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Review Article

Magnetic resonance imaging (MRI) guided proton therapy: A review of the clinical challenges, potential benefits and pathway to implementation

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ABSTRACT

Proton therapy and MRI-Linacs are two of the most exciting and fast growing technologies in radiation oncology. With over 100 MRI-Linacs and 100 proton therapy centres either in operation or under construction, an integrated approach that brings together the excellent soft tissue imaging of MRI with the superior dose conformity of proton therapy is compelling. The promise of MRI-guided proton therapy has prompted multiple research studies and the building of two pre-clinical experimental systems, taking us closer to realisation of this technology. Patients who would benefit most are those whose cancers have substantial tumour motion or anatomical variation, and those who are currently unable to receive safe dose-escalation due to nearby critical structures. MRI-guided proton therapy could allow more patients with pancreatic cancer, central lung cancer and oligo-metastatic cancers in the upper abdomen (e.g. liver and adrenal) to safely receive escalated curative doses. Head and neck, lung, brain and cervix cancers, where treatment accuracy is affected by inter-fraction tumour changes such as tumour regression or changing oedema, or normal anatomy variations, would also benefit from MRI-guidance. There will be new options to improve cure by functional MRI-guided biologically adapted proton therapy. This review focuses on the clinical aspects of MRI-guided proton therapy. We describe the clinical challenges in proton therapy and the clinical benefits from the addition of MRI-guidance. We provide updates on the design and beam modelling of in-line and perpendicular MRI-guided proton therapy systems, and a roadmap to clinical implementation.

Radiation therapy is a cornerstone of cancer treatment, recommended for half of all cancer patients [1]. Applying evidence-based radiotherapy increases local control and survival [2,3]. It is projected that 9.6 million people would benefit from evidence-based radiation therapy globally in 2025 [4]. Technology advances enabling better targeting of therapeutic radiation have transformed cancer patient outcomes. Most major advances in radiation therapy in the last two decades have come from improvements in imaging and better confidence in sculpting dose to the tumour. These advances include image-guided radiation therapy, intensity-modulated radiation therapy (IMRT), 4D-CT combined with IMRT, stereotactic ablative radiation therapy (SABR) and more recently MRI-Linac radiation therapy. They have resulted in higher tumour doses, reduced normal tissue dose, better cancer control and fewer side effects [5–11].

Comparative planning studies have suggested proton therapy may be more effective than photon therapy because of the compact nature of its dose distribution, which can be better confined to the target volume and better spare normal tissues than photon therapy (Fig. 1). Nearly one hundred proton centres have been established world-wide, yet despite the theoretical benefit, there is limited randomised evidence showing a clinical benefit [12]. One randomised study showed that proton therapy results in reduction in radiotherapy toxicity and postoperative mortality without a difference in survival compared with IMRT in oesophageal cancer [13]. Randomised trials have not shown a benefit to proton therapy in lung cancer [14] and hepatocellular carcinoma [15], where substantial tumour motion exists. In a randomised study comparing passive scattering protons with IMRT photons in patients with

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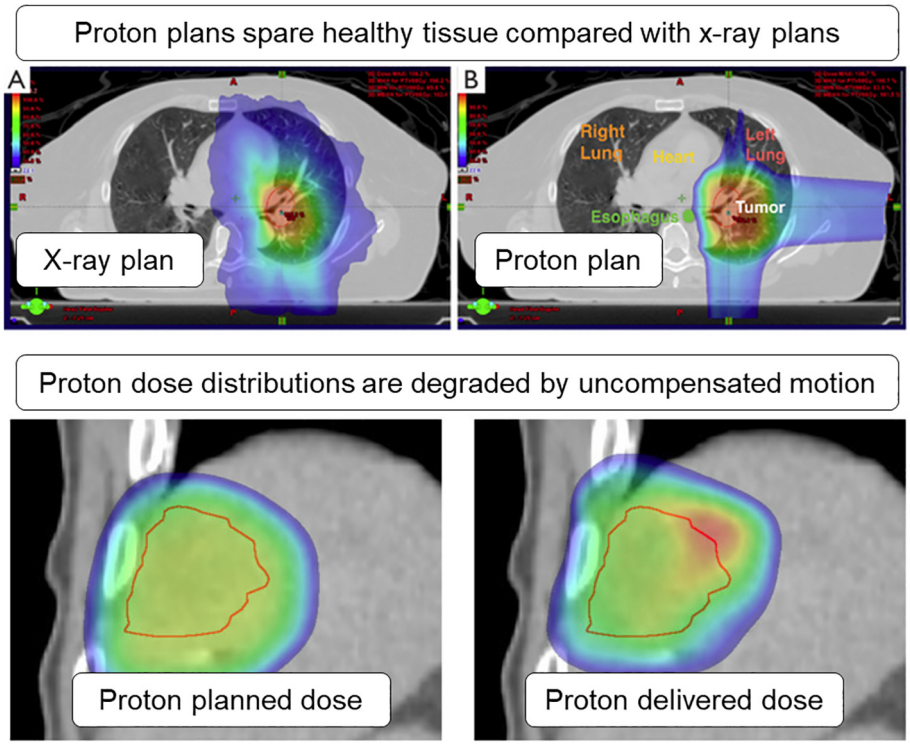

Fig. 1. (Top row) The dosimetric benefits of proton therapy is clearly demonstrated in this figure (Reproduced from Giap et al. [116] with permission) where for thorax treatment, proton therapy better spares heart and healthy lung. (Bottom row) However, proton therapy dose distributions are degraded by uncompensated motion (Reproduced from Colvill et al. [114] with permission).

advanced stage non-small cell lung cancer there was no local control benefit and grade 3+ pneumonitis was higher (10.5% vs 6.5%) in proton therapy despite more favourable proton therapy planned dose distributions [14]. The favourable toxicity profile of proton therapy for hepatocellular carcinoma has been demonstrated, however a survival benefit is yet to be shown [16,17]. A comparative study analysing the National Cancer Institute database showed no survival benefit in breast cancer with proton therapy compared to photon therapy [18]. Comparative evidence has shown a reduction in toxicity in some cancers where physiological motion is minimal, such as paediatric, adult brain and ocular melanoma [19]. A phase II trial comparing photon therapy with proton therapy in adult high-grade glioma was unable to detect a difference in rate of cognitive failure between treatment arms [20]. A systematic review showed that proton therapy was associated with lower cognitive impairment for paediatric brain tumours [21]. However, a systematic review (of level 3–4 studies) concluded there was insufficient evidence to either support or refute proton therapy for paediatric cancers [22].

A commonly cited reason for the missing clinical benefit of proton therapy is the lack of effective image guidance for proton therapy [23–27]. Proton therapy dosimetry is more susceptible to changes in tumour or normal tissue anatomy along the beam path than photon therapy, however image guidance for proton therapy has historically lagged behind that of photon radiotherapy, with guidance commonly based on 2D radiographs instead of volumetric images [28,29]. This can result in anatomical changes going undetected, leading to either under-dosing of tumour or over-dosing of normal organs. The extra margin required to account for these anatomical variations could also account for the missing clinical benefit. This situation is changing, with the first vendor supported X-ray volumetric image guidance in 2014 and all major vendors now offering some form of X-ray volumetric imaging. A variety of CT guidance solutions are now available: gantry, nozzle, or couch mounted cone beam computed tomography (CBCT), robotic C-arm CBCT, and CT-on rails [30]. However, in a recent survey of 19 participating European particle centres, only 50% had the capability to image the patient in the treatment position. Only one provided details of a 3D imaging protocol [28]. According to the Particle Therapy Co-Operative Group, of 96 operational proton therapy centres worldwide, 67 (61%) had been sold after 2014 and hence might be expected to include some form of volumetric imaging.

Due to the greater sensitivity of protons to anatomical changes, advanced integrated (in-beam) image guidance is essential for the success of proton therapy. Combining the optimal cancer targeting of proton therapy with the superior imaging of MRI in a fully integrated system may enable the predicted benefits of proton therapy to be realised. A rationale for MRI-guided proton therapy is shown in Fig. 2. The physics, software, and hardware aspects of MRI-guided proton therapy systems, and modelling and experimental investigations of the MRI interaction with protons have previously been addressed by Oborn et al., and Hoffmann et al. [26,31,32]. This review focuses on the clinical aspects of MRI-guided proton therapy. We describe the clinical challenges in proton therapy, the clinical indications and benefits from the addition of MRI-guidance, the latest updates in MRI-guided proton therapy systems design and concepts, and a roadmap to clinical implementation. The clinical indications are based on tumour anatomical characteristics and the surrounding normal tissues in clinical situations where the excellent soft-tissue contrast by MRI-guidance provides new opportunities for high-precision proton therapy with optimal sparing of healthy tissues. The tumour sites that would benefit from an integrated MRI-guided proton system are discussed in detail. These include (a) tumours with inter-fraction change (b) tumours with intra-fraction change (c) tumours requiring dose-escalation and

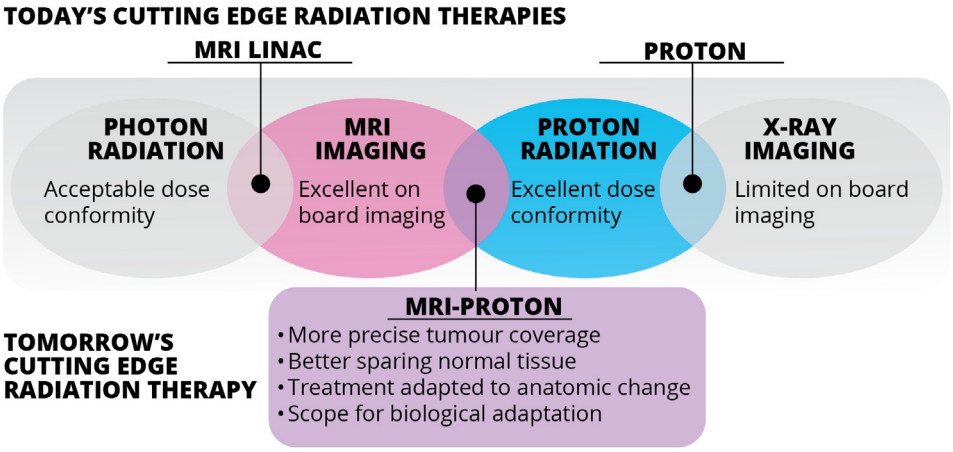

Fig. 2. MRI-guided proton therapy combines two fast-growing technologies in radiation therapy. However, the integration of the two technologies is fraught with challenges.

(d) tumours with biological heterogeneity. Clinical evidence for MRI-guidance from the MRI-Linac experience is discussed.

Clinical challenges and benefits of MRI-guidance for proton therapy

MRI is superior to X-ray imaging for radiotherapy guidance

Challenges that impede the accurate delivery of proton therapy with current X-ray (plain X-ray or CBCT) imaging guidance include (i) inability to see many tumours, (ii) inability to directly track moving tumours in real-time during treatment, and (iii) anatomical variation and organ motion. In proton therapy, the treatment volume is expanded to cover the tumour and account for anatomical uncertainty, and surrogates (e.g. fiducial markers, respiratory phase) are still used to aid targeting, limiting clinical potential. There may be unknown geographic miss of moving tumours, or movement of normal organs into the field.

Daily X-ray guidance exposes patients to small doses of extra ionising radiation. Even low doses of radiation may increase the risk of radiation induced second cancers [33,34]. Paediatric and young adult patients < 30 years old receiving radiotherapy have the largest relative increase in risk of radiation induced second cancer [35]. Typical imaging doses from CBCT are between 0.2 and 5 cGy [36] per fraction. For adult patients irradiated at 50 years, weekly MV-CBCT imaging for a 25 fraction breast radiotherapy course was modelled and found to increase the 10 year excess relative risk of contralateral breast cancer from 0.8 from treatment alone, to 0.9 with imaging [37]. Comparative planning studies have shown a two-thirds reduction of integral dose with proton therapy [38]. The reduced radiation dose in protons to normal tissues should reduce the risk of radiation induced second cancers. MRI-guidance, which does not involve ionising radiation, would further reduce the risk of second cancers from image-guidance.

Experience with MRI-Linacs has shown that MRI is an excellent modality to image soft tissue and therefore maximise the clinical potential of proton therapy through MRI-guided treatment. MRI allows superior imaging of complex tumour and normal tissue [39] and can be performed in real-time with the potential of real-time dose modification. Combining MRI with proton therapy to realise MRI-guided proton therapy would enable more accurate and effective dose delivery. MRI image guidance allows (i) excellent soft tissue contrast visualisation of tumour definition, (ii) ability to directly track moving tumours in real-time during treatment, (iii) better visualisation of normal organs and movement and (iv) functional MRI-guided differential dose delivery to biologically heterogeneous regions of tumour. MRI-guidance in an integrated system (in-beam imaging) enables both daily and real-time guidance. Daily pre-treatment MRI guidance detects anatomical changes that need to be addressed with daily adaptive replanning. Real-time (during treatment) MRI guidance detects tumour movement during 'beam-on' that may need to be addressed. MRI-guided proton therapy could expand the types of cancers that would benefit from proton therapy to include tumour sites where substantial tumour and physiologic motion exists. MRI-guided proton therapy could improve treatment accuracy, enabling accelerated treatment courses with ablative doses and fewer fractions, increasing patient convenience and the treatment cost-effectiveness.

MRI-guided proton therapy – advantages for assessing inter-fraction anatomical changes

Proton therapy is more sensitive to changes in tumour and normal tissue anatomy than photon therapy. Any changes in patient anatomy along the beam path can result in proton range uncertainties leading to under-dosing of tumour or overdosing of critical structures immediately distal to the target. This sensitivity is because the water equivalent thickness and proton stopping power are dependent on all the tissues that lie in the beam pathway [30,32,40]. Brain, central lung and gastrointestinal tumours (pancreatic, liver, oesophageal) and some normal organs (small bowel and duodenum) are difficult to visualise on X-ray imaging. The addition of MRI-guidance would provide certainty on tumour anatomy (including inter-fraction changes in tumour size and oedema) and tissues in the beam path that affect dosimetry, enabling a tighter planned target volume (PTV) margin to be used and more accurate targeting.

Inter-fraction anatomical changes include tumour motion [41,42], tumour target volume change (due to tumour growth, regression or change in oedema) [43–45], and changes in position of normal organs, all of which affect tissue density within the beam path resulting in range uncertainties and issues with tumour coverage. These inter-fraction changes are better detected on MRI than X-ray imaging. A paediatric cancer study assessing MRI detected anatomical changes during proton therapy found that 27% of paediatric patients had anatomical changes in their gross tumour volume or in the tissue density within the beam path, and over half of these resulted in a significant deterioration in plan quality [45]. Rhabdomyosarcomas and low grade gliomas had the highest rate of anatomical change at 100% and 24%, respectively. Anatomical change was associated with supra-tentorial or head and neck tumour location, and concurrent chemotherapy. Anatomical changes included changes in post-surgical fluid within the tumour bed, tumour progression from simulation to treatment commence-

ment, and tumour shrinkage during radiotherapy leading to displacement of critical normal structures, such as brainstem, into the high-dose volume.

Cancers that shrink rapidly during treatment such as lung, head and neck, and cervix, would also benefit from daily MRI-guidance. Non-small cell lung cancers treated with chemoradiotherapy have a 40% mean reduction in tumour volume by 15 fractions and 51% by end of treatment as demonstrated on CBCT [44]. Head and neck squamous cell cancers have a 7–48% reduction in tumour volume by 20 fractions and 6–66% by the end of treatment [46]. Cervix cancers have a 48–95% reduction in tumour volume by the end of external beam radiotherapy [47]. In cervix cancers, substantial bladder and rectal volume changes also occur despite use of bladder and bowel regimens to minimise daily differences [47]. Given that heart doses and their association with cardiac morbidity and mortality is now a recognised toxicity from lung radiotherapy [48], protons may have a role in reducing this, especially with more modern proton planning techniques, such as intensity modulated proton treatment (IMPT). In one non-randomised comparative non-small cell lung cancer study, IMPT patients had significantly lower lung, oesophageal and heart doses compared with passive scattering proton therapy, and significantly lower cardiac and lung toxicities [49]. The use of MRI-guidance could overcome some of the image-guidance challenges in treating lung cancer patients with proton therapy, enabling the predicted benefits in local control and toxicity to be realised.

MRI-guided proton therapy – advantages for assessing intra-fraction anatomical changes (moving tumours)

The delivery of proton therapy to moving tumours is more challenging than photon therapy. Moving tumours ideally require real-time imaging. Tumour motion not only affects the lateral extent of proton dose distribution, which can be accounted for with margins, but also causes range uncertainties [40]. Changes in tumour position depth can change the tissue density along the beam path, resulting in range errors. Tumour movement can result in large dose fluctuations ('interplay' effects), as tumours can move out of the pencil beam intended to irradiate it or receive extra dose by remaining within a pencil during the scan [50]. The PTV margin does not account for this uncertainty in proton therapy. The average range of lung tumour motion is 12 mm in the cranial-caudal direction for lower lobe tumours [41]. Pancreatic tumours move up to 20 mm in cranio-caudal direction and are poorly correlated with diaphragm or abdominal wall position surrogates [51]. Current motion management methods in proton therapy include the use of breath-hold or gating. Tracking is performed through the use of external surrogate tracking (external markers or surface imaging) or internal tracking (fiducial markers, respiratory phase, or marker-less tracking with fluoroscopy) [52]. Gating systems track tumour motion by tracking surrogates, yet a source of error is the correlation of surrogates with target position [53,54]. Current X-ray guidance is unable to directly visualise some tumours (e.g. liver), the use of surrogate markers is associated with uncertainty and errors in matching [54], and wider margins are necessary particularly in patients who are unable to tolerate breath-hold techniques. In respiratory triggered pulse proton therapy for liver tumours, intra-fractional uncertainties up to 5 mm and deviations of fiducial positions at time of treatment from their planned positions larger than 5 mm were observed in a quarter of patients [55]. Fiducial markers also pose problems with proton beam degradation if they lie within the beam path [52].

MRI-guidance enables direct matching to tumours, obviating the need for uncertain surrogates, and real-time monitoring of intra-fraction tumour motion to ensure accurate targeting of moving tumours. Tumour sites that could benefit from real-time MRI-guidance for proton therapy include lung, liver and pancreatic tumours that move on respiration, and prostate and uterine-cervix tumours that move with bladder filling and rectal gas motion. MRI-guidance with real-time imaging allows direct visualisation of lung and liver tumour motion and improves the accuracy of dose delivery. Gated treatment delivery allows the beam to be switched off if the tumour moves outside the beam target. MRI-Linac experience has shown the ability of MRI-guidance (2D cine MRI) to enable direct tumour target based gating without fiducial markers, in abdominal tumours including liver and pancreas [56,57]. This guidance could allow the theoretical advantages of proton therapy to be translated into an improvement in clinical outcomes, including better local control and reduced toxicity. A modelling study in liver tumours found that MRI-guided proton therapy can reduce the PTV volume by 40% compared with CBCT-guided proton therapy. MRI-guided proton therapy reduced the normal tissue complication probability by 48% compared with CBCT-guided proton therapy, and 31% compared with MRI-Linac [58].

MRI-guided proton therapy for improving dose-escalation

Locally advanced gastrointestinal tumours are difficult to treat using photon radiotherapy and remain mostly untested in proton therapy due to tumour motion and proximity to critical normal organs such as duodenum and small bowel impacting the ability to safely dose-escalate to tumoricidal doses. In pancreatic cancer, survival remains poor with photon radiotherapy with a 5 year survival of only 10% for patients with locally advanced inoperable cancer [59]. For patients undergoing abdominal SABR who are unable to receive maximum isotoxic doses, a detriment in local control and survival has been demonstrated with reduced biological equivalent dose (BED) [60]. Patients with ultra-central lung tumours close to critical structures, such as proximal bronchial tree, great vessels and heart, are also difficult to treat and currently at high-risk of toxicity or unsuitable for SABR.

The combination of improved detection of inter-fraction and intra-fraction tumour and normal organ changes provided by MRI guidance, combined with the superior proton dose characteristics, will enable safe high-precision dose-escalated proton therapy in abdominal (liver, pancreatic, adrenal) and central lung cancers. This would increase in the number of patients with primary or oligometastatic cancers in the abdomen or central lung eligible for curative dose-escalated proton therapy. MRI-Linac experience has shown that the addition of MRI-guidance has enabled safe dose escalation in abdominal cancers with excellent early clinical outcomes [11,61]. The ability of MRI-guided adaptive radiotherapy to improve tumour coverage or avoid a normal organ overdose that would have occurred due to anatomical variation has also been shown in abdominal SABR for primary or oligometastatic abdominal cancers [56,62]. Henke et al. showed that MRI-guidance for primary or oligometastatic abdominal cancers was able to achieve dose escalation in 20%, improve tumour coverage in 65%, and reverse a normal organ overdose in 75% of fractions. Patients were treated to a BED 100 Gy–150 Gy. At median follow-up of 15 months, there were no local progressions and no grade 3+ toxicity [56]. In a pancreatic cancer study by Rudra et al., dose escalation with MRI-guided adaptive radiotherapy resulted in a survival benefit (2-year survival for dose > 70 Gy vs. <70 Gy = 49% vs. 30%), while grade 2+ toxicity remained low [11]. Similarly in high risk lung cancer patients (central tumours, previous thoracic radiotherapy, or interstitial lung disease) clinical results from MRI-guided stereotactic adaptive radiotherapy have demonstrated the ability to dose escalate or re-optimise plans to improve the target coverage while maintaining normal tissue sparing with low levels of

grade 3+ toxicity [63]. Ninety-three percent of patients with high risk lung cancer were treated to a BED $\geq$ 100 Gy.

MRI-guided proton therapy could also create new radiotherapy options in more common cancers such as breast. MRI-Linac radiation therapy has already shown that MRI-guidance can be used to target and treat breast cancers with radiation therapy pre-operatively with a single ablative dose and this has led to pathologic complete response in over 40% of patients [64]. MRI-guided proton therapy would not only allow visualisation of breast tumours crucial for accurate targeting including in partial breast radiotherapy (a visualisation task that is challenging with standard X-ray imaging), but also enable cardiac sparing to reduce the risk of cardiac toxicity [65].

Functional MRI-guided proton therapy for assessing tumour biology and targeting tumour heterogeneity

Cancers are characterised by biological heterogeneity (e.g. variations in cellularity, vascularisation and oxygenation), which allows development of mechanisms of resistance to standard radiotherapy [66–68]. Targeting regions of radioresistance (e.g. hypoxia) with higher doses of radiation may increase chances of local tumour control [69]. X-ray techniques currently used for planning radiotherapy are unable to capture tumour biological heterogeneity. While IMRT and volumetric modulated arc therapy planning can increase, to a certain extent, the dose to the target without increasing the dose to healthy tissue, precise and effective dose escalation to hypoxic tumour subregions is still a challenge. IMRT can achieve dose modulation over small volumes of the order of 1 cm^3, which is a spatial resolution too large to target local variations in tumour hypoxia [70]. Dose escalation regimes achievable with IMRT are still limited by dose constraints to normal organs and do not achieve values high-enough to counteract hypoxia-induced radio-resistance.

Functional MRI-guided proton therapy may be suited for targeting tumour heterogeneity because it combines the ability of MRI to assess and map biological heterogeneity with superior proton dose-deposition characteristics, allowing the delivery of higher radiotherapy doses to biologically radio-resistant tumour regions while limiting dose to surrounding healthy tissue. Proton therapy has the ability to deliver radiation doses to a resolution range 3.5–6 mm^3 [23], which is greater than the resolution achievable with IMRT, making IMPT more suitable to escalate doses to radio-resistant sub-regions. The proton therapy Bragg peak could be used to selectively dose escalate to resistant tumour sub-regions to much higher levels than those achievable with IMRT, while avoiding normal tissues. Proton therapy has a higher relative biological effectiveness compared to photons, which increases in the distal part of the spread out Bragg peak [71]. Functional MRI allows imaging of tumour physiologic heterogeneity at resolution up to 1 mm. For example diffusion weighted imaging is correlated with cellularity [72–74], $R2^*$ imaging with hypoxia [75], and dynamic contrast-enhanced imaging with perfusion [74]. These techniques provide insight into tumour physiologic heterogeneity and factors of radio-resistance, and could be used to predict treatment response, personalise treatment and guide dose escalation [74,76]. MRI-guidance challenges the current paradigm that the tumour is treated as a uniform static whole, rather than as a heterogeneous dynamic tumour microenvironment. An MRI whole tumour 'virtual biopsy' creates new opportunities for adaptive biological targeting to overcome radio-resistance. Although off-line MRI could be used to personalise treatment to biological heterogeneity, there can be temporal heterogeneity in addition to spatial heterogeneity, particularly in oxygenation, and MRI-guidance from an integrated system would enable treatment to be adapted to the heterogeneity present at time of treatment. Combining the ability of MRI to image tumour heterogeneity, and higher biological effectiveness and efficiency of protons at delivering the dose to the target, functional MRI-guided biologically adapted proton therapy is likely to be the next frontier treatment for targeting cancer heterogeneity.

MRI-guided proton imaging and delivery requirements to address the challenges of anatomical changes

Site-specific MRI imaging and proton delivery capabilities are required to assess and address specific changes in anatomy, and fully utilise the additional information provided by MRI-guidance (Table 1). Proton plans are inherently more difficult to adapt to anatomical changes because, unlike photon plans they are generally not 'shift invariant' (this is because shifting the beam can result in alteration of dosimetry if there is altered anatomy in the beam path). Daily adaptive replanning will be a requirement to address even minor anatomical changes detected by MRI. For tumours with minimal motion, such as CNS and head and neck mucosal cancer, 3D anatomical MRI pre-beam together with daily adaptive planning capabilities are adequate to fully utilise pre-treatment information on daily changes in anatomy, including tumour regression and normal organ position.

For tumours with substantial motion, 3D MRI pre-beam and intra-fraction (real-time imaging) MRI monitoring of tumour motion is needed. Online pre-beam and intra-fraction 4D MRI has been successfully implemented in the clinical workflow for MRI-guided adaptive stereotactic radiotherapy delivered by MRI-Linac systems [77,78]. Gating experience from MRI-Linac systems has shown real-time tracking and gating capabilities using MRI is reliable and accurate with respect to spatial integrity and tracking accuracy [79]. Latency time between image acquisition and gating response needs to be short and has been shown to be between 300 and 500 ms on MRI-Linac systems [80]. Cine 2D MRI on MRI-Linac systems has been shown to be sufficient to enable gating, however work towards real-time 3D MRI are in progress. A more sophisticated adaptive approach than gated treatment delivery would be real-time tracking with dynamic treatment delivery. The proton beam position would need to shift by globally shifting the pencil beam scanning delivery pattern in alignment with lateral changes in tumour motion, and the proton beam energy would need to be adjusted to changes in anatomy within the beam path [32]. However, in the case of 3 dimensional tumour motion, major technological hurdles would have to be overcome to enable real-time tracking. Real-time experimental target tracking results with a particle therapy beam, accounting for changes in the lateral target position and depth, were published in 2007 [81]. This feasibility demonstration, well over a decade ago, has paved the way for the clinical implementation of real-time target tracking with a particle therapy beam. The lack of an available real-time target position monitoring system, such as MRI, has hampered the advancement of proton adaptation technology.

MRI is associated with anatomical distortion, and this needs to be addressed to ensure geometric fidelity, essential for both dose calculation and precise targeting, when adapting proton therapy to variations in patient anatomy. However this problem also exists with using CT in proton therapy; unlike in photon therapy, where the CT Hounsfield unit provides accurate tissue electron density information, in proton therapy uncertainties currently exist in the CT number to relative stopping power conversion of protons [40]. MRI-Linac systems have overcome the issue of geometric distortion with online distortion correction. MRI parameters can be adjusted to minimise geometric distortion (e.g. increasing the bandwidth). A similar requirement is needed for MRI-proton systems to ensure geometric accuracy in adapting proton therapy to

Table 1
Advantages of MRI-guidance, imaging and proton delivery requirements by tumour site.

Tumour site	Advantages of MRI-guidance	MRI requirements to assess anatomical change	Proton delivery requirements to address anatomical change
Tumours with inter-fraction changes			
Paediatric cancers	- Detect changes in tumour anatomy (shrinkage, growth, oedema, critical normal organ shift, tissue density change within beam path) that affect target coverage and dose to normal structures - No ionising radiation from X-ray imaging - Lower integral dose compared to photons	Daily 3D MRI (Pre-beam)	Daily adaptive plan based on daily anatomy
Brain	- Superior daily soft tissue imaging to detect changes in tumour anatomy (e.g. Oedema, growth or regression) and resulting displacement of adjacent normal structures (e.g. brainstem)		
Head and neck	- Superior soft tissue tumour imaging to detect changes in tumour anatomy (e.g. Oedema) and shrinkage		
Breast	- Superior soft tissue tumour imaging and ability to visualise tumour enabling targeting of tumour in the pre-operative setting - Better cardiac avoidance, particularly in the setting of internal mammary chain irradiation		
Uterine-cervix	- Superior soft tissue tumour imaging - Monitor daily changes in tumour/uterine-cervix position that occur as a result of changes in bladder and rectal motion		
Tumours with intra-fraction motion			
Lung	- Early stage: Real-time imaging of moving lung tumours. Ability to treat central tumours with SABR and avoid critical structures (proximal bronchial tree, oesophagus, great vessels, heart) - Advanced stage: Superior soft-tissue visualisation in advanced lung cancers with extension into mediastinum, vertebra, chest wall, brachial plexus - Better cardiac avoidance	Daily 3D or 4D MRI (Pre-beam) Real-time imaging of tumour (Beam-on) Intra-fraction 2D-cine or 3D/4D MRI monitoring of tumour motion	Gated treatment with on-the-day adaptive treatment OR Real-time tracking with dynamic treatment delivery [81]
Pancreas	- Direct visualisation of tumour and changes in normal tissue anatomy will enable safe dose escalation and ability to deliver curative intent treatment while better avoiding duodenum and small bowel		
Liver	- Direct tumour visualisation on MRI, obviating the need for surrogate markers and avoiding uncertainty of matching to surrogates. - Better visualisation of changes in normal tissue anatomy - Real-time imaging of moving liver tumours - Improved ability to safely dose-escalate and avoid normal tissues (e.g. normal liver, small bowel, duodenum		Change depth of Bragg peak based on real-time tracking
Oligometastatic disease (lung, liver and adrenal metastases)	- Direct tumour visualisation more accurate targeting compared to using surrogates - Real time monitoring and tracking of tumour and normal anatomy motion - Improved ability to safely treat to maximum isotoxic dose, or dose escalate - Increase eligibility of patients with oligometastatic disease for SABR		

patient anatomy. In MRI-guided proton therapy, there is a requirement to image the entire anatomy from beam entrance to tumour target volume, as all anatomy along the beam path affects dosimetry. The image distortion is higher at the patient periphery, which is further away from the imaging centre, and methods to correct this distortion or accurately model the entire anatomy are needed.

Physics challenges for design of MRI-proton systems

Choice of configuration – impact on magnet design and dosimetry

As with MRI-Linacs, two device configurations are possible for an MRI-guided proton therapy system: beam parallel (inline) to magnetic field and beam perpendicular to magnetic field. Fig. 3 shows exemplar horizontal (i.e. fixed-gantry) beamline inline and perpendicular MRI-proton therapy systems. A clear requirement is the unobstructed path for the proton beam to reach the patient inside the MRI scanner. For the inline orientation system, a major ramification is the extent to which the magnet must be 'split'. The patient must lie between the two poles of the magnet, requiring a complete and large split of at least 50 cm in the magnet, gradient coils, and RF coils. This MRI configuration will inevitably be more expensive and have lower performance than a more conventional 'closed bore' type system. A second major ramification of this configuration is that rotation of either the patient or the magnet is required to enable multiple beam angles - both are challenging [82–84].

In the perpendicular orientation system, a more conventional MRI system geometry is possible. In contrast with an MRI-Linac system [85], in an MRI-proton system it is not possible to radiate through the cryostat, and either a complete split, or a 'chimney' in conjunction with a rotating magnet or patient would be required. The implication is that for MRI-Proton therapy some form of split bore magnet (including gradient coils and RF) is required regardless of configuration. As noted above, such magnets are expensive compared to a conventional design, and this is particularly the case for higher field strengths [86–88]. If a complete split solution is adopted, the split width is substantially reduced compared to an inline system; a 30 cm treatment field size in a 70 cm bore magnet with scanning magnets positions 200 cm away would require a split of only ~20 cm.

A second aspect of configuration in integrated radiotherapy-MRI devices is the accurate delivery and radiation measurement. There are two aspects which limit this. Firstly, charged particle transport is fundamentally affected by the presence of magnetic fields. Although the underlying physics is well understood and encapsulated by the Lorentz equation, the effects can be both complex and difficult to predict. Unlike photons, protons themselves

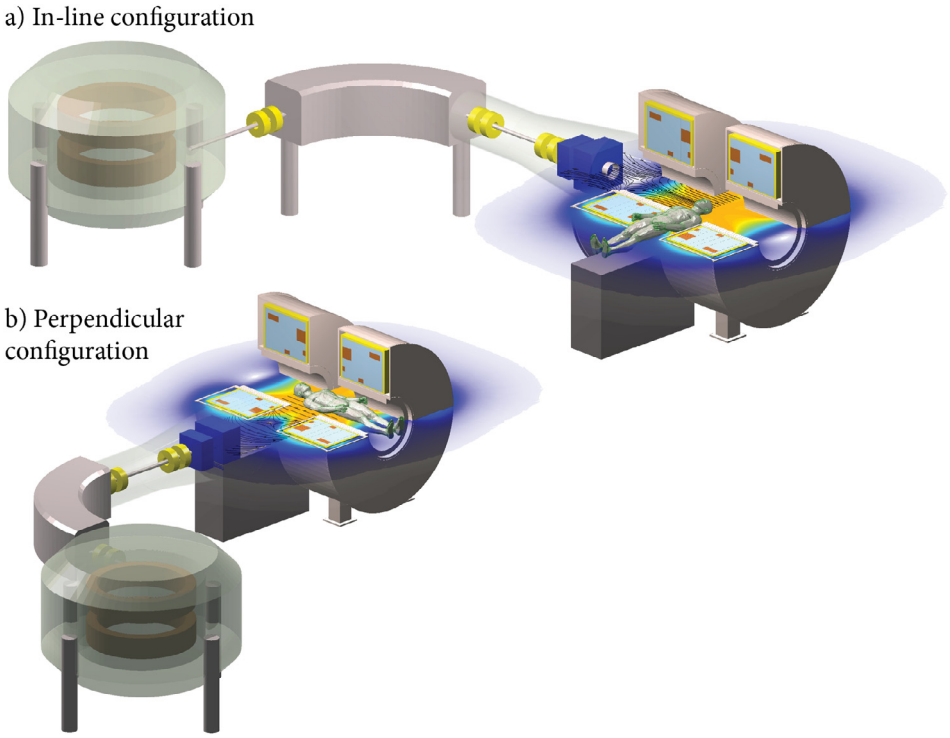

Fig. 3. Examples of a generic horizontal beamline (fixed-gantry) MRI-proton therapy systems with the magnet design based on the Australian MRI-Linac program. Options of upright patient rotation, gantry rotation and perpendicular systems have also been developed. Arrows indicate the magnetic field lines. Colours indicate the magnetic field magnitude. (a) Inline system where the proton beam travels parallel with the main field of the MRI field. (b) Perpendicular system where the proton beam travels transverse to the MRI main field direction.

are affected by magnetic fields. This means that the magnetic field affects not only the secondary electrons produced in the patient [89], but also the entire beam transport chain. The effects of proton beam transport through the fringe field of a 1.0 T MRI scanner have been assessed for both perpendicular and inline configurations [90]. In an inline field the protons are rotated around the central axis, whilst in the perpendicular configuration the beam bends away from the central axis, shown in Fig. 4. It has been demonstrated that these effects can be corrected for inline fields up to 1.5 T [91]. In addition to effects of transporting the beam through the fringe field of the scanner, there are effects on dose deposition within the patient, due to both the continued perturbation of the proton beam, and the effects on the secondary electrons. These effects have been studied in some detail for a range of field strengths and configurations [89,92–94]. Dedicated dose calculation algorithms for proton therapy have been proposed, which can enable substantial speed ups in dose calculation time without compromising accuracy [95]. The effect of magnetic fields on secondary electrons is smaller than in MRI-Linac therapy, as the energy of secondary electrons created by particle beams is lower [89,92] whilst the perturbation of proton trajectories in the patient is deterministic and can be handled with inverse planning. A potential problem is reduced robustness of plan delivery in the presence of anatomical changes, however such effects can also be mitigated by online adaptive strategies [96].

Choice of magnet technology

There are several viable magnet technologies for an integrated MRI-proton system. In the field of MRI-Linacs, most devices have utilised fairly conventional liquid helium cooled superconducting magnets [97,98]. The exception is the AuroraRT system, which utilises a magnet comprising both high temperature superconducting coils and iron yoke [87]. On one hand, a major advantage of 'yoked' systems is that the fringe field of the magnet is greatly reduced, which tends to minimise many imaging/beam integration challenges. On the other hand, such systems are limited to field strengths of around 0.5 T and have historically suffered from poor imaging stability, due to the thermally dependent magnetic properties of iron [99]. In addition, it appears that such designs may be more sensitive to the changing fringe field of scanning delivery systems compared with superconducting air core systems [31]. More recently, vendors in the radiology space have been moving toward either helium-free or very low helium designs. Like the AuroraRT system, a major advantage of such designs is that they do not require a quench pipe to the external environment, making siting and installation substantially easier. There has been a historic attitude in radiation oncology that higher field equals better images, however this is only true in some circumstances, and there is greatly renewed interest in high performance, low field MRI (in this context meaning < 0.5 T) within both industry and academia [97,100].

Experimental progress and status

Experimental progress towards MRI-proton therapy has been conducted by at least two research groups. OncoRay in Dresden, Germany, has conducted successful experiments with a proof of concept system [101]. In their work, a 0.22 T iron yoked C-shaped MRI was integrated with a proton pencil beam delivery system. MRI was shown as feasible during beam-on. The Dresden group have furthered this research with experiments conducted on the integration of a clinical pencil beam scanning (PBS) assembly and the same 0.22 T MRI scanner [102]. In this work, PBS was performed with concurrent MRI. Artefacts were observed due the magnetic fringe fields produced by the PBS assembly. In another study, the OncoRay group have studied the electron return effect for proton beams at 1 T [102]. At the MedAustron facility in Aus-

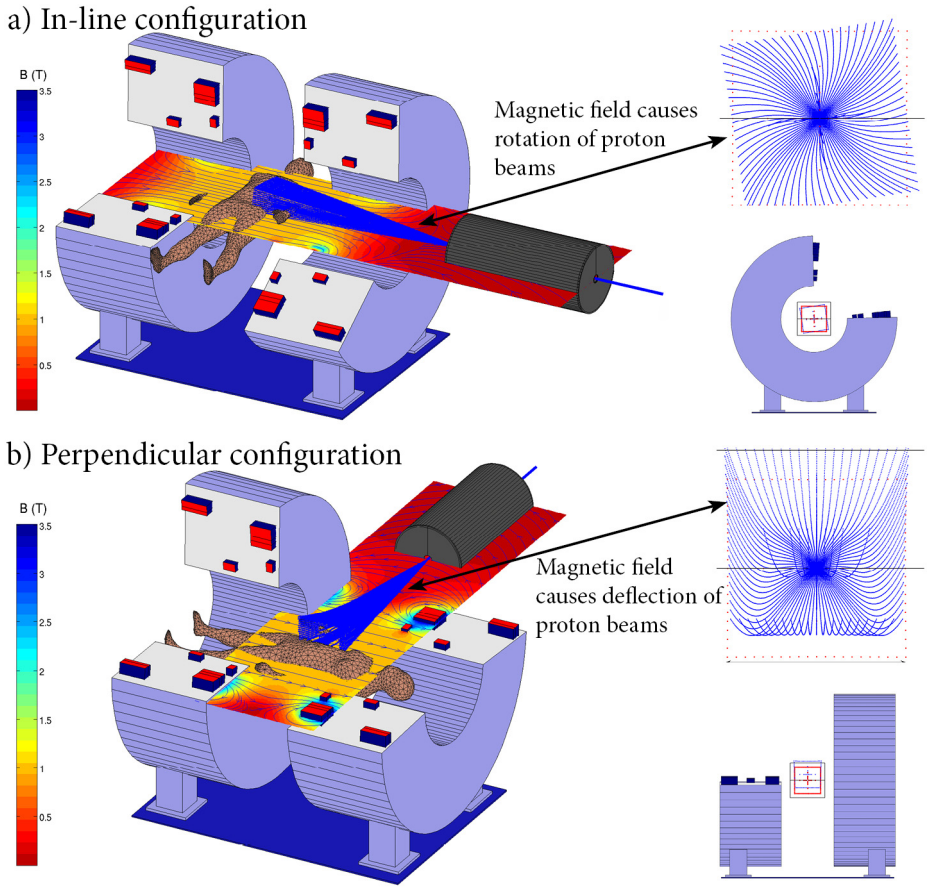

Fig. 4. The effect of the magnetic field on 300 MeV on a diverging MeV proton beam is shown for inline fields (top) and perpendicular fields (bottom). In-line fields cause rotation of proton beams around the central axis. Perpendicular fields cause deflection of the proton beam. The blue lines show the beam positions of a divergent proton source, showing the perturbation caused by the fringe field of the magnet. Without a magnetic field these would appear as a star-like array of straight lines.

tria, experiments have been conducted with 1 T dipole magnet system examining the dosimetry changes as well as dose planning studies for proton beams [103]. For these two studies, insignificant changes were observed due to the presence of the magnetic fields. The MedAustron group has also examined film response with proton beams in B-fields [89]. The ARTEMIS group in Heidelberg have a demonstrator system with a 0.25 T MRI scanner on rails with an envisioned patient rotation system [104].

Roadmap for clinical development and implementation

An obvious question stemming from this paper is to have a roadmap to develop a clinically and commercially viable MRI-guided proton therapy system. Both MRI-Linacs and proton therapy systems are growing markets. Revenues from the MRI-Linac guided radiation therapy systems market exceeded $220 million in 2018 with a projected 20% compound annual growth rate through 2028 [105]. There are 75 particle therapy centres worldwide with another 41 under construction [106], a more than $10B investment. MRI guidance for photon therapy has roughly doubled the cost of an integrated linac system to about 10 million Euro [107,108]. The relative additional cost of adding MRI is much less for proton therapy than photon therapy.

Integral to the deployment of MRI-guided proton therapy is the conduct of clinical trials to measure the health impact of the advanced technology and research programs to quantify current and future capabilities. The clinical trial outcomes should be benchmarked against non-MRI-guided proton therapy and MRI-Linac therapy to best estimate the impact of the combined MRI-proton therapy technology. Ideally, clinical trials should be in the form of randomised trials comparing MRI-guided proton therapy with photon therapy and these should be conducted to obtain evidence of clinical benefit and to support appropriate clinical dissemination and financial reimbursement [109]. We should do randomised studies, which provide high level evidence, and these should be conducted early in the clinical implementation of MRI-guided proton therapy, where there is more likely to be clinical equipoise. This approach will avoid the current situation with non-MRI-guided proton therapy, where there remains a paucity of randomised evidence to support its use despite the use of proton therapy world-wide for over a decade. Registry based clinical trials provide an alternative less costly method of obtaining comparative data [110,111]. The R-IDEAL framework to assess new technology can be used to obtain clinical evidence [112], however we should strive to obtain level 1–2 evidence in the form of randomised trials and pooled meta-analyses.

Progress towards an MRI-guided proton therapy system has seen a pre-clinical prototype device built in Dresden [25,103] and Heidelberg [104] and the announcement of the building of a clinical system at Dresden [113]. These are exciting times indeed.

Conflicts of interest

Related to the topic, Paul Keall is an inventor on an unlicensed US patent owned by Stanford University (#US8331531).

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