10TH ANNIVERSARY SERIES

Advances in clinical MRI technology

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Advances in MRI technologies have the potential to detect, characterize, and monitor a wide variety of diseases.

INTRODUCTION

Nuclear magnetic resonance (NMR) is the emission of electromagnetic signals by atomic nuclei in response to magnetic fields. NMR has long been of interest to the scientific and translational medical research communities, given its broad potential in chemical characterization, biosensing, and imaging (*1*, *2*). Early work by Haun *et al.* (*1*) showed the utility of a handheld micro-NMR device for rapidly characterizing fine-needle aspirates to diagnose cancer. Magnetic resonance imaging (MRI) produces images by measuring the radiofrequency signals arising from the magnetic moments of hydrogen protons abundantly found in water and lipids. In 2010, Wu *et al.* (*2*) used MRI and magnetic resonance spectroscopy to map the metabolomic profiles of prostate cancer samples. MRI has progressed to a great extent over the past 10 years; indeed, it has revolutionized contemporary medicine, building on advances in image reconstruction (parallel imaging and spatiotemporal reconstruction) developed over the past 20 years. It is estimated that more than 36 million MRI exams are performed annually on nearly 12,000 installed systems in the United States alone. Compared to other imaging technologies, MRI offers superb soft tissue contrast, multiple different contrast mechanisms, absence of radiation, and the ability to colocalize anatomic and functional or molecular information. Accordingly, MRI is routinely used clinically to evaluate disease in all major organ systems. In translational research, MRI has enabled progress in entire fields, including neuroscience, psychiatry, and oncology, among others. In this final installment of *Science Translational Medicine*'s 10th anniversary Focus series, we broadly discuss key technological advances achieved over the past decade and the future of clinical and translational MRI for disease management.

KEY TECHNOLOGICAL ADVANCES

The technical capabilities of current MRI systems have been driven largely by advances in computers, material science, engineering, and physics (Fig. 1). Although some extraordinary feats, such as single-atom imaging and ultrahigh-field anatomical imaging, have received considerable media attention, there are a myriad of incremental advances that have improved clinical imaging.

Better image quality and higher spatial resolution of today's MRI are largely due to advances in MRI pulse sequences (structured sets of alternating magnetic gradients used to probe for tissue properties) and hardware, including higher field strengths, improved multichannel coils, stronger gradients, and more homogenous magnets. Whereas it was common to image at 0.5 and 1.5 T several years ago, many magnets currently operate at 3 T. Today, coils that collect the body's MRI signatures are typically phased array, flexible printed, or blanket coils rather than the bulky cage coils used a decade ago (*3*). Beyond improving image quality, these advances have enabled functional MRI (the combination of morphological data with biological information) of the brain, vascular mapping, and real-time cardiac imaging. Engineering advances have also led to development of wide-bore and open magnets, allowing interventional procedures and surgeries and accommodating claustrophobic patients.

Faster imaging has become a clinical reality, although much work remains to be done in this area. Increasing imaging speed improves patient comfort and throughput, decreases cost, reduces motion artifacts, and enables imaging of joints and muscle function, such as in the heart. Newer approaches to achieve faster imaging include undersampling of *K*-space (partial Fourier reconstruction and parallel imaging), compressed sensing, and non-Cartesian sampling with constantly improving reconstruction algorithms.

Computational analysis and artificial intelligence (AI) play increasingly important roles in all aspects of MRI acquisition and data processing. For example, AI-based image reconstruction greatly reduces the time required for image reconstruction, producing images of comparable quality while providing the ability to reconstruct large datasets in near real time (*4*). In addition, the increasing availability of AI has laid the foundation for automated image post-processing, including segmentation and volumetric analysis. Volumetric analysis is particularly useful in imaging Alzheimer's dementia and medial temporal lobe quantification, although predominantly used in a research setting at present. Last, AI can be used for decision support to create automated reports, flag imaging abnormalities, or classify organ structures as normal or abnormal.

New techniques have emerged over the past several years. Perhaps the most noteworthy are integrated MRI–positron emission tomography (PET) systems that can synchronously map molecular information (glucose uptake and receptor density) onto anatomic structures. Because it can coimage multiple molecular probes, MRI-PET has particularly important applications in oncologic and neurologic imaging (*5*). Beyond these exciting advances in MRI-PET fusion imaging, advances in MRI pulse sequences have enabled other new imaging approaches. For example, innovative distinct pulse sequences allow quantitation of fat, fibrosis (elastography), iron content (hemochromatosis), and water content and distribution. The latter forms the basis of diffusion-weighted imaging (DWI) and MR tractography, which can physiologically, directionally assess brain tissue or myocardial fibers. Deuterium metabolic imaging (DMI) is a new spectroscopic technique that generates three-dimensional metabolic maps of ^{2}H-glucose or other ^{2}H-labeled substrates given systemically or orally. In the cancer field, intravenously administered gadolinium chelates (contrast agents) enhance

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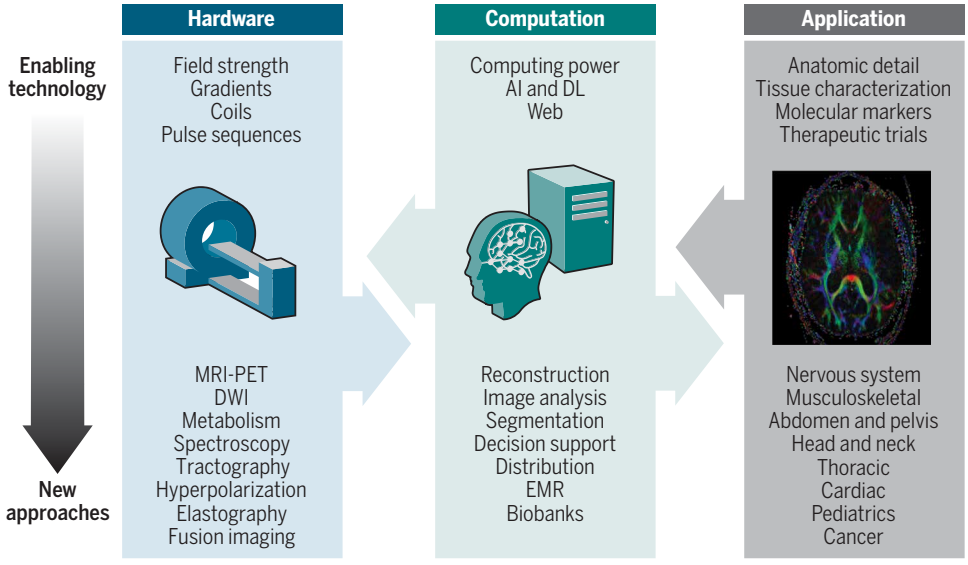

Fig. 1. Advances in clinical MRI. Depicted are previous and projected advances in magnetic resonance imaging (MRI). Complementary developments in imaging hardware and computational analysis are facilitating improved image quality, which has enabled a broadening of MRI applicability across organ systems and will likely continue to do so in the future. DWI, diffusion-weighted imaging; EMR, electronic medical record.

tumor detection and tissue characterization; however, their use may be problematic in patients with renal failure who are at risk of developing nephrogenic systemic fibrosis. Consequently, gadolinium-free alternatives are under investigation. MRI can be used with systemically administered magnetic nanoparticles for nodal staging in cancer (*6*); MRI can also be used to quantify innate immune cells in tissue (inflammation imaging) and predict the efficacy of nanotherapeutics (*7*). MR spectroscopy can measure metabolites such as phosphocholine, lactate, citrate, and creatine within tissues. Last, hyperpolarized MRI using labeled metabolites, such as ^{13}C pyruvate, allows basic metabolic measurements (*8*) that can safely and effectively detect key metabolic conversions in patients with a variety of diseases. For example, in prostate cancer, increased conversion of pyruvate to lactate can be measured and is associated with increased tumor aggression.

Although many current MR techniques focus on qualitative assessment of tissue characteristics (hypointense versus hyperintense lesions), significant advances in quantitative MR techniques are now being realized. MR fingerprinting quantitatively characterizes tissues; the resultant numerical values permit data collation across differing time points for individual patients and between differing datasets of patients for enhanced precision. Handling these large volumes of numerical data will be facilitated by established and emerging accomplishments in AI. Furthermore, image reconstruction for these datasets is complemented by concurrent advances in MR physics, including Bloch equation–based reconstruction techniques with dictionary mapping. These reconstruction techniques are necessary for accelerated data acquisition through undersampling while maintaining image quality. Similarly, advances in numeric T_1 mapping and extracellular volume analysis in cardiac MRI have improved our assessment of myocardial function. These permit, for example, the detection of diffuse cardiac fibrosis, which would otherwise go undetected on conventional late gadolinium-enhanced MRI, which is more sensitive to focal fibrosis.

THE NEXT DECADE OF CLINICAL MRI

Although clinical challenges abound for MRI, the opportunities are equally expansive. Looking forward, the most pressing clinical needs are shortening MRI acquisition times, optimizing image quality and content, automating analyses, perfecting fusion imaging, and enabling whole-body imaging. Approaches to achieve these goals will likely be similar to those described above. Deep learning (DL) algorithms are likely to play a central role in image acquisition (sub-Nyquist sampling strategies using DL), reconstruction (AUTOMAP), and automated image post-processing. More seamless integration of imaging results (including structured reporting and alerts of significant findings) into electronic medical records will be essential. Currently, this remains cumbersome because the different imaging technologies and platforms are not optimized to interact with and learn from each other. Below we discuss established, emerging, and still-needed clinical MRI applications for cancer and other diseases.

Cancer imaging using MRI for initial cancer diagnoses, staging, serial imaging in therapeutic trials, and recurrence/progression monitoring is already established. In general, MRI has been shown to accurately stage cancer; triage patients to appropriate therapy; and support patient follow-up, particularly for colorectal, gynecologic, and prostate cancers. It is generally accepted that MRI is the most sensitive imaging method for identifying early metastatic disease in the liver and brain. MRI is also routinely used to establish the extent of bone marrow involvement and to identify skin or satellite lesions in bone malignancies. Furthermore, MRI is increasingly relied upon to phenotype cancers by extraction of quantitative imaging features (radiomics) (*9*). Several newer applications in cancer imaging include the following: screening for breast cancer in high-risk populations carrying *BRCA* mutations; planning radiation treatment, whereby superior soft tissue contrast permits accurate boundary delineation and dose painting; and predicting and monitoring patient response to chemotherapy. Another example is using whole-body MRI in oncology staging, particularly for lymphoma in younger patients for whom radiation exposure should be limited. Intraoperative MRI will likely play an increasing role in neurosurgical oncology by providing real-time information about the precise spatial relationship between tumors and adjacent areas in the brain to optimize surgical resection while limiting inadvertent damage to healthy cerebral parenchyma. The continued evolution of open-bore scanners will further enable MRI-guided procedures in interventional oncology.

Of the many potential clinical advances likely to result from expanding imaging technologies, several hold notable potential. A key interest in neurologic imaging is to translate emerging ultrahigh-field MRI (>3 T), which increases the signal-to-noise ratio, into clinical practice. This will allow better anatomic and ultrastructural imaging and will likely open new doors to disease characterization. Although a few such ultrahigh-field systems are operational in clinical research settings,

practical challenges will need to be overcome for the approach to be adopted more broadly. Improved signal-to-noise ratio and increased imaging sensitivity as a function of higher field strength have had profound effects on advanced techniques such as blood oxygen level–dependent (BOLD) imaging, which may help uncover the neurobiology of complex processes in addiction and the locoregional actions of drugs targeting the central nervous system. For musculoskeletal imaging, a central goal is the ability to perform MRI with stress loading on joints. This may seem simple but will likely require new magnet designs. In cardiology, fast data acquisition will allow routine real-time imaging in patients with arrhythmias. Similarly, advanced thoracic imaging will require the development of image acquisition methods during quiet breathing rather than the current approach of breath holding, which often is difficult for patients. Important aspirations in abdominopelvic imaging include establishing MRI as a surrogate end point for metabolic disorders such as hemochromatosis and validating MRI as a readout in drug development and trial assessment (for example, in drug trials for nonalcoholic steatohepatitis).

While acknowledging the advances made in decreasing scan time and optimizing image acquisition over the past decade, there remains considerable potential for improving the patient experience in the MRI suite. At present, advanced imaging techniques, such as functional and cardiovascular MR, require protracted scan times (sometimes up to or more than an hour). Consequently, patients often become uncomfortable during the examination, and motion artifacts remain a considerable problem. Although retrospective motion correction algorithms are useful, adaptive dynamic imaging, including prospective motion correction currently in development, is expected to expand the applications of cardiovascular and functional MRI. Within the field of cardiovascular imaging, efforts are being made to combine these prospective motion correction algorithms with free breathing techniques to further enhance the patient experience. Previously, complex sequence acquisition required electrocardiogram gating, breath-hold sequences, and respiratory gating to achieve artifact-free images. New efforts are emerging on MR "multitasking," which continuously collects geometric data and resolves for these artifacts. Undoubtedly, the secondary gains from this progress will include enhanced image quality, shorter scan times, and improved throughput.

MRI biobanking programs by global initiatives seek to acquire multiorgan imaging from large cohorts of patients. Such biobank efforts also include genomic, proteomic, and metabolic outcomes and other patient data often collected at multiple time points. These large repositories (U.K. Biobank and The Cancer Imaging Archive; OpenNeuro) will be invaluable to advance research, education, and training. Although many of these programs are just beginning, they present an exciting opportunity in population-based health care, where MRI will improve understanding of disease mechanisms. The breadth of information acquired by biobanks presents its own challenges and will very likely require automated techniques for data collection and storage.

The advances in MRI technologies described here have not been realized without growing pains, and a considerable amount of work must be done to improve them further. The aspirations of the field are ambitious and will require a community of basic and translational scientists, as well as physicians, to achieve them. Such efforts have been catalytic in the past, as evidenced by the expeditious development of MRI in the past decade. Many new applications will necessitate prospective clinical trials and cost-effectiveness analyses so that emerging techniques can become reimbursable. Further broadening our horizons in MRI may not simply extend to increasing field strengths or improving sequence technology but to providing ubiquitously available low-field MRI at the bedside. Commensurate advances in the allied fields of AI and MR physics will be necessary to facilitate all of these improvements. Collaborative efforts and public-private partnerships will be essential to driving these technologies and realizing the full potential of MRI in the years to come (*10*).

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