Integrated MRI-guided radiation therapy: Opportunities and challenges

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Abstract
Magnetic Resonance Imaging, or MRI, can categorize cancerous and healthy tissues both anatomically and functionally with high spatial and temporal resolution. This non-invasive biological probe has been integrated with a radiation therapy device that can differentially target the most aggressive and resistant regions of the tumor. These treatment devices, combining imaging and targeting, have recently been clinically deployed, making the aspiration of integrated MRI-guided radiation therapy (MRIgRT) a reality. The two main clinical drivers for the adoption of MRIgRT are the ability to image and adapt to the patient anatomy changes that occur before and during treatment, and to also adapt to the biological characteristics of the tumor. Motion management and biological targeting can improve patient outcomes by increasing the radiation dose delivered to the tumor to improve the chance of cure and simultaneously reducing the radiation delivered to healthy tissue, thereby reducing treatment related toxicities. Together, the benefits are expected to result in increased survival and quality of life for cancer patients. In this review we describe MRIgRT as it is today, and the opportunities and challenges of this new weapon in the fight against cancer.

Key points

- Radiation therapy balances delivering dose to the target for therapeutic effect whilst minimizing damage to healthy tissue. However, human and cancer anatomy and physiology are dynamic, challenging our ability to image and target cancer during radiation therapy.
- MRI-guided radiation therapy (MRIgRT) images patients with MRI during treatment delivery enabling more precise cancer targeting with radiation, avoiding surrounding healthy tissue.
- MRIgRT enables differentially targeting tumor regions with higher radiation dose, providing new options to treat the most aggressive and resistant regions of the tumor.

- MRI-Linacs, which are MRIgRT devices that have integrated an MRI scanner and linear accelerator, are rapidly being clinically deployed: the opportunity for outcome improvements comes with the challenges of added complexity and cost.
- Rapid clinical utilization of MRIgRT is currently limited by increased capital, treatment and staffing costs and the paucity of medium to long term clinical data.

Glossary

Linac: A portmanteau of linear accelerator, a device that accelerates charged particles to create x-rays and delivers radiation therapy.

MRI: Magnetic resonance imaging, a widely used medical imaging procedure that measures magnetic properties of tissue. Often disease tissues, such as cancer, has different magnetic properties than surrounding healthy tissue, allowing for it to be precisely located. The location of the diseased tissue within the body is used for targeting disease with treatment beams during radiation therapy.

MRIgRT: MRI-guided radiation therapy, a process of exploiting the soft tissue imaging and flexibility of MRI for targeting disease, predominantly cancer, with radiation. Although MRIgRT can be used for pre-treatment cancer imaging and to measure treatment response, MRIgRT in the context of this paper focuses on the rapidly growing application of MRI guidance whilst a patient is receiving radiation therapy, enabled by MRI-Linacs.

MRI-Linac: An MRIgRT device that has integrated an MRI scanner and linear accelerator.

OAR: Organs at risk, healthy structures within the human body that are close to the tumor and at risk of being damaged during the radiation treatment.

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Magnetic Resonance Imaging, or MRI, can categorize cancerous and healthy tissues both anatomically and functionally with high spatial and temporal resolution. Imagine combining this non-invasive biological probe with a treatment device that can differentially target the most aggressive and resistant regions of the tumor. These treatment devices, combining imaging and targeting, have recently been clinically deployed, making the aspiration of integrated MRI-guided radiation therapy (MRIgRT) a reality. In this review we describe MRIgRT as it is today, the challenges, and tomorrow's opportunities for this new weapon in the fight against cancer.

The potential of technological advances in radiation therapy to improve patient outcomes is vast. Half of all cancer patients,[1] i.e. nearly 10 million of the 19.3 million new cancer cases each year,[2] would benefit from radiation therapy to help treat their cancers. Therefore, the ongoing revolution in radiation therapy technology has massive potential to improve human health. Radiation therapy is clinically effective with a 23% 5-year local control benefit and a 6% 5-year overall survival benefit.[3] Radiation therapy is one of the most cost effective cancer therapies at our disposal, at USD$13,000 per year of life gained.[3] Furthermore, there is a trend of technological innovation in cancer radiation therapy that has positively impacted survival and reduced toxicity. Examples include:

- For lung cancer, computed tomography (CT) simulation compared with conventional simulation was associated with a 23% lower risk of death (95% CI 0.18-0.27; 9<0.01).[4]
- Four-dimensional (4D) CT and intensity modulated radiation therapy (IMRT) compared with three-dimensional (3D) CT and conformal therapy resulted in a 65% median survival increase (median 1.4 vs. 0.85 years, p=0.04) and a 72% toxicity reduction (grade ≥3 pneumonitis 7% vs. 25% at one year, p=0.02).[5]
- The CHISEL trial of stereotactic ablative radiation therapy (SABR) compared with conventional treatment showed that local tumor control was improved in the SABR group compared with the (hazard ratio 0.32, 95% CI 0.13–0.77, p≤0.01).[6]

- For prostate cancer, a prospective randomized trial of imaging patients every day before radiation therapy compared to once per week prior to therapy found that the daily imaging arm had significantly higher biochemical control and lower rectal toxicity.[7]

An estimated 16% of the radiation treatments in the UK are indicated for MRIgRT.[8] If the foundations of the model used for this estimate are sound, assuming the indication for treatments is approximately the same as that for patients, extrapolating this proportion beyond the UK leads to the conclusion that 1.5 million patients globally would benefit from MRIgRT each year. Professional society recommendations for MRIgRT[9] include tumors whereby the soft tissue contrast provided by MRI-guidance provides new opportunities for safe, highly precise radiotherapy with optimal sparing of surrounding healthy tissues. Early MRI-Linac clinical experience suggests that tumor sites that would benefit include abdominal tumors (e.g. liver primaries and metastases, pancreatic cancer, oligometastases in the abdomen), [10-12] and high risk lung tumors (e.g. central lung tumors).[13]

Three companies are marketing MRIgRT systems. One company announced in June 2020 the order of the 100th MRI-linear accelerator (MRI-Linac),[*] with a paper describing treatment outcomes for over 900 patients published in 2021.[14] Another company announced in September 2020 the treatment of 10,000 patients on their 38 installed systems.[†] Globally, there are over 13,000 radiation therapy machines.[15] Therefore, MRIgRT systems currently represent approximately 1% of the total radiation therapy machines. To treat 1.5 million patients per year, if indeed this number is a representative of the global need, another 2,000 MRIgRT systems are needed.

The two main drivers of the adoption of MRIgRT are the need to image and account for the patient anatomy changes that occur before and during treatment, and the need to differentially target the most aggressive and resistant regions of the tumor, shown schematically in Figure 1. Human anatomy is constantly in motion due to normal physiology including breathing, digesting and heartbeats. On anatomy changes during radiation therapy, a 2016 Nature Reviews Cancer paper stated "*Current state-of-the-art techniques of photon-based radiotherapy … are approaching the physical limits of shaping high doses to the target volume. However, much is yet to be gained by improving motion control and imaging for radiotherapy*."[16] Demand for motion management results of a 41-country survey commissioned by the European Society for Therapeutic Radiology and Oncology found that 71% of radiation therapy centers wish to implement real-time motion management but are limited by resources and capacity.[17] In addition to anatomy changes, cancer and healthy tissue physiology are dynamic due to changing microenvironments. Motion management and biological targeting can improve patient outcomes by increasing the radiation dose delivered to the target to improve the chance of tumor control and minimize the amount of radiation delivered to healthy tissue to limit treatment related toxicities.

Main Text

Physical challenges of integration

MRI scanners and linacs are highly sensitive pieces of medical equipment which exhibit mutual electromagnetic interference. In the words of Professor Gino Fallone "MRI and linacs are allergic to each other".[18] From the perspective of the MRI scanner, the linac represents a magnetic source that degrades the magnetic field uniformity of the scanner which is integral for imaging. In addition, the linac is a source of radio-frequency (RF) interference which can also cause image artifacts.[19]

[*] https://www.elekta.com/pressreleases/98C2D12F7FD37C58/100th-elekta-unity-mr-linac-goes-to-st-george-s-hospital-in-new-zealand/

[†] https://investors.viewray.com/news-releases/news-release-details/10000th-patient-receives-treatment-viewrays-mridian-system

Meanwhile, the linac must operate within the static magnetic fringe field of the MRI scanner. The major effect is on the trajectories of electrons during the acceleration process. This effect causes beam perturbation up to and including complete beam loss, with the exact behavior dependent on specific field that the linac is operated in. Each MRI-Linac system has adopted a different approach to overcoming these issues. However, all involve some combination of magnetic shielding or magnet redesign to lower the fringe field magnitude around sensitive linac components to ensure safe and robust operation of the linac. Of these two approaches, use of passive shielding will cause further interference with the MRI scanner which must be compensated for, whilst magnet redesign is expensive and difficult. Shimming refers to producing counter-fields to cancel out the perturbing fields and can be used to compensate for the effect of the linac on the magnetic field uniformity. Passive shimming can be used for components that do not move relative to the MRI scanner, and active shimming for the components that do. However, active shimming for moving components is particularly challenging: care must be taken to ensure perturbation from moving components can be adequately compensated on a system specific basis. In addition to magnetic shielding, RF shielding to absorb or reflect RF waves can be used to overcome RF interference.

Many variables must be considered in the design of clinically feasible MRI-Linacs, including the magnetic field strength, the radiation beam energy, the space for the patient, the RF component design, and the gradient component design. One crucial top-level design decision is whether to have the radiation beam perpendicular to the magnetic field, maintaining a more conventional MRI system, or having the radiation beam inline with the magnetic field, maintaining beam symmetry. This decision has major ramifications for every aspect of the system design, with pros and cons to each choice. A schematic with a summary of these two approaches is shown in Figure 2. Further details on the MRI-Linac design challenges can be found in refs [20,21].

As a result of these challenges, the design of MRI-Linac systems is an exercise in compromise and MRI-Linac systems tend to be less performant than their stand-alone counterparts. For instance, the linac in MRI-Linac systems has less flexibility than modern linacs and is limited to delivering beams in a co-planar geometry, which is a limitation for some treatment sites. Similarly, the MRI systems in MRI-Linacs typically compromise on at least one of field strength, field homogeneity, or gradient strength compared to a standalone diagnostic system. In general, these limitations are compensated for by the advantages bestowed by system integration, which are discussed in the rest of this review. However, it is likely that there are some situations in which superior treatment could be delivered by a modern non-MRI linac and therefore appropriate patient selection will be important.

Functional MRI-guided biological targeting and adaptive radiotherapy

MRI is a versatile technique that allows different types of images of the patient to be acquired. Recent advances in functional MRI have enabled mapping of different aspects of the tumor biology, including cellularity with diffusion-weighted/diffusion-tensor imaging (DWI/DTI), vascularization with perfusion-weighted imaging (PWI), metabolism with magnetic resonance spectroscopy (MRS) and hypoxia with blood oxygen level dependent (BOLD) and oxygen enhanced (OE) MRI.[22] The incorporation of such techniques into clinical workflows is in its infancy, but hints at the potential of integrated MRIgRT systems to personalize patient treatments. Traditionally, this biological targeting process has been performed as an “offline process” by repeatedly imaging patients in between treatments and then using this information to change the treatment plan for subsequent treatments. With the advent of MRIgRT, this biological targeting process can now be performed efficiently and immediately prior to each treatment as an “online process”. As described in the “Physical challenges of integration” section the MRI scanners in the integrated MRIgRT systems have been modified to enable integration with an accelerator. Functional imaging techniques such as diffusion-weighted MRI are available and the feasibility of more sophisticated techniques has been demonstrated.[23-26] The ability to acquire functional MRI during as part of a standard treatment workflow substantially reduces

the logistical and economical hurdles associated with scheduling multiple independent appointments for conducting MRI biomarker studies. Further, by imaging during each treatment, the response to treatment can be monitored in unprecedented detail. This integration makes MRIgRT suitable for studies investigating the prognostic value of MRI biomarkers.[27]

A particularly relevant biomarker is hypoxia[28] given the negative association between hypoxia and survival across different cancer types. While feasible on MRI-Linac systems,[24] the ability of MRI to reflect true tissue hypoxia is still to be demonstrated. In some cancers, such as cervix, head-neck, and rectal cancers, perfusion has been shown to have prognostic value. Perfusion is typically measured with dynamic contrast-enhanced and dynamic susceptibility contrast MRI. However, to avoid administering gadolinium contrast agent daily, alternative techniques based on diffusion can be used.[29,30]

One clinical site where MRIgRT holds promise for biological targeting is for brain tumors. In neuro-oncology the challenges of performing invasive brain tumor biopsies highlight the need for imaging biomarkers to measure different aspects of the tumor biology. Brain tumors are highly heterogeneous in the cell type and tumor microenvironment (Figure 3a), resulting in a poor prognosis for brain cancer patients. The biological complexity of these tumors enables them to develop mechanisms of resistance to standard therapies that ultimately lead to recurrence.[31] Standard radiation therapy protocols do not account for biological heterogeneity of the tumor tissue, as clinicians do not have the tools to integrate this information to adapt treatment. As a result, radiation therapy targets are typically delineated based only on anatomical imaging and every patient receives the same homogeneous radiation dose irrespective of the sensitivity to radiation of different tumor subregions (Figure 3b). This therapeutic approach leads to local tumor recurrence in >95% of patients with glioblastoma, due to inadequate irradiation of areas of radioresistant tumor cells.[32] Consequently, the ability to non-invasively map different aspects of the tumor biology is needed to develop personalized treatment plans that would give each patient the best chance of improved survival.

In the context of radiation therapy, the inclusion of information about tumor biology for the development of personalized treatment plans offers two major advantages. First, by improving delineation of tumor infiltration, it allows a reduction in radiotherapy target margins, which results in sparing of critical brain structures from unnecessary radiation toxicity. Second, by enabling delivery of higher doses of radiation selectively to radioresistant tumor regions, it maximizes chances of improved local tumor control (Figure 3c). This strategy enables patient-specific heterogeneous prescription doses, safely escalating the radiation dose in radioresistant tumor regions, while reducing the dose to less aggressive tumor regions and critical brain structures.[33] For instance, recent clinical evidence has demonstrated that DWI and DCE MRI performed on high-grade glioma patients during the course of radiation treatment helped identify regions of evolving treatment resistant tumor, which could be adaptively targeted with a dose escalation boost.[34]

Accelerated imaging for MRIgRT

An advantage of MRIgRT is the ability to implement a fully MRI-guided workflow that allows direct target localization during treatment. However, MRI is an intrinsically slow imaging modality compared to x-ray imaging and the acquisition of high-quality images immediately prior to treatment (i.e. pre-beam imaging) contributes to the longer treatment times for MRIgRT.[35] The implementation of tumor tracking or gating techniques, which are particularly advantageous for sites affected by respiratory motion such as the lung and liver, requires real-time imaging during treatment (i.e. beam-on imaging) with latencies typically lower than a few hundred milliseconds.[36,37]

Many advanced techniques exist to accelerate pre-beam 3D or 4D MRI.[38] MRI techniques based on compressed sensing, which assume underlying sparsity to reconstruct images from less acquired data,

have been shown to reduce pre-treatment imaging time by up to 50% for MRIgRT.[39] Increasingly, continuous acquisitions based on radial sampling techniques[40] are proving advantageous for pre-treatment imaging due to their motion robustness and the ability to trade-off spatial resolution for temporal resolution when performing reconstructions, which can be beneficial for online verification of treatment plans.[41] While pre-treatment compressed sensing acquisitions are faster, the increased computational complexity of image reconstruction[42] has spurred the development of machine learning methods to accelerate MRI reconstruction for online plan adaptation.[43,44]

The ideal imaging strategy for intra-treatment patient imaging MRI treatment systems would yield real-time 3D information of both tumor and surrounding tissues, aimed at accurately tracking the tumor as well as describing organs-at-risk (OAR) motion to best guide the treatment delivery.[45] However, the current state-of-the-art method for real-time imaging of organ motion in MRIgRT systems is fast 2D intra-treatment MRI, which is limited to the acquisition of a few slices, compromising accurate treatment adaptation for 3D motion.[46]

To obtain real-time 3D imaging, a key opportunity exists in MRIgRT to exploit the extensive prior imaging data collected for radiation therapy treatment planning purposes, shown schematically in Figure 4. Pre-treatment 4D MRI can be used to create a patient-specific model of patient breathing and combined with in-room intra-treatment 2D MRI data to derive a time-resolved 3D description of tumor and healthy tissues motion.[47,48] Alternatively, direct 3D real-time intra-treatment imaging approaches without a 4D imaging prior have also been investigated.[45,48]

Implementing 3D tracking strategies with sufficiently low latency for real-time use remains a technical challenge. Again, machine learning techniques are particularly well poised to undertake image reconstruction,[49,50] motion estimation[51,52] and tumor segmentation tasks[53] that must be rapidly completed to implement real-time, predictive treatment adaptation. Beyond fast execution, it is expected that in MRIgRT, machine learning will allow superior tailoring of image reconstruction[54] and plan adaptation[55] personalized to each patient. While translation of adaptive treatments leveraging machine learning may face initial resistance from clinicians,[55] trials will benefit from the strong support for online image processing tasks that exist within the MRI community.[56,57]

Geometric fidelity

Geometric fidelity is essential for high-precision radiotherapy. However, MR images are subject to geometric distortion. Uncorrected image distortions in MRI can cause inaccurate target volumes, misplaced radiation doses and degrade treatment effectiveness. Geometric distortions in MRI can be divided into system-related distortions and patient-related distortions.[58] System-related distortion are caused by magnetic field non-uniformity and gradient field nonlinearity. For MRI-Linacs a source of uncertainty that may influence image quality is the interaction between the MRI and linac components.[59] However, MRIs acquired during dynamic therapy (e.g., moving gantry and collimator) have been shown to have stable image quality.[60] Patient related image distortion is primarily caused by susceptibility and chemical shift differences between tissues. These distortions, which are most apparent at air-tissue interfaces and fat regions, respectively, are reduced when imaging at lower magnetic field strengths.[61] To quantitatively measure system-related distortion, phantoms of known dimensions are imaged. The distortion increases as the distance from the magnet center increases.[62] Acquisition of phase difference maps using specialized MRI sequences can be applied to provide information of patient-related distortion, which have been reported to be of lower magnitude than system-related distortions. Recent evaluations in phantoms and patients highlight that local distortions near interfaces are more prominent for higher field strengths due to the susceptibility difference across the interface.[63] Vendor-provided algorithms and some advanced models such as electromagnetic modeling and machine learning techniques have been developed to correct system-related distortions. Methods such as applying fat saturation techniques or increasing the receiver

bandwidth can reduce patient-related distortions. Studies have shown that geometric distortions should be less than 2 mm, which is still challenging to achieve for a large imaging volume.[64]

Adaptive radiation therapy for MRIgRT

MRI-Linacs provide a wealth of information before, during and after treatment delivery, which gives rise to a challenge: how should this information be efficiently incorporated into an automated decision making process? In fact, the conceptual framework, adaptive radiation therapy (ART), was envisioned over thirty years ago. ART is an open loop radiation treatment process integrating systematic feedback and monitoring of treatment variations that are then used to inform treatment plan reoptimization during the treatment course.[65] Over the past decade, technological advances in rapid computing have enabled the ART process to be performed immediately prior to treatment while the patient remains in treatment position.[66] This 'online' ART process can be implemented to respond to daily size and shape variations of the tumor and OARs that are in close proximity to the tumor, local deformation, internal status (e.g., bladder/rectal filling in the pelvis or stomach/intestinal filling in the abdomen), and respiratory motion. By responding to daily changes in patient anatomy, isotoxic-based radiation therapy (e.g., escalation or de-escalation of tumor dose to maintain a clinically acceptable risk of toxicity based on the dose to OARs) has been demonstrated with promising outcomes.[67-69]

Online ART tasks such as recontouring, plan reoptimization, quality assurance, and plan approval are essential steps of an ART process. Early iterations of online ART workflows were implemented using CT on-rails in head and neck[70] and prostate[71] cancers, with plan reoptimization based on daily anatomy yielding improved OAR sparing, particularly in compensating large OAR deformations. The advent of MRIgRT has further pushed the boundary of implementing daily online ART for reducing toxicities. Emerging data suggest that using online MRI-guided ART has improved OAR sparing and enabled tumor dose escalation for many disease sites.[72-74] For example, in SABR for localized prostate cancer, low incidence of early gastrointestinal and genitourinary toxicities was observed in both clinician measurements and patient-reported outcomes.[75] The development of ART for MRIgRT has spurred parallel advances in conventional radiation therapy. The Ethos (Varian, Palo Alto, California, USA) is an online ART platform that integrates a higher quality iterative cone-beam CT for daily dose calculation and has recently been introduced into clinical practice.[76]

Real-time dose adaptation for MRIgRT

One of the driving factors towards MRI-Linac adoption is that conventional radiation therapy typically cannot image the movement of tumors within the human body during treatment. These movements occur naturally: breathing, swallowing, twitching, and digesting. The clinical impact of these movements can result in underdosing in 18% of prostate treatments,[77] a 30% increase in the irradiated volume for lung cancer patients[78] and a lower prescription dose for 55% of liver cancer patients.[79] Therefore, dynamic cancer targeting is needed for radiation therapy to improve clinical outcomes and reduce treatment toxicities.

To address the intra-treatment motion problem, an evolving class of technologies for dynamic targeting has demonstrated lower toxicity in a matched-pair analysis[80] and dosimetric improvements.[81,82] In addition to MRIgRT[ref], a number of non-MRI technologies have been developed for tumor visualization during treatment, e.g. the Real-time Tracking Radiotherapy system,[83] CyberKnife,[84] Calypso,[85] and ultrasound,[86].[87-90] The ability of MRIgRT devices to acquire images at the time of radiation delivery makes them ideal platforms for the management of intra-treatment tumor motion. In conventional radiation therapy, tumor motion is generally accounted for by irradiating a larger than necessary volume that encompasses the entire range of movement. An alternative is to motion the motion of external markers, typically gold, that are implanted directly into patients for the purposes of guiding radiation therapy. In contrast, MRI allows the radiation target to be directly imaged and its position and boundaries to be accurately delineated during treatment. MRI-

guidance enables real-time beam adaptation techniques that can reduce the irradiated volume to one that more tightly surrounds the target and avoids the unnecessary irradiation of healthy tissue.

The most common form of real-time adaptation for MRIgRT is the gating of the radiation beam, currently implemented on the ViewRay MRIdian.[91,92] A treatment boundary is defined on a pre-treatment MRI. As real-time MRI images are acquired, the radiation beam is triggered only when the target structure is within that boundary, for example, at one phase of the respiratory cycle. Beam gating prevents healthy tissue from irradiation if a target moves from its expected treatment position.

MRIgRT devices are also well suited for more advanced forms of real-time adaptation such as multi-leaf collimator (MLC) tracking, which has been demonstrated experimentally on MRI-Linac systems.[93] MLC tracking continuously modulates the shape and position of the beam in real-time in response to motion. Like beam gating, MLC tracking ensures geometric alignment between the target and the radiation beam, but additionally, the flexibility of the MLC allows for the shape of the beam to be adapted where necessary. For example, MRI-guidance enables the deformation of the target or the independent motion of multiple targets to be monitored during treatment and MLC tracking can adapt the beam in response to these more complex anatomical changes.[94,95]

Patient and staff education and safety

As with most medical imaging procedures, the vast majority of MRI procedures are performed without incident. However, there are several risks including projectile motion and forces on non MRI-compatible body implants. Most radiation therapy department have limited expertise in bringing MRI safely into the radiation therapy environment, which has clear implications in terms of safety training. MRI-Linacs are being installed with an inner projectile zone (roughly at 30 Gauss) marked on the floor. While this floor marking serves as an important final reminder to staff and visitors unfamiliar with the dangers of a magnetic field, full safety training needs to occur before entry to the MRI room. Safety should include an understanding of the risks associated with the static magnetic field, the oscillating gradient field and the RF field.[96] Professional bodies are beginning to address these needs, although, there is still variability in the practical execution. The introduction of safety expert accreditation in diagnostic MRI is an important step and will provide a way of formalizing this training in a manner similar to radiation safety governance. However, staff training needs to go beyond basic safety training. Initially, departments are choosing to recruit or involve radiographic and physics staff with MRI experience. Commercial MRI-Linac systems have also been operating with deliberately restricted protocols. Nevertheless, to exploit the technology to its full extent within radiation therapy, this equipment needs to be used by MRI knowledgeable radiation therapy staff. This is important to address the many issues likely to arise (e.g. compatibility of devices and equipment, through to optimization of imaging sequences) and to have the ability to proactively react to images as they are acquired. In 2021 two international guidelines on the use of MRI in radiation therapy were published.[97,98] These guidelines will help define a baseline of competence and standardization from which MRI guidance can develop more efficiently. Additional efforts are underway to provide guidance on staffing and training as it pertains to MRI-Linac technology. A recent report provides a single institution framework for establishing a MRI safety program in Radiation Oncology[99] and many programs follow MRI safety standards of practice from the American College of Radiology.[100]

Health economics

Value-based healthcare is essential, regardless of the underpinning funding strategy. Whilst MRIgRT theoretically presents many advantages and can be used for any radiation therapy indication, compared to conventional radiation therapy, MRIgRT is currently more expensive,[8,101] treatments are longer, and substantial structural and staffing investments are required.[102] Careful consideration of health economics is needed to ensure successful and lasting clinical utilization of MRIgRT. MRIgRT costs should be balanced by local control and treatment outcome improvements, treatment-induced

toxicity reductions, fewer treatments per patient, redundancy of implanted markers or theater costs, and/or the expansion of radiation therapy indications. Threshold analysis determined that only slight reductions in overall side-effects are required for MRIgRT to be cost-effective compared to conventional treatment for stereotactic prostate radiotherapy.[102] The number of patients treated had the greatest impact on the analysis. However, health economics modeling is currently challenged by scarce clinical data illustrating the efficacy of MRIgRT. The lack of high-quality and long-term data is largely due to MRIgRT being in its infancy, and contributed to by variations in patient populations, treatment modalities, treatment schedules, cancer type and stage, and outcome reporting. The rapid advancement of MRIgRT technologies can also quickly outpace existing data. The lifetime and capacity of MRIgRT systems, treatment uptake, required treatments per patient, and the rate of technology improvements are also largely unknown and treatment simulation resources, physician-person hours, and potentially increased patient travel costs need to be considered.

The current MRIgRT implementation burden is high, due to the substantial capital investment, lack of MRIgRT clinical effectiveness data, and uncertainty in MRIgRT technology progression and efficiency improvements. However, conventional radiation therapy is generally excellent value; it produces 40% of cancer cures yet currently uses only 5% of the UK National Health Service cancer budget.[103]

Clinical Indications where MRIgRT has made a difference

With so many advances in radiation therapy technology over the last decade, MRIgRT enters a crowded field. How and where will MRIgRT make a difference to patients? Although clinical experience of this new technology is still in its infancy,[10] there are already some examples of patient impact. MRIgRT allows us to adapt the plan daily for those with particularly variable anatomy and examples of patient-level impact include treating prostate patients with unfavorable bowel anatomy and multiple oligometastases, where patients were treated with MRIgRT, but dosimetry simulated as if treated on a conventional linac.[104] For one patient, target coverage of their oligometastasis dropped as low as 0% for one simulated treatment without MRIgRT.[105]

On a population basis, MRIgRT is allowing us to deliver higher doses to cancers, typically in the upper abdomen, where local control after radiation therapy is sub-optimal. Early studies suggest that MRIgRT can deliver high doses to liver metastases with good local control and low toxicity.[10,104,105] Van Dams *et al.* treated 20 patients to a median dose of 54 Gy in 3 treatments with daily MRI-guided adaptation, achieving an estimated 2 year local control of 80%, no acute grade 3+ toxicities and a single late grade 3-4 event.[106]

Replication of these results in pancreatic cancer, an area where radiation oncology has historically fallen short , would be a therapeutic game changer. A multicenter retrospective study of 44 patients treated with MRIgRT showed a significant correlation between the dose delivered to the pancreas and overall survival (OS), with 2 year OS of 49% for high dose (where dose was optimized for each treatment with MRIgRT) vs 33% (p=0.03) for low dose (also delivered with MRI guidance, but with no adaptation of the dose).[12] Whilst not randomized and prone to bias, this study does support the hypothesis that overall survival could be improved by MRIgRT. A prospective trial of 133 patients is ongoing to test whether the promising results seen in the retrospective study can be replicated.[107]

MRIgRT may provide an optimal solution for hard-to-treat lung cancers, such as central lung cancers near critical mediastinal structures like the trachea and great vessels. It is feasible to deliver 50 Gy in five treatments, but the initial trial failed to meet its primary endpoint of treating in less than 80 minutes.[108] A further study with 50 patients showed that the median treatment time has dropped to under an hour with more experience, and lung tumors considered to be high risk can be safely treated with low toxicity.[13]

With ever fewer treatments per patient, one could argue that a single pre-treatment plan is less relevant and, for single treatments, makes no sense at all. The ability to create a plan immediately prior to dose delivery is logical and when offered the choice of the pre-planned or daily plan, clinicians chose the reoptimized plan over the pre-plan on up to 91% of occasions.[10,13] MRIgRT is poised to enable the most patient- and health-system friendly option – single treatment per patient. Finazzi *et al.* detail their first experience of MRI-guided single treatment lung SABR, a technique where widespread adoption has been hampered by concerns about accuracy with other platforms. Ten patients received 35 Gy in a single dose using gated breath-hold and the authors conclude that this is a feasible technique, although one that would benefit from improvements in tracking and efficiency.[109]

Where is MRI-guided radiation therapy headed?

MRIgRT technology is not static – expect to see dramatic improvements as processes become faster and increasingly automated, and technologies such as real-time beam adaptation[37] leverage the ability of the MRI imaging capabilities for major efficiency and accuracy gains.

There is a growing momentum pushing radiation therapy towards fewer treatments per patient.[110-112] One of the key drawbacks of MRIgRT is the resource-intensity required per treatment, hence fewer treatments per patient become a logistic necessity. Due to this driver, and the augmented accuracy of daily adaptive replanning, most MRIgRT treatments have five or fewer treatment sessions per patient compared with around 20 for more traditional treatments.[113]

There are several broad areas where MRIgRT may impact the lives of cancer patients in the future. MRIgRT brings gains in accuracy due to superior pre-beam and beam-on imaging which can reduce side effects, particularly where daily adaptive replanning can reduce target volumes. The increased confidence in the location and extent of a tumour directly corresponds to treating less healthy tissue. The goal of this approach is to alter the plan while it is being delivered, thereby accounting for intra-treatment dynamic changes in OAR position or tumor motion. Technical development is already underway to make this goal a clinical reality.[114,115] The most fundamental, way that MRIgRT can impact patients is to offer hope of increasing cure rates. For some cancers, doses needed to cure are not currently possible due to proximity to OARs. However, as MRIgRT can spare OARs more consistently than standard linacs,[116] this offers the prospect of isotoxic (to standard) dose escalation, keeping toxicity levels constant while escalating the dose delivered to the tumor. Ultimately, if escalated dose could be delivered accurately to the tumor with minimal dose to OARs, then very few localized cancers would be incurable.

With these tools, MRIgRT gives us the opportunity to test new treatment paradigms not currently possible on any other machine, for example, fewer treatment sessions per prostate cancer patient.[117] The Hypofractionated Expedited Radiotherapy for Men With localisEd proState Cancer (HERMES) trial[‡] will randomize prostate cancer patients to two treatments vs five treatments of MRIgRT using daily replanning and intra-treatment MRI monitoring. Other trials of few treatments per patient are planned, notably in breast cancer. Large registries of patients will go some way to support these innovations[14] but randomized trials will be required to clarify which patients have most to gain and hence should be prioritized for MRIgRT.

MRI-Linacs have integrated functional MRI. Functional MRI enables dose to be directed biologically to the area of most aggressive or resistant disease.[118] Use of multiparametric MRI would enable dose to be personalized to the biology of the tumor, including response over time, and not just to the daily anatomy of the patient.[118] The integration of functional imaging in radiation treatments creates the prospect of biologically-guided treatment personalization to improve cure and therapeutic response. Based on observed changes in the tumor, not only in size and shape, but also in its physiological

[‡] https://clinicaltrials.gov/ct2/show/NCT04595019

properties, the dose may be modified during each treatment fraction. One can hypothesize that it may benefit outcome if the treatment dose is escalated specifically in those resistant areas that persistently show diffusion restriction in diffusion-weighted MRI, while reducing dose in areas that respond, as visualized by increased water diffusion. In this way, radiation oncology may shift from a fixed treatment paradigm, where a pre-defined treatment plan is delivered, split in several equal treatments, to biology guided adaptive radiotherapy, where dose level and dose distributions are adapted daily based on functional MRI and where even the total number of treatments is decided based on response.

We have previously discussed how the biological complexity of heterogeneous brain tumors strongly affects the spatial radiosensitivity within the single tumor mass. However, it is important to remember that the biology of the tumor and its surroundings changes during the treatment course. Therefore, the next frontier in radiation treatment, biology guided adaptive radiotherapy, will use functional imaging to reduce treatment volumes, identify radioresistant tumor regions, and adapt dose prescriptions for each treatment to reflect longitudinal changes in tumor tissues radiosensitivity occurring during treatment.[119] This advanced imaging will personalize treatments by delivering radiation therapy optimized to the tumor-specific and dynamic radiation sensitive biology. This approach has the potential to improve patient survival and quality of life by increasing chances of higher local tumor control and reduced toxicity to healthy brain tissue.[120] To make biology guided adaptive radiotherapy a clinical reality, several technological requirements need to be met. First, the functional imaging modality used to map the tumor biology needs to have high spatial resolution, accurately quantify the biological parameter of interest and be non-invasive, to make serial imaging feasible without putting a burden on patient scan time. Second, mathematical relationships used to convert the imaging parameters into an optimized prescription dose need to be developed and integrated into radiation treatment planning systems. Third, to facilitate dose prescription adaptation during a treatment course, the imaging functionality needs to be compatible with the radiation treatment unit. Functional MRI is a useful imaging modality for this purpose and MRI-Linac systems are designed to fulfill all these requirements.[121] At the moment, MRI-Linac systems are mainly utilized to track anatomical motion during treatment. However, the future of MRI-guided radiation therapy is headed towards expanding their capability to biological treatment adaptation.[122]

The MRI-Linac experience has already shown that the addition of MRI-guidance enables safe dose escalation[12,13] and this can lead to improved survival.[12] The potential impact of better image guidance could be even more pronounced for charged particle therapy, shown in Figure 5. Recent studies have investigated the feasibility of integrated MRI-guided proton systems.[123,124] MRI-guidance would allow full exploitation of the physical and biological advantages of particle therapy and enable new strategies to treat deep-seated and radioresistant cancers. T Real-time detection of anatomic and pathological variations is crucial for accurately targeting the tumor while avoiding adjacent critical structures, as well as accounting for any changes along the beam path which impact dose-deposition.[123] The biological advantages of particles include the higher relative biological effectiveness compared to photons, which is highest for heavy ions such as carbon ions,[125] thus being the key to overcoming radioresistance in hypoxic tumors[125] and suppressing angiogenesis[126] and metastatic potential.[127] In this context, functional MRI can allow a virtual tumor biopsy,[128] thus assessing biological characteristics such as hypoxia, cellularity and angiogenesis,[129,130] creating new opportunities for differential targeting of biologically resistant tumors with particle therapy.

MRI-guided particle therapy will combine the ability of MRI to exquisitely visualize anatomy and biological heterogeneity with the unique dose-deposition and biological properties of particle therapy creating new opportunities to potentially improve cure by biological dose escalation. Some cancers are difficult to treat with radiation therapy, due to a combination of tumor motion and proximity to

healthy critical organs limiting the ability to dose-escalate to tumoricidal doses,[131] and biological resistance such as hypoxia,[132] angiogenesis and metastasis.[133] Unresectable cancers that may benefit from MRI-guided biological dose escalation include pancreatic, central lung, liver, esophagus, brain and oligometastatic cancers. The potential advantages of MRI-guided particle therapy can be exploited to deliver a higher biologically effective dose while avoiding adjacent critical structures, such as duodenum and small bowel in pancreatic cancer, proximal bronchial tree, great vessels and heart in central lung cancer, and brainstem, optic chiasm, and optical nerves in brain cancer.

The introduction and development of MRI-guided radiation therapy is not happening in isolation. All modern non-MRI guided radiation therapy systems have x-ray image guidance tools. X-ray guidance can create 4D patient images in less than a minute[134] and measure the target position during treatment. Effort is underway to enable time-resolved 3D images that update in real-time during treatment, aligned with the 4D MRI developments. Respiratory signal monitoring and surface imaging are becoming more common,[135] and ultrasound imaging has for some decades been a relatively cost-effective real-time image guidance modality.[86] For MRIgRT to be beneficial for a given patient, the differential technology it offers must outweigh that of competing options.

Concluding section

Radiation therapy is an exciting medical specialty. It is at the fusion of fast-growing knowledge and development areas of technology, biology, and clinical care. The adoption of integrated MRI guided radiation therapy has advanced patient care, solved technical challenges previously deemed unworkable, and stimulated improvements in non-MRI-guided treatment technology. MRI-guided radiation therapy makes imaging biological changes before, during and after treatment accessible and enables personalized patient management changes. MRI-guided radiation therapy can improve treatment precision, meaning that shorter treatment regimens to improve the patient experience and decrease health care costs, as well as more ablative regimens with a high chance of treatment success, can be considered. The promise and enthusiasm for this new technology, as with other technologies, should be focused on performing carefully controlled scientific studies and clinical trials to advance knowledge and provide clinical evidence.

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Author contributions
All authors made a substantial contribution to the discussion of content, wrote the manuscript, and reviewed and/or edited the manuscript before submission.

Competing Interests
PK is an inventor on two patents relating to MRI-Linacs, US#8,331,531 and US#9,099,271. AT declares research funding from Elekta, Varian and Accuray. AT declares honoraria and travel assistance from Elekta. UH declares research funding from Elekta AB and Philips Healthcare. CB, CG-H, GL, PL, SL, CP, TP, SS, DW, BW have no competing interests.

Figures:

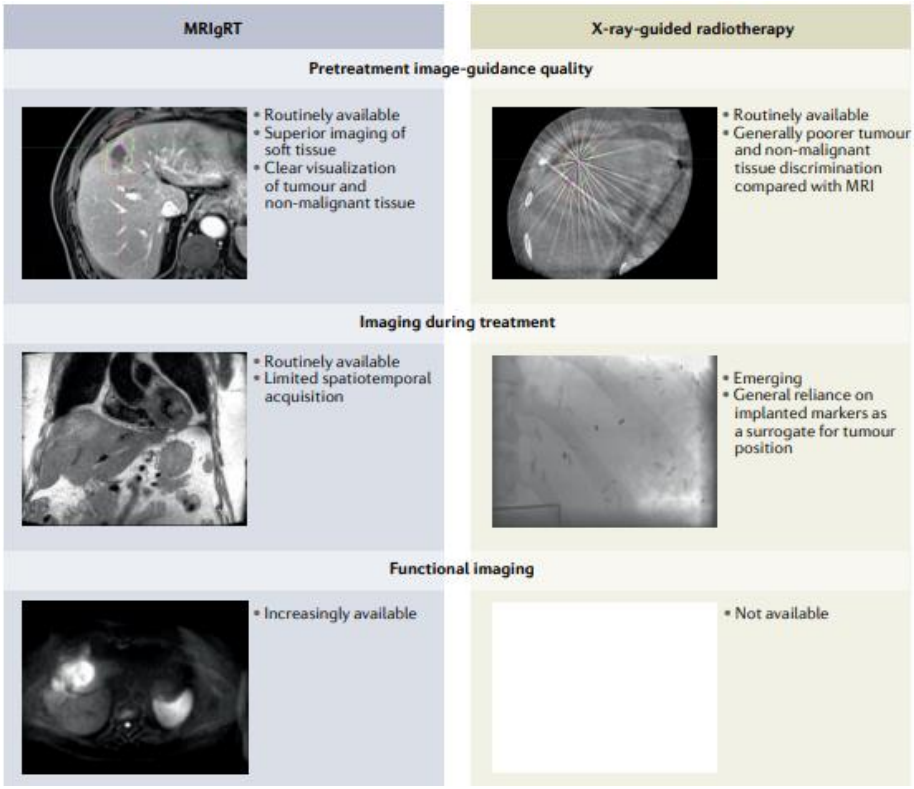
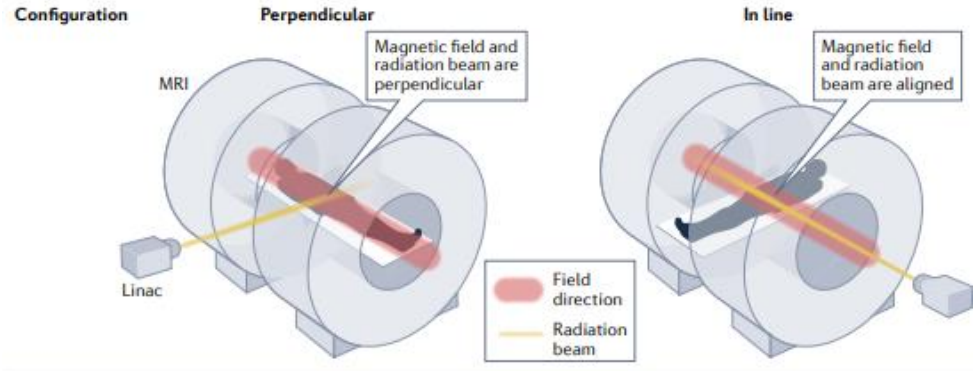


Figure 1. Comparisons between example liver cancer images acquired using MRI-guided and conventional x-ray guided radiation therapy. The routinely available quality of the anatomic image and growing availability of functional images are driving the MRI-Linac uptake.



Effect of field on therapy beam	Major: magnetic field bends charged particles, affecting beam generation and dose in patients	Minor: magnetic fields aligned with particle beam direction
Effect on MRI technology	Minor: close-to-standard hardware can be used	Major: specialized hardware designs are required
Multiple beam angles	Linac can be rotated independently of magnet	Either magnet or patient must be rotated to maintain configuration alignment

Figure 2. There are two main types of MRI-Linac, the perpendicular and inline configuration. The design differences, and implications, are shown. The radiation beam is depicted as yellow, the field direction is depicted as magenta.

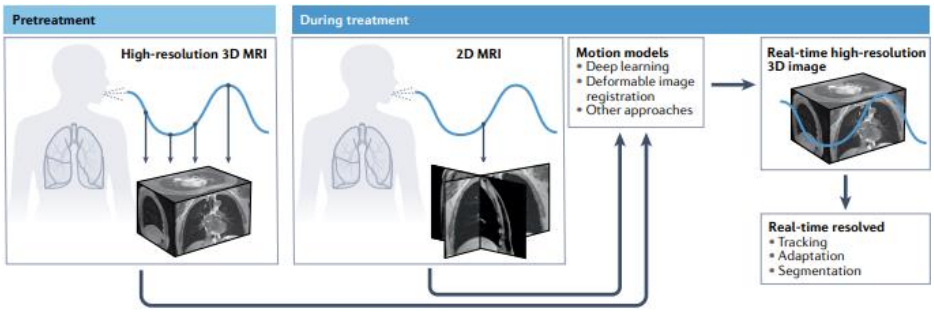


Figure 3. Functional MRI-guided biological adaptive radiotherapy to overcome treatment resistance **a)** Scheme representing three important components of tumor biological heterogeneity driving treatment resistance, cellularity, vascularization, and hypoxia, which can be obtained with DWI, PWI and qBOLD MRI techniques, respectively. **b)** Scheme representing radioresistance driving tumor recurrence in standard radiation treatment involving homogeneous dose delivery to the target. **c)** Scheme representing tumor control approaches with biologically-adapted radiation treatment involving heterogeneous dose delivery to the target. T_1 + C: T_1-weighted MRI post contrast administration; FLAIR: fluid-attenuated inversion recovery T_2-weighted MRI; DWI: diffusion-weighted MRI; PWI: perfusion-weighted MRI; qBOLD: quantitative blood-oxygen level dependent MRI.

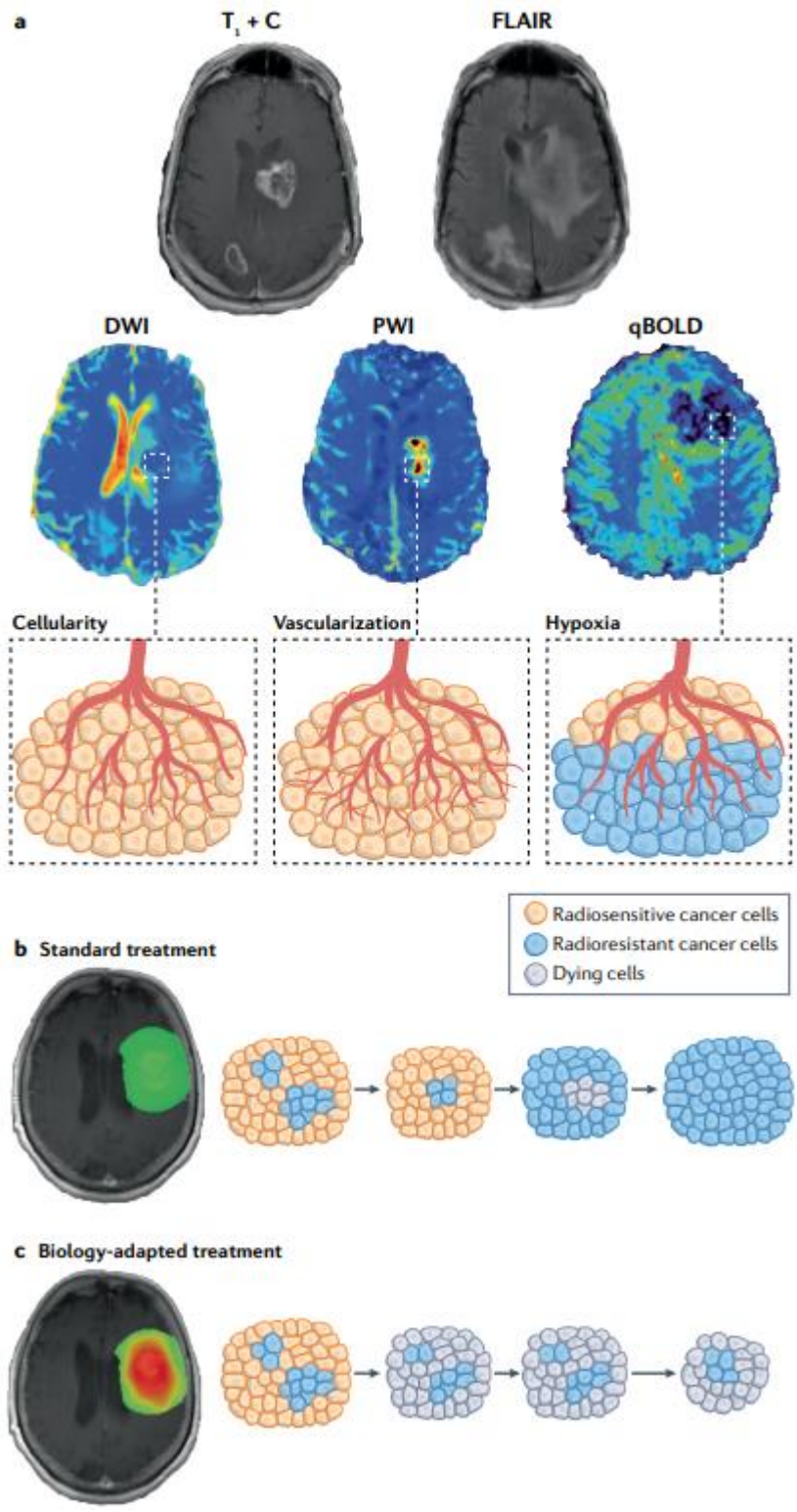


Figure 4. An important advance for MRI-guided radiation therapy is to develop methods to improve the spatial and temporal resolution of anatomic and functional imaging. An exemplar approach is shown.

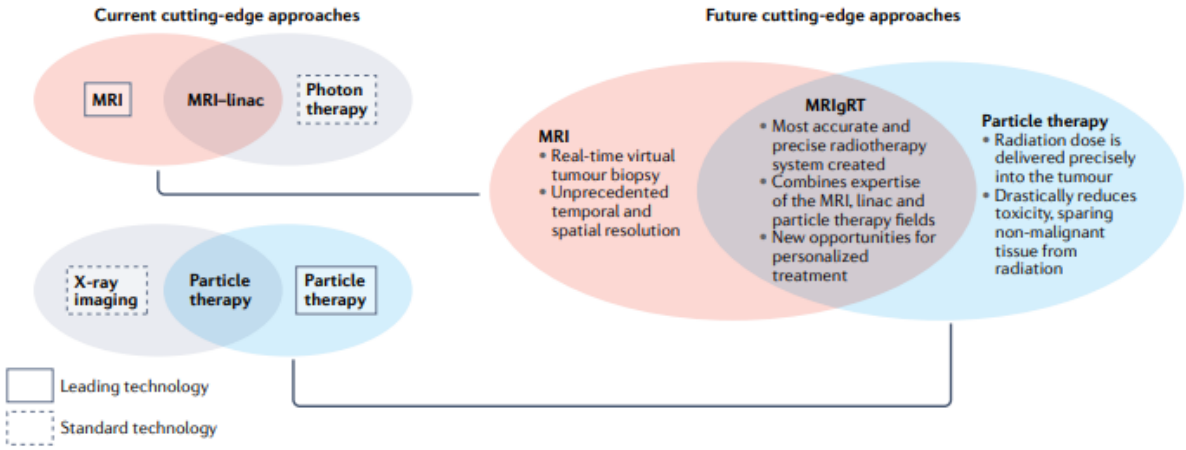


Figure 5. The potential of MRI-guided particle therapy to improve health outcomes.