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Systematic Review

Focused ultrasound–induced blood–brain barrier modulation for drug delivery in recurrent glioblastoma: A systematic review

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Background and objectives: Glioblastoma is the most aggressive primary adult central nervous system of malignancy, with a median overall survival of 12–18 months. Recurrence is almost inevitable and carries poor outcomes, with median overall survival of 2–9 months and progression-free survival of 1.5–6 months. Treatment options are limited, as locoregional therapies apply to selected patients, and systemic treatments are restricted by the blood–brain barrier. Focused ultrasound has emerged as a noninvasive method to transiently and reversibly increase blood–brain barrier permeability. This study aims to systematically evaluate the clinical efficacy and safety of focused ultrasound-mediated blood–brain barrier modulation to enhance drug delivery in recurrent glioblastoma.

Methods: A systematic search of PubMed, ScienceDirect, Scopus, the Cochrane Library, ClinicalTrials.gov, and Wiley Online Library identified studies published between 2015-2024. The review followed PRISMA guidelines, with risk of bias assessed using ROBINS-I and protocol registration in PROSPERO (CRD420251010548). Disagreements were resolved by consensus.

Results: Twelve clinical trials involving 841 patients met inclusion criteria. Focused ultrasound-mediated platforms included SonoCloud-1, SonoCloud-9, ExAblate Neuro, and NaviFUS, with 1–10 sonication sessions lasting 2.5–22 min. blood–brain barrier opening was achieved in 68–100% of procedures. Median overall survival ranged from 9.95–18 months and median progression-free survival (PFS) from 2.2–3.5 months. Several studies reported improved outcomes *vs* historical chemotherapy-only controls, including progression-free survival-6 rates of 42–52%. Adverse events were mostly mild and transient, with >85% graded as Grade 1 and no treatment-related mortality.

Interpretation and conclusions: Focused ultrasound-mediated blood–brain barrier modulation is a practical therapeutic adjunct that improves intracerebral drug penetration and might extend survival beyond traditional outcomes; providing a noninvasive approach suitable for patients where systemic dose escalation is limited by toxicity and access.

Keywords Blood–brain barrier; Clinical trials; Drug delivery; Focused ultrasound; Recurrent glioblastoma

Glioblastoma is a WHO grade IV, highly aggressive and diffusely infiltrating astrocytoma, representing the most common malignant central nervous system tumour in adults.[1] Despite standard treatment with maximal safe resection followed by radiotherapy and temozolomide, survival gains remain modest, with a median overall survival of 12–18 months and a five-yr survival rate below 7%.[2] Recurrence is nearly universal, and outcomes after relapse are poor, with a median overall survival of 2–9 months and progression-free survival of 1.5–6 months.[3,4]

A major obstacle in both newly diagnosed and recurrent glioblastoma is the blood–brain barrier, which prevents therapeutic concentrations of most systemic agents from reaching tumour tissue.[4,5] Existing strategies to overcome this limitation, including convection-enhanced delivery and nanoparticle-based approaches, are limited by nonuniform distribution, restricted penetration, or toxicity.[5-7] In contrast, focused ultrasound combined with intravenous microbubbles enables transient, localised, and reversible blood–brain barrier opening through mechanical cavitation,

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facilitating drug delivery without damage to surrounding tissue.[6-8]

Preclinical and early clinical studies demonstrate that focused ultrasound safely enhances intratumoural delivery of chemotherapeutics, antibodies, and nanoparticles.[6,8-10] Advances in implantable and MRI-guided systems allow repeated, drug-synchronised sonication, supporting personalised treatment strategies.[5,7] By improving targeted delivery without systemic dose escalation, focused ultrasound may reduce toxicity, particularly in frail or heavily pretreated patients, while offering a scalable, noninvasive option for resource-limited settings.[9,10] This systematic review evaluates clinical evidence on focused ultrasound-mediated blood–brain barrier modulation, examining device platforms, sonication protocols, therapeutic combinations, blood–brain barrier opening efficacy, survival outcomes, and safety to inform future research and clinical integration in recurrent glioblastoma.

Methods

Protocol registration: This systematic review was developed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The review protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD420251010548.

Eligibility criteria: Studies were selected based on the following inclusion criteria: studies including adult patients (≥18 yrs) with histologically or radiologically confirmed recurrent glioblastoma; interventions involving focused ultrasound techniques, including both transcranial and implanted systems, aimed at temporarily disrupting the blood–brain barrier to increase drug delivery; study designs limited to phase I–III clinical trials with available efficacy or safety data; and outcomes reporting at least one of the following: extent of blood–brain barrier opening, pharmacokinetics, drug bioavailability, tumour response, overall survival, progression-free survival, or adverse events. Studies were excluded if they were preclinical (*in vitro* or animal models), case reports, editorials, conference abstracts without full text, or did not involve focused ultrasound-mediated blood–brain barrier modulation.

Information source and search strategy: A comprehensive search was conducted across the following databases: PubMed, ScienceDirect, Scopus, the Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, and the Wiley Online Library. The search included all articles published up to July, 2025. The search terms combined MeSH and free-text words were as follows: ('focused ultrasound' OR 'FUS') AND ('glioblastoma' OR 'GBM') AND ('blood-brain barrier' OR 'BBB') AND ('drug delivery' OR 'chemotherapy') AND ('recurrent' OR 'relapsed').

Study selection and data collection process: Two independent reviewers (MAP and SAG) conducted title and abstract screening, followed by full-text evaluation for final inclusion. Any disagreements were resolved through discussion, and when necessary, by consulting a third reviewer (MFA), using a consensus-based approach. A PRISMA flow diagram was used to document the selection process. A formal kappa statistic for inter-reviewer agreement was not calculated.

Risk of bias assessment: The risk of bias was assessed for each included study *via* the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) tool.[11] The tool evaluates seven domains of bias: confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result.

Data extraction and management: Data were extracted *via* a standardised form that included the following: study details (authors, yr, country), patient demographics and sample size, focused ultrasound device type and protocol (frequency, duration, number of sessions), drugs administered and timing relative to sonication, and outcomes, which included the extent of blood–brain barrier opening, imaging confirmation, overall survival, focused ultrasound, tumour response, and adverse events.

Data analysis and synthesis: Owing to heterogeneity in study designs, focused ultrasound devices, and outcome reporting, a qualitative (narrative) synthesis was undertaken, and formal meta-analysis was not performed. Study characteristics, device parameters, drug regimens, and key clinical outcomes were summarised in tabular form. Time-to-event outcomes, including overall and progression-free survival, were extracted as reported in the original studies (median values, ranges, and/or survival rates at predefined timepoints such as progression-free survival -6 or overall survival -12). For the purpose of this review, overall survival was defined as the time from focused ultrasound-assisted treatment or trial enrolment to death from any cause, and progression-free survival as the time from treatment or enrolment to radiological or

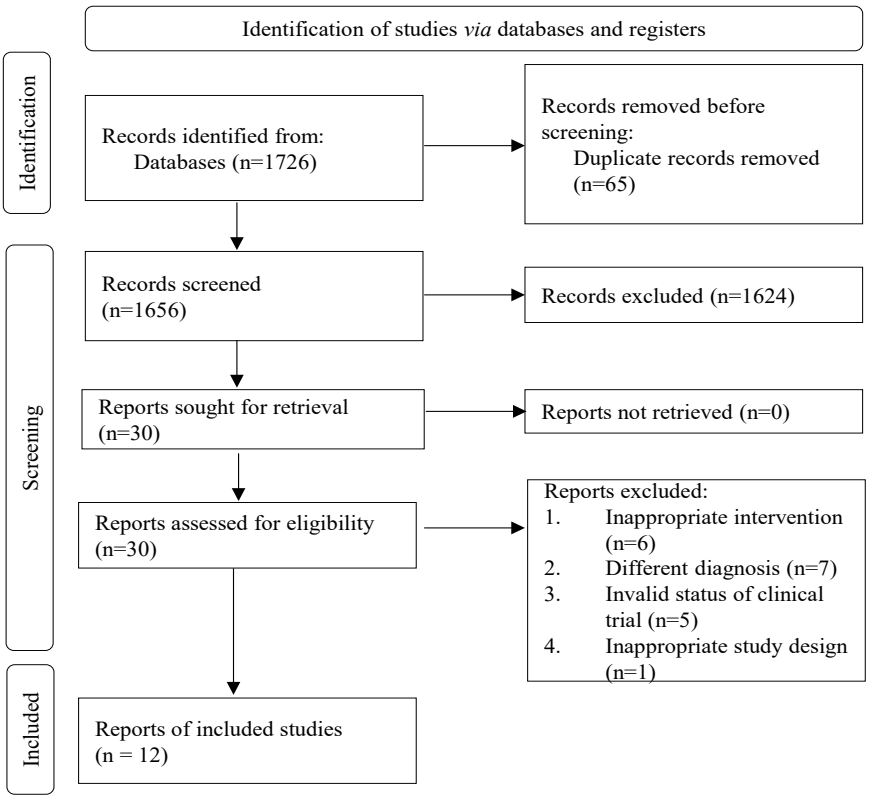

Fig. 1. PRISMA flowchart.

clinical disease progression or death, consistent with each trial's prespecified criteria.

Results

Study selection and characteristics: A total of 1,726 records were identified, with 65 duplicates removed. After screening 1,656 records, 30 full-text articles were assessed for eligibility; 18 were excluded due to inappropriate intervention (n=6), different diagnoses (n=7), invalid clinical trial status (n=5), or unsuitable study design (n=1). Most records were excluded at the initial screening stage because they were unrelated to focused ultrasound, did not involve blood–brain barrier modulation, or lacked clinical relevance to recurrent glioblastoma. Following full-text evaluation, 12 clinical trials met the inclusion criteria, of which 6 studies had published outcome data (**Fig. 1**).[8-10,12-19] These trials, conducted between 2014 and 2025, enrolled a combined total of 841 patients with histologically confirmed recurrent glioblastoma.[8-10,12-19] The studies included multicenter trials (n=1) and single-center trials (n=5) conducted across Europe, North America, and Asia. All were phase I, II, and II investigations, with designs ranging from single-arm nonrandomised feasibility to double-arm comparison studies. The mean sample size was 66 participants (range, 6-560), with patient ages ranging from 18-80 yrs in the adult cohort and 5-17 yrs in the paediatric cohort **(Table I)**[8-10,12-19].

A variety of focused ultrasound platforms were employed across studies: SonoCloud-1 (SC1) and SonoCloud-9 (SC9) as implantable devices, ExAblate Neuro as an MRI-guided transcranial system, and Navifocused ultrasound as a neuronavigation-based extracorporeal system **(Table II).** Several studies have investigated these devices in combination with chemotherapeutics such as carboplatin, bevacizumab, lomustine, temozolomide, and nab-paclitaxel, whereas others have evaluated device-only approaches. Collectively, these studies provide a comprehensive view of the evolving landscape of focused ultrasound–mediated blood–brain barrier opening strategies in recurrent glioblastoma, encompassing both adult and paediatric populations.[8-10,12-19]

Risk of bias assessment: Using the ROBINS-I tool, most studies showed a moderate risk of bias due to nonrandomised, open-label designs and lack of control arms. Selection and reporting bias were minimised through prospective registration and standardised

Table I. Study characteristics

Study reference (yr)	Cancer	Phase	Trial No.	Registry date	Intervention	Combination	Control	Sample size	Age (yr)	Gender	Country
Ref 12[12], 2025	rGBM	3	NCT05902169	June 13, 2023	SC9	CBP	SoC CCNU/ TMZ	560	≥18	All	USA
Ref 13[13], 2024	rGBM	3	NCT06496971	July 11, 2024	NFUS	MB, BEV	SoC BEV	32	18-80	All	Taiwan
Ref 14[14], 2024	rGBM	1 and 2	NCT06329570	March 26, 2024	NFUS	LUM, BEV	None	10	≥18	All	USA
Ref 10[10], 2024	rGBM	1 and 2	NCT03744026	November 16, 2018	SC9	CBP	None	38	58 (median)	All	France, USA
Ref 15[15], 2023	rGBM	2A	NCT04446416	June 24, 2020	NVFUS	BEV	None	6	≥20	All	Taiwan
Ref [16], 2023	rST-MBT	1	NCT05293197	March 24, 2022	SC9	None	None	24	5-17	All	France
Ref 9[9], 2020	rGBM, IDHwt	1	NCT04528680	August 27, 2020	SC9	Nab-PTX and CBP	None	57	≥18	All	USA
Ref 17[17], 2020	rGBM	1 and 2	NCT04440358	June 19, 2020	Exablate	CBP mono	None	13	18–80	All	Canada, Italy, South Korea
Ref 18[18], 2020	rGBM	1 and 2	NCT04417088	June 4, 2020	Exablate	CBP mono	None	30	Adult	All	USA
Ref 8[8], 2018	rGBM	Early Phase	NCT03626896	August 13, 2018	NFUS	None	None	6	≥20	All	Taiwan
Ref 19[19], 2014	rGBM	1 and 2	NCT02253212	October 1, 2014	SC1	CBP	None	27	≥18	All	France

Paediatric cohort (5–17 yr); all other trials enrolled in adult patients

BAL, balstilimab; BEV, bevacizumab; BOT, botensilimab; CBP, carboplatin; CCNU, lomustine; GBM, glioblastoma (glioblastoma multiforme); GS, gliosarcoma; IDH-wt GBM, IDH1 Wild-type glioblastoma; L-DOX, liposomal doxorubicin; LIPU-MB, low-intensity pulsed ultrasound with microbubbles; LUM, luminosan; MB, microbubble; MBT, malignant brain tumour; nab-PTX, albumin-bound paclitaxel; ND-GBM, newly diagnosed glioblastoma; NFUS, NaviFUS; rGBM, recurrent glioblastoma; rGBM (IDH-wt), Recurrent GBM (IDH Wild-Type); rST-MBT, supra-tentorial primary malignant brain tumour, Recurrence; SC1, sonoCloud-1; SC9, SonoCloud-9; SoC, standard of care; TMZ, temozolomide

Table II. Comparison of focused ultrasound devices

Device	Technology	Mechanism	Therapeutic approach	Treatment mechanism in GBM	Key advantage	Regulatory status/ clinical availability
SonoCloud 1 (SC1)	Low-intensity focused ultrasound (LIFU) with microbubbles for blood–brain barrier (BBB) opening	Uses ultrasound plus intravenous microbubbles to transiently open the BBB and enhance drug penetration	Noninvasive BBB disruption to enhance chemotherapy or biologic delivery	Facilitates enhanced drug delivery to tumour via BBB modulation	Allows repeatable, noninvasive BBB opening in targeted regions	Investigational; FDA Breakthrough Device and EMA orphan designation; not yet CE/FDA approved
SonoCloud 9 (SC9)	Enhanced LIFU array with multiple transducers and microbubbles for BBB opening	Similar to SonoCloud 1 but with multiple ultrasound emitters for improved spatial targeting	Noninvasive BBB disruption with higher precision and broader field coverage	Same as SonoCloud 1, but covers a wider area with a multi-array system	Higher precision and broader cortical coverage with a more scalable platform	Investigational; EMA orphan device designation; pivotal Phase III trial ongoing
ExAblate Neuro	High-intensity focused ultrasound (HIFU)	Focused ultrasound thermally ablates tumour tissue using real-time MR guidance	Tumour ablation *via* heat-induced coagulative necrosis	Directly ablates glioblastoma tissue *via* MR-guided thermal energy	MR-guided precise thermal ablation; effective for nonresectable or recurrent GBM	CE- and FDA-approved for movement disorders; GBM applications investigational
NaviFUS (NFUS)	Navigated high-intensity focused ultrasound with microbubbles for BBB opening	Uses MR- or neuronavigation-guided ultrasound to temporarily open BBB with microbubbles	Targeted BBB disruption to improve CNS drug delivery without thermal damage	Enables localised BBB opening for improved drug access to tumour area	Combines image guidance and BBB modulation; avoids thermal effects, enabling synergistic therapies	Class II US FDA 510(k) and TFDA-cleared platform; GBM BBB-opening use investigational

BBB, blood–brain barrier; FDA, United States food and drug Administration; EMA, European medicines agency; CE, Conformité Européenne (European Conformity) mark; TFDA, Taiwan food and drug administration; 510(k), US FDA premarket notification pathway

imaging protocols (**Fig. 2**). This risk profile is typical for early-phase device–drug delivery studies. [8-10,12-19]

Focused ultrasound protocols and blood-brain barier opening efficacy: The sonification parameters of the focused ultrasound systems evaluated in this study are summarised in **Supplementary Table I**. The SonoCloud 1 (SC1) and SonoCloud 9 (SC9) systems operate at a frequency range of 1.0–1.5 MHz with an acoustic intensity of 0.5–1.5 W/cm², delivering 10–20 ms pulses at a 10–30% duty cycle. Each treatment session lasted 30–60 min. SC1 utilised a 9-transducer implantable array, whereas SC9 applied a 9-transducer external array; both delivered pulsed sonication with microbubbles.[9,10,12,15,19]

In contrast, the ExAblate Neuro system operates at a lower frequency (0.5–0.7 MHz) but with higher intensity (1.0–3.0 W/cm²) and longer pulse durations (100–200 ms) at a 30–50% duty cycle, with treatment sessions lasting 1–3 h. This system employs a multi-element hemispherical transducer and delivers high-intensity focused ultrasound (HIFU) for thermal ablation, either continuous or modulated.[13,14]

The Navifocused ultrasound system demonstrated operational flexibility with a frequency range of 0.25–0.7 MHz and an intensity of 0.5–3.0 W/cm², applying 100–300 ms pulses at a 20–50% duty cycle for 30–90 minutes per session. Its single- or multi-element image-guided configuration enables non-thermal pulsed sonication with microbubbles.[8,16-18]

A summary of the efficacy of blood-brain barrier opening is shown in **Table III**[8-10,15,19,20]. The duration of sonication varied between 2.5 and 22 min per session. The number of sonications per cycle ranged from a single application to 10 sessions spaced over weeks. Most studies have employed intravenous microbubble contrast agents such as Definity® or SonoVue® to facilitate blood–brain barrier disruption. Successful blood–brain barrier opening was confirmed

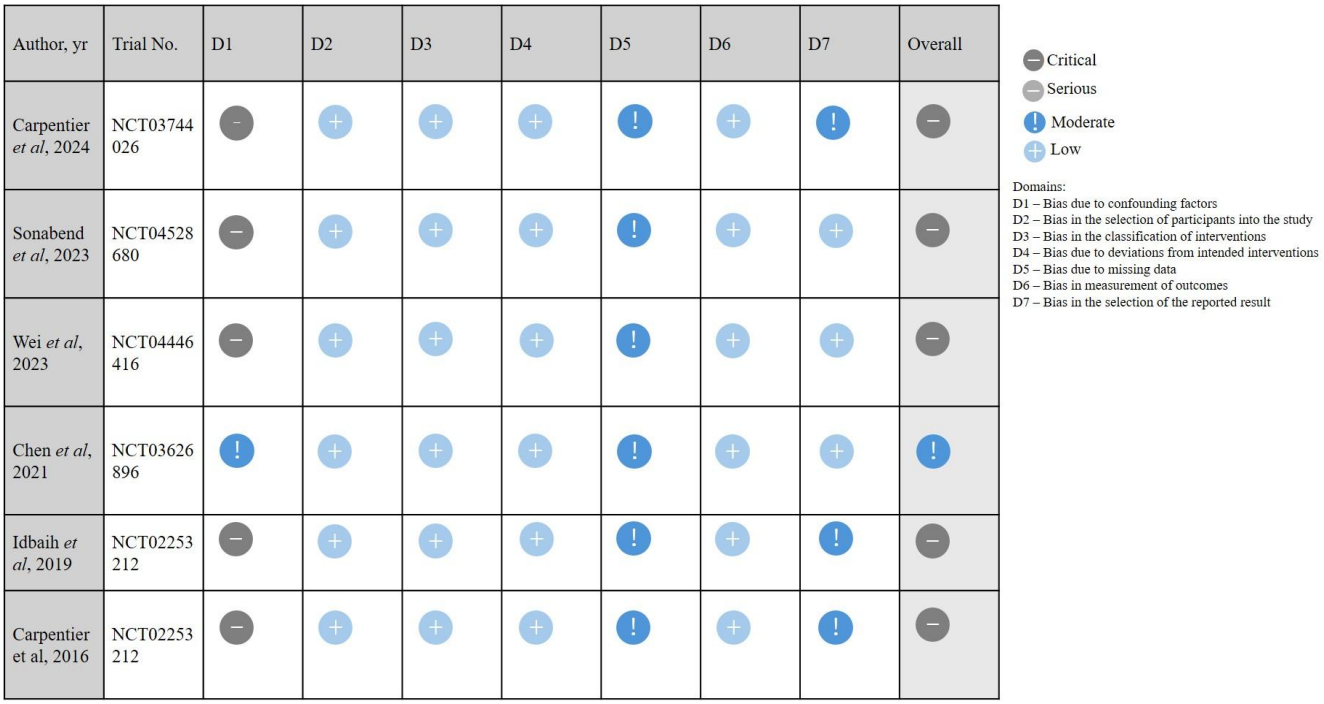

Fig. 2. Risk of bias assessment.

Table III. Blood-brain barrier opening on FUS devices

Author, yr	Device	Duration of procedure (median, range)	Total number of sonication	Number of sonication/ month (median, range)	Dose-limiting toxicity of ultrasound	Drug	Dose	BBB, %	BBB grade
Carpentier *et al*[10], 2024	SC9	5 min	90	N/A	Not Reached with dose of 1.15 MPa	CBP	Area under the curve (AUC5)	90	Grade 2–3: 90% | Grade 1–0: N/A
Sonabend *et al*[9], 2023	SC9	4.5 min	68	3 (range 2–6)	Not reached during cycle 1 of sonication and ABX chemotherapy	Nab-PTX	40–260 mg/m² (6 dose levels)	100	N/A
Wei *et al*[15], 2023	NFUS	N/A	156	N/A	Not reached	BEV	10 mg/kg	67	N/A
Chen *et al*[8], 2021	NFUS	14 min (5–22)	6	N/A	Not reached	None	None	N/A	N/A
Idbaih *et al*[19], 2019	SC1	9 min (4–16)	65	3 (1–10)	Not reached with dose of 1.15 MPa	CBP	AUC4 in 16 procedures, AUC5 in 48 procedures	80	Grade 1: 18, Grade 2: 8, Grade 3: 27
Carpentier *et al*[20], 2016	SC1	2.5 min	41	3 (1–10)	Not reached with dose of 1.10 MPa	CBP	AUC5 (adapted to AUC4 or AUC6)	68.29	Grade 0: 12, Grade 1: 10, Grade 2: 6

BBB Grade was defined on post-contrast MRI using a 0–3 scale adapted from Carpentier *et al*[10] and Idbaih *et al*[24]: Grade 0 = no ultrasound-induced contrast enhancement (no BBB opening); Grade 1 = contrast enhancement limited to the subarachnoid space; Grade 2 = contrast enhancement involving subarachnoid space and cortical gray matter; Grade 3 = contrast enhancement involving subarachnoid space, gray matter, and subcortical white matter. Counts in the 'BBB Grade' column refer to the number of sonications/emitter volumes achieving each grade. NA, not available

via gadolinium-enhanced MR sequences and ranged between 68.29% and 100%. Studies using SonoCloud-9 reported the highest consistency in blood–brain barrier permeability across multiple cycles.[8-10,15,19,20]

Drug combinations and pharmacokinetics: Carboplatin (CBP) was the most frequently evaluated chemotherapeutic agent, reported in five studies, and was typically administered within 30 min after sonication at target AUC4–AUC5 doses in 3–4-weekly cycles (**Supplementary Table II**). Temozolomide was investigated in two studies, either as standard concomitant chemoradiation (daily 75 mg/m²) or as adjuvant therapy (150–200 mg/m² on days 1–5 of a 28-day cycle). Albumin-bound paclitaxel (nab-PTX) was escalated across six dose levels (40–260 mg/m²), whereas bevacizumab was consistently given at 10 mg/kg every 2 wk. These regimens were integrated with focused ultrasound-mediated blood–brain barrier opening without modification of the systemic dosing schedules. [8-10,15,19,20]

Across several studies, analyses of cerebrospinal fluid (CSF) and tumour biopsies obtained after treatment demonstrated elevated intratumoural drug concentrations compared with conventional delivery methods. Median peak plasma or regional exposure to carboplatin and paclitaxel increased by approximately 1.5- to 3-fold following focused ultrasound-mediated delivery, while systemic doses were maintained at standard levels, suggesting that blood–brain barrier disruption primarily augments local rather than systemic drug exposure.[9,10]

Survival and clinical outcomes: The median overall survival among patients receiving focused ultrasound-assisted therapy ranged from 9.95 to 14.0 months (**Supplementary Table III**). Median progression-free survival varied from 2.6 to 3.5 months across the studies reporting Kaplan-Meier-based medians. None of the included trials reported a 6-month progression-free survival rate for the survival cohorts summarised in **Supplementary Table III**; the previously cited value of '42%' corresponded to the 12-month overall survival landmark in Idbaih *et al*[19] (2019), not to progression-free survival. With respect to radiological outcomes, partial tumour regression or disease stability was documented in approximately 30–55% of patients across the included studies.[9,10,19]

Safety and tolerability: Adverse events associated with focused ultrasound-assisted therapy were predominantly mild and transient as summarised in **Supplementary Table IV**. Grade 1 adverse events accounted for 85% of the reported events and included headache, dizziness, nausea, and fatigue, typically occurring within 24 h after sonication. Grade 2–3 adverse events represented 14% of events and primarily involved localised cerebral edema, transient motor or cognitive impairment, and mild intracranial hypertension. A single Grade 4 adverse event (1%) was reported in one patient who developed symptomatic intracerebral hemorrhage requiring surgical intervention. No deaths or permanent neurological deficits were directly attributed to the focused ultrasound procedure. Device-related complications, such as electrode malfunction or probe misalignment, occurred in fewer than 3% of cases. [8-10,15,19,20]

Discussion

Despite decades of investigation, therapeutic progress in recurrent glioblastoma remains limited because most systemic therapies cannot overcome the biological and anatomical constraints of the blood-brain barrier and the tumour's heterogeneity. This review identifies focused ultrasound-mediated blood–brain barrier opening as a promising strategy to address these barriers. Across included trials, focused ultrasound achieved high blood–brain barrier-opening rates with consistent reproducibility, demonstrating precise, image-guided modulation of permeability with individualised sonication parameters.

The value of focused ultrasound becomes clear when contrasted with existing treatments. Cytotoxic agents such as temozolomide and carboplatin achieve subtherapeutic intratumoural levels and are restricted by systemic toxicities.[2,21,22] Targeted therapies, including EGFR/EGFRvIII inhibitors, fail due to poor blood–brain barrier penetration, active efflux, and pathway heterogeneity, while immunotherapies are constrained by limited T-cell trafficking, antigen escape, and strong microenvironmental immunosuppression.[23-29] Bevacizumab, an FDA-approved therapy for recurrent glioblastoma, despite radiographic and progression-free survival benefit, does not extend overall survival.[30-32] These limitations underscore that many agents retain intrinsic activity but do not reach the tumour in effective concentrations.

Within this context, focused ultrasound-mediated blood–brain barrier modulation offers a biologically coherent approach to improving drug delivery. Across trials, focused ultrasound increased intratumoural carboplatin and paclitaxel levels by 1.5–3-fold without altering systemic dosing, echoing earlier SonoCloud

and Navifocused ultrasound pharmacokinetic findings.[9,10] As proposed by broader frameworks such as Song *et al*[33] (2023), focused ultrasound may also enhance immune-cell trafficking and biologic delivery, offering a strategy to address barriers that have limited immunotherapy efficacy in recurrent glioblastoma.

A major advantage of MRI-guided and neuronavigation-guided focused ultrasound is precise spatial and temporal control.[34] Adjustable sonication parameters allow blood–brain barrier opening to be synchronised with drug dosing, and higher blood–brain barrier-opening grades have been associated with longer progression-free survival and overall survival, suggesting a dose-response effect.[35,36] Several platforms, including implantable systems such as SonoCloud-9, support efficient, repeatable blood–brain barrier opening in an outpatient setting, reducing procedural burden and facilitating integration into routine clinical workflows.[19,37,38] Emerging evidence also suggests that the noninvasive, clinic-based nature of focused ultrasound may offer cost advantages over invasive delivery methods such as convection-enhanced delivery, although formal economic evaluations remain limited.[39,40] Our study also shows that focused ultrasound was also safe and feasible across studies, with predominantly mild, transient adverse events and no ultrasound-related dose-limiting toxicities, contrasting with the invasiveness and variable distribution of convection-enhanced delivery.

No studies to date have evaluated focused ultrasound-mediated blood–brain barrier opening in low- and middle-income countries (LMICs), reflecting broader limitations in MRI access, technical expertise, and capital investment. Nonetheless, focused ultrasound may ultimately be more accessible than other advanced neuro-oncology technologies because it does not require neurosurgical infrastructure and can be integrated into radiology-based settings. As lower-cost ultrasound platforms and portable or lower-field MRI systems become more available, focused ultrasound could help reduce global disparities in glioblastoma care.

Despite these findings, several limitations warrant consideration. Most evidence derives from early-phase, single-arm studies with small cohorts, limiting statistical power and increasing susceptibility to selection bias. Substantial heterogeneity in device platforms, sonication parameters, and chemotherapy regimens further hinders cross-study comparison. While BBB opening rates and short-term safety are well documented, long-term outcomes—including neurocognition, quality of life, and cost-effectiveness—remain insufficiently characterised, underscoring the need for standardised reporting and more rigorous trial designs.[8-10] Future research should prioritise large, multicenter trials to validate efficacy, optimise sonication parameters, and establish pharmacokinetic–clinical correlations using standardised protocols.[41-43] Integration of focused ultrasound with emerging therapies may enhance delivery of agents with limited CNS penetration,[44-48] supported by improved imaging and biomarker tools to monitor drug distribution and BBB permeability[38,41,42,45] Continued safety-focused studies and implementation-science efforts addressing workflow, patient selection, and cost-effectiveness will be essential for routine clinical adoption.

Author contributions: MARP: Conceptualisation and study design, PROSPERO registration, literature search strategy, study screening and selection, data extraction, synthesis and interpretation of findings, manuscript writing; SASG: Study screening and selection; data extraction and verification, quality/safety data appraisal, manuscript writing; MFA: Data extraction and verification, interpretation of clinical outcomes and safety, critical revision for intellectual content and clarity. All authors have read and approve the final printed version of the manuscript.

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