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The future of MRI in radiation therapy: challenges and opportunities for the MR community

On behalf of the ISMRM MR in Radiation Therapy Study Group

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Abstract

Radiation therapy is a major component of cancer treatment pathways worldwide. The main aim of this treatment is to achieve tumour control through the delivery of ionising radiation while preserving healthy tissues for minimal radiation toxicity. Since radiation therapy relies on accurate localisation of the target and surrounding tissues, imaging plays a crucial role throughout the treatment chain. In the treatment planning phase, radiological images are essential for defining target volumes and organs-at-risk, as well as providing electron-density information for radiation dose calculations. At treatment, onboard imaging informs patient set-up and could be used to guide radiation dose placement for sites affected by motion. Imaging is also an important tool for treatment response assessment and treatment plan adaptation. MRI, with its excellent soft tissue contrast and capacity to probe functional tissue properties, holds great untapped potential for transforming treatment paradigms in radiation therapy. The MR in Radiation Therapy ISMRM Study Group was established to provide a forum within the MR community to discuss the unmet needs and fuel opportunities for further advancement of MRI for radiation therapy applications. During the summer of 2021, the study group organised its first virtual workshop, attended by a diverse international group of clinicians, scientists, and clinical physicists, to explore our predictions for the future of MRI in radiation therapy for the next 25 years. This article reviews the main findings from the event and considers the opportunities and challenges of reaching our vision for the future in this expanding field.

Keywords: future MR radiation therapy ISMRM workshop

1. Introduction

Radiation therapy (RT), prescribed to approximately 50% of cancer patients, is a major component of cancer treatment pathways.(1,2) The aim of RT is to deliver a sufficiently high dose of ionising radiation to the tumour to control disease while limiting the dose to healthy tissues for minimal radiation toxicity. The most common RT modality, external-beam RT, delivers megavoltage beams of x-rays via a linear accelerator (Linac) mounted on a gantry that rotates around the patient. Carefully optimised treatment plans tailor beam profiles and photon intensities to focus the prescribed dose to the target volume(s) and minimise exposure to surrounding healthy tissue.(3,4) Typically, an RT course is run over 5–30 treatment sessions, called fractions, that span 1–9 weeks. This article focuses on external-beam RT, but some aspects are also applicable to other forms of RT, such as brachytherapy and proton therapy.

Imaging is performed at multiple points in the RT treatment chain with multiple objectives, which can be broadly categorised as: “Delineation and Dosing”, “Guidance and Targeting”, and “Response and Adaptation”.(5) Delineation and Dosing goals are met by acquiring computed tomography (CT) simulation (CT-Sim) images, often with complementary magnetic resonance imaging (MRI) or positron emission tomography (PET) scans. Using these images, radiation oncologists delineate targets and radiosensitive normal tissues. Delineated targets and critical structures inform the treatment planning process that simulates and optimises the planned dose distribution. Imaging is also used to inform Guidance and Targeting during treatment delivery. Onboard imaging is a vital component of modern Linac systems, which typically employ mounted x-ray systems capable of planar images and cone-beam CT (CBCT) to align the tumour target with the position specified in the treatment plan through rigid couch adjustments each day of treatment.(6) In some cases, imaging may also be used to adjust the radiation beams to compensate for internal anatomical changes,(7) a process referred to as adaptive therapy. Because courses of RT span multiple fractions, there is room for tumour response assessment with CT, MRI, or PET to inform online or offline

treatment plan adaptation.(8,9) These imaging techniques for Response and Adaptation objectives are active areas of clinical development.

While x-ray and CT-based technologies currently dominate imaging in RT, MRI is quickly growing in this application and has significant untapped potential to improve the field. **Figure 1** illustrates conventional, state-of-the-art, and our vision for the future of RT workflows. MRI's superior soft-tissue visualisation in comparison to CT will improve Delineation and Dosing, allowing for reduced uncertainty in target localisation and, therefore, more accurate treatments with the ability to safely deliver higher doses.(10–14) The availability of functional MRI, or quantitate MRI (qMRI), techniques, such as diffusion-weighted imaging (DWI) and oxygen-enhanced MRI (OE-MRI) could add useful contrasts and may be able to identify high-risk regions of the target that would benefit from dose boosts.(15) New standards for Guidance and Targeting have been created by the recent availability of commercial MR-linac systems that allow concurrent imaging during treatment for MRI-guided RT (MRgRT).(11,16–19) Lastly, Response and Adaptation could be advanced through MRI's potential for quantifying tumour radiation sensitivity.(20) Adapting dosing to treatment response between fractions may improve patient outcomes and could be achieved either using diagnostic MR systems(21) or MR-linacs.(22)

This article is a summary of the findings from a 2021 workshop held by the ISMRM MR in RT study group on the future of MRI in RT. The aim of the workshop was to explore study group members' predictions for the future of this expanding field in 25 years' time. An international assembly of MRI and RT scientists, clinicians, and clinical physicists met virtually to discuss the long-term opportunities and challenges of this expanding field of research. Given the nature of this topic, some predictions are based on current literature, but we also consider the consensus of expert opinions at the workshop, for which limited literature is available to cite. Here, we reach out to the MR community to elucidate the unmet needs that must be addressed for our vision in **Figure 1** to become a reality.

It should be noted that due to the tremendous flexibility of machine learning approaches, these will often be at the core of this article's suggestions for overcoming the limitations of MRI in RT. However, where machine learning is applied in future clinical workflows, a consensus should be established on the validation, testing, and quality assurance (QA) of the techniques.(23) Despite its great potential, machine learning should not be thought of as a silver bullet. It is well documented that machine learning solutions can behave poorly, for instance, when input data are out of distribution.(24,25). It is therefore important we are prepared to address this secondary set of challenges for clinical implementation.

2. Delineation

Delineation, or contouring, is performed by radiation oncologists using a combination of CT-Sim and co-registered MRI or PET scans to outline a set of 3D contours (i.e., treatment targets and critical structures). These contours are defined by ICRU(26) guidelines, and include the gross tumour volume (GTV), clinical target volume (CTV), planning target volume (PTV), and selected normal tissues, termed the organs at risk (OARs).(27) As illustrated in **Figure 2**, the GTV represents the extent of the primary tumour revealed by imaging and is outlined manually. The CTV extends the GTV to account for invisible, sub-clinical spread. A predefined GTV-to-CTV margin is typically used, although, depending on the treatment site, the CTV may instead be manually contoured or defined by the entire involved tissue (e.g., the prostate). The purpose of the PTV is to ensure CTV coverage, and it is built by adding additional margins that account for uncertainties in delineation, patient setup, physiological motion, and treatment delivery.

Autocontouring

Despite being labour-intensive(28,29) and frequently resulting in large inter- and intra-observer variations,(30,31) delineation of target volumes and OAR structures is conventionally performed manually. Machine learning-based, automated contouring (autocontouring) is one popular solution(32,33) that is currently being introduced in daily

practice. It promises greater reproducibility and accuracy of delineated structures, with a substantial reduction in clinical burden. Today, the feasibility of autocontouring treatment targets(28,34–39) and OARs(34,40–42) using MRI has been demonstrated and commercial solutions are rapidly being released. However, the success of autocontouring over the coming years will rest on balancing clinical, industrial, and regulatory interests.(43)

Automated contouring must be robust and flexible for clinical implementation to be feasible. For instance, autocontouring models should be able to rapidly adapt to new imaging protocols, without the need to obtain and annotate a new training set. Future solutions may include generating large sets of synthetic data with the desired contrast for training using generative adversarial networks (GANs) (41,44–46) and/or employ protocol-agnostic networks.(47,48) Autocontouring tools should also be able to handle inter-scanner differences, such as model, field strength, vendor, etc. Such flexibility would allow inter-institutional cooperation and access to vast heterogeneous training data across multiple centres. Therefore, federated learning, a technique for training deep neural networks in a decentralised fashion without exchanging original data between sites, could provide an invaluable resource in developing autocontouring solutions.(49)

For MRgRT on the MR-linac, the need to achieve low-latency autocontouring for mid-treatment tumour tracking presents another set of challenges. Because adapting targets to real-time changes make clinician approval infeasible, automated QA tools will be needed. Machine learning-based techniques for detection of erroneous or anomalous delineations(50) or delineation uncertainty maps offer solutions here.(51,52) State-of-the-art, online planning assisted with these tools could augment human review in treatment planning and allow smaller treatment margins by reducing inter-observer variation.

New contouring paradigms

An inherent limitation of RT delineation is that treatment volumes depend on the imaging modality or contrast employed. Specifically, GTVs extend only as far as what

can be revealed by the imaging and GTV-to-CTV margins must provide a conservative estimate of undetected microscopic expansion, sometimes several cm in magnitude.(53) In the future, advanced application of cutting-edge MRI methods (see **5 Quantitative MRI**) may hold the key to safely reducing GTV-CTV margins through improved visualisation and/or understanding of the underlying biology. These advances might allow novel contouring concepts to be implemented clinically, such as probabilistic margin optimisation(54) or even contourless planning. With changes in delineation concepts (including autocontouring), new methods for performing clinical evaluation of contours will also be needed. Geometric measures for evaluating contours (e.g., Dice similarity index) will no longer be clinically relevant.(55) Alternatively, dosimetric comparisons could be made compared with plans generated with ground truth reference contours (55–58).

The clinical implementation of new contouring paradigms relies on histopathological validation and large clinical trials so that standards and guidelines may be developed.(59) In transitioning to new contouring paradigms, the MR and RT communities will need to first determine target definitions by asking what should be delineated and why. Second, we must establish whether a delineation task can reliably be achieved. Third, how new contours are employed for dose prescription must be addressed. All three aspects would ideally form one consistent and robust clinical strategy.

Unmet needs

- Development and optimisation of autocontouring methods that are robust with heterogeneous inter-institutional data
- Clinical QA solutions for safe autocontouring for mid-treatment tumour tracking
- A re-examination of how target delineations are defined in collaboration with the RT community

3. Dose Calculation

Dose calculation is the computation of energy deposited by ionising radiation in the patient (i.e., radiation "dose"). Following delineation, treatment planning software is used to simulate the interaction between the patient and the planned treatment x-ray beams. An iterative process is used to update the beams to optimise the calculated dose in tumour targets and OARs. To model photon scatter and absorption within the patient, information is needed on the tissue elemental composition, where this is conventionally derived from dedicated CT imaging. In state-of-the-art RT and in the future, so-called synthetic CT (sCT)—CT-like images derived from MRI—will facilitate MRI-only workflows(60) and adaptive replanning on MR-linac systems(61) by providing up-to-date sCT maps free from registration errors. In addition, hybrid PET/MR systems give rise to a similar need for attenuation correction (62), where the culmination of research in both areas advances sCT generation techniques.(63)

While MRI cannot directly measure x-ray attenuation, many techniques for generating sCT have been proposed in the literature(64) and vendor-provided solutions already exist for sites such as brain and pelvis.(65–67) However, commercial sCT solutions are not available for more complex anatomies, such as the thorax, or tumour sites close to abnormal bony anatomy.(68) Where most vendor solutions are based on bulk density overrides or atlases, recent sCT research approaches employ machine learning architectures, such as GANs(63,69–72) that may provide solutions for more challenging datasets and anatomical sites. As discussed in the previous section, successful clinical implementation of machine learning-based methods for use in treatment planning will depend upon their robustness to clinical variability, such that they meet the quality standards defined by consensus guidelines,(12) and the development of suitable QA phantoms for end-to-end testing.

Today, sCT image volumes are designed to match the resolution and axial orientation of CT image volumes that are anticipated by the treatment planning software. Planning systems may soon be adapted to more conveniently handle other orientations that are facilitated by MRI(73) and, later, four-dimensional (4D) sCT or MRI-based motion

signals may inform the simulation software for more advanced treatment planning in moving anatomies.(74)

Looking further ahead, sCT may be only a steppingstone on the way to a new RT paradigm. One day, sCTs may never be directly reconstructed or seen by operators but, instead, *k*-space data fed to the planning system algorithm to generate a treatment plan using predefined library matching or machine learning approaches. On the other hand, reconstruction of synthetic electron density images might never leave treatment chains totally as intermediate representations may be key for optimal performance.(75) Moreover, human supervision of key intermediate steps will be needed for QA purposes and so is likely to remain desirable for years to come.

Unmet needs

- 4D-sCT methods suitable for adaptive MRgRT in complex anatomies, such as thoracic sites

4. Image Guidance

Image guidance is the process of using imaging at the treatment phase to inform up-to-date localisation of tumour targets and healthy tissues. Modern Linacs typically house onboard CBCT to facilitate alignment of the targets to the treatment plan model at the start of each fraction.(6) However, conventional image guidance is limited by poor soft tissue contrast and lack of online motion characterisation.(76) Residual targeting errors are generally accounted for by CTV-to-PTV margins, although large margins limit the dose that can be safely delivered while sparing nearby OARs.(77) Hybrid MR-linac systems promise to reduce PTV sizes through the superior localisation and targeting afforded by onboard MRI.(78) Accurate, low-latency motion characterisation will facilitate gated treatment,(79) tumour tracking during irradiation,(80–84) and could enable real-time adaptive replanning. Such precise treatments, delivered to smaller PTVs, will permit safe dose escalation(85,86) and hypofractionation(87) to improve patient outcomes and clinical efficiency. Moreover, management of bulk patient motion with real-time MRI could remove the need for uncomfortable immobilisation devices.

4D-MRI

In the RT context today, 4D-MRI generally refers to respiratory-correlated 3D-MRI, with image volumes acquired over several breathing cycles and retrospectively binned into respiratory phases.(88) Potential applications of motion characterisation using 4D-MRI include onboard treatment plan adaptation and retrospective dose calculations, where 4D-MRI serves as a precursor to volumetric real-time imaging.(79)

In the future, respiratory-correlated 4D-MRI could be replaced by truly time-resolved 4D-MRI (i.e., volumetric real-time imaging(88)), with potential applications in tracking, gating, and real-time dose monitoring. Current developments include employing motion models built from prospectively acquired 4D-MRI(89) to rapidly generate synthetic 4D-MRI updated by 2D imaging of the motion perpendicular to the treatment beam.(83) Alternatively, the use of higher-order surrogate signals(90) can resolve signal characteristics beyond respiratory motion,(91) enabling simultaneous resolution of peristaltic motion(92) or cardiac motion to aid cardiac gating for MRgRT of ventricular tachycardia.(93)

Real-time MRI

To fully realise the potential of motion management for MR-guided adaptive targeting, low-latency, high-fidelity data for precise spatial-temporal localisation is desirable. However, low-latency goal differs for each motion type. For instance, cardiac motion is on the sub-second scale, while organ filling extends over minutes.(76) Recommendations have been made for MRI latencies of 200-500 ms for respiratory motion,(94) although how fast this could be and still make a clinical impact is an open question that must be revisited as research progresses. Currently, when mid treatment adaptation is desired, time-resolved 2D MRI images are often obtained, rather than 4D-MRI.

Real-time adaptive image processing for MRI is an area of ongoing research.(95) To minimise latency, the amount of acquired data per frame must be reduced, which could be aided by accurate spatiotemporal motion models.(96,97) An alternative could be the

use of suitable low-rank subspace constraints,(98) or sparsely sampled *k*-space data interpreted by compressed sensing.(91) However, most of these accelerated MRI acquisition techniques, the gain in acquisition time results in longer reconstruction times. Fortunately, machine learning approaches that transfer computational processing to offline training of a network(99–102) may overcome long reconstruction times of accelerated acquisitions. In the future, latency may be further reduced when patient representations for treatment planning and image guidance may be composited from models that extract various representative states and their probabilistic variations. Tighter integration will gradually lift the need to exchange information between MRI scanners and Linacs in the form of images, opening opportunities for reducing latency through direct contour tracking from raw MRI data.(58,103)

Opportunities and challenges of real-time imaging for MRgRT are shared by interventional MRI.(104) We should therefore ensure that both fields learn from one another as solutions are explored in the coming years. Another area that will benefit is MR-guided proton therapy, where a full characterisation of target and OAR motion is crucial since steep dose gradients exist not only perpendicular to the beam, but also along the direction of the beam.(105)

Unmet needs

- Low-latency, high-fidelity precise spatial-temporal localisation of target volume and organs at risk
- Rapid online reconstruction of highly undersampled MRI data
- A tighter integration of MRI and RT systems for adaptive planning informed directly by *k*-space

5. Quantitative MRI

Biomarkers derived from quantitative MRI (qMRI) techniques allow for non-invasive assessment of morphological, biological, and functional processes in tissue and therefore promise several key roles throughout RT workflows.(106) First, qMRI could improve visualisation for delineation by incorporating advanced contrast mechanisms.

Second, qMRI biomarkers promise to provide metrics for RT response to allow adaptive treatment based on physiological responses(9) (e.g., necrosis) that manifest earlier than anatomical imaging features.(21,107) For instance, changes in cell density—a well-established marker for early response detection—can be measured indirectly using DWI for early response detection.(9) Third, qMRI techniques may offer a surrogate for tissue dose sensitivity, such that treatment dose boosts can be informed and adapted according to baseline measurements.(108) Several recent articles have been published on the use and level of evidence for different qMRI techniques in RT.(103,106,109) We particularly refer to Table 1 in (103).

MRI-derived biomarkers

An active area of MRI research that works to detect radiation sensitivity is the investigation of hypoxia, a well-established and important prognostic marker for radioresistance. Hypoxic tissues require up to threefold greater doses to achieve the same biological effectiveness.(110) Although there are several MRI approaches for assessing oxygenation (pO_2), they are predominately indirect. Tissue water T_1 is sensitive to pO_2 since the oxygen molecule is paramagnetic. The effect is small, but recent pre-clinical work demonstrated the feasibility of stratifying tumours based on pre-irradiation oxygen gas breathing to predict long term tumour control following radiation.(108) Meanwhile, T_2^* is strongly influenced by the concentration of deoxyhaemoglobin. Perfusion is also an indirect marker for hypoxia, which can be measured using dynamic contrast enhanced (DCE), arterial spin labelling, or intravoxel incoherent motion. A more direct way of measuring pO_2 is with dynamic oxygen-17 MRI;(111) however, this technique is expensive and suffers from weak SNR and so has not been commonly investigated.

Other commonly investigated qMRI techniques for RT include chemical exchange saturation transfer (CEST) and MR spectroscopy.(103) Recent analysis suggests radiation dose could be effectively adapted using a genomic-adjusted radiation dose model(112) and active investigations seek similar capabilities based on radiomics.(113) Ultimately, we believe a combination of several techniques will allow us to sample

complimentary information on the state of the tumour. These data will allow clinicians to generate better personalised treatment plans than ever before: targeting dose to (hypoxic) radioresistant tumour regions and reducing dose to regions it is no longer needed.

We expect that the impact of qMRI development for RT will not only improve RT outcomes but allow RT in cases that are currently considered unsuitable. For instance, lung cancer patients with severe lung function loss are often limited to surgery due to the risk of damage to remaining healthy tissue. However, with qMRI in combination with ventilation of hyperpolarised gases, functional regions of the lung can be clearly identified and considered, enabling RT as viable treatment in these patients. (114–117)

From research tool to clinical tool

Currently, qMRI for RT is predominantly a research tool, with most work focusing on establishing a link between MRI and treatment response. To translate qMRI to clinical use, the next step will be establishing quantitative imaging biomarkers (QIBs) from qMRI parameters. The general imaging biomarker roadmap of O'Connor et al. provides a useful framework for these next steps,(118) where there must be a transition from a promising QIB, to a potential QIB, and ultimately towards a clinically validated QIB.(119)

Today, evidence for QIBs in RT is limited: complex logistics and the added patient burden of extra MRI examinations(103) mean that analyses are often based on small patient cohorts or very few time points. To overcome these difficulties, functional imaging data for QIB studies could be collected on MRgRT systems at the time of treatment. Through systematic measurement of qMRI across treatment courses, large collaborative libraries could be built to detect which qMRI techniques generate truly prognostic QIBs. Such an initiative would require large collaborative networks that include experts from both MRI and RT communities, such as the Elekta MR-linac consortium, to collect data prospectively and systematically over many years. To supplement this, robust data-science frameworks should be established, which are often overlooked in qMRI studies.

When the prognostic value of a set of qMRI parameters has been systematically demonstrated in a large cohort, the next step of clinical validation is confirmation that the qMRI method also has predictive value (i.e., can be used to modify treatment). Investigations into predictive value can be conducted using interventional trials that adhere to the RT idea, development, exploration, assessment, and long-term evaluation (R-IDEAL) framework.(120) Although we must first ensure that any unknowns are first solved, like how qMRI parameter maps are translated into the dose prescription.

To systematically study the relation between qMRI parameters, dose, and treatment response requires comparing qMRI with clinical outcome measures at different treatment dose levels. Some insight can be gained by comparing results between periods where guidelines for dose prescriptions changed or countries that prescribe differing treatment doses. Ultimately, however, qMRI validation requires randomised trials with variable dose. Setting up such trials is challenging since current dose levels are the accepted clinical standard. Changing doses could benefit some patients but could result in a worse outcome for others. Therefore, informed, careful patient selection, and close collaboration between qMRI experts and oncologists will be essential. In particular, radiation oncologists should have a more advanced understanding of the underlying qMRI mechanisms so that they can be comfortable in adapting treatment.

Initial efforts towards consensus guidelines for qMRI on MRgRT systems have recently begun.(22) However, the current focus of qMRI in RT is on the target volume, where QIBs that monitor normal tissue toxicity(121) could be further explored. To further develop guidelines for RT QIBs, there are opportunities to learn from and work with the diagnostic qMRI community, building on pre-existing work. Such opportunities include initiatives for accurate and reproducible qMRI,(122) learning from the Quantitative Imaging Network,(123) and guidelines from the Quantitative Imaging Biomarker Alliance (QIBA) on DWI and DCE-MRI.(124) In adapting diagnostic recommendations for RT, we must remember that MR-linacs differ from conventional MRI systems.(125,126) For instance, images from MRgRT systems typically exhibit a lower signal-to-noise ratio

(SNR) than those obtained using diagnostic devices, and sometimes have unconventional field strengths.

Adaptive treatment

One major opportunity for qMRI which arose with the onset of MR-linac systems is daily tumour biology-based treatments. For instance, the availability of real-time qMRI techniques could improve RT efficacy by allowing treatment to be timed to when the tumour is at its most sensitive to irradiation, such as outside of hypoxic periods.(20,127–132) MRI might also be used to directly enhance treatment. For instance, radiation sensitivity could be increased with drugs targeted to the tumour tissue with MRI, using a similar approach as MR targeting.(133) Alternatively, hypoxia could be reduced by breathing hyperoxic or hyperbaric oxygen,(134) with qMRI used to confirm normoxic status.

Another application of qMRI in RT could be real-time visualisation of biological dose. Since radiation dosimetry can be assessed in vitro using Bang gels, one can envisage extension to in vivo applications.(135) Through a deeper understanding of the short-term effects of dose on tissue, we may find an MRI contrast mechanism, such as CEST or DWI, is sensitive to the short-term biological effect of the treatment beam. Such qMRI methods could be used for validation and adaptation of the planned treatment.

Protocol optimisation

The image quality of qMRI is notoriously poor when compared to conventional MRI. Because multiple images must be obtained to model and measure signal changes, image resolutions are low despite long acquisition times. Therefore, clinicians often prefer conventional MR images for tumour assessments. Technical improvements in acquisition speed and image quality will hence greatly aid implementation of qMRI in clinical workflows.

For state-of-the-art RT on MR-linacs, faster qMRI is imperative. Today, qMRI measurements are acquired during the opportunity-time created by manual contouring. With the adoption of autocontouring (see **2 Delineation**), the time available for qMRI

measurements for MRgRT will be shortened as this is used more clinically. Methods such as MR fingerprinting,(136) model-based image reconstruction,(137) and MR-Spin Tomography in Time-Domain(138) could enable substantially shorter acquisitions and could yield higher resolution qMRI images with improved accuracies. However, shorter acquisition times often come with a trade-off of longer reconstruction times. For online applications, the solution may be machine learning-based methods that permit rapid reconstruction,(102,139,140) and modelling(141–143). Ultimately, we may measure QIBs in tumours directly from under sampled raw *k*-space data to meet the goal of real-time monitoring and treatment adaptation.(144)

Unmet needs

- Established, standardised QIBs for RT derived from qMRI parameters
- Demonstration of the predictive value of QIBs across large multi-center cohorts
- Accelerated pipelines for acquisition, reconstruction, and interpretation of qMRI
- Improved image quality of qMRI parameter maps

6. Hardware

MRI for RT

Standalone MRI systems may be used for simulation imaging (i.e., MR-Sim). Compared to conventional diagnostic MRI scanners, these pre-treatment imaging systems must meet additional RT-specific requirements.(145) For instance, high spatial accuracy is important as geometrical image distortions can lead to under-exposure of the tumour site and unnecessary dose to healthy structures.(144) Geometric fidelity depends on magnetic field homogeneity and gradient linearity, which are typically worse at higher field strengths and can be compromised by the integration of the Linac system.(146) Unlike in diagnostic MRI, the geometric fidelity of MR images is critically important for RT applications. The implementation of MRI for RT has therefore largely focused on minimising and charactering(147) distortions as new techniques and QA procedures were developed.(148) Today, this issue is largely solved, but will remain an important factor to consider as the technology develops.

The installation of conventional MRI systems in RT departments can be complex and costly. Large scanner weights, the need to incorporate a quench pipe in shielding designs, and the undesirable interaction between MRI fringe fields and nearby Linacs are often challenging factors, and the need for MR-Safe(149) immobilisation devices and other devices (e.g., intravenous-contrast pumps) further adds to the cost. In addition, wide scanner bores are required to accommodate immobilisation equipment.

Several recent developments can help adapt diagnostic systems for RT purposes. The industry has recently developed diagnostic MR scanners with low helium content (e.g., < 8 l), which offer lower installation costs, reduced environmental impact, and no need for a quench pipe.(150) Another example is the increased use of low-field scanners, which can improve geometric accuracy.(151) However, improved geometric accuracy must be balanced with SNR loss and poor image quality below 1 T (particularly for qMRI). One possible future solution to boost low-field SNR is machine learning driven reconstruction.(152)

MR-linac systems

MRI is also present in RT in the form of MR-linac systems. These hybrid systems present several engineering challenges. For instance, the influence of the MR system fringe field on the Linac must be minimised. In addition, the radiofrequency (RF) radiation originating from the Linac must be shielded from the MRI sub-system. Furthermore, the MR sub-system design must be optimised to meet radiation attenuation requirements.

Currently, two MR-linac solutions are commercially available, which have taken different approaches to the integration of an MR scanner with RT beam-generation components.(126,153) Both MR sub-systems are based on diagnostic designs, which have been modified to meet RT workflow and dosimetric requirements while maintaining imaging performance (e.g., spatial integrity). The Unity (Elekta AB, Stockholm, Sweden) MR device(154) is based on a modified 1.5-T MRI (Philips Healthcare, Best, the Netherlands). The magnet is optimised to create a surrounding annulus of a low magnetic field to enable its decoupling from the rotating-gantry-mounted ferromagnetic

components that include the beam generation sub-systems. The magnet was also modified to create a radiation window by splitting the gradient coils.(155) The MRIdian (ViewRay Inc, Oakwood, USA) system houses a superconducting, 0.35-T, split-magnet design, using ferromagnetic shielding to isolate the Linac sub-systems on the ring gantry from the magnet. In both vendor designs, the gap between the two magnet cryostat components permits megavoltage x-ray beams to pass through with very little attenuation.(153) Non-commercially available MR-linac systems have focused on bi-planar rotatable MR designs(156) and the use of a standalone magnet with a non-rotatable radiation beam.(157)

To date, approximately 200 MR-linacs have been installed, which is limited compared to the global installed base of roughly 13,000 conventional Linacs. To provide improved access to MR-linacs, it is important that they become cheaper and simpler to use in the future. There are several challenges associated with the current designs. Firstly, the MR magnet structure offers limited access to the patient table inside the bore. Secondly, the overall size, weight and cost of the MR scanner adds complexity. The footprint of MR-linac systems may pose significant demands on the construction space required, greatly increasing installation costs. Thirdly, only a very limited range of coils, with low numbers of coil elements, are available. Fourthly, state-of-the-art treatments, like volumetric-modulated arc therapy, are not yet available for MR-linac systems.

As the MR-linac market grows, optimised components may start to differ from the mainstream diagnostic solutions to become more aligned with the unique needs of RT. Future iterations of MR-linac technology may include greater use of modelling for the MR magnet optimisation problem, such that additional Linac structural and performance specifications are considered. MR-linac designs could also put more focus on requirements for maximising patient access and minimising hardware size.(158) Vendors should facilitate easy MR-linac upgrades since these are essential to enabling rapid integration of novel treatment and imaging innovations.

Conversely, maintaining a similar blueprint could reduce overheads through the sharing of manufacturing, obsolescence, and supply costs. This could be aided further by

focusing on open-source hardware.(159) Comparable designs could facilitate fast and easy translation of MRI solutions to the MR-linac domain. Another advantage is that when MR-designs are similar, less retraining is required for in-house radiology experts.

In addition to imaging performance, RF coil design for MRgRT applications must balance patient set-up and dosimetric requirements.(160) For instance, in some MR-linac designs, the RF coil elevates above the patient to reduce the excess surface dose at the expense of SNR.(161) In future designs, excess surface dose may instead be reduced by constructing RF coils with inbuilt foam boluses, which allow the coils to be positioned closer to the patient to improve SNR.(162) Low-weight coils minimise body-contour deformations and ease patient set-up.(158) Another important design consideration relates to the local beam attenuation and positioning of sensitive electronics, which limit the number of coil elements and, consequently, the parallel imaging capabilities of the MR subsystem. RF coils utilising high impedance capacitors could enable a high number of coil elements to be employed while meeting the beam attenuation requirements.(163–165) Alternatively, high-density, disposable coils that allow electronics to be directly in the path of the radiation beam could be considered. Therefore, many new coil designs could be exploited to optimise image quality for MRgRT, including wireless, flexible(165,166) and disposable RF coils, as well as inbuilt bolus designs.

Unmet needs

- Easier access to MR-Sim and MR-linac systems: simpler installation, reduced costs, and reduced footprint
- Optimised MR-linac components that are more aligned with the unique needs of RT e.g., improved coil designs

7. Reducing Patient Burden

An important aspect for the success of MR in RT is minimising patients' treatment burden. In addition to well-being, patient burden(167) includes the time, difficulty and costs devoted to healthcare. Critical components of the treatment burden are the

number of visits to the hospital (including travel-time and costs), the duration that patients must hold the treatment position, and the comfort of this position.(168)

MR guided radiotherapy

The advent of MRgRT systems has initially increased the treatment burden for patients because treatment times per session have increased substantially compared to conventional Linacs. For example, the average treatment duration for prostate cancer has increased from 15–20 min on CBCT-Linacs(169) to 45 min on MR-linacs.(170) Liver treatment on the MR-linac is particularly long, ranging from 60 to 90 min.(171) Although 45 min is a generally acceptable examination time on diagnostic MRI scanners, at MRgRT, patients are set up in the treatment position, which can include a hard flat tabletop, fixation devices such as closely fitted full-head masks, and holding uncomfortable positions (e.g., arms above the head).(73) Furthermore, patients experience increased MRI-related acoustic noise(172) and anxiety due to limited space.(173,174) With the many repeated MRgRT sessions throughout an RT course, acoustic noise has a more substantial impact on hearing than for a one-off diagnostic MRI examination.

In the future, MRgRT on MR-linac systems presents several opportunities to reduce patient discomfort. Firstly, adaptive planning using onboard MR imaging could allow the couch to be made more comfortable, where the hard flat tabletop is no longer needed for consistent set-up. Secondly, future MR-linac models could be developed with wider bores to reduce claustrophobia and aid access to the patient. Thirdly, uncomfortable setup devices may be rendered unnecessary with online MRI tracking.(101) Fourthly, future developments in MRI, tumour tracking, and gated deliveries could remove the need for breath-hold imaging and treatment deliveries.(175)

Hypofractionation

Hypofractionation, increasing the dose per fraction and reducing the number of fractions, allows a biologically similar treatment plan to be delivered in fewer hospital visits.(171) However, the challenge of hypofractionated approaches is that treatment

becomes more sensitive to patient setup errors. MR-linac systems could make setup errors smaller to overcome these limitations. Consequently, clinicians are currently attempting to increase the dose per fraction in several MRgRT protocols.(176,177) By further improving image quality at planning and real-time monitoring during treatment, we can further reduce uncertainties and gain confidence in continuing the reduction of fraction numbers. However, it should be noted that spreading dose over multiple fractions allows healthy tissue to repair itself between sessions, receiving a lower effective dose. While hypofractionated treatment regimens are showing dramatic improvements to treatment response for many disease sites,(178–180) this is only possible with excellent geometric precision and, in some instances, tumour dose spread must be more heterogeneous to ensure that normal issues are preserved.

Next-generation workflows may be a one-stop-shop for which only 1–3 hospital visits are required. Once the patient is set up, the MR-linac acquires a fast MRI, target volumes and OARs are automatically contoured and, within seconds, an automated, single-fraction, high-dose treatment plan is developed and delivered, all during a single visit (**Figure 1**). By reducing clinic visits, this approach would increase clinical throughput and improve patient experience, especially for palliative patients. At present, “day-one” treatment planning would require substantial clinical resources and automation is strongly desired.

Unmet needs

- Increased patient comfort via removal of uncomfortable elements from MRgRT treatment chains, such as hard tabletops, immobilisation devices, and breath-holding
- Faster imaging and treatment to reduce time in the machine
- Improved image quality at planning and real-time monitoring during treatment to improve confidence in hypofractionation

8. Implementation and Dissemination

The implementation of MRI in RT will be accelerated and steered by the introduction of MRgRT on MR-linacs. Currently, however, only a few RT centres have MRI scanners installed in the RT department and MR-linacs only account for a small fraction (~1.5%) of all treatment machines in clinical use. We expect that developments will initially take different directions for non-academic and academic centres. In non-academic centres with MR-Sim only, the focus will be on targeting accuracy. For non-academic centres with an MR-linac, this will be combined with fast and automated hypofractionated RT and target tracking, where hypofractionation greatly reduces the cost of RT. In academic centres, experiments will focus heavily on development for qMRI methods. As the use of MRI for RT increases, guidelines(145) for its practical implementation should be reviewed and updated.

Clinical burden

Operating an MR-linac currently requires a large team of clinical and technical experts. Centres with MR-linacs often employ an on-site clinician for recontouring, two dual-trained RT-MR technologists during treatment, an on-call MR-RT physicist, and a large group of physicists available for quality control and maintenance. Even where the additional facilities and expertise required were minimal, the increased strain on staff resources caused by using an MR-linac is often significant, with treatment times typically doubling those of conventional systems.(109) The cost of developing and maintaining new support teams for MR-linac treatments is manageable for large cancer therapy centres but could be prohibitive for smaller (2-3 Linacs), community-based radiation therapy centres, which are typical across Europe and the United States.(181,182) We therefore predict that over the next few years, MRgRT will predominantly be conducted at larger specialised centres.

For the dissemination of MRgRT and MR-Sim to non-academic centres and for long-term usage in academic centres to be successful, logistic, environmental, and staff burdens must be reduced. Simple solutions to reducing clinical burden in the future

include transferring staff training to external parties and investing in AI-assisted workflows. Looking at the big picture, efforts should be made to reduce treatment times and simplify the operation of the MR-linac. Standardised MRI acquisitions for treatment planning and motion monitoring combined with AI-driven MRI-scanning methods reduces the complexity of MR knowledge needed by radiographers.(183) Similarly, AI-driven contouring and treatment planning will greatly reduce the time and staff requirements for on-table plan adaptation of treatments.(184) Looking further ahead, the operational burden on the physics staff could be reduced by increased automation of patient treatment and QA procedures and highly hypofractionated treatment courses.(176,185) Such a workflow would resemble the ultimate minimisation in operational burden and drive the uptake of MRgRT across all radiation oncology centres. Because automated workflows remove clinical decision making and hypofractionated treatments deviate from the current clinical standard, it is of vital importance that clinicians are included in the introduction of these new approaches.

Unmet needs

- Standardisation of MRI acquisitions for treatment planning and motion monitoring
- Collaborative development of automated workflows by researchers and clinical teams
- Easy (or automated) operation of MRI and MRgRT systems

9. Concluding remarks

MRI has become indispensable in modern RT pipelines and its role is expected to grow. Advances in tumour delineation, onboard image guidance, and imaging biomarkers afforded by MRI promise to transform RT over the next 25 years. With this paradigm shift, a rich spectrum of new challenges and opportunities is presented for the MR community.

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12. Figure Captions

Figure 1: The role of imaging for radiation therapy (RT) in conventional, state-of-the-art, and future workflows.

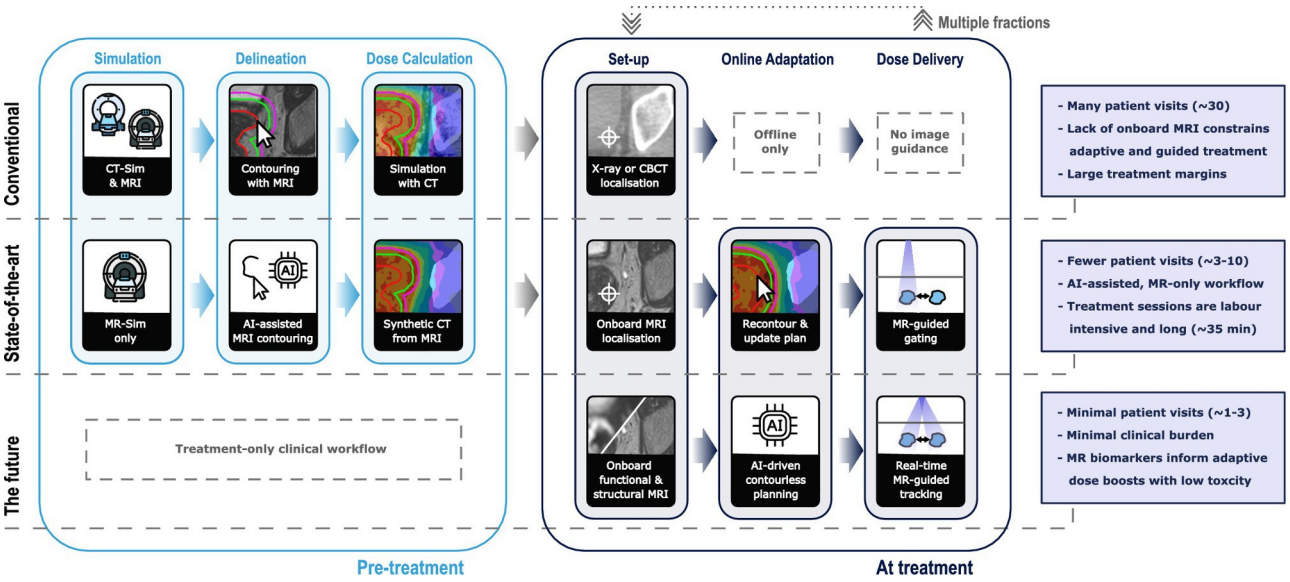
The conventional workflow (top row) begins the pre-treatment phase by scanning the patient in a computed tomography simulator (CT-Sim), where the patient set-up for treatment is simulated using the same flat-top coach and positioning devices. MR scans are also acquired and registered to the CT images. Target volumes are delineated manually on MRI and dose distributions are simulated and optimised using the CT images. At treatment, patient set-up on a Linac system is aided by onboard cone-beam CT (CBCT) or planar x-ray. The patient must return daily for repeated treatment fractions over the course of several weeks.

The middle row illustrates a state-of-the-art RT treatment chain. This MR-only workflow replaces CT-Sim with MR-Sim, reducing the burden on hospitals and patients. Artificial intelligence (AI) assisted contouring increases the efficiency and reliability of delineation (**2 Delineation**). Treatment plans are calculated using synthetic CT generated from MR-Sim images, eliminating CT-MRI registration errors (**3 Dose Calculation**). At treatment, hybrid MR-linac systems (**6 Hardware**) will facilitate the safe reduction of treatment margins via MRI-informed adaptation to the daily anatomy and gated deliveries for moving targets (**4 Image Guidance**). Treatment sessions are more labour intensive than conventional treatments but could lead to fewer patient visits overall (**7 Reducing Patient Burden**).

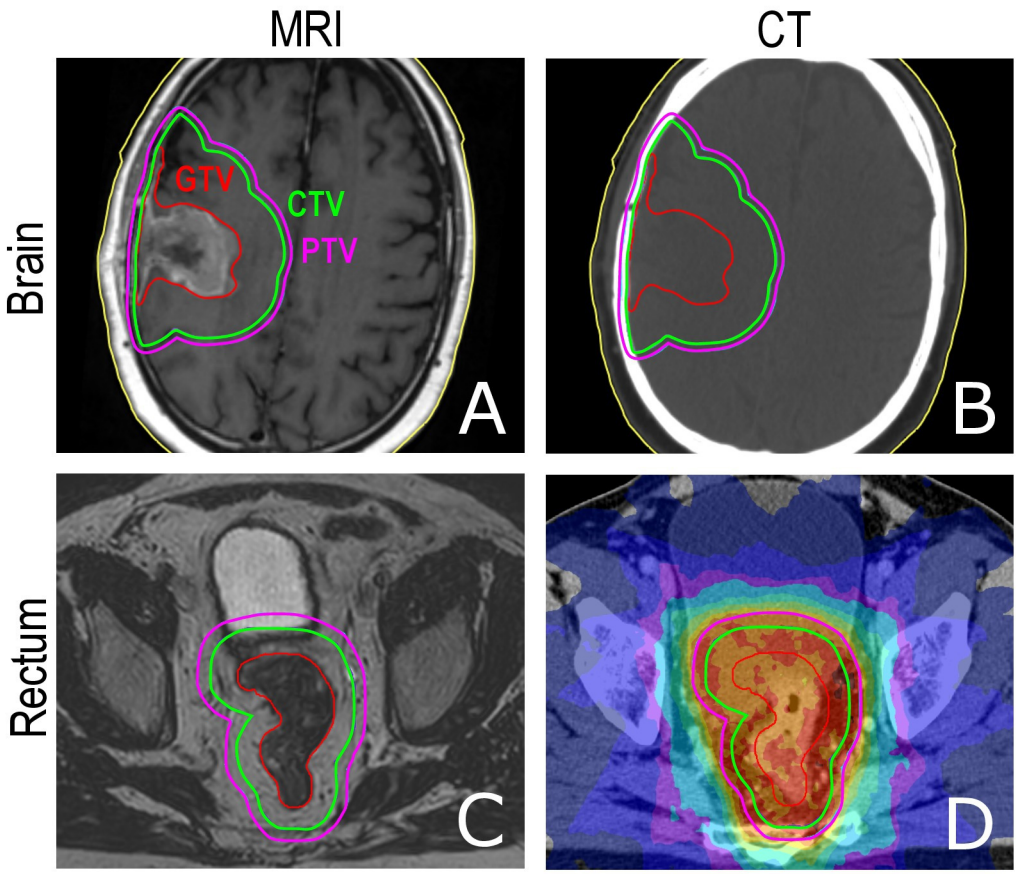
In the future (bottom row), an MR-linac-only workflow without a pre-treatment workup may be possible, where planning and treatment delivery is performed within minutes on the same system. Functional and structural MR imaging could inform AI-driven

algorithms to generate plans without input from clinicians. MR-derived biomarkers (**5 Quantitative MRI**) hold the potential to establish new, contourless dose planning approaches, with information now available to inform the safe delivery of high-dose boosts to targeted regions. Treatment plans could be delivered rapidly via real-time MR-guided tracking to continuously irradiate the target and safely (precisely) deliver dose distributions with steep spatial gradients. The presented workflow would greatly reduce patient and clinical burden (**8 Implementation and Dissemination**).

Figure 2: **A-B:** Radiation treatment contours for a patient with brain cancer. Here, the GTV (red) is contoured based on visible tumour tissue on MRI (**A**). The CTV (green) encompasses the GTV to account for subclinical spread not visible on imaging, based on anatomy and biological considerations. The PTV (magenta) is designed to account for patient set-up errors and beam inaccuracies, to ensure the prescribed dose is delivered to the CTV. The CT images (**B**) are not suitable for contouring here but are needed to provide electron density information for dose calculations. **C-D:** Radiation treatment for a patient with rectal cancer. Again, the GTV is contoured based on MRI visibility (**C**). The MRI is registered to a CT image, which is used to calculate and optimise the planned dose distribution illustrated by the colourwash overlay (**D**). Note that the CTV-PTV margin is large compared to the brain site treatment due to greater set-up uncertainty and intrafraction motion.



mrm_29450_figure_1.eps



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