

White paper

Transcranial Magnetic Resonance-guided Focused Ultrasound Surgery: *Current Applications and Progress for Non-Invasive Neurosurgery*

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The MRgFUS products and applications discussed in this document are currently used only for research. They are currently limited by United States Law to investigational use.

ABSTRACT

Transcranial Magnetic Resonance-guided Focused Ultrasound Surgery (tcMRgFUS) is a promising new technology for the non-invasive treatment of various brain disorders. With preclinical and clinical precedents set for the safety, efficacy, and reproducibility of MRgFUS for treating uterine fibroids, painful bone metastases, adenomyosis, breast tumors, and a host of other conditions, tcMRgFUS for cranial disorders could become a groundbreaking and potentially disruptive technology in the field of neurosurgery. The current report outlines the key features of tcMRgFUS and its potential clinical benefits, based on ongoing clinical studies for treating functional disorders and brain tumors, and on significant preclinical experience and research into other applications such as targeted drug delivery and treatment of stroke. The collaboration and synthesis of investigative efforts across various disciplines will aid in the development of these applications and may trigger a quantum improvement in the clinical management of brain pathologies.

INTRODUCTION

More than half a century ago, researchers began to seek an alternative to invasive neurosurgical procedures for brain disorders (Fry et al., 1942; Fry et al., 1955; Lynn et al., 1942). Recently, Magnetic Resonance-guided Focused Ultrasound Surgery (MRgFUS) has emerged as a well-established technology for non-invasive surgical ablation (Fennessy et al., 2007; Jolesz et al., 2005; Jolesz and McDannold, 2008). MRgFUS does not use ionizing radiation, thereby permitting multiple treatments, without the risk of cumulative radiation exposure and delivers immediate tissue response during the treatment. Since MRgFUS is non-invasive, the risk of infection, blood loss, and damage to nearby tissue is minimized (Chen et al., 2001).

For decades, therapeutic transcranial ultrasound was assumed impossible, due to disruption of the focused acoustic beam by the skull, and the production of damaging heat by the ultrasound. Novel technology using high-power phased array transducers and multiple



Figure 1: ExAblate 4000 system



Figure 2: *Transducer and Mechanical Positioning Unit*

channel driving electronics enabled a sharp focal point in the planned target. MR images provide intraoperative anatomical data to identify the target, and real-time thermo-sensitive images allow intraoperative feedback to evaluate treatment outcome and guide the therapy. The historical development of MRgFUS for brain therapy and the details of its physical principles have recently been reviewed (Jagannathan et al., 2009).

Principle of Operation

The ExAblate 4000 transcranial (tc) MRgFUS system (InSightec, Inc, Tirat Carmel, Israel) is a specialized system, integrating magnetic resonance imaging and high intensity focused ultrasound for investigational non-invasive, image-guided transcranial applications. The system enables intra-procedure MRI for therapy planning, and real-time MR thermal imaging feedback to monitor safety and efficacy. It is tightly integrated with an MR scanner and operates via a unique planning and treatment control workstation. MR imaging facilitates the accurate localization of the target region, safe delineation of the treatment margins, sustained real-time monitoring of tissue heating, and assessment of therapeutic outcome during and after therapy (Chen et al., 1999; Chung et al., 1999).

The ExAblate 4000 supports clinical studies with a unique patient interface, and provides tools for clinical,

preclinical, in vivo and in vitro research. A hemispherical, helmet-like, multi-element phased array transducer enables focal targeting of brain tissue through the intact skull. The system is integrated with a standard GE MRI system using a detachable treatment table. In the scanner room, the patient lies on the table with their head immobilized in a stereotactic frame, and the helmet like transducer positioned around their head. A sealed water system with an active cooling and degassing capacity maintains the skull and skin surface at a comfortably low temperature.

The entire setup is moved into the MR scanner and a series of conventional MRI scans are displayed on the ExAblate workstation and analyzed by the attending physician to determine the targeted regions. Pre-operative CT and inter-operative MR scans are co-registered reconstructing a model of the skull and brain anatomy for treatment planning and simulation. The treatment is based on multiple sonications that cover the targeted volume. Sublethal spots confirm the target localization accuracy and patient comfort prior to lesion generation. During energy delivery to each spot, thermal images provide real-time feedback of the treatment location and measure thermal rise, allowing the physician to adjust the parameters accordingly. Post-treatment contrast imaging confirms the treatment effect.

RESEARCH APPLICATIONS

The potential applications of tcMRgFUS are wide-ranging – The ExAblate 4000 tcMRgFUS system is under evaluation for clinical safety and efficacy in functional neurosurgery and tumor ablation, stroke, and targeted drug delivery are in pre-clinical phase.

Functional Neurosurgery

An important application for tcMRgFUS is for neuro functional disorders such as essential tremor, epilepsy, neuropathic pain, and Parkinson's disease. Currently, such disorders are treated using pharmaceutical therapy, deep brain stimulation, radiofrequency ablation, radiosurgery or resection of specific neural pathways. The risks associated with such invasive techniques include infections, hemorrhages, damage to non-targeted brain tissue, and targeting errors due to tissue shifting.

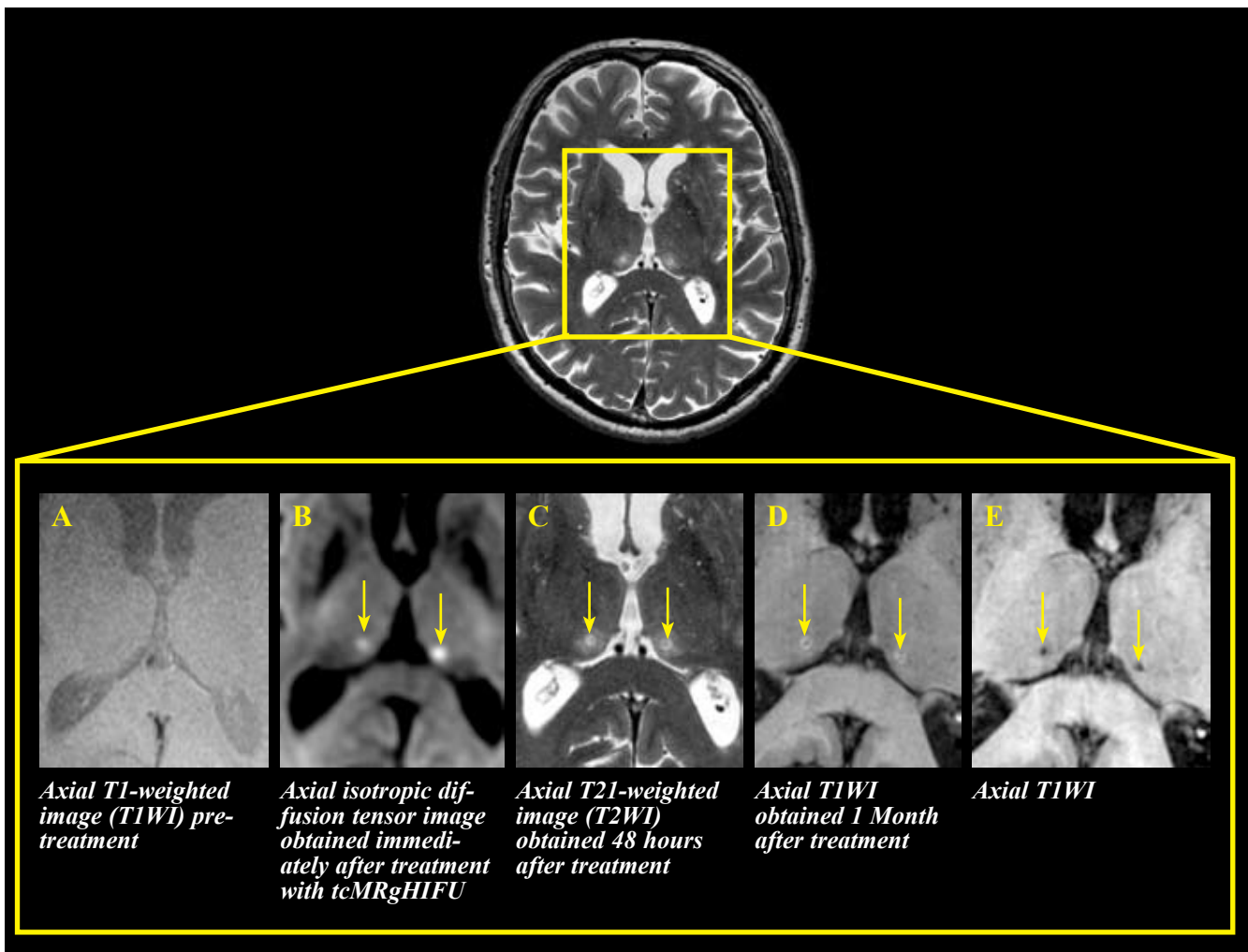


Figure 3: Pre- and Post-treatment magnetic resonance (MR) images showing one sonication lesion that was placed bilaterally in the posterior parts of each central lateral thalamic nucleus

Moreover, treatment in some situations is limited as a result of trajectory limitations and inaccessible targets deep within the brain. The benefits of tcMRgFUS as compared to the risks of other stereotactic neurosurgical techniques are discussed below.

Surgical Advantage

tcMRgFUS for functional neurosurgery may prove to be advantageous over other stereotactic neurosurgical techniques, such as deep brain stimulation, and stereotactic radiofrequency ablation. The major surgical advantage of tcMRgFUS is its noninvasiveness, obviating the need for an incision, burr hole, or penetrating

electrode, thereby reducing the risks of hemorrhagic and infectious complications. The overall risk of hemorrhagic complications for open stereotactic procedures is about 2% per electrode insertion, with a risk of permanent neurologic deficit of about 1%. Intraventricular hemorrhages occur in 5% of cases when the electrode traverses the lateral ventricular system (Sansur et al., 2007). With tcMRgFUS there is no implanted hardware, no concern of interference with external sources of electromagnetic noise, and no need for programming follow-up or battery replacement. tcMRgFUS may prove to be much more cost-effective since it avoids the need for device management and replacement, and health care costs maybe reduced.

Real-Time Monitoring and immediate physiological effect

tcMRgFUS uses real-time MRI monitoring and MRthermography (Jolesz et al., 1990; Jolesz et al., 1989; Jolesz and Blumenfeld, 1994; Jolesz and McDannold, 2008; Moonen et al., 2001; Salomir et al., 2006; Cline et al., 1992), to immediately confirm the anatomical targeting process, unlike stereotactic radiosurgery, which has associated placement errors (Deogaonkar et al., 2007; Elias et al., 2007). Stereotactic Radiosurgery (SRS) procedures (as an example the Gamma knife) use ionizing radiation to denature DNA and cause cell death within the area defined by the 50% isodose margins around the target. It requires a long time (median several months) (Duma et al., 1999; Niranjan et al., 2000; Ohye and Shibazaki, 2009) for the lesion to develop. Since the procedure does not require the use of intraoperative testing to verify the target and confirm the absence of side effects, the lesions observed on MR after 3 months are variable in volume and distribution, although the clinical effects seem consistent (Ohye and Shibazaki, 2009).

The clinical effect of the MRgFUS lesion can be evaluated immediately. While awake, the patient interacts with the treatment team, and is observed within the MR scanner bore for functional effect during therapy. The treatment can be aborted or altered if adverse effects or inaccurate targeting is noted. Unlike stereotactic radiosurgery, tcMRgFUS does not use ionizing radiation, thereby avoiding the risk of tumorigenesis.

Progress and Potential

Ablative tcMRgFUS is being investigated for functional neurosurgery, to eliminate damage to neural pathways in the brain thereby ameliorating symptoms in patients with disorders such as epilepsy and neuropathic pain (Martin et al., 2009). Following preclinical investigations with biological tissues, phantoms, and human ex-vivo preparations, the first clinical study to test the reproducibility, accuracy, feasibility and safety of tcMRgFUS for neuropathic pain was initiated. The study showed accurate targeting within 1 mm of the planned target, perfect safety, no adverse events, and a mean pain relief of 68% at 2 days post-treatment, based on preliminary findings (Martin et al., 2009).

This holds tremendous potential for non-invasive lesioning of deep brain targets, overcoming trajectory constraints, minimizing tissue damage, and reducing risks associated with invasive procedures.

Tumor Ablation

The incidence of brain tumors in the United States is over 200,000 new diagnoses annually [<http://www.cancer.gov/cancertopics/factsheet/risk/brain-tumor-study>, <http://emedicine.medscape.com/article/1157902-overview>]. The current treatment for brain tumors includes a combination of neurosurgery, radiosurgery, radiation therapy, and chemotherapy. However, the 5-year survival rate is approximately 30%, indicating that the clinical outcome is not optimal [<http://www.cancer.gov/cancertopics/factsheet/risk/brain-tumor-study>]. Even stereotactic radiotherapy, which is the gold standard of care in such cases, has an important caveat in that nearby healthy tissue reaches a threshold for the maximum allowable exposure to radiation. Therefore, tcMRgFUS may offer a significant advantage in that it can be repeated as often as it is required, without the risks of accumulated dose effects.

Principle of Operation

The proof of principle for brain tumor thermal ablation was demonstrated using heat created by radiofrequency energy, laser, and focused ultrasound (Hynynen et al., 2004; McDannold et al., 2004a; McDannold et al., 2004b; Vykhodtseva et al., 2000). These and other such studies underscore the accuracy, reliability and efficacy of MRI-controlled thermal ablation in animals and humans for various applications (Jolesz et al., 2004; Kacher and Jolesz, 2004; Yagel, 2004).

Progress and Potential

An important preclinical feasibility study (Cohen et al., 2007) demonstrated in a porcine open skull model that MRgFUS can accurately demarcate, target, and thermally ablate brain tissue, without any anatomical or histological damage to the untargeted surrounding tissue. A subsequent clinical trial was performed wherein three patients diagnosed with recurrent glioblastoma multiforme were treated with MRgFUS following cra-

niotomy (Ram et al., 2006). Two patients survived for over 30 months. This study demonstrated that focused ultrasound can be used with MRI to ablate brain tissue, and that MRI is particularly efficient as a way to plan the treatment and monitor its progress using thermal mapping. In its current design tcMRgFUS eliminates the need for craniotomy and its associated risks. A feasibility clinical study for elucidating the effectiveness of tcMRgFUS for glioblastoma multiforme patients is currently ongoing, and 4 of the 10 recruited patients have been treated (McDannold et al., 2010). Preliminary results show that focused ultrasound can thermally ablate target tissue via the intact skull. Minimal skull heating was demonstrated, and no neurological deficits were reported during or after the procedure.

Thrombolysis for Ischemic and Hemorrhagic Stroke

Hemorrhagic and ischemic strokes constitute the third most frequent cause of death in the United States. Of the 700,000 patients that are affected each year, many may benefit from tcMRgFUS in the future [<http://www.strokecenter.org>]. The leading current therapeutic target for ischemic stroke is the use of thrombolytic drugs such as tissue plasminogen activator (tPA), which must be administered within the first 3-5 hours of a stroke to be effective.

Principle of Operation

MR angiography combined with tcMRgFUS may have the potential to localize and dissolve the clot, beyond the 3-hour time window for which patients are deemed eligible for tPA treatment. Liquefaction of a blood clot is achieved by mechanical disruption, using less energy, thereby preserving the integrity of the clotted artery. The concomitant administration of thrombolytic agents with microbubbles and focused ultrasound enhance clot lysis (Stone et al., 2007; reviewed in Medel et al., 2009). This effect was mediated by a focused ultrasound-induced elevation in the level of tPA activity due to hyperthermia, and an elevation in tPA binding to fibrin (Stone et al., 2007).

Therefore, in the case of ischemic stroke, tcMRgFUS could be used to liquefy the clot confined inside a blood vessel, which can then dissipate through the normal circulation. This treatment modality is still undergoing pre-clinical research to optimize treatment parameters such as acoustic patterns that may be different than the ones required for thermal ablation. tcMRgFUS may also be beneficial in the treatment of hemorrhagic stroke. An already clotted brain volume as a result of hemorrhagic stroke may be dissolved using focused ultrasound to relieve intracranial pressure. The dissolved residues could then be evacuated using draining techniques.

Progress and Potential

An animal model was developed to enable the research of this potential application (Harnof et al., 2008). Naturally clotted porcine blood is implanted in a pig's brain through a burr hole. The clot is identified in MR imaging and targeted with special ultrasound parameters. The ultrasound dissolves the clot without using any chemical agents (tPA or microbubbles). In future potential clinical applications for hemorrhagic stroke treatment, tcMRgFUS can be used to liquefy the clot, and the liquefied clot would then be drained from the brain cavity via a minimally invasive procedure. This application requires further basic research to develop acoustic patterns that may differ from those that are required for thermal ablation. Pre-clinical research is ongoing, to collect data for beginning a feasibility clinical trial.

Targeted Drug Delivery

Principle of Operation

Delivering macromolecular drugs to the central nervous system (CNS) in a reproducible and controlled manner represents a challenging development in overcoming the obstacle of the blood-brain barrier (BBB) to drug delivery. The ability of ultrasound to open the BBB has been known for years, and was considered a highly favorable option for delivering effective therapeutic agents into the CNS. The effectiveness of focused ultrasound-mediated delivery of various pharmacologi-

cally-relevant sized agents across the BBB and into the CNS has been shown to be reproducible and controlled, using MRI to monitor the process (Choi et al., 2010). By enabling a localized, temporary, reversible opening of the BBB using focused ultrasound, location controlled drug delivery to CNS targets can be achieved.

Progress and Potential

Focused ultrasound mediates targeted delivery to the brain of various substances, including genes, antibodies, growth factors, and chemotherapeutic agents (Cho et al., 2002; Kinoshita et al., McDannold et al., 2005; Qin et al., 2008; Treat et al., 2007). Many chemotherapeutic brain tumor drugs are not effective because they are too large to cross the BBB. Focused ultrasound may enhance BBB permeability thereby improving tumor treatment. Microbubbles are a powerful vehicle for enhancing the ability of focused ultrasound to

increase BBB permeability (Meairs and Alonso, 2007). Microbubbles lower the threshold for the occurrence of the mechanical bioeffects involved in BBB disruption (i.e. cavitation), thereby facilitating BBB opening at lower acoustic intensities.

Similarly, nanoparticles are being investigated as drug delivery vehicles in combination with high intensity focused ultrasound. Nanobubbles containing a chemotherapeutic drug were injected into a mouse tumor model. They selectively accumulated in the tumors and combined to form larger microbubbles, which were exposed to ultrasound and triggered to release the drug (Rapoport et al., 2007). Compared to delivery of the drug alone, the encapsulated method was more effective at thwarting tumor growth. Targeted delivery of encapsulated chemotherapeutic agents to tumors later releasing the drug at the targeted tumor, eliminates many of the toxic side effects of these drugs and significantly improving quality of life during treatment.

SUMMARY AND FUTURE IMPLICATIONS

tcMRgFUS has the potential to be an extraordinary therapeutic tool for brain pathologies. As a non-invasive thermoablative technique, tcMRgFUS can be applied to tumors and functional neurosurgery targets. Its nonablative potential can be used to disrupt the BBB for enhanced delivery of therapeutic drugs, and lyse clots to treat ischemic and hemorrhagic stroke. A wealth of preclinical studies in a variety of experimental models has shown that tcMRgFUS is safe, feasible, reproducible, and efficacious. The benefits of tcMRgFUS for brain applications are summarized below:

- Non-invasive: reduces risk of infection, hemorrhage, and tissue damage
- Potentially reduces morbidity, recovery time, and health care costs
- Thermal ablation results in immediate bio-physical response
- Does not use ionizing radiation, thereby allowing repeated treatments and staged treatment procedures.

- Monitoring immediate tissue response to confirm treatment outcome
- Real-time MRI of target tissue and intra procedure control to monitor localization accuracy, therapeutic outcome, and safety

Several clinical trials have been initiated and others are underway to evaluate and develop tcMRgFUS for brain disorders, by improving treatment parameters and outcomes. As the technology is honed, tcMRgFUS may emerge as an invaluable neurosurgical tool, allowing clinicians to treat CNS disorders that were previously challenging, and open avenues for novel applications. The evolution of this therapy depends on collaborations between neurosurgeons, neuroscientists, biomedical engineers, physicists, and neuroradiologists. Enabling a fruitful collaborative environment can accelerate the development of tcMRgFUS to improve the therapeutic management of a wide spectrum of intracranial disorders.

Additional references and information can be found on the InSightec website: www.insightec.com

REFERENCES

1. Bradley WG Jr. MR-guided focused ultrasound: a potentially disruptive technology. *J Am Coll Radiol*. 2009;6:510-513
2. Chen L, Bouley DM, Harris BT, Butts K. MRI study of immediate cell viability in focused ultrasound lesions in the rabbit brain. *J Magn Reson Imaging*. 2001;13:23-30
3. Chen L, Bouley D, Yuh E et al. Study of focused ultrasound tissue damage using MRI and histology. *J Magn Reson Imaging*. 1999;10:146-153
4. Choi JJ, Wang S, Tung YS, et al. Molecules of various pharmacologically-relevant sizes can cross the ultrasound-induced blood-brain barrier opening in vivo. *Ultrasound Med Biol*. 2010;36(1):58-67
5. Cho CW, Liu Y, Cobb WN, et al. Ultrasound-induced mild hyperthermia as a novel approach to increase drug uptake in brain microvessel endothelial cells. *Pharm Res*. 2002;19:1123-1129
6. Chung AH, Jolesz FA, Hynynen K. Thermal dosimetry of a focused ultrasound beam in vivo by magnetic resonance imaging. *Med Phys*. 1999;26:2017-2026
7. Cline HE, Schenck JF, Hynynen K, et al. MR-guided focused ultrasound surgery. *J Comput Assist Tomogr*. 1992;16:956-965
8. Cohen ZR, Zauberaman J, Harnof S, et al. Magnetic resonance imaging-guided focused ultrasound for thermal ablation in the brain: a feasibility study in a swine model. *Neurosurgery*. 2007;60:593-600
9. Deogaonkar M, Walter B, Boulis N, Starr P. Clinical problem solving: finding the Target. *Neurosurgery*. 2007;61:815-824
10. Duma C, Jacques D, Kopyov O. The treatment of movement disorders using Gamma Knife stereotactic radiosurgery. *Neurosurgery Clinics of North America*. 1999;10:379-389
11. Elias W, Fu K, Frysinger R. Cortical and subcortical brain shift during stereotactic procedures. *Journal of Neurosurgery*. 2007;107:983-988
12. Fennessy FM, Tempny CM, McDannold NJ et al. Uterine leiomyomas: MR imaging-guided focused ultrasound surgery-results of different treatment protocols. *Radiology*. 2007;243:885-893
13. Fry WJ, Barnard JW, Fry EJ et al. Ultrasonic lesions in the mammalian central nervous system. *Science*. 1955;122:517-518
14. Harnof S, Hananel A, Schiff G, et al. MR guided focused ultrasound surgery for the treatment of intracerebral hemorrhage: In vitro proof of concept. *Stroke*. 2008;39:563 (abstract)
15. Hynynen K, Clement GT, McDannold N, et al. 500-element ultrasound phased array system for noninvasive focal surgery of the brain: a preliminary rabbit study with ex vivo human skulls. *Magn Reson Med*. 2004;52:100-107
16. Jagannathan J, Sanghvi NT, Crum LA, et al. High-intensity focused ultrasound surgery of the brain: part 1 - a historical perspective with modern applications. *Neurosurgery*. 2009;64:201-211
17. Jolesz FA, Bleier AR, Lauter RS. Laser surgery benefits from guidance by MR. *Diagn Imaging*. 1990;12:103-108
18. Jolesz FA, Blumenfeld SM. Interventional use of magnetic resonance imaging. *Magn Reson Q*. 1994;10:85-96
19. Jolesz FA, Hynynen K, McDannold N, et al. Noninvasive thermal ablation of hepatocellular carcinoma by using magnetic resonance imaging-guided focused ultrasound. *Gastroenterology*. 2004;127 (Suppl 5):S242-247
20. Jolesz FA, Hynynen K, McDannold N, Tempny C. MR imaging-controlled focused ultrasound ablation: a noninvasive image-guided surgery. *Magn Reson Imaging Clin N Am*. 2005;13:545-560
21. Jolesz FA, McDannold N. Current status and future potential of MRI-guided focused ultrasound surgery. *J Magn Reson Imaging*. 2008;27:391-399
22. Jolesz FA, Moore GJ, Mulkern RV, et al. Response to and control of destructive energy by magnetic resonance. *Invest Radiol*. 1989;24:1024-1027
23. Kacher DF, Jolesz FA. MR imaging-guided breast ablative therapy. *Radiol Clin N Am*. 2004;42:947-962
24. Kinoshita M, McDannold N, Jolesz FA, Hynynen K. Noninvasive localized delivery of herceptin to the mouse brain by MRI-guided focused ultrasound-induced blood-brain barrier disruption. *Proc Natl Acad Sci U S A*. 2006;103:11719-11723
25. Lynn JG, Zwemer RL, Chick AJ. The Biological Application of Focused Ultrasonic Waves. *Science*. 1942;96:119-120
26. Martin E, Jeanmonod D, Morel A, et al. High-intensity focused ultrasound for noninvasive functional neurosurgery. *Ann Neurol*. 2009;66(6):858-61
27. McDannold N, Clement GT, Black P, et al. Transcranial magnetic resonance imaging-guided focused ultrasound surgery of brain tumors: initial findings in 3 patients. *Neurosurgery*. 2010;66(2):323-32; discussion 332

- 28a. McDannold N, King RL, Hynynen K. MRI monitoring of heating produced by ultrasound absorption in the skull: in vivo study in pigs. *Magn Reson Med*. 2004; 51:1061–1065
- 28b. McDannold N, Vykhodtseva N, Jolesz FA, Hynynen K. MRI investigation of the threshold for thermally induced blood-brain barrier disruption and brain tissue damage in the rabbit brain. *Magn Reson Med*. 2004;51:913–923
29. McDannold N, Vykhodtseva N, Raymond S, et al. MRI-guided targeted blood-brain barrier disruption with focused ultrasound: histological findings in rabbits. *Ultrasound Med Biol*. 2005;31:1527-37
30. Meairs S, Alonso A. Ultrasound, microbubbles and the blood-brain barrier. *Prog Biophys Mol Biol*. 2007;93(1-3):354-62
31. Medel R, Crowley RW, McKisic MS, et al. Sonothrombolysis: an emerging modality for the management of stroke. *Neurosurgery*. 2009;65(5):979-93
32. Moonen CT, Quesson B, Salomir R, et al. Thermal therapies in interventional MR imaging. Focused ultrasound. *Neuroimaging Clin N Am*. 2001;11:737-747
33. Niranjana A, Kondziolka D, Baser S, et al. Functional outcomes after gamma knife thalamotomy for essential tremor and MS-related tremor. *Neurology*. 2000;55:443-446
34. Ohye C, Shibasaki T. Treatment of functional disorders with gamma knife thalamotomy. *Prog Neurol Surg*. 2009;22:170-181
35. Qin G, Li Z, O'Neill B, Li KC. High intensity focused ultrasound facilitated drug delivery using heat-sensitive partially polymerized liposomes. Presented at: *International Symposium on MR Guided Focused Ultrasound Surgery; Tyson's Corner, Va.* October 6-7, 2008
36. Ram Z, Cohen ZR, Harnof S, et al. Magnetic resonance imaging-guided, high-intensity focused ultrasound for brain tumor therapy. *Neurosurgery*. 2006;59:949–956
37. Rapoport N, Gao Z, Kennedy A. Multifunctional nanoparticles for combining ultrasonic tumor imaging and targeted chemotherapy. *J Natl Cancer Inst*. 2007;99:1095–1106
38. Salomir R, Delemazure AS, Palussiere J, et al. Image-based control of the magnetic resonance imaging-guided focused ultrasound thermotherapy. *Top Magn Reson Imaging*. 2006;17:139-151
39. Sansur CA, Frysinger RC, Pouratian N, et al. Incidence of symptomatic hemorrhage after stereotactic electrode placement. *J Neurosurg*. 2007;107:998-1003
40. Stone MJ, Frenkel V, Dromi S, et al. Pulsed-high intensity focused ultrasound enhanced tPA mediated thrombolysis in a novel in vivo clot model, a pilot study. *Thromb Res*. 2007;121:193–202
41. Thilo Hoelscher, Eyal Zadicario, David Fisher, William G. Bradley. Transcranial Clot Lysis Using High Intensity Focused Ultrasound. Presented at: *The 6th Annual World Congress for Brain Mapping and Image Guided Therapy Boston MA August 2009*
42. Treat LH, McDannold N, Vykhodtseva N, et al. Targeted delivery of doxorubicin to the rat brain at therapeutic levels using MRI-guided focused ultrasound. *Int J Cancer*. 2007;121:901–907
43. Vykhodtseva N, Sorrentino V, Jolesz FA, et al. MRI detection of the thermal effects of focused ultrasound on the brain. *Ultrasound Med Biol*. 2000;26:871–880
44. Yagel S. High-intensity focused ultrasound: a revolution in non-invasive ultrasound treatment? *Ultrasound ObstetGynecol*. 2004;23:216–217

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