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ABSTRACT

SUMMARY: Transcranial focused ultrasound (FUS) is a versatile, MR-guided, incisionless intervention with diagnostic and therapeutic applications for neurologic and psychiatric diseases. It is currently FDA-approved as a thermoablative treatment of essential tremor and Parkinson disease. However, other applications of FUS including BBB opening for diagnostic and therapeutic applications, sonodynamic therapy, histotripsy, and low-intensity focused ultrasound neuromodulation are all in clinical trials. While FUS targeting for essential tremor and Parkinson disease has classically relied on an indirect, landmark-based approach, development of novel, advanced MR imaging techniques such as DTI tractography and fast gray matter acquisition T1 inversion recovery has the potential to improve individualized targeting and thus potentially enhance treatment response, decrease treatment times, and avoid adverse effects. As the technology advances and the number of clinical applications increases, the role of the neuroradiologist on a multidisciplinary team will be essential in pairing advanced structural and functional imaging to further this image-guided procedure via a precision medicine approach. This multi-institutional report, written by an experienced team of neuroradiologists, neurosurgeons, and neurologists, summarizes current practices, the use of advanced imaging techniques for transcranial MR-guided high-intensity FUS, recommendations for clinical implementation, and emerging clinical indications.

ABBREVIATIONS: AC = anterior commissure; DBS = deep brain stimulation; dDRTT = decussating dentatorubrothalamic tract; ET = essential tremor; FGATIR = fast gray matter acquisition T1 inversion recovery; FUS = focused ultrasound; HIFU = high-intensity focused ultrasound; LIFU = low-intensity focused ultrasound; ML = medial lemniscus; MRgFUS = MR-guided focused ultrasound; MRgHIFU = MR-guided high-intensity focused ultrasound; ndDRTT = nondecussating dentatorubrothalamic tract; PC = posterior commissure; PD = Parkinson disease; SDR = skull density ratio; VIM = ventral intermediate nucleus

Transcranial MR-guided high-intensity focused ultrasound (MRgHIFU) is an incisionless, image-guided procedure that is currently FDA-approved for the treatment of essential tremor (ET) and Parkinson disease (PD).[1-3] Low-intensity focused ultrasound (LIFU) for BBB disruption and neuromodulation is presently under study and discussed separately.[4-13] Currently, neurosurgeons most commonly perform MRgHIFU followed by neuroradiologists and neurologists. A multidisciplinary team facilitates the preprocedural patient assessment, treatment, and postprocedural follow-up; technical optimization and interpretation of related imaging studies; and management of the support staff. There are currently no publications outlining good clinical practice for transcranial MRgHIFU, and implementation varies greatly across sites. While neurologists, neurosurgeons, or neuroradiologists can lead the multidisciplinary treatment team, in this report, we specifically provide recommendations for neuroradiologists treating patients with MRgHIFU. We also describe the current clinical applications and approach and discuss future applications.

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CURRENT INDICATIONS FOR TRANSCRANIAL MRgHIFU

Essential Tremor

ET is the most common movement disorder affecting >10 million individuals in the United States alone.[14] Prevalence increases

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with age with 5% of those older than 60 years of age having the diagnosis.[14] Fifty percent of ET cases are familial, though a genetic cause remains elusive. While tremor in ET most commonly affects the hands and arms, other regions may also be affected, including the head, voice, jaw, trunk, and legs. A key characteristic of tremor in ET is that it emerges with posture or action and less often presents at rest.[15] First-line pharmacotherapy includes medications such as propranolol and primidone. Unfortunately, these medical therapies often prove ineffective. Like other neurodegenerative diseases, ET is often progressive and can sometimes present with comorbid ataxia and cognitive deficits.[14] While not fully understood, ET may result from loss of cerebellar Purkinje cells,[14] leading to development of a dysfunctional motor circuit involving the cerebellum, red nucleus, ventral intermediate nucleus (VIM) of the thalamus, and primary motor cortex.

Due to decades of experience with lesional therapies and deep brain stimulation, VIM of the thalamus has emerged as the standard therapeutic target for ET. Unilateral MRgHIFU ablation of the VIM was FDA-approved for ET in 2016. Because this nucleus is not visualized on conventional high-resolution MR imaging, the VIM is typically targeted using "indirect" or coordinate-based methods. A limitation of indirect targeting is that it cannot fully account for the anatomic variability among patients, being especially important when considering volume loss in the elderly. Tractography generated from DTI enables direct targeting of the dentatorubrothalamic tract, a white matter pathway that is hypothesized to be the source of therapeutic benefit associated with VIM targeting. Tractography-guided MRgHIFU has been performed successfully at several sites.[16-21] Potential benefits include improved efficacy, decreased treatment times, and reduced adverse effects.[16-21] For example, one limitation of MRgHIFU has been adverse effects from injury to nearby structures such as the corticospinal tract and medial lemniscus. These tracts can be visualized with tractography, allowing the treating physician to avoid them. Although there is a paucity of articles directly comparing indirect targeting with tractography-based targeting, many centers are now use tractography-based targeting. One multiparametric method, 4-tract tractography, has now been replicated and successfully implemented across a variety of scanner vendors and postprocessing algorithms and software.[18,21]

Parkinson Disease

PD is a complex neurodegenerative disease characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta.[22] PD is associated with cytoplasmic inclusions (Lewy bodies and Lewy neurites) composed of insoluble aggregates of α-synuclein. PD pathology also includes other brain regions and nondopaminergic neurons.[23] Classic presentation is defined by its motor symptoms, which include asymmetric rest tremor, rigidity, and bradykinesia. However, PD is a heterogeneous disease with a wide phenotypic spectrum that can be classified by motor subtypes, specifically tremor-dominant and akinetic rigid subtypes.

Tremor-Dominant Parkinson Disease. Approximately 7% of patients with PD present with a tremor-dominant subtype. Unlike those with classic PD, these patients present primarily with asymmetric resting tremor and re-emergent tremor, tremor that emerges after a delay of several seconds with changing position as in moving the limb from rest to holding it against gravity. Unilateral VIM thalamotomy with MRgHIFU was FDA-approved for tremor-dominant PD in 2018. Like ET, the dentatorubrothalamic tract has also been targeted with some success.

Bradykinesia and Rigidity in the Setting of Parkinson Disease. FDA-approved deep brain stimulation (DBS) targets in PD include the subthalamic nucleus and globus pallidus internus.[24-26] Although the MRgHIFU clinical trials studying high-intensity focused ultrasound (HIFU) ablation of the globus pallidus internus or subthalamic nucleus noted a marginal benefit, MRgHIFU of the globus pallidus internus was approved by the FDA as of 2021 for the unilateral treatment of dyskinesia. Many European sites prefer to target the subthalamic nucleus.[27] MRgHIFU of the pallidothalamic tract is currently under investigation.[28,29]

Comparison of Therapeutic Options for Tremor

Patients with medically refractory tremor and substantial comorbidities, advanced age, asymmetric tremor, or a strong preference to avoid an open surgical procedure or implanted device may be better candidates for MRgHIFU than DBS. However, there is currently a paucity of long-term MRgHIFU data (>6 years).

MRgHIFU versus DBS. Although no prospective clinical trials have been conducted directly comparing MRgHIFU with DBS for tremor, a systematic retrospective meta-analysis compared unilateral MR-guided focused ultrasound (MRgFUS) thalamotomy with unilateral and bilateral DBS of the VIM for the treatment of ET (Table).[30] Bilateral DBS was superior to unilateral MRgHIFU in overall tremor control; however, because MRgHIFU was limited to unilateral treatment, post hoc analyses showed that the substantial factor in improvement was laterality rather than technique. Most interesting, quality of life was significantly greater with FUS than DBS; however, this was performed in a post hoc and retrospective analysis. Additionally, there is a paucity of long-term MRgHIFU data (longest follow-up data to date is 5 years). This is in stark contrast to DBS for which follow-up data from ≥10 years are available.

Recently, bilateral staged MRgHIFU was approved by the FDA. Preliminary clinical trial data suggest a higher risk of speech and gait adverse effects following bilateral MRgHIFU thalamotomy.[31] However, it has yet to be determined how overall tremor control following bilateral MRgHIFU compares with that in bilateral DBS.

Despite its limitations, MRgHIFU is a good alternative for patients with medically refractory tremor but substantial comorbidities that preclude DBS, comorbidities such as advanced age, coagulopathies, antiplatelet and/or anticoagulant use, and a strong preference against an open surgical procedure involving an implanted device. Last, DBS can be used to treat patients with recurrent, residual tremor or failed MRgHIFU.

Radiofrequency Ablation, Gamma Knife, and MRgHIFU. Radiofrequency and radiosurgery (gamma knife) VIM thalamotomy are alternate procedures for tremor control.[32] While both

Comparison of DBS versus MRgHIFU thalamotomy

	DBS	MRgHIFU
Infection risk	~2%–4%	None
Intracranial hemorrhage risk	~2%–3%	Very low, <1%, no reports
Imbalance/risk of gait ataxia	Not seen initially but can develop with time with stimulation; stimulation-related ataxia can occur in up to ~30% of patients with ET[48]	Initial transient imbalance is not infrequent and can gradually resolve during 3–4 weeks; higher risk of permanent worsening of balance in patients with pre-existing balance issues, joint replacement, or neuropathies
Risk of aspiration	Not seen	Possibly due to the head being fixed in supine position and occasional induced nausea
Tremor relief efficacy	80%–100%	70%–90% relief more typical, with known return of some tremor
Risk of thalamic pain syndrome	None	Possible, but not reported
Reversible	Yes	No
Anticoagulation	Must be held	Currently held; some evidence supporting not holding anticoagulation in the literature[34]
Possible "honeymoon" effect	Yes	Yes
Battery maintenance	Yes	No

have shown tremor benefit, MRgHIFU has several advantages over gamma knife: 1) no ionizing radiation; 2) the ability to gradually titrate up delivered energy; 3) the ability to refine the target on the basis of real-time patient feedback; and 4) avoiding the risk of a run-away lesion. The advantages of radiofrequency or gamma knife ablation over MRgHIFU include the ability to treat patients with nonpermissive skull density ratios (SDRs), decreased procedure-related pain in patients with low SDRs, and the potential for frameless, mask-based therapy.

Focused Ultrasound Principles and MRI Essentials

Focused Ultrasound. Because bone absorbs most of the ultrasound energy delivered to it, scalp and skull heating is a limitation of transcranial focused ultrasound (FUS). However, transcranial FUS treatments are made possible by the development of phased-array ultrasound transducers, which spread the ultrasound energy needed to create a thermal ablation in the brain over the entire head circumference.[33] A clinical, hemispheric, FDA-approved system containing 1024 phased-array elements that can each be pulsed at varying time intervals is widely used. The operator can steer and shape the intensity of the FUS beam by combining the resultant summation of these interference patterns. This ability allows the operator to correct for the ultrasound wave dephasing effects of the variations in skull thickness and density and deliver a thermally ablative ultrasound energy dose at a spatially precise target. The distortions in ultrasound coherence related to variable skull thickness and density are determined using CT of the head and specialized software.[3] The CT scan is registered to the MR images of the brain during treatment, and the CT-derived skull measurements are then used to calculate appropriate phase corrections. The final thermal lesion spot shape in the brain created by a hemispheric phased-array ultrasound transducer is a prolate spheroid with the longer axis in the craniocaudal direction, which can vary in size depending on the patient's skull thickness and shape.

MRI. MRI plays several critical roles in transcranial HIFU, providing anatomic information for preoperative planning, thermal monitoring, and target adjustment during the procedure and posttreatment assessment of lesion location, edema, and complications.

Safety

Patients should be screened for unsafe implants and claustrophobia, and, if necessary, give consent for the MRI. Vigen et al[34] have previously published MRI considerations for nonconditional pacemakers. The clinical FUS system is compatible with both 1.5T and 3T MRI scanners. See below for special sequences used for preoperative and intraoperative treatment-planning. Intracranial devices are at least relative if not absolute indications. MRgHIFU can be performed after DBS if the hardware has been removed, though surgical changes in skull density must be considered in HIFU target-planning.

CLINICAL MRgHIFU RECOMMENDATIONS

Roles, Training, and Certification.

Qualifications of Physicians Performing Transcranial MRgHIFU. Physicians performing transcranial MRgHIFU should have appropriate medical licensure and proper training for the clinical applications. For neuroradiologists and interventional neuroradiologists, these should include specialized training in FUS technology, pertinent imaging neuroanatomy, and clinical knowledge and training in patient assessment and management. For example, required training could include completion of FDA-approved FUS systems training and participating in movement disorder clinics under the supervision of a movement disorders neurologist. In addition, MRgHIFU training is recommended to include observed active learning of 10 MRgHIFU cases and clinical practice of at least 15 proctored MRgHIFU procedures for the specific FDA indications being reported. Currently, these requirements could be met through an advanced or integrated fellowship with appropriate documentation along with the fellowship certificate. Alternate pathways for training and certification in other specialties are beyond the scope of this article.

Multidisciplinary Team. A collaborative, multidisciplinary approach that maximizes patient safety is integral to highly specialized advanced image-guided procedures. Multidisciplinary teams

commonly include some combination of a movement disorders neurologist, a functional neurosurgeon, and a neuroradiologist. Although each subspecialty brings additional expertise and value, interchangeable roles can easily be distributed across a well-trained multidisciplinary team. Various tasks include confirming the patient's diagnosis, evaluating concurrent movement disorders (eg, dystonia), ensuring and documenting that the patient has failed first-line treatment, evaluating any potential functional overlay, ensuring appropriate MRI sequences and protocol development for targeting, head frame placement, operating the HIFU system console, reviewing the targeting before ablation, and, if necessary, adjusting the target during treatment on the basis of clinical feedback.

MRgHIFU is a technically demanding procedure that requires the coordination of multiple steps and may require real-time troubleshooting. The treating physician and team should be well-versed in pitfalls. Examples include the ability to evaluate and fix causes of cavitation, scalp heating, and the inability to deliver a therapeutic amount of energy. The physician may need to revisit the planning images for membrane folds, assess small water bubbles in the system, assess patient positioning, or modify the active elements, for example. Understanding the effect of increasing the time-versus-power settings for various clinical situations is essential. Comfort with each step and strong familiarity with the hardware and software are absolutely required.

Qualifications of FUS Scientists and Medical Imaging Physicists Involved in Clinical Treatments

Although not critical to a clinical program, FUS scientists and medical imaging physicists can be great assets for a successful clinical program. They should be well-versed in MR thermometry, image processing, MR and FUS physics, MRI safety, and other scientific aspects of FUS and its application to patient care. Furthermore, they should be available for consultation during a case if troubleshooting of technical factors is necessary.

Qualifications of MRgFUS Technologists

The MRgHIFU technologist should have a background in MRI and, when appropriate, vendor training. Observed learning including a review of the principles of FUS technology, technical aspects of the FUS systems, daily quality assurance, patient preparation, data acquisition, operational routines, technical troubleshooting, artifact identification, prevention, and elimination. The technologists should be a standard part of the MRgHIFU multidisciplinary team.

Clinical Workflow of MRgHIFU Patients

Evaluating the patient for MRgHIFU candidacy is a multidisciplinary process that begins with evaluation of the patient by a movement disorders neurologist. Once they establish that the patient's diagnosis is appropriate and that symptoms have become medication-refractory, interventional options are discussed. These options include MRgHIFU or DBS. If the patient and clinician decide to proceed with FUS, a referral is made to a provider trained in MRgHIFU. The preprocedural clinic visit includes a neurologic examination, review of prior imaging, discussion of the procedure day, including risks, benefits, and alternate treatment options. Although there have been no recent reports of intracranial hemorrhage after MRgHIFU, at several of the authors institutions, patients are instructed to hold anticoagulants and antiplatelets 7 days before and 2−3 days following the procedure. However, some institutions no longer require patients to hold anticoagulation medications before MRgHIFU.[35] Medications to treat tremor are commonly held overnight.

MRgHIFU Clinic

It is highly recommended to have a weekly clinic or be actively involved in a multidisciplinary movement disorder group in which patients are evaluated regularly. Evaluations include a complete history and neurologic examination, a review of medications taken, and a discussion on alternate treatment options (other medications, DBS). It is important to be well-versed in alternate treatment options, medications commonly used to treat these diseases, adverse effects from these medications, and other tremor conditions that can present with tremor but not be ET or tremor-dominant Parkinson disease. The neurologic examination should include a movement disorders examination, which can be learned through active participation in a movement disorder neurology clinic. Critically, it is essential that all patients undergo a formal evaluation by a movement disorders neurologist to evaluate their candidacy for MRgHIFU. Follow-up protocol can vary from site to site, and many centers now advocate for follow-up as needed.

IMAGING

Head CT without Contrast

It is critical to ensure that an appropriate protocol is used for a planning head CT, which requires full coverage of the vertex, use of a specific reconstruction kernel, and specific reformats. The SDR is calculated from this examination and represents the ratio (in Hounsfield units) of cortical-to-cancellous bone in the calvaria. The SDR can range from 0 to 1, and a value >0.40 predicts improved ultrasound skull penetrance. In some regions of the country, an SDR value of ≥ 0.40 is also required for Centers for Medicare & Medicaid Services reimbursement. Low-SDR skulls cause greater reflection and attenuation of ultrasound, which requires the use of higher-energy levels or longer duration of energy exposure to reach ablative temperatures in the brain. This requirement can result in increased patient discomfort during the procedure, larger lesions with substantially more edema, incomplete treatments, and potentially more adverse effects due to edema or lesion expansion. The treatment team reviews the head CT and SDR before the multidisciplinary discussion of the patient's treatment options. Other skull characteristics beyond the SDR can also impact the likelihood of treatment success or difficulty, in particular the presence of hyperostosis and skull roundness and skull thickness.[36]

Treatment-Planning Brain MRI

A treatment-planning MRI is highly recommended. Planning MR imaging should include an MR of the brain with and without contrast and include DWI, T1, T2, FLAIR, SWI, and postcontrast T1 sequences. Furthermore, additional advanced imaging sequences including DTI and white-matter-nulled sequences (eg, fast gray matter acquisition T1 inversion recovery [FGATIR]) can be considered. Task-based fMRI may also be appropriate (Figure).[16,18]

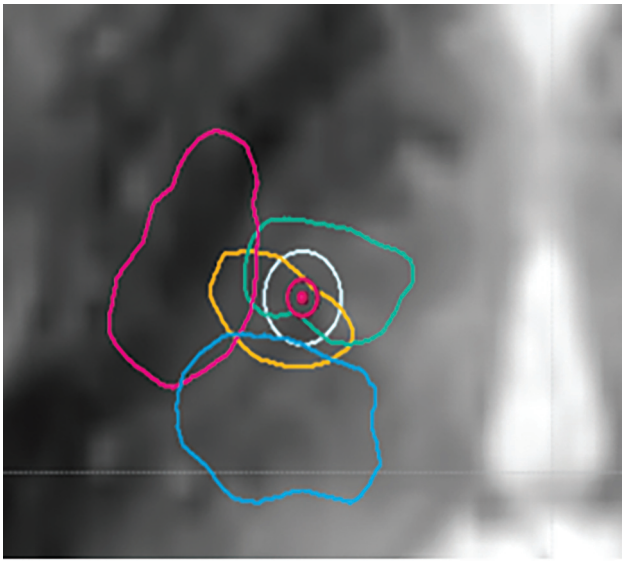

FIGURE Four-tract tractography. Axial FGATIR MR image through the level of the thalamus shows the relative position of the 4 tracts: corticospinal tract (red), ML (blue), dDRTT (yellow), dDRTT (green).

Tremor Treatment-Planning

Treatment-planning can be performed without advanced imaging sequences (DTI, FGATIR) for indirect targeting or with advanced image sequences for direct targeting. As noted, it is the authors' opinion that preplanning with advanced imaging improves clinical outcomes.[16-18]

Indirect Targeting for the Treatment of Tremor. After the anterior commissure (AC), posterior commissure (PC), and midline are identified, indirect treatment-planning is performed by marking targets at the standard indirect target coordinates (lateral-medial: 14 mm lateral to the midcommissural point or 10.5−11 mm lateral from the wall of the third ventricle; AC-PC: 25% of the AC-PC distance anterior to the PC; superior-inferior: 1.5−2 mm superior to the AC-PC line). Adjustments may be made on the basis of patient anatomy; for example, measurement from the lateral wall of the third ventricle may be preferred over the midline measurement in patients with an enlarged third ventricle.

Advanced Multiparametric Imaging-Based Targeting for the Treatment of Tremor. *Tractography-Guided Tremor Treatment.* DTI can be performed in several fiber-tracking software packages.[16-18,21] The diffusion tensor images are rigidly coregistered to both structural FGATIR and 3D TSE T2-weighted sequences. Coregistration and distortion-correction of DTI and anatomic images are performed. A corrected diffusion tensor image set is generated and used for fiber-tracking. Four fiber bundles are tracked, the nondecussating dentatorubrothalamic tract (ndDRTT) and decussating dentatorubrothalamic tract (dDRTT), corticospinal tract, and medial lemniscus (ML).[16,18] Although white-matter-nulled sequences cannot delineate the relative contributions of the decussating and ndDRTT fibers, the DTI-based fiber bundles can be anatomically confirmed using structural FGATIR images.

Exact practices vary from one institution to another. Some of the authors adhere to the following targeting protocol: After identifying the AC, PC, and midline, indirect coordinates are placed. Adjustments to the target are then made to target the posterior confluence of the dDRTT and ndDRTT, while avoiding the corticospinal tract and ML. The posterior margin is selected because the dDRTT has 2 arms: The more anterior arm inserts into the ventralis oralis posterior, and the more posterior arm enters the VIM. The ndDRTT enters only the VIM. The treatment coordinates and fiber bundles are overlaid on a coronal FGATIR image. The dentatorubrothalamic tracts can be easily identified on the coronal FGATIR images as a diagonal band extending from the red nucleus to the corticospinal tract. The fiber bundles and trajectory are overlaid on the structural FGATIR to confirm and finalize the targets. Fiber tracts can be imported into the treatment console for real-time visualization during ablation.

PROCEDURAL DAY WORKFLOW

Consent and Preprocedural Neurologic Assessment

The patient first gives informed consent to the treating physician, and a complete neurologic examination, including a movement disorders examination, is performed by the treatment team. This step is critical to establish a baseline for comparison of intraprocedural and postprocedural treatment responses (tremor testing) and adverse effects (somatomotor, somatosensory, and ataxia). The posture eliciting the greatest and consistent level of tremor should be determined. Normally, this may be with the patient holding the arms in a winged position.

The preoperative and postoperative neurologic assessment consists of speech evaluation, writing (specifically line drawing and Archimedes spirals), and tests of coordination (finger to nose, heel to shin, finger chase, alternating movement). The gait assessment evaluates ataxia with tandem walking and stance in stationary and tandem positions. Truncal ataxia is further assessed by having patients sit with arms outstretched and eyes closed without foot support. It is likely that the movement disorder examination findings will worsen in the event that tremor medications are withheld.

Medications

Although moderate sedative agents and general anesthesia agents can be used, these are generally avoided because they can substantially diminish the tremor before treatment and confound feedback during the procedure. Acetaminophen (1000 mg), fentanyl (25 mcg), ondansetron (4 mg), and dexamethasone (4 mg) can be given as needed.

Frame Placement

The goal of frame placement for the FUS procedure is to place the frame as low as safely possible to permit the use of the maximal number of elements. After placing the frame on the patient's head, marking pin sites, and sterilizing the skin in standard practice, we administer subcutaneous lidocaine at each site. MRI-compatible pins are then used to secure the headframe.

Water Membrane Placement

Chilled, degassed, deionized water is continuously circulated over the patient's scalp to keep the skull and scalp cool during the

procedure. Thus, a water membrane must be placed to create a watertight seal around the patient's scalp and frame.

Real-Time MRI Scan and HIFU Transducer Setup

The patient is placed on the MRI scanner, and the head frame posts are locked into brackets associated with the HIFU transducer. A 3D sagittal T1 or T2 sequence is then performed or MPRAGE if there are specific absorption rate limitations such as those related to an implanted device. The AC and PC are identified, and the images are reformatted in 3 planes. The midline is marked on a coronal image. If the indirect targeting method is to be used, the intraoperative MRI is registered to the head CT for ultrasound phase-correction; then, the indirect target tool can be used to place an initial target. If preoperative MRI examinations are being used, the intraoperative MRI is first registered to the treatment plan. It is critical that the AC, PC, and midline are marked to match the treatment-planning MRI.

Marking the first target will give the user the distance between the natural focus of the transducer and the target in all 3 directions. The natural focus of the transducer is manually adjusted until this distance is <1 mm in all 3 planes. A movement-detection scan is performed to ensure that the patient has not moved since the intraoperative scan. Fiducials are then placed on movement-detection images so that if the patient moves subsequently, the direction of motion can be identified.

Intraoperative Planning

During the planning stage of treatment, several additional steps are performed, including identifying and marking off intracranial calcifications and water membrane folds, to avoid transmitting energy through these areas. The system will calculate the number of active elements, the skull area, the distribution of the SDR, and a thermal dose-prediction based on usable ultrasound elements for assessment by the treating physician.

TREATMENT

Alignment Sonications

First, low-intensity sonications are delivered to the target to verify that the transducer and planned target are aligned. At the conclusion of alignment, a neurologic assessment is performed to evaluate tremor response and adverse effects. Effective targeting will result in temporary tremor reduction. Adverse effects can include numbness and tingling in the face or mouth or fingertips, weakness in the upper or lower extremity, and dysmetria.

Therapeutic Sonications.

If the patient demonstrates a tremor response without adverse effects after the alignment sonications, high-intensity FUS is delivered until a target thermal dose of 55°C to 60°C is reached, typically 57°C. The transducer is then positioned to the second target, and the process is repeated.

Conditions for Intraoperative Target Movements

General Approach. The initial target may be modified depending on the patient's response to individual sonications. Some examples are given below, but in general, the treatment team should consider the overall 3D anatomy of the thalamus, tracts, and the specific clinical scenario. The impact of any movement on the target relationship to white matter tracts should be considered on multiplanar images.

Poor Tremor Response in the Absence of Adverse Effects. If there is no tremor response when achieving a thermal dose of 50°C to 53°C, it is likely the target is suboptimal. Independent of the targeting methodology being used, the first consideration should be a posterior or lateral movement.

Sensory Adverse Effects. If a patient develops numbness, it is likely that the target is too posterior (ie, ventralis caudalis nucleus, somatosensory tracts). The target should be moved anteriorly before delivering a thermal ablative dose. Adverse effects encountered with subablative doses usually resolve within a few minutes.

Motor Adverse Effects. If the patient develops weakness, it is likely that the target is too lateral or inferior, affecting the corticospinal tract. The first consideration should be a medial or superior movement.

Nausea. During MRgHIFU, patients may experience nausea. Although preoperative medications (see medications) can alleviate it, the treatment team should have additional doses available if intraoperative nausea is identified. Suction should also be readily available to avoid complications such as aspiration.

Postoperative Adverse Effects

Common adverse effects that may develop following MRgHIFU include paresthesia around the mouth or within the fingertips, a subjective feeling of imbalance, ataxia, weakness, dysphagia, and dysarthria. One-third of patients develop a temporary subjective imbalance that typically resolves in 3–4 weeks. The possibility of permanent gait impairment should be discussed with patients with a pre-existing history of joint replacement surgery or peripheral neuopathy.[37] Some of the authors prescribe patients a short course of steroids to be taken in the event of edema-related adverse effects.

Postoperative MR Imaging Findings

Following the procedure, MR imaging can reveal a core of restricted diffusion at the center of the lesion. On T2-weighted images, the lesion can be further characterized into concentric zones.[38] Zone 1 is at the central core of reduced diffusion that reflects coagulative necrosis. Zone 2 is the surrounding T2 hyperintensity indicating cytotoxic edema. Zone 3 often does not present until 24 hours after the procedure and reflects vasogenic edema. It usually resolves in 1 week. SWI may identify small amounts of blood products, but no hemorrhage is identified within the lesion immediately after the procedure. At most centers, patients are often scanned immediately postprocedure or within the first few days of the procedure and then again at 3 months and 1 year. In our practices, we have modified this schedule to include imaging patients at 9 months in preparation for treating the contralateral side.

Discharge Protocol

MRgHIFU is an outpatient procedure. Patients typically are discharged home within 1–2 hours following completion of the procedure.

BILLING AND REIMBURSEMENT

The Centers for Medicare & Medicaid Services has authorized and implemented a CPT code for MRgHIFU for ET and tremor-dominant PD: 0398T. By means of this code, clinical transcranial MRgHIFU is a well-established reimbursable procedure by most insurers and is accepted as a standard of care in treating medication-refractory ET and tremor-dominant PD.[39] This category 3 code was recently approved by CPT to be changed to a category 1 code, implying that the Centers for Medicare & Medicaid Services must give it a value and establish further increasing potential for reimbursement.

QUALITY IMPROVEMENT AND QUALITY CONTROL

A critical component of establishing and maintaining a high-quality clinical transcranial MRgHIFU program is to invest in the training and education of all team members. For example, vendor training programs in which treating teams for new sites visit established sites to observe treatments can provide valuable teaching, experience, and support for all parties involved. Such programs foster intersite collaboration, which can, in turn, lead to technologic advances and improvement.

Additionally, a high-quality program needs regular and consistent quality control measures. Developing a clear protocol for assessing the technical quality of the system is vital. A common approach used by many treating sites involves performing a daily quality assurance at the start of each procedure day. The daily quality assurance ensures that the system is functioning as expected before being exposed to a patient. Thus, issues and problems can be identified before they risk harming a patient.

EXPERIMENTAL AND EMERGING APPLICATIONS

LIFU is used to describe the application of FUS energy in a range that does not result in significant tissue heating. LIFU is emerging as a new technology for noninvasively interacting with brain tissue that results in a variety of physiologic effects mediated by nonthermal mechanical stimulation.

BBB Opening

Abundant literature shows that FUS in combination with IV injected microbubbles allows a safe, targeted, and reversible BBB opening in both animal models and humans.[4-7,9-13,40] IV injected microbubbles oscillate when exposed to LIFU. Such stable cavitation can result in temporary BBB disruption through the opening of pores in the cell membrane, altering the integrity of interendothelial tight junctions and increasing transcellular vesicular trafficking. Such a BBB opening can be assessed on MRI with the use of IV gadolinium. Broadly speaking, this transcranial MRgFUS application has 2 main uses: liquid biopsy and therapeutic delivery. Currently low-intensity applications require a completely separate low-frequency MRgFUS unit. While there is substantial crossover in the operations, there are also key differences that require specialized training.

Liquid Biopsy of Glioma. Personalized treatment-planning requires knowledge of the somatic mutations specific to a particular tumor. However, surgical biopsy of gliomas is an invasive procedure, which is not always safe, feasible, or repeatable. Circulating tumor DNA can provide cancer-specific somatic mutation data. Unfortunately, an intact BBB often limits the release of circulating tumor DNA into the peripheral blood, thus making collection and detection challenging. A targeted FUS-mediated BBB opening, however, has been shown to increase the concentration of brain tumor circulating tumor DNA in the peripheral blood.[41] Thus, circulating tumor DNA can more easily be collected and then used to determine genetic mutations that can potentially guide prognostic and therapeutic considerations. In addition to being minimally invasive, such a liquid biopsy approach overcomes tissue-sampling bias and can target specific anatomic ROIs. Such an approach may one day allow discrimination of pseudoprogression from true disease progression.

Therapeutic Effect and Improved Delivery for Alzheimer and Other Neurodegenerative Diseases. Clinical trials are underway studying the safety and efficacy of a FUS-guided BBB opening in patients with Alzheimer disease (NCT03671889).[40,42] A preprocedural amyloid PET scan is performed to identify the specific regions of amyloid in a particular patient. These brain regions are then targeted for a BBB opening. The BBB opening procedure is repeated several times, followed by an amyloid PET to determine if there has been a reduction in amyloid levels. Blood is also collected before and at various time points after the procedure to determine if the BBB opening released amyloid into the blood stream. The patient undergoes serial cognitive and neuropsychiatric examinations to evaluate changes related to baseline.

Brain Metastases. Steady improvements in the overall survival of patients with oligometastatic disease has been achieved for many cancers using targeted therapies and monoclonal antibodies. However, limited efficacy has been observed in the treatment of brain metastases secondary to poor brain penetration of most therapeutic agents because of the limited ability to cross the BBB. Although small (<400 Da), relatively lipophilic molecules can cross the BBB, >90% of small molecules and nearly all large molecules (such as antibodies) are unable to cross it. Temporary disruption of the BBB using FUS in combination with microbubbles can be used to augment therapeutic delivery and potentially improve treatment response. A current clinical trial is combining a FUS-mediated BBB opening with systemic delivery of pembrolizumab to patients with brain metastases secondary to non-small-cell lung carcinoma.

Sonodynamic Therapy. Sonodynamic therapy involves the administration of a "sonosensitizer," ie, a chemical agent that, when exposed to LIFU, results in the generation of reactive oxygen species and cytotoxicity.[43] While similar in mechanism to photodynamic therapy, FUS energy used for sonodynamic therapy can penetrate deeper into tissue, thus enabling enhanced treatment of deep-seated tumors. Multiple clinical trials are currently assessing the efficacy of 5-aminolevulinic acid, a sonosensitizer that accumulates in tumor cells, used in conjunction with LIFU to treat glioblastomas in adults and diffuse midline gliomas in children.

Glioma. The ability to cross the BBB is an important determinant in the efficacy of chemotherapeutic agents used for treatment of gliomas. Unfortunately, most agents are large, hydrophilic, and

thus ineffective due to limited brain penetration. A BBB opening achieved through MRgFUS has been shown to increase the concentration of some of these drugs (such as etoposide) in the brain and improve survival benefits in preclinical trials.[44] This result has opened a new dimension in the treatment of gliomas, allowing the use of drugs that were not previously available. Additionally, preclinical trials have also shown how MRgFUS can increase the concentration of temozolomide in the brain, a standard-of-care drug that effectively crosses the BBB, thus leading to improved survival,[45,46] Such enhanced drug delivery will theoretically allow the use of lower doses of chemotherapeutic agents, resulting in reduced systemic adverse effects. There are several clinical trials underway currently testing the efficacy of drugs like carboplatin and bevacizumab in glioblastoma and doxorubicin and panobinostat in diffuse infiltrative pontine glioma (NCT04440358, NCT04446416, NCT05630209, NCT04804709). The authors of this article are also involved in evaluating the efficacy of pembrolizumab in recurrent glioblastoma.

LIFU Neuromodulation

LIFU neuromodulation is being investigated as a potential treatment for depression, addiction, and other neuropsychiatric conditions. The major differences between HIFU and LIFU are related to variations in parameters of acoustic frequency, acoustic intensity, pulse-repetition frequency, on-off duty cycle, and sonication duration. The net effect of LIFU treatment parameters is having lower tissue-energy deposition than HIFU, and the tissue changes related to LIFU are thought to be transient in comparison with the more permanent changes of HIFU. In animal models, LIFU has been demonstrated to variously stimulate or suppress neural activity, depending on the specific parameters used. Mechanisms of neural activation and suppression are poorly understood and are areas of ongoing investigation. Despite the uncertain mechanism of action, LIFU neuromodulation is actively being explored as a potential intervention in a variety of human neuropsychiatric conditions, including depression and addiction.[47] For example, a National Institutes of Health–sponsored clinical trial is underway studying LIFU to the anterior insula to modulate the drug cue response in cocaine addiction. One practical advantage of LIFU is the lower profile of the equipment that could eventually allow in-office treatments by practitioners.

CONCLUSIONS

Transcranial MRgFUS provides a multifaceted, noninvasive tool for diagnosing and treating diseases of the brain. Although MRgHIFU is currently FDA-approved only for treatment of ET and PD, there are several clinical trials underway using LIFU for both diagnostic and targeted drug-delivery purposes. Radiologists are specifically trained to perform image-guided procedures and neuroradiologists can advance the therapeutic effectiveness of MRgFUS by pairing it with advanced structural, functional, and metabolic imaging. Realizing the full potential of transcranial FUS will depend on the neuroradiologist's ability to lead and collaborate in a multidisciplinary team and integrate deep-seated background in imaging science with the anatomic, physiologic, and functional data to develop a clinical practice of image-guided medicine.

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