Initial experience with magnetic resonance–guided focused ultrasound stereotactic surgery for central brain lesions in young adults

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OBJECTIVE Magnetic resonance–guided focused ultrasound (MRgFUS) is an incisionless procedure capable of thermoablation through the focus of multiple acoustic beams. Although MRgFUS is currently approved for the treatment of tremor in adults, its safety and feasibility profile for intracranial lesions in the pediatric and young adult population remains unknown.

METHODS The long-term outcomes of a prospective single-center, single-arm trial of MRgFUS at Nicklaus Children’s Hospital in Miami, Florida, are presented. Patients 15–22 years of age with centrally located lesions were recruited, clinically consistent with WHO grade I tumors that require surgical intervention. This cohort consisted of 4 patients with hypothalamic hamartoma (HH), and 1 patient with tuberous sclerosis complex harboring a subependymal giant cell astrocytoma (SEGA).

RESULTS In each case, high-intensity FUS was used to target the intracranial lesion. Real-time MRI was used to monitor the thermoablations. Primary outcomes of interest were tolerability, feasibility, and safety of FUS. The radiographic ablation volume on intra- and postoperative MRI was also assessed. All 5 patients tolerated the procedure without any complications. Successful thermoablation was achieved in 4 of the 5 cases; the calcified SEGA was undertreated due to intratumor calcification, which prevented attainment of the target ablation temperature. The HHs underwent target tissue thermoablations that led to MR signal changes at the treatment site. For the patients harboring HHs, FUS thermoablations occurred without procedure-related complications and led to improvement in seizure control or hypothalamic hyperphagia. All 5 patients were discharged home on postoperative day 1 or 2, without any readmissions. There were no cases of hemorrhage, electrolyte derangement, endocrinopathy, or new neurological deficit in this cohort.

CONCLUSIONS This experience demonstrates that FUS thermoablation of centrally located brain lesions in adolescents and young adults can be performed safely and that it provides therapeutic benefit for associated symptoms.

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KEYWORDS ablation; brain tumor; epilepsy; focused ultrasound; hypothalamic hamartoma; pediatric; functional neurosurgery

TRANSCRANIAL magnetic resonance–guided focused ultrasound (MRgFUS) is capable of conformal target thermoablation without a skin or scalp incision or passing instruments through the brain.1,2 FUS was approved in 2016 by the US FDA for focal thalamotomy to treat refractory essential tremor in adults.3–6 Under an Investigational Device Exemption (no. GI60189), our group conducted a pilot study aimed at treating pediatric and young adult brain lesions using the InSightec Exablate 4000 MRgFUS device.

For appropriate candidates, an FUS ablation procedure has many possible advantages over open surgery or MR-guided laser interstitial thermal therapy (LITT). FUS may be a favorable alternative to stereotactic radiosurgery

ABBREVIATIONS ASM = antiseizure medication; FUS = focused ultrasound; HH = hypothalamic hamartoma; ICU = intensive care unit; LITT = laser interstitial thermal therapy; MRgFUS = magnetic resonance–guided FUS; POD = postoperative day; SEGA = subependymal giant cell astrocytoma; TSC = tuberous sclerosis complex.

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because it does not use ionizing radiation, which conveys advantages, especially in the pediatric population. Additionally, FUS is performed using real-time MR thermography monitoring of the thermoablation process that leads to immediate radiographic changes and clinical results. The current intracranial application of FUS is limited to deep, central brain lesions located within the treatment envelope, where acoustic beams can be optimally focused.7–9 In this pilot study, we aim to demonstrate the safety and feasibility of FUS in children as young as 8 years of age. Patients were recruited in incrementally decreasing age groups to demonstrate safety in young adults and adolescents prior to treating younger children, as agreed upon by the protocol with the US FDA. This case series of 5 patients, the first of whom was treated in 2017, represents our first efforts in the treatment of centrally located benign brain lesions in adolescents and young adults between 15 and 22 years of age. Abstracts of the first 3 cases have been previously presented in conferences.10,11

Methods

Study Population

This study was approved by the WCG IRB. Eligible patients were 8–22 years of age, with a minimum head circumference of 52 cm, who required intervention for a benign brain tumor consistent with WHO grade I pathology. Patients with known or radiographic features of malignant tumors, or lesions that required histopathology confirmation, were excluded. Patients with contraindications to MRI, or who were unable to undergo general anesthesia, were excluded. Participants were recruited in tiers of descending age groups to ensure that the safety profile of the procedure was appraised in a gradual and progressive fashion. Previous craniotomy or surgical intervention was not an exclusion criterion. Adult patients provided informed consent to participate. A full description of inclusion and exclusion criteria can be found online (https://clinicaltrials.gov/ct2/show/NCT03028246).

Outcome Variables

The primary outcomes of the study were FUS treatment safety and feasibility, in addition to radiographic changes in tumor volume in the postoperative period up to 12 months following the procedure. The incidence of treatment-related adverse events was noted, including medical, neurological, endocrinological, and radiographic outcomes. Secondary outcomes focused on the patient’s general physical profile, changes in neurological examination, and visual field testing, in addition to physician and patient impression of global change following FUS.

Surgical Procedure

We followed a modified surgical method, described in detail elsewhere.15 Briefly, after induction of general anesthesia, the patient was intubated and intravenous dexamethasone was administered. For patients with epilepsy, the preoperative antiseizure regimen was continued. A Foley catheter and leads for pulse oximetry, core body temperature, and cardiac monitoring were placed. The scalp was razor-shaved, prepped with povidone-iodine, and infused with local anesthetic at the pin sites for placement of a customized CRW frame (Integra LifeSciences). The patient was transported to the MRI machine (General Electric Discovery MR750w 3.0 T) and the head frame was secured to the phased-array device (InSightec Exablate 4000). Cooled, degassed water acoustically coupled the transducer array to the patient’s scalp. A series of high-resolution FLAIR and T2-weighted sequences were obtained and fused to previously acquired CT bone window images. These images were then used for phase correction of each individual operating piezoelectric driver within the 30-cm-diameter, 1024-element hemispherical phased-array ultrasound transducer attached to a four-axis positioner mounted on a modified GE Healthcare patient table. Elements for which the acoustic path crossed a density interface (i.e., frontal air sinuses, intracranial calcifications, or previous burr holes) were turned off to reduce off-target heating. The primary carrier frequency of the system was 650 kHz. Acoustic microphones housed in the transducer array and MR phase thermography were used to detect cavitation events and monitor the thermoablations, respectively. Tracking coils embedded within the transducer housing detected device array movement within the MR space. Image coregistration software detected any movement of the head relative to the device immediately before each sonication event. These safety features reduced the chance of off-target tissue damage.

A series of low-energy sonications using less than 200 W to raise tissue to 40°–45°C were used to detect and, if necessary, correct the alignment of the sonication centroid in 3 cardinal imaging planes (axial, coronal, and sagittal). Once the target and low-energy coalignment were completed, high-energy sonications with acoustic power up to 1500 W were undertaken to create a series of overlapping thermoablations to cover the region of interest. Goal peak temperature at target was 56°–60°C, a range known to create nearly instantaneous tissue coagulation and necrosis13 but reduce the occurrence of inertial cavitation.11

Following FUS ablation, the patient was monitored in the intensive care unit (ICU) for neurological assessment and routine biochemical bloodwork. MRI was performed at the time of FUS and at 3-, 6-, and 12-month intervals postoperatively. As indicated, endocrine laboratory work was performed preoperatively and at 6- and 12-month intervals following FUS ablation.

Results

A total of 5 patients (3 female, 2 male) between 15 and 22 years of age were recruited as of November 2019 and comprise this proof-of-concept trial (Table 1). All patients required treatment of central lesions that had either failed prior resection (3/5) or for which patients declined resection (2/5). Four patients had hypothalamic hamartoma (HH), and 1 patient had a subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC). All patients underwent uncomplicated FUS procedures without new endocrine, electrolyte, metabolic, or neurological sequelae. All 5 patients were discharged home on postoperative day (POD) 1–2 on a 5-day taper of oral dexamethasone with ranitidine. There were no
significant adverse events or readmissions to the hospital. One patient experienced a minor drug reaction, manifested as rash and itching, which responded to antihistamine treatment. The length of postoperative clinical follow-up ranged between 13 and 43 months (mean ± SD 24.8 ± 12.4 months, median 24 months). Radiographically, the patients underwent immediate postoperative MRI, followed by routine imaging at 3, 6, and 12 months postoperatively (Fig. 1).

**Patient 1: Small Residual Hamartoma**

The first patient of the series underwent FUS thermoablation of an HH in early March of 2017. This patient was a 21-year-old, right-handed woman with a history of gelastic seizures and precocious puberty. She had previously undergone a right frontal transventricular endoscopic resection of a Delalande and Fohlen type IIIA HH at age 16 years. She was initially seizure-free for 2 years, but then relapsed and experienced almost daily seizures despite an augmented antiseizure regimen consisting of clobazam, topiramate, and lamotrigine. She was also maintained on risperidone for oppositional defiant disorder. The gelastic events did not generalize. MRI revealed a small remnant of the lesion along the left hypothalamic wall. The HH and its vertical gliotic attachment plane immediately adjacent to the hypothalamus were targeted. After the low-energy

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**TABLE 1. Description of patient demographics, pathologic substrates, clinical variables, and treatment details**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patient No.</th>
<th>Mean ± SD (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs), sex</td>
<td>1 2 3 4 5</td>
<td>21, F 22, F 18, M 19, F 19, M 19.2 ± 2.7 (15–22)</td>
</tr>
<tr>
<td>Pathologic substrate</td>
<td></td>
<td>HH HH HH HH SEGA</td>
</tr>
<tr>
<td>Primary concern</td>
<td></td>
<td>Seizures, precocious puberty, neurodevelopmental delay, psychiatric disorder NOS (agression, suicide attempts, self-mutilation), Seizures, neurodevelopmental delay, hypothalamic obesity w/ BMI 44 kg/m², Seizures, precocious puberty, severe autism, neurodevelopmental delay, Hypothalamic obesity w/ BMI 31 kg/m², hyperphagia, Growth of SEGA despite mTOR inhibitor (everolimus) therapy; no seizures or cognitive issues</td>
</tr>
<tr>
<td>Prior interventions</td>
<td></td>
<td>Endoscopic rt-frontal transventricular resection of lt-sided HH, LITT, Gamma Knife radiosurgery, LITT, None, None</td>
</tr>
<tr>
<td>Target dimensions/description</td>
<td></td>
<td>4.2 × 2.1 × 3.3 mm; lt-sided HH remnant, 11.8 × 11.5 × 12.2 mm; lt-sided isthmus of HH, 18.0 × 18.0 × 17.0 mm; rt-sided isthmus of HH, 10.6 × 10.3 × 7.3 mm; lt-sided stalk of pedunculated HH, 18.5 × 10.5 × 13.5 mm; rt frontal SEGA</td>
</tr>
<tr>
<td>Treated volume</td>
<td></td>
<td>6.7 × 5.2 × 6.7 mm; 0.12 cm³, 6.0 × 2.5 × 2.3 mm; 0.04 cm³, 10.0 × 4.0 × 6.0 mm; 0.24 cm³, 5.9 × 3.9 × 4.3 mm; 0.05 cm³, NA*</td>
</tr>
<tr>
<td>Treatment duration, sec</td>
<td></td>
<td>13 35 31 41 39 31.8 ± 11.2 (13–41)</td>
</tr>
<tr>
<td>Max temp, °C</td>
<td></td>
<td>54 59 54 50 56 54.6 ± 3.3 (50–59)</td>
</tr>
<tr>
<td>Max energy, kJ</td>
<td></td>
<td>14 42 24 50 50 36 ± 16.2 (14–50)</td>
</tr>
<tr>
<td>Length of FU, mos</td>
<td></td>
<td>43 30 24 14 13 24.8 ± 12.4 (13–43)</td>
</tr>
<tr>
<td>Changes to primary concern</td>
<td></td>
<td>Seizure-free (while on ASMs), 95% seizure reduction, from 30 per wk to 1 every 2 mos, 90% seizure reduction, from 4–5 per wk to 1 every 3 mos, 13 kg weight loss, sustained &amp; complete resolution of hyperphagia, Enlargement of SEGA on follow-up MRI 13 mos after FUS</td>
</tr>
<tr>
<td>Physiological function</td>
<td></td>
<td>Hypothalamic dysfunction, hyperprolactinemia w/ galactorrhea, no post-FUS changes, Hypothalamic dysfunction &amp; obesity, no post-FUS changes, Hypothalamic dysfunction, no post-FUS changes, No pre- or post-FUS endocrine or electrolyte abnormalities, No pre- or post-FUS endocrine or electrolyte abnormalities</td>
</tr>
<tr>
<td>Changes to general behavior</td>
<td></td>
<td>Graduated from school &amp; off risperidone, no subjective behavioral improvement, Improved: better mood &amp; quality of life, Improved: increased focus, concentration, responding more to his primary caregiver, Improved: less antagonistic, better mood &amp; quality of life, Unchanged</td>
</tr>
</tbody>
</table>

FU = follow-up; mTOR = mammalian target of rapamycin; NOS = not otherwise specified.

* No appreciable post-FUS treatment MRI changes seen.
sonication alignment steps, we initiated a series of high-energy sonications starting approximately 4–5 mm from the wall of the third ventricle and moved the target progressively more medially toward the ependymal surface. At 1.5 mm from the ventricular wall during the penultimate sonication, cavitation was acoustically detected and transducer power shutdown was automatically tripped. We then obtained T2- and susceptibility-weighted imaging sequences to evaluate our progress and exclude an obvious intraparenchymal or intraventricular hemorrhage. Diffusion restriction did not extend completely through the hamartoma-hypothalamic interface, but it was visualized within the more lateral gliotic tissue within the left hypothalamus, suggesting that lethal peak temperatures had been achieved. After waiting for the pre-prescribed cooling period, we completed one final sonication and
achieved a peak temperature of 54°C. Postoperative imaging revealed complete coverage of the hamartoma remnant and its gliotic attachment plane with no evidence of off-target restriction or hemorrhage (Fig. 1A–C).

The patient awoke uneventfully from anesthesia. As per the protocol, she spent 1 night in the ICU and was then transferred to the floor the next day and discharged on POD 2. Biochemistry panels revealed no postoperative abnormalities. She remained neurologically intact and seizure-free for 9 months following FUS. Endocrine investigations remained normal for 12 months following FUS. Despite counseling, the patient became pregnant shortly after her FUS procedure and self-discontinued her antiseizure medications (ASMs). While off medication, she did experience generalized seizures but gave birth to her child and resumed her ASMs without further seizures.

### Patient 3: Large Residual Hamartoma

Patient 3 was an 18-year-old man with developmental delay, severe autism, seizures, and precocious puberty attributed to HH (Fig. 1G–I). He had comorbid left perisylvian polymicrogyria and focal cortical dysplasia. He underwent Gamma Knife radiosurgery at 4 years of age, but unfortunately, his seizures worsened at the onset of puberty, and he experienced 4–5 seizures weekly. He was believed to be a good candidate for FUS thermoablation. The targeted area of interest was a narrow isthmus of tissue connecting the large right-sided pedunculated hamartoma, measuring approximately 4 mm in diameter and 10 mm in length. The initial sonication series aligned the heating centroid at the center of the isthmus. Once the center of heating was identified, incremental sonications were performed, raising the temperature to an average maximum of 54°C. This required a series of 14 progressive sonications with increasing total energy and time. Intraoperative imaging revealed no evidence of hemorrhage or off-target heating. The cooling periods between sonications grew increasingly longer and the last 3 sonications were separated by nearly 30 minutes to allow for scalp/skull cooling. The patient recovered well postoperatively and was discharged home on POD 1 with a steroid taper.

At the 3-month follow-up, the patient experienced a total of 3 hypnopompic seizures, which involved shoulder lifting and head drops. At 24 months following surgery, he continues to experience an overall 90% reduction in seizure frequency, having only 1 seizure every 3 months for the previous 18 months. No endocrinopathy was detected at 12 months following FUS. Subjectively, his primary caregiver reports a sustained improvement in his focus, concentration, and social interactions.

### Patient 5: Subependymal Giant Cell Astrocytoma

Patient 5 was a 19-year-old male university student

Patient 5 underwent lesioning therapy that created an average maximum temperature of 50°C over the 6 × 4 × 4-mm treatment area. There was appreciable hyperintensity on T2-weighted MRI sequences, corresponding with the region of targeted interest. After the procedure, she experienced minor flushing and a transient rash, believed to be a drug reaction that resolved with diphenhydramine. She was discharged home on POD 2 with a steroid taper.

Immediately following FUS, the patient experienced controlled appetite without effort or further behavioral modifications. She lost 13 kg within the first 6 months after FUS and has maintained her weight loss with a lower BMI of 26 kg/m² over the ensuing year. No endocrinopathy was detected at 12 months after FUS thermoablation. Furthermore, she has been able to enjoy improved self-esteem and social engagements, without any postprocedural complications.
with TSC diagnosed in childhood, and a slowly enlarging midline SEGA (Fig. 2). Although he experienced no seizures, he began receiving everolimus for increasing SEGA size. The patient disliked the medication’s side-effects and wished to discontinue medical treatment.

As per protocol, under general anesthesia, the patient’s head was affixed in a CRW frame, and multiple images were taken to align the sonication centroid. To avoid the largest calcification in the SEGA, the treatment centroid was positioned at the superior border of the tumor and an effort was made to increase both wattage and time to achieve 25,000 kJ. A series of sonications were performed, each interrupted by cavitation events, which resulted in maximal heating to an average temperature of 56°C for only a few seconds. Attempts to move the target treatment area to other regions of the SEGA were unsuccessful in preventing cavitation events and the procedure was stopped. Target ablation temperatures were not reached, resulting in undertreatment. There were no hemorrhage, diffusion restriction, or significant MRI signal changes in the SEGA. The patient recovered uneventfully and was discharged home on POD 2. Follow-up MRI at 13 months post-FUS treatment showed that the SEGA had grown slightly and the everolimus therapy was restarted. This case represents a treatment failure due to cavitation, presumably due to the microscopic calcification within the SEGA.

**Discussion**

Using the Insightec ExAblate 4000 FUS system, we treated centrally located benign intracranial lesions in 5 adolescent and young adult patients between 15 and 22 years of age (Fig. 3). Consistent with the study design, patients were recruited in tiers of descending age groups, and these 5 patients serve as the trial’s experience with the oldest cohort. The participants included 4 patients with HH and either seizures or hypothalamic hyperphagia, and 1 patient with a SEGA associated with TSC. The FUS procedure was well-tolerated by every patient. No significant adverse events related to the general anesthesia, CRW frame application, or FUS treatment were observed. There were no unexpected radiographic findings of abnor-

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**FIG. 2.** Patient 5. Preoperative CT (A) and MR (B) axial images demonstrating a SEGA with calcification. There was known undertreatment that produced no FLAIR signal changes during the FUS procedure (C). At 13 months following FUS, there was interval SEGA growth, demonstrating treatment failure (D).

**FIG. 3.** Illustration of the FUS procedure for patient 5, involving application of the custom CRW frame and silastic cap (A), planning and target of the pedunculated left-sided HH stalk for disconnection of the lesion (B), and intraoperative thermoablation of the target (C). The blue outline in panel B on the left corresponds to the red areas on the right, which represent the areas of actual heating. Copyright Shannon Zhang (panels A and C). Published with permission.
siently visualized on the immediate postoperative MRI. The signal changes on follow-up MRI performed months after FUS were less perceptible compared to the intraoperative imaging. Of note, 2 of our cases showed consistent T2 hyperintensity on follow-up MRI, while 2 other cases demonstrated resolution of the T2-weighted and FLAIR signal changes over time. In this limited sample, MR signal evolution does not appear to correlate with the clinical outcome of FUS. The seizure and hyperphagia benefits of FUS have persisted for all 4 successfully treated HH patients, despite regression in the MRI changes over the ensuing months after thermoablation.

Conclusions
The 5 cases illustrated in this paper demonstrate that FUS appears feasible and safe for the treatment of benign central intracranial lesions and contributes to the current literature on the role of FUS ablation for movement disorders, psychiatric conditions, and epilepsy. Further work is necessary to refine optimal patient selection criteria, determine the long-term therapeutic durability of this approach, and demonstrate safety in younger children. As part of the tiered age-group recruitment process, this pilot trial will continue to enroll progressively younger patients to definitively demonstrate the safety of FUS in children.

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Dedication
To the memory of our friend and colleague Dr. Sanjiv Bhatia (1958–2018). As Professor of Neurosurgery and Chief of Surgery at Nicklaus Children’s Hospital, Sanjiv had the inaugural honor to launch the initial sonication alignment sequences for our first patient on March 7, 2017. We miss him dearly.

References


Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Ragheb, Tierney, Alavian, Altman, Bhatia, Jayakar, Miller. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: Ragheb, Tierney, Alavian, Altman, Duchowny, Jayakar, Resnick, Wang, Miller. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Ragheb. Statistical analysis: Tierney, Alavian, Altman, Bhatia. Administrative/technical/material support: all authors. Study supervision: Ragheb, Tierney, Alavian, Altman, Bhatia, Miller.

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