MR-guided focused ultrasound surgery, present and future

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MR-guided focused ultrasound surgery (MRgFUS) is a quickly developing technology with potential applications across a spectrum of indications traditionally within the domain of radiation oncology. Especially for applications where focal treatment is the preferred technique (for example, radiosurgery), MRgFUS has the potential to be a disruptive technology that could shift traditional patterns of care. While currently cleared in the United States for the noninvasive treatment of uterine fibroids and bone metastases, a wide range of clinical trials are currently underway, and the number of publications describing advances in MRgFUS is increasing. However, for MRgFUS to make the transition from a research curiosity to a clinical standard of care, a variety of challenges, technical, financial, clinical, and practical, must be overcome. This installment of the Vision 20/20 series examines the current status of MRgFUS, focusing on the hurdles the technology faces before it can cross over from a research technique to a standard fixture in the clinic. It then reviews current and near-term technical developments which may overcome these hurdles and allow MRgFUS to break through into clinical practice. © *2013 American Association of Physicists in Medicine*. [http://dx.doi.org/10.1118/1.4811136]

1. INTRODUCTION

Image-guided focused ultrasound surgery (FUS) is a quickly developing technology that uses high-intensity focused ultrasound (HIFU) along with MR image-guidance (MRgFUS;[1,2]) or diagnostic ultrasound image guidance (USgFUS;[3–5]) for therapeutic purposes. Image-guided focused ultrasound surgery (also sometimes referred to as HIFU-therapy or HIFU-surgery) has potential applications across a wide range of indications that span benign and malignant tumors, pain, vascular problems, and others.

FUS has the potential to be a disruptive technology in the context of certain subspecialties within radiation oncology, particularly for focal techniques such as stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) which have similar focal treatment and minimally invasive characteristics. However in other settings, FUS also has the potential to be an effective approach alongside traditional Radiation Oncology techniques.

In the United States, MRgFUS has been deployed clinically for the noninvasive treatment of uterine fibroids and bone metastases. Clinical trials are currently underway for a variety of other applications both within and outside the realm of oncology. In most of these cases the intent of the therapy is to locally destroy targets using heat; the system is capable of conformally heating targets to ablation temperatures while largely sparing normal tissue. However, research is also focusing on uses of MRgFUS as an adjuvant therapy to traditional radiation or chemotherapy,[6,7] and for the targeted delivery of therapeutic agents[8] that can be used by themselves or in tandem with radiation.

Recent symposiums and workshops and an increase in the number of focused ultrasound surgery publications demonstrate that the technology is viable and is likely to see significant development. MR-guided focused ultrasound surgery was also recently named by Time Magazine as one of the 50 most important inventions[9] (the second time MRgFUS has appeared in Time magazine[10]).

FIG. 1. Examples of currently available commercial MR-guided focused ultrasound systems. (a) Insightec OR MR-guided system (image courtesy of InSightec Ltd.). (b) Philips Sonalleve MR-guided system (image courtesy of Philips Medical Systems).

This edition of the Vision 20/20 series examines the current state of MRgFUS and some likely paths for its future development. This paper is divided into two main parts: Part I reviews the basic physics and biology of MR-guided focused ultrasound as well as indications currently cleared in the United Stated; Part II describes the challenges that confront MRgFUS as it evolves toward a more widely available clinical tool, along with a review of current developments that should overcome these challenges in the near future.

Part I. Physics and Biology

2. MR-GUIDED FOCUSED ULTRASOUND—BASIC PRINCIPLES AND CURRENT CLINICAL STATUS

2.A. Technology overview

2.A.1. Basic components

Current focused ultrasound surgery systems are roughly classified into two types based on the technique used for image guidance. Ultrasound-guidance combines the therapeutic high-intensity ultrasound with diagnostic ultrasound imaging for target localization and postprocedure verification. MR-guidance allows for both target localization and *in vivo* real-time monitoring of temperature through a technique called MR thermometry,[11] as well as postprocedure imaging (typically with contrast-enhancement) to verify tissue destruction.

Figures 1(a) and 1(b) illustrate two of the MR-guided systems currently on the market or in late-stage development. Table I describes the components of a typical FUS system.

The current commercially available MR-guided FUS systems use multielement phased array ultrasound transducers. These transducers are composed of a number of individual piezoelectric ultrasound elements. In most cases the transducers are constructed in a concave design to provide them with a natural focus. Beam steering and focusing is usually accomplished through a combination of mechanical translation and tilt (for gross positioning of the focal spot), and electronic steering (for fine control of the focal spot location). The degree to which electronic control of the transducers can adjust focal spot position and shape depends in part on the number of transducer elements and the overall geometry of the transducers.[12]

TABLE I. Major components of a clinical high-intensity focused ultrasound surgery system.

Component	Purpose
Multielement phased array ultrasound transducer	Generate focused, high-intensity ultrasound beams. Usually electronically steerable.
Water bath	Creates an acoustic window between transducer and tissue, assists in surface cooling
MR (MRgFUS) or diagnostic ultrasound (USgFUS) unit	Target localization and tracking / real-time thermometry
Customized MR table (for MRgFUS)	Allows the ultrasound transducer and water bath to fit in table and interface with MR unit
Accessory immobilization devices (body molds, immobilization masks, stereotactic frames, etc.)	Target immobilization
Motion tracking and gating devices	Assists with targeting of moving targets
Treatment planning and delivery software	Allows imaging and treatment planning to be integrated, used to predict treatment effects

In most cases, for MR-guided FUS systems the transducer is built into the MR treatment couch, however intracorporal transducers[13] and relocatable, strap-on transducers have also been developed and can be used for locations where fixed transducers in the treatment table cannot reach the intended treatment site.

2.A.2. Basic physics of MR-guided focused ultrasound

An ultrasound beam is composed of longitudinal mechanical waves with frequencies above the range of human auditory perception (i.e., greater than ~20 kHz). As the waves traverse the medium, they apply pressure to the particles (atoms or molecules) in the medium, causing them to oscillate back and forth. While the particles move only a tiny distance, the collective motion of the particles creates wave fronts of compression and rarefraction which transmit the ultrasound energy.[14]

2.A.2.a. Acoustic impedance, reflection, and acoustic windows. As ultrasound passes through hetereogenous media such as exists in the body, the beam encounters tissue types with varying physical and acoustic properties. At each of these interfaces, a proportion of the ultrasound energy is reflected back from the interface, and the remaining energy is transmitted. For diagnostic applications, it is the detection of the reflections which forms the basis of image creation. For therapeutic applications such as FUS, the goal is to minimize reflection and transmit sufficient energy to the targeted tissue to cause a desired biological effect.

Every medium has a characteristic property called the acoustic impedance (Z) (units $\text{g cm}^{-2} \text{ s}^{-1}$), which is the product of the physical density and the speed of sound in the medium:

$$Z = \rho c.$$

Maximum transmission through heterogeneous tissue interfaces occurs when the acoustic impedance of the tissue types on either side of the interface is equal. When the impedances are not equal, the fraction of ultrasound energy which is reflected increases in proportion to the difference between the acoustic impedances of the interfacing tissues. For example, due to large differences in acoustic impedance, ultrasound does not readily propagate from water or tissue into air (or vice versa).[15]

Thus, a critical component of every HIFU system is to have a robust acoustic window between the transducer and the target. A combination of materials including mineral oil, gel, and degassed water are used to create an interface between the transducer and the skin of the patient. Any air-filled organs (such as bowel) must be out of the path of the ultrasound beam. Bubbles, whether in the transducer-patient interface or within the patient's tissue can cause reflection and scattering of the ultrasound beam. Setup procedures for each treatment generally include instructions for removing bubbles at the transducer-patient interface, and treatment preparations can include techniques such as bladder and rectal filling to help move air-filled organs such as intestine out of the beam path.

2.A.2.b. Frequency vs depth vs sharpness. With HIFU, for a given transducer there is a direct tradeoff between the frequency of the ultrasound waves, the penetration depth, and the sharpness of the lesion. Ultrasound intensity for a plane-wave beam propagating in an absorbing medium attenuates (scatters and absorbs) exponentially

$$I = I_0 e^{-\mu x}, \tag{1}$$

where I is the intensity at any point x and I_0 is the intensity at the origin. The intensity attenuation coefficient, μ, describes the attenuation per unit length. μ is a power-law function of frequency,

$$\mu = a f^b, \tag{2}$$

where a and b are constants specific to the medium, and f is the frequency.[16] This relationship means that increasing the ultrasound frequency increases the absorption, i.e., more heating occurs per unit length, and also decreases the possible depth of penetration. The intensity at the focus is reduced due to pre-focal absorption. Likewise, a decrease in frequency increases the penetration of the beam, but makes it more difficult to create a sharply defined thermal focus.[16]

The attenuation coefficient also changes in tissue which has been coagulated, making it more difficult to ablate tissue which is located downstream of tissue which has already been ablated.[17]

Thus, the optimal frequency for HIFU varies by treatment and (for a given transducer radius of curvature) is always a balance between penetration depth and the ability to create a focus. It should also be noted that the sharpness of the focus also depends on geometric factors, such as the radius of curvature of the transducer, so there can be a complex set of engineering tradeoffs involved in developing a system.[16] For most extracorpeal abdominal and pelvic applications, a frequency close to 1 MHz is employed as a best trade-off between focus and penetration. For intracavitary and interstitial systems that require smaller penetration depths, higher frequencies of between 3 and 12 MHz are often used. Extracorpeal systems use lower frequencies in order to penetrate deep within tissue, and compensate for the difficulty in creating a focus by employing higher power levels.[16] For shallow applications such as cosmetic[18,19] and ocular[20-22] indications, frequencies greater than 2 MHz have been employed.

2.A.2.c. Thermal energy transfer. Transfer of thermal energy to tissue occurs primarily through two mechanisms.[15] The first, relaxation absorption, is described by the following relationship:

$$\beta_{\text{r,tissue}} \propto \sum_{n} \frac{f^2}{1 + \left(\frac{f}{f_{r,n}}\right)^2},$$

where $f_{r,n}$ are the various relaxation frequencies present in the tissue. For a homogeneous medium, the relaxation frequency corresponds to a relaxation time τ, which is the time required for elastic forces within the medium to return the medium to its original position after displacement from a pressure wave. If the frequency is such that the wave arrives at the same instant the medium is in its maximum elastic recoil (or

relaxation), the amount of energy extracted from the pressure wave is maximized. In general, there is a linear relationship between frequency and the relaxation absorption coefficient.[15]

The second mechanism of thermal energy transfer, called classical absorption, is due to friction between particles in the medium, and is proportional to the square of the frequency:

$$\beta_{classical} \propto f^2.$$

The interparticle friction converts the ultrasound energy into heat. As such, classical absorption is proportional to the viscosity of the medium.[15] For thermal applications of FUS, where temperature elevation is the desired endpoint, classical absorption is the primary mechanism for heating.[16]

2.A.3. Image guidance

Image guidance plays a critical role in focused ultrasound surgery. Imaging is required to identify and localize the therapeutic target and surrounding anatomy, to ensure the patient is correctly positioned with respect to the ultrasound transducer, and to verify that an appropriate acoustic interface exists between the transducer and the target. Real-time image guidance can provide targeting feedback during the treatment itself. For instance in thermal therapies a technique known as thermometry can be used to identify areas of tissue which have reached an appropriate ablation threshold and which areas remain to be treated.

Ultrasound-guided FUS (USgFUS) systems rely on diagnostic ultrasound to provide both anatomical and real-time treatment feedback. Feedback at real-time frame rates is possible by identifying areas of hyperechogenicity in treated tissue.[4] However, this method of ultrasound guidance is not optimal for determining absolute temperature changes or for spatial resolution of the treated tissue.[23] Ultrasound thermometry is possible with quite high temperature resolution, however the window of temperatures that can be mapped is small, and most methods depend on knowledge of tissue-specific parameters such as attenuation, speed of sound, and changes in backscattered energy with temperature, which are often poorly characterized at ablative temperatures.[3]

MR-guided systems (MRgFUS) use MR for diagnostic and planning imagery as well as for feedback during procedures in the form of MR-thermometry.

This is possible because a number of MR parameters including T1 and T2 relaxation, proton resonance frequency, and magnetization transfer coefficient have temperature dependencies which can be exploited. In proton-resonance frequency shift (PRF) thermometry, the most commonly used thermometry technique, temperature-dependent phase changes in gradient-recalled echo (GRE) pulse sequences are used to determine the temperature change.[24] Images acquired during a sonication are subtracted from baseline images acquired prior to heating.

The change in temperature can be represented as

$$\Delta T = \frac{\Delta \phi}{\gamma \alpha B_0 TE},$$

where $\Delta\varphi$ is the phase change, γ is the gyromagnetic ratio, B_o is the main magnetic field, and *TE* is the time to echo, and α is the PRF change coefficient for aqueous tissue (-0.01 ppm/°C).[25]

MR-thermometry can provide quantitative temperature measurements over the range of temperatures used in ablative and subablative FUS techniques are generally independent of tissue type for most soft tissues,[26] and can be acquired at near real-time framerates with customized pulse sequences.[27]

PRF-shift thermometry works best when the reference and sonication images are perfectly coregistered. Any misalignment, including that caused by patient shifts, internal organ movement, edema, and changes in tissue due to thermal coagulation, will result in artifacts in the resulting thermal map. This limits the use of PRF thermometry in situations of poor patient immobilization or respiratory organ motion.[28,29] Thermometry measurements within fatty tissue is also degraded[25] as the phase dependence of lipids is almost independent of temperature.[30] In situations of adipose tissue or mixed tissue types, fat suppression can be used to compensate.[30,31]

2.A.4. Physical tissue effects

Current clinical MRgFUS systems are designed mainly with target ablation as an endpoint. However, ultrasound (and high-intensity ultrasound in particular) has several physical effects in tissue, all of which can theoretically be used for treatment advantage:

- Thermal effects: ultrasound absorption in tissue causes microscopic-scale frictional heating of tissue generated by shearing caused by the longitudinal compression and rarefraction pressure variations of the ultrasound.[16] The amount of heating is predictable and repeatable and can be measured with techniques such as MR-thermometry.[32–34] It should be noted that when used for tissue ablation FUS thermal effects are significantly different from traditional hyperthermia therapies as used in oncologic settings.[35] Ablative FUS achieves much higher temperatures in a much shorter amount of time, and in a more localized area of tissue. Thermal effects causing ablation of tissue are currently the primary effects used in FUS.
- Mechanical affects: Rarefaction of the ultrasound wave can draw gas out of the surrounding tissue forming microbubbles. These bubbles will oscillate with the ultrasound waves and will grow in resonance to the waves until violently imploding.[36,37] The resulting mechanical action due to implosion shock waves and thermal effects due to broad-spectrum ultrasound emission is much greater than what is achieved with ultrasound waves alone.
- Acoustic streaming: Ultrasound waves passing through a fluid can transfer momentum to the fluid.[38,39] This can cause a velocity gradient, which in turn causes shear stress.

2.A.5. Biological tissue effects

The physical effects outlined above can be used alone or in combination to achieve a variety of desirable biological effects. These are summarized below:

- Local Ablation: At temperatures above a certain threshold (∼56°C for > 1 s, but varies for different tissue types) coagulative necrosis (ablation) occurs. The boundary between lethal and sublethal effects can be extremely sharp, on the order of a few cell-thicknesses. The area of necrosis is surrounded by a rim of damaged cells that typically die soon after exposure.[12] Thus, the effect of FUS on tissue that is thermally ablated is immediate and complete if all cells have been raised to the ablation threshold. In some settings such as tumors, this may be advantageous as compared to ionizing radiation, where the probability of cell death is a stochastic function of dose, and cell death can be temporally delayed because of the dependence on cell-division.[40]

- Thrombolysis: At low-frequency but high-intensity, with temperatures below that required for ablation, acoustic streaming can cause changes in cell membranes and the fibrin mesh that work to increase thrombolysis. This could play a role in the treatment of stroke or other thrombosis.[41]

- Arterial occlusion: At ablation temperatures, thermal coagulation of blood vessels can occur. This could make possible new treatment options for arteriovenous malformations and highly vascular targets.[42,43]

- Radiosensitization: High-intensity ultrasound at subablation temperatures can generate hyperthermia which causes radiosensitization or chemosensitization of targeted tissue.[44,45] This effect could play an important role in combination FUS/radiation therapies.[46]

- Soft tissue erosion (histotripsy): Short, high-intensity pulses of ultrasound can achieve mechanical erosion of soft tissues, especially at tissue/fluid interfaces. The boundary between damaged and interact tissue can be at a subcellular order of magnitude.[47]

- Sonication in the presence of microbubbles has been shown to alter cell membrane permeability at subablation temperatures.[48] Potential applications taking advantage of this effect include drug delivery, selective opening of the blood-brain-barrier (BBB),[49] and gene therapy.[50]

2.B. Current clinical status

The modern history of focused ultrasound surgery can be traced back to its first mention by Wood and Loomis in 1927.[51] In 1944, Lynn and Putnam proposed using ultrasound to destroy tissue.[52] Soon after, the Fry brothers described the creation of focal lesions in the central nervous system with high-intensity ultrasound.[53] Experiments soon demonstrated the ability to create lesions in deep-seated tissue in the brain,[54] and later the ablation of tumor tissue.[55] However, the ongoing development of FUS was inhibited by technical constraints including a lack of effective target visualization technologies, the inability to effectively refocus ultrasound after it has been distorted by tissue interfaces, large power requirements, and limits at the time on transducer design. The relative ease of delivery of focal ionizing radiation diverted efforts toward the development of techniques such as radiosurgery.[56]

Detailed studies of the acoustical properties of the human skull[57] demonstrated that under certain conditions it might be possible to focus ultrasound energy through the skull.[58] Methods were later developed that made this idea a practical reality,[59] applying phase-compensation techniques similar to older methods developed for diagnostic imaging.[60]

In parallel with advances in the creation of focal ultrasonic lesions came advances in imaging technology. Parker *et al.*, discovered that temperature variations can be mapped in an NMR image.[61] This insight led directly to the idea of using MR as a temperature-feedback device, a technique which is now the cornerstone of MRgFUS.

Beginning in the early 1990s, the developments in ultrasound delivery technology, computer modeling of ultrasound beams, and imaging began to coalesce. In 1992, reports emerged describing MR-guided FUS on *ex vivo* muscle tissue,[1] and the following year on *in vivo* tissue.[2] Several reports using US-guided systems for treating benign prostatic hyperplasia and prostate cancer appeared in the early 1990s.[62–64] By 1995, integrated systems for MRgFUS were being developed,[65] and improvements in MR-thermometry were being reported.[24] In 2000, large-scale arrays for transcranial FUS were developed that allowed the ultrasound energy to be spread out over a wide area, increasing the efficiency of ultrasound delivery to spots deep within the brain.[66] Shortly thereafter, time-reversal algorithms that could simulate the effect of and correct for the effect of the skull on the ultrasound focus were reported.[67]

Parallel to these developments were a series of clinical trials conducted in China in the 2000s for patients with hepatocellular,[68] renal,[69] bone,[70] pancreatic,[71] and other malignancies[72–74] using relatively simple US-assisted systems mechanically steered to their target. These early trials demonstrated the potential effectiveness of FUS for solid tumors with even manually guided devices.

In 2004, the first MR-guided ultrasound surgery system received FDA clearance for the treatment of uterine fibroids. In 2006, reports emerged discussing the use of microbubbles to enhance heating effects and thus reduce the power required to create a lesion.[75,76] Since 2004, the number of potential indications, clinical trials, and reports continues to expand. In Europe, several MR-guided and US-guided focused ultrasound systems have expanded beyond uterine fibroids in the clinical realm with CE marks for palliative treatment of bone metastases and treatments for prostate cancer. In 2012, the FDA announced clearance for the first time in the United States for a system for palliative treatment of bone metastases.

While approved clinical indications are still limited, MRgFUS is experiencing a wide-ranging surge of research and development. Several vendors are now marketing FUS devices, and there are a variety of new devices in the near-term

TABLE II. Current manufacturers of USgFUS and MRgFUS systems.

Company	Location	Device	Type
Chongqing Haifu (HIFU) Technology Company, Ltd.	Chongqing, China	Haifu System	USgFUS
Insightec, Inc.	Tirat Carmel, Israel	Exablate 2000, Exablate 4000, Exablate 2100	MRgFUS
US Hifu, LLC.	Charlotte, NC, USA	Sonablate 500 (prostate cancer)	USgFUS
EDAP TMS	Vaulx-en-Velin, France	Ablatherm (prostate cancer)	USgFUS
Philips Healthcare, Inc.	Boston, MA, USA	Sonalleve	MRgFUS
Profound Medical, Inc.	Toronto, ON, Canada	Prostate system	MRgFUS
Image Guided Therapy, Inc.	Pessac, France	TargetedFUS	MRgFUS

development pipeline. A range of clinical trials are now in progress or are planned.

2.B.1. Clinical systems manufacturers and FUS centers of research

There are several current manufacturers of "commercially available" FUS systems summarized in Table II. Most of these devices are still either under development or are considered investigational in the United States. At the time of this writing the InSightec Exablate has been cleared by the FDA for the treatment of uterine fibroids and for the palliative treatment of painful bone metastases.

FUS research is currently conducted at academic institutions worldwide, and there are three primary research organizations devoted to its development and clinical adoption summarized in Table III.

2.B.2. Current clinical indications for MRgFUS

2.B.2.a. Uterine fibroids. One of the most established current clinical indications for the use of FUS is in the treatment of uterine fibroids. Fibroids which are homogeneous and hypointense relative to skeletal muscle on pretreatment T2-weighted imaging seem to respond better than inhomogenous or higher intensity fibroids, presumably because the latter are more vascular and thus sink heat away from the treatment site. Clinical outcome also seems to correlate well with non-perfused volume (NPV) on contrast-enhanced T1-weighted imaging immediately posttreatment.[77,78]

Figure 2 shows representative pretreatment and post-treatment imaging from a patient treated in two sessions with MRgFUS. Figure 2(a) shows the fibroid pretreatment. Figure 2(b) was acquired immediately after the first treatment session. The NPV of fibroid was calculated to be approximately 67%. Figure 2(c) was acquired after the second session, and the NPV percentage approached 100%.

As of this writing, thousands of FUS uterine fibroid treatments have been carried out worldwide. The success rates in terms of symptom reduction for medium-sized fibroids are comparable to other therapies in this field, but with the advantage of a noninvasive, outpatient procedure.[79,80]

2.B.2.b. Bone metastases. Several ongoing trials in Europe, Asia, and the United States continue to investigate FUS for palliative treatment of primary and metastatic bone tumors. Because bone preferentially absorbs ultrasound energy and converts it to heat, bone tends to heat faster than soft tissue. The objective in palliative bone treatments is not necessarily to ablate the tumor itself, rather it is to heat the bone cortex and destroy or inactivate the nerves innervating the periosteum which is the origin of the pain.[81]

One advantage of FUS over standard radiotherapy regimens is that pain relief can happen very quickly with FUS. A small 2007 study of 12 patients at Sheba Medical Center found that with a mean follow-up of 59 days, 10 patients out of 12 (two patients died from disease progression within 1 month of treatment) reported substantial pain relief on questionnaires and visual acuity scale (VAS).[82] A 2008 study by Gianfelice *et al.* reported that 11 patients in the study with a mean pretreatment VAS score of 6.0 had a mean VAS score of 0.5 (92% decrease) at 3 months follow-up.[83] A multicenter study with 3-month follow-up on 25 patients found 72% of patients reporting significant pain

TABLE III. Scientific organizations promoting the adoption of focused ultrasound technology.

| Name	Year founded	Mission	URL
Focused Ultrasound Surgery Foundation	2006	To accelerate the development and clinical acceptance of MRgFUS	http://www.fusfoundation.org
International Society for Therapeutic Ultrasound	2001	Increase and diffuse knowledge of therapeutic ultrasound to the scientific and medical community	http://www.istu.org/
Society for Thermal Medicine	1986	Fostering interaction and innovation in the study of biological, physical, and medical applications of thermal therapy for cancer and other diseases	http://psfebus.allenpress.com/eBusSFTM/
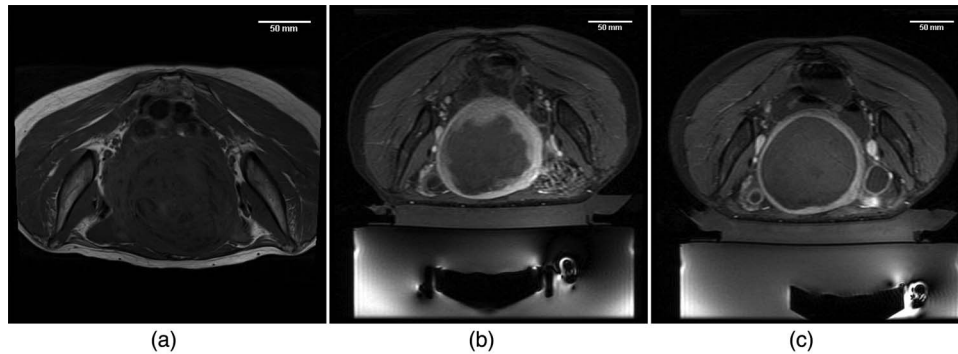
FIG. 2. MR-guided focused ultrasound for uterine fibroids. Images document the treatment of a fibroid patient treated in two MRgFUS sessions approximately 1 week apart. (a) Preprocedure: axial T1 spin-echo image of a patient with a large ($\sim$542 cm^3) uterine fibroid. Image shows some heterogeneity of the fibroid, as well as some possible necrotic areas. (b) Postprocedure 1: axial, postcontrast, fat suppressed, fast spoiled gradient echo pulse sequence. Image shows large nonperfused volume in the center of the fibroid. Volume calculations estimate that 63% of fibroid volume was nonperfused. (c) Postprocedure 2: axial, postcontrast, fat suppressed, fast spoiled gradient echo pulse sequence. Image shows the remaining volume of the lesion is now nonperfused. Approximately 100% of the fibroid volume was ablated. [Images courtesy of the University of Virginia Department of Radiology].

improvement, with mean VAS scores reduced to 1.8 from 5.9.[84] In all three studies no adverse events were recorded.

Part II. Challenges and Solutions

The long history of focused ultrasound demonstrates that although many of the individual technologies have been used in place for some time, it is only recently that focused ultrasound has emerged as a serious clinical possibility. Even now, while there is much potential for focused ultrasound, the number of proven clinical indications for MRgFUS remains quite small. Many barriers to entry—clinical, technical, and regulatory, must be overcome before MRgFUS becomes a standard fixture in the clinic. Part II of this paper explores some of the challenges MRgFUS must overcome before it can be more generally accepted, followed by near-term developments that may help it meet these challenges.

3. PHYSICS AND ENGINEERING CHALLENGES

3.A. Challenge: Cavitation detection and control

The mechanical effects of ultrasound energy in FUS can cause small gas bubbles trapped in tissue to oscillate, a process called cavitation. In noninertial cavitation, these bubbles undergo repeated cycles of linear or nonlinear rarefraction and compression. The bubbles in turn scatter the ultrasound waves, with the amount of scatter proportional to the incident pressure. As the pressure continues to increase, the bubbles reach a threshold size at which they violently collapse during the compression part of the cycle. This phenomenon is termed inertial cavitation.[37] The rapid heating characteristic of focused ultrasound can also cause boiling if the temperature in tissue reaches its boiling point ($\sim$100 °C).[85,86]

If boiling or cavitation occur where they are not wanted, they can produce enhanced heating,[87] displacement of the lesion,[86] and potentially significant damage to tissue. Noninertial cavitation can also have the opposite effect; microbubbles in the prefocal field cause an increase in attenuation of the ultrasound energy and can effectively shield the target from ablation.

Unfortunately, there are many parameters involved in the production of cavitation, and therefore cavitation prediction becomes quite complex and difficult to control. The threshold for cavitation depends on bubble size, bubble density, local temperature, incident acoustic pressure, and excitation frequency. These parameters (with the exception of excitation frequency) are all subject to change from moment to moment.[37] Thus, efforts to either predict or monitor targeted tissue for cavitation effects are being implemented or under development and would be a significant development for FUS.

3.B. Challenge: Calcifications

Tissues within the body that contain macro- or microscopic calcifications (such as intracranial calcifications) pose a theoretical risk in focused ultrasound treatments. Calcifications absorb ultrasound energy in a manner similar to that of bone. The additional absorption of energy can cause unwanted excessive heating away from the focus, and can also act as a shield, blocking ultrasound energy from reaching its intended target. In at least one experiment reported at the 9th International Symposium on Therapeutic Ultrasound, a sonication was stopped because of suspected far-field heating of a calcification.[88]

Macroscopic calcifications can often be visualized on CT imaging and can be managed through careful beam targeting and by the algorithms used for refocusing the ultrasound beams through bone.[89] However, microcalfiiciations that are too small to visualize on CT may be difficult to correct for.

3.C. Challenge: Standing waves and reflections

Like microscopic calcifications, the presence of standing waves in certain FUS indications, especially intracranial applications, presents a theoretical risk that has yet to be fully explored. Standing waves can occur when the ultrasound

beam path between two tissue interfaces is an integer multiple of half-wavelengths. Standing waves can be dangerous because they can cause areas of undesired heating and damage outside of the focus. In the brain, where the effect has been most studied, this can occur within the skull or brain tissue.[90] Targeting areas of tissue near interfaces (e.g., soft tissue/air, soft tissue/bone) can cause reflections that can shift the area of lesioning away from the planned location.[91] This effect has been shown to be especially prevalent in preclinical studies using animal models, where the smaller skulls (and often lower frequencies) involved in the studies make standing waves common.[92]

The transcranial low-frequency ultrasound-mediated thrombolysis in brain ischemia (TRUMBI) trial employing nonfocused, low-frequency (300 kHz) ultrasound in addition to tissue plasminogen activator (tPA) for thrombolysis in ischemic stroke patients showed an increased hemorrhage risk as compared to tPA alone.[93] Subsequent simulation found that standing waves could cause large increases in rarefractional pressure that exceeded the threshold for the development of inertial cavitation. The authors of the study theorized that standing waves could have been a factor in the increased hemorrhage risk.[94]

3.D. Challenge: Developing standards for exposure, "dose," calibration, and clinical acceptance

There is currently no clear agreement on the most appropriate parameters to measure in order to characterize the focused ultrasound beam. Likewise, there is little agreement on how to describe exposure for FUS, or the analog of "absorbed dose" as it is understood in traditional radiation oncology.[95] This creates several challenges for clinical focused ultrasound—it means there is no robust way to standardize treatment parameters for any given clinical situation. There is not necessarily any way to duplicate an experiment reported in a journal on a different treatment device. It also means that comparative treatments on different devices, or even different treatments on the same device, are quite difficult to execute.

There are currently no internationally accepted standards for calibration of high-intensity focused ultrasound machines,[96] although efforts to this effect are in progress.[95] One could argue that for purely thermal treatments being monitored by temperature imaging techniques such as MR-thermometry, precise calibration is not required as the temperature is being reported during the treatment. For purely ablative therapies, perhaps the only important consideration is that the time/temperature reached in the treatment crosses the threshold for ablation.

However, in most situations calibration will remain a critical component in the safety and effectiveness of FUS. FUS is used in situations where the target tissue may be surrounded by healthy tissue. Experiments thus far have shown that the effect relationship between CEM 43° and tissue damage is quite sensitive.[97] Small changes in heating time (for a given temperature) or temperature (for a given time) can have a large effect on tissue damage. Thus, miscalibration of equipment can di-

rectly put healthy tissue at risk of the target is overtreated. Conversely, unintentional undertreatment of the target may result in the need for repeat treatments or even disease progression. When operating under nonthermal conditions or in the presence of cavitation or microbubbles, temperature monitoring via imaging may not be as effective, and accurate calibration will likely become even more critical.

More practically for the widespread adoption of FUS technology, standards for calibration would help to provide the confidence in FUS that is a component that regulatory bodies and insurance companies look for as they make clearance and reimbursement decisions.[96]

When the emerging field is viewed broadly, FUS in some ways is inherently more complicated than ionizing radiation. Whereas currently ionizing radiation is most commonly used to deliver a known absorbed dose to a volume of tissue in one or more sessions, with FUS there are a variety of possible treatment techniques (subablative, ablative, mechanical, mechanism for drug delivery, etc.). For FUS, this complicates the development of a standard set of calibration procedures. In addition, many of the measurement tools available for diagnostic ultrasound (force balances, hydrophones, etc.) can be damaged by the high-temperatures and pressures found in high-intensity focused ultrasound beams.[96] However, without agreement on the most appropriate parameters and methods for quantifying them, there is great difficulty in comparing different FUS treatment techniques, or even comparing the same treatment technique on two different FUS systems.

Without standards for calibration, critical tasks such as acceptance testing of new clinical equipment become difficult. Gorny *et al.* describe acceptance tests they performed on a clinical FUS device for fibroid treatments. Their tests relied on MR-thermometry measurements of temperature and thermal spot location. No tests were performed on the actual calibration of the system, so there is no way to know if the power, frequency, and energy settings of the device were in fact accurate.[98] The risk would be that a different machine operated with identical settings and environmental conditions could deliver different results. This could complicate the ability of a treating clinician to apply their experience across different devices.

4. PHYSICS AND ENGINEERING: SOLUTIONS AND FUTURE DEVELOPMENTS

4.A. Cavitation detection

Of the major causes of unwanted heating discussed above, cavitation detection and control has been the focus of the majority of research efforts. Current clinical FUS systems follow two basic techniques to detect cavitation. US-guided systems attempt to detect bubble formation using B-mode ultrasound to look for hyperechogenicity at the focus; however, these systems cannot be used during the actual therapeutic sonications because the HIFU signal interferes with the B-mode images.[99] As enhanced temperature rise has correlated with bubble-formation,[87] MR-guided systems can instead monitor temperature rise and look for unplanned temperature rise as

a surrogate for cavitation. In either system, cavitation away from the immediate focus can evade detection.

Ongoing work on more sophisticated methods for cavitation detection takes advantage of the range of phenomena characteristic of cavitation. Sonoluminescence detectors can detect the light emission from bubble collapse. Laser scattering and laser interferometry can detect bubble clouds and individual bubbles, respectively.[100] Hydrophone-based cavitation detectors look for characteristic frequency signatures of cavitating bubbles.[101] A drawback to these methods is in localization of individual cavitation events and their efficacy *in vivo*. The use of dual receivers can allow for the localization of cavitation events to a fairly small detection volume.[102] However to be useful for focused ultrasound these detectors may need to work faster and also capture the time-course of cavitation events. Combination methods are in development which may begin to address these shortcomings, such as a dual-method system that combines passive (i.e., receive-only) ultrasound detection with ultrafast subtraction of B-mode ultrasound images relative to presonication reference images that can detect individual cavitation events.[103] Another promising method uses a passive ultrasound array combined with a beamforming algorithm to spatially and temporally map cavitation events.[99]

It may be that the required level of sophistication for cavitation detection is dependent on the clinical technique. For ablative techniques where a specific level of heating at a specifically planned location is the goal, inertial cavitation anywhere may be undesirable, so mapping the location of cavitation events may not be necessary. Conversely for cavitation enhanced techniques, histotripsy, and other techniques, the location of cavitation events becomes critical, and more sophisticated detection is likely to be required.[37]

4.B. Detecting and controlling standing waves and microcalcifications

Unexpected damage to healthy tissue attributed to standing waves has thus far been limited to lower frequency systems in the brain which have a good match between wavelength and skull dimensions. These systems operate at frequencies lower than those currently operated clinically; however, further studies will be required to determine safe operating envelopes in terms of anatomic areas of risk and operating characteristics in order to preclude standing wave formation. Techniques have been explored to prevent the formation of standing waves. One technique is to introduce small random modulations in ultrasound frequency to try to dampen standing waves within the areas of risk.[90]

Further studies will also be required in order to determine how best to image and detect microcalcifications, as well as to determine the minimum size a calcification needs to reach before it can cause clinically significant effects in terms of unwanted heating or beam distortion. Ultrashort echo time MR (UTE) imaging (discussed in more detail below) may be one method for detecting microcalcifications in tissue.[104]

Many tumors involve calcified tissue,[105–110] and this may become an important factor in determining whether FUS is indicated for clinical treatment in individual cases.

4.C. Standards for "absorbed dose" and calibration

4.C.1. Absorbed dose

As with ionizing radiation, "absorbed dose" cannot be directly measured for FUS. Exposure can be measured in terms of parameters such as acoustic power and pressure. A variety of proxies for absorbed dose have been proposed for FUS, including degree × minutes, specific absorption rate (SAR), power density, etc.

In the ablative systems currently on the market, the *de facto* standard for thermal dose is the thermal isoeffective dose:[111]

Cumulative equivalent minutes at 43°C (CEM43 °C)

$$= tR^{(43-T)},$$

where t is the time in minutes, T is the average temperature during the time interval, and R = 2 for T > 43 °C. In the case of FUS, where the temperature is changing quickly with time, the equation is summed over small time intervals, assuming a constant T over each interval. The thermal isoeffective dose describes the relationship between heating and time. The constant R has been estimated from *in vivo* and *in vitro* studies on a variety of tissue types using Arrhenius analysis of cell survival. The cutoff temperature of 43 °C was chosen arbitrarily by the authors of the report; however, it is close to the temperature at which the slope of the Arrhenius plots change in human tissue.

The isoeffective dose concept is popular because it is simple to understand, and if tissue tolerances are well known at a single temperature/time point, the equation can be used to extrapolate to various temperature/time combinations. However, the values for R are not well known at very high temperatures (>57 °C) generated with HIFU, are not proven at the temperature change rates associated with HIFU for thermal ablation, and are not necessarily constant across different tissue types.[97, 112] Isoeffective dose may be sufficient for temperatures up to 57 °C, and may be useful for describing the outer boundary of tissue damage. A direct Arrhenius relationship may be sufficient for describing thermal effects or damage within the higher temperature zone.[113, 114] Further research on tissue response to various thermal treatments may provide methods to better characterize "thermal dose," and may eventually be able to incorporate cavitation, FUS-mediated pharmokinetics, and other effects into some sort of "thermal dose equivalent" somewhat similar in idea to the "Effective Dose"[115] used to describe the overall biological damage associated with an exposure to ionizing radiation.

4.C.2. System calibration

There are a variety of candidate parameters that could be used in system calibrations. Ultrasound systems in similar frequency ranges are commonly characterized by radiation force measurements of the entire cross-section of the beam on a

target using a radiation force balance, and measures of the spatial and temporal distribution of pressure using piezoelectric hydrophones. Intensity and ultrasound power are derived from these pressure and radiation force measurements.[95]

In high-intensity beams, these traditional measurements are quite difficult to perform. The high thermal temperatures generated in the focal ultrasound field can change the response of hydrophones, and can damage the radiation force targets and hydrophones. Induced cavitation can shield the instruments from the beam, and can also cause mechanical damage. Assumptions used to derive intensity and power from pressure measurements are not valid for focal fields. Nonlinear harmonics can change the response of the pressure measurements.[95] Various groups are working on new techniques to allow measurements of these parameters in high-intensity fields and to allow direct measurement of intensity. For instance, Shaw and Hodnett propose a castor oil target and a buoyancy-based measurement to that can provide accurate power measurements in high-intensity focused fields.[96]

As discussed earlier, for thermal ablation treatments, it may be that all of these issues can be wrapped into a temperature measurement (performed in a phantom for calibration, and *in vivo* for actual treatments), since that is the ultimate endpoint of the treatment. This is the basic approach taken by the MR-thermometry community. However, questions remain regarding precision of the system to discern small changes in temperature and the spatial location of the temperature changes. For targets near critical normal tissues, this may become an issue. For procedures where ablation is not the primary endpoint temperature rise by itself is not a sufficient calibration parameter.[96]

5. CLINICAL AND FINANCIAL CHALLENGES

5.A. Challenge: Expanding clinical indications and gaining insurance coverage

As discussed above, in the Unites States at the time of this writing, treatment of uterine fibroids and bone metastases are the only FDA-cleared indications for commercial MRgFUS. While this would allow MRgFUS to become a niche treatment for a certain subset of patients, it is not likely to be sufficient to effect the widespread adoption of the technology or to displace existing alternative treatments. The number of clinical indications for MRgFUS must expand in the future if MRgFUS is to be more widely accepted.

Expanding clinical indications from the perspective of safety and effectiveness is only part of the challenge of gaining clinical acceptance of MRgFUS in an increasingly crowded treatment marketplace. Achieving insurance coverage and reimbursement for any new medical device is a tremendous barrier to entry. This is especially true when a device is new, and not simply an incremental improvement over an existing device. Even in the instance of uterine fibroids, very few insurance carriers reimburse for the procedure, and not in all parts of the country.

In the United States, insurance coverage decisions are driven primarily by Medicare and its Centers for Medicare and Medicaid Services (CMS). National coverage decision through the CMS are the preferred outcome, however local coverage decisions through Medicare local contractors are more common, leading to varying coverage rules in different areas of the country. Coverage decisions are not a completely transparent procedure, and the required data for efficacy, safety, and cost effectiveness are not standardized.[116] Reimbursement is likewise a complicated endeavor, with payment terms generally set by CMS and used as a benchmark by private insurers. If new technologies are assigned to payment groups where the payment does not cover the cost of the procedure for the provider, the provider will not have any incentive to adopt the new technology. Vendors of new devices, and providers hoping to adopt these devices, must therefore work closely with both specialty societies and CMS in order to achieve adoption.[117] It may be especially difficult for indications where there is a crowded field of existing treatment options. Thus, new indications for MRgFUS have an uphill battle to wage regarding insurance coverage and reimbursement. Without these, widespread acceptance will be difficult.

5.B. Challenge: Proving safety and effectiveness

Solving the reimbursement puzzle will be difficult unless the case can be made that MRgFUS is safe, and at least as effective as existing treatment options for any given indication. A recent paper in European Urology performed a systematic review of the literature looking at evidence for the use of MRgFUS for prostate cancer and applying a quasiobjective grading scheme for the quality of the evidence. They concluded the current evidence was of "very low quality, mainly due to study designs that lack control groups." They also took issue with the particular survival and biochemical control endpoints used in many of the studies.[118] This point of view was reiterated in a recent edition of the Point/Counterpoint series published in Medical Physics examining the evidence for MRgFUS vs radiation therapy for prostate cancer.[119]

MRgFUS is an emerging technology. By definition, it will not have a long track record of class 1 evidence supporting its use. However, as attempts to rein in healthcare costs increasingly gain a sense of urgency, proof of cost effectiveness will be vital for the success of MRgFUS.

6. CLINCIAL AND FINANCIAL SOLUTIONS AND FUTURE DEVELOPMENTS

6.A. The role of clinical and scientific societies

The focused ultrasound research and clinical community has organized around several clinical, and scientific organizations whose purposes are to accelerate basic and translational research with HIFU, facilitate collaboration among international centers of research, and perhaps most importantly, to build awareness of the technology and its potential with the public, with CMS and the insurance market. These societies are assisting the creation of interinstitutional collaborations, sharing of technical expertise, and acting as liaisons between industry and academic institutions and between industry and

regulatory agencies. In this sense, MRgFUS is not trying to gain a foothold in the medical marketplace organically, but rather through a deliberate strategy, one that may be unique in medicine.

We have discussed how to prevent MRgFUS from simply becoming a niche treatment modality; it must expand its range of generally accepted indications. Likewise, for FUS to gain approval for reimbursement in the United States it cannot remain a one- or two-indication treatment option. Table IV outlines clinical trials currently active or recruiting in the US clinical trials database (NCT) for breast cancer, functional neurosurgery, brain metastases, uterine fibroids, bone metastases, and prostate cancer. Much more work is taking place around the world on a wide range of indications and possibilities through preclinical and clinical trials, some which expand the possibilities for FUS by taking advantage of both ablative and nonablative techniques.

6.B. New clinical indications: Ablative techniques

6.B.1. Breast cancer

Local treatment of breast tumors was an indication targeted early on by researchers in the field because of its favorable soft tissue interface and relative ease of transmitting the required ultrasound energy.[120] Since this early feasibility study on breast fibroadenomas, several small feasibility trials have been completed investigating the use of FUS as a lumpectomy replacement. Gianfelice *et al.* showed that dynamic contrast-enhanced MRI could be used to evaluate the efficacy of a MRgFUS treatment for small breast lesions.[121] Wu *et al.* reported on a clinical trial with 48 patients randomized to radical mastectomy or HIFU followed by radical mastectomy. Histopathology showed complete necrosis of the tumors after HIFU. In 2005, the same group reported on another 22 patients treated as part of a nonrandomized prospective trial of HIFU followed by radiation, tamoxifen, and chemotherapy. After a median 54.8 month follow-up period they report an 89% recurrence-free survival, with good cosmetic results.[122] In 2007, Furasawa reported that after a mean of 14 months follow-up 20 out of 21 cases of ductal carcinoma remained recurrence-free, with 2 skin burns reported.[123] However, other results have been less encouraging, with Zippel *et al.* reporting that eight of ten patients had at least some amount of residual tumor at lumpectomy 7–10 days after MRgFUS.[124]

The reported studies thus far are early, single-instruction studies with small patient cohorts that provide very limited evidence for more widespread adoption.[125] Wider adoption is also limited by the technical issues including difficulty in measuring temperature via MR-thermometry due to the fat content of breast tissue,[25,31] extended treatment time and patient positioning requirements, as well as the politics of breast-cancer care which can have a significant impact on treatment options.[126] A successful multi-institution clinical trial may help open up breast cancer as a common indication for MRgFUS.

6.B.2. Prostate cancer

FUS is an attractive therapy for localized prostate cancer because it is minimally invasive, can be delivered in a single session, has good acoustic accessibility, and can be repeated if needed or combined with more traditional therapies if required. FUS systems for prostate cancer commonly make use of transrectal transducers which place the ultrasound beams in close proximity to the prostate. A number of clinical trials on significant numbers of patients with early-stage prostate cancer have been completed. Early results are comparable and in some cases better than that reported for traditional radiotherapy or radical prostatectomy. In one multicenter series of 803 mainly low and intermediate-risk patients, the study reported overall and cancer-specific survival rates at 8 years of 89% and 99%, and metastasis-free 8-year survival rate of 97%. Five-year biochemical-free survival rates were reported as high as 84% for low-risk patients.[127] Another series of 181 patients treated with USgFUS reported biochemical disease-free survival rates of 85%, 80%, and 78% at 1-, 3-, and 5-year follow-up. Complications included urethral stricture (22%), epididymitis (6%), rectourethral fistula (1%), transient incontinence (0.6%), erectile dysfunction (20%), and retrograde ejaculation (9%).[128] FUS has also been proposed as a salvage therapy after failure with radiotherapy.[129,130] The technique may be limited by the accuracy of staging. For patients with micrometastases who ultimately fail FUS, options may include salvage radiotherapy[131] or radical prostatectomy.[132] Also, while these results are encouraging, FUS is an emerging technology, and the quality of evidence for FUS is still immature.[118]

6.B.3. Liver and other abdominal targets

Radiofrequency ablation of hepatic tumors has been shown to be an effective technique to gain local control.[133] Focused ultrasound would provide a less-invasive improvement on this technique.[134] Moore *et al.*[135] and Yang *et al.*[136,137] conducted some early experiments on animal models. Chen looked at thermal lesion histopathology to confirm cell destruction within thermal lesions.[138]

In human patients, Kennedy *et al.* report on a safety and efficacy series using extracorporeal US-guided HIFU and finds transient pain and minor skin burns as the only complications.[139] Li reports a normalization of clinical symptoms in 83% of a cohort of 100 patients.[140] Leslie *et al.* reported on a phase II efficacy trial that showed MR-guided FUS to be feasible, and that postprocedure MR accurately predicts tumor ablation when compared to histology.[141] One difficulty in using FUS for abdominal targets is the presence of intervening anatomy such as ribs and bowel. Preferential absorption of energy in the ribs can distort the ultrasound focus. The presence of gas in the bowel can cause reflections, unwanted heating, and effectively prevent ultrasound energy from reaching the target. Bowel between the transducer and the target is often a contraindication for uterine fibroid procedures.[142] Quesson describes a method for identifying and turning off transducer elements that would result in beams passing through the ribs.[143]

TABLE IV. Trials currently active or recruiting in the US clinical trials database (NCT) for breast cancer, functional neurosurgery, brain metastases, uterine fibroids, bone metastases, and prostate cancer.

NCT No.	Title	Recruiting, Not yet recruiting, Completed	Conditions	Device/intervention	Sponsors	Phase
NCT01141062	Therapeutic MRI guided high intensity focused ultrasound ablation of uterine fibroids	Recruiting	Uterine fibroids	Device: Philips MR-guided HIFU	Philips Healthcare	Phase III
NCT00837161	Pilot study of mri-guided high intensity focused ultrasound ablation of uterine fibroids	Completed	Uterine fibroids|uterine leiomyomata	Device: Philips MR guided HIFU system	Philips Healthcare|Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)	Phase I|Phase II
NCT01097239	Examining the role of transrectal high intensity focused ultrasound (HIFU) in rectal pelvic cancer	Recruiting	Rectal cancer	Device: Sonablate 500 (High Intensity Focused Ultrasound (HIFU))	Imperial College London|Imperial College Healthcare NHS Trust	Phase I|Phase II
NCT01064960	Clinical trial protocol for therapeutic mri-guided high intensity focused ultrasound ablation of uterine fibroids in a 3T MRI scanner	Completed	Uterine leiomyomas	Device: Philips MR-guided HIFU system	Philips Healthcare|Philips Medical Systems	Phase III
NCT01422629	High intensity focused ultrasound (HIFU) to treat breast fibroadenoma	Recruiting	Breast fibroadenoma	Device: Ultrasonic ablation device	Theraclion	
NCT00897897	Therapeutic magnetic resonance imaging (MRI)-guided high intensity focused ultrasound (HIFU) ablation of uterine fibroids	Completed	Uterine fibroids	Procedure: HIFU	Philips Healthcare|Philips Medical Systems	
NCT01489787	Study to evaluate a high intensity focused ultrasound (HIFU) procedure in patient with liver metastases	Recruiting	Neoplasm metastasis	Procedure: HIFU|Procedure: HIFU|Procedure: HIFU	Centre Leon Berard|National Cancer Institute, France|CLARA	Phase I|Phase II
NCT01504308	Philips pivotal clinical trial for MRI-HIFU of uterine fibroids	Not yet recruiting	Uterine fibroids	Device: MR-HIFU treatment for ablation of uterine fibroids	Philips Healthcare	Phase II|Phase III
NCT01421407	Efficacy and safety of high intensity focused ultrasound (HIFU) device to treat secondary hyperparathyroidism	Recruiting	Secondary hyperparathyroidism|end stage renal disease|parathyroid hyperplasia	Device: Ultrasonic ablation device	Theraclion	
NCT01291498	High intensity focused ultrasound (HIFU) for parathyroid adenoma	Recruiting	Parathyroid adenomas	Device: High Intensity Focused Ultrasound	Oxford University Hospitals NHS Trust|Theraclion	

TABLE IV. (*Continued.*)

NCT No.	Title	Recruiting, Not yet recruiting, Completed	Conditions	Device/intervention	Sponsors	Phase
NCT01117246	Pilot study for palliation of pain in bone metastases by MR-HIFU	Completed	Secondary malignant neoplasm of bone	Device: High Intensity Focused Ultrasound	Philips Healthcare	Phase I|Phase II
NCT01309048	Magnetic resonance-guided high intensity focused ultrasound for palliation of painful skeletal metastases	Recruiting	Bone metastasis	Device: Philips MR-guided HIFU system	Philips Healthcare	Phase I|Phase II
NCT01060982	Observation of histological changes in parathyroid adenomas following high intensity focused ultrasound (HIFU) treatment procedure	Recruiting	Primary parathyroid adenomas	Device: Ultrasonic ablation device	Theraclion	
NCT01194648	High-intensity focused ultrasound in treating patients with localized prostate cancer	Recruiting	Male erectile disorder|prostate cancer|therapy-related toxicity|urinary incontinence	Procedure: high-intensity focused ultrasound ablation	University College London Hospitals	Phase II
NCT01239641	High intensity focused ultrasound ablation virus myomectomy to treat uterine fibroids	Recruiting	Uterine fibroid	Procedure: High intensity focused ultrasound	Chongqing Medical University	Phase IV
NCT00987675	High-intensity focused ultrasound ablation in treating patients with progressive prostate cancer	Recruiting	Prostate cancer	Procedure: high-intensity focused ultrasound ablation	University College London Hospitals	Phase II
NCT00295802	Ablatherm integrated imaging high intensity focused ultrasound for the indication of low risk, localized prostate cancer	Active, not recruiting	Prostate cancer	Device: Integrated Imaging High Intensity Focused Ultrasound	EDAP TMS S.A.	Phase II|Phase III
NCT01331954	Treatment of breast fibroadenoma with high intensity focused ultrasound (HIFU)	Recruiting	Breast fibroadenoma	Device: Ultrasonic ablation device	Theraclion	
NCT00988130	High-intensity focused ultrasound focal ablation in treating patients with progressive prostate cancer	Recruiting	Prostate cancer|sexual dysfunction and infertility	Procedure: high-intensity focused ultrasound ablation	University College London Hospitals	Phase II
NCT00180739	Safety trial of magnetic resonance (MR) guided focused ultrasound surgery (FUS) in women with uterine fibroids wishing to pursue pregnancy in the future	Completed	Uterine fibroids|pregnancy	Procedure: Magnetic Resonance Guided Focused Ultrasound	Imperial College London|InSightec	Phase IV
NCT00772317	A multicenter clinical study of the sonablate®500 for the treatment of locally recurrent prostate cancer with HIFU	Recruiting	Recurrent prostate cancer	Device: High Intensity Focused Ultrasound	USHIFU, LLC	Phase III
NCT00770822	Clinical study of the sonablate® 500 to treat localized (T1c/T2a) prostate cancer	Active, not recruiting	Prostate cancer	Device: HIFU (Sonablate® 500)|Device: Brachytherapy	USHIFU, LLC	
NCT01377519	Magnetic resonance guided focused ultrasound for uterine fibroids	Recruiting	Uterine fibroids	Procedure: MR Guided Focused Ultrasound	University of California, San Francisco	

TABLE IV. (*Continued.*)

NCT No.	Title	Recruiting, Not yet recruiting, Completed	Conditions	Device/intervention	Sponsors	Phase
NCT00573586	Treatment of localized prostate cancer with high intensity focused ultrasound using the sonablate® 500 system in Canada	Not yet recruiting	Prostate cancer	Device: Sonablate 500 (SB-500)	USHIFU, LLC	Phase IV
NCT01473485	ExAblate (magnetic resonance-guided focused ultrasound surgery) treatment of brain tumors	Recruiting	Glioma|metastatic brain cancer	Device: ExAblate Transcranial System	InSightec	
NCT00030277	High-intensity focused ultrasound in treating patients with locally recurrent prostate cancer	Completed	Prostate cancer	Procedure: high-intensity focused ultrasound ablation	Focus Surgery	Phase I
NCT01338467	Glaucoma treatment by circular cyclocoagulation using high intensity focused ultrasound with the EYEOP medical device	Recruiting	Glaucoma	Device: EYEOP device	EyeTechCare	
NCT00656305	ExAblate (magnetic resonance-guided focused ultrasound surgery) treatment of metastatic bone tumors for the palliation of pain	Recruiting	Bone metastases|multiple myeloma	Device: ExAblate 2000|Device: Sham	InSightec	Phase III
NCT00159328	Efficacy study of magnetic resonance (MR) guided focused ultrasound in the treatment of large fibroids	Completed	Uterine fibroids	Procedure: Magnetic Resonance Guided Focused Ultrasound	Imperial College London|InSightec-TxSonics	Phase IV
NCT01104272	Subcutaneous contouring using high intensity focused ultrasound	Completed	Body sculpting	Device: LipoSonix (Ultrasound treatment of Subcutaneous Adipose Tissue)	Medicis Technologies Corporation	
NCT00995878	The FIRSTT: comparing MRgFUS(MR-guided focused ultrasound) versus UAE (uterine artery embolization)for uterine fibroids.	Recruiting	Symptomatic uterine leiomyomas|fibroid|myomas	Procedure: Focused ultrasound (MRgFUS)|Procedure: Uterine artery embolization (UAE)	Mayo Clinic|Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)	Phase IV
NCT00030290	Ultrasound in treating patients with prostate cancer confined to the prostate	Completed	Prostate cancer	Procedure: high-intensity focused ultrasound ablation	Focus Surgery	Phase I
NCT00147108	MR-guided focused ultrasound surgery in the treatment of breast fibroadenomas	Completed	Breast fibroadenoma	Device: ExAblate 2000	InSightec	Phase III
NCT01091883	Study comparing the safety and effectiveness of magnetic resonance guided focused ultrasound (MRgFUS) and external beam radiation (EBRT) for treatment of metastatic bone tumors and multiple myeloma	Recruiting	Bone cancer|secondary malignant neoplasm of bone|pain	Device: Exablate treatment|Radiation: Radiation	InSightec	Phase III
NCT01304758	ExAblate transcranial MR-guided focused ultrasound in the treatment of essential tremor	Recruiting	Essential tremor	Device: ExAblate Transcranial MRgFUS System	InSightec	Phase I

TABLE IV. (*Continued.*)

NCT No.	Title	Recruiting, Not yet recruiting, Completed	Conditions	Device/intervention	Sponsors	Phase
NCT01226576	Focal MR-guided focused ultrasound treatment of localized low-risk prostate cancer: feasibility study	Not yet recruiting	Localized low-risk prostate cancer	Device: MRgFUS Treatment	InSightec	Phase II
NCT01232582	Safety and efficacy of MRgFUS for the treatment of low back pain	Recruiting	Lower back pain, facets joints osteoarthritis	Device: Exablate treatment	InSightec	Phase II
NCT01092988	A clinical study to evaluate safety of the ExAblate 2100 UF V2 system in the treatment of symptomatic uterine fibroids	Recruiting	Uterine fibroids|bleeding|pain	Device: Exablate 2100	InSightec	
NCT01142791	Safety study of ExAblate for the treatment of uterine fibroids	Recruiting	Uterine fibroids	Device: ExAblate	InSightec	Phase IV
NCT00365989	MR-guided focused ultrasound treatment of uterine fibroids with enhanced sonication	Completed	Uterine leiomyoma|uterine fibroids	Device: ExAblate 2000	InSightec	Phase III
NCT01085565	Focused ultrasound surgery in the treatment of pain resulting from metastatic bone tumors with the ExAblate 2100 conformal bone system	Recruiting	Bone cancer|secondary malignant neoplasm of bone|pain	Device: ExAblate 2100	InSightec	Phase II
NCT00295217	MR-guided focused ultrasound surgery in the treatment of uterine fibroids: Software V4.2 validation	Completed	Uterine fibroids|uterine leiomyomas	Device: ExAblate 2000	InSightec	Phase III
NCT01285960	ExAblate UF V2 system for the treatment of symptomatic uterine fibroids	Not yet recruiting	Uterine fibroid(s)	Device: ExAblate UF V2	InSightec	Phase III
NCT00981578	ExAblate conformal bone system treatment of metastatic bone tumors for the palliation of pain	Recruiting	Bone metastases	Device: ExAblate 2100	InSightec	Phase I
NCT01229826	Magnetic resonance elastography (MRE) of uterine fibroids	Recruiting	Uterine fibroids	Radiation: MR Elastography	Mayo Clinic	
NCT01328067	Study to evaluate the safety and effectiveness of MRgFUS compared with myomectomy for the treatment of uterine fibroids	Not yet recruiting	Uterine fibroids|bleeding|pelvic pain	Device: Exablate 2100|Procedure: Myomectomy	InSightec	Phase IV

6.B.4. *Lesioning for neuropathic pain and functional disorders*

Patients with chronic pain syndromes have for many years been treated with subthalamic lesioning using either radiofrequency lesioning[144] or radiosurgery[145] to interrupt pain pathways and improve symptoms. Stereotactic RF-lesioning conventionally requires a burr-hole through the skull, with the possibility of associated complications. Radiosurgical lesioning avoids this requirement, but necessitates large doses of ionizing radiation and has a delayed onset of symptomatic benefit. With FUS it may become possible to noninvasively place discrete lesions in the brain at very controlled target sites such as the subthalamic area in patients with chronic pain syndromes. Jeanmonod *et al.* describe a technique to treat neuropathic pain whereby 3–4 mm lesions are created in the posterior part of the central thalamic nucleus using MR-guided FUS. The study achieved an improvement in pain (by Visual Analog Scale) of 41% at one year. In all cases the patients reported somatosensory and vestibular effects during

the treatment, and a hemorrhage was reported in one case.[146] Another trial targeting the central lateral nucleus of the thalamus reported a mean 68% subjective pain reduction and no observed neurological deficits or side effects in a small cohort of nine patients.[147]

Trials at the author's (D.S.) institution have begun to investigate the use of focused ultrasound for movement disorders such as essential tremor[148] and Parkinson's disease. Current remedies for essential tremor and Parkinson's disease include the long-term insertion of deep brain stimulators.[149,150] While effective, stimulators are associated with a non-negligible morbidity[151–153] and occasionally require surgical revision.[154] FUS treatments for movement disorders follow a technique similar to those described above, and thus avoid the creation of a burr-hole as is required for the current remedies such as the insertion of deep brain stimulators. More data and longer term followup will be required to learn if ablative lesioning via FUS will lead to better outcomes than stimulators.

6.C. New clinical indications: Nonablative techniques

Most research that has reached the stage of clinical investigation both in the United States and abroad deals with ablative techniques as described above. However, there are a number of potentially interesting applications of FUS that do not rely solely on direct tissue destruction. These applications are in preclinical development and will likely not find their way into the clinic in the near-term; however, they may have significant consequence when they do.

6.C.1. Targeted drug delivery

One of the more promising future applications for FUS involves targeted delivery of drugs to specific organ and/or tumor sites. The theoretical advantages to this approach would be to create a high therapeutic concentration of the drug at the desired treatment site while limiting systemic side-effects. Drugs can be packaged into carriers such as liposomes,[155–157] microbubbles,[158] or nanoparticles.[159,160] These can then be injected systemically, however activation would only occur upon sonication at the intended target. Mechanisms of drug release can be through heat-activation,[161] lysis of the carrier, or by increasing the blood vessel permeability of the target[162] Dromi *et al.* demonstrated that the use of liposomes created to be sensitive to temperature, combined with a pulsed high-intensity ultrasound exposure, resulted in faster drug delivery and higher *in vivo* drug concentration[155] than the use of temperature-insensitive liposomes or the use of liposomes without ultrasound exposure.

The techniques for clinical drug delivery are being quickly refined.[157] Klibanov *et al.* summarize a range of techniques for creating liposomes for a variety of drug delivery models.[163] In one recent study by Eisenbrey *et al.*, researchers were able to deliver doxorubicin to a liver tumor in a rabbit model. They achieved a 50% reduction in doxyrubicin concentration in nontargeted areas of the liver, and a 110% increase in levels near the periphery of the tumor.[164] Klibanov *et al.* developed a construct of liposome coated microbubbles. The liposomes were loaded with calcein and thrombin. In an *in vitro* model consisting of canine blood, pulsed ultrasound resulted in destruction of the microbubbles, with significant release of calcein and a detectable increase in blood clotting.[165]

One technical challenge with drug delivery using microbubbles is ensuring the proximity of the microbubble to the intended target. Studies of the kinetics of microbubble transit through vessels show that they tend to travel along the central axis of the vessel.[166] For drug delivery, it may be desirable for the bubbles to burst and release their payload close to the vessel endothelium. Patil *et al.* address this problem by using ultrasound radiation force to push the microbubbles closer to the vessel wall before destroying them and releasing their payloads. Simultaneous imaging allows for real-time imaging monitoring of the microbubble accumulation. A high pulse-repetition frequency pulse is then applied to destroy the bubbles (Fig. 3).[167]

6.C.2. Blood-brain-barrier opening

The efficacies of chemotherapeutic agents are severely restricted in the brain. One reason is the blood-brain-barrier (BBB); a permeability barrier which prevents large molecules from penetrating into the parenchyma from the
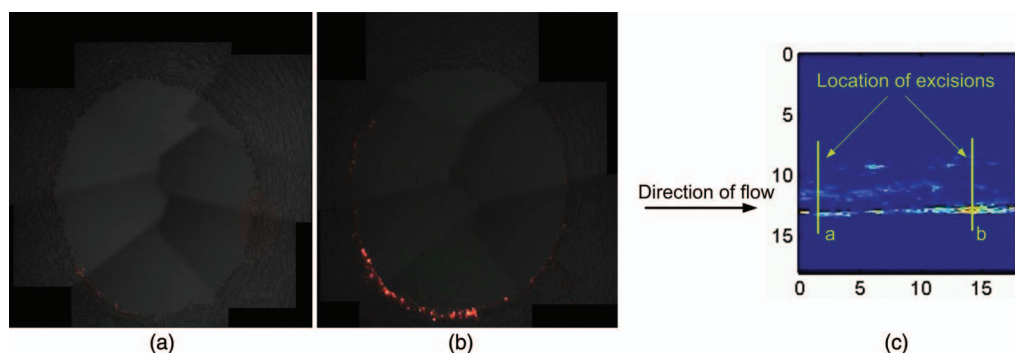

FIG. 3. Fluorescence microphotographs of two fragments (control and ultrasound-treated) of a swine artery after intravenous administration of DiI fluorescent-dye impregnated microbubbles (Ref. 167) (a) Fluorescence observed in the control fragment of the artery after microbubble administration. (b) Fluorescence observed in the ultrasound-treated fragment after microbubble administration and insonation with radiation-force ultrasound, followed by a "destruction" pulse to locally destroy the microbubbles. (c) Ultrasound image of the artery at the end of the applied ultrasound sequence with the locations of the excised control (a) and ultrasound-treated (b) fragments. [Figures courtesy of Abhay Patil, Philips Healthcare, and John Hossack, University of Virginia] (Ref. 167).
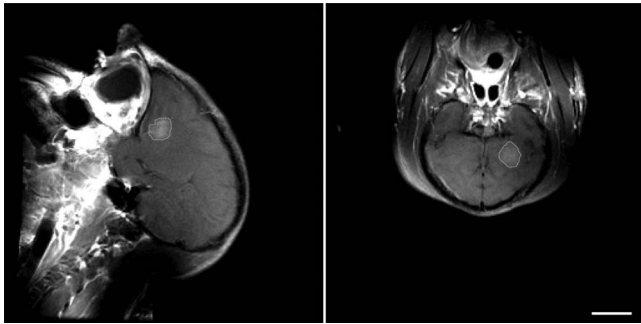
FIG. 4. Contrast-enhanced T1-weighted MRI showing blood-brain barrier disruption induced in a brain volume in a macaque by focused ultrasound and microbubbles. The disruption was produced in a 1 cm^3 volume using low-energy focused ultrasound pulses combined with a circulating microbubble ultrasound contrast agent. The sonications were applied transcranially using a clinical prototype MRI-guided focused ultrasound system (ExAblate 4000, InSightec). Note the lack of contrast enhancement in the ultrasound beam path. This noninvasive technique is being investigated to target the delivery of drugs that normally do not reach the brain due to the presence of the blood-brain barrier. [Image courtesy of Dr. Nathan McDannold, Brigham & Women's Hospital, Boston, MA.]

brain vasculature.[168] In many systemic chemotherapy treatments, it becomes almost impossible to deliver a therapeutic concentration of drug to the brain without an unacceptable risk of toxicity to the rest of the body. In the setting of brain tumors, the tumors themselves manifest aspects of the BBB (the blood tumor barrier or BTB), and in addition often have decreased density of capillaries, requiring elevated dosing for drugs to penetrate into tumor tissue in sufficient concentrations.[169]

FUS has been shown to have an ability to open the BBB,[170] albeit with some evidence of damage to the surrounding brain tissue. Hynynen *et al.* improved on this approach, using lower ultrasound intensities with microbubble contrast agents to selectively and reversibly open the BBB in rabbits.[171] Several researchers from the same group at Brigham and Women's Hospital have extended this work (Fig. 4). McDannold *et al.* looked at histological effects of the technique, finding little evidence that unwanted hypoxia or apoptosis would occur.[49] Hynynen *et al.* used ultrasound frequencies more compatible with transcranial FUS procedures.[171] Kinoshita *et al.* report on successful delivery of Herceptin (trastuzumab) through the BBB using the technique.[162]

While work to better understand the biological effects and refine the technique is ongoing, the early results suggest that FUS presents a unique capability for BBB-opening as it appears to be reversible, localizable, and noninvasive.

6.C.3. Sonothrombolysis

Although the thrombolytic potential of ultrasound has been known for many years,[172] it is only recently that the possibility of using ultrasound alone or in combination with thrombolytic agents such as recombinant tissue plasminogen activator (rTPA) has become an important area of investigation for FUS.[173] In the CLOTBUST phase I trial, stroke patients eligible for TPA therapy were randomized to either 2 h of moni-

toring with transcranial Doppler (TCD) ultrasound or placebo monitoring, along with a bolus of TPA.[174] The group monitored by TCD showed stronger outcomes based 24 h (44% vs 40% dramatic clinical improvement, $p = 0.7$) and at 3 months (42% vs 29%, modified Rankin scale, $p = 0.20$).[175] While not statistically significant, this trial showed the potential for FUS sonothrombolysis.

Success in this area would represent a major potential indication for FUS. Stroke remains a significant cause of long-term disability and a tremendous burden on the overall healthcare system.[176] The current state-of-the-art treatment for ischemic stroke is rTPA, however this is severely constrained in its eligibility criteria, with only 8% of patients generally able to benefit under current exclusion guidelines.[177]

6.C.4. Pain management

Studies as far back as the 1960s examined the effect of ultrasound on nerve conduction and the ability to create reversible nerve blocks.[178,179] The ability of FUS to create targeted, focal sonications makes it an attractive potential technique for the treatment of various pain pathologies such as facet rhizotomy and spasticity.[180] Foley *et al.* have demonstrated FUS to be capable of creating sciatic nerve blocks in rabbits.[181]

Work at the author's unit (W.G., unpublished data) is currently directed at decreasing the pain associated with lumbar spine facet joint disease. Facet joint problems are commonly treated by local injections of local anaesthetics, steroids, or sclerosants, etc., or local radio frequency ablation all aimed at limiting the pain fibers around the facet joints which are believed to cause the patients pain in this condition. Focused ultrasound, using relatively low power sonications targeted at facet joints, can be used to try to destroy the neural fibers running over the facets to decrease the pain felt from these areas. Early pilot work suggests excellent symptom improvement and very good improvement of disability in these patients with chronic back pain up to 6 months posttreatment. Much more work is clearly required in this area but the potential of FUS as a noninvasive method of treating chronic back pain is very attractive. This early study also suggests that focused ultrasound may be a very effective way of producing local nerve blocks which could be applied in many other areas where currently pain specialists use percutaneous needle placement guided by fluoroscopy or CT.[182]

6.C.5. Combined therapies—focused ultrasound and radiation

Focused ultrasound surgery is by definition a localized treatment. While margins can be taken around a tumor to account for subclinical disease, as with traditional surgery these may be insufficient to ensure the adequate control of highly infiltrative disease. Oncology patients also often have micrometastases not evident on current imaging modalities; these patients are often treated with large field external-beam radiation and/or systemic chemotherapy. In these cases, focused ultrasound could be an effective primary treatment
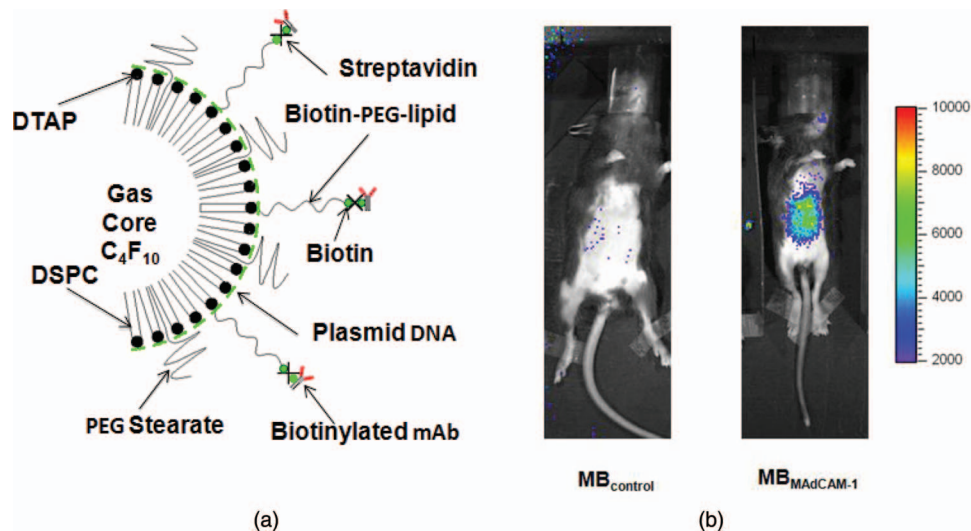
Fig. 5. FUS/microbubble-mediated gene transcription (Ref. 197). (a) A positively charged microbubble is complexed with a luciferase-encoding plasmid, and carries an antibody against a marker for Crohn's disease. Control bubbles carry a nonspecific Immunoglobulin G (IgG) antibody. Bubbles are injected intravenously and left to circulate for 2 days, with the targeted bubbles accumulating in the target intestinal inflammation zone and attaching to the Crohn's disease marker on the vascular endothelium. After the circulating bubbles exit the bloodstream, ultrasound is performed. Two days later, luciferin is injected, and optical imaging of the induced bioluminescence is performed. (b) Control vs experimental results. The left-hand figure shows an animal injected with control bubbles. Right hand figure shows animal injected with targeted antibody bubbles. Note the accumulation bubbles in the targeted animal, demonstrating transfection. [Image courtesy of Alexander Klibanov, University of Virginia] (Ref. 197).

option with the goal of controlling or debulking the grossly evident disease and mitigating acute symptoms. In one study of patients with localized prostate cancer, salvage external beam radiation was used to treat patients with local recurrence after focused ultrasound. At a median followup of 37 months, the disease-free survival rate was 64%.[131] Alternatively, FUS could be used as a salvage treatment after local failure with radiation, with one study reporting a 71% disease-free rate after whole gland ablation of the prostate after localized recurrence post- external-beam radiotherapy.[129] It has been known for some time that heat can be a potent radiosensitizer,[44,45] likely because heat insult prevents the cells from efficiently repairing sublethal DNA damage from radiation.[183] Hypoxic tissues do not show the same resistance to thermal insult as they do to ionizing radiation.[184] Thus, there is a possibility for a synergistic effect by combining FUS-delivered thermal energy and ionizing radiation. One potentially attractive idea would be to use ablative FUS to debulk the hypoxic areas of large tumors which do not normally respond well to radiation and then treat the surrounding tissue with traditional radiation.

One issue to be worked out is the optimal sequencing of FUS and radiation. At subablative temperatures, studies have found that tumor control and normal tissue reactions are highest when delivering concomitant radiation and hyperthermia.[185] Using high-intensity focused ultrasound, an increased reduction in cell survival has been found when radiation delivery follows ultrasound, but not if radiation precedes ultrasound.[186]

It is likely that in the future FUS will be used in combination with other chemo- and radiotherapies. Much work remains to determine the most effective combination treatments and the sequence in which they should be considered.

6.C.6. FUS-mediated gene therapy

Research has suggested that FUS can affect the efficacy of gene therapy, as well as provide a method for spatial and temporal control of gene expression.[187] FUS used to achieve sublethal temperature increases can affect the regulation of heat-shock proteins such as hsp70, which can then be used as promoters for gene insertion.[188] Also, in a method similar to that used for targeted drug delivery, pulsed HIFU-induced cavitation, often achieved through the use of microbubble contrast agents[189] or nanoparticles,[190] can cause an increase in the permeability of cellular membranes and result in more efficient uptake of DNA and subsequent gene expression.[50] This temporary increase in sonoporation would then allow for localized insertion of genetic material at the target and minimize the risks of systematic effects.[191] A variety of preclinical studies are reporting progress on *in vitro* and *in vivo* tissue models.[192–196] Figure 5 illustrates a conceptual framework for gene transfection in a murine model for Crohn's disease using microbbubbles loaded with targeted antibodies and luciferase-encoding plasmids.[197]

6.C.7. Cardiac disease

FUS has been explored for its potential to treat cardiac disease including arrhythmia, hypertrophic cardiac myopethy, and atrial fibrillation. Englel *et al.* reported on a preclinical study where they successfully created midmyocardial lesions in areas of the left and right ventricles of *ex vivo* canine hearts, and also in an *in vivo*, open-chest study where the ultrasound was gated to an electrocardiogram.[198] However, Mezner *et al.* describe a clinical study using balloon catheters to deliver HIFU in order to achieve pulmonary vein isolation in

32 patients with paroxysmal atrial fibrillation. While the technique achieved an 87% isolation rate, and a 56% atrial-fibrillation-free rate after a median follow-up of 3.8 years, the trial had to be halted because of severe complications.[199] FUS may one day be able to compete with similar techniques such as radiofrequency ablation, but much work remains to solve current technical hurdles.

6.C.8. Neuromodulation

One of the more exotic potential applications of FUS is to cause desired modifications in behavior by targeting various functional centers in the brain with low-power ultrasound. These treatments would be subablative; no tissue would be permanently damaged, but the neuromodulatory effects may nonetheless be durable.

The neuromodulation potential of ultrasound was first described by Fry *et al.* in the 1950s. They describe reversible reduction in visually evoked potentials in cats sonicated with high power ultrasound.[200] Rinaldi *et al.* in 1991 reported an ability to modulate the evoked potentials of an *in vitro* hippocampus by sonicating to a power of 80 W/cm^2 using 750 KHz ultrasound with a pulse repetition of 150 KHz and a duration similar to electrical signals found naturally to evoke potentials in the brain. Field potentials were found to decrease during ultrasound exposure, and were at least partially reversible.[201] Tyler *et al.* demonstrated that low-intensity, low-frequency ultrasound could be used to stimulate hippocampal circuits in *ex vivo* mouse brains.[202] This work was later extended to intact mice, and was used to disrupt seizure activity in epileptic mouse models.[203]

Work in neuromodulation is in a very preliminary stage, however it holds potential for a new class of clinical applications for focused ultrasound techniques.

7. TREATMENT DELIVERY CHALLENGES

7.A. Challenge: Time of treatment

Perhaps the most daunting technical limitation of current MRgFUS systems has to do with time of treatment. Current ablative treatments are slow; often several hours are required to ablate a midsized (50–100 cm^3) tumor such as a uterine fibroid. Some current devices use a large number of individual sonication spots to ablate a target. During each sonication, tissue in the near-field absorbs some amount of ultrasound energy, albeit not as much as in the focal area. Each sonication is therefore followed by a cooling period to prevent thermal-buildup that would result in unwanted near-field heating if the sonications were performed continuously. This reduces the effect of thermal buildup, but with the tradeoff of time for cooling and energy lost through outward diffusion.[204] Each sonication additionally requires MR prescan time for gradient and RF calibration as well as MR-thermometry scan time. A single sonication is, therefore, a several minute process, and there can be upwards of a hundred individual sonications in a given treatment. But because of locally variable heat diffusion of ultrasound energy away from each focus, some sonications

fail to cause ablation temperature in tissue and these locations must be repeated.[204]

The extended treatment times mean the patient is required to lie motionless on the treatment table for the duration of the treatment. And, since the most efficient way to get ultrasound energy to the target is through the shortest beam path length, it means that often the patient is asked to place their body weight on the tumor; often this is quite a painful request. It means that the treating physician, be it radiation oncologist, radiologist, surgeon, etc., is tied up performing the procedure for the duration, along with the rest of the treatment team, which can include anesthesiology, nursing, physics, etc. In the case of MR-guided FUS, it also goes without saying that the MR unit (which is so far not typically dedicated to FUS) is also allocated for the duration of the treatment; an expensive proposition for a device in extremely high demand.[205, 206]

7.B. Challenge: Presence of bone, implants, or intervening bowel

Bone absorbs ultrasound with an efficiency almost 90 times greater than that of soft tissue.[207] Thus, tumors lying in the shadow of bone require much greater energy to ablate than targets not shadowed by bone. Bone also defocuses the ultrasound focus, often requiring a corrective refocusing in order to achieve a focal spot.[208] When the bone absorbs this ultrasound energy, it heats much more efficiently than soft tissue.[209] This can lead to damage to the bone matrix, as well as unwanted burns to surrounding tissue.[210, 211] Similar issues may come into play when treating patients with metal implants,[212] patients with embedded metal fragments, or any nontissue debris that may be in the near-field of the focused ultrasound beams.

Similarly, tumors that lie near bone or implants, such as meningiomas in the brain, may be difficult to treat with focused ultrasound. The acoustic window available to reach the tumor is often constrained by bone, and the resulting defocusing and bone heating may be difficult or impossible to compensate for.

As with bone, gas that exists between the transducer and the focus can cause difficulties for treatment. Segments of bowel anterior to uterine fibroids is often a contraindication for treatment.[213] Gas in the bowel will effectively stop ultrasound energy from propagating further in the tissue and can reflect the energy back toward the transducer, potentially leading to unwanted near-field heating and burns.

7.C. Challenge: Protecting sensitive structures

In many situations where focused ultrasound might be considered a treatment option, the target lies close to critical structures that constrain the geometric pathways for energy delivery. Currently, commercial treatment planning systems for FUS provide functionality to create "no-pass zones" that effectively shield sensitive structures by restricting the available sonication locations and restricting the ultrasound beam directions. In some cases, for instance where a critical structure lies in the postfocus ultrasound field, this technique may

contraindicate FUS because there remains no path that can adequately cover the target. Another current solution is to restrict the minimum allowed distance between the target and nearby critical structures in order to minimize the energy that reaches the critical areas,[214] however this can exclude some otherwise indicated patients.

8. TREATMENT DELIVERY SOLUTIONS AND FUTURE DEVELOPMENTS

8.A. Treating through and around obstacles

Some methods for avoiding obstacles such as intervening bone, bowel, or metal implants are already in clinical practice. Beam paths can be adjusted to avoid the obstruction, and beam no-pass zones can be defined in the clinical treatment planning software to help optimize these beam paths.[213]

As described earlier, targets for focused ultrasound often involve interference from the ribs. Two strategies have emerged to deal with this problem. The first follows directly from the idea of refocusing energy through the skull; researchers are developing methods to correct for focal beam distortion caused by the ribs.[215,216] A second strategy is to detect the location of the ribs and then selectively turn off individual transducers in the phased array, effectively refocusing the beam through the intercostal space.[217,218] This latter method is in early clinical testing by some MRgFUS manufacturers.

For the case of intervening bowl, techniques such as filling the bladder with saline can in some cases push the bowel out of the beam path. Degassed water balloons used to compress the abdomen can also be helpful.[219]

8.B. Volumetric sonication

Most work in reducing treatment time has focused on methods to increase the sonicated volume. Early results focused on the use of phased array transducers[220] or temporal switching among predefined patterns of focal spots[221] to increase the ablated volume of each individual sonication. More recent work involves optimizing the locations of the individual focal spots into concentric circular patterns so that outward heat diffusion is effectively captured in the volumetric ablation. In effect, the heat already diffusing out of one location is used to minimize the energy required at the subsequent location.[204] Binary feedback can be used during sonication to optimize the sonication duration of each concentric layer.[222] These techniques are able to increase the volume of necrosed tissue per unit of applied energy, reducing overall power requirements and decreasing the treatment time. They also increase the uniformity of thermal dose within the targeted tissue, reducing the likelihood of undertreatment of parts of the volume as compared to the individual sonication spot technique.[204] Another possibility is to use transducers designed specifically to ablate larger volumes. Melodelima *et al.* report an eight-element toric transducer that can create a 19.5 mm diameter lesion in as little as 40 s.[223]

While large volume sonication remains a challenge in current clinical systems, there are few technical hurdles that would prevent larger sonication volumes from being included. This should help to reduce the overall time of treatment.[220]

8.C. Microbubbles for protecting critical structures and enhancing heating

Methods to directly shield a critical structure in the post-focus field would still allow the target to be treated without risk to the critical structure. One such method proposes to use bubbles (generated via cavitation or boiling) to shield postfocal tissue from unwanted temperature rise.[224]

Bubbles created in the focal zone can absorb, scatter, and reflect ultrasound energy, preventing unwanted temperature rise in postfocal tissue, especially at tissue/air or tissue/bone interfaces.[225,226] While work remains to control the density, location, and extent of the bubbles, this technique could form the basis of a method for shielding of critical structures that is more flexible than the current avoidance techniques.[214]

For certain applications, cavitation or injected microbubbles might be a theoretical asset. Cavitation has been shown to have the potential to locally enhance heating in the focal region.[37] Likewise, the presence of injected microbubbles in tissue has been shown to reduce the power and temperature requirements for soft tissue lesioning.[87,227–229] In locations where it is difficult to deliver sufficient energy for a lesion via standard techniques, enhanced techniques using cavitation or microbubbles may sufficiently increase the treatment envelope.

8.D. Indication-specific transducer designs

High intensity ultrasound technology has also been developed for delivering thermal therapy from directly within or adjacent to a deep target volume via intraluminal, endocavity, endoscopic, laparoscopic, or percutaneous approaches. Due to the enhanced spatial control and energy penetration afforded by ultrasound, these technologies may have significant advantages over the RF, MW, laser, and cryotherapy technology as currently applied for tumor ablation and hyperthermia therapy.[13,230,231] These ultrasound devices can direct or conform the heating volume to the target area while protecting or avoiding other tissues, and potentially treat larger volumes in shorter times. Although more invasive than external or extracorporeal HIFU devices, these are still considered minimally invasive surgical approaches. These technologies may be preferable for sites where bone or bowel are intervening or external acoustic windows are too narrow for treating deep seated targets with extracorporeal HIFU; or where localization of all power and energy propagation within the target tissue is critical; or a less complex and shorter duration procedure—albeit more invasive—is desired. Due to the size restrictions inherent to a catheter-based approach and the proximity of the particular applicator to the target region, many devices need not be geometrically or electronically focused, further reducing device and procedure complexity. Typically MRI, US, CT, or fluoroscopy techniques can be

used to guide the placement of these devices. Furthermore, many of these applicator configurations include MR compatible versions that can be used and monitored in real-time using MR temperature feedback. Many of these technologies are commercially available or are in the final stages of development and testing in clinical pilot studies. Some examples of this technology as currently under development or implemented in clinical studies are reviewed (transrectal HIFU systems, either MR or US directed, and cardiac interventions are covered in other sections).

Intraductal or intraluminal high-intensity ultrasound devices have been configured with a rotating planar transducer segment at the distal end of a flexible catheter,[232] which can be positioned under endoscopy and fluoroscopic guidance within tumor obstruction of the bile duct; varying applied power levels and rotation position were used to shape the thermal lesion over 360° at the site of treatment[233] in human pilot studies. Makin *et al.* created a 32-element array intrastitial transducer integrated into a complete assembly including a coupling balloon and piercing tip. This design was shown to be capable of complete liver tumor ablation *in vivo* in rabbits.[234, 235] There is a possibility of using dual-mode arrays to both deliver and monitor the conformal thermal ablation.[236] Larger diameter (10 mm) transesophageal applicators with rotating planar transducer segments have been devised and used in pilot studies for ablation of tumor volumes of the esophagus;[237] currently improved versions with phased arrays and MR compatible devices suitable for MR-guided procedures with fast MR temperature monitoring are under evaluation[238] and indicate potential for precision MR directed procedures.

Transurethral ultrasound devices have been devised for fast targeted ablation of prostate cancer and BPH. Device configurations for this application include linear arrays of planar[239–241] or curvilinear transducers[242] with dynamic rotation or stationary multisectored tubular arrays[13, 243] that can be used under MR guidance and control for accurate therapy delivery.[244] Dual frequency selection or modulation has been demonstrated an effective approach for controlling rate and depth of power absorption[245] to produce conformal target ablation. Recent human pilot studies demonstrate feasibility of very precise treatment of targets within the prostate using a rotating planar configuration with proven accurate MR feedback control.[246]

An endorectal ultrasound applicator, consisting of a multisectored tubular array, has been used for hyperthermia treatment of prostate cancer combined with external beam radiation therapy.[247] Delivering hyperthermia to the whole prostate gland is achievable, with no rectal toxicity, and shown to improve survival when delivered with external beam radiation.[248] MR compatible versions of this device and control algorithms for feedback control have been investigated demonstrate MR directed hyperthermia with this approach is feasible.[249] There is considerable potential for this technology to be implemented for thermal targeted drug delivery to the prostate.

Catheter-based ultrasound applicators based on arrays of multisectored tubular transducer segments have been applied for interstitial and endocervical delivery of hyperthermia

in conjunction with HDR brachytherapy[250, 251] for treatment of prostate and cervical cancer; clinical pilot studies have demonstrated enhanced thermal penetration and spatial control compared to alternative modalities for applying interstitial hyperthermia as an adjunct to radiation or chemotherapy. High-power configurations of these 13–14 g percutaneous applicators have been evaluated *in vivo* for fast and large volume ablations, shaped in length and angle by adjusting power delivered to each array element and sector activation pattern, and can be directional to direct energy toward the target volume while avoiding nontargeted adjacent regions.[252] Single or multiple applicators can be used under MRI guidance and thermal monitoring to target specific regions of tissue including brain[253] and prostate,[254] and generate conformal therapeutic heating (ablation or hyperthermia) over large and targeted volumes, with superior spatial control, target localization, and fast treatment.

As advances in endocavity and catheter-based devices coalesce with improvements in MR monitoring techniques, MR-guided minimally invasive high-intensity ultrasound is poised for clinical implementation in many sites either difficult to reach with external HIFU approaches or sites where ultrasound rivals current ablative technology as currently within the interventional radiology and surgery armamentarium. When considering drug activation or radiosensitization using heat, these minimally invasive techniques should provide an ideal modality for generating and maintaining localized temperature distributions 40 °C–43 °C for 30–60 min interval within a large volume, which can be difficult with external HIFU sources due to prefocal heating.[255] In consideration of MR-guided thermal ablation, the fast treatment times and conformal target localization will make these minimally invasive high-intensity ultrasound technologies more acceptable.

9. IMAGE GUIDANCE AND TREATMENT PLANNING CHALLENGES

9.A. Challenge: Internal organ movement

Internal organ movement, such as that caused by respiratory motion, is a well-known problem in radiation therapy.[256] With focused ultrasound, patient motion or internal organ motion can cause problems in targeting the focal spots, and can also cause artifacts in the thermometry used for real-time evaluation of the treatment.[257] FUS treatments also assume a very rapid temperature gradient outside of the targeted tissue, and thus rely on precise targeting to achieve a desired effect. Just as with stereotactic radiosurgery, accurate targeting in the setting of respiratory motion becomes an issue of vital importance.[258]

9.B. Challenge: Treatment planning

FUS treatments proceed through several general phases. Treatment planning is a set of procedures that result in a general treatment strategy and treatment parameters. Treatment monitoring during the procedure ensures that the target is being appropriately treated and nontarget tissue remains untreated. Postsonication evaluation involves a determination

of what tissue received optimal treatment and what remains to be treated.

The thermal spots generated by current FUS systems are often smaller in dimension than the targets they are used to treat. Complete target coverage may be achieved through the use of a collection of individual thermal spots arranged to cover the intended target,[259] or by using a volumetric sonication method.[222,260] However, there are often constraints that can restrict the number and/or orientation of these individual thermal spots such as nerves, bone, bowel, or other anatomy that can be damaged if ultrasound passes through them. In many cases these constraints require that the transducer be positioned in particular orientations relative to the patient's anatomy. In other cases, techniques that can reorient patient anatomy may be required (one example being filling the bladder with saline in order to push the intestines out of the beam path in fibroid treatments). It may be that certain regions of a tumor remain inaccessible due to normal tissue constraints. Finally, parameters driving the ultrasound beam must be optimized for depth of focus, lesion size, angle of the transducer relative to the target, etc., in some cases requiring a correction for beams passing through bony structures such as skull.[261,262] The treatment planning results in a treatment strategy that attempts to optimize the treatment to meet its objectives while respecting these constraints.

Figure 6 shows screen captures from the treatment planning systems of two manufacturers of MRgFUS systems. Each system has functionality to localize targets, define beam paths, visualize real-time thermal data, and monitor treatments for undesirable heating away from the target areas. During treatment planning, the target is defined, along with ultrasound no-pass zones intended to protect critical structures. The system will create a proposed targeting solution for the target, and will indicate areas of the target which cannot be treated with the current targeting plan due to constraints on the treatment.

Treatment planning on current clinical systems can take up a significant fraction of total treatment time, requiring a significant commitment from the treating physician to contour targets, define critical structures, and optimize beam directions.[263] In addition, not all current clinical treatment planning can automatically optimize sonication parameters. Nonlinear propagation can have a significant effect on temperature deposition patterns, but this is not always modeled in current treatment systems.[264,265] Instead, parameters generally useful for each indication are predefined and must be optimized by hand on a sonication-by-sonication basis. Physicians not familiar with ultrasound biophysics[266] may not be prepared to perform these optimization tasks.

10. IMAGE GUIDANCE SOLUTIONS AND FUTURE DEVELOPMENTS

10.A. Strategies to account for internal organ motion

As was discussed previously, classic PRF MR-thermometry techniques are suboptimal in the setting of patient or organ motion. Several strategies have been de-veloped which attempt to overcome this limitation through the inclusion of *a priori* information regarding anatomical movement in the image.

Referenceless thermometry techniques attempt to overcome the limitations of PRF thermometry by using areas of the image distant from the intended thermal focus as a surrogate for the baseline phase of the image. The technique is still subtraction-based. A region-of-interest (ROI) outside of the heated area of the treatment is created (usually by the operator). Surface fitting is then applied to identify and remove background variations not related to temperature.[267,268] Referenceless techniques are sensitive to the selection of ROIs, and to local susceptibility effects.[28] Recent work has refined the basic technique to include using the difference in PRF-thermal coefficients between fat and water to achieve a better temperature estimation at tissue boundaries.[269]

Multibaseline thermometry techniques trade the ROI-creation step for a preparatory imaging stage where a series of baseline thermometry images are acquired over the periodic movement cycle of the tissue of interest. These multiple baseline images are stored in a lookup table and are matched to incoming thermometry images taken during the subsequent sonication stage.[270,271] Multibaseline methods tend to work well for periodic motion, but fail in the presence of spontaneous motion that is not well represented by the presonication baseline acquisitions.[28]

Hybrid methods attempt to combine the advantages of both the referenceless and multibaseline techniques. This method models the total phase shift in an image as separate anatomical-induced shifts, temperature-induced shifts, and shifts due to respiratory motion, bowel filling, etc. The temperature of a given voxel is then determined by fitting the observed data to the model through minimization of a cost function. The hybrid method was shown to perform well in the setting of liver and heart, in situations of anatomical motion, and requires a smaller database of baseline images. Another strategy to account for organ motion and allow for continuous sonication is to use rapid imaging techniques combined with trajectory prediction models to update ultrasound targeting to track moving targets. One example reported by Ries *et al.*[272] makes use of high-spatial frequency (10 Hz) 2D MR image acquisitions. The inplane position of the target is determined using optical flow registration techniques. The out-of-plane position of the target is tracked using pencil beam navigators.[273] Artifacts induced in the MR-thermometry images are corrected by assuming a periodic motion profile for the targeted tissue and looking up the appropriate phase correction from a table generated in an initial training step. Figure 7 illustrates the method on an *in vivo* porcine kidney. Figure 7(a) shows the heat deposition without the motion correction system. Figure 7(b) shows the increased heating and steeper heating profile achieved with the motion tracking system.

10.B. MR-ARFI: MR acoustic radiation force imaging

Thermometry is not the only method for monitoring changes in tissue due to FUS. For some time elastography
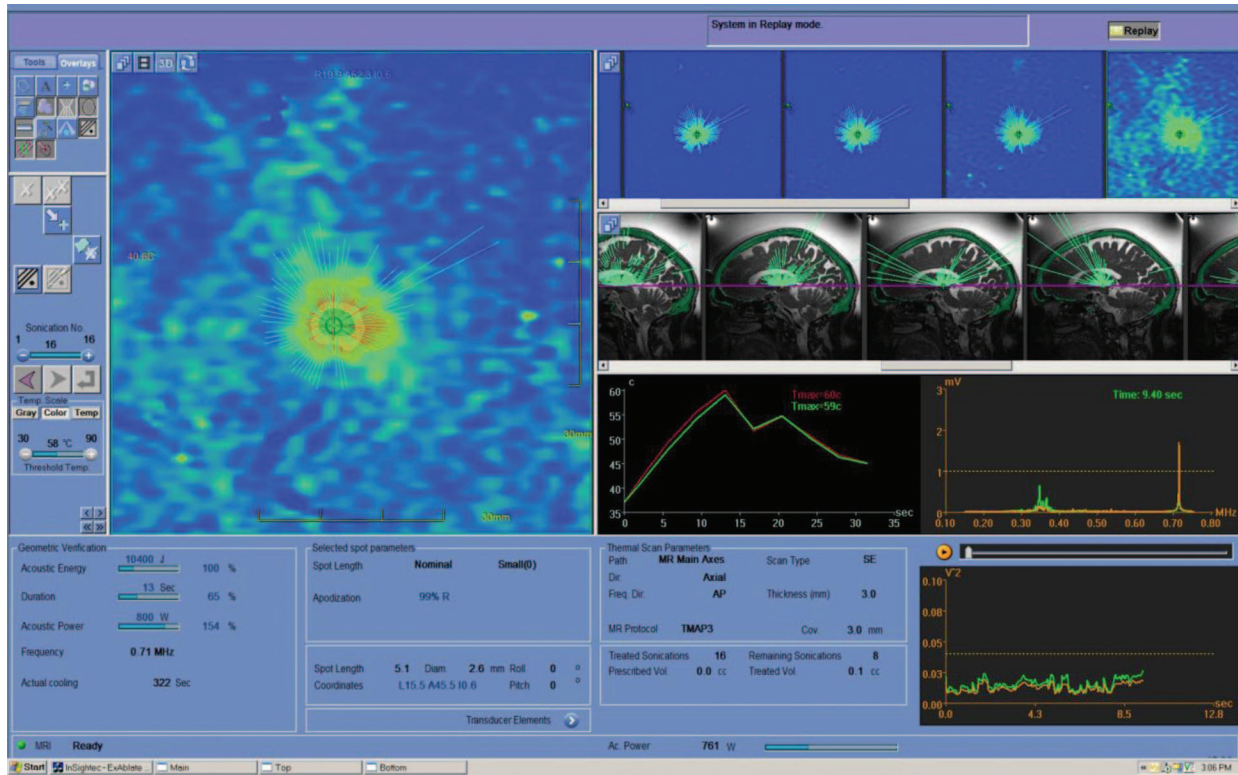
(a)
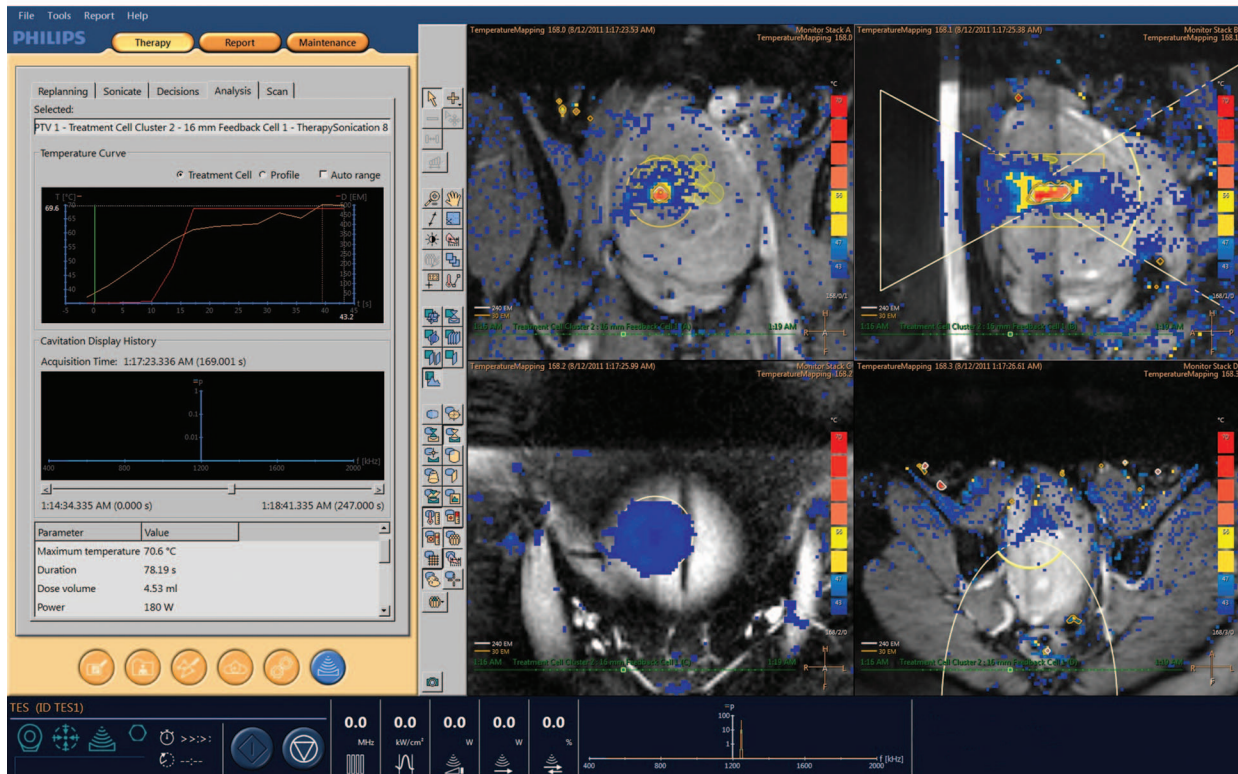
(b)

FIG. 6. Examples of treatment planning systems for MRgFUS. (a) Treatment planning for the InSightec Exablate Neuro. Planning screens allow the operator to set treatment parameters, monitor beam paths per transducer, thermal lesion location, time/temperature graphs, and ultrasound frequency spectrum. [Image courtesy of the InSightec Ltd.] (b) Treatment planning for the Philips Sonalleve MRgFUS system. This system allows the operator to monitor real-time temperature rise at the target, as well as in near-field and far-field regions [Image courtesy of Philips Healthcare].
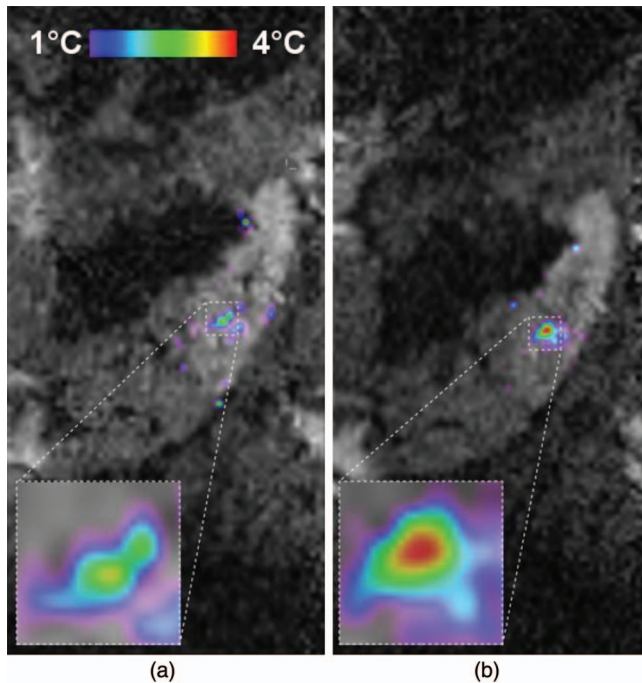
FIG. 7. Color-coded temperature map overlaid on T2* weighted anatomical MR images of porcine kidneys demonstrating a real-time motion compensation technique (Ref. 272). (a) Heating deposition without motion compensation. (b) Heating deposition with motion compensation. Notice the increase in heating magnitude and sharper temperature falloff. [Images courtesy of Mario Ries, Ph.D., Laboratory for Functional and Molecular Imaging, Bordeaux, France].

techniques have existed which can measure changes in mechanical tissue properties.[274] It was soon determined that the acoustic radiation force exerted on tissue by ultrasound could be used as a basis for measuring these viscoelastic changes.[275] More recently, MR acoustic radiation force imaging (MR-ARFI) techniques have been developed which can measure tissue displacements caused by the acoustic radiation force and create a map of local mechanical tissue properties in the form of an image.[276,277]

MR-ARFI uses an ultrasound beam impinging on tissue to cause a small longitudinal displacement of the tissue. Through a technique similar to PRF-shift thermometry, the displacement in tissue can be described by

$$\Delta x = \frac{\Delta \phi}{2 \gamma G_e \tau}$$

where $\Delta \varphi$ is the phase change, γ is the gyromagnetic ratio, G_e is the displacement encoding gradient strength, and τ is the displacement encoding gradient length. The displacing ultrasound pulse is synchronized with the displacement encoding gradients and assumes the tissue has reached a steady-state displacement while the encoding gradients are turned on.[276] Figure 8 illustrates the correspondence between ARFI images and MR-thermometry images during FUS ablation of an *in vivo* porcine liver.

MR-ARFI-based monitoring techniques provide a second method that can be used for monitoring treatments and can be correlated with thermometry techniques to provide more confidence in the results. ARFI techniques may also be quite
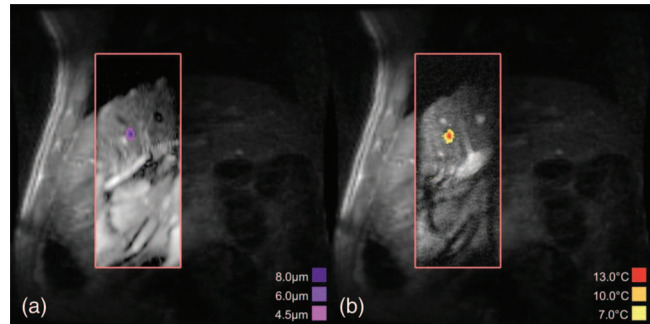

FIG. 8. MR-ARFI: (a) MR-ARFI and (b) MR-thermometry images acquired in the *in vivo* porcine liver. Both images are small FOV EPI acquisitions superimposed on a larger FOV gradient echo image acquired a few minutes before. After visualization of the displacement focus on MR-ARFI to verify the target location (Ref. 291), a steered HIFU ablation was performed with thermal monitoring, shown in the reduced FOV image on the right (Ref. 27). MR-ARFI images require only 3 J of energy, whereas a low temperature rise test ablation would require upwards of 800 J of energy. [Images of courtesy of Dr. Andrew B. Holbrook and Dr. Kim Butts Pauly, Stanford University].

important in monitoring some of the nonthermal applications for FUS outlined in this paper, including drug delivery and BBB-opening.

It should be noted that ultrasound-only variants of ARFI are being developed. One such technique, harmonic motion imaging (HMI) (Refs. 5 and 278) uses both therapy and diagnostic ultrasound transducers (sometimes combined). One transducer induces an oscillating displacement of tissue in the focal zone using the radiation-force property of ultrasound. The pulse-echo transducer then detects the RF echoes from the tissue and determines the tissue displacement. Investigations have shown that this technique can discern tumor inclusions from surrounding tissue in phantoms,[279] and measure increases in stiffness in tissues that have been heated to the level of coagulative necrosis.[280]

10.C. Ultrashort TE (UTE) MR imaging of bone

Certain indications for FUS require a refocusing of the ultrasound beams to correct for the absorption and scatter of the beams through bone.[262] This in turn requires information about the structure of the bone. Cortical bone has extremely short T2* decay times (<500 μs). Current clinical MR protocols have echo times that are much longer, such that the signal from cortical bone decays and little or no signal is recovered.[281] The bone therefore appears dark on the resulting images, and the bone structure is lost.

Because of this, imaging used to correct the ultrasound focus is typically provided by CT imaging which shows good bone to soft-tissue contrast. However, CT acquisition of bone information has some drawbacks; it exposes the patient to a small dose of ionizing radiation;[282] it can be inefficient in some centers to send a patient for a CT when the bulk of the procedure takes place in the setting of a MR, and the patient is not necessarily in treatment position at CT, therefore requiring a coregistration step to align the CT and treatment planning MR (or ultrasound) images.

A method to image bone on MR would mitigate many of these drawbacks, and especially for MR-guided FUS provides a convenient method for recovering the required bone structure information. Several groups have been investigating the use of ultrashort TE (UTE) imaging to recover signal from bone.[281,283–287] UTE imaging may also help detect other short T2* components in tissue, such as calcifications in the brain.[104] While technically feasible, these sequences rely on extremely fast gradient systems that are not yet widely available in the clinic. However, in the future it may become feasible to acquire the required bone structure directly from MR-imaging, eliminating the need for a separate imaging step.

10.D. Treatment planning

One potential advantage for the control of FUS treatments as compared to ionizing radiation treatments is that FUS provides real-time feedback of tissue temperature. This means it may be possible to eliminate the manual optimization of operating parameters required of the physician in current workflows. Arora *et al.* have developed a control system for FUS that automatically monitors the treatment against constraints for maximum target tissue temperature, avoidance structure tissue temperature, and power levels to prevent unwanted cavitation.[288–290] These sorts of closed-loop, automated control systems will likely further the goal of creating a "physician-friendly" device that is more likely to be accepted in the clinical community.

11. SUMMARY AND CONCLUSION

The idea to use ultrasound energy for therapeutic purposes is not a new idea; it has been explored and rejected several times over the years since it was first mentioned as a possibility. However, the confluence of imaging, computing, and ultrasound technology advancement over the last 10 years has revitalized the idea and brought it close to reality in the clinic.

This paper has explored some significant challenges that MRgFUS must overcome before it can find wide acceptance in the clinic. However, as we have tried to show, most of the challenges—technical, practical, and financial, are currently being addressed and seem likely to be overcome. MRgFUS is already a clinical reality. Whether it will become a more common clinical reality depends on whether the data accumulating about its clinical and cost effectiveness will allow it to compete and win in an ever more crowded marketplace of therapeutic techniques.

Medical Physicists and Radiation Oncologists would do well to pay attention to MRgFUS and its progress. If it succeeds, it is possible MRgFUS will have a disruptive effect on current practice in certain aspects of radiation oncology, and could one day even replace ionization radiation for the subset of indications where focal treatments have been shown to be efficacious (for instance, single-fraction radiosurgery for benign tumors, functional disorders, and small numbers of metastases). However, for most indications (especially oncologic indications) it is likely that MRgFUS will be used in conjunction with radiotherapy, just as radiotherapy is often used concomitantly or adjuvantly with surgery. MRgFUS will be one of a variety of tools the treatment team will have at its disposal, helping to promote an effective, multidisciplinary, multimodality treatment strategy.

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