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## REVIEW ARTICLE

# The future of image-guided radiotherapy will be MR guided

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## ABSTRACT

Advances in image-guided radiotherapy (RT) have allowed for dose escalation and more precise radiation treatment delivery. Each decade brings new imaging technologies to help improve RT patient setup. Currently, the most frequently used method of three-dimensional pre-treatment image verification is performed with cone beam CT. However, more recent developments have provided RT with the ability to have on-board MRI coupled to the teleradiotherapy unit. This latest tool for treating cancer is known as MR-guided RT. Several varieties of these units have been designed and installed in centres across the globe. Their prevalence, history, advantages and disadvantages are discussed in this review article. In preparation for the next generation of image-guided RT, this review also covers where MR-guided RT might be heading in the near future.

## INTRODUCTION: IMPORTANCE OF IMAGE-GUIDED RADIOTHERAPY IN RADIOTHERAPY

Radiation therapy has advanced in leaps and bounds over the past few decades. The introduction of accurate dose calculation algorithms, intensity-modulated radiation therapy (IMRT), image-guided radiotherapy (IGRT) and stereotactic body radiotherapy (RT) has changed our clinical practices. For example, in our clinic, it is now routine practice to treat early-stage lung cancer patients definitively with stereotactic body RT when, in years past, surgery was the standard of care.<sup>1-4</sup> Currently, tumour delineation is the weakest link in the delivery of accurate and precise RT.<sup>5,6</sup> In his 1989 Canon Rebel camera commercial, Andre Agassi proclaimed “image is everything”.<sup>7</sup> And we agree. After all, as physicist Harold Johns said “if you can’t see it, you can’t hit it, and if you can’t hit it, you can’t cure it”.<sup>6</sup> This need to “see” the tumour is the basis for IGRT. IGRT provides on-board (or in-room) imaging which helps guide the radiation treatment delivery process in order to safely deliver the treatment to the intended target.<sup>8,9</sup> This publication is limited in scope to discussing methods of on-board or in-room MR IGRT techniques in external beam treatments.

Currently, there are several imaging technologies available in radiation oncology to facilitate optimizing treatment positioning accuracy and precision such as megavoltage planar imaging, static kilovoltage planar imaging, ultrasound, cone beam CT (CBCT) and even

in-room CT-on-rails units, all of which still have worse soft-tissue contrast than MRI.<sup>10</sup> Common imaging modalities such as portal imaging and CBCT are quite useful for minimizing and correcting rigid misalignments but are lacking when it comes to adaptive RT techniques that aim to modify the treatment plan according to both geometric and anatomical changes on both an interfraction and intrafraction basis.<sup>10</sup>

The ultimate goal of MR-guided RT (MR-gRT) would be to exploit MR’s superior soft-tissue contrast and its ability to use imaging biomarkers that could potentially indicate a treatment response to adaptively modify the treatment in an online fashion. Instead of just adaptively changing the treatment plan due to anatomical changes without changing the original treatment intent as most current adaptive RT techniques do, MR-gRT when fully realized, will be able to change the treatment intent based upon the continuously acquired real-time data it will collect and be able to use biomarkers to identify responders compared with non-responders.<sup>10</sup> MR-gRT with real-time adaptive plan optimization will be a game changer in radiation oncology.

Before sophisticated methods became widely available for IGRT, the International Commission on Radiation Units and Measurements in 1999 gave guidance on accounting for tumour positional uncertainty with the use of creating margins surrounding the irradiated target.<sup>11</sup>

And as early as 2004, Raaijmakers *et al*<sup>13</sup> published the findings of their feasibility study to integrate a 6-MV linear accelerator (linac) with an MRI unit.<sup>12,13</sup> In a collaboration between Elekta Oncology Systems and Philips Medical Systems, the team designed a 6-MV linear accelerator that rotates about the gantry of a 1.5-T MRI system. The major goal of the study was to not just design the device but also to predict the impact of the transverse magnetic field on the radiation dose delivered by the linac. Computer simulations of the dose kernels were created using Monte Carlo algorithms for 1.5- and 1.1-T fields.<sup>12–16</sup> They discovered that the pencil beam dose would be asymmetric, and for larger radiation fields, the depth for the maximum dose is shallower by 5 mm than expected and the penumbra is increased. Their work in 2005 also determined that the increase of dose at tissue–air interfaces was due to electron return effect, where electrons in a magnetic field will move in a circular pattern and cause extra dose to be deposited. Despite these effects to the dose deposition, the team concluded that these effects could be taken into account by conventional three-dimensional conformal treatment-planning procedures and decided to investigate the magnetic field's impact on IMRT fields later. The construction for the first of these systems began in 2007 at the University Medical Center, Utrecht, Netherlands.<sup>12,17</sup>

In 2006, Kron *et al*<sup>18</sup> published a proposal for a combined MR-adaptive cobalt tomotherapy unit. They named their proposed device the “MiCoTo”, the nuclear MR-integrated cobalt tomotherapy unit. The appeal of cobalt RT is that there is a lack of interference between the MR unit and the linac. Other advantages of using a low-energy megavoltage photon-emitting source such as cobalt-60 (<sup>60</sup>Co) is that it ensures a constant dose rate with gantry rotation and makes dose calculation in a (0.25-T) magnetic field easier as the range of secondary electrons is limited in comparison to high-energy X-rays produced by a linac.<sup>18</sup> The tomotherapy ring was designed to sit between the MRI's two Helmholtz coils. Owing to using cobalt, there would be no impact of the MRI's fields on the dose rate or deposition and the dual-row multileaf tomotherapy collimator system would allow for intensity-modulated treatment.<sup>18</sup>

### CURRENT MR-GUIDED RADIOTHERAPY SYSTEMS

In 2014, the first commercial MRI-guided cobalt radiation therapy system began treating patients at Washington University, St Louis, MO. The unit is called the “MRIdian®” or “ViewRay system” (VRS).<sup>19,20</sup> The system has three doubly focused multileaf collimated <sup>60</sup>Co sources mounted on a ring, straddled by a 0.35-T MRI.<sup>20</sup> Both the therapy and the imaging system share the same isocentre, which allows for simultaneous imaging and treatment. In addition, the VRS has an integrated adaptive treatment-planning system (TPS) that allows the user to rapidly adapt the treatment plan and beam delivery based upon the MRI information.<sup>20</sup>

The VRS has three main components, namely the MRI, the RT delivery system and the adaptive RT TPS.<sup>20</sup> The VRS' MRI has a double-doughnut design with a 50-cm imaging field of view. It has a 75-cm diameter whole-body radio frequency (RF) transmit coil which covers the magnet gap and is thin, yet uniformly attenuating to prevent beam heterogeneities and to improve

patient comfort.<sup>20</sup> The RT system consists of three controlled <sup>60</sup>Co sources (initial dose rate 550 cGy min<sup>-1</sup>) with three 10.5 × 10.5-cm<sup>2</sup> fields at the isocentre from three gantry angles set 120° apart from one another.<sup>20</sup> During treatment delivery, the MR can continuously and simultaneously track in one sagittal plane at four frames/second or in three parallel sagittal planes at two frames/second using real-time deformable image registration-based beam control.<sup>20</sup> Finally, VRS' adaptive RT TPS uses Monte Carlo dose calculations, capable of delivering IMRT or conformal RT or even both, and it is fully capable to perform on-couch, real-time adaptive RT.<sup>20</sup> Its TPS is robust and time-efficient; it can calculate nine-field treatment plans within 30 s. The TPS can also perform its calculations with and without the effects of the MR field being present.<sup>20</sup> In September 2015, Wooten *et al*<sup>21</sup> published their report of their first RT treatment using the VRS at Washington University. Since then other sites have followed suit with clinically treating with their VRS such as the University of California, Los Angeles (Los Angeles, CA).<sup>22</sup>

Hu *et al*<sup>19</sup> evaluated the VRS' image quality as compared with the American College of Radiology's guidelines for the Washington University VRS and found that the system met all American College of Radiology and vendor specifications. Hu *et al*<sup>19</sup> measured slice position error to be <1 mm, slice thickness error was <0.5 mm and the resolved high-contrast spatial resolution was 0.9 mm. Geometric distortions for the 20- and 35-cm-diameter spherical volumes were 0.1 and 0.18 cm, respectively, for high spatial resolution three-dimensional images and 0.08 and 0.2 cm for two-dimensional (2D) high temporal cine images.<sup>19</sup>

The VRS is not the only MR-gRT option. Several other options exist and will soon be operating clinically. Namely, their largest difference from the VRS is that they are mostly MR units combined with linacs and have higher MR field strengths than the VRS (Table 1).

One such MR-linac system is Dr Fallone's rotating biplanar linac (RBL)-MRI system in the University of Alberta's Cross Cancer Institute, Edmonton, AB.<sup>23,24</sup> It is designed with an open biplane (0.6-T) magnet with a 6-MV linac that can be positioned either between the magnet planes or through one of the central openings of the magnet planes.<sup>23</sup> This allows for the radiation treatment field to be either parallel or perpendicular to the magnetic imaging field.<sup>23</sup> Like the VRS, this system allows for MR to image during radiation treatment delivery for real-time guidance.<sup>23</sup>

One of the main advantages of the RBL system is that it was designed to be delivered in small parts, which is ideal for standard-sized RT vaults, and it has a cryocooler which allows the unit to maintain superconducting temperatures without the use of cryogenic liquids, as most other MR-gRT systems require.<sup>23</sup> Similar to the VRS, the RBL system has real-time tumour tracking, an automated tumour-contouring algorithm, tumour-position predictive algorithms supported by neural networks and the capability to move the multileaf collimators (MLCs) in real time with the tumour.<sup>23</sup> One thing that

Table 1. MRI-guided radiotherapy units

MR dimensions	Radiation unit specifications	Location	Manufacturer/ publication
0.35-T whole-body scanner, 70-cm bore	Three-headed $^{60}\text{Co}$ system; 5.5 Gy min $^{-1}$ at isocentre	FDA-501(k) cleared. First installation at Washington University, St Louis, MO	20
0.35-T whole-body scanner, 70-cm bore	Three-headed $^{60}\text{Co}$ system; 5.5 Gy min $^{-1}$ at isocentre	VU University Medical Center, Amsterdam, Netherlands	20
0.35-T whole-body scanner, 70-cm bore	Three-headed $^{60}\text{Co}$ system; 5.5 Gy min $^{-1}$ at isocentre	Seoul National University Hospital, Seoul, Republic of Korea	20
0.35-T whole-body scanner, 70-cm bore	Three-headed $^{60}\text{Co}$ system; 5.5 Gy min $^{-1}$ at isocentre	Sylvester Comprehensive Cancer Center, University of Miami, Coral Gables, FL	20
0.35-T whole-body scanner, 70-cm bore	Three-headed $^{60}\text{Co}$ system; 5.5 Gy min $^{-1}$ at isocentre	University of California, Los Angeles, Los Angeles, CA	20,22
0.35-T whole-body scanner, 70-cm bore	Three-headed $^{60}\text{Co}$ system; 5.5 Gy min $^{-1}$ at isocentre	University of Wisconsin Carbone Cancer Center, Madison, WI	20
1.5-T MR scanner, 70-cm bore	Mobile MR scanner, 6-MV linac (IMRT, VMAT, CBCT)	Princess Margaret Hospital, Toronto, ON	IMRIS and Varian; <sup>25</sup>
1.5-T MR scanner (Philips Achieva®), 70-cm bore	6-MV linac (Elekta)	University Medical Center Utrecht, Utrecht, Netherlands	Elekta and Philips Healthcare; <sup>15</sup>
1.5-T MR scanner (Philips Achieva), 70-cm bore	6-MV linac (Elekta)	Sunnybrook Health Sciences Center, Toronto, ON (pending)	Elekta and Philips Healthcare
1.5-T MR scanner (Philips Achieva), 70-cm bore	6-MV linac (Elekta)	The Froedtert & Medical College of Wisconsin Cancer Center, Milwaukee, WI (pending)	Elekta and Philips Healthcare
1.5-T MR scanner (Philips Achieva), 70-cm bore	6-MV linac (Elekta)	Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands (pending)	Elekta and Philips Healthcare
1.5-T MR scanner (Philips Achieva), 70-cm bore	6-MV linac (Elekta)	Institute of Cancer Research, London, UK (pending)	Elekta and Philips Healthcare
1.5-T MR scanner (Philips Achieva), 70-cm bore	6-MV linac (Elekta)	The Christie NHS Foundation Trust, Manchester, UK (pending)	Elekta and Philips Healthcare
1.5-T MR scanner (Philips Achieva), 70-cm bore	6-MV linac (Elekta)	MD Anderson Cancer Center, Houston, TX	Elekta and Philips Healthcare
0.6-T MR scanner, 60-cm bore	6-MV linac	Prototype at Cross Cancer Institute, Edmonton, AB	Research System; 23
1-T MR scanner, 80-cm bore	6-MV linac	Design study	28

CBCT, cone beam CT; FDA, US Food and Drug Administration; IMRT, intensity-modulated radiation therapy; linac, linear accelerator; VMAT, volumetric modulated arc therapy.

Fallone's<sup>23</sup> group did first was to quantify the signal-to-noise ratio (SNR) reduction as a function of the radiation-induced current due to the photon radiation's impact on the MR coils which was in the order of 15–18% at 250 MU min $^{-1}$ . To compensate for this, they created methods to improve SNR using build-up or image processing in *k*-space.

Perhaps one of the most comprehensive MR-gRT facilities in existence is the Princess Margaret Cancer Centre (PMCC) which has a rail-mounted 1.5-T MR scanner that can operate in three different suites: an MR simulation suite, an MR-guided brachytherapy (Nucletron; MicroSelectron high dose rate, iridium-192, 10 Ci) suite and an MR-guided external beam suite (Varian;

TrueBeam, 6-MV, 1400 MU min $^{-1}$ ).<sup>25</sup> PMCC's system has a MR coil specifically designed for radiation oncology with extended field-of-view capabilities for head and neck and pelvic imaging.<sup>25</sup> Automated shielding doors (6.4 cm for the brachytherapy suite and 20.3 cm for the external beam suite) allow the MR scanner to enter suites safely.<sup>25</sup> Similar to the design of most CT-on-rails external radiation therapy beam designs, PMCC's MR-on-rails is designed to advance over a patient after they have been translated 3.1 m between the Truebeam linac's isocentre and the MRI isocentre.<sup>25</sup> Despite the comprehensive nature of all of the MR suites that this facility has, it lacks one of the hallmark features of other MR-gRT units, real-time adaptive planning, tracking and imaging using MR. Still, it does offer

their patients more frequent response assessment in the treatment position. Nominally, there is currently a 120-s time delay from MRI to treatment delivery which they hope to reduce to <90 s.<sup>25</sup>

Lagendijk et al<sup>27</sup> at the University Medical Center in collaboration with Elekta AB (Stockholm, Sweden) and Philips (Best, Netherlands) developed a fully integrated MR-linac unit which includes a 1.5-T Achieva® Philips MRI and an Elekta 6-MV accelerator in a ring configured in the mid-transversal plane about the MR.<sup>14,26,27</sup> The team is still working to create a real-time Monte Carlo-based TPS that will allow for online, during-treatment adaptive planning for their unit.

Finally, Australia's MRI-linac program is similar in some regards to Fallone's RBL system in that it is also an open-bore 1-T magnet with the capability of delivering radiation inline and perpendicular to the orientation of the magnetic field.<sup>28</sup> What is unique about Australia's design is that they are considering whether to rotate the patient or rotate the MR-linac itself.<sup>28,29</sup> Mounting the linac inline to the magnetic field has several advantages: no beam attenuation or Compton scatter to the patient from irradiating through the cryostat; lower exit dose; no need to control for eddy currents or have dynamic shimming; the magnetic field has less impact on the electron gun; electron transport; and the waveguide operation.<sup>28</sup> However, the inline orientation would require more engineering since it is not common. The easier orientation for the MR-linac would be to follow a perpendicular approach with the linac sandwiched in-between the magnet biplane doughnuts, similar to the Fallone's RBL system. This design allows for better imaging performance, lower skin dose, no need to rotate magnet or patient and lower constraints on the magnet, gradient coil and RF design.<sup>28</sup>

Keall's group has made considerable effort to describe and measure the impact of the magnet on the linac's components ranging from the electron gun to the MLCs. Their finite-element modelling study showed that the MLC does not create significant inhomogeneities in the MRI field for source-axis distances at 140 cm or beyond, that dynamic shimming is not required during treatment and the 1500 N force between the magnet and the MLCs is manageable.<sup>28</sup> However, his team did report that the electron gun should be modified in the linac to prevent current loss.<sup>28-30</sup> An unshielded gun in the perpendicular orientation can be more sensitive to the magnetic field and accelerate electrons orthogonally away from the waveguide.<sup>28</sup> In order to reduce skin dose in the inline orientation, Keall's group suggests optimizing magnet design, using bolus, magnetic scrapers and helium regions placed strategically between the linac and the patient.<sup>28</sup>

We believe MR will play a major role in the future of radiation therapy. MR simulators have already started appearing in some clinics. Even MR only simulation and treatment planning are taking hold in certain body sites.<sup>31</sup> Also, the application of pseudo-CT density data and synthetic CT are promising in enabling MR image only treatment planning.<sup>32,33</sup> Dedicated MR simulators are available with coils and immobilization specifically designed to work in the RT and MR setting. Also, several groups have dedicated

their research to developing suggestions for suitable imaging protocols for MR-gRT imaging techniques (Table 2).<sup>34-51</sup> Tables 1 and 2 were created based upon a literature review.

## BIOMARKERS AND MRI

Owing to its high contrast detail of soft tissue, MRI can contribute uniquely to the RT imaging needs. For example, the high contrast of MRI will enable contouring of intrahepatic lesion without MR contrast administration.<sup>52</sup> In addition, it has the ability to improve contouring accuracy in many disease sites including the prostate, brain, nasopharynx etc.<sup>53</sup> and in critical structures such as the brachial plexus and salivary glands. In addition to morphological imaging, MRI has the capability to provide functional imaging. Higher cell proliferation rate in cancer leads to higher cell density and this decreases extracellular space, which in turn reduces the mobility of water molecules. This leads to a decrease in the apparent diffusion coefficient in cancerous regions compared with normal tissues. Thus lower apparent diffusion coefficient can be used for tumour detection as well as treatment response and prediction.<sup>54,55</sup> Similarly, diffusion tensor imaging has been shown to improve delineation of difficult-to-treat high-grade gliomas than using only  $T_1$  weighted images.<sup>35</sup> Dynamic contrast enhanced MRI has been shown to be useful in evaluating late cardiac toxicity due to radiation therapy.<sup>56</sup> MRI is extremely useful in guidance of brachytherapy insertions as well as post-implant evaluation.<sup>57-60</sup> MR as an on-board image modality carries the inherent advantages (high contrast, functional information, better tumour and normal tissue discrimination) to image guidance. MRI is specifically useful in visualizing the brachial plexus, spinal cord, intrahepatic lesions, brain etc.<sup>10</sup> In addition, it adds no radiation dose; it is possible for some clinical sites to image in the treatment orientation; and ultrafast techniques are available to reduce motion-induced blur for imaging guidance in hypofractionated treatment settings. It is to be noted that recent developments such as multiplexed sensitivity encoding and simultaneous multislice potentially provide sufficient spatial resolution to be used for real-time image guidance.<sup>61,62</sup>

The ability of magnetic spectroscopy imaging (MRS) to diagnose areas of high metabolic activity linked to tumour cell proliferation is particularly useful for RT treatment planning because of better gross tumour volume delineation.<sup>27</sup> MRS can also help during image guidance by daily tumour imaging facilitating simultaneous integrated boost treatments. MRS has the potential to differentiate recurrence from scar tissue in previously irradiated sites.<sup>28</sup> The fundamentals of MRS stem from the fact that the resonant frequencies of metabolites can be resolved using strong-enough magnetic fields.<sup>63,64</sup> The common and relatively abundant metabolites are creatine which is an energy marker, choline which is a cell membrane marker and *N*-acetylaspartate which is a neuronal marker.<sup>65</sup> The ratio of these markers to one another can be used to differentiate abnormal tissue from the normal one. Poptani reported, in 1995, that intracranial lesions can be characterized using *in vivo* proton MR spectroscopy.<sup>29</sup> Since then MRS has been studied in various sites including the prostate, brain, breast etc.<sup>63,66-68</sup> With the availability of MR simulators and IGRT systems, serial monitoring of these metabolites becomes practical and hence

Table 2. Site-specific suggested MR sequences

Anatomical location	Acquisition sequence	Reference
Brain	$T_1$ 3D gradient echo	34,36
	Post-Gd- $T_1$ standard spin echo	35,36
	Proton density fluid-attenuated inversion-recovery	35,36
	$T_2$ FLAIR	36,53
Head and neck	Post-Gd- $T_1$ standard spin echo	36,37
	$T_2$ weighted sequence with fat saturation	36,38
	$T_1$ 3D gradient echo (pre- and post-contrast)	36,53
Breast	$T_1$ inversion-recovery (STIR) sequences	36,39
	$T_2$ weighted 3D FSE (XETA)	36,40
	$T_1$ weighted TSE	36,41
	$T_1$ 3D gradient echo	36,53
GYN	TSE $T_2$	36,42
	$T_2$ weighted FSE	36,53
	$T_1$ 3D gradient echo	36,43,44,53
Prostate	$T_2$ weighted FSE	36,45
	$T_1$ 3D gradient echo	36,53
Rectum	$T_2$ weighted FSE	36,46
	$T_1$ and $T_2$ STIR	36,48
	$T_1$ 3D gradient echo	36,53
Liver	Cine-MRI, FIESTA	49
	3D true fast imaging gradient echo	50
Lung	Cine-MRI, true-FISP	51

3D, three-dimensional; FIESTA, fast imaging employing steady-state acquisition; FLAIR, fluid-attenuated inversion-recovery; FSE, fast spin echo; Gd, gadolinium; STIR, short tau inversion-recovery; true-FISP, true fast imaging with steady state free precession; TSE  $T_2$ , turbo spin echo  $T_2$ ; XETA, extended echo-train acquisition.

biological progression can be readily evaluated during the course of radiation treatment.

The absence of fluorine-19 ( $^{19}\text{F}$ ) in soft tissue makes it an ideal contrast agent for spectroscopy. However, in order to obtain sufficient SNR, the density of  $^{19}\text{F}$  needs to be increased on the molecular basis which is accomplished through perfluorination in which all  $^1\text{H}$  atoms in a hydrocarbon chain are replaced with  $^{19}\text{F}$  atoms.<sup>64,69</sup> These perfluorocarbons (PFCs) are similar to common organic compounds in their molecular structure except that they are very electronegative. This produces the desired chemical shift to be effective as a contrast agent.<sup>64</sup>  $^{19}\text{F}$  nuclear MR can be used for functional lung imaging, cell tracking using PFC emulsions and *in vivo* monitoring of fluorinated drugs and their metabolites such as chemotherapy agents.<sup>64</sup> In addition,  $^{19}\text{F}$  can bind with a biomolecule acting as a ligand. This property is exploited in measuring oxygen concentration as the later affects paramagnetic effects of the former. Hyperpolarized PFCs and  $^3\text{He}$  have been used to evaluate lung function parameters such as ventilation distribution, ventilation/perfusion ratios and regional oxygen partial pressure.<sup>63,64,66–68</sup> PFC is also ideal for cell trafficking

and migration as the absence of  $^{19}\text{F}$  in tissue makes detection of PFC in cells possible in real time.<sup>69,70</sup>

### CHALLENGES OF MRI-GUIDED RADIOTHERAPY

MR-gRT has an array of advantages over traditional types of IGRT platforms, but it does have some limitations that must be addressed. For each treatment site, the work is still being carried out to determine the optimal MRI sequences that should be utilized for the imaging demands of that organ/clinical setup. In addition, these sequences should also be efficient or timely.

A recent work by Paulson et al<sup>71</sup> provides information on full consensus agreements based on feedback from a series of questionnaires regarding site-specific MRI simulation. For brain MRI simulations, the article suggests that geometric distortions be  $<1\text{ mm}$  for stereotactic treatments and  $<2\text{ mm}$  for non-stereotactic brain treatments.<sup>71</sup> Also, there was full consensus established for using post-contrast  $T_1$  weighted image as the reference simulation image to be co-registered to planning CT.<sup>71</sup> For head and neck treatments, the authors suggest that the tumour region be identified using fat-suppressed, post-contrast  $T_1$  weighted sequences and oedema should be identified using  $T_2$

weighted turbo spin echo sequences.<sup>71</sup> For prostate simulations, no consensus was reached regarding consistent organ-filling methods between CT and MRI simulation.<sup>71</sup> However, full consensus was achieved for using axial multislice 2D  $T_2$  turbo spin echo images with 3-mm slice thickness and <1 mm in-plane spatial resolution in order to contour the seminal vesicles and prostate gland.<sup>71</sup> The study found that for the prostate and cervix, there is no consensus or agreement on imaging the patients on flat table arrays in immobilization devices for their MR simulation. For cervix MRI simulations, there was agreement for acquiring multislice 2D  $T_2$  weighted turbo spin echo images in both the axial and sagittal planes as well as using the  $T_2$  weighted image as the reference set to be co-registered to the planning CT.<sup>71</sup>

Beyond the work that still needs to be carried out to offer agreed-upon MRI simulation protocols, there are other issues with MR-gRT such as the magnetic field's impact on secondary electrons. The presence of magnetic field can cause effects on the secondary electrons as noted earlier, and robust techniques in the dose calculation algorithm for the unit must account for these effects. It is possible for the magnetic fields to cause warping of the dose and hot spots at material interfaces.<sup>72</sup> This requires the TPS to account for and reduce the electron return effect. Alternatively, work has been carried out to create new units that have the magnetic field positioned in parallel to the radiation beam which eliminates electron return effect.<sup>23,73</sup>

Furthermore, MRIs are normally acquired in a position without immobilization tools unlike that of a RT treatment position. The length of time for an MRI acquisition greatly exceeds the time of a RT treatment and therefore can lead to blurring of the MRI data set. Quality assurance (QA) must be performed to ensure the geometric accuracy of the MRI data set, and MR images lack electron density information that is needed for RT dose calculations.<sup>74</sup> The American Association of Physicists in Medicine's Task Group 142, lists guidelines for daily tolerances for the coincidence between imaging and treatment isocentres which is  $\leq 2$  mm for non-stereotactic treatments and  $\leq 1$  mm for stereotactic treatments.<sup>75</sup> One report has shown that their 3-T MRI protocol yields geometrically accurate planning data sets with  $\leq 0.6$  mm external fiducial reference deviations.<sup>76</sup> Therefore, there is evidence that MRI data sets may be useful without being registered to CT scans for use in RT treatment planning.

However, implanted metal devices in the patient may cause artefacts in the MR images, such as signal loss, intense areas of signal accumulation and distortions in the area near the implant, even if they are non-magnetic.<sup>74</sup> The MR image is reconstructed from the RF signal coming mainly from protons, and the electron density information is lacking. However, MRI can be used to estimate electron density.<sup>74</sup> Alternatively, MRI data sets can be registered with CT data set for treatment planning purposes. MRIs can also be segmented into small partitions that can provide electron density estimates. MRI manufacturers are working on RT applications which would provide these estimates for MR-RT consoles.<sup>74</sup>

Finally, QA devices must be manufactured for thorough testing of the magnetic field effects on the radiation beam. Current QA devices need to be made MR compatible, and also, online tools for during-treatment detection of transit dose need to be made suitable for these units. ArcCHECK-MR (Sun Nuclear Corporation, Melbourne, FL) is a cylindrical QA water-equivalent phantom containing diode arrays in a spiral pattern with a plug insert which allows for ionization chamber reference dosimetry.<sup>77</sup> Houweling *et al*<sup>77</sup> measured maximum dose differences <1.5% when they compared their ArcCHECK-MR readings for their MR-gRT unit compared with their conventional non-magnetic-field linac.

## THE FUTURE OF IMAGE-GUIDED RADIOTHERAPY MR-proton units

The excellent soft-tissue contrast of MRI can be combined with tissue-sparing properties of particle beams to reduce dose to normal tissues therefore dose escalation without significant adverse effects can be realized. Despite MR-guided cobalt and linac units just being unveiled at a few locations worldwide recently, Raaymakers *et al*<sup>78</sup> have been evaluating the feasibility of MRI-guided proton therapy units since 2008.<sup>17,78</sup> One of the advantages this team observed when they did simulations of 90-MeV proton beams in the presence of a 0.5-T magnetic field was that the proton beam dose distribution was not affected much.<sup>17,78</sup> They calculated no effect of the magnetic field on the proton beam at tissue-air interfaces and minimal disruption of the dose distribution since the secondary electrons produced by proton beams have low energy.<sup>78</sup> A more recent work from the same group has shown through the use of the Monte Carlo software Tool for Particle Simulation that intensity-modulated proton therapy in a transverse 1.5-T magnetic field is dosimetrically possible and that the resultant dose distribution for 0-T and 1.5-T intensity-modulated proton therapy plans have equivalent dose distributions.<sup>79</sup> It should be noted that Wolf and Bortfeld<sup>80</sup> performed analytical calculations that indicated the lateral deflections of proton beams in the presence of even small magnetic fields on the order of just 0.5 T could still be significant (1 cm and larger).

Another group performed Monte Carlo simulations of proton treatments for several sites, including the lung, liver, prostate, brain, skull-base and spine, with 0.5- or 1.5-T magnetic fields.<sup>81</sup> Their simulations showed that targets with minimal tissue heterogeneity such as the liver or spine, suffered the least from dose distortions. Low magnetic fields (up to 0.5 T) had no impact on target coverage or on normal tissue toxicity. However, higher magnetic field strength in certain sites caused severe underdosage of target which could be remedied by changing beam angle and beam isocentre.<sup>82</sup>

## CONCLUSION

IGRT has advanced in concert with our understanding of the underlying biology of cancer we aim to treat. From static megavoltage ports to CBCT, on-board imaging capability has greatly increased and thus improving our ability to target volume accurately and precisely. The clinical benefits of these new combined MR-gRT units remains to be evaluated, but with the growing number of units with each year, it is a matter of time before we see the results.

MR-gRT solutions are being made rapidly to overcome the obstacles associated with MR-only workflows encompassing QA devices, novel dose calculation algorithms that can account for magnetic field dose perturbances, fast automated contouring algorithms and imaging protocols for intrafraction motion monitoring and plan adaptation.<sup>61,77,84,85</sup> Another potential solution to the issue of cost-effectiveness of this technology would be to determine if the addition of off-line MRI simulations might improve the accuracy of current day IGRT while improving patient throughput on MR-gRT systems.

Currently, with the help of CBCT and kilovoltage imaging, radiation oncologists are well equipped to identify and treat anatomical structures. With on-board MR systems, they will have the capability to target based on function information. The next important step in curing disease lies in identifying the clinical target volume, the biologically active margin of

difficult-to-visualize cancer cells that extends beyond the obvious, visible tumour mass. Our next goal will not only be targeting the current disease but also in having the data to know what future area to target since it will become the disease that causes a metastasis tomorrow. So far, MRI has been shown as a means to measure background parenchymal enhancement which was associated with increased risks of developing breast cancer.<sup>83</sup> Breakthroughs similar to this breast cancer study imply that our field is not only on the way beyond just treating today's tumour but also being able to obtain the real-time biological and anatomical data needed to effectively treat cancer before it even starts. With the help of online MR guidance, radiation oncologists will soon be able to image biomarkers during treatment and be able to adapt the plan or even change the treatment intent based upon real-time data which could shed light on treatment or disease progression. For these reasons, we believe that the future of IGRT will be MR guided.

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