

COMMENTARY

Premarket Approval Through the 510(k) Process: Lessons from the Translation Process of Magnetic Resonance Elastography

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Innovations in medical imaging technologies have revolutionized medicine and generated examples of rapid translation to the clinic. Magnetic resonance elastography (MRE) is a noninvasive technique to quantify tissue stiffness. In this commentary, key events in the translation of MRE from laboratory into clinical practice are highlighted. We focus on key science and technology, application to chronic liver diseases, key clinical studies, the US Food and Drug Administration (FDA) approval process, and its influence on current and future medical practice.

THE EVOLUTION OF DIAGNOSIS

Manual palpation has been dated from at least 1500 BC as a technique for abdominal cavity diagnosis in the Egyptian Ebers Papyrus. Hippocrates described it as well to assess organ stiffness in the year 400 BC. The discovery of the X-ray technology, in 1895, and magnetic resonance imaging (MRI), in 1974, further enhanced clinician's assessment capacity to diagnose masses by visually observing changes to tissue composition and structure.

WHAT IS MRE?

An MRE is an MRI-based technique that allows quantitative imaging of tissue elastic modulus, or, in other words, using MRI for noninvasive palpation. Elastography is based on a principle that propagating mechanical waves move more rapidly in stiffer material than in soft material. The equation $v = f \cdot \lambda$ describes the relationship between the wave frequency (f), wave length (λ), and the propagation velocity (v). Theoretically, a technique that allows tracking of mechanical waves in tissue and measuring their wavelength would allow for assessment of tissue stiffness (elastic modulus). In 1992, elastography was described as a method that would allow quantitative imaging of strain and the elastic modulus distribution through soft tissues.¹ In 1995, elastography was combined with MRI, allowing the spatial mapping and quantification of harmonic mechanical waves in tissues and the visualization of propagating mechanical waves.²

EARLY MRE INVESTIGATIONS

The 1995 publication by Muthupillai *et al.*² described a groundbreaking MRI-based technique for quantitative mapping of physical response of agar gel phantoms to harmonic mechanical excitation (**Figure 1**). The resulting images allowed calculation of regional mechanical properties of the imaged material. Results demonstrated that the shear modulus obtained with MRE in gel material correlated with independent measurements of shear modulus. The most developed application in human studies is in the liver, in which many studies demonstrated the reliability of MRE to noninvasively assess liver fibrotic changes and even to differ fibrosis staging.^{3,4} In 2007, Yin *et al.*⁵ demonstrated MRE's potential to assess liver stiffness with a mouse model, strengthening the results of human studies. Nonetheless, as liver MRE was developed in humans, the assessment of MRE was done mostly in patients.

FINDING THE CLINICAL APPLICATIONS FOR MRE

Chronic liver diseases and clinical impact

The liver is an organ located in the abdominal right upper quadrant whose main functions include protein synthesis, bile production, drug metabolism, and glycogen storage. Chronic liver injury is related to alcoholism, viral infections, autoimmune disease, and obesity; leading to liver scarring, fibrosis, and failure. According to the Centers for Disease Control, between 2.7 and 3.9 million people in the United States have chronic hepatitis C and between 850,000 and 2.2 million have chronic hepatitis B.⁶ Furthermore, as obesity and metabolic syndrome have increased in prevalence, the population of patients with nonalcoholic fatty liver disease has grown as well. In the United States, about one-third of the population has nonalcoholic fatty liver disease, with the prevalence ranging between 10 and 50% depending on diagnostic modalities used for diagnosis.⁷

Chronic liver injury progresses from inflammation and fibrosis to the irreversible endstage liver cirrhosis. In liver fibrosis and cirrhosis, normal liver cells are replaced by increasing amounts of scar tissue as a consequence of repeated damage, leading to progressive stiffness.

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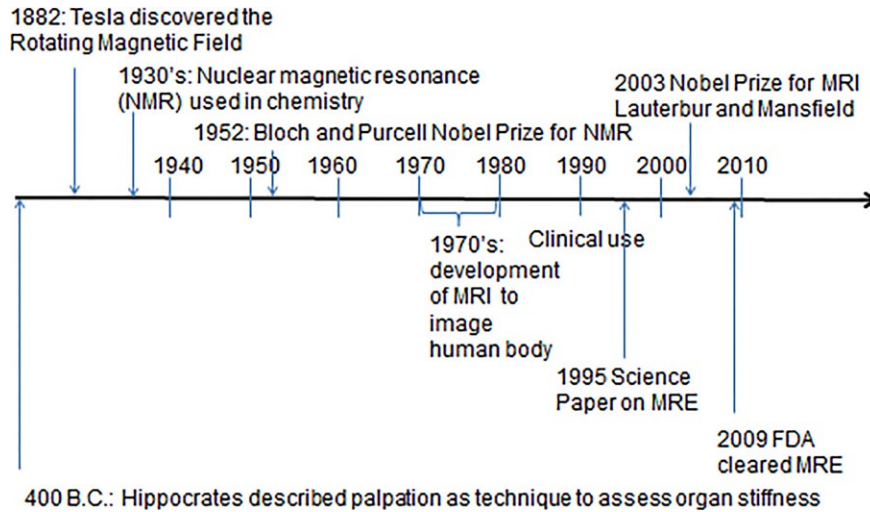


Figure 1 Timeline for translation of magnetic resonance elastography (MRE) technology. FDA, US Food and Drug Administration; MRI, magnetic resonance imaging.

Consequently, liver function becomes hindered. Patients develop portal hypertension with related complications, such as esophageal varices with subsequent bleeding. Additional complications include hepatic encephalopathy and hepatorenal syndrome, leading to kidney damage and potential need for dialyses. Cirrhosis can lead to fulminant liver failure requiring immediate liver transplantation. As disease evolution is initially indolent, preliminary and noninvasive testing become highly useful tools to catch the disease early in its history. The importance of early detection of liver fibrosis lies in the fact that it can be reversed if the harmful liver stimulus is removed.

Liver fibrosis progresses silently and the “gold standard” method for diagnosis is liver biopsy. Liver biopsy is a highly invasive procedure, which can lead to complications, such as pain, infection, hemorrhage, pleural cavity leakage, pneumothorax, sepsis, and, in rare cases, death. Approximately 2–3% of patients require hospital admission for management of complications and the mortality of percutaneous liver biopsy is about 1:10,000.⁸ Liver biopsies rely on operator experience, and sampling variability and interpretations can vary due to interobserver variability.

An MRE has a reported sensitivity of 98% and specificity of 99% for all stages of liver fibrosis, whereas discriminating moderate and severe fibrosis with a sensitivity of 86% and a specificity of 85%. An MRE is safe and effective, and is a potential screening test for liver fibrosis and cirrhosis.⁹ A shear stiffness cutoff of 2.93 kPa can be used to distinguish normal and fibrotic liver, whereas normal liver is softer.⁹

LIVER MRE AND TRANSLATING TECHNOLOGICAL INNOVATIONS INTO CLINICAL PRACTICE

In 2017, Serai *et al.*⁴ prepared a meta-analysis using data from studies spanning 10 years to assess liver stiffness with MRE. This analysis revealed that a measured change in hepatic stiffness of 22% or greater indicates that there is a true change

in stiffness when performed at the same site with the same equipment and acquisition sequence. They stated limitations, such as operator dependence, and assessed challenges in areas near the liver margins and the driver, which should be avoided as high wave reflections could artificially increase result values.⁴ Nevertheless, they determined that MRE is reliable in terms of the repeatability of MRE results and that ongoing improvement in hardware and software could further increase the product’s reliability as a diagnostic tool.⁴

EXPANDING APPLICATIONS OF MRE

Many pathological processes affect the tissue mechanical property. MRE is currently under study for application to pathologies of other organs, including the brain, breast, prostate, heart, kidneys, lungs, and skeletal muscle.^{3,10}

FDA REVIEW AND INDUSTRY INVOLVEMENT

The FDA defines class I devices as those posing minimal to moderate risk. These devices are typically exempt from the traditional FDA review processes. Class II devices pose a higher risk than class I, requiring regulatory oversight to ensure safety and effectiveness. Class III is the devices with a higher risk potential, leading to the most rigorous pathway known as the premarket approval process. MRE was classified as a class I device, cleared through a process known as the 510(k) mechanism, which classifies a device as having substantial equivalence if there is a predicate device. These devices are defined as FDA-approved, safe, effective devices with similar technology to the ones intended for approval. MRE produces an acoustic frequency vibration and then uses MRI for the measurement of displacement caused by the vibrations leading to measurements of stiffness. Consequently, headphones were used as predicate devices, allowing for a faster than average approval.⁶

MRE was patented by the Mayo Foundation for Medical Education and Research, Rochester, MN. The Mayo Foundation founded Resoundant, a company producing MRE software and hardware, including an abdominal driver for generating acoustic waves. GE, Siemens, and Phillips licensed the MRE technology from Resoundant, and subsequently obtained clearance via 510(k) process from the FDA to market MRE as an upgrade on conventional MRI scanners (2009 GE, 2012 Siemens, and 2014 Phillips). A cross-vendor validation assessment was performed and demonstrated reproducibility and consistency between vendor platforms for the device.

BARRIERS TO TRANSLATION AND KEYS TO SUCCESS

Although an MRE holds great promise in increasing diagnostic accuracy and monitoring therapeutic outcomes, it shares many of the same limitations as an MRI. For example, MRI cannot be used in patients with implanted devices due to its magnetic field. MRI also has body size limitations, as some morbidly obese patients are not able to fit into the scanner.

There are several key factors that contributed to the successful translation of MRE into clinical management of patients with chronic liver disease. The process of assessing elastic imaging began during the late 1980s. The patent for the MRE device was obtained in 1997 and, in 2009, the FDA approved its process.² The development of MRE at the Mayo Clinic under Dr. Ehman allowed for thorough investigation of MRE in animal and human studies. Other key factors in successful translation included widespread availability of MRI scanners, the noninvasive nature and low cost of MRE being supplemental to the clinical MRI, and short duration of added MRE to total MRI time for individuals undergoing imaging. Current work is toward technique improvement, its use for other tissue pathologies, and determining its clinical impact.

LESSONS LEARNED

The translational path of MRE reveals many broadly generalizable lessons regarding the translation of imaging devices, the use of predicate devices for the approval of medical devices, and the 510(k) mechanism. Imaging devices tend to undergo faster approval than more invasive devices, as they often use the predicate device and 510(k) mechanisms. Consequently, imaging-dependent processes can be quickly implemented in medical practice, aiding practitioners to perform more accurate procedures and tests while minimalizing risks. It is important for stakeholders to work together for technology enhancement and distribution

to the market to ensure rapid and safe translation, as well as reproducible results. Furthermore, the encouraging results in models in additional organ systems could lead to similar results in the future, including advancing treatment for other pathologies, including neurodegenerative diseases and cancers.

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