherapy

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Recognizing the potential of quantitative imaging biomarkers (QIBs) in radiotherapy, many studies have investigated the prognostic value of quantitative MRI (qMRI). With the introduction of MRI-guided radiotherapy systems, the practical challenges of repeated imaging have been substantially reduced. Since patients are treated inside an MRI scanner, acquisition of qMRI can be done during each fraction with limited or no prolongation of the fraction duration. In this review paper, we identify the steps that need been taken to move from MR as an imaging technique to a useful biomarker for MRI-guided radiotherapy (MRgRT).

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Introduction

The potential of functional imaging methods in radiation oncology was identified over 2 decades ago when Ling et al.¹ proposed to improve the therapeutic ratio between tumor control and treatment-related toxicity by pursuing biological conformality. Positron emission tomography (PET) and functional MRI techniques have since been shown to image biologically relevant properties about the physiology and function of the tumor and its surroundings.^{2–7}

In particular, MRI is a versatile technique that allows acquisition of multiple anatomical and functional images in a single scan session. For example, diffusion-weighted MRI (DWI), probes the microanatomy of tissue and is often integrated into clinical exams. Dynamic susceptibility-contrast MRI (DSC-) and dynamic contrast-enhanced (DCE-) MRI are frequently used to measure perfusion and permeability of the microvasculature. Other techniques, such as blood

oxygen level-dependent MRI (BOLD), oxygen-enhanced (OE-) MRI, and chemical exchange saturation transfer (CEST) are not as widely used, but may have the potential to characterize hypoxia and tissue metabolism.^{8,9} In recent years, multi-parametric MRI techniques, such as MR fingerprinting, have further improved functional MRI acquisition efficiency.¹⁰ This versatility has allowed MRI to image several of the cancer characteristics that are necessary to sustain tumor growth and proliferation.^{11,12}

Obtaining MR images with absolute levels of quantification is demanding and resource intensive because of hardware and software differences across centers, so semi-quantitative scoring systems based on visual interpretation have been proposed. For example, the BI-RADS system for breast cancer and the PI-RADS system for prostate cancer are now widely used in clinical decision-making.¹³ While useful in a diagnostic setting, such systems are intrinsically subjective, lacking objective quantification. To use quantitative MRI (qMRI) in clinical decision-making for radiation oncology, it would be necessary to demonstrate that qMRI can serve as a quantitative imaging biomarker (QIB). Kessler et al. in the Terminology Working Group of the Quantitative Imaging Biomarker Alliance (QIBA) defined a QIB as “an objective characteristic derived from an in vivo image measured on a ratio or interval scale as an indicator of normal biological processes, pathogenic processes or a response to a therapeutic intervention.”¹⁴ Thus, quantitative imaging metrics reflect relevant information about a biological process by measuring biophysical parameters that could be used as biomarkers, rather than relying solely on relative differences in

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image signal intensities (of arbitrary scale and units), as in routine diagnostic imaging.¹⁵

Many steps must be taken to advance an imaging modality to a clinically useful biomarker. O'Connor et al.¹⁶ proposed a 'biomarker roadmap' that shows the steps in 3 domains: technical, clinical, and economical. Two translational gaps are identified. To cross the first gap, 1 must demonstrate that an imaging parameter can be measured accurately and reliably, and that this parameter is associated with a biological property or clinically relevant characteristic. Only then is it useful to apply the imaging parameter in a clinical trial with the aim of demonstrating that clinical decisions can be based on the imaging parameter. After this has been achieved, the second translational gap has been crossed, and the imaging parameter can be considered a biomarker for routine clinical use.

Within the context of radiotherapy, 3 categories of applications for QIBs can be distinguished: 1) prediction of clinical outcomes; 2) early assessment of response, typically used after neo-adjuvant radiotherapy, for decision-making about further treatment; 3) biological image-guided adaptive radiotherapy (BIGART).¹⁷ Most clinical studies have focused on the prediction of clinical outcomes using images acquired prior to treatment. Although up to now repeated imaging has been challenging on a practical level, several studies have investigated changes in qMRI during the course of radiotherapy, suggesting that changes in quantitative parameters potentially are quite informative.¹⁸⁻²² Nonetheless, while many candidate biomarkers have been identified, at this stage no quantitative MRI biomarker has been sufficiently validated to warrant routine clinical use in radiation oncology decision-making.

With the introduction of MRI-guided radiotherapy (MRIGRT) systems, the practical challenges of repeated imaging have been substantially alleviated. Since MRIGRT patients are treated inside an MRI scanner, acquisition of qMRI can be done during each fraction with very limited or no prolongation of the fraction duration. Indeed, the acquisition of qMRI has been demonstrated on both the commercial 0.35T and 1.5T systems.²³⁻²⁵ The MRI scanner designs in these systems deviate substantially from those of standard diagnostic systems.²⁶ Significant MR hardware modifications had to be done to allow for minimally degrading the radiation beam and decoupling the MRI and linear accelerator electromagnetic functions, which reduced the imaging system performance relative to purely diagnostic equivalent systems. Therefore, an extensive effort has been directed at the technical validation of qMRI sequences to establish accuracy and repeatability. To integrate the technical validation in clinical trials, a trial design has been proposed with a minimal additional burden for the patient or cost.¹⁷ The design proposes to include 1 additional MRI exam on the MR-linac prior to the start of irradiation to provide test-retest data and to allow direct comparison against qMRI data acquired from MRI simulation on a diagnostic system.

Importantly, if consistency with diagnostic systems can be demonstrated, the radiation therapy can benefit from the work done on such systems to establish the relationship between the MRI parameter and biologically relevant

quantities, reducing the requirements for additional biological validation. For example, the relation between micro-anatomy and ADC has been shown²⁷ in the diagnostic imaging field and so this should apply to the ADC measured on an MR-linac. The same reasoning applies to the relation between perfusion parameters and characteristics of the microvasculature.²⁸ Likewise, qMRI studies on diagnostic systems establishing a link with clinical outcome should be transferable to MRI-guided radiotherapy systems.

The number of centers that have access to MRIGRT systems is growing rapidly. Importantly, collaborative communities such as the Momentum network²⁹ facilitate collaboration and exchange of data, supporting multicenter validation of QIBs. A similar collaboration has been initiated in Australia, where the ADAPT-MRL registry will provide a platform for technical and clinical studies.³⁰ Nonetheless, many challenges need to be overcome before crossing the second translational gap as defined by O'Connor et al.¹⁶

In this paper, we will review the current state of technical and clinical validation of qMRI research on MRI-guided radiotherapy systems. We focus on quantitative MRI techniques, such as DWI and relaxometry. Methods extracting quantitative measures such as texture features in a radiomics approach fall outside the scope of this review. We further discuss the opportunities that are currently being considered for clinical applications of qMRI biomarkers in MRIGRT and identify the additional steps that need to be taken to bring qMRI biomarkers to routine clinical decision-making, in particular for BIGART.

QIBs on MRI-Guided Radiotherapy Systems

Because MRI-guided radiotherapy systems have been in clinical use for a relatively short time, the use of qMRI on these systems is still in its early stages. Benefiting from the earlier work on diagnostic systems, the research on MRI-guided radiotherapy systems is almost exclusively dedicated to the validation phase (Domain 2 of the imaging biomarker roadmap¹⁶). Although cost-effectiveness has not yet been investigated, the additional cost of acquiring QIBs appears limited as there is typically time available during adaptation of the treatment when the scanner is unused.²⁶ While the roadmap of O'Connor et al. addresses multiple use cases, MRI-guided radiotherapy provides a unique opportunity for BIGART. Establishing the prognostic value of qMRI techniques is therefore not a purpose in itself, but rather 1 of the steps towards demonstrating that adaptation based on such biomarkers is useful. [Figure 1](#) summarizes the steps in technical and clinical validation that are necessary before we can implement BIGART clinically.

Technical Validation of qMRI on MRI-Guided Radiotherapy Systems

Technical validation is needed to make sure that qMRI measurements can be done routinely and yield consistent

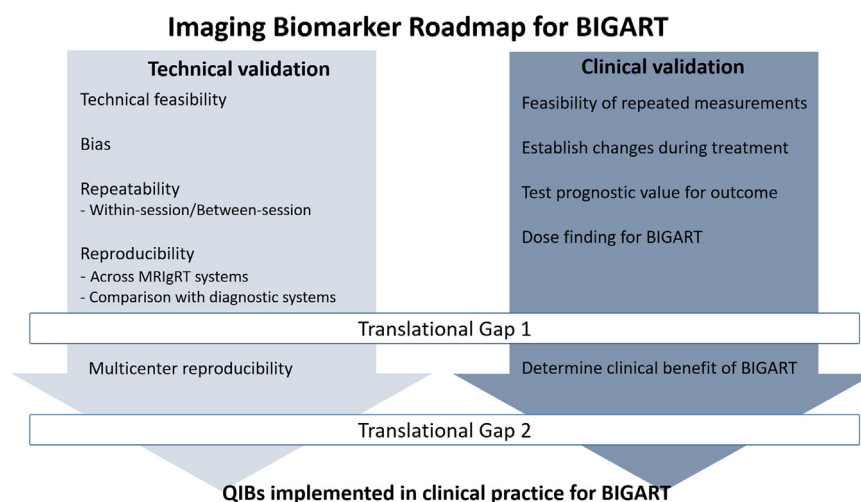


Figure 1 Overview of the steps in technical and clinical validation of imaging biomarkers that are required to demonstrate that they can be used for biological image guided adaptive radiotherapy. (Color version of figure is available online.)

results.¹⁶ Technical validation aims to measure the bias, repeatability, and reproducibility of qMRI values (Fig. 1). Bias describes the difference of a measurement from the ground truth and is typically established using MRI phantom images. Repeatability and reproducibility are both measurements of precision.¹⁶ Repeatability relates to the variation in qMRI values after repeated measurements over time on the same subject and machine.³¹ Good repeatability is especially important to distinguish treatment-related qMRI value changes that potentially have clinical relevance from random session-to-session qMRI-measurement variations. Reproducibility is related to qMRI measurements acquired under different conditions, for example in a multicenter setting with different MR-Linacs or in studies that use diagnostic imaging systems. QIB measurement reproducibility is particularly important in studies of patients undergoing follow-up MRI exams on diagnostic systems after earlier MRigRT treatments and their corresponding qMRI image values. Both repeatability and reproducibility can be measured using phantoms, but in-vivo measurements provide more realistic precision estimates in the clinical trial setting.³¹ Table 1 gives an overview of the status of technical qMRI validation done on MRI-guided radiotherapy systems.

Diffusion-Weighted MRI (DWI)

DWI is by far the most widely studied qMRI technique on MRigRT systems, mainly using echo-planar imaging (EPI) sequences. Technical feasibility was demonstrated with a few patient examples both on the 0.35T and 1.5T systems.^{23,24,32} As the gradient strength of the MR-Linacs is typically lower than that of diagnostic systems, the duration of the diffusion-encoding gradients is longer, resulting in a prolonged echo times and reduced signal-to-noise ratios.³³ A more subtle effect may be that the diffusion time, which is the time that water molecules require to diffuse between the 2 gradients, is also longer than on diagnostic systems. This means that greater spatial distances are probed, potentially

resulting in the MR images being sensitive to different micro-anatomical distance scales. This may have an impact on the measured values of the ADCs.³³

For the 0.35T system, it was shown that the ADC variation and geometric distortions were dependent on the gantry angle at acquisition with an EPI sequence.³⁴ Following this, Nadrini et al.,³⁵ investigated the optimal sequence settings by taking the geometric distortions, gantry angle, and a reduced signal-to-noise ratio (SNR) into account. They suggested acquiring data at a gantry position of 0° and using a diffusion gradient in the slice direction. Acquisition with their optimized parameter settings could be done in 78 s.

On the 1.5T system, active shimming is used to create a donut-shaped volume around the cryostat of near-zero magnetic field strength. The sensitive components of the accelerator are positioned in this volume. As a consequence, the gantry orientation has a negligible impact on the static field (B₀) homogeneity.³⁶ Indeed, no difference in ADC was observed in patient experiments between a static gantry at different gantry angles, and no effect was seen comparing ADC values obtained with static and rotating gantries.³³ This suggests that DWI acquisition could be done during irradiation on the 1.5T system, as long as the MRI was not being used for tumor tracking.

Consensus EPI-based protocols have been developed for the 1.5T system that take into account the modifications of the MRI-system.³³ To offset the reduced signal-to-noise ratio, it has been suggested to limit the acquisition of high b-values to 500 mm²/s. Kooreman et al. showed that the ADC can be measured with a 5% accuracy within a 7 cm radius of the isocenter.³³ The ADC errors increased further away from the isocenter. This was in line with the findings of Subashi et al.³⁷ and was partly related to gradient nonlinearity.³⁸ However, the effect appeared larger than observed on diagnostic systems and was also attributed to eddy currents resulting from the split coil design. This spatial variation was not present when scanning in the slice direction.

Table 1 Overview of Studies Investigating the Technical Validation of qMRI on MRI-Guided Radiotherapy Systems

Reference	qMRI	Phantom	In-Vivo: Tumor Site (No. of Subjects)*	System	Technical Development	Bias	Repeatability [†]	Reproducibility [‡]
DWI								
Yang et al. 2016 ²³	ADC	NIST/QIBA	n.a.	0.35T	n.a. [‡]	yes	No	no
Gao et al. 2017 ⁴⁰	ADC	NIST/QIBA + uniformity phantom	GBM/sarcoma (n = 8p)	0.35T	development of TSE-DWI, spatial integrity	yes	Inter	no
Kooreman et al. 2019 ²⁴	ADC	NIST/QIBA	Prostate (n = 1p)	1.5T	technical feasibility	yes	Intra	4×1.5T
Kooreman et al. 2020 ³³	ADC	NIST/QIBA	Prostate (n = 11p)	1.5T	spatial accuracy, choice of b-values, effect of gantry rotation	no	Intra Inter	no
Paulson et al. 2020 ^{23,24,32}	ADC, f	n.a.	Pancreas (n = 1p)	1.5T	technical feasibility	no	no	no
Lawrence et al. 2021 ⁴³	ADC	n.a.	CNS (n = 59p)	1.5T	n.a.	no	Intra Inter	1.5T and 1.5T MRI
Almansour et al. 2021 ³⁹	ADC	n.a.	Prostate (n = 13p)	1.5T	image evaluation	no	no	1.5T and 3T MRI
Lewis et al. 2021 ³⁴	ADC	NIST/QIBA	n.a.	0.35T	geometric distor- tions, effect of gantry angles	yes	no	1.5T, 1.5T MRI, 3T MRI
McDonald et al. 2022 ⁴¹	ADC	NIST/QIBA	head-and-neck (n = 10p + 10v)	1.5T	comparison of acqui- sition methods	yes	Inter	1.5T and 1.5T MRI
Nardini et al. 2022 ³⁵	ADC	PMMA sphere + home- made	n.a.	0.35T	SNR, uniformity, effect gantry rotation	no	no	0.35T and 1.5T
Subashi et al. 2022 ³⁷	ADC	NIST/QIBA	n.a.	1.5T	n.a.	yes	Inter (4x)	no
Habrich et al 2022 ⁴⁴	ADC	n.a.	head-and-neck (n = 11p)	1.5T	n.a.	no	Intra	no
Relaxometry								
Kooreman et al. 2019 ²⁴	T2/T1	Eurospin T05	Prostate (n = 1p)	1.5T	technical feasibility	yes	Intra	4×1.5T
Bruijnen et al. 2020 ⁴⁵	MRF: T2/T1	Eurospin T05	liver, brain abdo- men (n = 1p + 1v)	1.5T	technical feasibility	yes	Intra Inter	no
Nejad-Davarani et al. 2020 ⁴⁶	T1, PD, and R2*	NIST/ISMRM	Brain (n = 4p)	0.35T	technical feasibility	yes	Inter	no
Mickevičius et al. 2021 ⁴⁷	MRF: T1/T2	NIST/ISMRM	pelvis, thigh, brain, and head/ neck (n = 1v)	0.35T	technical feasibility	yes	Intra	3×0.35T

(continued on next page)

Table 1 (Continued)

Reference	qMRI	Phantom	In-Vivo: Tumor Site (No. of Subjects)*	System	Technical Development	Bias	Repeatability [†]	Reproducibility [‡]
Subashi et al. 2022 ³⁷	T2/T1	NIST/ISMRM	n.a.	1.5T	n.a.	yes	Inter (4x)	no
Akdag et al. 2022 ⁴⁸	T2/T1	Eurospin T05	Heart (n = 5v)	1.5T	technical feasibility	yes	Intra	1.5T and 1.5T MRI
Kooreman et al. 2022 ⁵⁰	T1 ρ	home-made	n.a.	1.5T	n.a.	no	Intra	no
Vascular properties and oxygenation Kooreman et al. 2019 ²⁴	K ^{trans}	home-made	Prostate (n = 1p)	1.5T	technical feasibility	yes	Intra	4×1.5T
Kooreman et al. 2021 ⁵⁹	D, f, D*	n.a.	Prostate (n = 43p)	1.5T	n.a.	no	Inter [§]	no
Dubec et al. 2023 ⁶⁰	OE-MRI: T1, $\Delta R1$	Eurospin T05	head-and-neck (n = 5p + 5v)	1.5T	technical feasibility	no	Inter (phantom) Intra (in-vivo)	1.5T and 1.5T MRI
CEST Chan et al. 2021 ⁶¹	MTR _{amide} , MTR _{NOE} , asymmetry	home-made	n.a.	1.5T	technical feasibility	no	no	no

* p = patient, v = volunteer.

[†] Intra = intrasession repeatability, inter= intersession repeatability.[‡] N.a. = not applicable.[§] This was not pure test-retest, but a comparison between fraction 1 and 2 under the assumption that the treatment effect was negligible.

The DWI image quality on the 1.5T system was scored lower than on a 3T diagnostic system.³⁹ The diagnostic confidence and lesion conspicuity could be improved by examining the 1.5T images in combination with the diagnostic images. The geometric distortions in DWI images were similar between 1.5T MR-linac and diagnostic 3T systems.

EPI sequences are particularly sensitive to magnetic field distortions, such as those that could be caused by the linear accelerator and the corresponding modified MRI scanner design. Therefore, Gao et al. developed a TSE-based acquisition on the 0.35T system using a diffusion-prepared turbo spin echo readout (DP-TSE).⁴⁰ Compared to an EPI sequence, this TSE DWI had less distortion. However, destructive interference between spin echoes and stimulated echoes could reduce the SNR in TSE-based DWI sequences. McDonald et al. showed the feasibility of the “split acquisition of fast spin echo signals” (SPICE) on the 1.5T system, where the spin echo and stimulated echo contributions were acquired separately to improve SNR.⁴¹

Bias

All studies used the NIST/QIBA diffusion phantom to test ADC measurement bias.⁴² The first study reporting DWI on the 0.35T system showed that the bias in ADC was less than 5%.²³ A similar bias (<3%) was observed for EPI and TSE based sequences at 0 °C, whereas at room temperature the bias was lower for the TSE based sequence (4% for TSE, 8% for EPI).⁴⁰

Two studies on the 1.5T system compared the ADC bias of the central water-vial with the QIBA tolerance levels (<3.6% or $< 0.04 \times 10^{-3} \text{ mm}^2/\text{s}$). Kooreman et al reported a bias between 0.0 and 0.7% on 4 different 1.5T systems using an EPI sequence.²⁴ McDonald et al. reported that the bias with an EPI sequence for head-and-neck ($0.026 \times 10^{-3} \text{ mm}^2/\text{s}$) was also within the QIBA limits, whereas the biases of SPICE and TSE acquisitions were larger than the limits, $0.057 \text{ mm}^2/\text{s}$ and $0.123 \times 10^{-3} \text{ mm}^2/\text{s}$, respectively.⁴¹

Kooreman et al. reported a median ADC bias for all phantom vials ranging between 1.9% and 2.7% on 4 different 1.5T systems using the EPI reference sequence of the phantom.²⁴ Subashi et al.³⁷ reported a median bias of -0.8% averaged over 4 weeks. An overestimation of 8.6% was observed for the vial with the lowest ADC value ($0.128 \times 10^{-3} \text{ mm}^2/\text{s}$). The mean ADC values in the inner ring of the phantom were significantly different from the outer ring for 4 out of the 6 vials, illustrating the spatial dependence of ADC accuracy.

McDonald et al. compared the bias of 3 different acquisitions: EPI, SPICE, and TSE. The biases of the EPI and SPICE acquisitions were below $0.1 \times 10^{-3} \text{ mm}^2/\text{s}$ for most vials in the phantom.⁴¹ They also observed an overestimation of the ADC for the lowest ADC values. Furthermore, the TSE acquisition showed an underestimation of the ADC values for almost all vials.

Repeatability

In this review, we used the following definition of repeatability: repeated measurements with the same subject on the

same imaging system, but at different moments in time. This could be during the same scan session (intrasession repeatability), or on a different scan session or day (intersession repeatability). In some studies, the latter has been called reproducibility, but it will be interpreted here as repeatability. Estimates of the repeatability are often reported as the within-subject standard deviation (wSD), within-subject coefficient of variation (wCV), the repeatability coefficient ($\text{RC} = 2.77 \times \text{wSD}$), or the relative repeatability coefficient ($\%\text{RC} = 2.77 \times \text{wCV}$).¹⁵

In phantoms, the median relative difference within the same session ranged between 1.3 and 2.2% on 4 1.5T systems using the phantom reference sequence.²⁴ The long-term repeatability within 5 months was 1.7%. Similar values with the phantom reference sequence were found by Subashi et al: a median coefficient of variation of 1.3% (range 0.5%-2.2%) over 4 weeks.³⁷ The %RC for the central water-vial reported by Kooreman et al.²⁴ was greater than the recommended QIBA tolerance, which could be attributed to the lower SNR on the MR-linac compared to diagnostic systems. This is partly due to the absence of a head coil and may have particularly affected the measurement at a b-value of 2000 s/mm^2 , as recommended in the QIBA protocol for repeatability assessments.¹⁵ When using protocols with lower maximum b-values, the repeatability coefficients were within the tolerance values.⁴¹ The within-session RC of an EPI sequence ($0.011 \times 10^{-3} \text{ mm}^2/\text{s}$) was greater compared to a SPICE sequence ($0.008 \times 10^{-3} \text{ mm}^2/\text{s}$) and TSE sequence ($0.004 \times 10^{-3} \text{ mm}^2/\text{s}$). This difference was even larger for the between-session RC: $0.030 \times 10^{-3} \text{ mm}^2/\text{s}$ for EPI, $0.025 \times 10^{-3} \text{ mm}^2/\text{s}$ for SPICE, and $0.003 \times 10^{-3} \text{ mm}^2/\text{s}$ for TSE.

On the 0.35T system, the maximum CV for ADC was below 5%.⁴⁰ The standard deviation of ADC values measured with the DP-TSE sequence was greater than the standard deviation of the single-shot EPI sequence. This could have been caused by the relatively lower number of averages from DP-TSE where outliers could have a large impact.⁴⁰

In prostate, the RC between 2 consecutive fractions was $0.09 \times 10^{-3} \text{ mm}^2/\text{s}$ for noncancerous prostate and $0.37 \times 10^{-3} \text{ mm}^2/\text{s}$ for tumors.³³ Note that this study was not a formal test-retest study as 1 radiation fraction was given between the 2 measurements, but its effect was considered negligible. In the brain, an intrasession wSD ranging from $0.0065 \times 10^{-3} \text{ mm}^2/\text{s}$ to $0.045 \times 10^{-3} \text{ mm}^2/\text{s}$ (wCV 0.9 to 2.0%) was reported for the tumor region and several normal appearing structures.⁴³ The intersession wSDs were slightly greater, ranging from 0.0097×10^{-3} and $0.12 \times 10^{-3} \text{ mm}^2/\text{s}$ (wCV 1.4%-4.8%). Two studies investigated ADC measurement repeatability in head-and-neck on the 1.5T system using EPI protocols with similar b-values. The intrasession RC was $0.457 \times 10^{-3} \text{ mm}^2/\text{s}$ (31.3%) for the tumor region, $0.310 \times 10^{-3} \text{ mm}^2/\text{s}$ (23.5%) for suspicious lymph nodes, and varied between 0.138×10^{-3} and $0.281 \times 10^{-3} \text{ mm}^2/\text{s}$ (9.4% and 21.8%) for submandibular and parotid glands.⁴⁴ The RC was lower for structures with larger volumes. Similar values were reported in another study, the intrasession wCV was 9.6% for the tumor, 7.8% for the

lymph nodes, and 5.4% for parotid glands.⁴¹ For SPLICE, the intrasession wCV was 7.8%, 7.2%, and 3.2% for tumor, lymph nodes, and parotid glands, respectively. For TSE, the wCV was 7.6%, 10.8%, and 5.7%. For all structures and all sequences, the intersession wCV was about 2% greater.

Reproducibility

The ADC measurement reproducibility with a phantom across 4 different 1.5T systems was 2.2%.²⁴ For the 0.35T system, ADC values, calculated using 4 b-values ranging from 0 to 800 s/mm² at 0.35 T, were lower than those produced on 1.5 T and 3 T systems using 4 b-values ranging from 0 to 2000 s/mm.^{2 34} For a reference ADC of 1.127×10^{-3} mm²/s, the corresponding difference was -0.00085×10^{-3} mm²/s at 3 T, 0.0083×10^{-3} mm²/s at 1.5 T, and -0.116×10^{-3} mm²/s at 0.35 T.³⁴ However, another study observed no significant differences between ADC values between a 0.35T system and a 1.5T diagnostic scanner.³⁵ The results showed a maximum difference of 0.03×10^{-3} mm²/s.³⁵ The differences in the 2 studies might be explained by differences in the diffusion schemes and choice of b-values.³⁵

Lawrence et al. compared ADC measurements in the brain, comparing the 1.5T MR-linac system against a 1.5T diagnostic scanner.⁴³ The interscanner difference was -8.1% for both the tumor and normal tissue (NAWM: -7.3%, NAGM: -9.0). The largest difference was found for the CSF (-20%). In prostate cancer, the mean ADC values were higher on the 1.5T system (mean of 1.07×10^{-3} mm²/s $\pm$ 0.4×10^{-3} mm²/s) compared against a 3T diagnostic scanner (mean 0.8×10^{-3} mm²/s $\pm$ 0.2×10^{-3} mm²/s).³⁹ The differences were not statistically significant.³⁹ For head-and-neck, volunteers were scanned on both the 1.5T MR-linac and a 1.5T diagnostic system.⁴¹ The bias and repeatability of the parotid glands were similar between both systems.

Relaxometry

Technical feasibility of relaxometry measurements on MRgRT systems has been demonstrated for different tumor sites.^{24,45-48} Standard clinically available sequences were used for T1 and T2 mapping: the variable flip angle (VFA) approach for T1 mapping^{24,37,46} and multiecho spin echo (ME-SE) sequences for T2 mapping.^{24,37} Akdag et al. developed T1 and T2 sequences for measurements in the heart using cardiac triggering in combination with breath holds on the 1.5T system.⁴⁸ For T1 mapping a modified look-locker sequence (MOLLI) was used and for T2 mapping a black blood-prepared gradient spin echo sequence was used.

Another relaxation parameter is T1 ρ , which is the T1 relaxation in the rotating frame. T1 ρ is mainly influenced by protein-water interactions and therefore is sensitive to the presence of protein molecules. In a heterogeneous environment, it reflects the combined effects of diffusion, chemical exchange, and molecular motion.⁴⁹ Kooreman et al. implemented a T1 ρ sequence on the 1.5T system, which required additional research options for the prepulse.⁵⁰

In addition to the individual parameter acquisitions, several studies developed sequences to estimate multiple parameters from 1 acquisition. Nejad-Davaraini showed the initial feasibility of STrategically Acquired Gradient Echo (STAGE) acquisition on the 0.35T system in the brain to simultaneously estimate T1, T2*, and proton density (PD).⁴⁶ Bruijnen et al. developed an MR fingerprinting technique (MRF) for brain and abdomen on the 1.5T system to simultaneously estimate T1 and T2 values.⁴⁵ Similarly, Mickevicius et al. implemented MRF for the 0.35T system showing that a full 3D volume could be obtained in less than 6 mins.⁴⁷

B1 field inhomogeneities can impact T1 and T2 measurement accuracy. Subashi et al. observed a 2% deviation from the nominal B1 field in an ROI of 35cm in a homogeneous phantom.³⁷ However, B1 inhomogeneities in patients can be very different than in phantoms. In fact, Kooreman et al. showed that a consistent B1 map was obtained in 3 patients for 5 fractions.⁵¹ For example, the B1 varied between left and right iliac arteries with about 20%:103% vs 80%.

Bias

Different Phantoms Have Been Used to Assess the Bias of Relaxometry Measurements, Commercial, Standard, and Home-Made⁵²

Nejad-Davarani et al. reported a %bias of $7.0\% \pm 2.5\%$ when comparing VFA to reference inversion recovery measurements on the 0.35T system. The median %bias for T1, as measured with the VFA method was between 2.7% and 14.3% on 4 different 1.5T systems.²⁴ The bias reported by Subashi et al. fell inside this range.³⁷ With a Modified Look-Locker Inversion Recovery (MOLLI), Akdag et al showed a maximum %bias of -3.2% compared to reference inversion recovery measurements on the 1.5T system.

Kooreman et al. observed that the T2 values were consistently underestimated with a multiecho spin echo (ME-SE) sequence over the entire range of T2 values in the a commercial phantom.²⁴ The median %bias ranged between 10.4 and 14.1% on 4 different 1.5T systems. This was in line with similar measurements on diagnostic systems.^{53,54} Using the NIST/ISMRM phantom, Subashi et al. did not find a systematic underestimation of T2 with a similar sequence: %bias was -3.9% (range -3.6 to 8.8%).³⁷ Akdag et al. showed a maximum %bias of -2.5% using a gradient and spin-echo (GraSE) sequence compared against an ME-SE reference sequence.⁴⁸

Bruijnen et al. showed that accurate T1 and T2 values could be measured with MRF on the 1.5T system.⁴⁵ The correlation coefficient for a 276 times-undersampled dataset was 0.999 between T1 estimated with MRF and T1 estimated with inversion recovery. For T2, the correlation coefficient was 0.975 between T2 estimated with MRF and T2 estimated with a ME-SE sequence. Mickevicius et al. showed that T1 was underestimated with MRF on the 0.35T system compared to inversion recovery reference values.⁴⁷ The %bias varied depending on the method chosen for B1 correction between 6.3% and 9.7%. For T2 mapping, an

underestimation ranging between 9.2 and 18.6% was observed. Only small additional errors were observed due to high undersampling: 0.65% for T1 and 4.05% for T2 values.

Using STAGE, a systematic underestimation ($9.5 \pm 2.2\%$) of T1 values was observed compared to reference measurements with inversion recovery.⁴⁶ STAGE-T1 values were significantly lower than VFA-T1 values for 7 of 11 vials. For PD the %bias was $8.05\% \pm 6.85\%$. A strong correlation (0.998) was obtained between R2* values and the MnCl2 concentrations in the phantom (0.013–1.704 mM/L).

Repeatability

Repeatability of relaxometry parameters has so far only been investigated with phantoms. The intrasession relative difference of T1 ranged between 0.5% and 5.1% on 4 different 1.5T systems with VFA.²⁴ The intersession difference was 1.8%. Similarly, an intersession %CV over 4 weeks of 1.1% was reported on another 1.5T system.³⁷ This indicates that while the accuracy of the VFA method is relatively low, the bias is constant over time. The intersession %CV over 6 weeks on the 0.35T system was $3.6\% \pm 0.7\%$.⁴⁶

For T2 estimated from ME-SE, the within-session relative difference ranged between 0.4 and 1.2% on 4 different 1.5T systems.²⁴ The intersession relative difference was slightly larger (1.4%) as measured on 1 of the systems. Similarly, Subashi et al. reported an intersession %CV over 4 weeks of 0.5%.³⁷

For, T1 ρ the intrasession RC was 0.9 ms for phantom.⁵⁰ The T1 ρ values in the femoral heads were stable during treatment.

T1 and T2 values estimated with MRF on the 1.5T system were very stable over time: average standard deviations over time were 6.4 ms for T1 and 2.3 ms for T2, suggesting that the T1 stability was slightly better. Also, on the 0.35T system, the T1 stability was better than T2 with MRF: RC = 21.6 ms for T1 and 51.5 ms for T2,⁴⁷ both less than 5%.⁴⁷ Using STAGE on the 0.35T system, the intersession %CV was $4.7 \pm 2.4\%$ for T1, $7.5 \pm 5.8\%$ for PD, and $10.1 \pm 9.9\%$ for R2*.

Reproducibility

The reproducibility of relaxometry parameters has been investigated in fewer studies. Kooreman et al. showed that the %CV of T2 values estimated with ME-SE was quite low (2.9%) across 4 different 1.5T systems, indicating that the T2 underestimation was consistent across these systems.²⁴ For T1 with VFA, the variation between 1.5T systems was larger: %CV was 11.2%. The variation increased for greater T1 values.²⁴ For cardiac MRI, Akdag et al. showed that the maximum %biases for T1 and T2 on the 1.5T system (-4.4% and -8.8%) were in a similar range as for a 1.5T diagnostic system (-3.2% and 8.6%).⁴⁸ Comparison of T1 and T2 maps in 5 volunteers showed comparable image quality and similar mean T1 and T2 values of the myocardium between the 2 systems.⁴⁸ With MRF, there were no significant differences in T1 and T2 values between 3 different 0.35T systems.⁴⁷ The mean %biases between 2 of the scanners were 2.9% for T1 and 2.7% for T2.⁴⁷

Vascular Properties and Oxygenation

Characteristics of tissue vascularity, such as perfusion and permeability are often measured with intravenous contrast agents. Contrast agents are increasingly used on MRI-guided radiotherapy systems to improve target conspicuity.⁵⁵ Wang et al. tested the chemical stability of gadolinium chelates in solutions under irradiation and found no significant change in chemical composition or displacement of gadolinium ions from their chelates using mass spectrometry, even after a dose of 30 Gy.⁵⁶ Mahmood et al. confirmed this finding with NMR spectroscopy, using radiation doses of up to 100 Gy.⁵⁷

On the 0.35T system, a free-breathing 3D golden angle radial stack-of-stars sequence was used to acquire DCE-MRI data in patients with liver cancer and investigated its feasibility for semiquantitative tissue perfusion analysis.⁵⁸ Dynamic signal intensity curves featured with characteristic contrast baseline signal, in-flux slope, and plateau region were seen in both phantom data and liver patient data. Greater contrast enhancement and in-flux slope were also captured in the tumor ROI as compared to surrounding normal liver tissue.

The technical feasibility of dynamic contrast-enhanced (DCE-)MRI was demonstrated for prostate cancer on the 1.5T system using a spoiled-gradient echo sequence.²⁴ This required installation of a power injector to administer the contrast agent. Direct evaluation of DCE parameter accuracy is challenging and requires flow phantoms. Kooreman et al. evaluated individual components of the DCE analysis pipeline according to QIBA recommendations: bias in baseline T1 values, stability of the signal during acquisition, and bias in concentration values when signal intensities are converted to concentration values.²⁴ The signal was stable during 5 mins of acquisition on 4 1.5T systems (%CV was between 0.1 and 0.6%).²⁴ However, the concentration values were underestimated (23.5% at 0.5 mM to 62.0% at 9.8 mM). The between-session difference was 17.9% and the reproducibility between 4 1.5T systems was 16.9%.

Intravoxel-incoherent motion (IVIM) MRI is gaining interest as it does not require the injection of a contrast agent. So far, only 1 study investigated the technical validation of IVIM parameters on MRIGRT systems.⁵⁹ On the 1.5T system, similar RC values for the diffusion coefficient (D) were reported as for ADC. The RCs were higher for the perfusion parameters of IVIM: 0.05 and 0.16 (58 and 181%) for the perfusion fraction (f) and $15.3 \times 10^{-3} \text{ mm}^2/\text{s}$ and $76.4 \times 10^{-3} \text{ mm}^2/\text{s}$ (53 and 262%) for the pseudo-diffusion coefficient (D*) in noncancerous tissue and tumor respectively. The RC varied with the size of the region of interest. Importantly, the RCs for f and D* were large compared to the mean values of tumor and noncancerous prostate, suggesting that the signal-to-noise needed to be improved to achieve reliable measurements of perfusion with IVIM.

Dynamic volumetric oxygen-enhanced MRI (OE-MRI) is a promising emerging technique to measure tissue oxygenation.⁸ In this technique, changes in R1 (ie, 1/T1) are measured, induced by inhaling 100% oxygen. Dubec et al. presented the first in-human implementation of OE-MRI on the 1.5T system tested in head-and-neck cancer.⁶⁰ Room

modifications were necessary to enable the gas challenge. The acquisition consisted of a baseline 3D inversion recovery turbo field echo (IRTFE) T1 map with 5 inversion delays followed by a 3D dynamic IRTFE sequence with 1 inversion delay of 1100 ms and a temporal resolution of 12s. The intrasession difference of baseline T1 values was 6.9 ± 6.6 ms for phantom measurements. The mean difference with a 1.5T diagnostic system was 2.3 ± 22 ms. The signal was stable during the dynamic measurements, with a maximum drift of $\Delta R1 = 6.0 \times 10^{-5} \text{ min}^{-1} \text{ s}^{-1}$. In a group of head-and-neck cancer patients, it was shown that OE-MRI was feasible on the 1.5T system and well tolerated by the patients. The intersession RC of T1 measurements was 59 ms and the RC for $\Delta R1$ was 0.020 s⁻¹. The OE-MRI DR1 curves were similar in shape and magnitude when comparing 1.5T system measurements with those from the diagnostic system.

Metabolic Imaging

One study showed technical feasibility of chemical exchange saturation transfer (CEST) imaging on the 1.5T system.⁶¹ A CEST implementation that was previously developed for diagnostic 1.5T systems was used.⁶² From the data, the magnetization transfer ratio (MTR) asymmetry, $\text{MTR}_{\text{Amide}}$, and MTR_{NOE} parameters were derived. To evaluate the sensitivity of CEST detection on the 1.5T system, a phantom was developed with different ranges of ammonium chloride (NH₄CL) concentration. The MTR asymmetry increased with increasing concentration, from $0.41\% \pm 0.18\%$ (mean $\pm$ SD within ROI) at 7.8mM NH₄CL to $34.7\% \pm 1.1\%$ at 1000 mM NH₄CL.

Clinical Validation of qMRI on MRI-Guided Radiotherapy Systems

Clinical validation describes the phases towards clinical implementation of imaging biomarkers (Fig. 1): 1) clinical feasibility with case studies, 2) observational studies showing changes in qMRI parameters during the radiation treatment, 3) prognostic studies investigating the link between changes during treatment with outcome, 4) planning and dose-finding studies to determine how to translate qMRI parameters into dose and 5) clinical trials to determine the clinical benefit of BIGART. Table 2 gives an overview of the studies related to clinical validation.

Several studies have demonstrated the clinical feasibility of repeated measurements of qMRI in head-and-neck, brain, sarcoma, pancreas, and rectum.^{23,46,63,64} The first study demonstrating the potential of qMRI measurements for BIGART was the study by Yang et al. where temporal changes of ADC were investigated in 3 head-and-neck cancer patients and 3 patients with sarcoma.²³ ADC measurements were done every 2 to 5 fractions on the 0.35T system. The results show that the temporal responses were different for individual patients; some showed an increase, while others showed a decrease in ADC. Similar results were also seen in rectal cancer cases on the 0.35T system.⁶⁴ In the previously mentioned STAGE study,⁴⁶ tumor changes were shown simultaneously through a quantitative change in 0.35T system T1,

R2*, PD maps, and image intensity change in 3T morphological MRI from a cohort of 4 brain cancer patients.

Changes during treatment in larger patient cohorts have been investigated in rectum, prostate, brain, and sarcoma. In rectal cancer, Ingle et al. showed that ADC increased in all 7 patients. The increase in some patients was larger than 50%.⁶⁵ In 12 patients, a small increase in T1 ρ in the tumor was observed.⁵⁰ The added benefit in terms of treatment response monitoring needs to be demonstrated.

In prostate, 2 studies investigated changes during treatment. However, no relation to clinical outcome has been investigated so far. All IVIM parameters increased in the tumor and noncancerous prostate tissue, except the diffusion coefficient D (similar to ADC) in noncancerous tissue.⁵⁹ The increase in D was larger for patients with a higher Gleason grade than for patients with a lower Gleason grade. Since the whole prostate gland was treated, inflammation may have caused the increase in f and D* for both tumor and prostate tissues.⁵⁹ Similarly, increases in all IVIM (except D in healthy tissue) and DCE parameters were observed in a follow-up study, suggesting there is an overall biological response which can be measured with both techniques.⁵¹ Small but significant correlations were found between some IVIM and DCE parameters.

In glioma patients, ADC changes during treatment were greater than the RC in 14 of 20 patients.⁴³ In 4 patients an increase in ADC was reported, in 7 a decrease, and in 3 both an increase and decrease, showing that different ADC temporal patterns occur during treatment in individual patients. These changes need to be linked to treatment outcomes in future studies. Changes during treatment were also observed in CEST parameters $\text{MTR}_{\text{Amide}}$ and MTR_{NOE} in a group of 54 CNS patients.⁶¹ In a group of 10 high-grade glioma patients, it was demonstrated that repeated measurements of multiparametric MRI measurements, including ADC, T1, T2, and CEST were feasible during treatment.⁶⁶ A correlation was observed between median ADC and the volume of the hyper-intense FLAIR region in all patients and all time points.

For soft tissue sarcoma, a novel deep-learning prediction framework along with generative adversarial network (GAN)-based data augmentation was introduced with DWI to separate response into 3 categories corresponding to their postsurgery pathologic treatment effect (TE) scores ($\text{TE} \leq 20\%$, $20\% < \text{TE} < 90\%$, $\text{TE} \geq 90\%$).²⁰ The model's patient-based prediction achieved a mean accuracy of 97.1%. Another study used longitudinal DWI based radiomics features⁶⁷ from the same patient cohort to differentiate patient response into 2 groups ($\text{TE} < 50\%$, $\text{TE} > 50\%$). This study successfully demonstrated the value of multitime point DWI acquisition for treatment response prediction.

Future Prospects

To date 3 platforms for MRI-guided radiotherapy are commercially available with varying main magnetic field strengths. For 2 of these, it has been established that the acquisition of quantitative MRI is feasible. Particularly diffusion-weighted MRI has been extensively studied. The bias of

Table 2 Overview of Studies Investigating Clinical Validation of qMRI for BIGART on MRI-Guided Radiotherapy Systems

Tumor site	Reference	No. of subjects	Treatment Schedule	System	qMRI Parameters	No. of qMRI Measurements Per Subject	Link to clinical parameters	Clinical Validation Phase
Prostate	Kooreman et al. 2021 ⁵⁹	43	20×3Gy	1.5T	D, f, D*	20	ISUP, ADT	Establish changes during treatment
Rectum	Kooreman et al. 2022 ⁵¹	20	20×3Gy	1.5T	D, f, D*, K^{trans} , k_{ep} , v_e	20 for IVIM, 5 for DCE	none	Establish changes during treatment
	Shaverdian et al. 2017 ⁶⁴	3	50.4-54Gy (1.8 Gy fraction per day)	0.35T	ADC	4, 6, and 7	FDG-PET	Feasibility of repeated measurements
	Ingle et al. 2022 ⁶⁵	9	Phase 1: 5×1.8Gy to GTV; Phase 2: 25×1.8Gy to GTV, mesorectum, pelvic nodes	1.5T	ADC	10 (daily in phase 1, weekly in phase 2)	TRG response	Establish changes during treatment
	Kooreman et al. 2022 ⁵⁰	12	5×5Gy	1.5T	T1rho	5	complete and incomplete response	Establish changes during treatment
Brain	Nejad-Davarani et al. 2020 ⁴⁶	4	25-30×2Gy	0.35T	T1, PD, and R2*	7-8 (pretreatment, once a week during RT, and post-treatment)	none	Feasibility of repeated measurements
	Lawrence et al. 2021 ⁴³	59	30×2Gy/15×2.67 Gy/5×5.5Gy	1.5T	ADC	daily	none	Establish changes during treatment
	Chan et al. 2021 ⁶¹	54	30×2Gy/15×2.67Gy	1.5T	MTR_{amide} , MTR_{NOE} and asymmetry	5-6 (once a week)	tumor type and grade	Establish changes during treatment
	Tseng et al 2022 ⁶⁶	10	30×2Gy	1.5T	ADC, T1, T2, CEST asymmetry	daily (each time a different technique)	relation to the location of tumor recurrence	Establish changes during treatment
Abdominal	Hall et al. 2020 ⁶³	10	6×5Gy/5×6.6 Gy/5×10Gy/5×15Gy/3×20Gy	1.5T	ADC, T2		none	Feasibility of repeated measurements
Head-and-neck Sarcoma	Yang et al. 2016 ²³	3		0.35T	ADC	4-7	none	Feasibility of repeated measurements
	Yang et al. 2016 ²³	3		0.35T	ADC	4-7	none	Feasibility of repeated measurements
	Gao et al 2020 ²⁰	30	5×6Gy	0.35T	ADC	3	none	test prognostic value for outcome
	Gao et al 2021 ⁶⁷	30	5×6Gy	0.35T	ADC	3 (15000 synthetic)	TE score	Test prognostic value for outcome

ADC measurements on both 0.35T and 1.5T systems has been determined in phantoms and lay within 3% at the center of the MRI, with an increasing bias towards the outer parts of the field of view. The repeatability was somewhat less than what is typically present in diagnostic systems and depended on the volume of the region of interest studied. Consequently, the repeatability varied between different tumor sites. Yet, the data gave an indication of the ADC changes that might be detected in tissue during fractionated radiotherapy. The reproducibility between MRI-guided radiotherapy systems and diagnostic systems depends critically on the choice of acquisition parameters, in particular the b-values used to calculate ADC. When a clinical biomarker study involves pretreatment or follow-up measurements at a diagnostic system, it is therefore recommended to include a measurement of reproducibility in the trial design.¹⁷ Relaxometry mostly focused on the measurement of T1 and T2 values but also included T1 ρ , T2*, and B0. Again, accuracy and repeatability for MRIgRT platforms appear in line with diagnostic systems.

For prostate cancer, Kooreman et al.⁵⁹ demonstrated that ADC values correlate with relevant tumor characteristics, such as Gleason grade, in line with studies on diagnostic platforms.⁶⁸ While increases in ADC and perfusion parameters were observed during the course of radiotherapy, the changes were quite small and barely detectable on an individual level. Since more and more patients are being treated using ultra-hypofractionated schedules of 5 fractions, and 2 fractions such as in the Hermes trial,⁶⁹ the window of opportunity for response measurements during treatment is shrinking. There is a trend towards focal boosting treatment strategies, increasing the dose specifically to the tumor inside the prostate gland. Here qMRI, such as DWI may be useful to delineate the gross tumor volume in an on-line setting.

There are some early indications that an increase in ADC value of rectal cancer during treatment on the 1.5T system, with or without chemotherapy, was associated with pathological complete remission.⁶⁵ To improve the likelihood of organ sparing, strategies have been proposed to boost the dose to the tumor.⁷⁰ In a BIGART approach, I could speculate about directing the boost specifically to the persistently poor-responding part of the tumor, as identified by QIBs.

As changes in ADC were seen in most patients with high-grade glioma, Lawrence et al. suggest that further data on the relationship between ADC and physiological changes in brain tumors could inform plan adaptation using DWI.⁴³ Chan et al. investigated CEST to monitor response during radiation treatment. If CEST signals detected during radiation could reveal areas of residual active tumor or areas of increased tumor metabolism, then alternative treatment strategies including CEST image-guided dose escalation could be applied.⁶¹

After determining ADC measurement repeatability in patients with head and neck cancer, Habrich et al. proposed that ADC-based patient stratification as well as assessment of treatment response during the course of radiotherapy might be realized.⁴⁴ As a first step towards biological image-guided adaptive radiotherapy, the University Hospital Tübingen

began a phase I dose-finding study in head-and-neck cancer patients, adding an adaptive boost to an ADC-based high risk subvolume with dose levels increasing to 5×6.5 Gy (clinicaltrials.gov Identifier: NCT05160714).

Within the field of on-line MRIgRT, we can benefit from the vast body of research that has been conducted in diagnostic settings using diagnostic MRI scanners. When the bias of QIB measurements on MRI-guided radiotherapy systems has been established and the reproducibility with measurements on diagnostic systems confirmed, results on the prognostic value of QIBs could be easily translated. Longitudinal studies, investigating the prognostic value of changes in qMRI parameters are facilitated by the availability of MRIgRT systems and such studies are likely to rapidly increase in number. Here, in turn, the diagnostic field potentially can use the results from QIB validation studies on MRI-guided radiotherapy systems, in particular by selecting optimal time points for measurements in a setting where daily measurements are not feasible in a diagnostic setting. The novel opportunity of biomarker measurements in MRIgRT lies in the use of qMRI for adaptation using the predictive value of QIBs for BIGART.

While the acquisition of quantitative MRI sequences is now feasible on MRIgRT systems, there are limitations that need to be resolved by the manufacturers. Many of the sequences are not available as a standard option for all users. Also, SNR is limited compared to diagnostic systems and further improvements would be warranted. For example, improved receive coils could increase SNR.⁷¹ A limiting factor in the routine use of qMRI in MRIgRT is that the extraction of quantitative parameters from the acquired images is often not standardized, let alone integrated into the acquisition process. The exception is DWI, where ADC maps typically are generated automatically on the scanners, and this may explain why most work so far has focused on this technique.

To enable the steps as outlined in Figure 1, the manufacturers need to follow a similar roadmap. Technical validation is possible with non-standard sequences in research settings and relatively small clinical trials. This has also been sufficient to establish that changes in qMRI parameters happen during treatment. However, to test the prognostic value for outcome, larger multi-center studies are required, and this means that sequences and analysis methods need to be widely available and standardized. To make the next step towards biological image-guided adaptation, the acquisition and processing of qMRI need to be integrated into on-line treatment planning. The treatment planning software will need to process a combination of anatomical images and quantitative parameter maps to define target volumes and dose prescriptions.

Conclusion

Quantitative MRI can be used to monitor changes in the characteristics of tumors and normal tissue over time. In the context of MRIgRT, most research has so far focused on the technical validation of qMRI on MRI-guided radiotherapy systems. For DWI and relaxometry, multiple studies have

demonstrated accuracy, repeatability, and reproducibility in phantoms as well as in patients. More sophisticated techniques, such as metabolic imaging with CEST or perfusion imaging and oxygen-enhanced MRI have also been translated to MRI-guided radiotherapy systems.

The focus of research is now shifting toward clinical validation. Because repeated measurements have become practically feasible during fractionated radiotherapy, a unique opportunity for establishing the prognostic value of QIBs has been created. With a growing number of MRIgRT system installations, large multicenter studies are also becoming possible. While daily imaging is not feasible in the diagnostic setting, some of the results of this research may translate to the diagnostic setting when an optimal time point can be defined at which QIBs should be acquired. The unique opportunity for use of QIBs lies in BIGART. On MRI-guided radiotherapy systems, the first steps are now taken towards interventional studies, investigating the frequent adaptation of the treatment based on QIBs. By bringing 2 concepts in radiotherapy together, adaptive radiotherapy and dose painting, its full potential as a treatment modality of cancer could be reached.

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