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Focused ultrasound for brain metastases

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Abstract

Brain metastases (BMs) increasingly represent a significant cause of morbidity and mortality in cancer patients. The efficacy of systemic therapies for BMs, in contrast to extracranial metastases (EMs), remains limited secondary to a host of challenges. These include insufficient drug delivery due to the blood–brain barrier and blood-tumor barrier, the unique immunological milieu in the tumor microenvironment and cerebrospinal fluid, the diversity of immunogenomic landscapes in BMs across genetically distinct malignancies, the branching evolution of BM from EMs, and the challenges in longitudinally obtaining information regarding clinically actionable genetic alterations in BMs for precision oncology. These complex, long-standing challenges require treatment strategies that address multiple problems concurrently, as represented by the potential of focused ultrasound (FUS) for enhancing effectiveness of several existing BM-specific management strategies. Beyond historically investigated applications of FUS for BMs, including thermoablation and histotripsy, new frontiers include enhanced drug delivery of systemic therapies, plasma sono-liquid biopsy of BM-derived factors, radiosensitization, and immunomodulation. These applications, as discussed here, enable multiple combinatorial opportunities of FUS with targeted- and/or immunotherapies for BMs. With multiple ultrasound delivery platforms (including MR-guided, neuro-navigation-guided, and implantable devices) being investigated in neuro-oncology trials worldwide, this review provides strategies for designing and optimizing future research efforts.

Key Points

- Transcranial FUS for BM is now clinically feasible due to integrated image guidance, real-time monitoring, and closed-feedback-loop power control.
- Major need for multicenter trials, with nested translational investigations, and FUS research consortia (like ReFOCUSED) multicenter trials.

Brain metastases (BMs) increasingly represent a significant cause of morbidity and mortality in cancer patients.[1,2] Despite advancements in standard-of-care (SOC) therapies, median survival after a new diagnosis of BM remains around four months.[3] In the United States, 70,000–400,000 new cases of BMs are estimated to be diagnosed annually,[4,5] with 10%–40% of individuals with solid tumors developing BMs across their clinical course.[1,6] BMs most frequently arise from lung cancer, breast cancer, and melanoma, amongst others.[7,8]

Unfortunately, the remarkable clinical benefit that has been seen for extracranial metastases (EMs) from advances in novel targeted agents and immunotherapies has not translated well to BMs.[7,9] The prolongation in survival due to better tackling of systemic disease, with under-targeting of intracranial disease, is slowly being reflecting as rising clinical burden of BMs. The efficacy of systemic therapies for BM is limited due to a host of reasons, including insufficient intracranial drug delivery due to the blood–brain barrier (BBB),[10–12] the unique immunological milieu of the cerebrospinal fluid (CSF) in BM patients,[13] the diversity of immunogenomic landscapes in BMs across genetically distinct malignancies,[14,15] the branching molecular evolution of BM from EMs,[16–19] and the challenges in obtaining

information regarding clinically actionable genetic alterations in BMs, particularly in a longitudinal fashion.[11,20] These complex and long-standing challenges require treatment paradigms that address multiple problems concurrently, as represented by the potential of focused ultrasound (FUS) for enhancing effectiveness of several existing management strategies.

Major consensus efforts and professional society guidelines have both converged, with regard to recommendations for future neuro-oncology research, on (i) acknowledging and tackling the BBB-related challenges in CNS drug delivery of systemic therapies, and (ii) targeting the unique molecular alterations in BMs.[7,10,11,20–22] Both of these issues remain to be well-resolved. Historically, the former has seen long-standing efforts at optimizing drug discovery,[10,22] while the latter is being worked upon through incremental advances in liquid biopsy in plasma and CSF.[23] However, even these "optimized" efforts have had modest success in developing BM-specific therapeutics.[11,24] Meanwhile, conventional plasma-based diagnostics have demonstrated (i) a low sensitivity for capturing of brain-specific gene alterations at baseline and tracking clonal evolution, (ii) a limited CNS-specific prognostic value, and (iii) a poor surrogacy for intracranial disease burden.[23,25,26]

These long-standing challenges set the stage for the promise of FUS for BM patients, including both high-intensity FUS (HIFU), which primarily focuses on thermal effects of sonication, and low-intensity FUS (LIFU), which primarily utilizes mechanical effects of sonication. While other reviews in this issue have described the history of FUS development as well as the completed and ongoing investigations of ultrasound-based management strategies for patients with primary brain tumors (PBTs),[27,28] and in pediatric neuro-oncology,[29] here we describe the state of the clinical and translational evidence of various applications of FUS for patients with BM and provide ideas for designing and optimizing future research efforts.

History of Brain-Directed FUS

Investigation into the utility of ultrasound-enabled therapeutics began over a century ago, with one of the earliest documented uses of brain-directed FUS being in 1942 by Lynn and Putnam, who lesioned cerebral tissue in 37 animals.[30] Initial efforts to reduce ultrasound beam distortion and achieve the desired local effect, without significant scalp heating, were done through removing a part of the skull (i.e. intracranial HIFU). In the 1950s, the famed brothers William and Francis J. Fry demonstrated the use of acoustic energy for brain lesioning via a four-transducer HIFU system with planoconcave lenses that required removal of skull.[31] They worked to develop this platform clinically with Robert Heimburger, the first neurosurgeon using FUS to treat brain neoplasms (in 1968).[32] Later, Lars Leksell also attempted to modify their system, using his own stereotactic frame and a new transducer system to improve accuracy.[33–37] Unfortunately, he abandoned this line of investigation given the lack of imaging essential for the procedure and the requirement for creation of a skull window for sonication. Meanwhile, the Fry brothers, in collaboration with Eggleton, had founded the Interscience Research Institute in Illinois, US, which was the first research center dedicated to FUS for brain diseases, and worked to demonstrate a partial lesioning of the basal ganglia using FUS performed postcraniotomy,[34,38–40] Lindstrom in 1954 also reported using FUS as an alternative to lobotomy for patients suffering from metastatic cancer and cancer-related pain.[41,42] Meyers and Fry in 1962 reported using FUS for multiple neurological diseases, especially Parkinson's disease and movement disorders.

After exciting advances in FUS for breast and thyroid neoplasms, the year 1991 saw publication of the first trial of radiotherapy combined with FUS hyperthermia for malignant PBTs.[43,44] The early 1990s saw FUS being combined with image guidance, leading to emergence of MR-guided FUS.[45] Hynynen and Jolesz later were amongst the first to successfully demonstrate transcranial MR-guided FUS using a large phased array transducer and the skull as a lens for beam focusing.[46] This group was also the first to demonstrate use of FUS for BBB opening (BBBO) in a precise, controlled fashion, later incorporating more optimized phased array approaches with CT-based planning.[47–49] In 1999, MR thermometry was developed for real-time monitoring of FUS delivery.[48,50] The late 2000s saw the earliest publication of microbubble-enhanced focused ultrasound (MB-FUS) for drug delivery,[51] followed closely by other reports validating this approach.[52–63] With safety and precision ensured by real-time monitoring and closed-feedback-loop power control for HIFU,[48,50] and recently LIFU,[64] transcranial FUS became clinically feasible. Overall, these developments have set the stage for various ultrasound-enabled management strategies for brain tumors, delivered using a multitude of available device platforms (Table 1).

FUS for Thermal Ablation of BM

Preclinical investigations several decades ago demonstrated that ultrasound could be utilized for the precise destruction of specific brain regions.[77–79] HIFU, in particular, involves delivery of high-intensity sonication waves which range between 100 and 10,000 W/cm^2 to cause thermal ablation of targeted regions. The high-intensity waves vibrate the molecules within the tissue, often inducing a state of hyperthermia. This denatures the proteins in cancer cells while fragmenting their DNA. In addition, sustaining a temperature above 56 °C even for a few seconds can cause coagulative necrosis, which leads to the death of targeted neoplastic tissue.[80]

Thermoablation as a Local Therapy

HIFU-based thermoablation has been hypothesized as a local disease control strategy for BM. Local disease control strategies, in addition to systemic therapy, are frequently employed in targeting BMs, and include surgery, whole-brain radiotherapy (WBRT), and stereotactic radiosurgery (SRS),[81–84] with SRS alone now preferred for patients with

Table 1. Clinical platforms for the delivery of ultrasound for brain tumors

Manufacturer[a]	Platform[a]	Delivery type	Transducer	Integrated intra-op guidance	Proprietary?	References
Acoustic MedSystems	ACOUSTx	Catheter-based	1–2 elements	None	Prop	65
Alpheus Medical	CV01	Transcranial	N/A	None	Prop	66
CarThera	SonoCloud-1	Implantable	Single element	None	Prop	67,68
	SonoCloud-9	Implantable	9 elements	None	Prop	69
Cordance Medical	NeuroAccess	Transcranial	15 elements	Neuro-navigation	Prop	70
Delsona Therapeutics	UltraNav	Transcranial	Single element	Neuro-navigation	Prop	71
Insightec	Exablate 3000	Transcranial	512 elements	MR-guided	Prop	72
	Exablate 4000	Transcranial	1,024 elements	MR-guided	Prop	73,74
NaviFUS Corp.	NaviFUS	Transcranial	Single element	Neuro-navigation	Prop	75
OpenWater	Open-LIFU 2.0	Transcranial, Wearable	128 elements	Neuro-navigation	Open	76
Zeta Surgical	Zeta	Transcranial	Single element	Neuro-navigation	Prop	–

[a]Information regarding commercial platforms was collected near the end of 2024 and may not be current. This is not meant to be an exhaustive list, as indications and applications related to specific devices in this space are rapidly evolving.
Refs., references; intra-opp., intra-operative; Prop, proprietary platform; Open, open-source platform.

limited number of BMs.[85–88] Several local salvage therapy options, including re-resection, repeat SRS or WBRT,[48,72] are used at BM recurrence.

However, regardless of setting, clinical evidence in support of HIFU thermoablation so far has been underwhelming. In brain diseases, the efficacy of HIFU (delivered using Exablate Neuro) was seen to be limited for thermoablation of PBT, as seen in trials reported by Ram et al. (2006, $N = 3$),[89] and McDannold et al. (2010, $N = 3$),[48,72] although these trials did stage the stage for technological evolution and feasibility for demonstration of efficacy of HIFU for Parkinson's disease and essential tremor.[90] The thermoablation trials also did demonstrate safety of HIFU for lesioning of small targets, with no major changes observed in nontarget-adjacent tissue or skull. Another clinical trial conducted in Zurich reported the safety and feasibility of using transcranial MR-guided FUS for noninvasive treatment of centrally located brain tumors, and BMs from breast and lung cancers (NCT01698437).[91]

Clinically, HIFU thermoablation has been hindered by several long-standing factors, many of which remain to be resolved. First is the issue of the heating of the skull, which is acoustic energy dose-dependent and limits extended ablation.[90] Second, large volume HIFU targeting is recognized to also lead to undesired local effects, like brain edema and local hemorrhage, despite HIFU procedures being guided by advanced imaging techniques (such as MRI) to help guide precise targeting and real-time MR thermometry for adaptive control. Finally, these trials were conducted in small sample sizes using older FUS delivery platforms, where high-resolution image guidance, precision targeting, and real-time monitoring capabilities were more limited. Thus, some of the above considerations may change, given the rapid ongoing FUS device evolution worldwide, which may lead to HIFU thermoablation becoming clinically feasible.[90]

FUS for CNS Drug Delivery

Rationale and Fundamentals

The BBB has been a long-standing challenge for effective delivery of systemic therapies to BMs, despite advancements in novel targeted and immune-based therapeutics that enable better tackling of EMs.[92] The prolongation in overall survival (OS) of advanced cancer patients due to better tackling of EMs, combined with limited intracranial efficacy of systemic therapies, allows for greater time during the disease course for development of BMs. Thus, CNS is increasingly becoming one of the first sites of disease relapse in metastatic cancer patients treated with SOC approaches.[93–96]

FUS-mediated BBBO relies on temporary mechanical disturbance of tight junctions in brain regions through activated (vibrating) microbubbles.[47,49] Here, microbubbles (MBs) are administered intravenously and allowed to disperse systemically in circulation, which is followed by LIFU (combined approach called MB-enhanced FUS or MB-FUS) targeted to brain regions containing the tumor or in close proximity to the resected tumor.[97] When MBs circulate within the targeted sonication zone (i.e. the acoustic field), they undergo volumetric oscillation, a phenomenon that results in cyclic MB expansion and contraction. This mechanical stimulus on nearby endothelial cells leads to transient disruption of the tight junction proteins as well as changes in endothelial efflux proteins, enhanced interstitial transport, and activation of inflammatory cascades.[98,99] Thus, MB-FUS leads to both structural barrier disruption and functional efflux activity downregulation, albeit transiently.

Typical MB formulations used for MB-FUS BBBO have 1-10 microns diameter and consist of a gas core (commonly perfluorocarbon or sulfur hexafluoride) encapsulated by a

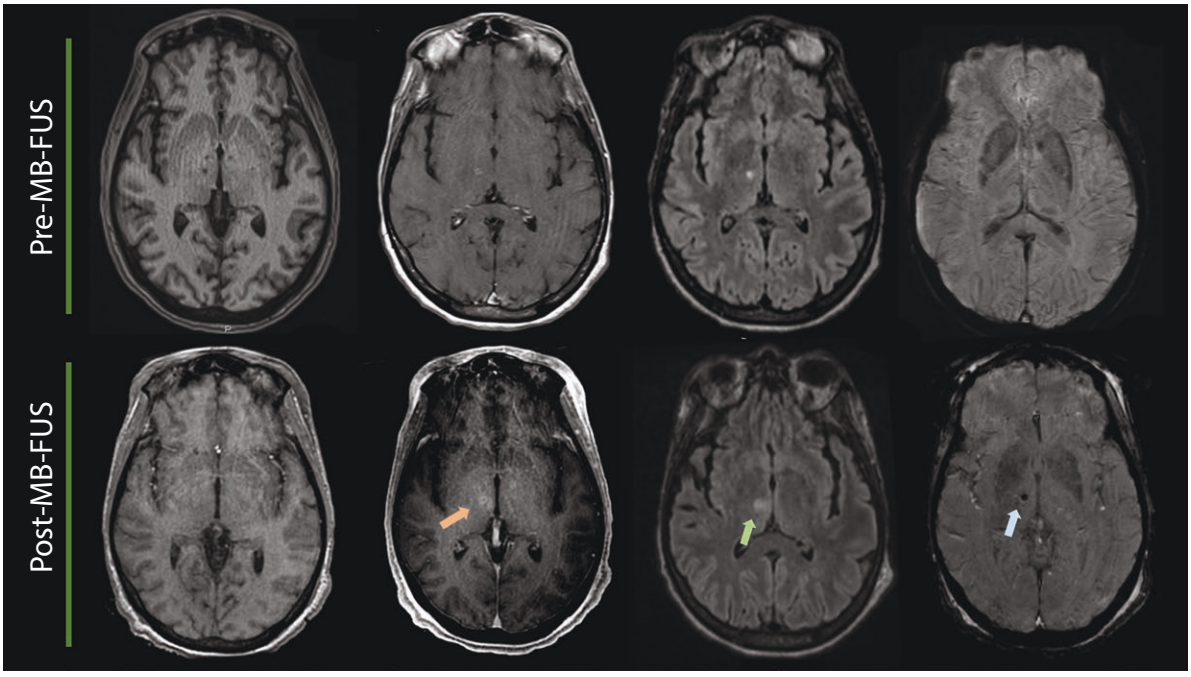

Figure 1. Case of transcranial low-intensity focused ultrasound for a patient with BMs. This adult patient was treated with 220 KHz FUS delivered using Insightec Model 4000 Type 2/2.1 (Insightec, Tirat Carmel, Israel) for blood–brain barrier opening (BBBO) for delivery of systemic therapy. Images show pre- and post-MB-FUS. Pink arrow (2nd column) indicates new or enhanced areas of enhancement after BBBO treatment, green arrow (3rd column) indicates minimal increase in FLAIR signal single arrow, and blue arrow (4th column) indicates a new area of susceptibility signal change on gradient echo (GRE) or T2* imaging, suggesting local erythrocyte extravasation, albeit at a small scale. There was no major clinical impact of this susceptibility signal change.

stabilizing shell that is typically composed of either lipids, proteins, or polymers. The MB size and shell composition influence MB circulation time, stability under ultrasound exposure, and responsiveness to acoustic pressure. Smaller MB may penetrate capillaries more efficiently and sustain prolonged circulation, whereas larger bubbles can exhibit stronger acoustic responses, potentially enhancing mechanical effects on endothelial junctions. Lipid-based shells offer high biocompatibility and flexibility, promoting controlled cavitation and reversible BBB disruption, while stiffer polymer shells may resist rupture, potentially requiring higher ultrasound intensities to achieve similar effects.[55,60,61,100,101] Regardless of the MB type used, BBBO (analogous to a two-way street) allows for both increased brain penetration of therapeutic compounds as well as leakage of brain tumor contents into circulation, as discussed later.[102]

Preclinical Studies

Several studies across different animal models have shown the safety and technical feasibility of MB-FUS BBBO for enhanced brain delivery of therapeutics,[51,54,57,59,60,62,63,103–109] including in BMs.[98,108,110,111] However, it must be recognized that there exist major differences for drug delivery for normal brain (in healthy animal models), PBT models, and BM models, given unique attributes of the BBB and the blood-tumor barrier.[92]

Trastuzumab has been shown to be an effective treatment against HER2-positive breast cancer, but its utility for brain metastasis is limited due to its large size and resulting low BBB permeability. A study in rat models of HER2 + breast cancer BM compared combinatorial MB-FUS + trastuzumab, to MB-FUS alone, trastuzumab alone, and no treatment groups. About 40% of MB-FUS + trastuzumab group had complete tumor resolution, an effect not observed in any other group. MB-FUS + trastuzumab also led to 32% increase in median survival vs 13% with trastuzumab alone.[110] In murine models of HER2 + breast cancer BM, FUS-mediated BBB disruption resulted in increased extravasation of doxorubicin and ado-trastuzumab emntansine. This effect was mediated by not only transient disruption of tight junctions in the barriers, but also increased interstitial convective transport.[98] The pharmacodynamics of FUS-mediated drug transport were shown here to be dependent on tumor vascular phenotype and reactivity of the drug to the tumor microenvironment, with clinical implications for trial design.

Clinical Studies

While several clinical trials of ultrasound-enabled drug delivery for PBTs have been published,[69,112] as summarized in other reviews in this supplement,[28,113] trials for BMs have been fewer and continue to be ongoing, with a representative case of MB-FUS for BMs being shown in Figure 1.

Overall, the body of evidence related to MB-FUS-enhanced brain drug delivery (for any disease indication) suggests that MB-FUS can be used for targeted delivery of systemic therapies, from small to very large-sized, in a highly consistent, repeatable fashion.

The first trial to evaluate MB-FUS-enabled drug delivery for BM was conducted in Toronto (NCT03714243), where breast cancer BM patients were treated with a clinically relevant radiotracer-labeled trastuzumab (^{111}In-BzDTPA-trastuzumab) designed to be visualized on single-photon emission computed tomography (SPECT). Twenty combination treatments were administered across $N = 4$ patients. No serious adverse effects were reported. On SPECT, trastuzumab uptake was increased. All target tumors also showed either stability or reduction in size by the end of the study.[73]

Currently, there is an ongoing multicenter, North American, multi-phase, pivotal trial investigating the use of MB-FUS BBBO for enhancing the efficacy of systemic therapies for BMs, called LIMITLESS (BT012, NCT05317858), from the ReFocused Consortium (Figure 2). The randomized controlled phase of LIMITLESS is randomizing patients with BMs from non-small cell lung cancer to MB-FUS plus systemic therapy or systemic therapy alone.[114]

FUS for BM-specific Liquid Biopsy

Rationale

Due to the heterogeneous nature of BM, robust characterization and analysis of patient-specific pathology is essential in designing effective, personalized treatment strategies. Furthermore, data across differing tumor types has increasingly demonstrated that, despite shared ancestry, the primary tumor and all metastatic regions evolve independently during the disease course, particularly in response to therapy.[15,16,115] In over 50% of patients with any metastatic disease, BMs contain clinically meaningful genetic alterations that are absent in the matched primary tumor, demonstrating branched evolution, subtype switching, and unique pathways of intracranial progression.[15,17] BMs also have distinct immune landscapes, with unique tumor immune microenvironment interactions (TIME).[116] These distinctions are further modified by differential therapeutic selection pressure for EMs vs BMs.[16,117] Thus, BM-specific liquid biopsy studies are needed to improve diagnostic and therapeutic monitoring.[15,16,115]

Unfortunately, baseline and longitudinal molecular profiling of BMs, despite being strongly warranted, remain limited by logistical constraints in obtaining tumor tissue from BMs. The need to characterize this tissue has propelled interest in liquid biopsy methods, which characterize cell-derived factors in biofluids such as blood, urine, or CSF. Due to the minimally invasive nature of this approach, the tumor can be closely monitored through repeated sampling to track tumor evolution and response to therapy. While liquid biopsy has revolutionized monitoring of peripheral tumors,[14,16,118–120] its applicability had remained limited for intracranial malignancies. Conventional biomarkers for liquid biopsy, such as circulating tumor DNA (ctDNA) and circulating tumor cells, are unable to effectively traverse the BBB and enter peripheral circulation from the brain. Therefore, traditional liquid biopsy tools have a low performance for intracranial metastases, both for detection and longitudinal monitoring.[121,122] The need to enrich acquisition of tumor-derived factors from BM has propelled interest in FUS-mediated liquid biopsy, also known as sonobiopsy or sono-liquid biopsy (SLB).

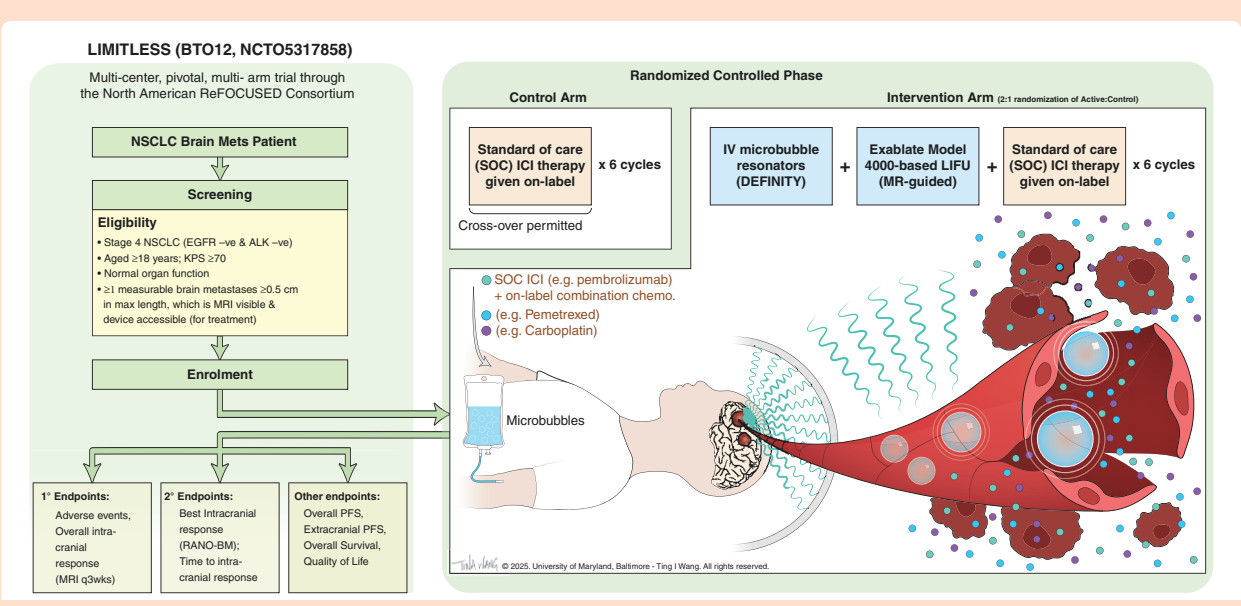

Figure 2. Summary of the Randomized Component of the LIMITLESS (BT012) Trial. This multi-component, multi-phase trial with a randomized component is enrolling under FDA investigation device exemption (IDE number G210314) and Health Canada Investigational Testing Authorization (ITA number 334144).

Table 2. Differences between high-grade gliomas and BMs, and their relevance to ultrasound-enabled diagnostics and therapeutics

Characteristic	High-grade gliomas	Brain metastases	Clinical Implications, esp. with respect to FUS
Epidemiology	2–3 cases per 100,000 individuals[132]; ~14,000 new patients diagnosed in US annually[132]	8–14 cases per 100,000 individuals[4,5]; 70,000–400,000 new patients diagnosed in United States annually[20]	Both HGG and BM present unique challenges to trial design, conduct, & enrollment,[10,133] - compounded in drug + device trials (like MB-FUS BBBO). Clinically greater need is perceived for HGGs due to sustained lack of avl. effective therapies.[133]
Tissue/Cell of Origin & Molecular Alterations in Tumor	Common precursor origin of most HGGs, with several shared critical molecular alterations (but substantial cellular & molecular heterogeneity)	Varying primary tissue-of-origin (breast, lung, etc.) with each primary tumor having different subtypes with unique molecular profiles	For BMs, tissue-of-origin & molecular profile data could be used for more individualized FUS Rx planning (given corresponding biophysical differences corresponding with these properties)
Extracranial disease (& in systemic circulation)	Absent (→ tumor cells, & derived factors, can come into systemic circulation only from CNS)	Present (→ tumor cells, & derived factors, come into systemic circulation from both within & outside CNS)[134]	MB-FUS-enabled SLB of brain neoplasms is less feasible for BMs (as plasma is preenriched from extracranially originating tumor cells/derived factors)
Number of lesions	Single; rarely satellite lesions or multifocal lesions	Typically, ≥1 lesion. BMs get classified as oligometastatic disease if 1–4 & polymetastatic disease if ≥5 lesions.	≥2 distant lesions: (A) make implantable ultrasound approach less feasible, & (B) warrant multiple sonications (for any therapeutic FUS Rx) → Multiple sonications safe in early preclinical studies,[110] but a recent study indicates greater sterile inflammation with multiple MB-FUS Rx.[101] → Prospective clinical (with nested radiological & molecular) studies needed.
Cumulative lesion volume	Variable volume of single lesion	Cumulative volume variable, dependent on lesion number & growth pattern	Technical efficacy of HIFU thermoablation becomes greatly limited with larger treated volumes (hindering clinical use).[135]
Intracranial location	More common in cerebral lobes but could be present elsewhere. Cerebellum is infrequently involved. Brainstem HGG is an uncommon but a very challenging entity.	Typically supratentorial, classically at gray-white junction, but could be present elsewhere. Cerebellum is relatively more involved (10%–15% cases) than HGGs	(A) Cerebellum not yet covered in FUS Rx envelope (B) Brainstem can be Rx with FUS but very limited experience & safety data (relevant for brainstem HGGs) (C) Development & optimization of advanced FUS spatial targeting approaches[64] needed to effectively treat a diversity of target locations (peripheral & deep) with reduced procedural time (without losing precision or safety).
Peri-lesional infiltration into brain parenchyma	Tumor cells in HGG, esp. GBM, infiltrate far beyond enhancing lesion deep into brain parenchyma (several cm) → unresectable & remain shielded by BBB[136] → seed recurrence	BMs are typically less infiltrative. Surgical resection is an effective first-line Rx (+/– other Rx) for oligometastatic disease	(A) Resection cannot eliminate distant infiltrating HGG cells →Treating infiltrating HGG cells through MB-FUS-enhanced drug delivery may be critical. (B) Less brain parenchymal involvement (& corresponding lower targeting risk) in BMs
Tumor growth pattern	More complex (irregular 3D geometry)	Generally, more circumscribed growth.	(A) Different ease of planning Rx for HGGs vs. BM for any FUS mode (B) Well-recognized challenges to lesion thermoablation for HIFU for complex targeting.[137]
Adjacent brain edema & T2 MRI changes	More brain edema & T2-MRI changes in HGGs	Less edema (esp. for oligometastatic disease)	
Brain endothelium & BBB	Greater pore diameter in HGGs,[138] but substantial regional differences (core has largest pore size & disrupted BBB, while periphery has minimally disrupted BBB)[136]	5–10 fold smaller pore diameter,[138] that sterically hinders diffusion of large Rx agents[138] (like MAbs). HGG-like regional heterogeneity in pore size has not been reported. Significant variation across different solid tumors in BBB integrity of their BM (e.g. more in TNBC than HER2 + BC)[139]	(A) Need to integrate MB-FUS with (i) regional tumor differences,[138] (ii) tissue-of-origin based variations in BBB integrity,[139] & (iii) different pathways of drug payload delivery (e.g. with ADCs like T-DXd). (B) Disease-state-based (i.e. resected or unresected lesion) targeting approaches are needed, given differential drug permeability (e.g. nonenhancing tumor areas have relatively preserved astrocyte–endothelia relationship[140]).
Tumor vessel morphology & spatial density	Frequently, thick, tortuous vessels with glomeruloid structure, & higher spatial density, (although substantial heterogeneity). HGGs have greater retention of partial BBB components.	Vessels resemble those of primary cancer (e.g. lungs, breast) & often regionally have fewer BBB components (like normal astrocyte relationships). Lower microvessel density than HGGs.	(A) Potential utility of using radiomics & perfusion (DSC) MRI data for FUS Rx planning, esp. for safety (e.g. avoid RBC extravasation through optimal MB-FUS dosing). (B) Optimization of sonication parameters may be needed when translating Tx from HGGs (where more MB-FUS drug delivery trials have been done) to BMs.

Table 2. Continued

Characteristic	High-grade gliomas	Brain metastases	Clinical Implications, esp. with respect to FUS
Current SOC Tx Approach	Maximal resection followed by adjuvant RT and chemoTx (at first line). Several Rx. options at recurrence avl., all with limited real-world effectiveness.	Rx of oligometastatic BMs with resection & SRS. Tx options for polymetastatic BMs, based on several factors, includes SRS, WBRT, systemic Rx (based on tissue-of-origin & molecular profile). Several lines of Rx are avl., including effective systemic Tx at recurrence	(A) MB-FUS will expand repertoire of avl. Tx for both HGGs & BMs as systemic Tx actively + passively limited by BBB → With MB-FUS, a new framework for brain tumor drug discovery needed. (B) For any one specific indicated Rx, optimal MB-FUS parameters need to be established (in a disease-state-optimized fashion), beyond one-size-fits-all.
Common systemic Tx & their brain penetrance	Temozolomide (MW:194 Da) is first-line chemoTx (better brain penetrance than other chemoTx), but brain concentration reaches ~18% of plasma.[141]	Tx options range from small molecule inhibitors like dabrafenib (MW: 519 Da) for melanoma to MAbs like pembrolizumab (MW:146 kDa) for PD-L1 positive cancers. Specific Tx depends on tissue-of-origin & molecular profile,	(A) MB-FUS may (i) improve brain penetrance of chemoTx, esp. larger compounds that are primarily limited by BBB permeability, & (ii) may downregulate BBB P-Gp efflux activity[142,143] → may improve efficacy of small molecule Rx susceptible to BBB efflux activity. (B) Major clinical utility of ADCs (very large size) for BMs, where MB-FUS BBBO could be of significant benefit as combo.

Rx, treatment, Tx, therapy, esp., especially, GBM, glioblastoma, MAb, monoclonal antibody, TNBC, Triple-negative breast cancer, HER2+-BC, HER2-positive breast cancer, SOC, Standard-of-care, T-DXd, Trastuzumab-deruxtecan, avl., available, RT, radiation therapy, RBC, red blood cell, ADC, Antibody-drug conjugates, combo, combination.

Preclinical Studies

Several preclinical studies in brain tumors (albeit not specifically in BMs) have positioned this technique for clinical usage.[123] FUS-mediated BBBO temporarily permits the passage of tumor-derived factors into peripheral circulation. Studies in rodent and porcine models of glioma showed increased detection of tumor biomarkers in the plasma following FUS administration,[124–127] as also described in another paper in this supplement.[128] These factors can be subject to downstream analysis for tumor characterization. SLB theoretically does allow for spatial sampling (by precise lesional targeting, followed by plasma acquisition) for better characterization of BM heterogeneity.

Clinical Studies

Clinical trials of SLB for brain tumors have focused on PBTs,[129] including a neuro-navigation-guided sonobiopsy trial by Yuan et al. in 2023 (NCT05281731) and exploratory analysis of MR-guided MB-FUS trial by Meng et al. in 2021 (NCT03616860, NCT03739905)[70,130] These trials demonstrated that FUS sonication increased levels of plasma cfDNA, neuron-derived extracellular vesicles, brain-specific protein S100b, and tumor-specific methylation signal, without any structural or inflammatory damage. Currently, there are two major ongoing trials designed to further evaluate SLB for brain tumors (albeit both for primary PBTs): the multicenter LIBERATE trial (BT015/NCT05383872)[131] and the single-center BRAINFUL trial (NCT04940507), both uncontrolled trials. LIBERATE aims to evaluate (i) safety, (ii) concordance of molecular alterations detected in tumor tissue and plasma cfDNA, and (iii) achievement of 2-fold or higher increase in plasma cfDNA post-MR-guided MB-FUS. BRAINFUL aims to evaluate temporal changes in plasma and CSF following MR-guided MB-FUS, as the primary endpoint.

However, the aforementioned studies are being conducted for PBTs, which differ from BMs in several aspects, including SLB (Table 2).[15,17] Next-generation sequencing investigations of ctDNA from glioma vs BMs have shown their distinct gene mutation profiles.[144] It is expected that, similar to PBTs, the plasma yield from BM patients would improve with MB-FUS BBBO.

However, the fundamental issue, yet to be resolved so far, is the accurate differentiation and characterization of BM-derived ctDNA in an enriched sea of all tumor DNA (originating from primary tumor, BM, and different EMs) in the plasma of metastatic cancer patients (Table 2). Further, increased plasma cfDNA fragmentation post-FUS has also been reported.[145] Once these issues are resolved, work will then be needed to determine whether this BM-derived plasma ctDNA consistently corresponds with the intracranial disease burden and whether longitudinal noninvasive BM-specific monitoring of molecular alterations can reach sufficient accuracy for integration into SOC. If achieved, it would allow for an adaptive theragnostic paradigm for management of BMs, where (i) BM-specific molecular features are periodically captured using SLB, (ii) SLB findings used to create bespoke treatment paradigms, and (iii) novel targeted therapies are delivered using MB-FUS-enabled BBBO, thus enabling precision oncology that adapts to disease evolution. Given that FUS offers a substantial advantage for repeat noninvasive sampling, longitudinal SLB could potentially be used to help differentiate pseudo-progression from real progression on therapy, a persistent challenge in neuro-oncology.

FUS for Histotripsy

HIFU can be utilized for histotripsy, a nonthermal ultrasound approach for local tissue fractionation or homogenization (informally referred to as an "invisible tissue blender").[146–150] Using a low-duty cycle and a pulse length in milliseconds (for boiling histotripsy),[146–150] or microseconds (for shock scattering or intrinsic thresholds),[147] tumor tissue can theoretically be pulverized. Here, peak negative pressures, using short, high-intensity pulses, are of over > 10 MPa in boiling histotripsy, over 15 MPa in shock scattering, and over 25 MPa for the intrinsic threshold.[151] Thus, similar to thermoablation, histotripsy theoretically can allow for intracranial tumor control. This tumor cell killing also leads to anti-tumor immune responses, thus contributing to FUS-enabled immunomodulation, as described later.[121,122]

Preclinically, HIFU-based histotripsy has been utilized for precise brain lesioning, with several downstream biomechanical effects.[122,129] Further, the collateral damage from this tissue fractionation has been demonstrated to be limited to 200 μm from the histotripsy margin in large animal models, with sharp boundaries between histotripsy-treated and untreated brain tissue.[152] The limiting factor for histotripsy's clinical translation has been the potential for this procedure to result in intraparenchymal bleeding or edema.[135]

Efforts at advancing histotripsy safety by better characterization of impact of different tunable parameters are needed. In this regard, a recent study indicated that histotripsy delivery with fewer pulses and less targets enabled reduced bleeding, while enhancing tumor fractionation.[135] Given the historical literature, this does suggest that histotripsy is less likely to be a viable approach for polymetastatic brain disease (more than 5 BMs). Similarly, efforts are also needed to preclinically characterize short and long-term locoregional impact of histotripsy with modern phased array multielement transducer platforms with image-guidance (i.e. more precisely targeted platforms), as also recently reported in a large rodent characterization study.[153] Another study using a handheld, intracranial catheter-based histotripsy device found that structural variation between rodents was the greatest contributor to downstream endpoint of achieving accurate ablation.[137] Optimizing sensitive real-time feedback and safety monitoring can help advance clinical histotripsy investigations.

A new transcranial neuro-navigation-guided histotripsy device has been developed for clinical use with 750 kHz, 360-element phased array transducer, with a corresponding preclinical platform.[154,155] Another histotripsy device is based on a biocompatible sono-lucent cranioplasty implant, that is inserted after brain tumor resection, enabling sonication through the implant with minimal sonication beam distortion.[156] A Canadian group has reported a slightly more invasive catheter-based approach, having co-registered ultrasound guidance,[157,158] with reportedly limited collateral cellular damage (upto 100 μm distance from histotripsy margin).[159] Real-time ultrasound imaging is also being combined in studies with Doppler overlay-based approaches for better intra-procedural guidance.[160] These recent device developments and innovations indicate renewed interest histotripsy, but significant ground remains to be covered for clinical translation.[160]

FUS for Sonodynamic Therapy

Analogous to photodynamic therapy (PDT), sonodynamic therapy (SDT) is fundamentally premised on the targeted activation of certain compounds (sonosensitizers) in specific locations at the desired time, which causes them to become cytotoxic.[161] Agents for SDT, many also used in PDT, are delivered systemically and then get activated by sonication in regions of interest (i.e BMs), causing precisely delivered cytotoxicity.[162,163] The acoustic energy also leads to local protoporphyrin IX (PpIX) activation, followed by reactive oxygen species (ROS) generation and tumor cell demise.[164,165] Some investigators have reported that SDT damage is through Type 1 reaction (free radical and radical ions), while PDT damage is through Type II reaction (highly reactive singlet oxygen), with both impacting tumor vasculature, as seen under albumin-gadolinium DTPA imaging.[166]

5-aminolevulinic acid (5-ALA), fluorescein, and TMZ are common sonosensitizers being investigated for brain-directed SDT. Immunogenic cell death using liposomal TMZ delivery for SDT has also been preclinically reported.[167] Beyond these, a recent systematic review has reported the use of sinoporphyrin sodium, hematoporphyrin monomethyl ether, and Rose Bengal in some animal model studies.[168] Recently, a portable benchtop model for conducting small animal SDT investigations has been reported.[169]

In a cell viability assessment study for melanoma BMs, B16F10 melanoma cells were treated with FUS alone, 5-ALA alone, or FUS + 5-ALA (SDT group). The latter group had significantly lower cell viability, than the other two groups, which among them had no significant difference.[170] Building on such efforts, flow cytometric evaluation of ROS generation building in BM models of SDT is needed. These findings align with prior in vitro evaluation of rat C6 and human U87 GBM cells, where cell viability reduction was 5%, 16%, and 47% in 5-ALA, FUS, and FUS + 5-ALA groups, respectively, with corresponding much higher increase in Caspase-3 induction.[171] Another work, albeit not in BMs, has reported that SDT using liposomally encapsulated sonosensitizer hematoporphyrin combined with immune checkpoint inhibitors (ICIs) led to hindered primary tumor growth and delayed lung metastasis.[172]

The molecular targeting enabled by spatial and temporally controlled cytotoxic activation of sonosensitizer molecules is the main promise of the precision therapeutic approach of SDT,[161] with potentially minimized off-target toxicity reported from animal models.[163,167,171,173,174] However, its feasibility for BMs remains to be clinically demonstrated.

FUS for Radiosensitization

Preclinical Evidence

Preclinically, the investigation of ultrasound for radiosensitization has been ongoing for several years.[164,175]

Fletcher et al. conducted an in vivo study comparing the effect of radiation therapy (RT) with or without MB-FUS in healthy and F98 (glioma) rat models. Animals receiving 4Gy RT + MB-FUS showed BBBO and had significantly tumor volume differences compared to 4Gy RT-only group.[176] The dramatic decrease of tumor growth when combining FUS with RT has also been seen in a study with allogeneic subcutaneous C6 glioma model where exaggerated DNA damage was identified as primary mediating mechanism.[177] Another in vitro study run also confirmed the presence of enhancement of DNA damage through FUS with human head and neck, brain (GBM), and prostate cancer cells.[178]

In an in vitro FUS-induced cavitation study for sensitizing cancer cells to RT, temporal, additive effects of FUS were seen affecting the activity and survival of the cancer cells, paving the way for animal studies.[179] Meanwhile, the in vivo mouse model study out by Chen et al. investigating RT + FUS for GBM found that survival was not improved in 2Gy RT + FUS cohort when comparing to the 5Gy RT cohort, unlike the improvement shown compared to 2Gy RT cohort. More rigorous preregistered validation efforts are needed.[180]

Clinical Evidence

A seminal work by Guthkelch and colleagues published over three decades ago first demonstrated the safety and feasibility of postcraniotomy FUS hyperthermia combined with external beam (RT) in a trial of $N = 15$ patients with malignant PBTs.[43,44] This was albeit done using a much more crude version of current platforms. Modern clinical utility of the post-FUS radiosensitization for brain tumors remains to be well delineated as compared to other FUS applications. The pilot trial conducted by Chen et al. with $N = 6$ patients resulted, post-RT-FUS, in three progressive disease and three stable disease patients, with or without additional therapies.[180] Another trial leveraging MR-guided MB-FUS carried out by Dasgupta et al. treated eight breast cancer patients, with MB-FUS treatments before 1st and 5th fractions of RT. Complete response was seen in 3/8 tumors at 3-months, with no enhancing diseases. No major complications or reactions to the combined modality treatment were observed.[181] However, BM-specific clinical studies for FUS radiosensitization have not been reported yet.

FUS for Immunomodulation

Different modes of ultrasound have all been shown to impact locoregional and systemic immune profile in a differential fashion,[75,121,163,172,182–187] as also reviewed in depth in this special supplement.[188] FUS-mediated BBBO could potentially enable delivery of systemically delivered immunotherapies, such as ICIs, interleukins, and chimeric antigen receptor (CAR)-T cells, into the brain.[184,189,190]

Preclinical Evidence

While considerable evidence exists for PBTs, investigation of FUS for immunomodulation in BM models has been limited. BBB opening has been reported for synergistic improvement of the utility of ICIs and CAR T-cell therapies.[182,191,192] A rat glioma model study by Chen et al. of FUS showed the presence of post-FUS-treatment BBBO proven by an increased gadolinium penetration, along with heightened K_{trans} and V_e maps. Immunohistological analysis at days 0 and 7 post-FUS done with 0.63 Mechanical Index (MI) FUS found increased CD8 + lymphocytes, but no significant changes in CD68 + macrophages or FOXP3 + lymphocytes. This was different from the 0.81-MI FUS cohort that showed significantly increased immunogenic response, especially with CD4 + levels.[75] Other studies have also reported enhanced antineoplastic immune activity and increased model survival with FUS.[182,191] Another study assessed the immunomodulatory effect of fluorescein-mediated SDT in a murine malignant glioma model (C57BL/6N). This combined in vitro and in vivo experiment showed a decrease in myeloid-derived suppressor cells.[163] Increased tumor antigen presentation,[121] inducement of a local sterile inflammatory response,[186] increased dendritic cell recruitment,[184] enhanced release of extracellular vesicles (specifically from FUS hyperthermia),[193] and increased tumor-infiltrating lymphocytes have all been implicated as putative mechanisms of FUS-induced immunomodulation,[190] although much of this data is not specific to BM models.

Clinical Evidence

The trial by Chen et al. also investigated FUS for immunomodulation. Here, while a dose-dependent BBBO was present, there were no immunological responses, contrary to the prolonged immunostimulation seen in preclinical glioma models.[75] This conflicting scenario could be potentially due to (i) species-specific (e.g. murine vs human) differences in sensitivity to FUS and tissue thresholds for various biophysical changes, which trigger local inflammatory response, or (ii) possible extravasation of immune cells with varying BBBO in preclinical but not in investigations, or other unclear reasons. Meanwhile the ongoing LIMITLESS (BT012) trial is also evaluating elements of not only BBBO-enabled drug delivery, but also potential downstream anti-tumor activity through immunomodulation (through combination of pembrolizumab, an immune check with MB-FUS) for patients with NSCLC BMs.

Unanswered Questions

Immunomodulation currently represents a rapidly evolving frontier with major excitement, but several unclear aspects remain:

- For BM patients, do different FUS modes lead to differential local and regional immune response? If so, how do these compare to other treatment modalities for BMs, especially radiotherapy (as well others like ablation with laser or radiofrequency or cryo-based approaches), and should these modes be harnessed differently for different tissue-of-origin BM?
- In looking to optimize FUS for immunomodulation, which factors hold the most clinical utility (such as

Table 3. Clinical trials of ultrasound-enabled management strategies for patients with BMs

Trial NCT (Alt. name)	Approach—application	Disease	Key end points	Location	*N*	Device	Status
Published or Completed[a] Trials							
NCT00147056 (BT002)	HIFU—Thermoablation	Metastatic cancer	Safety, Feasibility	USA	10	ExAblate	N/A[b]
NCT01473485 (BT003)	HIFU—Thermoablation	HGG & any BM	Safety, Feasibility	Canada	10	ExAblate	N/A[b]
NCT01698437	HIFU—Thermoablation	HGG & any BM	Safety, feasibility	Switzerland	3	ExAblate 4000	Published[80,91]
NCT03714243 (BT006)	LIFU—BBBO	Breast cancer BM	Safety, Feasibility	Canada	10	ExAblate 4000	Pub-lished[73]
NCT04021420 (SONIMEL-01)	LIFU—BBBO	Melanoma BM	Safety	France	21	SonoCloud-9	N/A[b]
Ongoing Trials							
NCT05317858 (BT012)	LIFU—BBBO	NSCLC brain mets	Safety, Radiologic Response	USA, Canada, South Korea	$	ExAblate 4000	Ongoing

[a]Based on the estimated study completion date in the trial registry.
[b]Marked "Unknown Status" on ClinicalTrials.Gov; results may have been either (i) unpublished), or (ii) presented only without publication, or (iii) published but without NCT ID provided in the publication.
Reg, registration; Alt. alternate; N, Actual (or planned) patient enrollment; $ Being updated.
The table was created based on a search of ClinicalTrials.Gov, Cochrane CENTRAL, and the International Clinical Trials Registry Platform, with last update as of April 2025.

further optimizing and standardizing sonication parameters, specific therapeutic combinations with MB-FUS BBBO, timing of MB-FUS BBBO, targeting strategy of partial HIFU thermoablation for enhanced antigen presentation, etc)?

FUS would optimally be combined with various approved ICIs being used for BM therapy in a tumor-specific, disease-state-optimized fashion.

Challenges and Opportunities for Future FUS Research

Optimizing Future FUS Investigations

While the promise of FUS needs to be considered in conjunction with the known high historical failure rates of new diagnostics and therapeutics in neuro-oncology, directed and specific efforts at optimizing future FUS investigations can help move the field forward in a more efficient and more expeditious manner (Tables 3 and 4). In particular, this will include learning from prior failures and logistical issues in neuro-oncology (for instance, compliance issues with tumor-treating fields), as well as other fields that have implemented approaches (such as novel trial designs) and systems enabling large pragmatic RCTs (such as registry-based randomization). Given the limitations of comparative effectiveness research from retrospective chart reviews and nondisease-specific national databases,[220] FUS RCTs that utilize appropriate endpoints and are conducted through multicenter collaborations are urgently needed (such as NCT05902169/SONOBIRD phase 3 trial), while pursuing greater diversity and minority enrollment in clinical trials.[221] These collaborations would be enabled by the development of FUS-specific academic institutional partnerships in the form of either subconsortia nested within broad-focus research consortia (such as NRG or NCTN) or independent transcranial technology-specific research consortia, such as ReFOCUSED (Research Consortium for Transcranial Focused UltraSound-Enhanced Drug Delivery and Diagnostics). Given the demonstrated success of directed research collaboratives [e.g. radiosurgery-specific like International Radiosurgery Research Foundation, radiation-oriented like RTOG], The establishment of FUS-specific institutional partnerships will help enable both clinical trials and real-world investigations, as discussed elsewhere in this supplement.[222]

FUS collaborations and investigations will be aided by open-source efforts, in particular, the de-identified sharing of trial and other individual patient data (IPD) datasets. These will not only enable pooled evidence syntheses (such as in IPD meta-analyses), but also potential questions that arise as the field evolves rapidly. De-identified open-source sharing of longitudinal imaging of brain tumor patients undergoing FUS would be particularly impactful, analogous to "NYUMets," currently the world's largest publicly available database of BM patients followed longitudinally with MRI.[223] Such open-source efforts are critical to setting the foundations for use of artificial intelligence and machine learning-based approaches for FUS.[224] A notable open-source effort (Table 1) is Open-LIFU 2.0 (by OpenWater), a transcranial, image-guided platform,[76] where information about device manufacturing and operations is on a public repository. Investigators can either

Table 4. Optimizing future clinical trials of focused ultrasound for brain tumors

Challenge	Potential solution(s)	Remark(s)
General challenges to device trials in neuro-oncology		
Difficulties in patient recruitment in neuro-oncology due to rigid criteria and burden posed by trial enrollment	Adopt pragmatic, patient-centered, decentralized trials with digitally enabled recruitment and digital-first monitoring/follow-up approach[194,195]	Enabled by remote patient monitoring (RPM)[196]
	When designing protocols, investigators carefully reconsider each criterion (many are copied from older trials)	Refer to FDA Guidance on "Cancer Clinical Trial Eligibility Criteria"[197]
Logistical & economic difficulties of randomization in device trials	Implement registry-based randomization to optimally enroll a larger population[198]	Nesting such efforts in existing brain tumor registries
Intrinsic high-failure in neuro-oncology trials	Prespecified go/no-go thresholds for explicit early decision-making to halt or continue therapeutic development	Implementing such explicit decision-making rules will reduce resource waste
Determining efficacy signal from single-arm (uncontrolled) device trials[199]	Use of modern causal inference frameworks with external cohorts[199,200]	Recognize considerations of "vibration of effects"[201] and "garden of forking paths"[202]
	Prespecification of statistical analysis plan for multivariable adjustment, with sensitivity analyses for robustness[203]	
Multiple similar, but underpowered, device trials running at different trial sites	Enable greater participation by reducing unnecessary barriers without compromising quality & safety[204]	These steps enable multicenter collaborations, which are foundational for adequately powered clinical investigations[205]
	Detailed public registration (with updates)[206] & publication of trial protocol early	
	Greater dissemination of protocol prior to and during trial accrual	
Difficulties balancing desired power & resources available to achieve power[207–209]	Implementation of adaptive trial designs (such as biomarker- and platform-adaptive)	InSIGHT and GBM-AGILE as exemplar adaptive trials[194,210]
	More efficient composite primary endpoint (e.g. time savings model or composite ordinal longitudinal model (OLM)) & combined overall benefit:risk evaluation[211]	OLMs tackle issue of wide confidence/uncertainty intervals
Inefficiency in data from old trials not being used for interpreting findings	Consider implementing prespecified Bayesian analytical approaches[212]	Optimizing prior information use decreases resource waste
Limited translational information extracted from a single trial	Recognize surgical device trials are a unique controlled experiment, and incorporate nested multi-omics analysis in them	Upfront planning for extracting more translational data
Logistical barriers to pooling data from multiple FUS trials	Support de-identified individual patient data (IPD) sharing to enable IPD-MA	NCI Cancer Research Data Commons as centralized repository
	Trial sponsors joining CSDR	
Increasing considerations related to costs of novel therapies & downstream impact on patient access[213]	Conduct prospective, industry-independent investigations on costs and accessibility of FUS for brain diseases.	Emergence of multiple platforms with similar technical efficacy will give rise to cost-effectiveness questions
Specific challenges related to FUS trials for brain diseases		
Multiple FUS platforms being investigated in numerous FUS trials with high variation in adjustable parameters	Standardization of FUS treatment protocols, enabled by creation of a unified dosage paradigm for LIFU[64] (similar to CEM43 for HIFU)	Multidisciplinary collaboration is critical, utilizing expertise from beyond neuro-oncology
Significant variability in capturing and reporting clinical & technical variables in FUS trials for brain diseases	Multistakeholder development & field-wide implementation of common data elements (CDE), as part of FUS research standards[214]	Reporting of minimum technical data supported by CDISC, FDA, and NIH NINDS (similar to stroke CDE)[215]
Ensuring confirmation of BBB opening	Beyond the metric of new contrast opening on T1w MRI, potential for use of radiolabeled agents & SPECT for confirmation	Consider pre- and postdynamic contrast-enhanced MRI

Table 4. Continued

Challenge	Potential solution(s)	Remark(s)
Regulatory concern for reliable noninvasive peri-procedural safety monitoring	Develop & implement a framework for standardized MR-based monitoring & reporting	SIPs & standardized frameworks will enable optimal imaging-based safety assessment & reporting
	Implement standardized imaging protocols (SIP), incorporating MR sequences that capture vascular changes (e.g. T2*)	
Technical & methodological barriers to pooling data from multiple FUS trials	Work to delineate factors critical to technical & clinical success in FUS trials for brain diseases	Need to quantify effect of co-administered therapeutics on relationship of these factors to sonication success
	Multistakeholder development and field-wide implementation of COS for reporting procedural/technical outcomes[216–218]	Development of a unified dosing paradigm and COS for FUS delivery will both enable IPD-MA
Unclear choice of systemic therapy being combined with MB-FUS BBBO[219]	Recognize drug activity against brain tumors in vitro (where BBB does not hinder its action) vs its efficacy in vivo (previously a challenge without BBBO but now feasible with FUS)	E.g. lipophilic carboplatin which benefits from BBBO[219]
	Work on regulatory barriers to investigating safety & efficacy of combining FUS with multiagent therapies (esp. in brain drug delivery)	Facilitated by advocacy efforts with patient-focused organizations
Lack of FUS-specific national academic research collaborations	Development of brain-directed FUS research collaboratives, modeled after other technology-specific and disease-specific consortia	Nested within consortia running brain tumor trials (such as NCI ETCTN, NCTN, & NRG) or separate consortia like ReFOCUSED

EHR, electronic health record, CDISC, Clinical Data Interchange Standards Consortium; COS, core outcomes set; IPD, individual patient data, CSDR, https://ClinicalStudyDataRequest.com; CDE, Common Data Elements, T1w T1-weighted. ETCTN, NCI Experimental Therapeutics Clinical Trials Network; NINDS, National Institute of Neurological Disorders and Stroke.

order the device off-the-shelf or manufacture this device themselves. Such approaches can theoretically enable more cost-efficient trials, and, hopefully, patient-funded, patient-driven FUS studies.

Trialists investigating FUS also need to consider development and adoption of a standardized core outcomes set (COS) and Common Data Elements (CDE) for conduct and reporting of FUS trials.[214,216] Field-wide adoption of COS will not only improve reporting of trials, but also enhance reporting across retrospective studies of FUS, particularly tackling "outcome-reporting bias."[225] COS adoption is increasingly recommended by regulatory authorities as well.[216,226] Given the current absence of any ongoing or completed efforts at COS for FUS and of COS for BM, development of high-quality COS following COS-STAD and COMET guidelines represents a need for the field.[216,217,226] These should be guided by multidisciplinary research prioritization efforts, with a notable NCI effort for BMs.[11] Similar efforts are also warranted at developing FUS-specific CDEs, potentially in the umbrella of preexisting collaboratives such as Clinical Data Interchange Standards Consortium and the National Institute of Neurological Disorders and Stroke (NINDS) CDE.[215] Similarly, development of standardized imaging protocols and reporting frameworks for transcranial FUS peri-procedural safety assessment are also needed.[227] Such global consensus-based efforts involving patient advocates, potentially organized and supported by the Society for Neuro-Oncology, European Association for Neuro-Oncology, and/or NINDS, will support future team science and convergence science efforts.

Adaptive trial designs may potentially be of utility in this evolving space, given the logistical challenges encountered in RCTs in neuro-oncology.[194,228,229] Adaptive trial designs relevant for enrolling FUS for brain tumor patients include biomarker-adaptive and platform-adaptive (for instance, which can be used for BM patients with targetable driver mutations in primary tumor to combine with MB-FUS-boosted drug delivery) and population enrichment designs (for instance which may be used to identify subgroups where HIFU may be most impactful). Adaptive platform trials permit utilization of a common core protocol, with additional modular blocks for different arms, that have prespecified stopping triggers. The use of master protocols and common trial infrastructure reduces administrative burden in multicenter collaborations and facilitates standardized assessment. Regular interim analyses evaluate whether one or more arms (such as control or FUS arm) may be withdrawn for futility or advanced for further investigation, as part of a perpetual platform. Adaptive trials for FUS for BM may be planned learning from prior successes of adaptive trials in solid tumors.[230–232]

Finally, agreement remains to be established on the optimal sonication parameters (including procedural settings for MB-FUS BBBO for BM cases), surrogate technical indicators, and monitoring approaches for safety and

technical completion. Substantial treatment protocol heterogeneity (for same P.I.C.O.) and considerable variations in institutional approaches to monitoring exist, warranting field-wide efforts at treatment protocol standardization for future multicenter investigations (Table 4). This optimization, in addition to potentially enhancing technical and clinical efficacy of future FUS investigations, will also enable future IPD meta-analyses.

Appropriate Endpoints, Safety Assessments, and Patient-Reported Outcomes

Given the rapid technological evolution and multiple ongoing trials of various devices in different phases, trial endpoint selection must be carefully done (Table 4), with specific thought given to technical, clinical, and patient-reported outcomes (PROs).[233–235]

In terms of technical outcomes, the end biomechanical effect of FUS needs to be captured and reported, instead of intermediate variables, going forward. For instance, for MB-FUS, this represents the microbubble activity,[64] rather than the pressure differential or sonication power. Appropriate endpoints are critical for device trials and in neuro-oncology trials, as well-illustrated previously with the sobering results from the use of PFS (a surrogate endpoint) in brain tumor trials of anti-VEGF agents.[236] However, lessons must also be learnt from the landmark oligometastatic BM RCTs, some of which prespecified OS as a primary endpoint in a trial investigating utility of brain-directed local therapy (OS being driven by systemic disease).

Given that both benefits and harms must be appropriately captured and reported, comprehensive safety assessment in FUS trials remains paramount. Safety evaluation ideally needs to be both clinical and imaging-based and carried out both intra- and postprocedure in a standardized fashion,[227] given that noninvasive peri-procedural safety monitoring is a current regulatory concern.[237] For instance, gradient echo sequences (GRE)/T2*-weighted MR imaging can capture subtle changes in susceptibility signal, which indicate erythrocyte extravasation (Figure 1).[64] Dynamic susceptibility-weighted imaging (DSI) during the procedure can help capture acutely developing areas of blossoming, indicating a need to stop the sonication at the target. However, acute vs delayed signal changes on intra-procedural DSI and/or postprocedural T2* imaging and their downstream relationship to desired and undesired bioeffects are yet to be characterized.

Finally, despite increasing recognition of the utility of PROs, most works for BM don't encompass PROs such as quality of life (QoL) and return to functional status (RTF) after treatment. These variables are also typically not captured in large centralized databases, like SEER, NCDB in the US, or in the electronic medical record (due to logistical challenges).[238] However, these PROs carry major relevance for patients with BMs, who frequently have concomitant EMs in multiple organs—with clinical implications of high-morbidity cranial surgeries. Given the increasingly recognized noninvasive nature of FUS (which minimally impacts QoL or RTF), PROs will be particularly important for FUS investigations, potentially even to be used as part of composite outcomes for trials [such as for an ordinal longitudinal model (OLM)-based endpoint]. For instance, a potential trial comparing HIFU vs resection for isolated brain metastasis would benefit from an OLM-based endpoint incorporating health state utility values or QoL data, which would also increase trial power. A RANO review has discussed considerations regarding neurocognitive, neurological, and QoL outcomes in BM trials.[238]

Considerations in Combining FUS and Systemic Therapies

Unique considerations and questions also present themselves with regards to timing and combinatorial approach for FUS with systemic therapies. Currently, it is unclear if BBBO through MB-FUS should be done concurrently with systemic therapies prior to development of metastases (in order to prevent or delay occurrence of BMs), or when metastases have already developed (for intracranial tumor control), in order to provide maximal patient benefit.[219] The sequencing of FUS and ICIs is also a question of major interest, given that tumor ablation or fractionation-based FUS applications can theoretically boost intracranial efficacy of ICIs (given concurrently with FUS or post-FUS). Here, adding partial or fractionated tumor ablation using HIFU may be of some utility to boost antigen presentation, synergistically with ICIs.

Further, given the large repertoire of systemic therapies now available for metastatic cancer patients, many of which had limited BM-specific efficacy, drug selection for combination with MB-FUS in clinical trials will require additional considerations. Many of the drugs that are not used for BMs specifically (having anti-tumor activity but not intracranial efficacy), can become reasonable choices for investigation in conjunction with MB-FUS. Combining MB-FUS with large-sized, intravenous agents that are delivered monthly could be potentially more feasible for clinical use than oral small-molecule drugs that are taken daily.

Trials of FUS plus systemic therapy may be combined with longitudinal multi-omic approaches, functional genomic analyses, and deep mutational scanning to extract more translational data per trial.[239] When used on scRNAseq data collected prospectively and longitudinally from clinical trial participants, functional class scoring methods like gene set enrichment analysis (GSEA/GSVA), along with pathway topology methods like signaling pathway impact analysis can help investigators better understand therapeutic response and/or drug resistance.[102] Incorporating in such trials recommendations made by the Methodology for the Development of Innovative Cancer Therapies (MDICT) guidelines will also help trial efficiency.[207–209]

Conclusions

Several opportunities are on the horizon for the use of FUS for patients with BMs, with the greatest promise held by the enhanced brain drug delivery of systemic therapies, followed by radiosensitization and immunomodulation,

and plasma liquid biopsy of BM-derived biomarkers. FUS-enhanced efficacy of systemic therapies could be used, in the future, in a synergistic manner with FUS-enhanced SLB, creating a potential new adaptive theragnostic paradigm for brain tumor patients. Given the demonstrated utility of MB-FUS for enabling delivery of small to large-sized therapeutics, directed efforts through multicenter trials and FUS consortia (like ReFOCUSED) are now warranted to optimize FUS for BM in a disease-state-based, tumor-specific fashion. Across all FUS modes, the relationship between adjustable FUS (sonication) parameters and downstream clinical and molecular bioeffects in BM patients, as well as the optimal timing of FUS treatments, are yet to be well-characterized; for FUS for enhancing efficacy of systemic therapies, investigations are needed to identify optimal combinations from the large available repertoire of conventional chemotherapies, targeted therapies, and immunotherapies. More optimized FUS delivery will lead to improved technical and clinical efficacy with decreased treatment time without reduction in either precision or safety.

Keywords

acoustics | brain metastasis | microbubble | neuro-oncology | sonication

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Conceptualization: A.O. and M.S.A.; Visualization: A.O., B.M., P.A., and D.G.; Project administration: A.O.; Supervision: M.S.A.; Writing – original draft: A.O. and B.M.; Writing—review & editing: All authors.

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