The Transformation Of Radiation Oncology Using Real-Time Magnetic Resonance Guidance, A Review

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Abstract:
Radiation therapy (RT) is an essential component of effective cancer care and is used across nearly all cancer types. The delivery of RT is becoming more precise through rapid advances in both computing and imaging. The direct integration of magnetic resonance (MR) imaging with linear accelerators represents an exciting development with the potential to dramatically impact cancer research and treatment. These impacts extend beyond improved imaging and dose deposition. Real-time MR-guided RT is actively transforming the work flows and capabilities of virtually every aspect of radiation therapy. It has the opportunity to change entirely the delivery methods and response assessments of numerous malignancies. This review intends to approach the topic of MR-based RT guidance from a vendor neutral and international perspective. It also aims to provide an introduction to this topic targeted towards oncologists without a specialty focus in radiation therapy. Specialty implications, areas for physician education, and research opportunities are identified as they are associated with MR-guided RT. The uniquely disruptive implications of MR-guided RT are discussed and placed in context. We further aim to describe and outline important future changes to the specialty of radiation oncology that will occur with MR-guided RT. The impacts on radiation therapy caused by MR-guidance include target identification, radiation therapy planning, quality assurance, treatment delivery, training, clinical workflow, tumor response assessment, and treatment scheduling. In addition, entirely novel research areas that may be enable by MR-guidance are identified for future investigation.

Introduction:

Clinical evidence supports the use of radiation therapy (RT) in over 50% of all cancer patients. With global cancer cases to reach 24.9M by 2035, further advances in RT are important to improve cancer outcomes and to minimize side effects[1]. Image-guided radiation therapy (IGRT) has represented an important advance in radiation therapy for well over a decade[2]. IGRT has been widely adopted by the radiation oncology community and is used in the majority of radiation treatments [3,4]. Radiation oncologists are amply trained in the acquisition and interpretation of CT images used for IGRT. Contemporary IGRT allows for increasingly precise target localization along with tumor and normal structure position verification in three dimensions[2].

Magnetic resonance (MR) imaging offers superior soft tissue discrimination, increased sensitivity for tumor detection and dynamic biological and functional data about tumors and normal tissues. MR imaging has been used for well over a decade to help define and direct radiation therapy volumes in many cancer sites. MR imaging's role in radiation therapy has largely remained limited to the initial radiation planning stages, i.e. before treatment begins. MR imaging devices have recently merged with radiation delivery devices (linear accelerators) to form an entirely novel radiation therapy paradigm categorized as MR-guided radiation therapy (or "MRgRT)". MRgRT possesses the ability to acquire an MR image immediately before, during, and after the patient is treated with radiation therapy, all with the patient in the same treatment position. In this review, we summarize the current approaches to MRgRT and highlight its implications and opportunities on oncology at large.

Methods:

An experienced cohort of radiation oncologists and medical physicists were assembled, bringing together users of the two commercially available MRgRT systems. Each author had intimate familiarity with the logistics and technical challenges associated with MRgRT in the two currently available commercial units. A literature search was conducted via PubMed using the key words "*MR-Guided radiation therapy* (766 items reviewed)", "*MR Linac* (248 items reviewed)", "*ViewRay* (54 items reviewed) ", and search results were curated. We restricted our search to English-language articles published from 1995 to 2018 and those that focused on single unit MRgRT devices. Abstract only publications were excluded. Research articles focused on combining MR images with RT treatment were also excluded as they were extensive in nature and considered beyond the scope of this review. The literature search was restricted solely to series focused on the combination MR-linear accelerator-based devices; articles examining in-room MR solutions, or "MR on rails" were also excluded.

Discussion and Observations:

The current state of MRgRT is rapidly evolving and expanding. This technology is positioned to dramatically impact the treatment of thousands of cancer patients annually. It will also rapidly introduce entirely novel research questions and opportunities. MR guidance has some similarities, but also crucial differences, to other recent technological developments in the delivery of radiation therapy. Figure 1 presents a general overview of workflow differences introduced with MR Guidance.

Radiation therapy has undergone several transformations over the past fifteen years. The routine use of CT simulation required a primary knowledge expansion on the part of radiation oncologists who had to familiarize themselves with cross-sectional and three dimensional anatomy as depicted on CT-based imaging. Since the introduction of CT-based planning other major technological advances in the form of intensity-modulated radiation therapy (IMRT) and proton therapy have been introduced. The introduction of IMRT represented a considerable improvement in radiation dose sculpting and normal tissue avoidance. Protons and heavy ions represent further gains in dosimetric conformality. MRgRT is unique in its contribution of extremely high quality imaging at the time of treatment. To help illustrate the impact of MRgRT, we have divided the discussion into several categories outlining the current and anticipated changes to the discipline of radiation therapy following the introduction of MRgRT.

Differences between MRgRT and other technological advances in radiation therapy:

While IMRT and proton therapy have resulted in important improvements in radiation dose deposition, neither has addressed two central problems facing radiation therapy. These specific challenges that remain inadequately addressed include 1) high doses of radiation delivered to normal organs in very close proximity to the treated tumor (which is often unavoidable secondary to the need for a planning target volume (PTV) expansion to account for daily set up uncertainties) and 2) personalization of radiation therapy via active monitoring of biologic tumor response. Total dose deposition, and conformality of dose, have been an understandable focus of radiation oncology technological advancement for decades. This has motivated the development of IMRT, IGRT, and proton therapy. Important to realize is that radiotherapy planning involves delivering dose not only to the tumor volume but also a rim of surrounding normal tissue to take into account systematic and random errors such as calibration uncertainty and organ motion. While the high dose conformality with IMRT and proton therapy have enabled dose escalation, the radiation oncology community has seen that dose escalation alone may fail to improve outcomes[5]. This might be limited by the need for a PTV expanding into some critical local structures. Indeed, CT based strategies for dose escalation are often compromised by the large uncertainty of tumor and normal structures with low soft-tissue contrast on CT images. Moreover, current CT-based methods suffer from an incapability of monitoring tumor and normal structure movement during radiation delivery. MR guidance directly addresses and improves upon these issues. The ability to determine the location of the tumor and adjacent normal organ/tissue boundaries, together with the ability to account for intra- and inter-treatment motion, will reduce radiation dose to normal organs, thereby

widening the therapeutic window. A summary of major technologic developments in radiation oncology and their potential contributions to clinical oncology research can be seen in *Table 1*.

Existing technological implementations of MRgRT*:*

At the time of writing this article, there are two commercially available MRgRT technologies. These devices are manufactured by ViewRay (ViewRay Technologies Inc, Oakwood, Ohio) and Elekta (Elekta AB, Stockholm, Sweden). There are also at least two devices that are in active development, one is by an Australian-based development group[6] and the second is the Aurora-RT system (MagnetTx Oncology Solutions, Edmonton, Alberta, Canada) [7]. These devices are gaining rapid and wide market traction (eg. 36 Elekta Unity systems have been sold and approximately 51 from ViewRay). Key differences between devices are presented in *Table 2*. The discussion will focus on the two commercially available devices, namely the ViewRay MRIdian and Elekta Unity MR Linac systems. The ViewRay MRI-cobalt device has been FDA approved since May 22, 2012, and Viewray MRIdian linear accelerator has been approved since February 24, 2017 and the Elekta Unity system received FDA approval on December 5th, 2018. There are numerous published series describing the initial clinical experience and case mix using the ViewRay MRIdian device (Table 2)[12,32-46]. To date, ViewRay has produced two different systems consisting of their first device, a split 0.35 T magnetic resonance scanner with a ring gantry and 3 multileaf collimator-equipped ^{60}Co heads (no longer in production) followed by their second device, capable of 6 MV photon production combined, again, with a 0.35 T MR.[8] The Elekta Unity system is a 1.5 T MR produced by Philips combined with a 7 MV linear accelerator produced by Elekta[9,10]. Details regarding each of these systems is presented in Table 2.

Implications of MR guidance on radiation treatment volumes:

As mentioned above, at the core of radiation therapy is the PTV[11]. This PTV margin is needed to account for inter- and intra-fractional variability of set-up of the tumor and normal structures. Typically ranging from 3 mm to 15 mm, the PTV structure extends considerably into adjacent normal organs or tissues that do not contain tumor. The need to incorporate a PTV margin with the associated exposure of adjacent normal structures currently limits the dose and fractionation schemes to what is tolerated by normal tissues rather than what is required to achieve tumor control. A fundamental change that will likely be seen with MR guidance is that using MRI immediately before and during a treatment delivery will enable accurate delineation and monitoring of tumor and normal structures at every treatment. This will result in much smaller irradiated volumes. For example, the elimination of PTV margins in the treatment of breast cancer has resulted in a 52 % reduction in the PTV volume, which likely has important implications for cosmetic outcomes[12]. This will result in lower doses of radiation to normal structures very close to the tumor. *Figure 2* visually illustrates differences, and potential benefits, of smaller PTV expansions.

While exciting and promising, this change also has important implications on physician and other radiation caregiver time. Such an MRI guidance strategy requires a radiation oncologist

and medical physicist to spend additional time at the machine to adapt treatment delivery on a daily basis, as tumor and normal organ changes are detected[13]. *Figure 1* highlights some of these key differences in workflow that may be presented with MRgRT. Radiation oncologists and radiation therapists will have to adapt their schedules to account for the additional time necessary to monitor the tumor and normal organs now seen continuously with MRgRT.

Training and education in MRgRT for radiation oncologists:

Routine use of MRI will require considerable "up-skilling " and education of radiation oncology professionals. Although MR has benefits at the time of simulation, it is not routinely used across the world. To optimize response evaluation, regional organ definitions, and data provided by various MRI sequences, these sequences will need to be understood by radiation oncologists. Radiation oncology societies will need to work with MR societies to develop educational programs to ensure radiation oncologists, medical physicists, dosimetrists and radiation therapists/radiographers are adequately trained in MR utilization, assessment and safety. In addition, the images acquired during the process of radiation treatment planning and delivery may be of value to other specialties, particularly in medical systems in which MR resources are scarce. An infrastructure through which treatment images could be easily shared with oncology colleagues may also be necessary for radiation oncology departments to consider.

Reimbursement Associated with MR Guidance:

Additional physician and medical physicist time and effort will be a component of the MRgRT workflow. This includes, but is not limited to, time spent at the treatment machine in delineating tumor and normal structures, adapting treatment plans based on the daily MRI, observing real-time tumor and normal structure changes, and evaluating treatment response from functional imaging[14]. Professional society groups involved with developing reimbursement codes may need to consider if additional billing codes are needed (and if they are justified) to account for this type of treatment delivery. Until such reimbursement codes are clarified, guidance as to the use of existing codes will be necessary to appropriately account for the time, effort and risk involved in the delivery of MRgRT. It is imperative that radiation oncology research groups prove the value of these added efforts through high quality, peer-reviewed, prospective research by showing measurable clinical improvements in cancer specific outcomes, and/or reduction of toxicity as compared to existing radiotherapy delivery technologies. To justify this additional time, effort, and cost, value must be proven. For this purpose, efforts are underway through two active research consortia to collect such data to prove the value-added of these technologies[15,16].

Unique Challenges Associated with MR Guided Radiation Therapy:

Radiation therapy deposits radiation dose via secondary charged particles, primarily electrons. The exposure of these electrons to a strong magnetic field changes the manner in which radiation dose is deposited. One well described effect, entitled the electron return effect,

presents such an example of this challenge[17]. This effect is the result of electrons moving in a circular pattern in the presence of a magnetic field, as opposed to a more linear path in the absence of a magnetic field. This effect results in a complicated radiation dose effect, particularly at tissue-air interfaces. Fortunately, advanced treatment planning software can model this dose effect and this can be accounted for in the process of radiation therapy planning[18]. It should also be considered that dose calculation in the presence of B-Fields is a novel and important challenge. MR images are also subject to geometric distortion which can alter the appearance of normal anatomy or the target. Such distortion must be carefully considered during a treatment course[19,20]. The potential impact on the patient of spending prolonged lengths of time in a confined space must also be carefully considered. Claustrophobia is a common concern, and the impact on patient-reported quality of life has been examined, in total approximately 5% of patients seem to have found this treatment unacceptably long[21]. Moreover, robust quality assurance methods of radiation treatment plans may require an entirely novel approach, given the influence of the magnetic field [22].There is also a necessity for compromises in the functionality of both the MR imaging device, along with the radiation delivery device when combining these units given the technical complexity of combining these devices. Such compromises may lead to longer treatment times. During this treatment time there may be an increase need to account for the movement of normal organs. In addition the process of online adaptive re-planning will introduce entirely novel challenges, with regard to physician time and workflow. Finally, MRgRT will present unique challenges with increasing need for improvements in mechanism for automation, archiving imaging, deformable image registration, exquisite Rad Onc attention to ferrous materials, and dose accumulation using MRI.

Future Directions, routine MR-based tumor response monitoring:

The collection and application of these MRI-based data may enable the delivery of the most effective dose to an individual tumor biology rather than the highest dose of radiation that can be delivered to a given tumor based on histology, stage, and location. Reduction in the PTV and improvements in tumor targeting will represent important, if linear, steps forward towards better and more conformal treatments for patients treated with MRgRT. While they are critically important, such innovation by itself would not represent a true transformation of radiation therapy. The ability to routinely acquire daily, functional MR imaging, and subsequently act on those data, directly in the treatment setting, presents an entirely new paradigm for the specialty. Imaging-based biomarkers will represent the future of cancer treatment delivery, and numerous candidate biomarkers have been extensively discussed and published[23]. Radiation oncology is well positioned to embrace this shift and MR guidance is optimally suited to enable response-based, personalized, radiation therapy. Indeed, the future of a biological, image-guided, adaptive radiation therapy, (BIGART) is very exciting. There are multiple established, MR-based response metrics in patients undergoing treatment for cancer. A summary of a variety of these metrics can be seen in Table 3. Most of these have been examined in patients being treated with chemotherapy and some have been examined in patients undergoing radiation therapy (Table 3). To date, the routine acquisition of diagnostic quality MRIs during a course of radiation therapy has been prohibitively expensive and

inconvenient for patients. Time on an MRI scanner is a highly limited resource at nearly all hospitals. The introduction of MR linac, with the capability to acquire many MRI sequences routinely during daily treatment, introduces a novel method of data collection. Rapidly, centers will start observing changes on MRI that occur in both the tumor and normal tissues during a treatment course. These changes, uniquely seen on MRI, can then be tested as early biomarkers correlated with cancer specific outcomes. Contrast agents during treatment may also hold promise for investigation[24]. The potential for early changes in MR (e.g. diffusion weighted imaging) to be correlated with long term outcomes has been shown in multiple tumors during a course of treatment with radiation, summarized in Table 3. These findings need robust prospective validation, which routine use of MRIGRT may provide. In addition to the use of current functional MR sequences, the MR Linac workflow allows for quantitative feature extraction using radiomic approaches to develop imaging-based biomarkers. This concept of daily response assessment may introduce an entirely novel dose prescription method into radiation therapy. Specifically, rather than treating to a pre-specified "historic" dose, a patient's treatment dose could be determined by an imaging biomarker goal. One could envision targeting a specific apparent diffusion coefficient level (for example) as the goal for a patient's treatment. This would represent a distinct paradigm change from the historic method of prescribing dose founded on a population basis. The future of dose prescription in radiation therapy could become a biologically adaptive, imaging biomarker driven, dose for a specific patient. Moreover, MR based functional imaging could represent radiosensitive or radioresistant subvolumes of disease that may benefit from differential dosing strategies. A visual representation of this potential "threshold" based dosing strategy is seen in *Figure 3*. Consortium-based collaboration, validation, and qualification will be absolutely critical to validite the clinical significance of the imaging metrics that are acquired during a course of radiation. The implications of a shift of this nature are extremely promising for patients. One of the most frequently asked patient questions during a radiation treatment course, "*is this working?*", could be answered by the radiation oncologist with a much greater degree of confidence. *Table 3* summarizes the potential imaging-based response characteristics. It becomes feasible to visualize a future of radiation therapy driven by tumor-specific, imaging signatures, of treatment response. This could enable personalization of radiation therapy dosing strategies or the potential for routine, functional adaptive dose-painting strategies[25].

Conclusions:

MR-guided radiation therapy is an exciting and rapidly advancing area of cancer research, accelerating with both computational and hardware advances. MR guidance is positioned to transform many aspects of radiation therapy as we currently know them. Even more novel integration of MRI into treatment delivery devices is also under development, such as MR-guided proton therapy [26,27]. Oncology research teams should prepare for innovative clinical trials involving personalization and adaption of radiation therapy to a level that has simply not been seen thus far within the specialty of radiation oncology.

Table 1 –Technological Advances in Radiation Therapy			
Technological Development	**Changes To Radiation Therapy**	**Clinical Trials Enabled By Technological Development**	**Limitations of Technological Development**
CT-guided Intensity-modulated radiation therapy (IMRT)[28]	▪ Significant improvements in radiation dose conformality and reduction in radiation doses to critical normal structures ▪ Ability to avoid or reduce doses to local structures	▪ Reduction in doses of radiation to critical organs at risk (e.g. Parotid glands in head and neck cancer)[29] ▪ Dose escalation strategies	▪ Expensive ▪ Insufficient soft-tissue contrast, limiting treatment adaptation ▪ Limited "beam-on" tumor monitoring during treatment delivery
Proton Therapy	▪ Reduction in radiation dose to normal structures ▪ Ability to completely eliminate dose to some normal structures	▪ Trials focused on clinical improvements enabled by reductions in moderate radiation doses to normal tissues[30,31]	▪ Very expensive ▪ Insufficient soft-tissue contrast in image guidance ▪ Inability to reduce highest radiation doses to normal organs ▪ Limited treatment adaptation
MR-Guided Intensity Modulated Radiation Therapy	▪ Substantial improvement in soft tissue imaging during treatment ▪ Online treatment adaptation based on MR-defined "anatomy of the day" ▪ Beam-on imaging with MR may enable considerable reductions in high doses to normal organs ▪ Detection of radiation response of tumor and normal structures	▪ Anatomically and biologically adaptive radiation therapy, based on changes seen on daily MRI during a treatment course (e.g. daily DWI) ▪ Intra-treatment, or "beam-on", monitoring of normal organ and tumor movement ▪ NTCP reduction with dose reduction, particularly of local structures in close proximity to the tumor	▪ Expensive ▪ Risks and complexity associated with the use of MRI ▪ New training needed ▪ Novel effects of MRI on radiation dose distributions ▪ Limited patient eligibility (not an option for those with contraindications to MR based imaging)
MR- magnetic resonance, DWI- diffusion weighted image, NTCP- normal tissue complication probability			

Table 2: Types of MR Linac Technologies					
Commercial Name	**Manufacture**	**MRI Field strength**	**Bore Size**	**Beam Strength**	**Clinical Outcome Publications***
Commercially available					
ViewRay[8] - Co-60 - Linac	ViewRay Technologies Inc, Oakwood, Ohio	0.35 Tesla	70 cm	Co-60 source 6 MV	[12,32-46]
Elekta Unity [47,48]	Elekta AB, Stockholm, Sweden	1.5 Tesla	70 cm	7 MV	[48,49]
In Development					
Australian MRI Linac System[6]	Australian MRI-Linac Program	1 Tesla	82 cm	6 MV	N/A
Aurora-RT System[50]	MagnetTx, Edmonton, Alberta, Canada	0.6 Tesla	60 cm	6 MV	N/A
* Clinical outcome publications involved the treatment of patients with reported outcomes. MV- megavoltage, cm - centimeters, Co-60 - Cobalt-60					

Table 3: Potential Imaging Biomarkers Of Treatment Response To Be Acquired Using an MR Linac

Candidate imaging biomarkers	Candidate Imaging Metric	Tumors site with diagnostic significance	Example clinical series showing clinical significance of imaging changes during radiation therapy
Diffusion-weighted imaging[51]	▪ ADC	▪ Primary brain ▪ Rectal Adenocarcinoma ▪ Head and Neck ▪ Pancreatic Adenocarcinoma ▪ Cervical ▪ Prostate ▪ Liver	▪ Rectal Adenocarcinoma [52,53] ▪ High-grade glioma [54] ▪ Pancreatic Adenocarcinoma [55] ▪ Cervical cancer [56] ▪ Prostate [57] ▪ Liver [58]
IVIM[59]	▪ Perfusion fraction ▪ D_{slow} ▪ D_{fast}	▪ Primary brain ▪ Rectal Adenocarcinoma ▪ Head and Neck ▪ Pancreatic Adenocarcinoma ▪ Cervical ▪ Prostate ▪ Liver ▪ Esophageal	▪ Rectal cancer [60] ▪ Head and neck [61,62] ▪ Cervical cancer [63,64] ▪ Bone metastases [65] ▪ Esophageal [66]
DCE-MRI [67*]	▪ K^{Trans} ▪ v_e ▪ v_p ▪ Blood Flow ▪ IAUC	▪ Primary brain ▪ Secondary brain ▪ Bone Metastases ▪ Rectal Adenocarcinoma ▪ Head and Neck ▪ Pancreatic Adenocarcinoma ▪ Cervical cancer ▪ Prostate ▪ Pancreatic Adenocarcinoma	▪ Head and Neck [68] ▪ Prostate [69] ▪ Secondary brain tumors[70] ▪ High-grade Glioma[71] ▪ Liver [72]
Relaxometry[73]	▪ T1 map ▪ T2 map ▪ BOLD	▪ Primary brain ▪ Secondary brain ▪ Pancreatic Adenocarcinoma	N/A
CEST [74]	▪ Metabolite maps	▪ Primary brain ▪ Secondary brain	▪ High grade glioma [75-77]

* Limited by the need for exogenous contrast agents, IVIM - Intravoxel incoherent motion, DCE - Dynamic contrast-enhanced, CEST - Chemical exchange saturation transfer (CEST), ADC- Apparent diffusion coefficient, BOLD- Blood oxygen level dependent, IAUC- Initial Area Under the Curve

References:

1. Atun R, Jaffray DA, Barton MB, et al. Expanding global access to radiotherapy. *Lancet Oncol.* 2015;16(10):1153-1186.
2. Jaffray DA. Image-guided radiotherapy: from current concept to future perspectives. *Nat Rev Clin Oncol.* 2012;9(12):688-699.
3. Jaffray DA, Carlone MC, Milosevic MF, et al. A facility for magnetic resonance-guided radiation therapy. *Semin Radiat Oncol.* 2014;24(3):193-195.
4. Simpson DR, Lawson JD, Nath SK, Rose BS, Mundt AJ, Mell LK. A survey of image-guided radiation therapy use in the United States. *Cancer.* 2010;116(16):3953-3960.
5. Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol.* 2015;16(2):187-199.
6. Keall PJ, Barton M, Crozier S, Australian Mri-Linac Program icfIIICCCLHSUUoNQSWS, Wollongong. The Australian magnetic resonance imaging-linac program. *Semin Radiat Oncol.* 2014;24(3):203-206.
7. Fallone BG, Murray B, Rathee S, et al. First MR images obtained during megavoltage photon irradiation from a prototype integrated linac-MR system. *Med Phys.* 2009;36(6):2084-2088.
8. Mutic S, Dempsey JF. The ViewRay system: magnetic resonance-guided and controlled radiotherapy. *Semin Radiat Oncol.* 2014;24(3):196-199.
9. Lagendijk JJ, Raaymakers BW, Raaijmakers AJ, et al. MRI/linac integration. *Radiother Oncol.* 2008;86(1):25-29.
10. Lagendijk JJ, Raaymakers BW, van Vulpen M. The magnetic resonance imaging-linac system. *Semin Radiat Oncol.* 2014;24(3):207-209.
11. Burnet NG, Thomas SJ, Burton KE, Jefferies SJ. Defining the tumour and target volumes for radiotherapy. *Cancer Imaging.* 2004;4(2):153-161.
12. Acharya S, Fischer-Valuck BW, Mazur TR, et al. Magnetic Resonance Image Guided Radiation Therapy for External Beam Accelerated Partial-Breast Irradiation: Evaluation of Delivered Dose and Intrafractional Cavity Motion. *Int J Radiat Oncol Biol Phys.* 2016;96(4):785-792.
13. Tyran M, Jiang N, Cao M, et al. Retrospective evaluation of decision-making for pancreatic stereotactic MR-guided adaptive radiotherapy. *Radiother Oncol.* 2018;129(2):319-325.
14. Kontaxis C, Bol GH, Lagendijk JJ, Raaymakers BW. A new methodology for inter- and intrafraction plan adaptation for the MR-linac. *Phys Med Biol.* 2015;60(19):7485-7497.
15. Kerkmeijer LG, Fuller CD, Verkooijen HM, et al. The MRI-Linear Accelerator Consortium: Evidence-Based Clinical Introduction of an Innovation in Radiation Oncology Connecting Researchers, Methodology, Data Collection, Quality Assurance, and Technical Development. *Front Oncol.* 2016;6:215.

16. C2T2 Consortium [Web Page]. https://viewray.com/clinical-trials/#.
17. Raaijmakers AJ, Raaymakers BW, Lagendijk JJ. Integrating a MRI scanner with a 6 MV radiotherapy accelerator: dose increase at tissue-air interfaces in a lateral magnetic field due to returning electrons. *Phys Med Biol.* 2005;50(7):1363-1376.
18. Chen X, Prior P, Chen GP, Schultz CJ, Li XA. Technical Note: Dose effects of 1.5 T transverse magnetic field on tissue interfaces in MRI-guided radiotherapy. *Med Phys.* 2016;43(8):4797.
19. Weygand J, Fuller CD, Ibbott GS, et al. Spatial Precision in Magnetic Resonance Imaging-Guided Radiation Therapy: The Role of Geometric Distortion. *Int J Radiat Oncol Biol Phys.* 2016;95(4):1304-1316.
20. Emmerich J, Laun FB, Pfaffenberger A, et al. Technical Note: On the size of susceptibility-induced MR image distortions in prostate and cervix in the context of MR-guided radiation therapy. *Med Phys.* 2018;45(4):1586-1593.
21. Tetar S, Bruynzeel A, Bakker R, et al. Patient-reported Outcome Measurements on the Tolerance of Magnetic Resonance Imaging-guided Radiation Therapy. *Cureus.* 2018;10(2):e2236.
22. Hackett SL, van Asselen B, Wolthaus JW, et al. Consequences of air around an ionization chamber: Are existing solid phantoms suitable for reference dosimetry on an MR-linac? *Med Phys.* 2016;43(7):3961.
23. O'Connor JP, Aboagye EO, Adams JE, et al. Imaging biomarker roadmap for cancer studies. *Nat Rev Clin Oncol.* 2017;14(3):169-186.
24. Wojcieszynski AP, Rosenberg SA, Brower JV, et al. Gadoxetate for direct tumor therapy and tracking with real-time MRI-guided stereotactic body radiation therapy of the liver. *Radiother Oncol.* 2016;118(2):416-418.
25. van der Heide UA, Houweling AC, Groenendaal G, Beets-Tan RG, Lambin P. Functional MRI for radiotherapy dose painting. *Magn Reson Imaging.* 2012;30(9):1216-1223.
26. S.Schellhammer LK, J.Smeets, C.L'Abbate, S.Henrotin, E.Van der Kraaij, A.Lühr, S.Quets, J.Pawelke, A.Hoffmann. First in-beam MR scanner for image-guided proton therapy: beam alignment and magnetic field effects. *Radiotherapy and Oncology.*127(Supplement 1):S318-S319.
27. Raaymakers BW, Raaijmakers AJ, Lagendijk JJ. Feasibility of MRI guided proton therapy: magnetic field dose effects. *Phys Med Biol.* 2008;53(20):5615-5622.
28. Bortfeld T. IMRT: a review and preview. *Phys Med Biol.* 2006;51(13):R363-379.
29. Nutting CM, Morden JP, Harrington KJ, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. *Lancet Oncol.* 2011;12(2):127-136.
30. Liao Z, Lee JJ, Komaki R, et al. Bayesian Adaptive Randomization Trial of Passive Scattering Proton Therapy and Intensity-Modulated Photon Radiotherapy for Locally Advanced Non-Small-Cell Lung Cancer. *J Clin Oncol.* 2018;36(18):1813-1822.
31. Sio TT, Lin HK, Shi Q, et al. Intensity Modulated Proton Therapy Versus Intensity Modulated Photon Radiation Therapy for Oropharyngeal Cancer: First Comparative Results of Patient-Reported Outcomes. *Int J Radiat Oncol Biol Phys.* 2016;95(4):1107-1114.

32. Fischer-Valuck BW, Henke L, Green O, et al. Two-and-a-half-year clinical experience with the world's first magnetic resonance image guided radiation therapy system. *Adv Radiat Oncol.* 2017;2(3):485-493.
33. Acharya S, Fischer-Valuck BW, Kashani R, et al. Online Magnetic Resonance Image Guided Adaptive Radiation Therapy: First Clinical Applications. *Int J Radiat Oncol Biol Phys.* 2016;94(2):394-403.
34. Boldrini L, Cusumano D, Chiloiro G, et al. Delta radiomics for rectal cancer response prediction with hybrid 0.35 T magnetic resonance-guided radiotherapy (MRgRT): a hypothesis-generating study for an innovative personalized medicine approach. *Radiol Med.* 2018.
35. Thomas DH, Santhanam A, Kishan AU, et al. Initial clinical observations of intra- and interfractional motion variation in MR-guided lung SBRT. *Br J Radiol.* 2018;91(1083):20170522.
36. Park JM, Shin KH, Kim JI, et al. Air-electron stream interactions during magnetic resonance IGRT : Skin irradiation outside the treatment field during accelerated partial breast irradiation. *Strahlenther Onkol.* 2018;194(1):50-59.
37. Chen AM, Cao M, Hsu S, et al. Magnetic resonance imaging guided reirradiation of recurrent and second primary head and neck cancer. *Adv Radiat Oncol.* 2017;2(2):167-175.
38. Raghavan G, Kishan AU, Cao M, Chen AM. Anatomic and dosimetric changes in patients with head and neck cancer treated with an integrated MRI-tri-(60)Co teletherapy device. *Br J Radiol.* 2016;89(1067):20160624.
39. Yang Y, Cao M, Sheng K, et al. Longitudinal diffusion MRI for treatment response assessment: Preliminary experience using an MRI-guided tri-cobalt 60 radiotherapy system. *Med Phys.* 2016;43(3):1369-1373.
40. Padgett KR, Simpson GN, Llorente R, Samuels MA, Dogan N. Feasibility of Adaptive MR-guided Stereotactic Body Radiotherapy (SBRT) of Lung Tumors. *Cureus.* 2018;10(4):e2423.
41. Henke L, Kashani R, Yang D, et al. Simulated Online Adaptive Magnetic Resonance-Guided Stereotactic Body Radiation Therapy for the Treatment of Oligometastatic Disease of the Abdomen and Central Thorax: Characterization of Potential Advantages. *Int J Radiat Oncol Biol Phys.* 2016;96(5):1078-1086.
42. Henke L, Kashani R, Robinson C, et al. Phase I trial of stereotactic MR-guided online adaptive radiation therapy (SMART) for the treatment of oligometastatic or unresectable primary malignancies of the abdomen. *Radiother Oncol.* 2018;126(3):519-526.
43. Palacios MA, Bohoudi O, Bruynzeel AME, et al. Role of Daily Plan Adaptation in MR-Guided Stereotactic Ablative Radiation Therapy for Adrenal Metastases. *Int J Radiat Oncol Biol Phys.* 2018;102(2):426-433.
44. van Sornsen de Koste JR, Palacios MA, Bruynzeel AME, Slotman BJ, Senan S, Lagerwaard FJ. MR-guided Gated Stereotactic Radiation Therapy Delivery for Lung, Adrenal, and Pancreatic Tumors: A Geometric Analysis. *Int J Radiat Oncol Biol Phys.* 2018;102(4):858-866.

45. Mehta S, Gajjar SR, Padgett KR, et al. Daily Tracking of Glioblastoma Resection Cavity, Cerebral Edema, and Tumor Volume with MRI-Guided Radiation Therapy. *Cureus.* 2018;10(3):e2346.
46. El-Bared N, Portelance L, Spieler BO, et al. Dosimetric Benefits and Practical Pitfalls of Daily Online Adaptive MRI-Guided Stereotactic Radiation Therapy for Pancreatic Cancer. *Pract Radiat Oncol.* 2018.
47. Raaymakers BW, Lagendijk JJ, Overweg J, et al. Integrating a 1.5 T MRI scanner with a 6 MV accelerator: proof of concept. *Phys Med Biol.* 2009;54(12):N229-237.
48. Raaymakers BW, Jurgenliemk-Schulz IM, Bol GH, et al. First patients treated with a 1.5 T MRI-Linac: clinical proof of concept of a high-precision, high-field MRI guided radiotherapy treatment. *Phys Med Biol.* 2017;62(23):L41-L50.
49. Winkel D, Bol GH, Kiekebosch IH, et al. Evaluation of Online Plan Adaptation Strategies for the 1.5T MR-linac Based on "First-In-Man" Treatments. *Cureus.* 2018;10(4):e2431.
50. Fallone BG. The rotating biplanar linac-magnetic resonance imaging system. *Semin Radiat Oncol.* 2014;24(3):200-202.
51. Padhani AR, Liu G, Koh DM, et al. Diffusion-weighted magnetic resonance imaging as a cancer biomarker: consensus and recommendations. *Neoplasia.* 2009;11(2):102-125.
52. Shaverdian N, Yang Y, Hu P, et al. Feasibility evaluation of diffusion-weighted imaging using an integrated MRI-radiotherapy system for response assessment to neoadjuvant therapy in rectal cancer. *Br J Radiol.* 2017;90(1071):20160739.
53. Sun YS, Zhang XP, Tang L, et al. Locally advanced rectal carcinoma treated with preoperative chemotherapy and radiation therapy: preliminary analysis of diffusion-weighted MR imaging for early detection of tumor histopathologic downstaging. *Radiology.* 2010;254(1):170-178.
54. Hamstra DA, Galban CJ, Meyer CR, et al. Functional diffusion map as an early imaging biomarker for high-grade glioma: correlation with conventional radiologic response and overall survival. *J Clin Oncol.* 2008;26(20):3387-3394.
55. Dalah E, Erickson B, Oshima K, et al. Correlation of ADC With Pathological Treatment Response for Radiation Therapy of Pancreatic Cancer. *Transl Oncol.* 2018;11(2):391-398.
56. Ho JC, Allen PK, Bhosale PR, et al. Diffusion-Weighted Magnetic Resonance Imaging as a Predictor of Outcome in Cervical Cancer After Chemoradiation. *Int J Radiat Oncol Biol Phys.* 2017;97(3):546-553.
57. Park SY, Kim CK, Park BK, et al. Early changes in apparent diffusion coefficient from diffusion-weighted MR imaging during radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys.* 2012;83(2):749-755.
58. Eccles CL, Haider EA, Haider MA, Fung S, Lockwood G, Dawson LA. Change in diffusion weighted MRI during liver cancer radiotherapy: preliminary observations. *Acta Oncol.* 2009;48(7):1034-1043.
59. Federau C. Intravoxel incoherent motion MRI as a means to measure in vivo perfusion: A review of the evidence. *NMR Biomed.* 2017;30(11).
60. Nougaret S, Vargas HA, Lakhman Y, et al. Intravoxel Incoherent Motion-derived Histogram Metrics for Assessment of Response after Combined Chemotherapy and Radiation Therapy in Rectal Cancer: Initial Experience and Comparison between Single-Section and Volumetric Analyses. *Radiology.* 2016;280(2):446-454.

61. Paudyal R, Oh JH, Riaz N, et al. Intravoxel incoherent motion diffusion-weighted MRI during chemoradiation therapy to characterize and monitor treatment response in human papillomavirus head and neck squamous cell carcinoma. *J Magn Reson Imaging.* 2017;45(4):1013-1023.
62. Lu L, Li Y, Li W. The Role of Intravoxel Incoherent Motion MRI in Predicting Early Treatment Response to Chemoradiation for Metastatic Lymph Nodes in Nasopharyngeal Carcinoma. *Adv Ther.* 2016;33(7):1158-1168.
63. Zhu L, Wang H, Zhu L, et al. Predictive and prognostic value of intravoxel incoherent motion (IVIM) MR imaging in patients with advanced cervical cancers undergoing concurrent chemo-radiotherapy. *Sci Rep.* 2017;7(1):11635.
64. Zhu L, Zhu L, Shi H, et al. Evaluating early response of cervical cancer under concurrent chemo-radiotherapy by intravoxel incoherent motion MR imaging. *BMC Cancer.* 2016;16:79.
65. Gaeta M, Benedetto C, Minutoli F, et al. Use of diffusion-weighted, intravoxel incoherent motion, and dynamic contrast-enhanced MR imaging in the assessment of response to radiotherapy of lytic bone metastases from breast cancer. *Acad Radiol.* 2014;21(10):1286-1293.
66. Li FP, Wang H, Hou J, et al. Utility of intravoxel incoherent motion diffusion-weighted imaging in predicting early response to concurrent chemoradiotherapy in oesophageal squamous cell carcinoma. *Clin Radiol.* 2018;73(8):756 e717-756 e726.
67. O'Connor JP, Jackson A, Parker GJ, Roberts C, Jayson GC. Dynamic contrast-enhanced MRI in clinical trials of antivascular therapies. *Nat Rev Clin Oncol.* 2012;9(3):167-177.
68. You D, Aryal M, Samuels SE, Eisbruch A, Cao Y. Temporal Feature Extraction from DCE-MRI to Identify Poorly Perfused Subvolumes of Tumors Related to Outcomes of Radiation Therapy in Head and Neck Cancer. *Tomography.* 2016;2(4):341-352.
69. Bonekamp D, Wolf MB, Edler C, et al. Dynamic contrast enhanced MRI monitoring of primary proton and carbon ion irradiation of prostate cancer using a novel hypofractionated raster scan technique. *Radiother Oncol.* 2016;120(2):313-319.
70. Farjam R, Tsien CI, Lawrence TS, Cao Y. DCE-MRI defined subvolumes of a brain metastatic lesion by principle component analysis and fuzzy-c-means clustering for response assessment of radiation therapy. *Med Phys.* 2014;41(1):011708.
71. Bisdas S, Smrdel U, Bajrovic FF, Surlan-Popovic K. Assessment of Progression-Free-Survival in Glioblastomas by Intratreatment Dynamic Contrast-Enhanced MRI. *Clin Neuroradiol.* 2016;26(1):39-45.
72. Coolens C, Driscoll B, Moseley J, Brock KK, Dawson LA. Feasibility of 4D perfusion CT imaging for the assessment of liver treatment response following SBRT and sorafenib. *Adv Radiat Oncol.* 2016;1(3):194-203.
73. Gilani IA, Sepponen R. Quantitative rotating frame relaxometry methods in MRI. *NMR Biomed.* 2016;29(6):841-861.
74. Wu B, Warnock G, Zaiss M, et al. An overview of CEST MRI for non-MR physicists. *EJNMMI Phys.* 2016;3(1):19.
75. Mehrabian H, Myrehaug S, Soliman H, Sahgal A, Stanisz GJ. Evaluation of Glioblastoma Response to Therapy With Chemical Exchange Saturation Transfer. *Int J Radiat Oncol Biol Phys.* 2018;101(3):713-723.

76. Mehrabian H, Lam WW, Myrehaug S, Sahgal A, Stanisz GJ. Glioblastoma (GBM) effects on quantitative MRI of contralateral normal appearing white matter. *J Neurooncol.* 2018;139(1):97-106.
77. Mehrabian H, Myrehaug S, Soliman H, Sahgal A, Stanisz GJ. Quantitative Magnetization Transfer in Monitoring Glioblastoma (GBM) Response to Therapy. *Sci Rep.* 2018;8(1):2475.