Medical
Research
Journal

FOCUSED ULTRASOUND–MEDIATED BLOOD–BRAIN BARRIER OPENING IN NEURO-ONCOLOGY: CLOSED-LOOP CAVITATION CONTROL, PRECISION DRUG DELIVERY, AND THE PROPOSED SONO-BRIDGE FRAMEWORK

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Abstract

Background. The blood–brain and blood–tumor barriers restrict homogeneous drug delivery to infiltrating brain-tumor cells, particularly beyond contrast-enhancing regions. Microbubble-enhanced focused ultrasound can temporarily and spatially increase vascular permeability through controlled mechanical interactions with cerebral microvessels.

Materials and methods. Prospective clinical trials, phase I–II studies, pharmacokinetic investigations, translational experiments, and technical reports published through July 2026 were synthesized. Evidence was organized according to skull acoustics, targeting, microbubble exposure, acoustic-emission monitoring, permeability imaging, drug properties, tumor phenotype, treatment timing, and toxicity.

Results. Noninvasive magnetic-resonance-guided, neuronavigation-guided, and implantable ultrasound platforms have repeatedly produced reversible barrier opening in glioblastoma, high-grade glioma, and brain metastases. Implantable low-intensity pulsed ultrasound increased delivery of albumin-bound paclitaxel and carboplatin in recurrent glioblastoma. The multicenter BT008NA phase I–II study combined repeated transcranial microbubble-enhanced focused ultrasound with adjuvant temozolomide and reported feasible barrier opening, acceptable safety, exploratory survival signals, and enhanced plasma tumor-biomarker release. Clinical evidence also supports increased trastuzumab delivery to HER2-positive brain metastases. However, drug penetration remains influenced by molecular size, plasma pharmacokinetics, extracellular diffusion, efflux transport, interstitial pressure, and regional tumor heterogeneity.

Conclusion. Focused ultrasound is a drug-delivery platform rather than an independent antitumor treatment. Safe translation requires individualized acoustic planning, real-time cavitation control, temporal coordination with systemic therapy, quantitative confirmation of permeability, and prospective demonstration that increased drug exposure improves patient-centered outcomes.

Keywords: focused ultrasound; blood–brain barrier; glioblastoma; microbubbles; cavitation; drug delivery; brain metastases; temozolomide; nanoparticle therapy; sonobiopsy.

ОТКРЫТИЕ ГЕМАТОЭНЦЕФАЛИЧЕСКОГО БАРЬЕРА ФОКУСИРОВАННЫМ УЛЬТРАЗВУКОМ В НЕЙРООНКОЛОГИИ: ЗАМКНУТОЕ УПРАВЛЕНИЕ КАВИТАЦИЕЙ, ПРЕЦИЗИОННАЯ ДОСТАВКА ЛЕКАРСТВ И ПРЕДЛОЖЕННАЯ МОДЕЛЬ SONO-BRIDGE

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Аннотация

Актуальность. Гематоэнцефалический и гематоопухолевый барьеры ограничивают равномерное проникновение лекарственных средств к инфильтрирующим клеткам опухолей мозга, особенно за пределами контрастирующейся части новообразования. Фокусированный

ультразвук в сочетании с микропузырьками способен временно и пространственно избирательно повышать проницаемость церебральных микрососудов посредством контролируемого механического воздействия.

Материалы и методы. Синтезированы проспективные исследования, испытания I–II фаз, фармакокинетические и трансляционные работы, опубликованные до июля 2026 года. Доказательства систематизированы по акустическим свойствам черепа, наведению, дозированию микропузырьков, акустическим эмиссиям, визуализации проницаемости, свойствам препарата, фенотипу опухоли и токсичности.

Результаты. Неинвазивные МР-направляемые, нейронавигационные и имплантируемые системы многократно обеспечивали обратимое открытие барьера при глиобластоме, глиомах высокой степени и метастазах. Имплантируемый низкоинтенсивный импульсный ультразвук повышал доставку альбумин-связанного паклитаксела и карбоплатина при рецидивной глиобластоме. Многоцентровое исследование BT008NA сочетало повторное транскраниальное ультразвуковое воздействие с темозоломидом и продемонстрировало осуществимость, приемлемую безопасность, исследовательский сигнал выживаемости и усиленный выход опухолевых биомаркеров в плазму. Увеличение проницаемости также способствовало доставке трастузумаба при HER2-положительных метастазах мозга. Однако поступление препарата определяется не только фактом открытия барьера, но и размером молекулы, длительностью циркуляции, связыванием с белками, межклеточной диффузией, эффлюксными транспортерами, интерстициальным давлением и неоднородностью микроциркуляции.

Заключение. Фокусированный ультразвук является платформой доставки, а не самостоятельным универсальным противоопухолевым методом. Безопасное применение требует индивидуального акустического планирования, контроля кавитации, точной синхронизации с системной терапией, количественной оценки проницаемости и подтверждения клинической эффективности в рандомизированных исследованиях.

Ключевые слова: фокусированный ультразвук; гематоэнцефалический барьер; глиобластома; микропузырьки; кавитация; доставка лекарств; метастазы головного мозга; темозоломид; нанотерапия; сонобиопсия.

NEYROONKOLOGIYADA FOKUSLANGAN ULTRATOVUSH YORDAMIDA GEMATOENSEFALIK TO‘SIQNI OCHISH: KAVITATSIYANI YOPIQ SIKLDA BOSHQARISH, PRETSIZION DORI YETKAZISH VA TAKLIF ETILGAN SONO-BRIDGE MODELI

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Annotatsiya

Dolzarblik. Gematoensefalik va gematoo‘sma to‘siqlari dori vositalarining infiltrativ miya o‘smasi hujayralariga, ayniqsa kontrast to‘playdigan hududdan tashqariga bir xil yetib borishini cheklaydi. Mikropufakchalar bilan kuchaytirilgan fokuslangan ultratovush serebral mikrotomirlarga boshqariladigan mexanik ta’sir ko‘rsatib, tomir o‘tkazuvchanligini vaqtinchalik va fazoviy tanlangan tarzda oshirishi mumkin.

Material va usullar. 2026-yil iyul oyigacha e’lon qilingan I–II faza klinik sinovlari, prospektiv tadqiqotlar, farmakokinetik hamda translyatsion ilmiy ishlar tahlil qilindi va umumlashtirildi. Olingan dalillar bosh suyagining akustik xususiyatlari, ultratovush nurlanishini yo‘naltirish usullari, mikropufakchalarni dozalashtirish, akustik emissiyalar, gematoensefalik to‘siq o‘tkazuvchanligini vizualizatsiya qilish, dori preparatlarining fizik-kimyoviy xususiyatlari, o‘smaning molekulyar-fenotipik xususiyatlari hamda davolash bilan bog‘liq toksiklik ko‘rsatkichlari bo‘yicha tizimlashtirildi.

Natijalar. Magnit-rezonans nazoratidagi noinvaziv, neyronavigatsion va implantatsiya qilinadigan ultratovush tizimlari glioblastoma, yuqori darajali glioma hamda miya metastazlarida to‘siqning qaytar ochilishini ta’minladi. Implantatsiya qilinadigan past intensivlikdagi impulsli ultratovush retsidiv glioblastomada albumin bilan bog‘langan paklitaksel va karboplatin yetkazilishini kuchaytirdi. Ko‘p markazli BT008NA tadqiqoti takroriy transkranial ultratovushni temozolomid bilan birlashtirib, texnik amalga oshirish mumkinligi, qabul qilinadigan xavfsizlik, yashab qolishga oid dastlabki signal va plazmaga o‘sma biomarkerlarining ko‘proq chiqishini ko‘rsatdi. HER2-musbat miya metastazlarida trastuzumabning o‘sma to‘qimasiga yetkazilishi ham oshirilgan. Biroq dori penetratsiyasi molekula hajmi, plazmadagi aylanish vaqti, oqsillar bilan bog‘lanish, hujayralararo diffuziya, efflyuks tashuvchilari, interstitsial bosim va o‘sma mikrosirkulyatsiyasining heterojenligiga bog‘liq.

Xulosa. Fokuslangan ultratovush mustaqil universal antitumor davolash emas, balki dori yetkazish platformasidir. Xavfsiz klinik joriy etish bemorga mos akustik rejalashtirish, real vaqtda kavitatsiyani boshqarish, sistemali dori yuborilishi bilan aniq sinxronlashtirish, o‘tkazuvchanlikni miqdoriy tasdiqlash va randomizatsiyalangan tadqiqotlarda klinik foydani isbotlashni talab qiladi.

Kalit so‘zlar: fokuslangan ultratovush; gematoensefalik to‘siq; glioblastoma; mikropufakchalar; kavitatsiya; dori yetkazish; miya metastazlari; temozolomid; nanoterapiya; sonobiopsiya.

Introduction. Glioblastoma and other infiltrative primary brain tumors remain therapeutically challenging despite maximal safe resection, radiotherapy, alkylating chemotherapy, molecular characterization, and increasingly sophisticated immunotherapeutic and targeted approaches. One major reason is that the visible contrast-enhancing tumor represents only part of the biological disease. Infiltrating tumor cells extend into surrounding brain where the blood–brain barrier may remain structurally and functionally intact, reducing the concentration of many systemically administered agents [1, 2, 3]. The blood–brain barrier is formed by specialized endothelial cells connected through tight and adherens junctions, a continuous basement membrane, pericytes, astrocytic end-feet, transport proteins, metabolic enzymes, and immune-regulatory elements. This neurovascular unit maintains ionic homeostasis and protects the central nervous system from toxins and fluctuating plasma composition. The same physiological protection excludes most large molecules and many potentially effective anticancer drugs [3, 6, 10]. Brain tumors can disrupt the barrier and create a heterogeneous blood–tumor barrier. Contrast enhancement indicates leakage of gadolinium-based agents but does not establish unrestricted drug penetration. Tumor vessels remain spatially heterogeneous, with regions of fenestration, abnormal basement membrane, high interstitial pressure, irregular perfusion, thrombosis, and relatively intact endothelium. Consequently, drug concentrations vary within the enhancing tumor and decline further in infiltrated nonenhancing brain [5, 11, 16]. Several strategies have attempted to overcome this obstacle. These include direct intratumoral injection, convection-enhanced delivery, intra-arterial therapy, osmotic barrier disruption, implantable polymers, receptor-mediated transport, intranasal administration, nanoparticle carriers, and molecular modification of therapeutic agents. Each approach has limitations related to invasiveness, spatial coverage, off-target toxicity, reflux, catheter distribution, systemic exposure, or dependence on specific transport pathways [4, 7, 14].

Focused ultrasound combined with intravenously administered microbubbles offers a fundamentally different strategy. Acoustic energy is concentrated within a selected intracranial volume. Circulating microbubbles oscillate in response to the acoustic field and generate mechanical forces at the microvascular wall. Under controlled conditions, these effects transiently increase paracellular and transcellular permeability without producing thermal ablation [8, 9, 25]. The opening is usually verified by contrast-enhanced MRI and closes over hours, although the duration depends on acoustic pressure, microbubble properties, vascular biology, and the size of the delivered agent. Spatial targeting enables treatment of tumor, peritumoral brain, or a distributed set of volumes while limiting exposure of unaffected regions [10, 13, 23]. The term focused ultrasound includes several biologically distinct interventions. High-intensity focused ultrasound can thermally ablate tissue. Sonodynamic therapy activates a systemically administered sensitizer to generate cytotoxic

reactive species. Histotripsy uses mechanical cavitation to destroy tissue. Low-intensity pulsed focused ultrasound with microbubbles aims primarily to modulate vascular permeability. These modalities should not be combined conceptually merely because they all use acoustic energy [2, 3, 18]. Clinical barrier-opening systems can be divided into three broad groups. Magnetic-resonance-guided transcranial systems use large phased arrays and CT-based skull correction to focus ultrasound noninvasively. Neuronavigation-guided systems use smaller transducers and image-based targeting outside the MRI scanner. Implantable devices replace a segment of skull with an ultrasound emitter or multiple emitters, facilitating repeated outpatient treatments through a fixed acoustic window [6, 13, 28].

The therapeutic effect of barrier opening cannot be evaluated independently from the accompanying drug. Ultrasound may increase local vascular permeability, but clinical benefit requires that the therapeutic molecule be present in the circulation during the permeability window, remain pharmacologically active, diffuse through the extracellular compartment, reach the relevant tumor cells, and exert a meaningful antitumor effect [11, 12, 20]. The same ultrasound parameters may not be optimal for temozolomide, antibodies, nanoparticles, viral vectors, immune cells, or albumin-bound chemotherapy. Molecular size, charge, protein binding, plasma half-life, tumor uptake, efflux transport, and intracellular target engagement influence the final pharmacological effect. Recent clinical evidence has moved beyond proof of barrier opening. Implantable systems have been combined with carboplatin and albumin-bound paclitaxel. Transcranial MR-guided ultrasound has increased trastuzumab delivery into HER2-positive brain metastases. The 2025 BT008NA study combined repeated microbubble-enhanced focused ultrasound with standard adjuvant temozolomide in newly diagnosed high-grade glioma and generated an exploratory survival signal requiring randomized confirmation [15, 17, 27]. Focused ultrasound may also enable diagnostic trafficking from brain to blood. Temporary vascular permeability can increase the release of cell-free DNA, RNA, proteins, and extracellular vesicles into plasma. This process, termed sonobiopsy or sono-liquid biopsy, may improve noninvasive molecular surveillance of brain tumors [7, 14, 19].

Materials and Methods. This manuscript was designed as a structured integrative review with an original treatment-selection and workflow synthesis. Prospective phase I and phase II clinical studies, pharmacokinetic investigations, first-in-human trials, translational experiments, acoustic-control studies, and clinically relevant device reports published through July 2026 were evaluated. The principal concepts included focused ultrasound, low-intensity pulsed ultrasound, blood–brain barrier opening, blood–tumor barrier, microbubbles, acoustic cavitation, passive cavitation detection, glioblastoma, high-grade glioma, brain metastases, diffuse midline glioma, temozolomide, carboplatin, albumin-bound paclitaxel, trastuzumab, doxorubicin, immunotherapy, sonobiopsy, and liquid biopsy. Evidence was classified into nine domains. The first domain was device architecture, including MR-guided phased arrays, neuronavigation-guided transducers, implantable single-emitter devices, and implantable multi-emitter systems. The second domain was acoustic planning, including skull thickness, density ratio, incidence angle, attenuation, phase correction, frequency, pressure, burst length, pulse repetition, and treatment volume. The third domain was microbubble biology, including formulation, diameter, concentration, injection timing, circulation kinetics, and interaction with ultrasound. The fourth domain was cavitation monitoring, including harmonic, ultraharmonic, and broadband acoustic emissions, stable and inertial cavitation, closed-loop control, and safety thresholds. The fifth domain was barrier confirmation, including contrast-enhanced MRI, dynamic contrast-enhanced MRI, permeability maps, susceptibility imaging, diffusion imaging, and acoustic-emission mapping. The sixth domain was pharmacology, including drug concentration, molecular size, plasma half-life, protein binding, carrier system, extracellular diffusion, target engagement, and systemic toxicity. The seventh domain was clinical safety, including hemorrhage, edema, seizure, headache, neurological deficit, sterile inflammation, infection, device complication, and repeated-treatment tolerance. The eighth domain was clinical efficacy, including radiological response, progression-free survival, overall survival, pharmacokinetic enhancement, biomarker release, and quality of life. The ninth domain was implementation, including patient selection, treatment timing, anesthesia, MRI occupancy,

multidisciplinary staffing, manufacturing, cost, repeatability, and integration with standard neuro-oncological care. No new patient cohort was created and no independent pooled meta-analysis was performed. Study results were interpreted according to trial phase, sample size, comparator, device, accompanying therapeutic agent, tumor phenotype, and endpoint. Tables represent an original synthesis of published evidence and not fabricated clinical data.

Results. The endothelial component of the BBB restricts paracellular passage through claudins, occludin, junctional adhesion molecules, and associated cytoplasmic proteins. Transcellular transport is limited by low rates of vesicular trafficking, while ATP-binding cassette transporters actively remove many lipophilic drugs from endothelial cells and brain parenchyma [16, 23, 30]. Small lipophilic molecules can cross more readily than hydrophilic or macromolecular agents, but molecular size alone does not predict clinically useful delivery. Temozolomide enters the brain better than many conventional cytotoxic drugs, yet its intratumoral distribution remains heterogeneous and its efficacy is limited by DNA-repair mechanisms, stem-cell states, and tumor evolution. Large molecules such as monoclonal antibodies have extremely restricted passive brain penetration. Their systemic activity against extracranial tumors does not guarantee equivalent activity against intracranial lesions. Nanoparticles, liposomes, viral vectors, and cellular therapies face additional barriers related to vascular extravasation, tissue diffusion, immune clearance, and particle size [21, 24, 31]. In glioblastoma, contrast-enhancing regions show barrier disruption, but the infiltrative margin may remain protected. This creates a pharmacological sanctuary in which residual cells survive treatment and later repopulate the surgical cavity. Barrier opening is therefore most relevant not only in the enhancing tumor but also in the surrounding infiltrated brain. The optimal target cannot be defined by T1 contrast enhancement alone. FLAIR abnormality, diffusion characteristics, amino-acid PET, perfusion, spectroscopy, surgical cavity geometry, expected recurrence pattern, and functional anatomy may need to be incorporated into the sonication plan [23, 30, 32].

Mechanism of Microbubble-Mediated Permeability. Clinical microbubbles contain a gas core stabilized by a lipid, protein, or polymer shell. Their diameter is generally comparable with that of red blood cells, allowing them to remain within the vascular compartment during diagnostic use. When exposed to an acoustic field, microbubbles expand and contract. At controlled pressures, stable cavitation produces repetitive oscillation and local mechanical effects, including endothelial shear stress, transient separation of tight junctions, increased vesicular transport, and modulation of the basement membrane. At higher pressures, bubbles can undergo inertial cavitation, characterized by rapid collapse and broadband acoustic emissions. This can damage microvessels, cause erythrocyte extravasation, petechial hemorrhage, edema, inflammation, ischemia, or larger hemorrhage [1, 10, 13]. The objective is therefore not maximum barrier opening. It is the lowest acoustic exposure that creates sufficient and spatially homogeneous permeability for the selected therapeutic agent without producing clinically relevant vascular injury. Barrier opening is affected by acoustic frequency, peak negative pressure, burst duration, repetition frequency, number of sonications, microbubble dose, bubble diameter, infusion method, vascular density, skull attenuation, and tissue pathology. A fixed pressure applied to every patient cannot guarantee a uniform biological response [3, 10, 18, 27].

Table 1. Biological Sequence of Focused-Ultrasound Barrier Opening

Stage	Principal process	Desired effect	Potential failure
Microbubble administration	Circulating gas-filled particles enter cerebral vessels	Uniform vascular availability	Variable concentration or rapid clearance
Acoustic focusing	Ultrasound energy converges within target volume	Spatially selective exposure	Skull-induced defocusing or off-target energy
Stable oscillation	Repetitive bubble expansion and contraction	Reversible endothelial permeability	Insufficient opening

Excessive cavitation	Violent oscillation or collapse	No therapeutic objective	Petechiae, edema, hemorrhage, vessel injury
Vascular permeability	Paracellular and transcellular transport increase	Drug extravasation	Heterogeneous or incomplete delivery
Interstitial distribution	Drug moves through extracellular space	Exposure of infiltrating tumor cells	High pressure, binding, matrix restriction
Barrier restoration	Endothelial function recovers	Temporary and controlled exposure	Prolonged leakage or inflammation
Treatment effect	Drug reaches biological target	Tumor control	Pharmacological resistance despite adequate delivery

Device Platforms. MR-guided transcranial systems use a hemispherical phased-array transducer containing hundreds or more than one thousand elements. Preoperative CT estimates skull thickness and density, allowing phase and amplitude correction. MRI defines the target, confirms contrast leakage, and assesses edema, diffusion abnormality, and susceptibility changes. This approach is noninvasive and flexible. Different intracranial regions can be targeted during subsequent sessions without surgery. Its limitations include MRI dependence, long procedure time, frame or helmet positioning, skull-energy loss, patient discomfort, limited availability, and difficulty treating some peripheral or skull-base targets [4, 14, 19, 25]. Neuronavigation-guided systems use a smaller extracranial transducer aligned with preoperative imaging. The patient can be treated outside the MRI suite, while acoustic emissions provide procedural feedback. MRI is still commonly required to confirm opening. The approach may reduce cost and treatment complexity but depends on accurate registration and transducer coupling. Implantable systems place an ultrasound emitter within a skull window created during tumor surgery. Repeated treatments can be performed without transcranial attenuation by intact bone. Early single-emitter platforms opened a relatively small cylindrical region, whereas multi-emitter devices such as SonoCloud-9 cover a larger volume around the resection cavity [5, 16, 20]. Implantation adds surgical risk, infection risk, device maintenance, and dependence on the original implant location. The fixed geometry may not cover distant or multifocal recurrence. Its advantage is repeatability and reduced acoustic uncertainty after the device has been positioned. Selection among platforms should reflect whether the patient is already undergoing craniotomy, the expected number of treatment cycles, tumor location, skull anatomy, need for distributed targeting, MRI compatibility, institutional resources, and the possibility of future recurrence outside the initial field.

Table 2. Comparison of Clinical Focused-Ultrasound Platforms

Feature	MR-guided transcranial array	Neuronavigation-guided transcranial system	Implantable ultrasound device
Surgical implantation	Not required	Not required	Required during craniotomy
Skull attenuation	Requires phase correction	Requires patient-specific acoustic planning	Reduced through implanted acoustic window
Target flexibility	High	High to moderate	Predetermined by implant position
MRI during treatment	Integrated	Usually separate confirmation	Separate post-sonication imaging
Repeated outpatient use	Feasible but resource-intensive	Feasible	Designed for repeated activation
Treatment volume	Multiple steerable focal spots	Device-dependent	Determined by number and geometry of emitters

Cavitation monitoring	Integrated or external sensors	Acoustic-emission based	Device-specific
Main advantage	Precise noninvasive spatial targeting	More accessible extracranial workflow	Reliable repeated delivery near resection cavity
Main limitation	MRI time and skull acoustics	Registration and coupling accuracy	Implant surgery and fixed coverage

Acoustic Planning and Skull Effects. The skull is the principal acoustic obstacle. Cortical and trabecular bone differ from soft tissue in density, sound speed, attenuation, and impedance. Ultrasound rays travelling through different skull regions acquire different phase shifts, causing defocusing unless corrected. Higher frequencies provide smaller focal volumes but undergo greater skull attenuation and heating. Lower frequencies penetrate bone more effectively and create larger focal regions but may reduce spatial precision. The optimal frequency therefore differs between thermal ablation and permeability modulation. Skull-density ratio, thickness, curvature, target depth, incidence angle, and distance from the transducer influence transmitted pressure. CT-based acoustic simulation is commonly used to estimate these variables and exclude patients in whom adequate focusing cannot be achieved safely. Air in the frontal sinus, mastoid cells, surgical cavities, or wound can distort transmission. Prior cranioplasty, titanium hardware, bone cement, and irregular postoperative skull anatomy require individualized assessment. In implantable systems, replacing bone with an acoustic device reduces attenuation but introduces alignment and coupling constraints. The implant must remain stable, integrated with the scalp, and free of infection. The acoustic field should be characterized after implantation rather than assumed from preoperative design.

Cavitation Monitoring and Closed-Loop Control. Passive cavitation detectors receive acoustic emissions generated by oscillating microbubbles. Stable cavitation produces harmonic and ultraharmonic signals, whereas inertial collapse generates broadband emissions. An open-loop protocol applies predetermined acoustic pressure based on population or preclinical data. A closed-loop system adjusts pressure during treatment according to detected bubble activity. Closed-loop control aims to compensate for differences in skull transmission, microbubble concentration, vascularity, and target anatomy [2, 6, 10, 13]. A common strategy gradually increases pressure until a cavitation threshold is detected, then reduces the exposure to a predefined fraction of that level. More advanced systems calculate cumulative acoustic-emission dose, spatial maps, or frequency-specific features throughout the treatment. Cavitation information must be interpreted carefully. The absence of detected emissions may indicate insufficient bubble activity, poor sensor alignment, skull attenuation, or technical failure. Strong emissions may reflect effective opening or unsafe vascular interaction depending on spectral pattern and context. The 2025 analysis of BT008NA procedural data demonstrated that acoustic-emission dose was associated with spatial and quantitative control of barrier opening, supporting personalized feedback-based sonication rather than uniform pressure delivery [11, 15, 17, 20]. The future objective is a fully closed-loop system that predicts the pressure required for each focal volume, detects microbubble arrival, adjusts exposure in real time, maps cavitation spatially, and stops automatically when permeability is sufficient or an unsafe signal appears.

Imaging Confirmation and Quantification. Contrast-enhanced T1-weighted MRI is the most common confirmation method. New enhancement within the sonicated volume indicates gadolinium extravasation. The enhancement should correspond spatially with the intended target and resolve on subsequent imaging. Binary confirmation does not measure how much permeability increased. Dynamic contrast-enhanced MRI can estimate Ktrans, plasma volume, and other pharmacokinetic parameters. These metrics may correlate more closely with therapeutic delivery than visual enhancement alone. Susceptibility-weighted imaging and T2*-weighted gradient-echo sequences detect microhemorrhages. Diffusion imaging evaluates ischemia or cytotoxic injury. FLAIR identifies edema or sulcal signal alteration. The absence of visible hemorrhage does not prove the absence of microscopic vascular injury. Conversely, isolated asymptomatic susceptibility foci may not predict permanent neurological harm. Standardized definitions of radiological toxicity are required. Gadolinium is smaller than many therapeutic agents. Successful gadolinium leakage

cannot guarantee delivery of an antibody, nanoparticle, viral vector, or cell. Imaging biomarkers should therefore be validated against direct measurement of the specific therapeutic whenever feasible. PET-labelled drugs, intraoperative tissue sampling, cerebrospinal-fluid concentration, plasma pharmacokinetics, and microdialysis can provide complementary evidence. Direct paired sonicated-versus-unsonicated tissue concentration remains one of the strongest pharmacological validation methods.

Pharmacokinetic Principles. The systemic drug should reach an effective plasma concentration during the barrier-opening window. Short-half-life agents may require administration immediately before or during sonication. Long-circulating antibodies or liposomes provide a broader temporal window but may remain in plasma after the BBB begins to close. Greater brain entry does not automatically improve therapeutic ratio. If systemic toxicity limits dose, focused ultrasound may allow greater intracranial exposure without increasing plasma concentration. Alternatively, the same systemic dose may produce additional brain toxicity after opening. Albumin-bound paclitaxel is normally excluded from the brain but has potent antitumor activity. Focused ultrasound provides a rationale for exposing glioblastoma cells to a drug class that is otherwise pharmacologically inaccessible. Carboplatin penetrates the CNS incompletely. Repeated implantable ultrasound has been combined with carboplatin to increase local delivery around the surgical cavity. Temozolomide already crosses the BBB to a clinically relevant extent. The rationale for FUS is not to convert an impermeable drug into a permeable one but to increase and homogenize exposure in infiltrated brain. Whether this improves benefit depends strongly on MGMT promoter methylation and other resistance mechanisms [1, 2, 10, 13]. Antibodies such as trastuzumab have limited passive brain entry. Their long plasma half-life and target specificity make them attractive candidates for FUS-mediated delivery, but Fc-mediated immune effects, receptor heterogeneity, and systemic cardiotoxicity remain relevant. Nanoparticles can carry high drug payloads, protect unstable molecules, and incorporate targeting ligands. Their size and matrix interactions can restrict diffusion after vascular extravasation. Opening the endothelial barrier solves only the first stage of delivery.

Table 3. Drug-Specific Requirements for Ultrasound-Mediated Delivery

Therapeutic class	Principal barrier	Potential FUS advantage	Remaining limitation
Temozolomide	Heterogeneous exposure in infiltrated brain	Increased and more uniform tissue concentration	MGMT-mediated resistance
Carboplatin	Limited CNS penetration and systemic toxicity	Regional delivery around surgical cavity	Myelosuppression and DNA-repair resistance
Albumin-bound paclitaxel	Very poor spontaneous brain penetration	Enables entry of an otherwise excluded cytotoxic drug	Neuropathy and myelosuppression
Monoclonal antibodies	Large molecular size	Regional antibody extravasation	Limited interstitial diffusion and target heterogeneity
Liposomal drugs	Particle size and vascular exclusion	Local carrier extravasation	Slow tissue penetration and reticuloendothelial uptake
Viral vectors	Endothelial and immune barriers	Regionally enhanced gene delivery	Neutralizing antibodies and long-term safety
Immune cells	Vascular adhesion and microenvironment	Potentially increased trafficking	Immunosuppressive tumor niche

Radiosensitizers	Insufficient tumor concentration	Increased local exposure before radiotherapy	Normal-brain radiosensitization
Molecular probes	Poor access to tumor tissue	Improved imaging or theranostic uptake	Need for specific biological target

Clinical Evidence in Recurrent Glioblastoma. Early implantable-ultrasound trials established that repeated barrier opening was feasible. The single-emitter SonoCloud device was activated during carboplatin infusion in patients with recurrent glioblastoma. Repeated sessions were tolerated and MRI demonstrated localized permeability changes [3, 6, 15, 18]. The SonoCloud-9 phase I–II trial expanded treatment volume through nine emitters. Thirty-three patients received 90 sonications with carboplatin. Up to nine emitters were activated without a dose-limiting toxicity, and successful barrier opening was evaluated using post-sonication MRI [5, 11, 16, 20]. The study was single-arm and primarily designed for safety and technical performance. Clinical outcome observations cannot establish efficacy because of selection, recurrent-disease heterogeneity, previous therapy, and absence of a randomized comparator. A separate phase I study combined the nine-emitter implant with albumin-bound paclitaxel in recurrent glioblastoma. The device was implanted after tumor resection and activated every three weeks for up to six cycles. The study established feasible repeated opening and enabled pharmacokinetic comparison of sonicated and unsonicated brain regions [4, 7, 14, 19]. The clinically important result was not merely MRI enhancement. Tissue analyses demonstrated substantially greater paclitaxel exposure in sonicated brain. This confirmed that a macromolecular chemotherapy formulation that normally has minimal CNS penetration could be delivered pharmacologically relevantly. The study also showed that paclitaxel and carboplatin toxicity must be interpreted separately from ultrasound toxicity. Myelosuppression, neuropathy, and systemic adverse events may increase if a potent but toxic agent is repeatedly administered.

Evidence in Newly Diagnosed High-Grade Glioma. BT008NA was a multicenter, open-label phase I–II study combining repeated transcranial microbubble-enhanced focused ultrasound with standard monthly adjuvant temozolomide. Thirty-four patients were enrolled across five sites in the United States and Canada. Barrier opening was visualized after all treatments. No treatment-related deaths occurred. Most adverse events were low grade, although neurological, hematological, disease-related, and procedure-related events required structured evaluation. The reported median progression-free survival was 13.5 months, and median overall survival was 31.3 months. Comparison with an externally constructed control cohort suggested a potential survival advantage, but the study was not randomized and was not originally powered to establish efficacy [2, 3, 10, 18]. The result is clinically encouraging because the intervention was integrated with newly diagnosed treatment rather than reserved for recurrence. Nevertheless, external controls cannot fully account for favorable performance status, extent of resection, molecular characteristics, supportive care, center selection, and unmeasured prognostic variables. A randomized controlled trial is necessary before the survival observation can be attributed to FUS. Stratification should include MGMT promoter methylation, IDH status, extent of resection, corticosteroid exposure, age, performance status, and tumor location. The study also collected plasma biomarkers before and after sonication. Changes in circulating cell-free DNA concentration and fragment characteristics appeared concordant with patient-specific disease trajectories in exploratory analyses. This links treatment delivery and disease monitoring within one procedure.

Brain Metastases and Antibody Delivery. Brain metastases may show contrast enhancement yet remain incompletely accessible to systemic antibodies. In HER2-positive breast cancer, trastuzumab is highly effective extracranially but has limited brain penetration. MR-guided focused ultrasound was used to open the barrier in patients with HER2-positive brain metastases receiving trastuzumab. PET imaging with radiolabelled trastuzumab showed increased antibody uptake within sonicated lesions [6, 11, 12, 20]. This study directly demonstrated delivery of a therapeutic macromolecule rather than only leakage of gadolinium. It established a pharmacological proof of mechanism for antibody delivery. Clinical efficacy remains uncertain because the cohort was small, lesions were heterogeneous, and patients received other oncological treatments. Larger

studies must determine whether repeated regional delivery improves intracranial response, neurological progression-free survival, or survival. FUS may be particularly relevant for lesions resistant to small-molecule HER2 inhibitors or for antibodies targeting EGFR, VEGF, immune checkpoints, or tumor-specific antigens. Each molecule requires independent safety and distribution assessment.

Diffuse Midline Glioma and Brainstem Disease. Diffuse midline glioma is a compelling application because the tumor is unresectable and the brainstem barrier limits drug delivery. At the same time, the anatomical tolerance for edema, hemorrhage, or targeting error is extremely low. Preclinical studies have demonstrated enhanced delivery of etoposide, doxorubicin, antibodies, and other agents into pontine tumor models [30–33]. Clinical translation requires conservative cavitation control, precise acoustic correction, cranial-nerve and long-tract monitoring, and careful selection of drug toxicity. A permeability change that would be tolerated in frontal white matter may be clinically significant in the pons. Trials should initially emphasize safety, pharmacokinetics, and biomarker response rather than expecting early survival proof. Pediatric age, skull development, sedation, repeated MRI, and long-term vascular effects require additional consideration.

Immunological Effects. Barrier opening is not biologically neutral. Mechanical interaction can alter endothelial signaling, cytokine expression, leukocyte trafficking, microglial activation, and antigen release. Excessive acoustic exposure can produce sterile inflammation. Controlled exposure may create a transient immunological window that facilitates immune-cell or antibody access [1, 3, 10, 13]. Preclinical glioma studies have combined FUS with doxorubicin and PD-1 blockade. Ultrasound-enhanced doxorubicin delivery altered the tumor immune microenvironment and improved response to checkpoint inhibition in experimental models [5, 11, 16, 32]. Early compassionate or exploratory clinical observations are insufficient to establish efficacy but support the concept that FUS may serve as both a delivery and immune-modulation platform.

The direction of the immune effect depends on acoustic dose, tumor model, microbubble exposure, accompanying drug, corticosteroids, radiation, and treatment schedule. Inflammation should therefore be measured rather than assumed to be beneficial.

Sonobiopsy and Two-Way Barrier Trafficking. Brain-tumor liquid biopsy is limited because tumor-derived nucleic acids and proteins are diluted in plasma and restricted by the BBB. Cerebrospinal-fluid analysis provides higher sensitivity in selected tumors but requires lumbar puncture or ventricular access and may not be safe in all patients. Focused ultrasound can facilitate two-way trafficking. Therapeutic molecules move from blood into brain, while tumor-derived material moves from brain into blood. The first prospective human sonobiopsy trial used neuronavigation-guided FUS in patients with high-grade glioma. Plasma collected after sonication showed increased concentrations of brain-derived and tumor-associated biomarkers without serious procedure-related toxicity [7, 9, 19, 28]. BT008NA incorporated repeated biomarker sampling and suggested that plasma cfDNA trajectories might reflect disease behavior. These observations remain exploratory and require validation against MRI, methylation analysis, tumor-specific mutations, and clinical progression. Sonobiopsy could improve diagnosis when tissue biopsy is dangerous, permit molecular surveillance during treatment, and detect clonal evolution. It may also create false signals from normal-brain injury, inflammation, or transient release unrelated to viable tumor burden. The timing of blood collection is critical because biomarkers are cleared rapidly. Standardized pre-sonication and serial post-sonication samples are needed.

Table 4. Clinical Evidence and Its Appropriate Interpretation

Clinical application	Principal study type	Main demonstrated outcome	What remains unproven
Recurrent GBM with carboplatin	Implantable phase I–II studies	Repeated opening and acceptable procedural safety	Randomized survival benefit
Recurrent GBM with albumin-bound paclitaxel	Phase I pharmacokinetic trial	Increased regional drug delivery	Comparative efficacy and optimal dose

Newly diagnosed high-grade glioma with TMZ	BT008NA phase I–II study	Feasibility, safety, exploratory survival signal	Causal survival benefit
HER2-positive brain metastases	Small MRgFUS pharmacokinetic study	Increased trastuzumab uptake	Improved intracranial disease control
Diffuse midline glioma	Preclinical and early feasibility programs	Enhanced drug penetration	Human efficacy and long-term brainstem safety
Sono-liquid biopsy	First-in-human prospective studies	Increased circulating biomarker release	Diagnostic sensitivity, specificity, and outcome impact
FUS plus immunotherapy	Mainly preclinical investigations	Immune modulation and enhanced experimental response	Reproducible clinical antitumor efficacy

Safety and Adverse Events. The main acute safety concerns are microhemorrhage, larger intracranial hemorrhage, edema, ischemia, seizure, headache, transient neurological deficit, and inflammatory change. Risk increases with excessive acoustic pressure, high microbubble dose, unstable cavitation, vascular abnormality, coagulopathy, thrombocytopenia, anticoagulation, recent hemorrhage, uncontrolled hypertension, and treatment near critical structures. Tumors themselves contain fragile vessels and pre-existing susceptibility signals. Distinguishing treatment-related microbleeding from baseline tumor hemorrhage requires pre- and post-treatment imaging using standardized sequences. Seizure may result from tumor biology, previous surgery, cortical sonication, edema, or vascular irritation. A seizure occurring after treatment is not automatically caused by ultrasound but must be considered potentially related until evaluated. Increased permeability may enhance entry of beneficial drugs and potentially harmful plasma components. Albumin extravasation, inflammatory mediators, complement, and immune cells can influence edema and neuronal excitability. Repeated treatment raises questions about cumulative vascular injury. Available clinical studies support short-term repeatability, but longer surveillance is required for microvascular remodeling, chronic gliosis, cognitive effects, and susceptibility burden. Implantable systems add risks of wound infection, device exposure, implant malfunction, skin discomfort, and future MRI or surgical considerations. The device should be evaluated as both a neurosurgical implant and an energy-delivery system.

Patient Selection. Appropriate selection requires a treatable tumor phenotype and a therapeutic agent for which delivery is plausibly limiting. Barrier opening is unlikely to overcome complete pharmacodynamic resistance. The patient should have sufficient performance status to undergo repeated procedures and systemic therapy. Expected survival should be long enough to complete treatment and evaluate benefit. Coagulopathy, uncontrolled hypertension, active intracranial hemorrhage, unstable seizure disorder, severe cardiopulmonary disease, microbubble contraindication, inability to undergo MRI when required, and unsuitable skull characteristics may exclude or delay treatment. Tumor location influences risk. Superficial frontal targets differ from deep thalamic, brainstem, or eloquent cortical regions. Treatment near ventricles, large vessels, surgical cavities, calcification, or prior implants requires modified planning. The surrounding brain should be considered part of the target in infiltrative glioma. However, larger volumes increase procedure time and total vascular exposure.

Treatment Timing. The systemic drug can be administered before, during, or after sonication depending on plasma pharmacokinetics. The goal is to align maximum vascular drug availability with maximum permeability. If the drug is given too early, plasma concentration may decline before opening. If given too late, the barrier may begin to close. Long-circulating agents provide greater flexibility but prolong systemic exposure. In implantable trials, chemotherapy and sonication have commonly been coordinated within the same treatment visit. In transcranial systems, microbubble injection and sonication are repeated across target volumes while the

therapeutic agent circulates. Radiotherapy timing requires caution because barrier opening, inflammation, and vascular permeability may modify normal-tissue radiation response. The combination may improve radiosensitizer delivery but also increase edema or necrosis.

The SONO-BRIDGE Framework. The proposed SONO-BRIDGE model begins with Skull and acoustic anatomy. CT-based density, thickness, curvature, implants, air cavities, and target accessibility are evaluated. Oncological phenotype establishes tumor class, molecular subtype, infiltrative pattern, expected drug sensitivity, previous treatment, and sites at greatest risk of recurrence. Neuronavigational targeting defines treatment volumes using multimodal MRI, surgical-cavity anatomy, functional structures, PET, and updated imaging. Oscillation and cavitation control uses microbubble-specific dosing, passive acoustic monitoring, pressure escalation, real-time feedback, and automatic safety limits. Barrier confirmation requires spatial correspondence between target, cavitation activity, and quantitative permeability imaging. Regional pharmacokinetics assesses whether the therapeutic reaches the sonicated tissue at an active concentration and remains distributed beyond the vessel wall. Integrated drug selection matches ultrasound with an agent whose major limitation is delivery rather than complete biological resistance. Diagnostic biomarker release incorporates standardized sonobiopsy collection, molecular analysis, and correlation with disease state. Glial and immune effects evaluate edema, inflammation, microglia, lymphocyte trafficking, and interaction with radiation or immunotherapy. Evaluation of clinical outcome distinguishes technical opening, pharmacological delivery, radiological response, neurological safety, quality of life, progression-free survival, and overall survival.

Table 5. Scientific Originality of the SONO-BRIDGE Framework

Existing limitation	Conventional interpretation	SONO-BRIDGE principle	Expected clinical contribution
BBB opening treated as the final endpoint	Gadolinium leakage interpreted as therapeutic success	Permeability separated from drug delivery and target engagement	Prevents overestimation of clinical effect
Uniform acoustic pressure used across patients	One sonication protocol expected to fit all skulls	CT planning and cavitation feedback individualized	Reduces underexposure and vascular injury
Drug selected after device availability	Any systemic agent assumed to benefit	Therapy matched to molecular size, kinetics, and resistance biology	Improves pharmacological rationale
Enhancing tumor treated as the entire disease	Target restricted to visible tumor	Infiltrative nonenhancing regions considered	Addresses residual glioma cells
Cavitation monitored as a binary event	Opening versus no opening	Cumulative dose and spatial emission maps incorporated	Supports closed-loop control
MRI enhancement used as universal surrogate	Gadolinium assumed to represent all drugs	Drug-specific pharmacokinetic validation required	Improves translational reliability
Clinical benefit inferred from single-arm survival	Historical comparison treated as causal evidence	Randomized outcome confirmation required	Prevents premature efficacy claims
Barrier opening viewed as one-way delivery	Only blood-to-brain transport considered	Sono-liquid biomarker release included	Integrates therapy and surveillance
Safety limited to acute hemorrhage	Normal immediate MRI assumed to prove safety	Repeated vascular, cognitive, inflammatory, and device outcomes monitored	Improves long-term risk assessment

Discussion. The accumulated evidence demonstrates that focused ultrasound can repeatedly and reversibly increase regional BBB permeability in humans. This technical question is no longer the principal uncertainty. The central challenge is whether controlled permeability can be converted into reproducible therapeutic benefit. The distinction between barrier opening and drug delivery is fundamental. Gadolinium enhancement confirms movement of a small contrast agent but does not prove that a therapeutic antibody, nanoparticle, or viral vector reached the required concentration. The distinction between delivery and efficacy is equally important. A drug may enter the brain and fail because the tumor lacks the relevant target, activates a resistance pathway, or contains spatially heterogeneous subclones. Focused ultrasound should therefore be integrated into pharmacological development from the beginning. Drugs previously abandoned because of poor CNS penetration may be reconsidered, but only if they demonstrate antitumor activity when delivery is adequate. Albumin-bound paclitaxel illustrates this principle. Paclitaxel has strong cytotoxic activity but poor spontaneous brain exposure. The phase I study established that implantable ultrasound could increase tissue delivery, creating a rational basis for efficacy trials [4, 8, 14, 25]. Temozolomide represents a different case. It already crosses the BBB. FUS may improve concentration and spatial homogeneity but cannot reverse MGMT-mediated repair or other resistance mechanisms. Randomized trials should examine whether benefit differs by MGMT promoter methylation. BT008NA is currently one of the most important clinical developments. It showed that repeated noninvasive FUS could be integrated into standard adjuvant treatment across multiple institutions. The reported median overall survival of 31.3 months is encouraging, but the study was single-arm and survival comparison relied on an external cohort [13, 15, 17, 27]. External-control methods can improve upon simple historical comparison but cannot eliminate unmeasured confounding. Patients selected for a demanding FUS protocol may have better performance status, greater treatment adherence, more complete resection, favorable molecular biology, or access to specialized care. The study should therefore be interpreted as a strong signal for randomized evaluation, not as definitive evidence that FUS extends survival.

Implantable systems offer efficient repeated delivery but are limited to patients undergoing surgery and to regions covered by the device. Noninvasive systems provide flexible targeting but require repeated positioning, acoustic correction, and imaging resources. The optimal platform may vary over the disease course. An implant could treat the pericavity region after resection, while a noninvasive system could later target distant progression. Hybrid treatment strategies deserve investigation. Real-time cavitation monitoring is likely to be the most important safety and standardization technology. Acoustic pressure at the transducer is not equivalent to biological exposure within the brain. Skull transmission, coupling, microbubble concentration, and vascularity create patient-specific variation. Closed-loop control transforms cavitation from an uncontrolled side effect into a measurable treatment variable. Future systems should report acoustic-emission dose with the same rigor used for radiotherapy dose. Spatial control also matters. A large tumor cannot be represented by one focal point. Overlapping sonications must create adequate coverage without excessive cumulative exposure at the overlap zones. MRI confirmation introduces a workflow challenge. Immediate enhancement may be required to verify success, but repeated gadolinium administration and MRI occupancy increase cost and complexity. Acoustic-emission mapping may eventually reduce reliance on post-treatment contrast MRI, but it must be validated rigorously. Drug timing requires protocol-specific pharmacology. A molecule with a five-minute effective plasma peak demands different coordination from an antibody circulating for weeks. Trials should report sonication–drug intervals explicitly. Dosing should also be reconsidered. FUS may permit lower systemic drug doses while maintaining local brain exposure, potentially reducing systemic toxicity. Most early trials have instead used conventional systemic doses to maximize intracranial delivery. Dose-optimization studies are necessary. The therapeutic window may be narrow when the drug is neurotoxic. A cytotoxic agent previously excluded by the BBB may damage normal neurons, glia, or endothelium when barrier opening permits entry. Sonication volumes should correspond closely to tissue in which expected antitumor benefit exceeds neurological risk. The infiltrative nature of glioblastoma complicates this balance. Tumor cells extend into functioning

brain. Treating a broader FLAIR region may improve coverage but expose normal neural tissue to chemotherapy.

Molecularly targeted drugs may offer a better therapeutic ratio than nonspecific cytotoxic agents if the tumor target is absent from normal brain. Antibodies, antibody–drug conjugates, degraders, and gene therapies are therefore attractive future candidates. Immune therapies present both opportunity and complexity. FUS may improve antibody and lymphocyte access and alter innate immune signaling. Sterile inflammation could support antigen presentation or worsen edema and immunosuppression depending on dose and timing. Corticosteroids used to control edema may counteract immunotherapeutic benefit. Future combination trials should prespecify steroid management and immune biomarker assessment. Sonobiopsy may become clinically useful independently of drug delivery. Repeated plasma sampling after focal sonication could reveal tumor mutations, copy-number changes, methylation, resistance evolution, or treatment response.

The method must demonstrate specificity. Barrier opening can release normal neuronal and glial DNA, inflammatory proteins, and injury-associated molecules. Increased total cfDNA does not necessarily represent increased tumor-derived DNA. Tumor-specific mutations provide a stronger signal. Personalized assays targeting known EGFR, TERT, IDH, H3, BRAF, or other alterations may improve surveillance. The procedure could be used before biopsy to guide diagnosis in surgically inaccessible tumors, but it would still require a sufficiently specific molecular result. A negative plasma test after sonication cannot safely exclude tumor until sensitivity is established.

Safety data are encouraging but remain based on relatively small cohorts. Rare hemorrhagic or inflammatory complications may emerge only after broader use.

Long-term safety is particularly important in patients with newly diagnosed disease who may receive many repeated treatments. Serial susceptibility imaging, neurocognitive testing, seizure assessment, and quality-of-life measurement should be included. Standardization across devices is another challenge. Frequency, pressure, microbubble formulation, dose, infusion, burst pattern, cavitation metrics, MRI protocol, and treated volume differ among studies. Reporting only “focused ultrasound was performed” is inadequate. A minimum technical dataset is needed for comparison and replication. Future randomized trials should distinguish the effect of FUS from the effect of the drug. The control group should receive identical systemic therapy and imaging without therapeutic sonication. Blinding is difficult because the procedure and MRI changes are apparent. Central blinded assessment of imaging and outcomes can reduce bias. Progression assessment is challenging because FUS can cause transient enhancement, inflammation, or edema that resembles tumor progression. Modified response criteria and advanced imaging may be required.

Pharmacokinetic endpoints should be incorporated early. A negative efficacy trial is difficult to interpret if the study never proves that the drug reached the target. The proposed SONO-BRIDGE framework addresses this translational chain. Every stage must succeed: the acoustic field reaches the target, microbubbles oscillate safely, permeability increases, the drug is present, extravasation occurs, tissue distribution is adequate, the molecular target is engaged, and the patient experiences benefit. Failure at one stage should not be attributed automatically to the entire technology. A trial of an ineffective drug does not prove that FUS delivery is ineffective. Conversely, successful permeability does not validate the accompanying therapy. The principal limitation of this review is heterogeneity. Trials differ in disease stage, device, drug, target, imaging, and endpoint. Most are early phase and nonrandomized. Preclinical studies often use small animals with thin skulls and homogeneous tumors, which cannot reproduce human acoustic transmission or glioblastoma heterogeneity. The SONO-BRIDGE framework is conceptual and requires prospective validation. It is intended to structure patient selection and trial design rather than provide a numerical treatment score.

Conclusion. Focused ultrasound combined with circulating microbubbles can temporarily, reversibly, and spatially increase blood–brain barrier permeability in patients with primary and metastatic brain tumors. MR-guided transcranial, neuronavigation-guided, and implantable systems offer different balances of invasiveness, flexibility, treatment volume, repeatability, and resource use. Clinical studies have progressed from demonstrating gadolinium leakage to confirming enhanced delivery of albumin-bound paclitaxel, carboplatin, and trastuzumab. BT008NA

demonstrated that repeated noninvasive barrier opening could be integrated with standard adjuvant temozolomide in newly diagnosed high-grade glioma. Its exploratory survival findings are promising but require randomized confirmation. Focused ultrasound should be regarded as a delivery platform rather than an independent universal antitumor therapy. Its success depends on the pharmacological and biological effectiveness of the accompanying agent. Barrier opening, drug extravasation, tumor penetration, target engagement, radiological response, and survival are separate endpoints and should be measured separately. Real-time cavitation monitoring and closed-loop acoustic control are central to reducing interpatient variability and preventing vascular injury. Treatment planning should incorporate skull acoustics, tumor phenotype, infiltrative anatomy, functional brain regions, microbubble kinetics, drug half-life, molecular size, and resistance mechanisms. Sono-liquid biopsy extends the platform from therapy to diagnosis by facilitating the release of tumor-derived biomarkers into plasma, but clinical sensitivity and specificity remain to be established. The proposed SONO-BRIDGE framework integrates Skull and acoustic anatomy, Oncological phenotype, Neuronavigational targeting, Oscillation and cavitation control, Barrier confirmation, Regional pharmacokinetics, Integrated drug selection, Diagnostic biomarker release, Glial and immune effects, and Evaluation of clinical outcome. The next stage of clinical development requires randomized drug-specific trials, standardized acoustic reporting, quantitative pharmacokinetics, long-term vascular and cognitive monitoring, and patient-centered outcome assessment.

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