



Review Article

Quantitative magnetic resonance imaging on hybrid magnetic resonance linear accelerators: Perspective on technical and clinical validation

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ABSTRACT

Many preclinical and clinical observations support that functional magnetic resonance imaging (MRI), such as diffusion weighted (DW) and dynamic contrast enhanced (DCE) MRI, might have a predictive value for radiotherapy. The aim of this review was to assess the current status of quantitative MRI on hybrid MR-Linacs. In a literature research, four publications were identified, investigating technical feasibility, accuracy, repeatability and reproducibility of DW and DCE-MRI in phantoms and first patients. Accuracy and short term repeatability was < 5% for DW-MRI in current MR-Linac systems. Consequently, quantitative imaging providing accurate and reproducible functional information seems possible in MR-Linacs.

1. Introduction

Functional magnetic resonance imaging (MRI) has been shown in a number of recent studies to provide not only beneficial information for target volume delineation [1,2], but more importantly also prognostic information with respect to outcome after radiotherapy (RT) [3,4]. In terms of quantitative MRI techniques in a clinical context, so far mainly diffusion weighted imaging (DWI) and dynamic contrast enhanced (DCE) MRI have been used to predict RT response [5,6]. DWI is a functional MRI technique to visualize diffusion properties of water in tissues and thus cellular density [5], whereas DCE measures tissue perfusion and permeability [6].

There is growing evidence that diffusion weighted (DW) MRI may provide prognostic information to predict RT treatment outcome in head and neck cancer (HNC) [7–11]. Also for other tumor sites, such as brain tumors [12,13], cervical cancer [14] or rectal cancer [15], the prognostic value of DW MRI for RT outcome prognosis has been shown. The majority of these studies correlated functional biomarkers derived from functional MRI before the start of RT with observed outcome following therapy. Some studies also investigated the optimal time point of

imaging and showed that biomarkers acquired in the first weeks of therapy might be beneficial for prognosis prediction [16]. Vandecaveye et al. [16] reported that DW MRI during RT allowed for a more accurate response prediction compared to anatomical imaging and correlated significantly to two-year loco-regional control (LRC) in HNC.

Other studies showed that also DCE MRI may yield prognostic information with respect to RT outcome [6,17]. For example, Halle et al. identified a prognostic parameter from DCE MRI data to predict RT response in cervical cancer [17]. Consequently, functional MRI yielded promising results in the light of developing prognostic models for RT outcome prediction. Such predictive models relating quantitative biomarkers derived from functional MRI to RT outcome might serve in the future as a basis for RT interventions aiming for personalized dose prescriptions. However, the direct use of functional imaging information for RT dose optimization requires quantitative imaging information [18,19].

Studies on optimal imaging time points are ongoing. Those are challenging due to a limited availability of imaging appointments and high burden to the patient when using separate, stand-alone MRI scanners.

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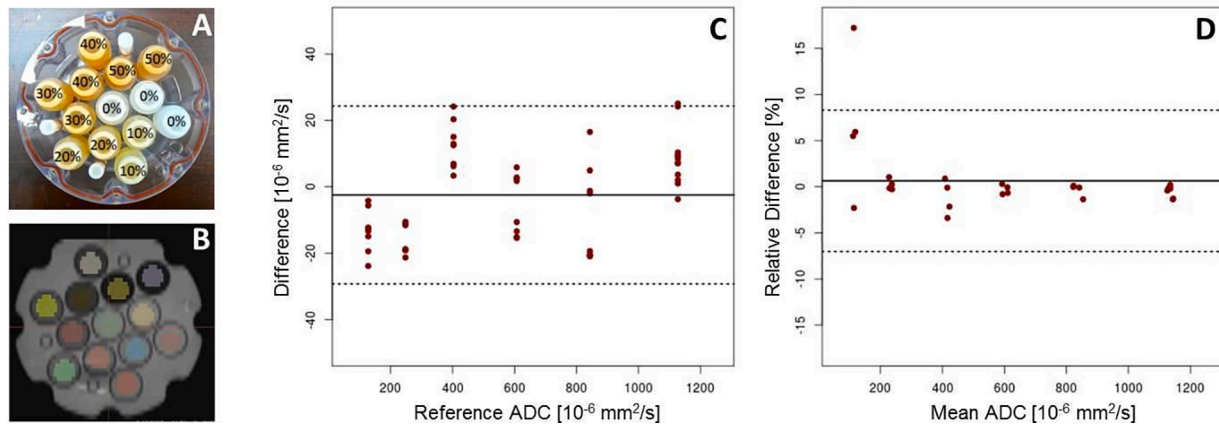


Fig. 1. Assessment of accuracy and repeatability with respect to ADC determination based on DW MRI at the 1.5 T MR-Linac using a dedicated diffusion phantom. (A) Diffusion Phantom (Model 128, Qalibre MD, Boulder, USA) containing inserts prepared with different known diffusion coefficients. (B) Regions of interest used to analyze ADC values in the different probe areas, acquired with an EPI-based DW MRI sequence ($b = 0, 200, 500 \text{ s/mm}^2$; TE/TR = 117/6683 ms; voxel size: $1.53 \times 1.53 \times 4 \text{ mm}^3$). (C,D) Bland-Altman plots showing accuracy and short term repeatability of ADC assessed in four measurements on two different days, including bias (full line) and LoA (limits of agreement, dashed line). (C) Accuracy of ADC assessment with a bias of $-2.5 \cdot 10^{-6} \text{ mm}^2/\text{s}$ and LoA $\pm 26.8 \cdot 10^{-6} \text{ mm}^2/\text{s}$. (D) Repeatability analysis presents a bias of 0.6%, LoA = $\pm 7.6\%$. Median accuracy and reproducibility were -0.31% and 0.31% , respectively.

Recently, combined devices of MRI and linear accelerator (MR-Linac) have been introduced clinically [20–25], which allow for daily online-adaptive MR-guided RT [26–31]. Two different systems with magnetic field strengths of 0.35 T [32] and 1.5 T [33] are currently commercially available. In addition to daily anatomical MRI during RT, MR-Linac treatment machines provide an optimal basis for un-biased biomarker studies, as functional imaging can be done sequentially, at any time point during RT [34]. A recent review by Datta et al. [34] discussed challenges related to the technical implementation of functional MRI techniques on combined MR-Linac systems. However, the MR scanner design in combined MR-Linacs is different compared to diagnostic MR-scanners in terms of technical parameters such as gradient strength, slew rate and eventually also field strength as well as the use of radio-opaque radiofrequency coils adapted to the RT-specific patient positioning [32,35]. Therefore, after implementation of functional MRI on MR-Linacs, their capacity to provide quantitative imaging and thus accurate, repeatable and reproducible quantitative imaging biomarkers (QIB) needs to be investigated before initiating clinical studies [36,37]. Consequently, the aim of this work was to review the current status regarding technical and clinical validation of quantitative imaging using hybrid MR-Linac systems.

2. Methods

A literature research was performed in the database PubMed (www.pubmed.ncbi.nlm.nih.gov) using the search terms “MR-Linac / MRI-Linac” AND “functional / quantitative MRI” OR “diffusion-weighted imaging” to assess the current status of functional MRI using combined MR-Linacs. Search results were screened for original papers. Reviews and studies investigating issues related to stand-alone MRI scanners during RT were excluded from analysis.

3. Results

A total of eight articles were found during the literature research, out of which two were review articles focusing on the management of lung cancer using MR-Linacs [31] and on the technical challenges when implementing functional MRI [34]. Two articles were not related to combined MR-Linac systems. After curation of the search results, four articles were reviewed and will be discussed in the following.

3.1. 0.35 T MR-Linac / MR-guided tri-cobalt 60 system

Yang et al. [38] have demonstrated the general feasibility of acquiring longitudinal DWI on the combined 0.35 T MRI-guided tri-cobalt 60 radiotherapy system, the precursor of today’s 0.35 T MRI-Linac. In this study, a multi-slice spin echo single-shot echo planar imaging (EPI) pulse sequence to measure diffusion was implemented and tested in phantom studies. Tests were performed on the diffusion phantom recommended by the Quantitative Imaging Biomarker Alliance (QIBA) [37] which contains inserts with different known diffusion coefficients. Results of this phantom study demonstrated that apparent diffusion coefficients (ADC) measured on the 0.35 T MRI-guided RT system matched with the reference ADC values within $< 5\%$ error. Furthermore, this study provided proof-of-principle data in six patients with head-and-neck cancer (HNC) or sarcoma, where ADC value changes during fractionated RT were acquired and reported [38].

As DW MRI using single-shot EPI suffers not only from limited resolution but also from severe spatial distortion and potentially inaccurate ADC value determination at low field strengths, the same group developed a diffusion prepared turbo spin echo (TSE) readout sequence to measure diffusion in tumors [39]. Similarly, a QIBA diffusion phantom was used to benchmark the accuracy and repeatability of the TSE-DW MRI sequence in addition to assessing geometrical distortions using a spatial integrity phantom. The spatial integrity of the TSE sequence was shown to be $< 1 \text{ mm}$ within a radius of 100 mm which was much lower compared to the EPI sequence for DW imaging [39]. Experiments with the diffusion phantom demonstrated that both sequences provided accurate quantitation of ADC at a temperature of 0°C , which was $< 3\%$ with respect to the reference values. At room temperature, EPI-based ADC values showed 8% of variation compared to reference, whereas TSE based ADC determination was accurate within 4%. TSE experiments showed reasonable repeatability with a coefficient of variation $< 5\%$ [39]. Also in this study, proof of concept was provided for clinical usability of DW MRI using TSE sequences, although using longer acquisition times compared to EPI-based DWI, by reporting preliminary clinical experience on six patients.

Wojcieszynski et al. reported on the semi-quantitative use of MRI contrast agents to improve tumor visibility for online contouring and tracking on a 0.35 T MRI-guided RT system in 5 patients [40]. This initial report on clinical feasibility demonstrated increased signal-to-noise ratios of contrast-enhanced MRI at hybrid MRI-guided RT machines, which may be a first step towards future usage of DCE-MRI at MRI-Linac systems.

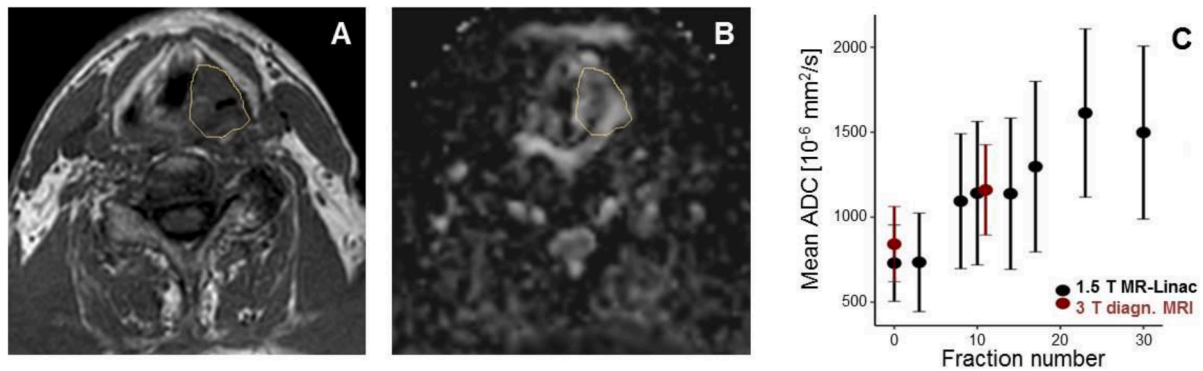


Fig. 2. Sequential DWI measurements acquired on the 1.5 T MR-Linac (Unity, Elekta AB, Stockholm, Sweden) in a HNC patient. This patient was treated in the context of a phase 2 feasibility trial (NCT04172753), which had been approved by the ethics committee of the University Hospital Tübingen, and gave written informed consent. (A) Anatomical T1-weighted MRI acquired on the 1.5 T MR-Linac after two weeks of RT (fraction 10) with gross tumor volume (GTV) delineated. (B) ADC map derived from EPI-based DW MRI ($b = 200, 500, 800 \text{ s/mm}^2$, TE/TR = 107/10392 ms, voxel size: $3 \times 3 \times 4.8 \text{ mm}^3$). (C) Mean ADC values in the tumor region sequentially assessed during the course of fractionated RT, in comparison to two DW-MRI scans acquired at a diagnostic 3 T MR scanner (Vida, Siemens Healthineers, Erlangen, Germany). The error bars visualize the standard deviation of the ADC distribution inside the GTV. ADC values are continuously increasing during RT, which may be a sign of individual treatment response.

3.2. 1.5 T MR-Linac

In a recent multi-center phantom study, the performance of the 1.5 T MR-Linac system regarding quantitative MRI was assessed [41]. In this study, four MR-Linac systems at four different institutes were used to investigate accuracy, repeatability and reproducibility of measuring T1- and T2-relaxation times, ADC values and DCE imaging using dedicated phantoms. Kooreman *et al.* showed bias and limits of agreement (LoA) of $11 \pm 238 \text{ ms}$ and $-6 \pm 63 \text{ ms}$ for T1- and T2-relaxometry, respectively. For ADC determination, a bias of $(0.007 \pm 0.027) \cdot 10^{-3} \text{ mm}^2/\text{s}$ were found in addition to a short term repeatability of $0 \pm 9\%$. A median relative coefficient of variation of 0.6 was reported to DCE MRI on the MR-Linac systems. Reproducibility was shown to be 11.2% for T1, 2.9% for T2, 2.2% for ADC, and 18.4% for DCE [41]. Consequently, this study demonstrated that quantitative MRI on the 1.5 T MR-Linac is feasible, repeatable, and accurate within the observed limits. These are important requirements for a future use of MR-Linac for response monitoring and RT interventions based on daily quantitative MRI.

4. Discussion

This literature review demonstrates that so far only a few studies were carried out to investigate the use of MR-Linac systems for the acquisition of functional and quantitative imaging [38–41]. Those few studies report that on both currently commercially available MR-Linac systems, DWI and also DCE MRI seems to be technically feasible in dedicated phantoms and also in first proof-of-concept patient examinations. Accuracy and short term repeatability was shown to be below 5% for DW MRI in the 0.35 T and also in the 1.5 T MR-Linac. Fig. 1 presents an example, where accuracy and repeatability of DWI were assessed on a 1.5 T MR-Linac using a dedicated phantom. Clinical usage of combined MR-Linacs seems to be feasible even though the systems present with MR system specifications (e.g. gradient strength, slew rate, etc.) which are different to state-of-the-art diagnostic systems, as accuracy and reproducibility of quantitative imaging has been demonstrated in first experiments.

Nevertheless, most studies so far investigated quantitative imaging characteristics of MR-Linacs only in phantom experiments. In order to overcome the first translational gap according to [36], not only technical validation in phantom studies but also clinical validation studies of proposed quantitative imaging biomarkers are needed. Therefore, systematic assessment of sequential quantitative MRI in patients with different tumors needs to be carried out as a next research step towards quantitative MRI-based personalized RT interventions. To realize this,

the MR-Linac is an optimal tool, as it inherently provides the opportunity for sequential imaging during fractionated RT. Test-retest studies in patient cohorts are required to investigate reproducibility of quantitative parameters measured on combined MR-Linacs. Such test-retest experiments in addition to studies assessing cross-correlations with quantitative MRI obtained from diagnostic MRI scanners are absolutely necessary before biomarker studies with outcome correlations can be done. In Fig. 2, a proof-of-concept data set is shown where DWI was performed in a HNC patient during RT on the MR-Linac and mean tumor ADC values were compared to those measured with a diagnostic MR system. In addition, also questions about optimal imaging time points for assessing quantitative information with prognostic information and optimal timing of quantitative MR-based interventions may be answered with patient studies at the MR-Linac in the near future.

So far published data on accuracy and repeatability of DW MRI on hybrid MR-Linacs were concerning mean ADC values averaged over bulk tumor or phantom regions [38,39,41]. However, biological interventions such as e.g. dose painting based on functional MR information measured on combined MR-Linacs require spatially resolved information about diffusion properties of the tumor to identify resistant sub-regions. To quantify the level of accuracy and reproducibility of voxel-based DW MRI on MR-Linacs, further phantom and patient studies are needed. Furthermore, not only quantitative information acquired accurately, but also reproducibly and with a high level of repeatability is required. In addition, geometrically accurate images are needed for dose painting interventions. Consequently, DWI needs to be characterized in terms of geometrical distortions. Due to potentially significant geometric distortions of $> 1 \text{ mm}$, Gao *et al.* [39] have developed and implemented a diffusion prepared TSE sequence on the 0.35 T MR-guided tri-cobalt 60 system. This sequence does not suffer from geometrical distortions but comes with much lower signal-to-noise ratios, which causes much longer acquisition times. Therefore, optimal quantitative imaging protocols suitable for longitudinal patient studies need to be carefully selected to provide optimal trade-offs for different aspects providing geometrically useful, accurate information measured in a realistic time frame. However, sequence parameters need to be chosen in a way to take into account the technical characteristics and related limitations of the respective MR systems and may thus differ from settings of comparable sequences on modern diagnostic MRI scanners.

In conclusion, first studies have shown the potential of combined MR-Linacs for quantitative imaging providing accurate and reproducible functional information in tumor tissues comparable to diagnostic MR scanners. With the ability of providing sequential functional information

during the whole course of fractionated RT, geometrically aligned with the RT plan, future use for investigating prognostic quantitative imaging biomarkers appears feasible. However, as most studies so far presented only phantom experiments, test–retest studies in clinical cohorts are required as a next step towards quantitative MR-based RT interventions.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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