Focused Ultrasound for Pediatric Diseases

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Focused ultrasound (FUS) is a noninvasive therapeutic technology with multiple pediatric clinical applications. The ability of focused ultrasound to target tissues deep in the body without exposing children to the morbidities associated with conventional surgery, interventional procedures, or radiation offers significant advantages. In 2021, there are 10 clinical pediatric focused ultrasound studies evaluating various musculoskeletal, oncologic, neurologic, and vascular diseases of which 8 are actively recruiting and 2 are completed. Pediatric musculoskeletal applications of FUS include treatment of osteoid osteoma and bone metastases using thermal ablation and high-intensity FUS. Pediatric oncologic applications of FUS include treatment of soft tissue tumors including desmoid tumors, malignant sarcomas, and neuroblastoma with high-intensity FUS ablation alone, or in combination with targeted chemotherapy delivery. Pediatric neurologic applications include treatment of benign tumors such as hypothalamic hamartomas with thermal ablation and malignant diffuse intrinsic pontine glioma with low-intensity FUS for blood brain barrier opening and targeted drug delivery. Additionally, low-intensity FUS can be used to treat seizures. Pediatric vascular applications of FUS include treatment of arteriovenous malformations and twin-twin transfusion syndrome using ablation and vascular occlusion. FUS treatment appears safe and efficacious in pediatric populations across many subspecialties. Although there are 7 Food and Drug Administration–approved indications for adult applications of FUS, the first Food and Drug Administration approval for pediatric patients with osteoid osteoma was obtained in 2020. This review summarizes the preclinical and clinical research on focused ultrasound of potential benefit to pediatric populations.

The primary goal of this State of the Art Review is to educate readers about focused ultrasound and highlight some of the promising published and ongoing research of potential benefits to pediatric populations. Focused ultrasound (FUS) is a noninvasive therapeutic technology with multiple applications for the treatment of various pediatric diseases. FUS concentrates multiple intersecting beams of ultrasound energy on a precise target in the body. Imaging guidance precisely identifies anatomic targets and monitors efficacy and safety. Each individual beam passing through tissue has no effect, but multiple beams of ultrasound energy converging at a single focal point result in important biological effects.[1] FUS may be especially advantageous in the pediatric population because it targets tissues deep in the body without exposing children to the morbidities associated with conventional surgery or the risks of radiation.

The Food and Drug Administration (FDA) has approved numerous FUS treatments for adults for uterine

abstract

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fibroids, painful bone metastases, prostate enlargement and cancer, essential tremor, and tremor-dominant Parkinson's disease. In November 2020, the FDA approved FUS (with Humanitarian Device Exemption) as a treatment of osteoid osteoma (OO) in the extremities, which typically impacts the pediatric population.[2] The feasibility, safety, and efficacy of FUS are being studied for over 131 clinical indications, and recent studies evaluating FUS for pediatric applications have increased from 3 in 2012 to 17 in 2019.[3] Table 1 highlights current clinical trials for pediatric-focused ultrasound applications.

SEARCH STRATEGY AND SELECTION CRITERIA

A literature review was conducted through PubMed, Google Scholar, Medline, and Elsevier to identify English language studies using combinations of the following search terms: "pediatric," "focused ultrasound," "treatment," and "high intensity focused ultrasound." Primary articles within the last 20 years that included technical explanations of the focused ultrasound machines and published clinical studies if the patients/subjects were pediatric patients (age 0–21 years) with some adult patients (>21 years) exhibiting typical pediatric diseases were identified. Further analysis of these articles' references identified preclinical papers within the last 30 years addressing disease processes and mechanisms of action. The various diseases were separated into the following major categories: musculoskeletal, oncologic, neurologic, and vascular applications.

MECHANISMS OF ACTION

FUS can produce mechanical or thermal energy to elicit a range of permanent or reversible bioeffects on treated tissue. Although over 60 different mechanisms of action are being investigated, 4 mechanisms are currently applied to pediatric diseases (Fig 1). High-intensity focused ultrasound (HIFU) using a 650-kHz transducer can induce thermal ablation and mild hyperthermia for targeted drug delivery while low-intensity focused ultrasound (LIFU) using a 220-kHz transducer can be used for neuromodulation and blood brain barrier (BBB) opening. Various clinical FUS devices are listed in Table 1 with details regarding the type of imaging guidance, manufacturer, and number of transducer elements.

Thermal Ablation

In general, thermal ablation via HIFU has been approved by numerous regulatory bodies worldwide to treat malignant and benign tumors of the breast, prostate, and liver, as well essential tremor, tremor-dominant Parkinson's disease, and uterine fibroids.[3] Thermal ablation occurs as acoustic energy is absorbed, elevating temperature in a precise location and causing cell death by coagulative necrosis with minimal damage to surrounding tissue[4] (Fig 1A). Imaging guidance for HIFU ablation can be performed with either MRI or ultrasound (US). Magnetic resonance HIFU (MR-HIFU) allows for precise anatomic guidance and monitoring of tissue temperatures to ensure successful heating above a dose threshold. US-HIFU allows for improved temporal resolution along with the usual anatomic targeting, but does not allow for direct measurement of temperature. Instead, US-HIFU provides observable changes in tissue echogenicity that can monitor treatment in real time using a centrally located diagnostic transducer.[5] The volume of HIFU ablation lesions can be as small as a grain of rice (10 mm^3) and as large as 10 mm × 40 mm with a sharp border between treated and untreated areas.[4]

Targeted Drug Delivery

FUS can increase the local delivery and absorption of various therapeutics into tumors and thus improve efficacy due to a variety of mechanisms. These mechanisms include vasodilation, most plausibly through release of nitric oxide, increasing cell membrane permeability, or sonoporation, and hyperthermia.[6] FUS-mediated local hyperthermia can release encapsulated therapeutic agents ranging from genes to chemotherapies from a carrier vehicle such as a temperature-sensitive liposome, microbubble, or nanoparticle. Such agents are only released into the target by the FUS beam (Fig 1B), delivering them in high concentrations to a precise location while minimizing systemic side effects.

Blood Brain Barrier Opening

The blood brain barrier (BBB) is a layer of tightly joined cells lining cerebral blood vessels that selectively limits substances from entering neural tissue. However, this barrier also limits approximately 99% of potential therapeutic agents from entering the brain and only allows molecules <400 Da to pass.[7] LIFU allows for three main effects: (1) controlled, temporary, and reversible opening of BBB tight junctions via mechanical stretching from oscillating microbubbles, (2) Increases in transcytotic vesicles along the BBB, (3) decreases in efflux proteins reducing the amount of molecules pumped out of cerebral tissue[8,9] (Fig 1C). LIFU allows for diffusion of molecules as large as

TABLE 1 Pediatric Focused Ultrasound Clinical Trials

Name	Pathology	Phase, Status	Location	Age	Guidance (Manufacturer) No. of Transducer Elements	NCT
Musculoskeletal						
Compare effectiveness of MRgFUS vs CTgRFA for osteoid osteomas	Osteoid osteoma	III, recruiting	Stanford Medical Center, UCSF Imaging Center	8 y and older	MRI (Insightec) 208 elements	NCT02923011
Safety and feasibility of MR-guided high intensity focused ultrasound ablation of osteoid osteoma in children	Osteoid osteoma	N/A, complete	Children's National Research Institute, Washington, DC	Up to 25 y	MRI (Profound Medical) 256 elements	NCT02349971
MR-HIFU treatment of painful osteoid osteoma	Osteoid osteoma	II, not yet recruiting	Children's National Research Institute, Washington, DC	Up to 30 y	MRI (Profound Medical) 256 elements	NCT04658771
MR-guided high intensity focused ultrasound for pain management of osteoid osteoma and benign bone tumors in children and adults	Osteoid osteoma, benign bone tumor, pain	N/A, completed	The Hospital for Sick Children, Toronto, Ontario, Canada	5 to 40 y	MRI (Profound Medical) 256 elements	NCT02618369
MRI guided HIFU for palliation of painful skeletal metastases in children	Bone metastases, pain	N/A, recruiting	The Hospital for Sick Children, Toronto, Ontario, Canada	5 to 17 y	MRI (Profound Medical) 256 elements	NCT02616016
Oncologic						
MR-guided high intensity focused ultrasound on pediatric solid tumors	Relapsed pediatric solid tumors, refractory pediatric solid	I, recruiting	Children's National Medical Center, Cincinnati Children's Hospital Medical Center	≤30 y	MRI (Profound Medical) 256 elements	NCT02076906
A phase I study of lyso-thermosensitive liposomal doxorubicin and MR-HIFU for pediatric refractory solid tumors	Relapsed and/or refractory pediatric malignant solid tumors	I, recruiting	Children's National Medical Center	Part A: ≤21 y; part B: ≤30 y	MRI (Profound Medical) 256 elements	NCT02536183
Neurologic						
Noninvasive focused ultrasound (FUS) with oral Panobinostat in children with progressive diffuse midline glioma (DMG)	Diffuse intrinsic pontine glioma, thalamic gliomas, diffuse midline glioma, H3 K27M-mutant	I, recruiting	Columbia University Irving Medical Center	4 to 21 y	Neuronavigation with MRI (TheraWave Bio Inc.) 1 element	NCT04804709
A feasibility safety study of benign centrally-located intracranial tumors in pediatric and young adult subjects	Benign centrally-located intracranial tumors	N/A, recruiting	Miami Children's Research Institute—Nicklaus Children's Hospital	8 to 22 y	MRI (Insightec) 1024 elements	NCT03028246
Vascular						
Ultrasound-guided high intensity focused ultrasound to treat twin-twin transfusion syndrome	Twin-twin transfusion syndrome	N/A, recruiting	Imperial College London	12 to 17 wk gestation	USgHIFU (no other information available)	IRAS Project ID: 260359

HIFU, high intensity focused ultrasound; N/A, not applicable; NCT, National clinical trial identifier number.

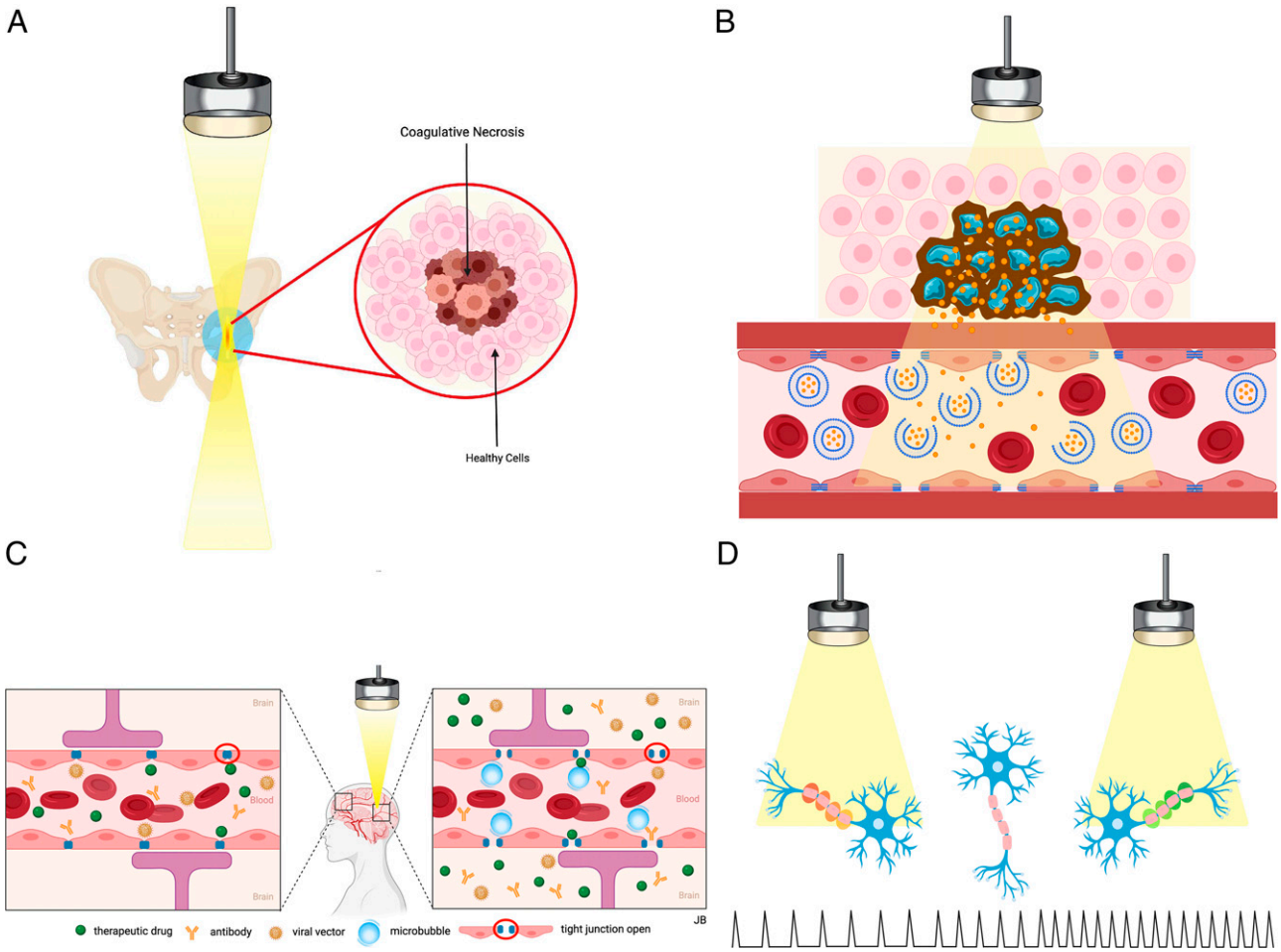

FIGURE 1

A, Thermal ablation. As the HIFU beam (yellow) focuses on a targeted anatomic lesion, the area is heated to a threshold temperature causing coagulative necrosis. The nontargeted healthy cells remain intact immediately adjacent to the ablated, necrotic cells with a narrow zone of transition. B, Targeted Drug Delivery. The focused ultrasound beam (yellow) enhances drug delivery by releasing medications from thermosensitive liposomes only within the tumor vessels, sparing surrounding and distant normal cells from potential drug toxicity. C, Blood Brain Barrier Opening. The focused ultrasound beam opens the BBB in a target location by oscillating the injected intravenous microbubbles that exert mechanical pressure on the endothelium and subsequently widen the tight junctions to allow molecules such as drugs, viral vectors, and antibodies to pass into the brain. D, Neuromodulation. With various parameters of the LIFU beam (yellow), neuronal signal may be suppressed (red axons) or stimulated (green axons).

185 kd.[10] LIFU has been shown to disrupt the BBB in a noninvasive, safe, and targeted manner for a therapeutic window up to 24 hours immediately after treatment.[11,12] To date, numerous clinical studies for adults are currently investigating BBB opening with LIFU to deliver a variety of neurotherapeutics for glioblastomas and metastatic disease to the brain.[13] Recently, the first clinical study for LIFU BBB opening in the pediatric population is now recruiting patients with diffuse intrinsic pontine glioma (DIPG).

Neuromodulation

Neuromodulation refers to the alteration of nerve activity by delivering changes directly to a targeted area. Neuromodulation is achieved using pulsed LIFU which is based on repeated bursts of energy of short duration. The mechanical effects of pulsed LIFU can either reversibly decrease the functionality of targeted neurons or trigger the activation and propagation of neural signals[14,15] (Fig 1D). The thermal effects of LIFU can also temporarily suppress neural signals in a targeted area by slightly raising the temperature without cell death.[16] These neuromodulatory effects can cause a range of therapeutic benefits such as suppressing epileptic seizures, modulating targets responsible for psychiatric disorders, and blocking nerves to treat pain.

CLINICAL APPLICATIONS

Musculoskeletal

Osteoid Osteoma

OO accounts for 11% of benign bone tumors and is most commonly found

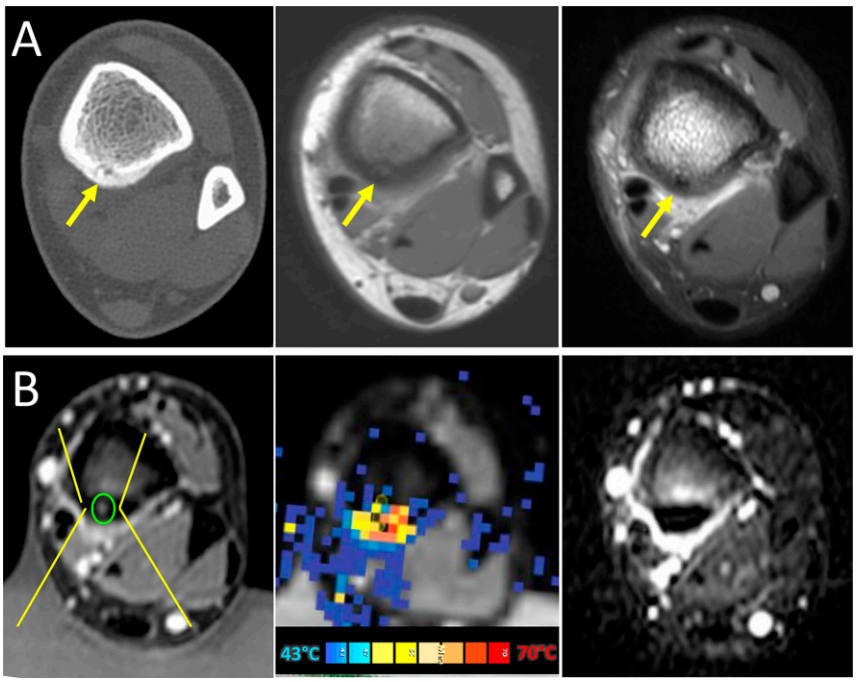

FIGURE 2

Osteoid osteoma. 17-year-old boy with left leg pain worse at night and temporarily relieved with Ibuprofen. No history of trauma. A, Diagnostic. Axial CT (left) and MRI (middle and right) images demonstrate the central nidus and periosteal reaction along the tibia (arrows). B, Focused ultrasound. MRI planning image (left) with beam path (yellow lines) focused on the nidus (green circle). Elevated temperature in nidus (yellow/orange) during sonication on MR thermometry image (center). Posttreatment postcontrast image (right) demonstrates nonperfusion (arrow) of the nidus. Courtesy of Karun Sharma, MD, PhD.

in the diaphysis of long bones in patients 10 to 30 years of age.[17] It characteristically causes severe nocturnal pain due to prostaglandin release, with symptoms typically alleviated by nonsteroidal anti-inflammatory drugs (NSAIDs).[18] However, this treatment only provides short-term relief and long-term use can lead to gastrointestinal and other side effects.[19] Current standard treatment uses computer tomography image–guided percutaneous radiofrequency ablation (CT-RFA), which is less invasive than surgical resection with a higher efficacy.[20] However, potential complications of CT-RFA include bleeding, infection, skin and muscle burns, and nerve injury.[21]

MR-HIFU ablation of OO has FDA and international approval in Europe, Russia, and China as a noninvasive alternative treatment option to precisely target OO lesions without damaging surrounding healthy tissue (Fig 2). Napoli et al reported that the first use of MRI-HIFU to treat a cohort of 6 patients with painful OO revealed that it was technically feasible and safe with clinical improvement in pain at 6 months.[20] In 2017, the same authors reported in a prospective study that 42 out of 50 patients (mean age: 18, age range: 16–25) with OO demonstrated a 3-year clinical benefit with improvements in pain, sleep, and overall quality of life.[22] Arrigoni et al reported 32 of 33 pediatric patients with OO had complete pain relief after one MR-HIFU treatment session. All patients stopped NSAID use after the procedures.[23] In a prospectively enrolled safety and feasibility study, Sharma et al published that 8 of 9 patients treated with MR-HIFU and 9 of 9 patients treated with RFA (entire cohort mean age: 16, age range: 7–24) had total pain resolution and cessation of analgesics after 4 weeks and suggested MR-HIFU offers a noninvasive, precisely-controlled ablation of OO without the need for ionizing radiation.[24] In all of the FUS studies detailed above, there were no serious adverse events or skin burns.[20,22,24]

At present, there is an ongoing randomized Phase III trial at the University of California, San Francisco and Stanford University designed to compare the effectiveness of MR-HIFU with CT-RFA for OO (NCT02923011). A pivotal trial on safety and efficacy of MR-HIFU ablation of OOs in children is ongoing (NCT04658771).

Bone Metastases

Skeletal metastases may occur in pediatric patients with cancer, including those with hematologic and solid tumor malignancies.[25] A study of 2652 children in Denmark

reported the incidence of bone metastases as 1.9 per 1000 person-years during a mean follow-up of 7 years.[26] These metastases can cause severe pain, reduced quality of life, increased health care costs, and increased risk of death. The primary options for treatment of painful bone metastases include pain medication, radiation therapy, and surgery.

MR-HIFU has been proven to be effective for pain palliation in adult patients with bone metastases. A phase III randomized, placebo-controlled, multicenter trial of MR-HIFU performed with 147 patients (median age: 61.7, range: 19.1–83.6) found that 64% of patients reported pain reduction at 3 months, with 20% obtaining complete pain relief and two-thirds of patients achieving clinical response within 3 days. The most common complication was procedure-related pain, however 60% of all adverse-effects resolved on the same day.[27]

HIFU has worldwide approval to treat painful bone metastases. MR-HIFU is currently recommended as a second-line therapy after radiation failure and as a first-line therapy with any contraindication to radiation therapy.[27] Importantly, HIFU can be repeated as necessary as there is no radiation toxicity, although patients with bone metastases to the skull and vertebrae are currently excluded.

Due to the proven efficacy in adults, there is now a clinical trial in Toronto, Canada (NCT02616016), investigating MR-HIFU for pain palliation in patients 5 to 17 years of age with bone metastases.

SOFT TISSUE ONCOLOGIC

Desmoid Tumors

Desmoid tumors are locally aggressive soft tissue tumors that can occur anywhere in the body. These tumors affect an estimated 1 to 2 per 500 000 people worldwide with almost 900 to 1500 new cases per year in the United States.[28] The median age at diagnosis is close to 30 years and the clinical course in children is similar to adults.[29] Desmoid tumors can infiltrate surrounding tissues and thus can be very difficult to resect, leading to a 50% recurrence rate after surgery.[30] Radiotherapy (RT) can be a therapeutic option for patients who cannot undergo or decline surgery. RT alone or combined with surgery in patients with incomplete resection can achieve long-term local control in approximately 70% to 80% of desmoids, regardless of the volume of the initial tumor.[31] However, Rutenberg et al reported that pediatric patients had lower rates of locoregional control than adults with control rates of 20% versus 63% in those less than 18 years and 18 to 30 years old respectively ($P = .08$).[32] RT is therefore often avoided in the pediatric population due to reduced efficacy, impact on growth of normal structures, and risk of secondary malignancy. In patients without clinical symptoms, desmoid tumors can be observed and for those cases which are unresectable, medical therapy with systemic chemotherapy or molecularly targeted agents can be used.[33]

US-HIFU and MR-HIFU have been used to treat extra-abdominal desmoid tumors in pediatric patients with most reported cases in the lower extremities and buttocks. In 2011, five pediatric patients with an average initial tumor volume of 9.92 mL were treated with a maximum of two US-HIFU treatments, resulting in ablation of 86% (range: 78%–92%) of the tumor volume.[34] In 2017, seven pediatric patients with an average initial tumor vol of 240 mL (range: 4–772 mL) had an average decrease in tumor vol of 73% (range: 39%–100%) over a maximum of four MR-HIFU treatments.[35] An additional four pediatric patients with extra-abdominal desmoid tumors treated with MR-HIFU showed similar success rates with an initial average tumor volume of 321 mL (range: 98–770 mL) and mean tumor ablation of 66% (range: 15%–85%).[36,37] A teenager with a debilitating desmoid in the palm of his right hand in close proximity to the nerves was successfully treated with MR-HIFU[35] and remains symptom-free without recurrence at five years (Fig 3).

The most common adverse effects of HIFU therapy were skin burns, most of which were reversible and treated with topical ointments, although a few patients had more severe burns or burns complicated by infection.[33] Skin burns are a complication of HIFU but not LIFU and most commonly with desmoids and fibroids compared with OO. In a case series of 15 patients with desmoids aged 7 to 66 years, 7 of whom were under 18, Ghanouni et al[35] reported that 8 of 15 had a skin burn. Of the 6 with a second-degree burn, the average distance between the tumor and skin was 4 mm. Of the two with a first-degree burn, both occurred along a surgical scar. Some patients also suffered from nerve injury after HIFU therapy due to the desmoid tumor abutting or encasing the nerve.[33] However, an active skin cooling device has been introduced to reduce the risk of skin burns, which may mitigate some of these events.[38] Overall, the rate of these adverse effects should also decrease with increased physician experience and improved software targeting.

There is currently an ongoing safety and feasibility clinical study at Children's National Hospital in Washington, DC, and Cincinnati Children's Hospital investigating the use of MR-HIFU in thermal ablation of relapsed and refractory pediatric

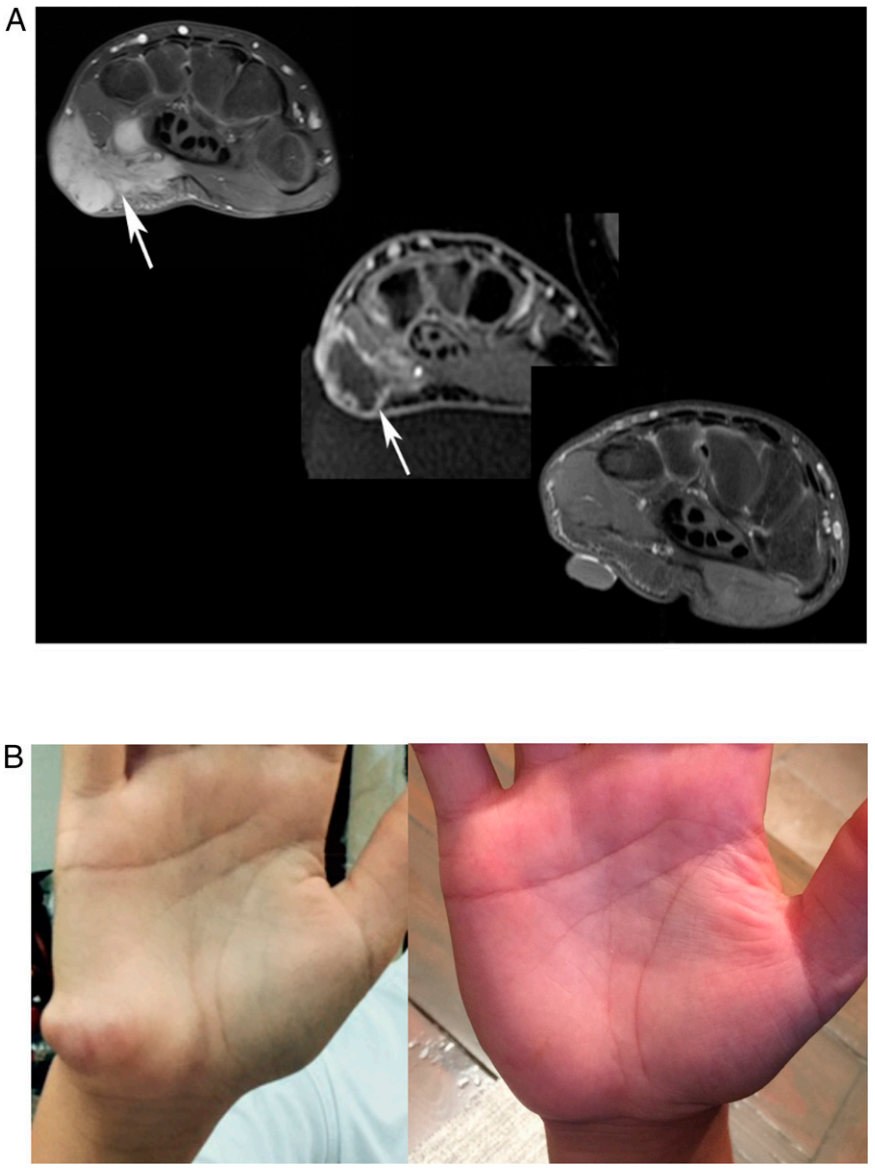

FIGURE 3

Desmoid tumor. A 14-year-old boy with lump on palm of right hand unable to play lacrosse. A, Axial MRI 6 months before HIFU treatment (upper left) demonstrates enhancing desmoid (arrow). Immediate post treatment scan (middle) shows nonperfusion and ablation with some surrounding enhancement (arrow). Twelve months after treatment (lower right) confirms no tumor or residual enhancement. B, Picture of hand with mass before (left) and 12 months after (right) HIFU procedure with complete resolution. Courtesy of Pejman Ghanouni, MD, PhD.

solid tumors including desmoid tumors (NCT02076906).

Soft Tissue Sarcomas

Osteosarcoma, Ewing sarcoma, and soft tissue sarcomas account for nearly 14% of all pediatric malignancies.[39] Children with metastatic or recurrent sarcoma have a poor prognosis with a five-year overall survival rate of 20% to 25%.[39] Neuroblastoma is the most common extracranial pediatric tumor, and is responsible for greater than 10% of childhood cancer-related mortality.[40] Current standard therapy for most sarcomas and high-risk neuroblastomas is systemic chemotherapy combined with surgery and/or radiation.

A preclinical study in mice models with subcutaneous neuroblastoma shows benefit of HIFU thermal ablation alone and in combination with Adriamycin.[41] In addition, HIFU histotripsy combined with checkpoint blockade immunotherapy (αCTLA-4 and αPD-L1) shows impressive survival benefit in a murine neuroblastoma model.[42] The advantage of HIFU and immunotherapy combined is synergistic in enhancing the antitumor response and triggering an abscopal effect in which the local therapy can upregulate immunomodulators that target cancer cells distant to the primary malignancy. This upregulation of immunomodulators is thought to confer long-term immunity and slow subsequent de novo tumorigenesis.[43]

In a study investigating the anatomic feasibility of MR-HIFU therapy in 121 pediatric patients with sarcoma and 61 patients with neuroblastoma, 64% of primary sarcomas and 25% of primary neuroblastomas were targetable with MR-HIFU. However, less than 20% of sarcoma and neuroblastoma metastases were targetable with most targetable lesions located in the extremities or pelvis.[39] In the future, respiratory motion compensation may increase the percentage of targetable tumors.[39] In a study with MR-HIFU and abdominal neuroblastomas, the majority of patients had potentially targetable lesions with a mean targetable volume ranging from 15% to 79%.[44] The potential benefits of FUS therapy for these pediatric tumors include increased efficacy and fewer complications compared with invasive surgeries and RT. Currently, there are Phase 1 clinical studies investigating the safety and feasibility of using MR-HIFU for refractory and relapsed solid tumors with targeted drug delivery

(NCT02536183) and thermal ablation (NCT02076906) as demonstrated in Table 1.

NEUROLOGIC

Epilepsy

An estimated 3 million adults and 470 000 children in the United States have active epilepsy.[45] Current treatments include medication, surgery, radiofrequency or laser ablation, deep brain stimulation (DBS), and stereotactic radiosurgery, all of which have limitations and side effects. FUS therapy has shown success in both preclinical studies and clinical case reports at reducing seizure frequency in adult patients with active epilepsy.

There are several mechanisms by which FUS can treat epilepsy: thermal ablation, neuromodulation, and BBB opening and targeted drug delivery. In 2016, Monteith et al reported that HIFU thermal ablation of mesial temporal lobe epileptic foci is feasible in laboratory models.[46] In 2020, Chen et al found that pulsed LIFU effectively suppressed epileptic activity in animal models and Lin et al reported that pulsed LIFU suppressed epileptiform activities in human pathologic slices by increasing the neural excitability of local inhibitory neurons.[47,48] In preclinical studies, MR-LIFU opened the BBB allowing for the delivery of drugs to targeted epileptic foci, leading to an overall decrease in seizure frequency.[49] Airan et al reported a novel method for using FUS to deliver drugs across the blood brain barrier,[50] which successfully released propofol from nanoparticles silencing drug-induced seizures in rats.[51]

With respect to clinical applications, Parker et al conducted a modeling and feasibility study of MR-HIFU for ablation of mesial temporal circuits in 10 adult patients with essential tremor and 2 patients with mesial temporal sclerosis.[52] The theoretical modeling concluded that MR-HIFU offers a noninvasive option for seizure tract disruption that could result in immediate seizure relief in certain candidates. A recent case report published by Abe et al demonstrated the success of MR-HIFU in treatment of mesial temporal lobe epilepsy in a 36-year-old woman. After a short temporary interval of increased frequency of seizures 1 month post-MR-HIFU treatment, she remained seizure-free with the ability to slowly wean her seizure medication without relapse. Although thermal ablation was the intended mechanism of action for this patient, suboptimal temperatures were achieved during FUS treatment, leading the authors to conclude that neuromodulation was the probable mechanism of action.[53] As part of an ongoing study at Brigham and Women's Hospital, entitled, "Low Intensity Focused Ultrasound Treatment for Drug Resistant Epilepsy: An Efficacy Trial" (NCT 03868293), a 26-year-old woman with drug-resistant epilepsy and mesial temporal lobe sclerosis with a baseline of 1 to 2 seizures per month was treated with LIFU neuromodulation and remained seizure-free for 6 consecutive weeks after 8 sonication sessions over 4 weeks.[54,55]

Currently, there are no clinical studies involving the pediatric population, but there are 6 clinical trials worldwide studying FUS therapy for epilepsy in adults applying thermal ablation and neuromodulation.

Hypothalamic Hamartoma and Other Benign Brain Tumors

Hypothalamic hamartomas (HHs) are rare, benign tumors that emerge during fetal development. HH is estimated to occur in 1 in every 50 000 to 100 000 patients worldwide.[56] There are 2 major clinical phenotypes of HH: (1) central precocious puberty and (2) epilepsy and neurobehavioral symptoms. Historically, treatment has been related to the clinical presentation with medical management to suppress pubertal development and stereotactic targeted radiation therapy, radiofrequency lesioning, or surgery for epilepsy.[57] In 11 patients treated with surgical resection, 3 patients became seizure-free, 8 had over 90% reduction in seizures, and all patients experienced significant improvement in behavior and cognition.[58]

HIFU therapy is a noninvasive alternative to surgical resection or disconnection of the HH and can potentially be used to treat other centrally located benign brain tumors in the pediatric population. Using MRI guidance, the FUS beams can ablate the hamartoma or ablate the connection between the hamartoma and hypothalamus to "disconnect" it from the surrounding brain circuitry (Fig 4). The Focused Ultrasound Foundation newsletter highlighted 2 cases in which pediatric patients with symptomatic HH were treated. The first patient suffering from debilitating seizures initially responded to surgical resection but reoccurred after several years. After a single FUS procedure, MRI scans showed complete ablation of the residual hamartoma and the patient was discharged the following day and "remains seizure-free[59]." The second patient was a 15-year-old girl with hyperphagia gaining an average of 18 pounds every 6 months, but immediately after FUS treatment, her hyperphagia symptoms disappeared. She has experienced no side effects and has

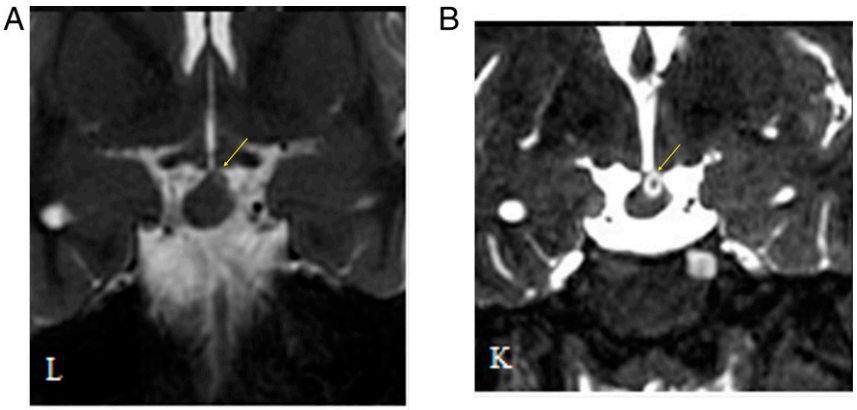

FIGURE 4

Hypothalamic hamartoma. Twenty-one-year-old woman with gelastic seizures and hypothalamic obesity. After HIFU, she became seizure-free and her weight stabilized. A, Coronal T2 image demonstrates remnant of previously resected hamartoma (yellow arrow) along left side of third ventricle. B, Post-HIFU treatment coronal T2 image with new hyperintensity at targeted location (yellow arrow). Courtesy of John Ragheb, MD.

lost 28 pounds since the procedure.[60]

Currently a phase I clinical trial at Nicklaus Children's Hospital in Miami, Florida, is investigating the use of the Insightec Exablate Neuro system in treating benign intracranial tumors, including HH, in pediatric and young adult subjects (NCT03028246).

Diffuse Intrinsic Pontine Glioma

DIPG is an extremely aggressive brain tumor arising from the brain stem and affecting nearly 200 to 400 children in the United States every year.[61] DIPG is uniformly fatal and is the leading cause of childhood brain tumor death. Median survival is nine months with 90% of children dying from the disease within 2 years of initial diagnosis.[62]

A preclinical study by Sewing et al stated that high-grade glioma and DIPG cells were sensitive to anthracyclines, specifically doxorubicin, while sparing normal human astrocytes. Convection-enhanced delivery allowed for adequate concentrations of doxorubicin at the tumor site.[63] Alli et al published that brain stem MR-LIFU BBB opening was feasible and effective allowing for increased and focal doxorubicin delivery in mice.[64]

As there is now ample data from adult clinical trials demonstrating safety and feasibility of BBB opening in patients with brain tumors, a pediatric clinical trial using FUS to improve the delivery of oral Panobinostat in DIPG tumors has started recruitment at Columbia University (NCT04804709).

VASCULAR

Congenital Vascular Malformations

Congenital vascular malformations (CVM) have a prevalence of 4.5% and can be divided into high-flow (arteriovenous malformations and fistulas) and low-flow (venous and lymphatic malformations) lesions. Venous malformations (VM) are the most common subtype of CVM with an incidence of 1 to 2 in 10 000 and a prevalence of 1%, most frequently seen in the head and neck (40%), extremities (40%), and trunk (20%).[65] Though VMs are present at birth, they are not always clinically evident until later in life and can cause local and systemic complications leading to significant morbidity, pain, and discomfort.[66]

The current first-line treatment of VMs is sclerotherapy, which requires a safe route of access and ability to visualize the vascular malformation continuously throughout the procedure.[67] However, if the lesion is unable to be visualized or if access is unfeasible, other treatment modalities such as surgical resection or ablation are considered.

In 2015, van Breugel et al[68] published a case report of an 18-year-old boy with a VM in the lower extremity treated with MR-HIFU with qualitatively sustained pain reduction for 13 months posttreatment. In 2017, Ghanouni et al reported statistically significant improvement in pain and reduction in lesion size without any complications in five patients (median age: 36 years, range: 18–54 years) with painful VM of the extremities treated with MR-HIFU[67] (Fig 5).

Twin-Twin Transfusion Syndrome

Twin-twin transfusion syndrome (TTTS) is a severe complication occurring in 15% of monochorionic-diamniotic twin pregnancies caused by abnormal placental anastomoses that create unbalanced blood flow among twins in utero.[69] TTTS, if left untreated, is 80% to 100% fatal for fetuses, and is the leading cause of death and disability in twins.[69] Fetoscopic laser photocoagulation of placental anastomoses is considered the current standard of treatment, despite meta-analysis data showing no significant survival or neurologic benefit. Laser-treated TTTS is still associated with a perinatal mortality rate of 30% to 50% and a 5% to 20% chance of long-term neurologic deficit.[69]

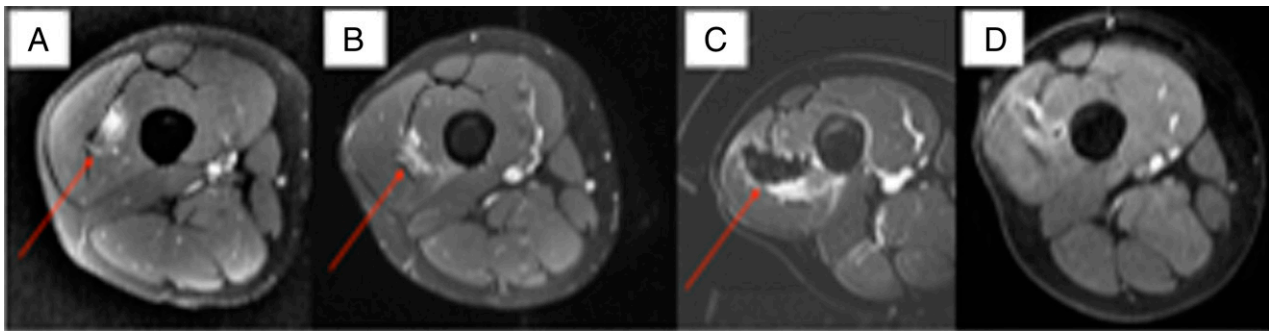

FIGURE 5

Vascular malformation. An 18-year-old boy with pain in lateral right thigh. A, Axial MRI with enhancing vascular malformation before surgery (red arrow). B, Axial MRI 3 months postsurgical excision with recurrence (red arrow). C, Immediate post-HIFU MRI with nonperfusion and ablation of the nidus on postcontrast MRI (red arrow). D, Three-month post-HIFU axial MRI with no residual malformation or pain. Courtesy of Pejman Ghanouni, MD, PhD.

HIFU therapy has the potential to be effective in treatment of TTTS via vascular occlusion, based on preclinical results reporting the consistent occlusion of placental vessels and cessation of blood flow in a pregnant sheep model.[70] The vascular and metabolic fetal responses and short-term safety suggest potential translation to human pregnancies. Okai et al described the successful use of HIFU to noninvasively occlude blood flow for twin reversed arterial perfusion in a human fetus, which offers potential for HIFU treatment of conditions resulting from abnormal placental vasculature.[71] Compared with more conventional invasive therapies for maternofetal vascular complications, HIFU may provide a noninvasive alternative to occlude vascular anomalies while minimizing injury to the mother, the fetus, and the uterus.

Currently, the Imperial College London is planning a first in-human phase 1a study of noninvasive HIFU vascular ablation in the treatment of TTTS (Integrated Research Application System Project ID: 260359).

Pulmonary Hypertension

There are two published preclinical studies exploring the potential benefit of using FUS to treat pulmonary hypertension by creating atrial septal defects in large animal models, one in dogs[72] and the other in pigs.[73]

CONCLUSIONS

This review highlights a wide range of current and potential pediatric applications amenable to treatment with FUS. This unique and noninvasive therapy can treat pediatric musculoskeletal conditions including OO and bone metastases using ablation. Soft tissue tumors including desmoids, sarcomas and neuroblastomas can be treated with HIFU ablation alone, or in combination with targeted chemotherapy delivery. Neurologic applications with FUS include treatment of benign and malignant brain tumors with thermal ablation and BBB opening with targeted drug delivery respectively as well as ablation and neuromodulation for epilepsy. Pediatric vascular applications of FUS include treatment of both CVM and TTTS using ablation with vascular occlusion. With increasing FUS experience in the adult population, other pediatric applications will likely follow and improve the care of children with a variety of diseases.

ABBREVIATIONS

BBB: blood brain barrier
CT-RFA: computer tomography image–guided percutaneous radiofrequency ablation
CVM: congenital vascular malformations
DIPG: diffuse intrinsic pontine glioma
FUS: focused ultrasound
HH: hypothalamic hamartoma
HIFU: high-intensity focused ultrasound
LIFU: low-intensity focused ultrasound
MR-HIFU: magnetic resonance–guided high-intensity focused ultrasound
NSAID: nonsteroidal anti-inflammatory drug
OO: osteoid osteoma
RT: radiotherapy
TTTS: twin-twin transfusion syndrome
US-HIFU: ultrasound-guided high-intensity focused ultrasound
VM: venous malformation

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