An update on the role of focused ultrasound in neuro-oncology

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Purpose of review
Brain tumor treatment presents challenges for patients and clinicians, with prognosis for many of the most common brain tumors being poor. Focused ultrasound (FUS) can be deployed in several ways to circumvent these challenges, including the need to penetrate the blood–brain barrier and spare healthy brain tissue. This article reviews current FUS applications within neuro-oncology, emphasizing ongoing or recently completed clinical trials.

Recent findings
Most clinical interest in FUS for neuro-oncology remains focused on exploring BBB disruption to enhance the delivery of standard-of-care therapeutics. More recently, the application of FUS for radiosensitization, liquid biopsy, and sonodynamic therapy is garnering increased clinical attention to assist in tumor ablation, early detection, and phenotypic diagnosis. Preclinical studies show encouraging data for the immunomodulatory effects of FUS, but these findings have yet to be tested clinically.

Summary
FUS is a burgeoning area of neuro-oncology research. Data from several forthcoming large clinical trials should help clarify its role in neuro-oncology care.

Keywords
blood–brain barrier, brain tumors, focused ultrasound, liquid biopsy, tumor ablation

INTRODUCTION

Brain tumors can be categorized as primary to the central nervous system or metastatic from systemic cancers, including melanoma, lung cancer, and breast cancer [1–4]. Brain tumors account for substantial morbidity and mortality, posing significant challenges for clinical management. Brain tumor treatment remains challenged by the blood–brain barrier (BBB), which restricts the penetration of systemic therapies, an immunosuppressive micro-environment and difficulties of developing therapies with minimal toxicity to healthy brain tissue [5–9]. For example, patients diagnosed with the most common primary brain malignancy, glioblastoma multiforme (GBM), face a poor prognosis with median survival of 14–15 months [3,10,11]. Furthermore, little change in standard-of-care treatment has occurred since the Stupp protocol was adopted in 2005 [3,10,12]. As such, novel treatments must be evaluated to improve clinical outcomes for these patients.

Focused ultrasound therapy (FUS) is an emerging technology that addresses these issues. Specialized devices, such as a curved transducer, lens, or phased arrays, direct ultrasound to precise targets [13]. By maximizing energy delivery to targeted tissues, FUS noninvasively exerts biological effects with great spatial precision and minimal effects on intervening tissue [13,14]. The therapeutic effects of FUS depend on ultrasound parameters such as transducer frequency, pulse duration, duty cycle, power, and tissue properties [13,15,16]. Off-target effects with cranial applications can result from scatter at interfaces between tissues with large differences in acoustic impedance (e.g. soft tissue and bone), or energy absorption by bone [17]. Low-intensity FUS (LIFU) is primarily utilized for BBB opening, radiation sensitization, neuromodulation, and sonodynamic therapy

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KEY POINTS

- Treating brain tumors with FUS is an emerging field under investigation for safety and feasibility in multiple ongoing phase I–III clinical trials.
- Most FUS applications in neuro-oncology utilize BBBO to facilitate therapeutic penetrance, with increasing interest in liquid biopsy, radiosensitization, histotripsy, and immunomodulation.
- Although thermoablation via MR-guided FUS is approved for lesioning in functional neurosurgery, technical limitations still prevent the ablation of large volumes of tissue and tumors in superficial locations.

(SDT) whereas high-intensity FUS (HIFU) is utilized for thermal ablation (Fig. 1) [16,18–21]. Other FUS applications include hyperthermia, histotripsy, and mechanical microbubble-enhanced ablation (Table 1). Currently, FUS devices investigated in clinical trials stem from several manufacturers, most commonly utilizing the Insightec ExAblate, Carthera Sonocloud, or NaviFUS devices (Fig. 2). The ExAblate device (Insightec, Haifa, Israel) consists of a hemispherical phased array of 1024 extracranial FUS transducers for precise, noninvasive HIFU lesioning at 650 kHz (Exablate 4000 Type 1) or LIFU applications such as BBB opening (Exablate 4000 Type 2) operating at 220 kHz [22]. The NaviFUS system (NaviFUS, Taiwan) operates at 500 kHz and uses optical neuronavigation to position a 256-element transducer over a target, allowing noninvasive BBB opening and other LIFU applications with only a single set of pretreatment MRI and computed tomography (CT) images for guidance treatment planning and guidance [23,24]. Both the Exablate and NaviFUS devices monitor cavitation signals to facilitate LIFU dosing [25,26].

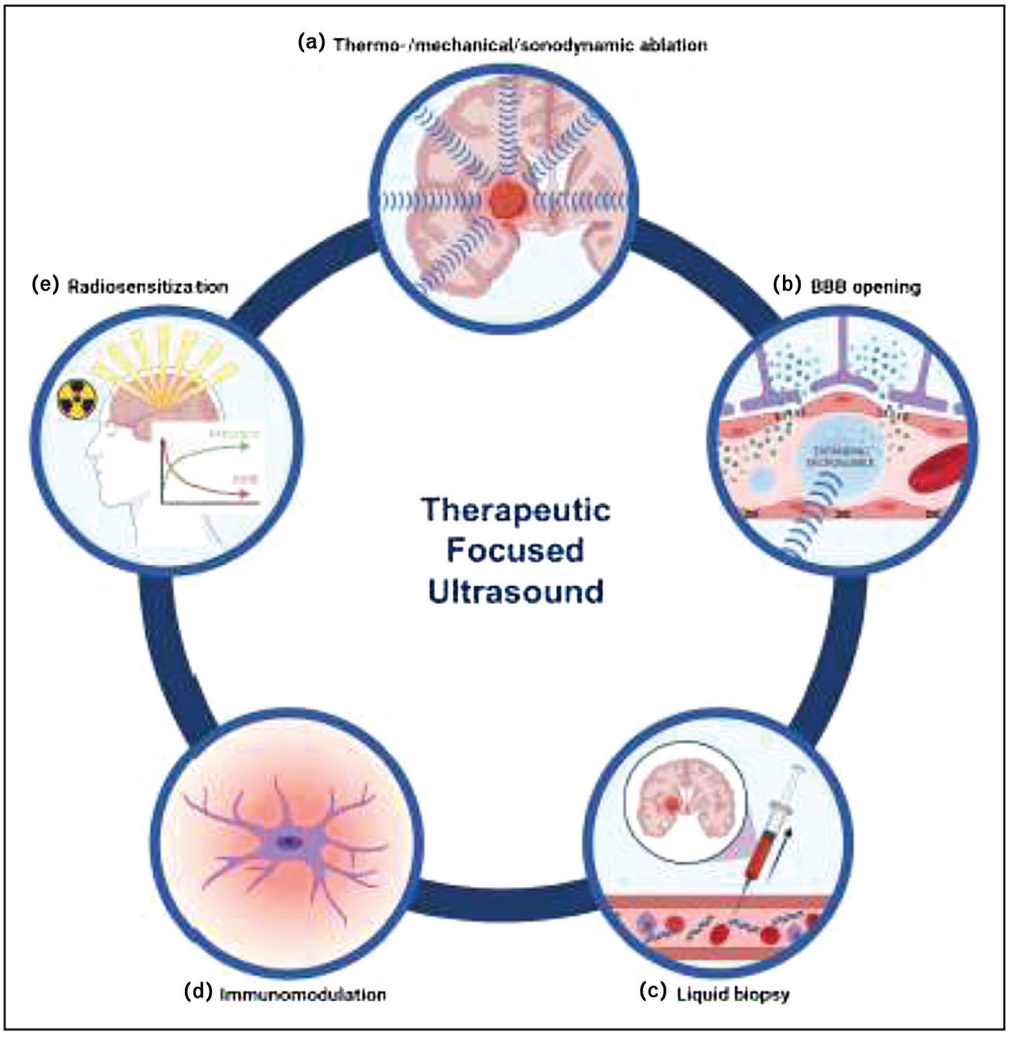

FIGURE 1. Summary of biological effects induced by focused ultrasound. FUS can induce multiple effects on target tissues based on sonication parameters, intensity, the presence of ultrasound sensitive molecules (e.g. microbubbles, sonosensitizers), and the induction of mechanical vs. thermal effects. Reproduced from Meng *et al.*, 2021 [89]. FUS, focused ultrasound.

Table 1. Summary of biological effects of focused ultrasound

FUS modality	FUS intensity	Mechanical vs. thermal effects	Additional therapeutic	Description
Blood–brain barrier opening	LIFU	Mechanical	Yes – intravenous microbubbles (e.g. DEFINITY, Sonovue, Optison)	Transient openings of the BBB to increase therapeutic penetrance and modulate biological processes.
Sonodynamic therapy	LIFU	Mechanical	Yes – sonosenzitizing agent (e.g. 5-ALA, fluoroscein)	Conversion of inactive drugs into cytotoxic therapies.
Liquid biopsy	LIFU	Mechanical	Yes – intravenous microbubbles (e.g. DEFINITY, Sonovue, Optison)	Enriching circulating levels of tumor biomarkers through BBB opening or mechanical effects on tissue.
Histotripsy	HIFU	Mechanical	No	High-amplitude, brief FUS pulses generate endogenous microbubbles that mechanically liquify tissue.
Radiosensitization	LIFU/HIFU	Thermal/ mechanical	Hyperthermia: no Nonthermal: yes – intravenous microbubbles (e.g. DEFINITY, Sonovue, Optison)	Enhancing tissue response to radiation via hyperthermia or mechanical effects.
Thermal ablation	HIFU	Thermal	No	Focal heating of targeted tissue induces coagulative necrosis.
Microbubble-enhanced ablation	HIFU	Mechanical	Yes – intravenous microbubbles (e.g. DEFINITY, Sonovue, Optison)	Exogenous microbubbles serve as a substrate for mechanical ablation of tissue via FUS

FUS, focused ultrasound; HIFU, high-intensity focused ultrasound; LIFU, low-intensity focused ultrasound.

With a different approach, the Sonocloud devices (Carthera, Paris, France) involve intracranial implantation of one, three or nine 1 MHz FUS transducers (Sonocloud-1/3/9) at the intended target [27,28▪,29]. Sonocloud systems offer less controllable targeting once implanted but allow repeated BBB opening in the long-term, without the need for online image guidance. ExAblate devices provide high accuracy at arbitrary deep brain targets with real-time MRI monitoring [30], which on the other hand poses limitations such as scalability and cost. NaviFUS strikes a balance between the two, allowing arbitrary targeting of, for example, new lesions or extents of tumor growth without the need for concurrent MRI guidance with more precision than Sonocloud devices but less than Exablate. NaviFUS can also be limited in its ability to target deep brain structures [31]. Additional emerging FUS devices include the neuronavigation-based ImaSonics, and Therawave devices and conformal cap-based Concordance NeuroAccess device [23,24].

The objective of this review is to provide an update of the recent device developments and clinical trial results for LIFU and HIFU in neuro-oncology.

BLOOD–BRAIN BARRIER DISRUPTION

One of the most exciting applications of FUS is for transient BBB disruption (BBBD). The BBB limits exposure of brain parenchyma to most hydrophilic and large-molecular-weight substances in systemic circulation, with tight junctions between capillary endothelial cells limiting paracellular transport. Transcellular transport is simultaneously limited by reduced vesicular transport and multidrug resistance (MDR) transporters such as P-glycoproteins [13,32,33]. Combined, these features limit the entry of many therapeutics into brain tissue, impairing treatment efficacy [34,35]. Importantly, MDR transporters may still significantly limit drug delivery where the BBB is otherwise disrupted, as often seen in CNS tumors [36]. Physical BBB opening (BBBO) with FUS and other approaches may circumvent these limitations. Intra-arterial mannitol allows BBBO at downstream capillaries but results in a target area dependent on the vascular distribution [37].

LIFU with intravascular microbubbles (i.e. ultrasound contrast agents widely employed in diagnostic ultrasound [38,39]) can disrupt the BBB with high spatial specificity [40–43]. Exogenous microbubble administration reduces the energy requirements of FUS BBBO, obviating the need to generate endogenous microbubbles [17]. When excited by ultrasound, the microbubbles oscillate through periods of expansion and contraction, exerting mechanical stress on capillary walls [44]. This mechanical force transiently disrupts tight junctions of capillary endothelial cells, enhances transcellular transport systems, and downregulates MDRs [40,44–46]. Additionally, microbubble activity within targeted tissues can be assessed and

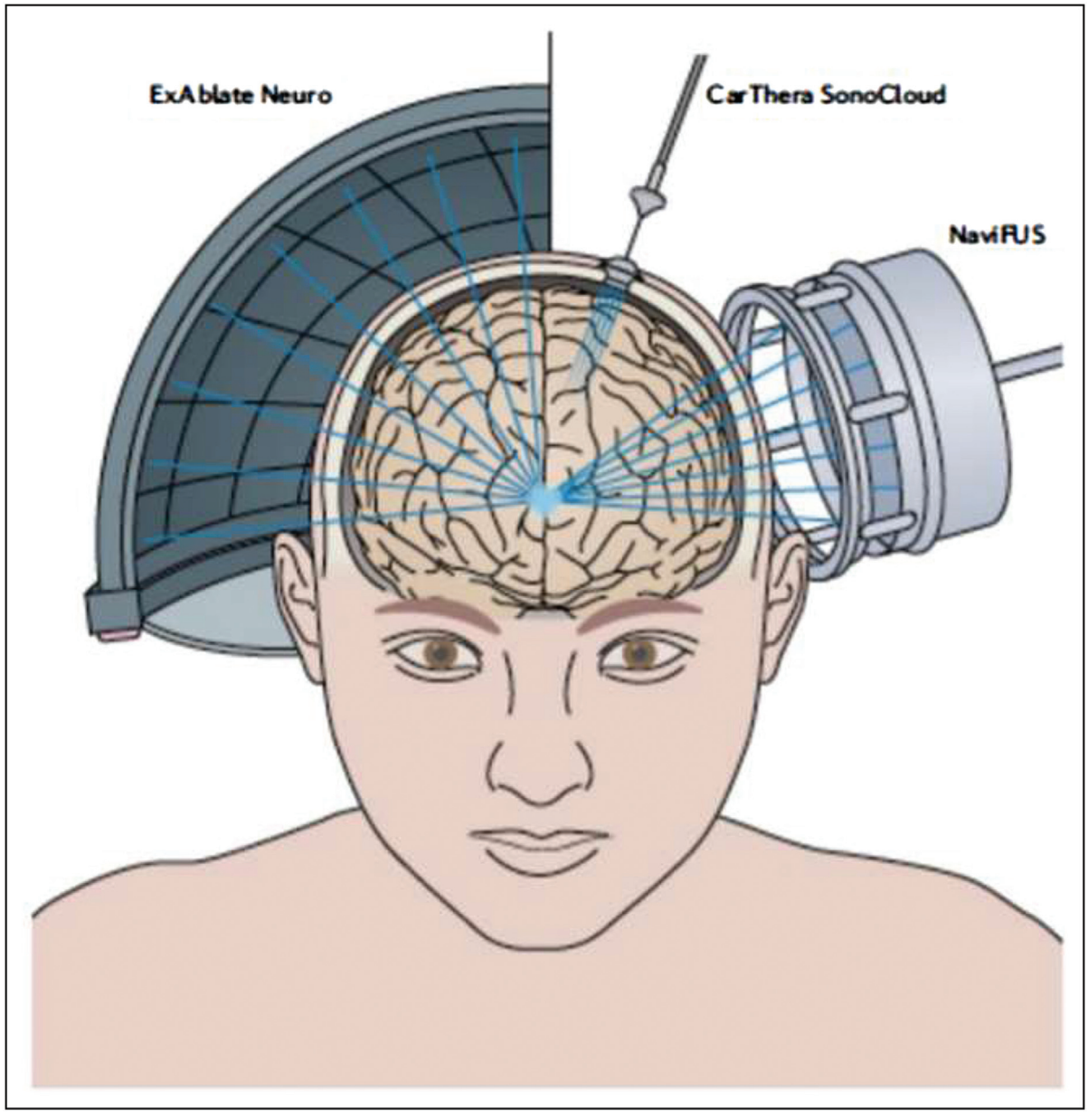

FIGURE 2. Commonly investigated ultrasound devices for neuro-oncology. The ExAblate device utilizes MR images with a transcranial phased array of ultrasound transducers. The CarThera SonoCloud device requires intracranial implantation of ultrasound transducers. The NaviFUS device is a transcranial handheld neuronavigated device capable of inducing LIFU. Reproduced from Meng *et al.*, 2021 [13]. LIFU, low-intensity focused ultrasound.

controlled with cavitation feedback methods measuring reflected ultrasound, allowing precision ultrasound 'dosing' at individual targets [26,47].

Ongoing clinical trials for blood–brain barrier opening

Most ongoing clinical trials are investigating the role of LIFU-induced BBBO for chemotherapeutic drug delivery to brain tumors (Table 2). For instance, FUS BBBO for enhancing temozolomide delivery in patients with GBM is being evaluated in several phase 1/2 trials (NCT04614493, NCT03551249, NCT03616860, NCT03712293, and NCT04998864). Similarly, prompted by promising results of preclinical studies [48,49,50▪], several clinical trials are investigating FUS BBBO to enhance carboplatin and/or paclitaxel delivery in recurrent glioblastoma (rGBM) (NCT04528680, NCT05902169, NCT03744026, NCT04440358, NCT04417088). Achieving therapeutic concentrations of carboplatin and paclitaxel in CNS tumors is limited by the BBB [28▪,50▪,51,52▪,53]. However, a 4.2-fold increase ($P = 0.0098$) in carboplatin penetrance following BBBO has been observed

Table 2. Summary of ongoing and recently completed trials using focused ultrasound for brain tumor treatment registered on ClinicalTrials.gov

NCT number	Disease	Trial progress	FUS Device	FUS indication	Trial description	Study location (number of centers)
NCT03028246	Benign pediatric brain tumors	Ongoing	ExAblate 4000	Thermal ablation	Open label, estimated 10 participants	USA (2)
NCT03322813	Infiltrating glioma/ oligodendrocytoma	Completed	ExAblate 4000 Type 2	BBBO prior to surgical resection	Phase 0 clinical trial, 4 participants	USA (1)
NCT03551249	High-grade glioma	Completed	ExAblate 4000 Type 2	BBBO for temozolomide delivery	Phase 1 clinical trial, 20 participants	USA (4)
NCT03616860	Glioblastoma	Completed	ExAblate 4000 Type 2	BBBO for temozolomide delivery	Phase 1 clinical trial, 14 participants	Canada (1)
NCT03712293	Glioblastoma	Completed	ExAblate 4000 Type 2	BBBO for temozolomide delivery	Phase 1 clinical trial, 9 participants	South Korea (1)
NCT03744026	Recurrent glioblastoma	Completed	Sonocloud-9	BBBO for carboplatin delivery	Phase 1/2a clinical trial, 38 participants	USA (3), France (4)
NCT04021420	Metastatic melanoma	Ongoing	Sonocloud-9	BBBO for nivolumab delivery	Phase 1/2 clinical trial, estimated 21 participants	France
NCT04417088	Recurrent glioblastoma	Ongoing	ExAblate 4000 Type 2	BBBO for carboplatin delivery	Phase 1/2 clinical trial, estimated 30 participants	USA (4)
NCT04440358	Recurrent glioblastoma	Ongoing	ExAblate 4000 Type 2	BBBO for carboplatin delivery	Phase 1/2 clinical trial, 13 participants	Canada (1), Italy (1), South Korea (1)
NCT04446416	Recurrent glioblastoma	Completed	NaviFUS	BBBO for bevacizumab delivery	Phase 1 clinical trial, 6 participants	Taiwan (1)
NCT04528680	Recurrent glioblastoma	Ongoing	Sonocloud-9	BBBO for paclitaxel and carboplatin delivery	Phase 1/2 clinical trial, estimated 57 participants	USA
NCT04559685	High-grade glioma	Ongoing	ExAblate	Sonodynamic Therapy with 5-ALA	Phase 1 clinical trial, estimated 30 participants	USA (1)
NCT04614493	Glioblastoma	Ongoing	Sonocloud-9	BBBO for temozolomide delivery	Phase 2 clinical trial, estimated 66 participants	Multicenter (International)
NCT04804709	Progressive diffuse midline glioma	Ongoing	NaviFUS	BBBO for panobinostat delivery	Phase 1 clinical trial, 3 participants	USA (1)
NCT04845919	Glioblastoma	Ongoing	ExAblate 4000 Type 2	Sonodynamic Therapy with 5-ALA	Phase 2 clinical trial, estimated 5 participants	Italy (1)
NCT04940507	Glioblastoma	Ongoing	ExAblate 4000 Type 2	Liquid biopsy	Phase 1 clinical trial, estimated 50 participants	Canada (1)
NCT04988750	Recurrent glioblastoma	Ongoing	NaviFUS	Radiation sensitization following temozolomide and bevacizumab treatment	Open label, estimated 8 participants	Taiwan (1)
NCT04998864	Glioblastoma	Ongoing	ExAblate 4000 Type 2	BBBO for temozolomide delivery	Phase 1 clinical trial, estimated 5 participants	Italy (1), Spain (1)
NCT05123534	Diffuse intrinsic pontine glioma/diffuse midline glioma	Ongoing	ExAblate 4000 Type 2	Sonodynamic Therapy with 5-ALA	Phase 2 clinical trial, estimated 40 participants	USA (4)
NCT05281731	Glioblastoma	Ongoing	Imasonics	Liquid biopsy	Open label, estimated 40 participants	USA (1)
NCT05293197	Malignant pediatric brain tumor	Ongoing	Sonocloud-9	BBBO for carboplatin delivery	Phase 1 clinical trial, estimated 24 participants	France
NCT05317858	Nonsmall cell lung cancer brain metastases	Ongoing	ExAblate 4000 Type 2	BBBO for pembrolizumab delivery	Phase 3 clinical trial, estimated 20 participants	USA (4), Canada (1), South Korea (3)
NCT05370508	Recurrent glioblastoma	Ongoing	ExAblate 4000 Type 2	Sonodynamic therapy with 5-ALA	Phase 1/2 clinical trial, 8 participants	USA (5)
NCT05383872	Glioblastoma	Ongoing	ExAblate 4000 Type 2	Liquid biopsy	Phase 1 clinical trial, estimated 57 participants	USA (14), Canada (1)
NCT05615623	Diffuse intrinsic pontine glioma	Ongoing	ExAblate 4000 Type 2	BBBO for doxorubicin delivery	Phase 1/2 clinical trial, estimated 3 participants	Canada (1)

Table 2 (*Continued*)

NCT number	Disease	Trial progress	FUS Device	FUS indication	Trial description	Study location (number of centers)
NCT05630209	Diffuse intrinsic pontine glioma	Ongoing	ExAblate 4000 Type 2	BBBO for doxorubicin delivery	Phase 1/2 clinical trial, estimated 10 participants	USA (2)
NCT05733312	Glioma	Ongoing	ExAblate 4000 Type 2	BBBO for TME characterization	Phase 1 clinical trial, estimated 6 participants	USA (1)
NCT05762419	Diffuse intrinsic pontine glioma	Ongoing	NaviFUS	BBBO for etoposide delivery	Phase 1 clinical trial, estimated 10 participants	USA (1)
NCT05864534	Glioblastoma	Ongoing	Sonocloud-9	BBBO for balstilimab, botensilimab, and doxorubicin delivery	Phase 2 clinical trial, estimated 25 participants	USA
NCT05879120	Recurrent glioblastoma	Ongoing	ExAblate 4000 Type 2	BBBO for pembrolizumab delivery	Phase 2 clinical trial, estimated 10 participants	USA (1)
NCT05902169	Recurrent glioblastoma	Ongoing	Sonocloud-9	BBBO for carboplatin delivery	Phase 3 clinical trial, estimated 560 participants	USA (3), Belgium (3), France (3), Germany (1), Italy (1), Netherlands (1), Spain (1)
NCT06039709	Recurrent glioblastoma	Ongoing	NaviFUS	Sonodynamic therapy with 5-ALA	Phase 1 clinical trial, estimated 11 participants	USA (1)
NCT06329570	Recurrent glioblastoma	Ongoing	NaviFUS	BBBO for bevacizumab delivery	Phase 1/2 clinical trial, estimated 10 participants	USA (1)

5-ALA, 5-aminolevulinic acid; BBBO, blood–brain barrier opening; RS, radiosensitization; SDT, sonodynamic therapy; TME, tumor microenvironment.

preclinically, suggesting FUS may be used to overcome this limitation [48].

A recent phase 1/2 study in 33 rGBM patients using the Sonocloud-9 device showed successful BBB disruption at 90% of sonicated targets [52▪]. Additionally, a patient cohort ($n = 12$) treated with intravenous carboplatin immediately prior to sonication displayed a promising mean overall survival of 14 months [52▪]. These findings have prompted further investigations, including a phase 3 clinical trial comparing FUS BBBO for carboplatin delivery with oral lomustine or temozolomide with an estimated enrollment of 560 patients (NCT05902169). Recruitment for this study began in January 2024 and remains ongoing, with study completion expected in June of 2028.

FUS BBBO is also being investigated in phase 1/2 trials for increasing the penetrance of doxorubicin (NCT05615623, NCT05630209) and etoposide (NCT05293197) to diffuse intrinsic pontine gliomas or diffuse midline gliomas in pediatric patients. With the Sonocloud-9 device, BBBO is being evaluated alongside carboplatin administration for pediatric populations with recurrent supratentorial brain malignancies (NCT05293197).

Blood–brain barrier opening and immunomodulation

Considerable interest exists in FUS BBBO for immunomodulation, not only via increased delivery of immunotherapies [54–56] but also through induction of local immunological responses [25,57–59]. In separate phase 2 trials for novel and recurrent GBM, BBBO is being investigated for enhanced delivery of concurrent doxorubicin, balstilimab, and botensilimab or pembrolizumab, respectively (NCT05864534 and NCT05879120). BBBO induced by the ExAblate device is currently being evaluated alongside pembrolizumab administration in a phase 3 trial for nonsmall cell lung cancer brain metastases (NCT05317858). Recent and ongoing trials are also investigating FUS BBBO-induced immunological responses as secondary or exploratory endpoints (e.g. NCT04614493 and NCT03626896) [25].

LIQUID BIOPSY

Liquid biopsy is a rapidly evolving diagnostic technique utilizing noninvasively obtained blood, urine, and other body fluid samples to screen for the presence of tumor biomarkers, including circulating tumor DNA (ctDNA) and circulating tumor cells (CTC) [60,61]. Liquid biopsy is particularly promising for earlier detection of recurrent tumors, diagnosis of lesions unsuitable for biopsy, tailoring treatments based on individual tumor phenotypes, and better prognostic determinations [62–64]. Early detection of genetic changes in the tumor during treatment will facilitate the tailoring of therapy based on that information. Reliable liquid biopsy of brain tumors has proved difficult as ctDNA and

CTCs are restricted from entering systemic circulation by the BBB [61]. Primary brain tumors exhibit poor ctDNA detectability, with less than 50% of patients presenting with detectable ctDNA levels [61]. Indeed, detectable levels of ctDNA are present in less than 10% of patients with gliomas [61]. Cerebrospinal fluid provides a higher yield of ctDNA and represents another avenue of investigation alongside FUS [65].

FUS BBBO has demonstrated promise by liberating brain tumor biomarkers into systemic circulation in preclinical models and human patients [66–69]. Prior reports in mouse and porcine GBM models show increased ctDNA expression of EGFRvIII and TERT C228T mutations following BBBO [69]. Currently, two ongoing studies aim to increase systemic concentrations of tumor biomarkers by transiently inducing BBBO in GBM patients using LIFU (NCT05383872 and NCT05281731). Additionally, partial tumor ablation with HIFU is being clinically evaluated to increase ctDNA concentrations, with the diagnostic value being assessed against a control group of patients undergoing HIFU thermal ablation for essential tremor (NCT04940507).

RADIOSENSITIZATION

Radiation therapy is a standard of care for patients presenting with both brain metastases [70,71] and primary brain tumors [12,72,73]. Whole-brain radiation therapy has long been a mainstay of treatment for patients with brain metastases. However, cognitive decline following treatment has pushed clinicians to favor radiosurgery as a more localized therapy [74–76]. Increased cumulative radiation therapy exposure is associated with radiation necrosis and may increase the risk of cognitive deficits following treatment, particularly in pediatric patients [77,78]. Cumulative radiation exposure is of particular concern for patients presenting with recurrent tumors [79]. For example, a 5–7% incidence of radiation necrosis was reported in pediatric brain tumor patients following reirradiation with conventional radiation doses [80], and rates as high as 24% have been reported at the highest cumulative doses in patients with GBM [79]. As off-target effects of radiation increase alongside administered radiation dosage, a current focus exists on developing radiosensitizers to minimize radiation administration while achieving the same therapeutic benefit [81–83].

One historical method to induce radiosensitization is tissue hyperthermia, which increases the radiation sensitivity of targeted tissue by multiple mechanisms, including impaired DNA damage repair, immunomodulation, and increased tissue perfusion and oxygenation [84,85]. A 1998 phase 3 clinical trial in GBM patients showed a significant 2-year survival increase of 16% in patients receiving hyperthermia alongside radiation compared with those receiving radiation therapy alone [86]. Despite this, clinical interest in hyperthermia has declined because of concerns regarding overall treatment toxicity and the requisite invasiveness of hyperthermia induction [85]. However, FUS has reinvigorated clinical interest in hyperthermia for radiosensitization by noninvasively producing localized hyperthermia with real-time MR thermometry monitoring [87–89]. Only one pilot study of scanning FUS hyperthermia for radiosensitization in the absence of MRI guidance has been completed, and it was reported in 1991 [90]. This trial suggested the feasibility of this approach, successfully achieving hyperthermia during at least one treatment for all 11 patients reported, with evidence of radiation and/or thermal necrosis at the treated site in all patients for whom postmortem tissue was available [90].

In addition to hyperthermia, numerous preclinical studies have identified a mechanical radiosensitizing effect of LIFU with microbubbles on various tumor tissues, with up to 10-fold increases in cytotoxicity reported in some cancers [91–94]. In this formulation, FUS appears to achieve radiosensitization via a mechanism distinct from hyperthermia, involving augmented ceramide production in endothelial cells and altered tissue perfusion [91–93]. Recent preclinical studies support the radiosensitizing effects of LIFU with microbubbles in glioma models [92,95▪]. These findings have led to establishing an ongoing open-label clinical trial utilizing FUS for BBBO during reirradiation of rGBM (NCT04988750). Preliminary results of this study suggest the combination of FUS with radiation therapy is feasible, although one patient developed grade 3 radiation necrosis [95▪]. Future results are expected to detail the dosimetric effects of radiation therapy. Further clinical trials are necessary to determine the feasibility and effectiveness of FUS-induced radiosensitization.

TUMOR ABLATION

Tumor ablation can be achieved with FUS via thermal ablation, histotripsy, microbubble-enhanced ablation, and SDT. Thermal ablation utilizes HIFU to heat target cells past 55 °C, inducing coagulative necrosis [96]. Although thermal ablation is clinically approved for treating movement disorders, brain tumors remain problematic in part because of tumor volume and common locations [89]. McDannold *et al.* [97] first showed that FUS can noninvasively elevate intracranial temperatures in three brain

tumor patients but could not achieve the required temperature thresholds for coagulative necrosis. In 2014, the first successful treatment using thermal ablation was conducted by Coluccia *et al.* in a GBM patient [98]. Notably, this ablation only involved a small volume (0.7 cm^3) of a larger tumor (6.5 cm^3) [98]. Although feasible, thermal ablation for brain tumors remains limited to very small volumes because of skull heating and the associated need for cooling periods between sonications [98,99]. The impact of skull heating and attenuation of acoustic energy restricts thermal ablation to deep centrally located targets where many transducers spread across a large surface area of the skull can be focused [100]. Targets too close to the skull surface result in excessive reflection of ultrasound energy due to high incident angles of many transducers, resulting in only a small number of transducers able to effectively contribute to target heating, while targets near the skull base are limited by heating of the underlying bone behind the target [87,100] One report showed that to avoid undesired tissue damage, thermal ablation can only lesion targets located between 2 and 4 cm deep to the skull [101]. As a result of these factors, thermal ablation currently receives minimal clinical interest.

Histotripsy and microbubble-enhanced ablation utilize cavitation endogenous microbubbles generated by FUS or exogenous intravascular microbubbles to mechanically disrupt targeted tissues [100–103]. Currently, histotripsy is being evaluated in multiple clinical trials for ablation of liver, pancreatic, and renal cancers (NCT06282809, NCT04573881, NCT04572633, NCT05432232, NCT05820087). The nonthermal mechanisms of histotripsy and related techniques present an opportunity to overcome the limitations of skull-heating in thermal ablation [104]. Furthermore, while histotripsy can generate endogenous microbubbles at a focal target for nonthermal ablation [103], exogenous microbubbles may present an additional opportunity to restrict effects to highly vascular tissues such as tumors or grey matter while limiting effects in less vascular tissues such as white matter tracts [100,102]. Notably, unlike coagulative thermal lesions, histotripsy liquifies target tissue, resulting in the rapid release of a large number of antigens in their native conformation and promoting abscopal immunological responses [105,106]. The generation of precise lesions of arbitrary shape with minimal edema or hemorrhage has been demonstrated in a porcine model following partial craniectomy [107]. Furthermore, histotripsy in the porcine brain has been demonstrated through cadaveric human skull fragments [108], and microbubble-enhanced nonthermal ablation has been successfully achieved through the intact skull of nonhuman primates using ExAblate 4000 [100]. Although these early reports are promising, no clinical trials using histotripsy for brain tumors are ongoing.

SDT utilizes LIFU to induce reactive oxygen species at the sonication target, thereby converting preadministered small, nontoxic molecules (sonosensitizers) into cytotoxic compounds capable of inducing tumor cell death [109–111]. 5-aminolevulinic acid (5-ALA) is often the sonosensitizer of choice as it shows strong preclinical BBB penetration, however, other sonosensitizers, including fluorescein, can also be utilized [112,113]. Multiple early-phase clinical trials are using SDT with a 5-ALA sonosensitizer for the treatment of multiple types of gliomas (NCT05123534, NCT04845919, NCT04559685, NCT05370508, NCT06039709) [114▪,115]. Preclinical studies have identified fluorescein accumulation only at sites with BBBO associated with tumor localization, suggesting the specificity of fluorescein for tumors yet to be clinically explored [116]. In other studies, temozolomide has shown increased cytotoxicity when combined with SDT [117], as well as induction of antitumoral immunological responses [118,119]. Such results raise the possibility of SDT to overcome chemoresistant and immunosuppressive phenotypes often observed in brain tumors such as GBM.

CONCLUSION

Studies employing FUS for neuro-oncological indications have focused on BBB disruption with LIFU for enhanced drug delivery. Future studies should seek to deliver a wider range of therapeutics, including a greater variety of monoclonal antibodies, cellular immunotherapies, and gene therapies. Notably, therapeutics with poor BBB permeability may be particularly well suited to delivery with FUS, as their effects within the CNS are likely to be limited only to targeted brain regions. Similarly, delivery of drugs using delivery vectors optimized for combination with FUS, such as ultrasound-sensitive drug-loaded nanodroplets or nanoparticles that release payloads at the sonication target while simultaneously forming microbubbles supporting local BBB disruption, provides an exciting opportunity to increase local drug concentrations further while limiting off-target effects [120].

Additionally, future trials should seek to capitalize on the synergistic effects of FUS with existing treatments. For example, FUS BBBO can enhance chemotherapies' delivery and increase tumors' sensitivity to radiation, making it an attractive adjunct to standard-of-care chemoradiation. Similarly, FUS for nonthermal ablation presents an exciting opportunity to enhance the delivery of immunotherapies

such as immune checkpoint inhibitors while stimulating local and systemic immune responses, potentially augmenting local and abscopal antitumoral immune responses [106,121,122]. Indeed, one can envision the possibility of using FUS in an integrated fashion throughout the entire clinical care pathway of neuro-oncological diseases, from liquid biopsy to diagnose and monitor lesions, FUS ablation for incision-less surgery, to FUS BBBO for augmenting drug delivery and radiation response, with various combinations thereof to diagnose and manage recurrent illness. Overall, FUS represents an intriguing and tailored approach to brain tumor treatments with applications ranging from inducing BBBO to tumor ablation. Future research is required to validate these reports and determine the efficacy of FUS in neuro-oncology.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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