Neuro-Oncology Advances
8(S4), vdaf019, 2026 | https://doi.org/10.1093/noajnl/vdaf019

Focused ultrasound in pediatric neuro-oncology: Current applications and future directions

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Abstract

Focused ultrasound (FUS) is a minimally invasive procedure with recent applications to patients with neurosurgical conditions. To date, most neuro-oncologic applications of FUS have occurred in the adult population to target high-grade gliomas and brain metastases. Its potential applications in pediatric neuro-oncology are only just starting to be realized. In children, high-intensity focused ultrasound (HIFU) has been used to treat benign intracranial lesions such as hypothalamic hamartomas and subependymal giant cell astrocytomas. Experience is now accruing with the use of low-intensity focused ultrasound (LIFU) in conjunction with systemically administered microbubbles in children to disrupt the blood–brain barrier (BBB) using magnetic resonance-guided focused ultrasound (MRgFUS). The pediatric brain tumor for which this application has been used is diffuse intrinsic pontine glioma (DIPG), a typically fatal neoplasm in children ages 5–7 years. Here, the history of FUS is reviewed, the principles of FUS therapy are delineated, and a discussion of its applications in neuro-oncology with a focus on pediatric neuro-oncology is provided. Innovations in MRgFUS are ushering a new and exciting era of minimally invasive treatments for children with brain tumors.

Key Points

- MRgFUS is a minimally invasive therapeutic strategy to treat patients with neurosurgical conditions including movement disorders, epilepsy, and brain tumors.
- High-intensity focused ultrasound (HIFU) creates an area of thermal ablation within a targeted tumor.
- Low-intensity focused ultrasound (LIFU) is used in conjunction with systemically administered microbubbles to enable chemotherapeutics to cross the blood–brain barrier.
- Both HIFU and LIFU are currently under investigation as potential treatments for pediatric brain tumors.

The field of pediatric neuro-oncology has advanced considerably in the past 2 decades. Whereas previously there were relatively few treatment options for children with malignant brain tumors, today, a variety of therapies can be implemented with the expectation of improved survival rates and lessened morbidity. This has been made possible for a few significant reasons. First, our understanding of pediatric brain tumors has changed significantly since the advent of detailed molecular characterization of these tumors and the identification of targeted drug therapies against specific pathways, mutations, and fusion anomalies. Second, progress has been made toward the realization and practice of minimally invasive neurosurgical procedures from which children recover more rapidly than before, and with fewer neurological consequences. Lastly, the concept of "incisionless" surgery has arisen through the promulgation of refined radiation

delivery strategies such as 3D-conformal radiation therapy, gamma-knife radiosurgery, and proton beam therapy. To add to these incision-free strategies, the exciting field of focused ultrasound (FUS) is quickly evolving to be a novel brain tumor treatment with expanding applications. In this review, we will discuss the history of FUS and its medical applications, the basic mechanisms of action of FUS, its current and extended applications, preliminary data obtained through clinical applications in pediatric neuro-oncology, and future possibilities of FUS with continued refinement and improvement in the technical side of the devices that are currently available.

History of Focused Ultrasound in Brain and Neuro-oncology Applications

The prospect of using FUS to ablate well-defined lesions in tissues was first proposed in 1942 by William Fry and colleagues at the Bioacoustic Research Laboratory at the University of Illinois. They developed a device that aligned 4 ultrasonic transducers to precisely target a lesion without injuring surrounding tissue.[1] This was followed by the first preclinical study in which FUS was used to produce circumscribed lesions in the brain.[2] In 1956, Lindstrom described the use of FUS, delivered through a small craniotomy, as an alternative to traditional surgical lobotomy in patients with carcinomatosis and cancer-related pain.[3] Shortly thereafter, FUS was investigated in the treatment of movement disorders, including Parkinson's disease and hyperkinetic disorders.[4,5] Heimberger was the first to use FUS to treat a patient with brain cancer.[6] In 1991, Guthkelch and Hynynen reported on a phase I clinical trial in which FUS hyperthermia was used via craniectomy to treat patients with malignant brain tumors.[7]

Tandem advances in FUS technology and the development of magnetic resonance imaging (MRI) led to increasingly precise applications of the procedure, enabling real-time visualization and monitoring of targeted brain regions. This approach, termed magnetic resonance-guided focused ultrasound (MRgFUS), not only permitted focal thermal ablation of specific brain regions at high frequencies[8–11] but at lower frequencies, with concurrent systemic administration of microbubbles, was discovered to temporarily disrupt the blood–brain barrier (BBB).[10,12–15] This transient disruption enabled the crossing of large molecules, such as short interfering RNA and antibodies, into targeted brain regions.[16] The first commercial MRgFUS device to be approved by the United States Food and Drug Administration was the ExAblate 2000, developed by Insightec (Haifa, Israel), in 2004. The device was initially approved for the treatment of uterine fibroids, and in 2006 was subject to the first clinical investigation of high-intensity MRgFUS for thermal ablation of recurrent high-grade gliomas in adults.[17] High-intensity MRgFUS has also demonstrated utility in the treatment of non-neoplastic lesions in deep brain regions such as hypothalamic hamartomas, where traditional surgical approaches can be associated with significant morbidity.[18]

In addition to the thermoablative capabilities of high-intensity MRgFUS, the low-intensity configuration of the technology has also been used to enhance the delivery of chemotherapy to intracranial neoplasms. The feasibility of repeated and transient BBB disruption using pulsed ultrasound was shown in a phase I/II study delivering carboplatin across the BBB for patients with recurrent glioblastoma using an implantable ultrasound device (SonoCloud-1, Carthera Inc.).[19] In 2022, the first phase I clinical trial to investigate MRgFUS-mediated BBB disruption to augment treatment for pediatric diffuse intrinsic pontine glioma was initiated in Toronto, Canada (NCT016, NCT05615623). From this brief historical review, it is clear that great progress has been made in the usage of FUS in its various iterations into clinical trials for patients with brain tumors. Its applications to pediatric neuro-oncology, however, are only starting to be realized.

Principles of Focused Ultrasound Therapy

In recent decades, tandem advancements in neuroimaging and ultrasonic technology have enabled increasingly precise and minimally invasive applications of FUS in humans.[20] Broadly, FUS leverages mechanical, acoustic energy generated by piezoelectric ultrasonic transducers to exert effects at distant targets in the brain. This acoustic energy must travel through several layers of tissue (eg, skin, soft tissue, skull, etc.) before it reaches the desired intracranial target, and at each layer, some of this energy is reflected while the remainder continues to be transmitted. The use of phased-array ultrasonic transducers, comprised of many (typically > 1,000) individually controllable piezoelectric generators, can focus the delivery of acoustic energy to a specific brain region. The intrinsic characteristics of the ultrasonic waves generated by these transducers, specifically their oscillatory frequencies and wavelengths, affect how they propagate through biologic tissue.[21] Furthermore, the intensity of the energy delivered to the targeted tissue, defined as the power or energy per unit area of the sound wave, is dependent on the density and speed of sound of the medium it is traveling through and can be regulated by adjusting the angular frequency and amplitude of the generated ultrasonic waves. High-intensity focused ultrasound (HIFU) typically uses intensities > 1,000 W/cm^2,[22] whereas low-intensity focused ultrasound (LIFU) operates at much lower intensities, typically < 5 W/cm^2.[23]

Mechanistically, HIFU acts by inducing thermal and mechanical changes in the tissue. The acoustic energy of the FUS is absorbed and converted to thermal energy, elevating tissue temperatures up to 60–100 °C within seconds.[21] In neuronal tissue, temperatures greater than approximately 60 °C lead to protein denaturation, coagulative necrosis, and cell death, a process characterized as thermal ablation.[24–26] In addition to its thermal effects, HIFU can result in non-thermal mechanical effects in biological tissue. The most important of these is a process termed "cavitation," where ultrasonic energy induces the formation, oscillation, and potentially the collapse of microscopic gas bubbles within tissue. If these microbubbles collapse, known as "inertial" (or "transient") cavitation,

Table 1. Features of the Commercial FUS Devices That Are Currently Available

System	Manufacturer	Features
ExAblate	Insightec Inc. (Haifa, Israel)	• 1,024 independent elements in the phased-array transducer • Intraoperative thermometry for safety • Headframe required
UltraNav	Delsona (NewYork, US)	• Uses neuro-navigation and optical guidance • Headframe and skull pins not required
NaviFUS	NaviFUS (Taipei City, Taiwan)	• Active tracking of cavitation effects • Tested in clinical trials for adult GBM • Headframe and skull pins not required
TargetedFUS	Image-GuidedTherapy (Pessac, France)	• 256 independent elements in the phased-array transducer • Real-time thermometry and MR-imaging available
SonoCloud®	Carthera Inc. (Lyon, France)	• Implanted device • Activated via an externally controlled transdermal needle • Repeated treatments possible in short intervals

they can release a substantial amount of highly localized energy resulting in mechanical cell and tissue damage and the generation of reactive oxygen species leading to oxidative stress.[27] These effects must be carefully monitored and controlled during HIFU procedures to limit tissue damage only to lesional areas.

Cavitation caused by FUS can also be leveraged to transiently disrupt the BBB, typically using exogenous, systemically administered microbubbles. Precisely regulating the delivery of FUS can induce "stable" cavitation, whereby microbubbles oscillate at the same frequency as ultrasound waves.[28–30] At low intensities (LIFU), these bubbles expand and contract in a relatively controlled manner without collapsing, and the mechanical stress induced during this process allows for sonoporation—transient pores on cellular membranes for drug entry.[12,25,28,29,31] LIFU has also shown promise as a tool for neuromodulation in the treatment of various neurological disorders.[32] While the mechanisms for LIFU neuromodulation are currently unclear, hypotheses include changes in electrophysiological-mechanical coupling,[33] opening of mechanosensitive ion channels,[32,34] microtubule resonance,[35] and thermal effects.[36,37]

Factors such as acoustic shadowing, reverberation, and refraction that are normally considered in diagnostic ultrasound imaging also apply to therapeutic FUS. In particular, the proximity of the treatment region to the skull is an important variable. Reflection or refraction of the ultrasonic waves passing through the skull can lead to altered FUS strength and locations. In both HIFU and LIFU, the effects of repeated FUS sessions on neurocognitive and biological responses must also be accounted for. Studies have shown that FUS activates the auditory pathways, which in turn leads to changes in nonauditory regions through cross-modal mechanisms.[38,39] Drug dosing also needs to be taken into consideration as efficacy and uptake will vary due to the degree of BBB permeability, affected by individual variations in FUS effects due to factors such as skull anatomy. There is a shorter duration of drug activity as well; the BBB does not remain open permanently and FUS sessions are limited due to safety concerns. Some tumors may require continuous dosing for drug efficacy to be seen. In comparison to HIFU, mechanisms and biological changes in LIFU are not as well characterized. This may result in confounding and uncontrolled variables in LIFU treatments. In HIFU, each treatment session can take several hours and is not as favorable compared to other minimally invasive treatment methods that require less time. There have also been reports of burns and pain after HIFU due to FUS energy being localized to an area of the tissue.[40] There is currently no reliable method to monitor lesion production in addition to limited thermometry techniques. The more commonly used magnetic resonance thermometry only allows for quasi-real-time monitoring, and ultrasound thermometry is able to measure at real-time but does not come with commercially available FUS devices.[41,42] These present as challenges to safe and complete tumor ablation.

Currently, there are 5 different commercially available FUS devices (Table 1). The ExAblate system, produced by Insightec Inc., includes a high-frequency apparatus (650–720 kHz) for thermal ablation and a low-frequency device (220–230 kHz) for microbubble-mediated BBB disruption. These systems require the use of a helmet containing a phased-array transducer of 1,024 independent piezoelectric elements. The helmet is typically fixated to the patient's head using a stereotactic frame. Chilled, degassed deionized water separates the patient's head from the transducer elements to facilitate delivery of the FUS and to cool the scalp in order to avoid thermal injury.[43] Proprietary software calculates the required amplitude and phase for each individual transducer element for the FUS beams to pass through the skull to the target. Intraprocedural MRI is also used to facilitate real-time guidance and thermal monitoring. For LIFU, 1.1–3.3 μm microbubbles composed of an inert, low-solubility gas, typically perfluorocarbon, are injected intravenously. The microbubbles oscillate within vessels at the site of the FUS delivery, leading to the breakdown of the BBB through alterations in ZO-1, caveolae, and tight junctions. This disruption of the BBB is transient, and completely reversible within hours of LIFU therapy.[44–46] In the ExAblate system, intraoperative thermometry via magnetic resonance is used as an added safety feature. Typically, the BBB restricts molecules larger than 400 Da from crossing. However, the use of LIFU in the presence of microbubbles allows molecules, drugs, or reagents as large as 185 kDa to cross, thus providing an opportunity for the delivery of

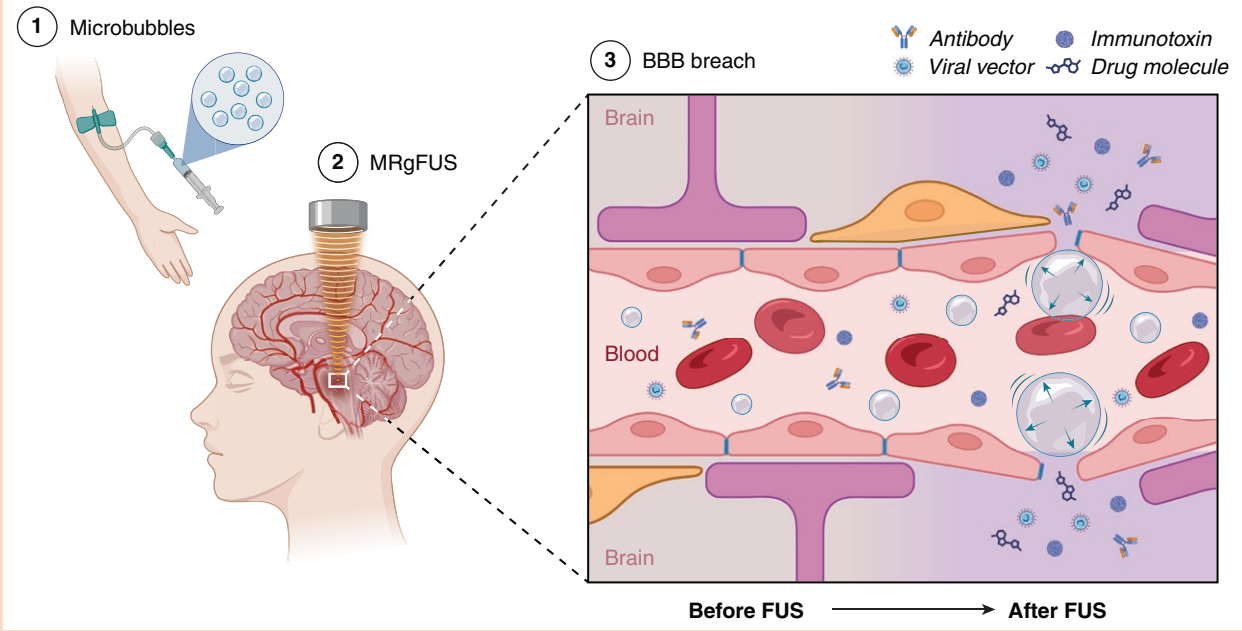

Figure 1. Use of magnetic resonance-guided focused ultrasound (MRgFUS) to disrupt the blood–brain barrier (BBB). In the presence of systemically administered microbubbles, MRgFUS can be used to target specific regions of the brain. In the vicinity where MRgFUS is targeted, the microbubbles oscillate, expand, and cause a temporary breach in the BBB enabling the passage of antibodies, large drug molecules, viral vectors, and immunotoxins into the parenchyma of the brain.

antibodies, cellular therapies, and immunotoxins to the target sites in the brain (Figure 1).[43]

The UltraNav, manufactured by Delsona, is another standalone system that uses LIFU for BBB disruption. An advantage of the UltraNav is that it is used with neuronavigation and optical guidance, obviating the need for a headframe or surgery. This system may be of particular value in the pediatric population since head stabilization with skull pins is not required.

NaviFUS is another FUS therapeutic system that does not require head fixation or general anesthesia. It is primarily used for BBB opening and can actively track cavitation effects. The NaviFUS has been tested in trials for adults with recurrent glioblastoma (NCT03626896) but has not yet been used in the pediatric population. Its ability to target deep and central lesions in the brain has not been determined.

Image-guided therapy has a phased-array system coupled to MRI containing 256 independent channels for volumetric ablation. Real-time thermometry and MR-imaging are advantages of this system and seem likely to move into clinical trials in the near future.

In addition to the standalone systems described above, one method of delivering FUS is through implantable devices. Specifically, the SonoCloud device by Carthera Inc. is implanted in a skull window beneath the skin via a craniotomy. The device is activated using a transdermal needle connected to an external control unit. The BBB can be disrupted for several hours, allowing for a therapeutic window for drug delivery to the targeted region. By administering therapies when the BBB is disrupted, drugs can reach the brain in higher and more effective concentrations. An advantage of this system is that drug treatments can be repeated effectively at short intervals. Carthera has developed several versions of SonoCloud, including the SonoCloud-1 and SonoCloud-9 devices. These MRI-compatible devices are designed to disrupt large regions of the BBB to increase the therapeutic efficacy of drugs in targeted brain regions and are currently in clinical trials for glioblastoma and brain metastases.[47]

There are several important considerations when selecting patients for FUS therapy. Due to the theoretical risk of intracranial hemorrhage, patients with coagulopathies or low platelet counts should be excluded. Another important criterion is the patient's skull density ratio (SDR), which measures the ratio of cancellous to cortical bone in the skull, with lower SDR values indicating higher skull density.[48] Patients with a low SDR will have lower sonication efficiencies as the FUS waves are subject to greater reflection and attenuation.[43,48] For similar reasons, the presence of intracranial calcifications, scalp masses, or hyperostosis frontalis may preclude these patients from entry into study trials. In general, the use of an MR contrast agent such as gadolinium is used to assess extravasation into the target area as an indicator of drug delivery. T2* gradient echo sequences by MR are often used post-procedure to assess for any possible intracerebral hemorrhage.[18]

Current Applications of Focused Ultrasound Therapy

FUS offers several key modalities for the treatment of neurological disorders, including: thermal ablation,

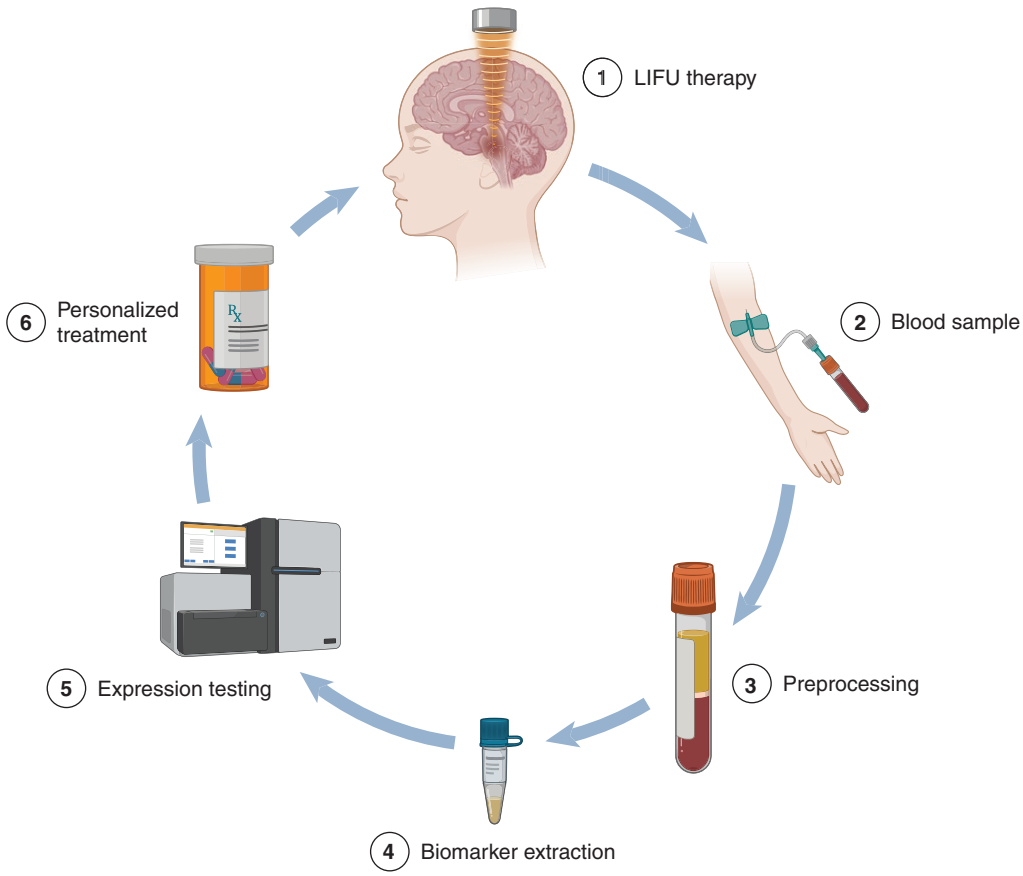

Figure 2. Use of low-intensity focused ultrasound (LIFU) to disrupt the blood–brain barrier (BBB) and to enable the collection of blood-borne biomarkers from the target site. Using this noninvasive strategy, patients with central nervous system diseases can be followed at intervals for levels of biomarker expression, and to determine responses to treatment.

targeted drug delivery, and neuromodulation. In neuro-oncology, thermal ablation has been performed for a variety of malignant and benign tumors. Several ongoing studies are examining the delivery of a variety of agents across the BBB.[49] Neuromodulation is achieved through the use of pulsed LIFU with repeated short-duration bursts of energy and is being investigated as a strategy to suppress seizure onset, modulate targets for psychiatric disease, and to provide nerve blocks for pain relief, as some examples. The important roles of FUS therapy in neuromodulation or thermal ablation, such as in the treatment of patients with essential tremor, Parkinson's disease, or other movement disorders, have been previously reviewed elsewhere.[20]

An interesting and relatively new application of FUS treatments is the ability to initiate the release of blood biomarkers through the use of LIFU therapy (Figure 2). These MRgFUS-generated liquid biopsies may prove to be an effective, noninvasive manner to examine blood samples for circulating biomarkers such as circulating tumor DNA (ctDNA), circulating tumor cells, cell-free DNA, extracellular vesicles, and methylation fragments.[50]

Focused Ultrasound Applications in Neuro-oncology

To date, the majority of FUS therapeutic trials in neuro-oncology have been conducted in adults. In one of the first such trials, Mainprize et al. treated 5 patients with high-grade gliomas using MRgFUS and intravenously injected microbubbles to enhance the delivery of systemic chemotherapy, including liposomal doxorubicin and temozolomide.[51] In this study, there were no adverse events and biochemical analysis of sonicated versus nonsonicated tissues suggested that chemotherapy delivery is feasible and quantifiable by means of liquid chromatography-mass spectrometry.

Anastasiadis et al. demonstrated an increase in fluorescein accumulation in surgically resected gliomas in patients undergoing MRgFUS and microbubble administration in a phase 0 clinical trial.[52]

Meng et al. reported on the use of MRgFUS to enhance the delivery of trastuzumab in patients with Her2-positive

brain metastases.[53] In this study, 4 patients were treated, and 111In-BzDPTA-NLS-trastuzumab was used for SPECT imaging. This was the first study to show spatial delivery of targeted monoclonal antibody therapy across the BBB using MRgFUS. The authors demonstrated the presence of radioisotope penetration in the sonicated region, a better and more reliable indicator of drug concentration than the use of gadolinium alone.

In another trial using the implantable SonoCloud system, Carpentier et al. conducted a phase I clinical trial in which patients with recurrent glioblastoma received LIFU, microbubbles, and albumin-bound paclitaxel. In 17 patients, there was a 3–7 times increase in the concentration of albumin-bound paclitaxel in the regions of the sonicated brain.[47]

Focused Ultrasound in Pediatric Neuro-Oncology

Focused ultrasound is particularly well-suited to be considered for the treatment of brain tumors in children. Many pediatric brain tumors are well-circumscribed, low-grade histopathology, and are in a targetable location within the brain. In this setting, high-frequency ultrasound holds great potential. Interestingly, in 2014, HIFU was used by neurosurgeons at the Hospital for Sick Children to treat patients with osteoid osteomas (NCT02618369). The results were encouraging, with excellent long-term outcomes.

Presently, pediatric neuro-oncology patients typically require the use of a stereotactic headframe to prevent head movement during treatment. Application of such a frame can pose challenges in the unanesthetized young child. As a result, almost all pediatric patients require sedation and/or general anesthesia to undergo the procedure. There are ongoing efforts by FUS device manufacturers to produce a "frameless" head holder system to obviate the need for skull pins prior to the initiation of treatment.

Another concern in the pediatric population is that they are more prone to perioperative hypothermia caused by general anesthesia due to children's decreased efficacy in homeostatic temperature regulation, lower weight-to-surface-area ratio, thinner skull and scalp leading to increased heat loss, and lesser subcutaneous adipose tissue for insulation compared to adults.[54,55] Instruments such as MRI machines require specific environmental temperatures, typically between 18 and 22 °C, thus special consideration is needed to prevent perioperative hypothermia. This can include the use of Bair Huggers or TransWarmers during anesthesia.[54]

One of the first studies in pediatric neuro-oncology included patients treated with HIFU for thermal ablation of hypothalamic hamartomas (HHs) and subependymal giant cell astrocytomas (SEGAs).[18] In Tierney's study, 5 children were treated using FUS at a frequency of 650 kHz and an acoustic power of 1,500 W, generating internal brain temperatures between 56 and 60 °C.[18] The authors noted a significant reduction in seizure frequency, no post-operative neurological deficits, and no endocrine hormone deficiencies. Their only treatment failure was in a child with tuberous sclerosis and SEGA. The advantages to take into consideration with HIFU versus gamma-knife radiosurgery are the immediacy of the results, the avoidance of ionizing radiation therapy, and the ability to retreat immediately in unexpected situations (Figure 3).[18]

Syed et al. have provided a preliminary report on the use of sonodynamic therapy with 5-aminolevulinic acid (ALA) for pediatric patients with diffuse intrinsic pontine glioma (DIPG) in a phase II study (SDT201, NCT05123534). This is a noninvasive drug delivery strategy that involves the sensitization of target tissues with a nontoxic chemical agent and subsequent exposure of the sensitized tissues to LIFU. When both elements are combined, a cytotoxic event occurs through the generation of reactive oxygen species leading to necrosis and apoptosis, occurring only within the tumor tissue where ALA is concentrated.[56–58]

MRgFUS for Delivery of Chemotherapy across the Blood–Brain Barrier in DIPG

DIPG is a fatal pediatric brain tumor occurring in children ages 5–7. Children typically present with a short clinical history with a combination of cerebellar, cranial nerve, or long-tract neurological findings. In neuroimaging studies, DIPG is typically localized to the pons. Given its intrinsic localization in the brainstem, DIPG cannot be resected in any significant manner.[59,60] Surgical biopsy of these lesions is becoming increasingly more frequent as molecular and genetic alterations of this tumor are becoming progressively better characterized and more useful for providing prognostic information.[61] DIPG is characterized by H3K27M mutations, amplifications of PDGFR-A, mutations in the ACVR1 gene, and MYC amplifications.[62] Once the diagnosis of DIPG is established, the standard treatment is comprised of fractionated radiation therapy over a 6-week time frame to a total dose of 54 cGy. Following successful completion of a course of radiation therapy, considerations may be given towards any one of several ongoing clinical trials for DIPG (see www.dipg.org). It should be noted that despite a myriad of previous clinical trials and the presence of numerous active clinical trials, there has been no treatment that has reliably extended survival for children with this devastating disease.[62]

Against this backdrop, some years ago, we envisioned that DIPG would be an ideal tumor for targeted drug delivery to the brainstem using MRgFUS. DIPG is typically a nonenhancing pontine tumor signifying an intact BBB. In preliminary studies, we determined that it was safe and feasible to target the normal pons using MRgFUS to disrupt the BBB in a preclinical model in mice.[63] We then determined using a high-throughput drug screening assay that DIPG cell lines were exquisitely sensitive to doxorubicin.[63] We demonstrated an increase in the concentration of doxorubicin in the normal pons of mice treated with MRgFUS and microbubbles versus controls.[63] We next developed preclinical models of DIPG in which orthotopic tumors in the pons were targeted with MRgFUS following the administration of microbubbles and the delivery of doxorubicin.[64] We showed a 4-fold increased concentration of doxorubicin within the implanted orthotopic tumors in the pons with MRgFUS and microbubbles compared to

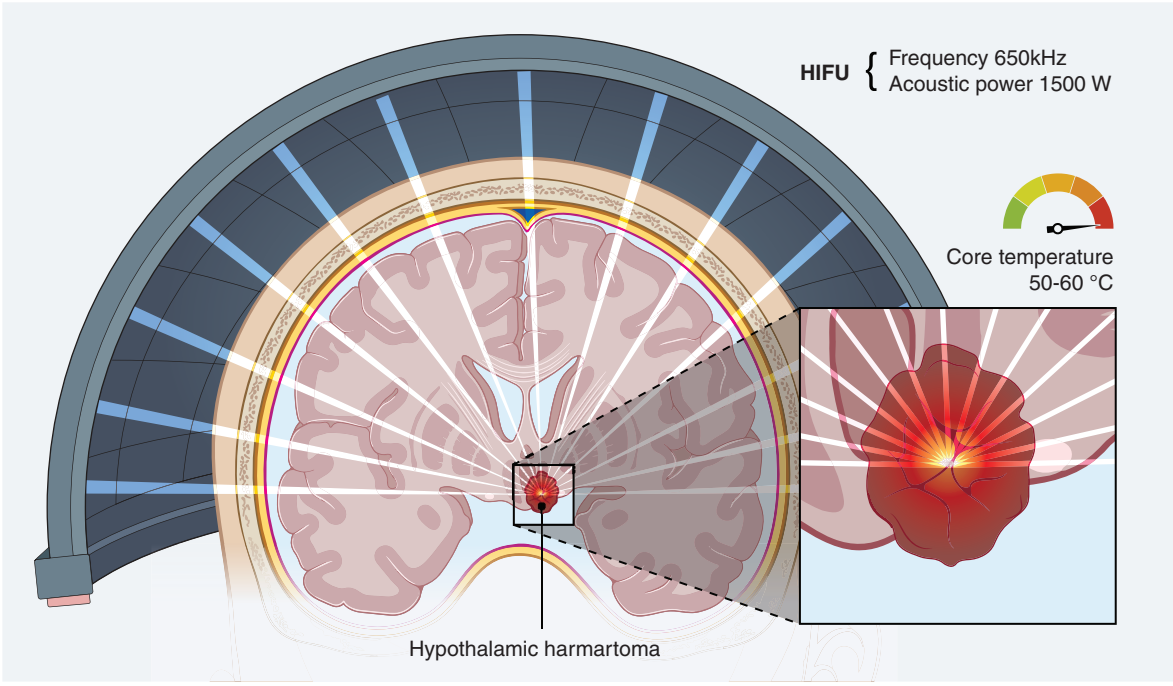

Figure 3. Magnetic resonance-guided focused ultrasound (MRgFUS) application for hypothalamic hamartoma (HH). HH is a deep, central malformative lesion that is typically well-circumscribed, and exhibits a minimal growth rate over time. For HH, high-intensity focused ultrasound (HIFU) is used to create a precise thermal burn within the tumor in efforts to disconnect the lesion from the surrounding hypothalamus. Such deep, central, and slow-growing lesions in children may be optimal targets for MRgFUS and HIFU. Image shows coronal section of the brain through the level of the hypothalamus.

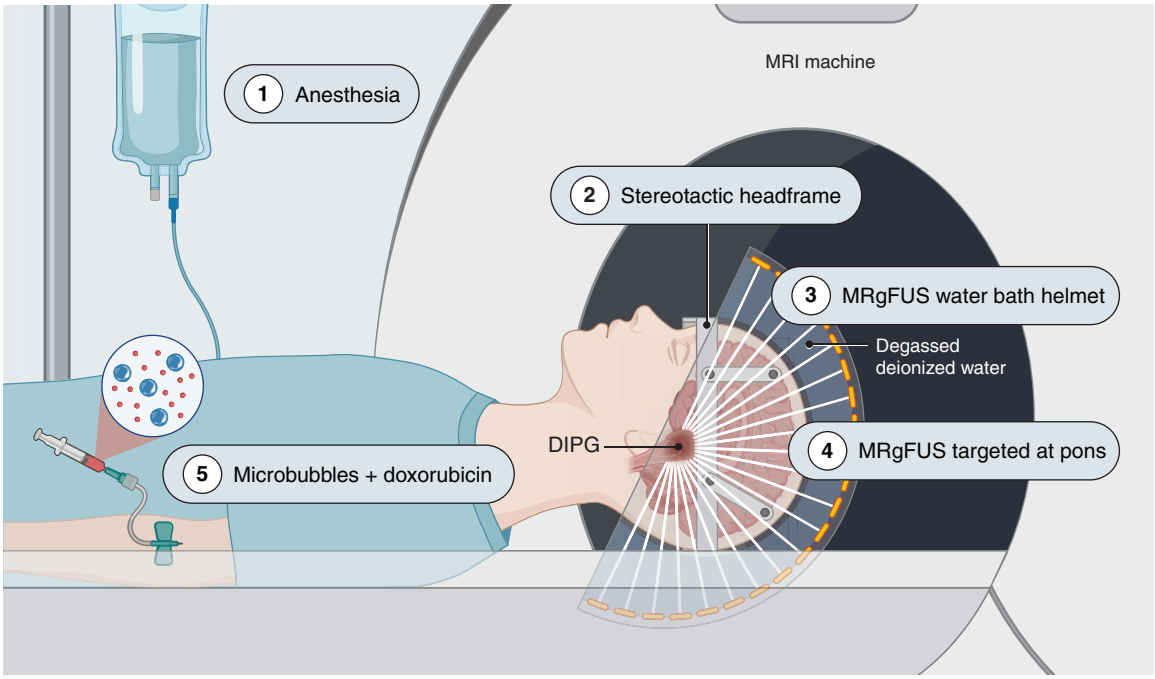

Figure 4. Magnetic resonance-guided focused ultrasound (MRgFUS) to treat diffuse intrinsic pontine glioma (DIPG). Children with DIPG are anesthetized, placed in a stereotactic headframe, and then placed into the MRgFUS water bath helmet where cold, degassed deionized water is used to cool the scalp and prevent thermal irritations. The ultrasound beams are focused on the pons using the principle of blood–brain barrier (BBB) disruption using microbubbles and the subsequent delivery of doxorubicin.

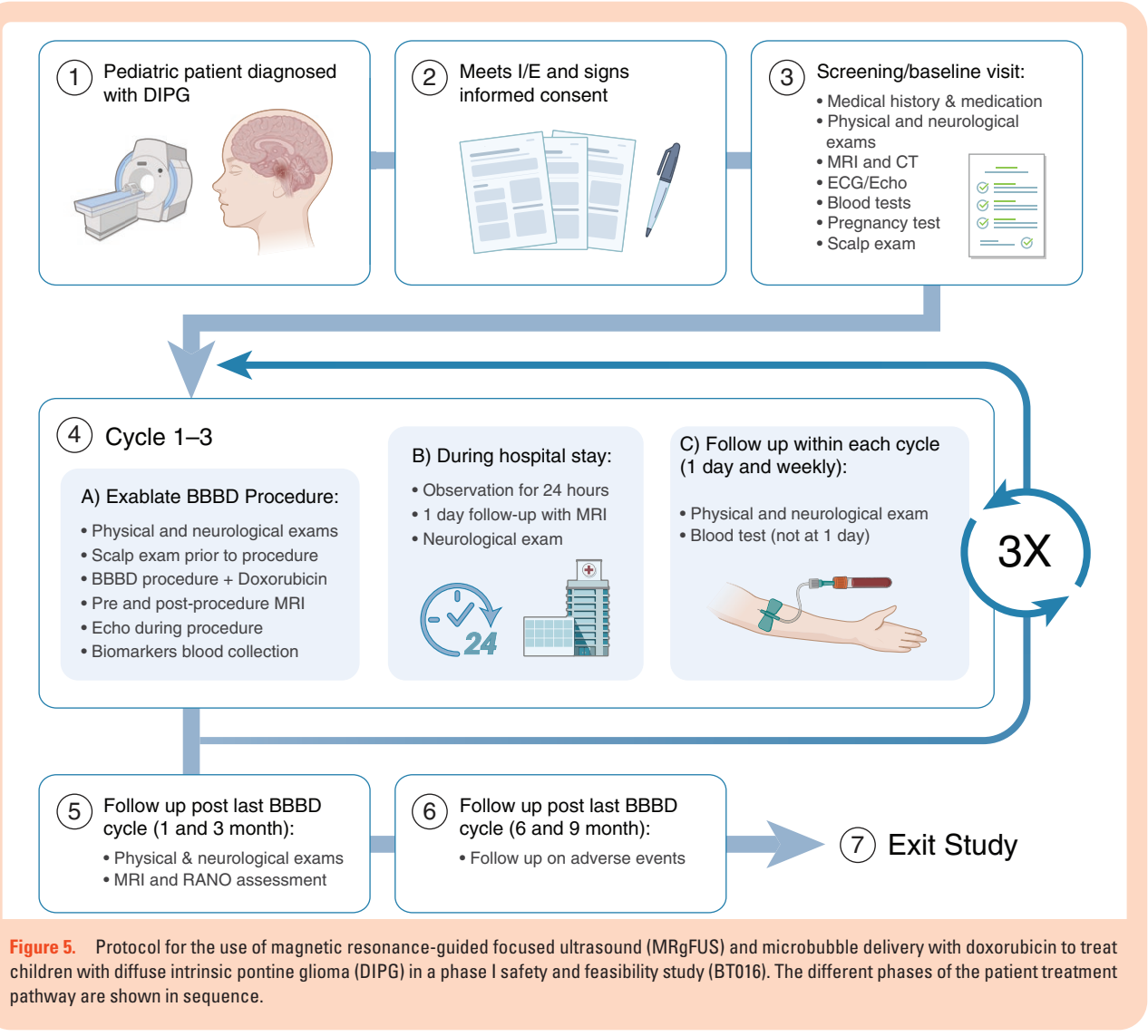

Figure 5. Protocol for the use of magnetic resonance-guided focused ultrasound (MRgFUS) and microbubble delivery with doxorubicin to treat children with diffuse intrinsic pontine glioma (DIPG) in a phase I safety and feasibility study (BT016). The different phases of the patient treatment pathway are shown in sequence.

controls, and a decrease in the volumetric growth rate of these tumors by virtue of suppression of the Ki-67 index.[64]

Based on these encouraging preliminary data, we developed a novel phase 1 clinical trial to assess the safety and feasibility of MRgFUS and doxorubicin delivery in children with DIPG (Figures 4 and 5). This phase I study (BT016, NCT05615623) is actively recruiting children with DIPG. To date, 5 children have each undergone three BBB disruptions, spaced apart at 1-month intervals, in addition to treatment with doxorubicin using MRgFUS and microbubble administration (Figure 6). There is a total of 3 sonication treatments, with each treatment cycle lasting 4–6 weeks. For sonication, the acoustic power is set to a maximum of 60 W, with the sonication mode set to either the stop sonication mode or the modulated power mode. Under the stop sonication mode, sonication occurs at a constant power equal to the maximum acoustic power set. The modulated power mode allows the physician to define the desired cavitation dose, to a maximum of 3.0 V*s, as well as gain at low, medium, or high. The system will then apply the appropriate power needed to achieve the prescribed sonication dose, based on real-time closed-loop acoustic feedback. The treatments have been well tolerated; there has been no evidence of brainstem hemorrhage in any of the patients treated and the chemotherapy side effects have been minimal.

A recent paper by Keating et al. reviewed several clinical trials that utilize MRgFUS as a treatment for pediatric brain tumors. One study utilizes HIFU to thermally ablate low-grade gliomas (BT005, NCT03028246), and 2 other studies focus on DIPG (SDT201, NCT05123534; BT016, NCT05615623), which include the phase I study mentioned above.[54] Typical workflow for this particular clinical study is as follows. Prior to transfer to the MRI suite, the patient undergoes anesthesia induction and is intubated along with cardiopulmonary monitoring. The type and degree of anesthesia are managed by the anesthesiologist throughout the procedure. Extended skull fixation pins and crossbar are then used for headframe placement, with the silicone membrane and lubricant applied onto the scalp to maintain a watertight seal. The patient is then transferred to the MRI room. There, the headframe is connected to the

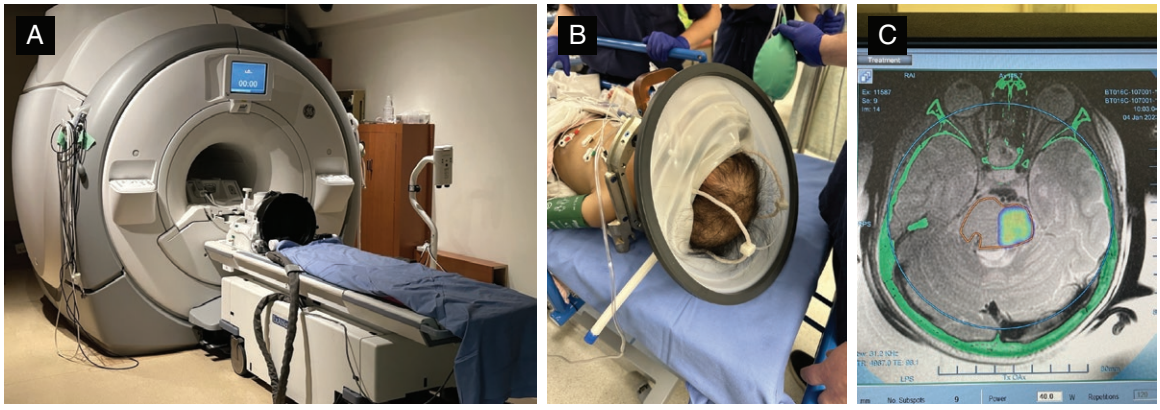

Figure 6. Case example of a child with diffuse intrinsic pontine glioma (DIPG) in a phase I safety and feasibility study (BT016). (A) Magnetic resonance imaging (MRI) scanner equipped for delivery of low-frequency focused ultrasound. The patient's head is placed into the head holder where cold water will be placed and continuously circulated during sonication. (B) A stereotactic head frame is placed on a child under general anesthesia. A head ring is then placed with a silicone diaphragm that serves to prevent water leakage during the delivery of low-frequency ultrasound. (C) MR-scan post sonication and delivery of doxorubicin demonstrating blood–brain barrier (BBB) disruption involving 50% of the pons in this first treatment of a child with DIPG.

FUS transducer on the MRI machine with water filled at the interface between the transducer and the patient's head. Pre-treatment MRI is conducted and used to map out the targeted region; doxorubicin is administered intravenously through a central venous catheter before microbubbles are injected prior to the administration of FUS to facilitate BBB disruption in the brainstem. The patient is then transferred out of the MRI suite for headframe removal, and extubation, with overnight monitoring in the pediatric intensive care unit.[54]

Overall, Keating et al. found that the average sonication time is 116 min across the 4 studies, with an average anesthetic time of 295 min. They observed that workflow is improved over time as the medical team becomes familiar with the MRgFUS process. Several technical difficulties are also highlighted. In some cases, the transducer helmet had become damaged due to the physical pressure between the helmet and the headframes, which had to be inferiorly positioned to ensure coverage of the entire tumor. This issue was resolved upon switching to a different transducer helmet with a larger coverage area, reducing the need to adjust the helmet between different targeted regions. Pockets of air and folding of the membrane surrounding the headframe also hindered sonication as due to the increased reflection of FUS waves. Alleviating the folds, lowering the power setting, and increasing repetitions allowed for proper sonication.[54]

Following the completion of this phase I trial, subsequent studies will attempt to augment treatment by harnessing the immune system in children with DIPG. There is preclinical evidence that MRgFUS, specifically LIFU, can lead to immunomodulation.[65] While DIPG is a relatively inert, immunologically "cold," tumor, the use of LIFU to open the BBB within the pons may convert it into an immunologically "hot" tumor. This may occur through the upregulation of proinflammatory cytokines and chemokines enabling the penetration of systemically delivered immune cells, checkpoint inhibitors, CAR-T cells, and immunotoxins in far greater concentrations than what could be achieved without BBB disruption. Immunotherapy has the benefit of a longer half-life, fewer systemic side effects, and a greater amplification effect than conventional chemotherapy.[65]

Future Applications of MRgFUS in Pediatric Neuro-Oncology

We are only now beginning to appreciate the diverse applications for which MRgFUS is well-suited in pediatric neuro-oncology. In future studies, discrete and well-circumscribed pediatric low-grade gliomas (pLGGs) may be suitable targets for MRgFUS and HIFU when surgery and standard chemotherapy regimens are not possible. In addition, one can envision the potential use of MRgFUS to treat non-neoplastic epileptiform lesions such as focal cortical dysplasia and bottom of sulcus dysplasia. In these conditions, MRgFUS may be considered a viable, minimally invasive substitute to laser interstitial thermal therapy.

As MRgFUS technology continues to advance, innovations in hardware, software, and neuroimaging sequences and protocols will expand the types of reagents that can be administered across the BBB for maximum therapeutic effects. This is an exciting time for the use of these minimally invasive procedures in the treatment of pediatric brain tumors. Results from carefully designed and well-executed clinical trials will help identify patients and pathologies that will best respond to this innovative technology.

Keywords

blood–brain barrier | brain tumor | focused ultrasound | pediatric neuro-oncology

Funding

This work was supported through grants received from the Canadian Institute of Health Research (CIHR), Brain Cancer Canada, the Wiley Family Fund, Meagan Bebenek Foundation (Meagan's HUG), Brainchild, the Fiorini fund, Insightec, and the Focused Ultrasound Foundation. This article appears as part of the supplement "Role of Focused Ultrasound in Brain Tumor Management," sponsored by Focused Ultrasound Foundation and Centre of Excellence in Focused Ultrasound at Sunnybrook Health Sciences Centre.

Conflict of interest statement. None declared.

Authorship Statement

Conceptualization: C.L., M.L., N.L., S.K., K.H., and J.R. Writing—original draft: C.L., J.R., and K.M. Writing—review and editing: C.L., M.L., N.L., S.K., K.H., K.M., and J.R. Figures and visualization: S.K. Supervision: J.R.

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