MRI-linac systems will replace conventional IGRT systems within 15 years

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POINT/COUNTERPOINT

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MRI-linac systems will replace conventional IGRT systems within 15 years

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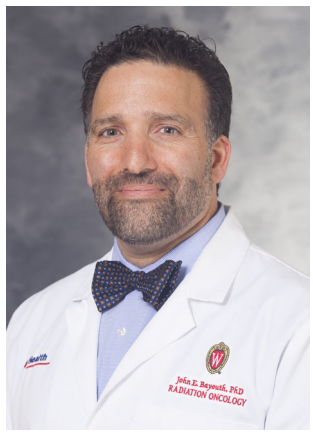
1. OVERVIEW

The introduction of novel hybrid technologies, including CT-linacs, MRI-linacs, and PET-linacs has the potential to revolutionize the practice of radiation oncology, likely resulting in better-quality patient care with improved outcomes. CT has long been the standard of care modality in radiation therapy; however, MRI provides superior soft tissue contrast, is inherently multiparametric offering both anatomical and functional information in addition to spectroscopy, and presents many advantages for motion management during treatment. In this regard, the concept of MRI-guided radiation therapy (MRgRT), which is now commercially available, has emerged as a promising technique for the treatment of a number of malignant diseases. The availability of in-room MRI guidance for patient setup and treatment delivery enables improved delineation of target volumes and organs at risk for adaptive therapy as well as real-time motion management during treatment. Hence, the clinical advantages of MRI-guided treatment delivery systems with respect to conventional cone-beam CT-guided–RT, referred here as IGRT, are being debated. While some think that MRI-linac is a relevant technology that should replace IGRT in the future, others think that the concept is still in its infancy and that IGRT will still remain the *de facto* standard in the clinic. This is the topic addressed in this month's Point/Counterpoint debate.

Arguing for the proposition is John Bayouth, PhD. Dr. Bayouth is a tenured Professor and the Bhudatt Paliwal endowed chair in the Department of Human Oncology at the University of Wisconsin in Madison. Nationally, he has served in the presidential chain of both the American Association of Physics in Medicine (AAPM) and the Society of Directors of Academic Medical Physics Programs (SDAMPP), and within various committees of the American Society of Radiation Oncology (ASTRO), the Radiological Society of North America (RSNA), and the American Board of Radiology (ABR). His primary area of research includes acquisition and analysis of 4DCT images to quantify longitudinal pulmonary functional changes following radiation therapy. He is currently PI of an NCI funded (R01 CA166703) Investigator Initiated Clinical Trial whose goal is to design and deliver radiation treatment plans that will improve pulmonary function of radiation therapy patients. Dr. Bayouth is also responsible for the clinical development and implementation of MRgRT (ViewRay) at UW-Madison, which has treated nearly 500 patients since September 2014.



Arguing against the Proposition is Daniel Low, PhD. Dr. Low obtained his Ph.D. in Physics from Indiana University, Bloomington and, after a postdoctoral fellowship at M. D. Anderson Cancer Center, Houston, TX, moved to Washington University Mallinckrodt Institute of Radiology, St. Louis, MO, where he eventually became Professor of Radiation Oncology. In 2010, he moved to his current position at UCLA, where he is Professor of Radiation Oncology and

Vice Chair of Medical Physics. Dr. Low is certified by the American Board of Medical Physics in Radiation Oncology Physics and the American Board of Radiology in Therapeutic Medical Physics. He has been very active in both the AAPM and ASTRO and currently serves as Chairman of the ASTRO Science Council. Dr. Low's major research interests include modeling respiratory motion and applications of magnetic resonance imaging in radiotherapy. He is a Fellow of the AAPM and has published over 250 papers in refereed journals.

2. FOR THE PROPOSITION: JOHN BAYOUTH, PH.D.

2.A. Opening Statement

MRI-linac systems will replace conventional IGRT systems within 15 years because:

1. We treat an ever-changing soft tissue disease;
2. Hypofractionated treatments will become standard of care;
3. Image guidance should be continuous to enable adaptation to intrafractional anatomic changes.

Radiation Oncology mostly addresses neoplastic diseases of soft tissue, and MRI is the best soft-tissue imaging modality. Multiple studies have shown that MRI provides the most accurate and reliable imaging modality for segmentation of tumors and organs-at-risk.[1] Internal anatomy is always changing: morphologically (size, shape, location) with changing physiological processes of the tumor microenvironment, such as oxygenation levels, cellularity, and vascularity, and regions of high tumor burden.[2] MRI is the best imaging modality to characterize these changes.

Hypofractionation is likely to become the standard of care, due to increases in cancer incidence and reduction in healthcare funding. Hypofractionation is highly effective in the curative setting for managing the most common tumor sites: prostate,[3] breast,[4] and lung.[5] The increased need for high resolution, high-temporal frequency imaging necessitates a non-ionizing imaging modality, which MRI provides. Is there a role for hypofractionation in palliative radiotherapy, which constitutes nearly half of RT patients? Most certainly. A recent survey[6] found that hypofractionation for palliative radiotherapy "delivers palliation that is time efficient, cost-effective, and minimally toxic. Evidence suggests that the reluctance of radiation oncologists to provide single-fraction treatment acts as a barrier to referrals from palliative care professionals." The reluctance is likely born from a combination of precision and financial concerns, which I argue would dissipate if reimbursement was independent of fractionation and physicians had the high precision imaging for patient alignment, motion management, and optimization of the treatment plan for each fraction provided by MR-linac systems.

Seeing what you are doing is addictive; this addiction will lead to broad application throughout Radiation Oncology. Imagine a surgeon in the operating room standing before the patient prepared on the table. The surgeon asks for the scalpel, but before cutting the nurse asks "would you like me to turn off the lights?" Ridiculous, right? Why would you choose to perform the surgery without seeing what you are doing? Unfortunately, much of external beam radiation therapy is delivered in this way – we knew where the anatomy was before we started, but once the beam is turned on we are in the dark. Real-time imaging during treatment and routinely adjusting the patient when their internal anatomy drifts out of alignment (holding their breath with a different tidal volume,[7] peristalsis of bowel, etc.) leaves a powerful impression. I believe Level 1 clinical evidence will demonstrate its positive impact on the therapeutic ratio, making MR-guided radiation therapy the standard of care.

For some, the proposition that such a change would occur in 15 years may seem overly ambitious. Well, 15 years ago the RTOG completed its first clinical trial to assess the safety and efficacy of IMRT in head and neck cancer.[8] Today, we cannot imagine treating without IMRT and I believe the same will be true for MR-linac systems.

3. AGAINST THE PROPOSITION: DANIEL LOW, PH.D.

3.A. Opening Statement

MRI-guided radiation therapy is a recently commercialized technology that has the potential for revolutionizing the treatment of some cancers.[9,10] MRgRT provides a number of definitive and potential advantages over conventional x-ray–based image guidance, including the fact that MR imaging delivers no ionizing radiation dose, can be conducted in real time, and has excellent to outstanding soft tissue contrast. The fact that MRgRT delivers no ionizing radiation dose means that imaging protocols are limited only by specific absorption rate limits, which, when combined with being able to image during radiation treatments, enables real-time gating at a quality heretofore unattainable.[11]

Potential advantages include the ability to acquire "functional image" data. The quotes are intended to emphasize that, while the MRgRT systems are able to employ pulse sequences that measure biological values or their surrogates, there is little evidence as to the clinical value of these data. For example, the apparent diffusion coefficient (ADC), measured using diffusion weighted imaging (DWI) may be an indicator of intra-tumor cell death and therefore an indication

of treatment efficacy.[12,13] If such information was available before a treatment course was completed, an adaptive process could be developed that boosted radiation insensitive regions and improve local control.

Given the known and potential advantages of MRgRT, what keeps it from replacing all conventional x-ray based systems? At the least, there are some patients who cannot be in an MR scanner, whether through claustrophobia, or metal in their bodies.[14,15] Also, there is no documented evidence that MRgRT has any advantages over conventional IGRT in tumors for which intrafraction motion is negligible and in which x-ray–based localization is adequate, for example in the brain. MRgRT systems do not allow noncoplanar beams and electron beams, both of which are used extensively for many treatments. Finally, the perturbation of the secondary electron fluence by the magnetic field, at least for high-field systems, may impact some tumor sites such as whole breast.

The current cost of MRgRT systems is greater than conventional IGRT systems, partly because their capital cost is greater but partly because site preparation and installation costs are greater. As of this writing, one of the two commercially available MRgRT systems requires a large vault and the machine needs to be delivered through an access port in the shielding, leading to most machines having been installed in new and dedicated vaults. Both commercially available systems require radiofrequency shielding, an unnecessary requirement for conventional IGRT systems.

The balance of improved soft tissue contrast and the ability to provide real-time imaging with no dose for tumor positioning and gating are compelling arguments for the value of MRgRT for tumors in the thorax and abdomen, while functional imaging shows promise for future advantages. On the other hand, the increased purchase and installation expense and the fact that not all patients can be treated in the magnetic field retains significant value for conventional IGRT systems moving forward. The ultimate balance between the two systems will be based on the perceived and real benefits of MRgRT over conventional IGRT, which, while already significant, are not universal.

4. REBUTTAL: JOHN BAYOUTH, PH.D.

MRgRT systems may replace conventional IGRT systems, but not all radiotherapy equipment. Other linacs will deliver electron therapy, total-body irradiation, stereotactic radiosurgery, and the rare cases of contraindications for MRgRT.

Dr. Low provides a great perspective and several reasonable challenges that I will attempt to address. (a) Some patients are unable/unwilling to enter an MRI. True, but a small minority. Estimates show ~ 3 million joint replacement implants, ~1 million pacemakers, and ~ 0.2 million defibrillators worldwide. Over 95% of individuals receiving these devices are over 50 years old and the world's population above this age is ~ 2 billion. So, less than 1% of those needing RT likely have these devices. As for claustrophobia, several methods have been established to enable claustrophobic individuals to get through CT and MRI.[16] (b) MRgRT has no proven advantage. . .in sites without intrafraction motion, for example the brain. True, level 1 evidence is lacking. However, we see soft tissue and target volume changes with daily MRgRT. While the value added for brain target volumes is less clear, these are dependent upon edema that can change during treatment. The limitations of x-ray–based IGRT are less sensitive. (c) Noncoplanar beams and electron RT are not possible with MRgRT. Again, true, but x-ray IGRT is not indicated for electron treatment setup, and IGRT systems often do not allow/provide accurate image guidance with couch rotation. (d) The electron return effect may impact care. Complications have not been reported in patients treated 0.35 T MRgRT (>3,000 patients in 5 + years), and soon we will have data with higher field strengths. Returning electrons have lower energy and can be absorbed by thin materials placed over the patient.

Technical solutions likely exist for all of these issues. Fifteen years is ample time to demonstrate the added benefit of MR guidance, for example reduced toxicity and increased hypofractionation. The value proposition of MRgRT will be clear if the benefits outweigh the differences in equipment costs.

5. REBUTTAL: DANIEL LOW, PH.D.

My esteemed colleague makes many outstanding points in his opening statement. Soft tissue tumors are indeed what we treat, and when they are embedded within other soft tissue, are more straightforward to visualize (either by a human or algorithm) and therefore target using MR imaging. This is especially important for those soft tissue tumors lying within mobile and radiation dose-sensitive organs such as the small bowel and duodenum. My colleague also makes an excellent point that hypofactionation will likely increase in relative frequency due to superior outcomes and reduced overall cost, necessitating improved image guidance.

While both of these points strengthen the justification for MRgRT, neither supports the replacement rather than the supplementation of x-ray–based IGRT by MRgRT. X-ray–based IGRT remains relatively cost-effective and is likely to remain so given the relatively high cost of MR versus cone-beam CT. Manufacturers have not yet maximized the image quality of cone-beam CT and the introduction of machine learning methods is likely to improve both image quality as well as localization using those images. Unless cone-beam CT hits an unexpected image quality limitation, we have not yet seen the apex of its performance.

Another important distinction is the ability to use noncoplanar beams with traditional linear accelerators. Noncoplanar beams have been exploited for intracranial stereotactic radiosurgery since before CT-based treatment planning, but it is the promise of highly noncoplanar radiation therapy, also termed 4-pi, that may further distinguish noncoplanar versus coplanar therapy.[17–20]

The concept that one would not want a surgeon that turns of the light is spurious. Surgery involves many forms of imaging, from the eyes (which we would certainly not want

our surgeon to close) to fluoroscopy. I imagine that the reason that there is a foot pedal in fluoroscopy rooms is because even surgeons do not need to "see" all the time. There is a cost to constant fluoroscopic visualization, primarily radiation dose to the patient and the surgeon. For radiation therapy, the added cost is of the physician's, physicist's, dosimetrist's and/or therapist's time, whomever ends up being responsible for visualizing, verifying, and monitoring the MR images as they arrive during treatment. It is challenging to imagine why this image stream would be important for some treatments, for example an intracranial treatment combined with some form of real-time external optical imaging to monitor patient immobilization.

In summary, while I feel that MRgRT is a revolution, not just an evolution, in radiation therapy, this does not mean that it will replace all IGRT due to increased cost and complexity and the added time and effort required for its implementation. The functional and anatomic imaging it provides, however, will in the future make it one of the, if not *the* leading, radiation therapy modality.

CONFLICT OF INTEREST

Dr. Bayouth and Dr. Low have no relevant conflict of interest.

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