EDITORIAL

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MRI in Radiation Oncology: Underserved Needs

Since their inception, the ISMRM and its predecessor societies have acknowledged the important role of electron spin resonance and MR in the diagnosis, staging, and treatment of cancer. There are many examples of this, including an ISMRM Study Group dedicated to MR of cancer, the recent ISMRM Workshop and associated *Magnetic Resonance in Medicine* Virtual Issue (1) on the topic of "MR in Cancer: Challenges & Unmet Needs," and of course the publication by this journal of much work describing advances in basic science and novel imaging techniques that have been of great use to that field. Despite these efforts, we believe that there remain underserved needs, most notably from within the radiation oncology community.

When the United States enacted the National Cancer Act into law in 1971, it initiated what has commonly been referred to as the "war on cancer." A major tool in this battle has been the use of high-energy radiation sources, including linear accelerators and cobalt-60 systems. To date, the number of high-energy radiation therapy systems deployed worldwide stands at approximately 13,360, with 8,960 in developed nations and approximately 4,400 in developing nations (2). Progress has been rapid; the combination of patient immobilization devices that ensure accurate and consistent radiation therapy treatment setup, sophisticated image guidance techniques, multiple photon beam arrangements, multileaf collimators, and intensity-modulated radiation therapy techniques have enabled therapeutic doses of radiation to be accurately delivered to the target volume while increasingly sparing dose to adjacent non-cancerous organs at risk (OAR). Particle therapy—of which proton therapy is the most common—is the next radiotherapy frontier. Proton therapy promises to further improve the efficacy of radiation therapy by significantly reducing the dose delivered to adjacent healthy tissue, allowing the reduction of radiotherapy-related side effects (3,4), which can improve options for combined therapies (ie, with chemotherapy and/or surgery). Currently, the number of non-US operational proton therapy centers stands at 32 and within the United States alone there are 25 proton centers in operation, under construction, or in development (5).

The current state of the art image-guided high-precision radiation therapy requires the use of imaging technologies with both high contrast and spatial resolution to visualize the target volume and adjacent tissues, both before the initiation of treatment (a process known as simulation) as well as during and after treatment. These needs have resulted in the adoption and further development of numerous imaging technologies including CT, projection radiography, ultrasound, and electronic portal imaging that allow real-time visualization of the radiation therapy treatment (6,7). MR, with its superior soft tissue contrast, its ability to obtain both anatomic and functional information, and most recently its ability to quantify biomarkers of disease stage and response to treatment [eg, see (8–11)], is increasingly being integrated into the radiation therapy treatment planning process. The recent advent and widespread commercial availability of 3T, 70-cm-bore MR scanners with flexible, high–channel count RF surface coils that can be used alone or in combination has enabled patients to be imaged in the same position that they will receive their treatment (ie, the treatment position). It should be no surprise that the radiation oncology community has acknowledged the valuable role that MR can play in the clinical practice of radiation therapy, as witnessed by its rapid adoption into their routine clinical practice. This growth is reflected in the annual increase in the number PubMed listings that include both the terms "MRI" and "radiation oncology"; in 2014 there were 536, compared with only two in the year 1985. When comparing publications over the entire preceding decade (2014-2004) this number increased by over 400% (2004 = 133 publications). Concomitantly, within our own clinical practice we have witnessed a surging number of requests for MR radiation therapy planning scans.

The need for MR-guided radiation therapy treatment planning using not only standard MR imaging but also advanced techniques will only increase due to the predicted worldwide increase in the annual incidence of oncologic disease. The number of worldwide cancer cases is expected to grow to 16.5 million by 2020, an increase of approximately 3.3 million compared with 2010 (2). Given these sobering statistics, it is useful to consider how our MR community can become better engaged in addressing unmet or underserved needs in radiation oncology. The ISMRM and the readership of *Magnetic Resonance in Medicine* are uniquely positioned to provide the expertise to advance this emerging application of MR.

From the following discussion, it should become clear that much of the technology that is needed has already been developed or is actively being developed by the MR community for non–radiation oncology applications, including intraoperative MR, positron emission tomography MR (PET-MR), and a host of others. Although references are provided, it should be understood that we are citing only a small representative sample of the published work. What remains is the adaptation of these technologies and techniques to meet the unique requirements placed on an imaging study for radiation oncology applications. For example, when motion correction techniques were developed in diagnostic imaging, the main

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objective was to produce images with reduced ghosting and blurring to improve the diagnostic accuracy of the radiologist's interpretation. In distinction, motion correction techniques are currently being integrated into MR imaging for radiation therapy planning to prospectively acquire data when the target is at a fixed or predetermined position (12–14) or to retrospectively sort MR image data acquired continuously throughout the respiratory cycle for fusion with a four-dimensional (4D) CT radiation planning data set (15).

The emergence of MRI guidance for radiation therapy treatment planning has provided a unique clinical opportunity for the MR community to positively impact the care of cancer patients. Despite the advantages of MRI, there are a number of challenges that need to be addressed before implementation into routine radiation treatment planning. We believe that simply opening up the channels of scientific communication about these different perspectives and facilitating collaboration between the MR and radiation oncology communities will go far to advance both fields. The complex nature of cancer demands a multidisciplinary approach to understand its biological basis and to develop improved diagnostic and therapeutic tools. A close partnership between members of both the MR and radiation oncology community is critical to the successful integration and growth of MRI into radiation treatment planning. Thus, the expertise of both specialties is essential to improve care to these seriously ill patients. Open communication and collaboration will help avoid a silo mindset that could lead to inefficient use of resources and wasteful duplication of effort.

IMPROVED MRI IMAGE QUALITY FOR TARGET AND OAR DELINEATION

The optimal coverage of the treatment target and delineation of OAR impose specific requirements for spatial coverage, resolution, and contrast that may not be met with diagnostic imaging parameters and protocols. Specifically, the scanned FOV needs to be sufficiently large to provide adequate visualization of the target as well as surrounding radiosensitive OARs. Relatively high resolution is also required for radiation therapy applications. For radiation planning outside of the brain spatial resolution better than $1.0 \times 1.0 \times 3.0$ mm^3 is typically preferred while for the brain, a spatial resolution better than $1.0 \times 1.0 \times 1.5$ mm^3 is desired. Further, 3D sequences acquired with isotropic voxels are ideal since this translates to optimal rendering in all three principal planes, which is readily tailored for the radiotherapy image segmentation and planning process. Adaptation of existing pulse sequences and protocols as well as the development of new techniques are needed in order to improve tumor conspicuity, particularly in regions that have been traditionally challenging for MR such as the base of skull and head and neck.

SPATIAL FIDELITY OF THE MR DATA SET

Accurate target and OAR delineation requires that MR images have high spatial fidelity within the entire FOV. In MR, geometric distortion arises from both system and patient-specific sources. System sources include gradient nonlinearity and B_0 field inhomogeneity. Although several correction methods have been investigated and implemented [eg, see (16–23)], resulting in residual distortion of approximately 0.5 mm as in the case of small field of view imaging of the prostate (23), there remains a need to improve the spatial accuracy of the MR data beyond the conventionally accepted limit of a 35- to 40-cm field of view centered at the magnet isocenter. Correction of patient-induced geometric distortion (eg, from B_0 effects) still remains challenging and is further complicated due to the fact that it is difficult to quantitatively evaluate the effectiveness of distortion correction methods in individual patients.

TUMOR RESPONSE ASSESSMENT

MR has the potential to provide a range of biomarkers for monitoring tumor response following radiation alone or for monitoring adjuvant therapy treatments. MR spectroscopy (24,25), diffusion-weighted imaging (26,27), dynamic contrast-enhanced perfusion imaging (25), and MR elastography (10) are examples of advanced MR techniques that have the potential to provide quantitative biomarkers to meet this need. Emerging biomarkers such as tissue conductivity and permittivity are also being studied (28). However, improvements in these and other methods are needed in terms of spatial coverage and spatial resolution for radiation therapy planning. Additionally, their accuracy and reproducibility need to be quantified using new quality assurance measures or by modification and optimization of existing measures. Quantitative MRI analysis platforms that generate biomarker information need to readily exchange postprocessed information with radiation treatment planning systems, improving accessibility across disciplines.

MOTION REDUCTION AND MOTION MANAGEMENT

The presence of motion creates challenges when imaging radiation therapy patients with MR. Respiration-induced motion severely degrades image quality, adding uncertainty to the exact location of the target and OARs, particularly when imaging within the thorax and abdomen. Breath-hold acquisitions are a simple and effective way to reduce artifacts caused by respiratory motion but can impose limits on the spatial coverage and resolution required for radiation therapy. Motion tracking techniques such as respiratory gating and navigator echoes as well as retrospective techniques such as PROPELLER (29) can be used to both quantify the amount of motion and reduce motion-induced artifacts. However, they need to be adapted further to the specific needs of radiation therapy planning.

There is also the need to quantify the amount of motion present during respiration for a time span similar to what is experienced during a normal radiation therapy treatment for both the target and OARs. 4D CT for respiratory motion characterization for radiotherapy planning was clinically implemented in the early 2000s [eg, (30)] and has since become a gold standard. However, 4D CT lacks soft tissue and tumor tissue contrast and imparts ionizing radiation, which necessarily limits acquisition time and thereby the degree to which variable breathing motion can be sampled and characterized. 4D MR imaging has the potential to address both of these needs. However, the relatively slow acquisition speed of most existing 4D MR techniques limits spatial and temporal resolution. In addition, not all MRI sequences are compatible with 4D MRI, resulting in limited options for visualizing the tumor and surrounding tissues. Particularly for characterizing breathing motion, whether with prospective triggering or retrospective sorting, it is desirable to develop a class of solutions with multiple contrast options that speed up image acquisition and improve spatial and temporal resolution. The ultimate goal is to integrate 4D MRI data seamlessly with the radiotherapy planning system vendor's tools.

REAL-TIME GUIDANCE FOR RADIATION DELIVERY

Research over the past decade into the development of hybrid therapy MR systems is starting to transition toward clinical trials and, ultimately, clinical integration (31). As such, the concept of MRI-guided radiation therapy is now becoming a clinical reality. In many respects, these systems are in their infancy, and further improvements are still needed in terms of the integration of MR and radiation therapy systems, not only in terms of general issues like spatial coverage and spatial and temporal resolution, but also more specific issues such as the effect of eddy currents on MRI image quality induced by intratreatment gantry motion.

METAL ARTIFACT REDUCTION

Patients with implanted foreign metal objects continue to be problematic in MR. Existing metal reduction techniques [eg, (32–35)] show promise but have not been adapted to the needs of radiation therapy patients. For example, some of these techniques are limited to two-dimensional acquisitions, whereas MR for radiation planning may require the use of 3D acquisition techniques. As the number of patients with metal implants increases, it is necessary to explore methods to reduce image artifacts produced by such implants, because these artifacts may mask the target and OARs on MRI images and make accurate delineation very challenging.

HARDWARE MODIFICATIONS TO SETUP PATIENTS IN TREATMENT POSITIONS

To minimize setup errors between imaging and treatment, it is desirable to image the patient in the MR scanner in the treatment position. This typically involves the use of an indexed flat table top and often with some type of immobilization device. Many diagnostic RF coils have been designed to be placed as close as possible to the patient, but this is suboptimal for radiation planning because they leave insufficient room for immobilization devices. For therapeutic purposes, hardware modifications including more flexible RF coils used alone or in combination are required to accommodate patient setup in treatment position.

MR-BASED TREATMENT PLANNING

Currently, CT is used as the primary image dataset for radiotherapy treatment planning. MR is commonly used as the secondary dataset and is fused to CT images to transfer target and OAR contours (14). The fusion process introduces uncertainties and potential errors into the treatment planning process, especially when deformable fusion is required. There is considerable interest in changing this workflow and making MR the primary image dataset for radiotherapy treatment planning. This will likely require MR to provide reliable surrogates for electron density information for dose distribution calculation. This is an active area of PET-MR [eg, (36–39)], and several methods have been proposed to supply electron density information using segmentation-based bulk density estimates, atlas registration (40,41), or probabilistic (ie, Bayesian) approaches (42). However, substantial work is needed to improve the accuracy of electron density information obtained from MR images.

In conclusion, the increasing integration of MRI into the routine clinical practice of radiation therapy represents a major opportunity to increase the accuracy and safety of radiation therapy, and thereby improve treatment outcomes, including improved survival rates and decreased radiation-induced side effects. It is our hope that this editorial will promote the development of several initiatives toward this goal.

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