MR Guided Focused Ultrasound surgery: New Clinical Applications

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Key take-home points

- MR guided focused ultrasound is a non-invasive therapeutic intervention which can cause thermo-coagulation of tissue.
- The combination of MR Target visualization, MR thermometry and MR monitoring provide a unique the combination of features of this exciting technique
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- New clinical applications are in the treatment of
  - o Essential Tremor
  - o Prostate cancer
  - o Palliation of Bone metastases.
  - o New applications in gynecology

Introduction

Tissue destruction by thermal ablation occurs when the targeted delivery of heat or cold causes a rapid change in temperature (>55°C for heat or <–20–50°C for cold) in the local tissue environment. Imaging can be used to localize and target the thermal effects to the target/tumor for treatment, control the energy deposition, and assess treatment response. Therapeutic applications of ultrasound (US) have been tried and tested for many decades in clinical medical care. The primary mechanism applied to date has been the application of high intensity focused ultrasound (HIFU) to cause local tissue thermo-coagulation through local temperature elevation. This is caused by the mechanical motion of adjacent tissues due to the rapid passage of US waves. The majority of clinical cases have been performed using a combination of two US devices, one for therapeutic US delivery and one for diagnostic imaging.

Currently, US and magnetic resonance (MR) imaging are used to guide therapeutic US, and the latter can provide all of these features, including quantitative temperature measurements in vivo through the temperature sensitivity of the water proton resonant frequency (1). The ability to use MR techniques to perform real-time thermometry makes MR the most reliable and comprehensive modality available for real-time (noninvasive) temperature monitoring. New US techniques that may allow for detection of thermal changes, through the use of contrast agents, and US-triggered drug delivery are under investigation.

Methods

MR guided focused ultrasound surgery (MRgFUS) is now an established clinical tissue ablation technique. There are several devices either on the market or in development. The ExAblate 2000 from InSightec Inc. was the first to receive both CE mark and FDA clearance for the treatment of uterine fibroids. Since then, other applications have been introduced and are currently either cleared or in clinical trials. These include new approaches for uterine fibroids, palliation of the pain from bone metastases in patients who have failed radiation therapy and most recently treatment of medication refractory essential tremor.

MRgFUS systems all use the following essential components: MR compatible transducers, phased array US technology, MR thermometry typically based upon detection of proton resonance frequency shifts, MR tissue characterization sequences (typically after intravenous (IV) injection of Gadolinium based contrast agents) to define ablation or non-perfused tissue after the procedure. MR devices: Most of the major MR vendors either have or are developing MRgFUS platforms, which operate at either 1.5T or 3.0T.

Some MR imaging parameters (such as T1-weighted, diffusion) are temperature sensitive and have been evaluated as methods for guiding thermal therapies (2-5). One parameter, the water proton resonant frequency (PRF), has been found to be particularly well suited for thermometry. The water proton resonant frequency changes with temperature through heat-induced changes in the hydrogen bonds in water, which affect electron screening of the nucleus (4). This can be mapped by using phase difference images generated from gradient echo sequences (2) Fig 1. Importantly, its temperature sensitivity does not depend significantly on tissue type and is not significantly affected by the thermal coagulation process. These unique features are most important to the success of MR thermometry. The main limitations of the technique are its motion sensitivity and its inaccuracy in fat tissues.

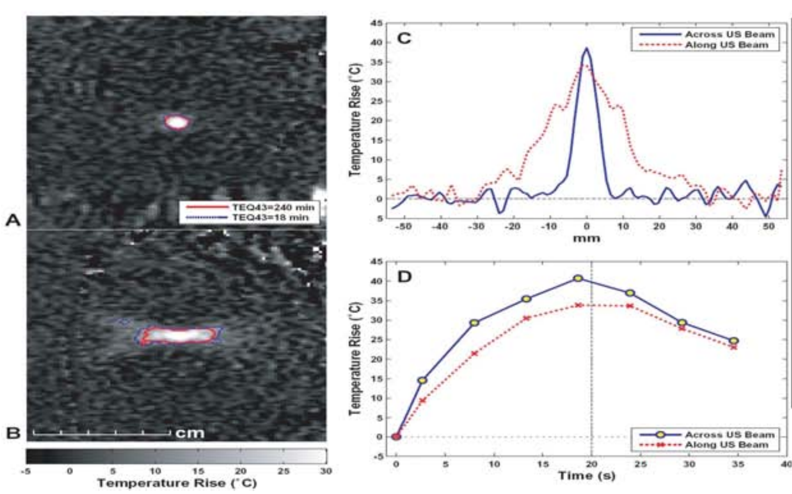

Figure 1 MR Thermometry:PRF
Temperature images acquired during sonications to ensure correct targeting of the focal coordinate. *A* and *B* were acquired in short and long axis to the beam *A*, sonications were performed with temperature imaging perpendicular to the ultrasound beam direction. *B* sonications were performed with imaging along the beam direction. C &D are graphic displays of the temperature elevation

Gynecological applications: Fibroids, Infertility and Adenomyosis

The first clinical application of MR guided FUS has been in the treatment of symptomatic uterine fibroids. Uterine fibroids are common benign neoplasms of the uterus, which can cause bleeding, pressure symptoms or contribute to infertility. The current treatment options include hysterectomy, myomectomy (laparoscopic myomectomy or robotic myomectomy/morcellation), uterine artery embolization, hormonal therapy or doing nothing. Sadly for many reasons the latter is by far the most common approach. The non-invasive nature of FUS has much appeal in this disease, along with the ease of treatment-few hours with little to no recovery necessary (7).   Thus MR-guided FUS has been broadly accepted as an option for the treatment of uterine fibroids. To date, more than 6000 patients have been treated with MR-guided FUS worldwide, with more than 5400 performed in routine clinical practice. MR-guided FUS outpatient-based treatment is technically feasible and reproducible and significantly reduces symptoms in more than 75% of women with fibroids treated (8). The best results are seen when the non-perfused volume is high and recommendations are to achieve at least 60% non-perfused volume.

In the recent reports of clinical experience, with proper selection of patient population, the treatment volume is often more than 50% of the total fibroid volume (8). Immediately on completion of MR-guided FUS treatment, with the fibroids shrinking by about 39% at 6 months.

The rate of side effects is generally low. Transient adverse effects include mild skin burn, nausea, short-term buttock or leg pain, and transient sciatic nerve pals. Another ongoing evaluation of the clinical application of MR-guided FUS of uterine fibroids is its effect on fertility. A clinical trial is underway to evaluate the efficacy and safety of MR-guided FUS in the enhancement of fertility in women with non-hysteroscopically resectable uterine fibroids who have a diagnosis of otherwise unexplained infertility Technical Improvement One of the main limitations of FUS in treating large tumors such as uterine fibroids is the long treatment time required. Initially the approach to clinical treatment has been conservative to avoid the thermal build-up that occurs along the ultrasound beam path when multiple overlapping sonications are delivered in succession. Newer strategies have been developed, including the use of the so-called interleave mode, to increase the treatment volume and decrease treatment time. By redefining the sonication order by minimizing overlap between sonications, less heat absorption in the tissues through which the ultrasound beam passes—known as the “pass zone”—can be achieved, and cooling time can be largely reduced.

Another promising advance is “enhanced sonication,” which uses microbubbles to enhance the heating at the focal point without reducing the overall energy deposition rate. This technique uses cavitation—a nonthermal mechanism to cause physical destruction of tissue and cells. In contrast to a continuous power transmission that lasts about 20 seconds to gradually heat at the focus, the enhanced sonications use high-power bursts to generate microbubbles that cause energy reflection and greater energy absorption and heating at the spot location. Therefore, although the total energy is the same, the volume of tissue ablated per individual sonication/treatment spot can be enlarged to allow for larger treatment volumes in shorter time periods. To determine the reliability and efficacy of enhanced sonication, clinical tests have recently begun.

Brain: Essential Tremor

Traditional neurosurgical approaches to deep-seated tumors usually result in some degree of normal brain damage due to the dissection down to the tumor. It has been known since the mid-20th century that FUS can destroy targeted tissue without injuring the normal brain and thus there has been extensive research to develop FUS as an “ideal” neurosurgical method (9).

In this procedure, ultrasound exposure is accomplished by using phased-array transducers surrounding the skull. The phase shifts caused by the irregular skull bone can be compensated for by the thickness measurements generated from x-ray computed tomography (CT) data. The phase corrections permit focusing at relatively lower frequencies. A prototype FUS phased-array research system for trans-skull brain tissue ablation using a 500-element US phased array operating at frequencies of 700– 800 kHz has been developed (10). After designing a working transducer model, Hynynen and Jolesz (10) noted that a focus distorted by the insertion of a human skull fragment in a water bath could be restored by simply adjusting the driving phase of each element in a spherically curved transducer array with transducer elements large enough to make practical, high-gain arrays feasible. The passage of the US wave is then modified appropriately to allow for the beam attenuation of the skull and re-phases the beam before passing into the brain itself. Initial work with this phase conjugation used a small receiver placed in the head to demonstrate that it was possible to deliver a signal through the closed skull. A second high-intensity focused ultrasound (HIFU) treatment system produced by SuperSonic Imagine (Aix en Provence, France), has been developed, with promising results in an animal model, showing focal brain thermal ablation without any skull heating. A clinical system designed for the MR-guided FUS thermal surgery of the brain through the intact skull has been developed and tested in a small number of patients

(11) (fig 2). The ultrasound beam was generated originally by a 512-channel phased-array system.

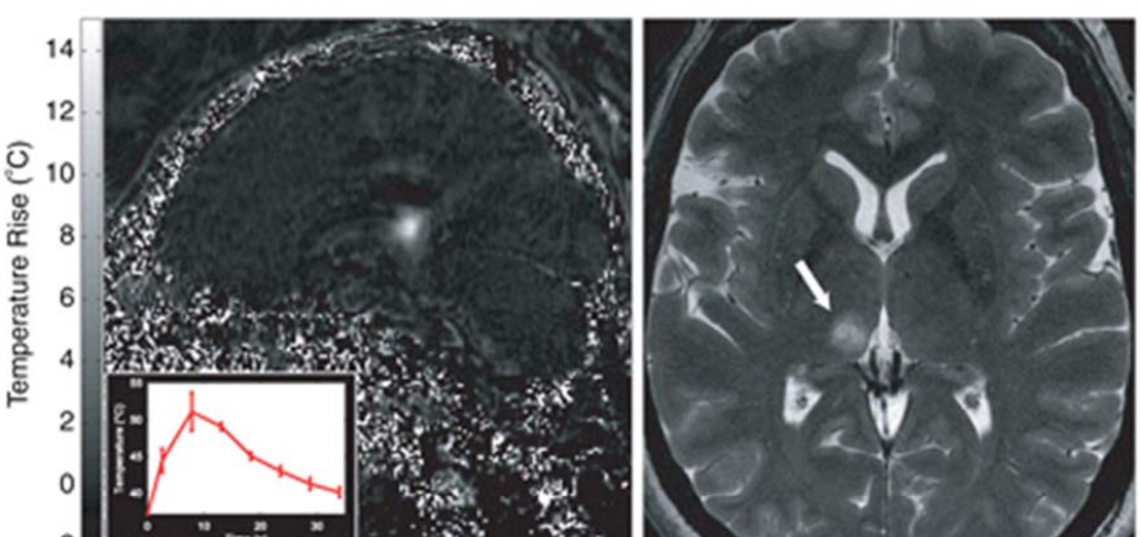

Figure 2:
MR-guided FUS in the brain for functional neurosurgery. A right centrolateral thalamotomy was performed with transcranial MR-guided FUS in a 50-year-old female patient with chronic therapy-resistant neuropathic pain in the left trigeminal nerves V2 and V3. Two locations were sonicated to create a lesion of suitable size to cover the target area. Left: MR temperature map at peak heating (inset = temperature/time curve in 3 × 3 voxel region at the focal point). Right: Axial T2-weighted image shows the resulting lesion (arrow). (Images courtesy of University Children's Hospital, Zurich, Switzerland.)

These critical developments have lead to many new and exciting neuro-applications of MRgFUS. In 2012 the first major application was published by Elias et al (N Engl J Med 2013 Aug 15; 369 97) 640-8) from UVA, reporting the application of MRgFUS for treatment of essential tremor. They reported a pilot study of 15 patients treated with MRgFUS, targeted at he unilateral ventral intermediate nucleus of the thalamus. All patients had severe medication-refractory essential tremor. The procedure improved tremor symptoms by 75% in all 15 and adverse events included transient sensory cerebellar, motor and speech abnormalities, with persistent parasthesias in 4. Clearly larger trials and more work remains to be done but none the less this study indicates the enormous potential of this technique for functional brain disorders. Beyond this the future may also see the application of MRgFUS for use in opening the blood-brain-barrier. This protective barrier is a major obstacle for drug delivery as large molecules are unable to pass into the brain, such as Herceptin for treatment of breast cancer brain metastases.

Bone FUS has been used in clinical practice for treatment of primary bone tumors and palliation of pain from bone metastases. A recent multicenter trial presented, using the ExAblate device, showed a significant reduction of the pain, as recorded on the visual analogy scale, in 72% of patients at 3 months after treatment (12). They also reported a 67% reduction in the use of opioid pain medication. Initial experience for pain relief is very promising. It has great potential to be valuable in patients who cannot receive more radiation to a particular site, due to limitations in normal tissue tolerance or as the risk of fracture in the peri-irradiation period would be very high. The FUS treatment for palliation of pain from bone metastases differs from tumor ablation. Due to the high absorption in bone, the ultrasound energy requirements for FUS ablation in bone are much lower than in other targets; approximately only 30% of the soft tissue energy is required. One can take advantage of the high absorption in bone by placing the focal point beyond the bone surface. Because very little of the energy is transmitted into the bone, the ablation is localized to the periosteal bone–soft tissue interface. The pain palliation is thought to be due to FUS denervation of the nerves in the periosteal layer of bone. New applications of MRgFUS in bone diseases include the palliation of metastatic bone pain and also for relive of pain in knee osteoarthritis (13)

Prostate New focal therapies for prostate cancer are increasingly being sought out by and used in patients who are seeking cancer control with reduced side effects. FUS treatment of prostate cancer has been first reported using US-guided FUS. Unfortunately, grayscale US is limited in its depiction of focal tumors, which can be either hypo- or hyperechoic. Furthermore, during sonications, US imaging does not accurately depict thermal changes within the heated zone. However, hyperechoic regions may appear, presumably due to cavitation through the boiling or the intense negative pressures associated with high-intensity ultrasound exposures. These regions, while not predictive of the resulting thermal lesions, provide some level of feedback to the operator. There is considerable effort underway to improve the technique. Research groups have investigated US-based thermometry methods and US elastography methods to detect thermal coagulation.

Successful treatment is defined by radiologic, pathologic, and biochemical markers of disease. Adverse effects from US-guided FUS, include urinary retention (8.6% patients), stress incontinence (13.1%), bladder outlet obstruction (3.6%), urinary tract infection (13.8%) and urethrorectal fistula (1.2%). Other studies have identified greater degrees of impotence, in approximately 50% of patients.

Newer approaches using MR as the imaging guidance method offer a potential advantage over US by allowing improved thermometry and tumor visualization. It is hoped that this will lead to reduced adverse effects, as it more accurately monitors temperature in the volume of ablation allowing for real-time adjustment of energy delivered. We and others are investigating MR-guided FUS using a transrectal approach in a canine model as a potential therapeutic approach for prostate cancer Fig 3. Others are investigating the use of transurethral ultrasound devices for MR-guided thermal ablation. The first human clinical trial is underway with MR-guided FUS performed prior to radical prostatectomy. Transducers have been positioned on a transurethral device or on an intrarectal device, to deliver the ultrasound beam. Clearly the engineering challenges involve the need to ensure safe and effective delivery of the ultrasound beam in the MR environment and with the anatomic constraints presented by the prostate and its locoregional structures. For safe and effective treatment the operator will need to have full control of the focal spot size and localization, to avoid heat delivery to critical structures such as the neurovascular bundles.

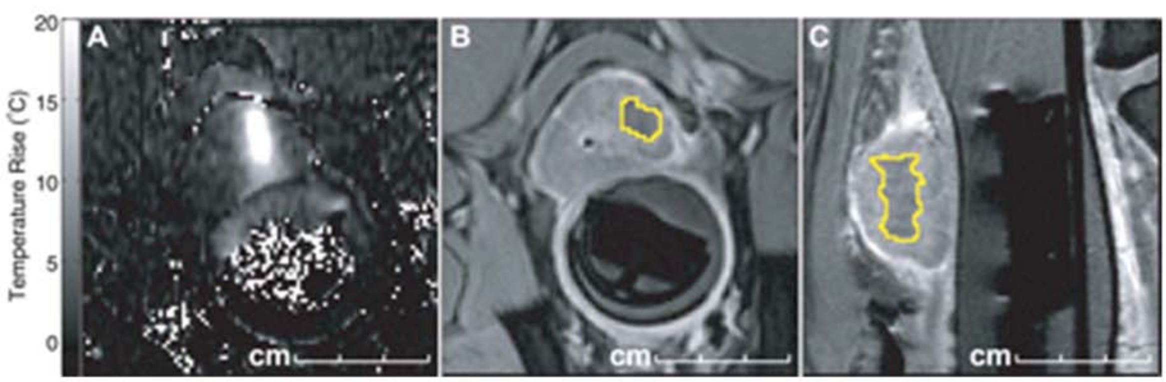

Figure 3:
Preclinical MR-guided FUS of the prostate. Three images from an animal study show, *A*, axial phase image with thermal change (high-signal-intensity area centrally) from an individual sonication delivered by transrectal FUS transducer device (InSightec), then, *B*, axial T1-weighted and, *C*, sagittal T1-weighted images after the procedure and after injection of intravenous gadolinium show the focal ablation as an area of nonperfusion (yellow).

In conclusion, image-guided FUS effectively combines two technologies, MR imaging or US and FUS, into an image-guided therapy delivery system for noninvasive tumor ablation or the targeted delivery of drugs, both of which can either replace or complement surgery or radiation therapy.

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