REVIEW ARTICLE

Ultrasound-Stimulated Microbubbles in Cancer Therapy: A Review of Clinical and Translational Evidence

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Abstract: Ultrasound-stimulated microbubbles (USMB) have evolved from a diagnostic contrast technology into an investigational cancer therapy. Acoustically driven microbubble cavitation generates localized mechanical effects that can permeabilize cell membranes, disrupt tumor vasculature, and transiently open biological barriers. This review synthesizes the clinical and translational evidence for USMB-based oncologic therapy across its three principal applications: radiosensitization, drug delivery, and thermal ablation. A narrative review of English-language literature was conducted using PubMed/MEDLINE through April 2026. Radiosensitization is most clinically advanced in liver malignancies, supported by phase 2 randomized data in hepatocellular carcinoma and an efficacy signal in intrahepatic cholangiocarcinoma, with early-phase trials in breast and head and neck cancer. USMB-enhanced drug delivery is most developed in glioma, where implantable and noninvasive focused-ultrasound systems for blood–brain barrier opening have shown feasibility, pharmacokinetic enhancement, and a recent overall-survival benefit; pancreatic cancer provides the strongest randomized evidence outside the brain and liver. Thermal-ablation enhancement remains predominantly preclinical. USMB shows growing clinical promise across multiple tumor types, but the evidence base is constrained by small, heterogeneous trials, the absence of completed phase 3 studies, and off-label agent use. Standardized protocols and larger randomized trials are needed before routine clinical adoption.

Key words: Ultrasound-stimulated microbubbles; Ultrasound-triggered microbubble destruction; Cavitation; Sonoporation; Radiosensitization; Drug delivery, BBB opening, Thermal ablation, Cancer therapy

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Cancer remains one of the leading causes of death worldwide, with approximately 20 million new cases and 9.7 million deaths in 2022. Global cancer incidence is projected to reach 35 million new cases annually by 2050, driven largely by population growth and aging [1]. Despite substantial advances in chemotherapy, radiotherapy, and locoregional ablative techniques, treatment outcomes for many solid tumors remain limited by a set of persistent physiological and mechanical barriers. Radiotherapy resistance is frequently driven by tumor hypoxia arising from aberrant tumor vasculature [2]. Poor intratumoral drug penetration reflects heterogeneous vascularization, elevated interstitial pressure, and dense stromal matrices [3]. Thermal ablation efficacy can be limited by perfusion-mediated heat loss, a phenomenon commonly referred to as the "heat-sink" effect, in which blood flow near the ablation zone dissipates thermal energy and reduces lesion formation [4]. Because these barriers are largely structural and physiological rather than molecular [5], they are

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often difficult to address with new pharmacologic agents alone, motivating the investigation of physical strategies that can directly modify the tumor microenvironment.

Ultrasound-stimulated microbubbles (USMB) have emerged as one such strategy [6]. Microbubbles are gas-filled, micron-sized particles (approximately 1 to 10 micrometers in diameter) consisting of a low-solubility gas core, typically a perfluorocarbon or sulfur hexafluoride, stabilized by a lipid, protein, or polymer shell. Their size confines them to the intravascular compartment in tissues with intact endothelium, and the large acoustic impedance mismatch between the gas core and surrounding blood makes them highly echogenic, which is the basis of their original development as diagnostic contrast agents [7]. When exposed to an ultrasound field, microbubbles undergo volumetric oscillation (termed stable caviation) and, at sufficient acoustic amplitudes, inertial cavitation. These cavitation states produce localized mechanical effects including microstreaming, shear stress, shockwaves, and microjets and can transiently permeabilize cell membranes, perturb the vascular endothelium, and open tight junctions in specialized barriers such as the blood-brain barrier (BBB) [8,9].

The same core phenomenon of cavitation can be applied to disrupt the tumor microvasculature to enhance radiation response, permeabilize biological barriers for drug delivery, and amplify local energy deposition during thermal ablation. As a result, USMB has been investigated in parallel across these three principal therapeutic applications in oncology [10]. The first human trials of USMB-based cancer therapy were reported approximately a decade ago [11,12] and the clinical evidence base has expanded substantially over the past several years, with multiple phase 1 and phase 2 trials reported across a range of tumor types and therapeutic applications, motivating a consolidated review of the current state of clinical and translational evidence.

This review synthesizes clinical and translational evidence for USMB-based cancer therapy, organized around three principal therapeutic applications: radiosensitization, drug delivery, and thermal ablation. Each section is structured by organ system, prioritizing clinical studies where available, with selected preclinical evidence included where clinical data remain limited. The review also briefly summarizes microbubble agents currently used in clinical and translational research and discusses current limitations and future directions.

Data Collection and Analysis

This article is a narrative review of clinical and translational evidence supporting the use of USMB, including ultrasound-triggered microbubble destruction (UTMD), in oncologic therapy. A PubMed/MEDLINE search was conducted for English-language publications through April 2026 using terms related to USMB, UTMD, focused ultrasound, cavitation, sonoporation, radiosensitization, drug delivery, BBB opening, thermal ablation, and cancer. Reference lists of relevant articles and recent reviews were also screened to identify additional studies.

The review was organized around three principal therapeutic applications of USMB: radiosensitization, drug delivery, and thermal ablation. For each application, clinical studies were prioritized where available, and preclinical studies were included selectively to provide mechanistic context or where clinical evidence

remained limited. Emerging areas of investigation, including immunomodulation, were not covered in this review, as the available clinical data in these areas remain limited at this time. Selected observations related to immune activation are noted where they arise within the three primary therapeutic categories, and immunomodulation is briefly discussed as an emerging direction in the final section of this review.

Clinically Available Microbubble Agents

Most clinical and translational USMB studies have used one of four second-generation ultrasound contrast agents originally approved for diagnostic imaging. Second-generation agents are characterized by low-solubility fluorinated-gas cores stabilized by lipid, albumin, or phospholipid shells, which provide longer circulation times and greater acoustic stability than the air-cored first-generation agents that have largely been withdrawn [7,13]. Their regulatory approvals and clinical adoption vary by region. It should be noted that all therapeutic applications of these agents discussed in this review are off-label, as none of the four agents currently holds regulatory approval for therapeutic use. Table 1 summarizes the key characteristics and regulatory status of these agents.

In addition to these clinically approved agents, several investigational microbubble formulations have been developed for therapeutic applications and appear later in this review. However, none of these investigational formulations is currently approved for routine clinical therapeutic use.

Radiosensitization

Radiosensitization is one of the most clinically translated therapeutic applications of USMB in solid tumors. Unlike conventional radiosensitizers, which typically enhance radiation response through direct effects on

Table 1 Clinically available second-generation microbubble contrast agents and their approved diagnostic indications [7,13,14].

Agent	Manufacturer	Shell	Gas Core	Mean diameter (μm)	Approved Indications	Regions of approval
Definity (Luminity in EU)	Lantheus	Lipid	Octafluoropropane (C_3F_8)	1.1-3.3	Echocardiography	US, Canada, EU, Australia
Lumason/SonoVue	Bracco	Phospholipid	Sulfur hexafluoride (SF_6)	1.5-2.5	Echocardiography; focal liver lesions; vesicoureteral reflux	US, EU, China,
Optison	GE Healthcare	Albumin	Octafluoropropane (C_3F_8)	3.0-4.5	Echocardiography	US, EU
Sonazoid	GE Healthcare	Phospholipid	Perfluorobutane (C_4F_{10})	2-3	Focal liver lesions; focal breast lesions (Japan)	Japan, South Korea, Taiwan, China, Norway

tumor cell DNA damage or repair pathways, USMB-mediated radiosensitization acts primarily through cavitation-induced mechanical priming of the tumor vasculature [15]. Several mechanisms have also been proposed, including disruption of the tumor microvasculature through the acid sphingomyelinase (ASMase)–ceramide pathway, reversal of tumor hypoxia via oxygen-carrying microbubbles, and additional cellular and immunologic effects that remain primarily preclinical.

Cavitation of microbubbles within tumor blood vessels generates mechanical stresses that damage endothelial cells and amplify radiation-induced tumor injury. This effect arises from a mechanically induced vascular insult in which high-pressure ultrasound triggers inertial cavitation, producing forces that disrupt endothelial membranes and activate the ASMase–ceramide signaling pathway. Ceramide accumulation promotes endothelial apoptosis, leading to microvascular collapse within the tumor while sparing adjacent normal tissue. Collectively, this antivascular mechanism amplifies radiation response without requiring radiation dose escalation [15-17].

Tumor hypoxia, a major determinant of radiotherapy response, limits the generation of DNA-damaging reactive oxygen species and promotes radioresistance, particularly in head and neck and breast cancers [18,19]. In preclinical models, USMB has been used to transiently increase tumor oxygenation through two complementary approaches: direct oxygen delivery using gas-core microbubbles loaded with oxygen [18] and the combination of oxygen delivery with metabolic inhibitors that reduce tumor oxygen consumption, prolonging the reoxygenation window available to radiotherapy [20,21]. These approaches remain preclinical but provide a mechanistically distinct strategy for overcoming hypoxic radiotherapy resistance.

Beyond vascular disruption and hypoxia reversal, emerging preclinical evidence suggests that USMB may also enhance radiation response through additional cellular and immunologic effects. Microbubble cavitation has been reported to increase tumor cell apoptosis beyond the direct vascular injury, contributing to the overall therapeutic response. In parallel, USMB appears to modulate the tumor immune microenvironment, with Increased infiltration of $CD45^+$ immune cells observed following ultrasound-triggered microbubble destruction, suggesting that cavitation-induced vascular injury may initiate secondary immunologic responses [22]. Additional preclinical work has further implicated inhibition of Progesterone Receptor Membrane Component 1 (PGRMC1)- mediated autophagy as a potential contributor to radiosensitization [23]. These mechanisms remain largely preclinical, and their individual clinical contributions are not yet well defined, but collectively they broaden the biological rationale for USMB-based radiosensitization.

Liver cancer

Promising clinical evidence for the use of USMB-radiotherapy sensitization has emerged in liver cancer over the past several years. In a phase II randomized trial involving 98 participants with hepatocellular carcinoma (HCC), Wessner et al. reported that adding UTMD, delivered with two-dimensional ultrasound guidance, to Yttrium-90 transarterial radioembolization (Y90-TARE) significantly improved response rates, increasing complete or partial responses from 66% to 96%, without additional treatment-related toxicity. Notably, overall survival was also prolonged, with a nearly 50% reduction in mortality hazard in the UTMD group [24]. An example of UTMD captured on contrast-enhanced ultrasound during treatment, showing peak intratumoral microbubble enhancement followed by loss of enhancement after the high-mechanical-index pulse, is shown in figure 1. These findings build on earlier pilot work by Eisenbrey et al., a first-in-human randomized pilot trial in 28 HCC participants, which demonstrated the feasibility and safety of integrating UTMD sessions into standard Y90-TARE protocols without redistribution of Y90 microspheres outside the liver, no changes in vital signs or liver function, and good patient tolerability [17].

Subsequent clinical evaluation by the same group extended this approach to patients with intrahepatic cholangiocarcinoma (ICC) and metastatic liver disease, tumor types less responsive to locoregional therapy. The trial introduced 3D volumetric cavitation to broaden

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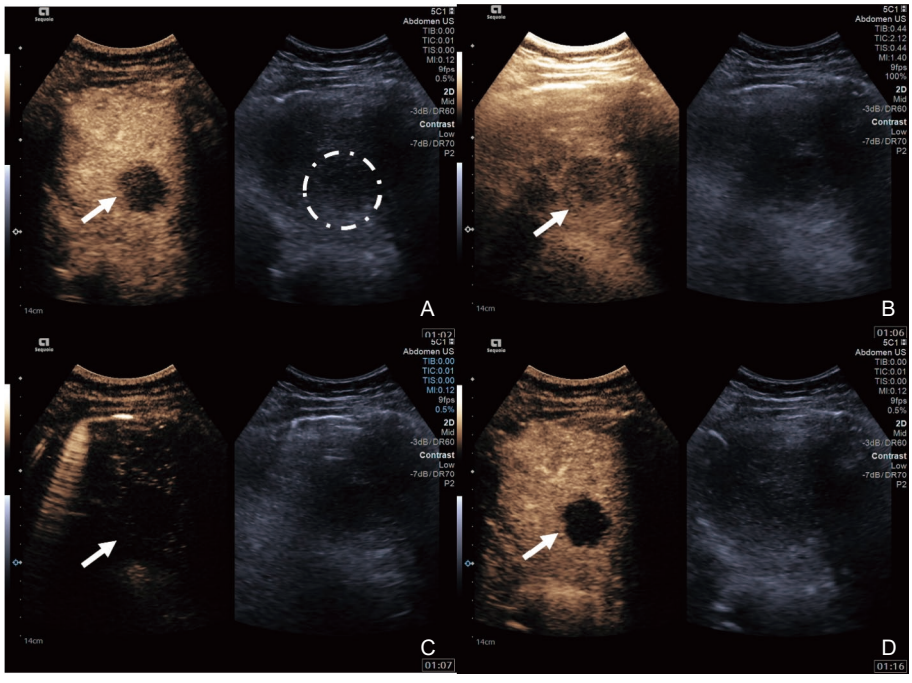


Figure 1 UTMD performed during Y90-TARE treatment of hepatocellular carcinoma in a 70-year-old man with a 3.1 cm segment 4A HCC (arrows), who subsequently achieved complete radiologic response on long-term follow-up imaging. Dual-screen acquisition is shown in each panel, with nonlinear contrast-mode imaging on the left and corresponding B-mode imaging on the right for anatomic reference. (A) Pre-contrast baseline; (B) Peak intratumoral and parenchymal enhancement following intravenous microbubble infusion; (C) Application of the high-mechanical-index destructive pulse; (D) Immediate post-pulse image demonstrating absence of contrast within the tumor, confirming microbubble destruction.

tumor-volume coverage relative to the 2D approach used in earlier studies. Among 15 UTMD-treated participants and 15 matched controls, the addition of volumetric UTMD to Y90-TARE was feasible and well tolerated. Imaging-based response evaluation demonstrated a trend toward improved tumor response, with a complete response observed in 50% of UTMD-treated participants compared with 27% in the control group, and no cases of progressive disease in the UTMD group versus 33% in the control group (P = 0.06). When analysis of tumor response explored only ICC participants, the improvement became statistically significant (P = 0.02), with a complete response rate of 56% in UTMD-treated participants compared with 9% in controls [25]. These findings suggest that vascularly mediated radiosensitization may extend beyond hepatocellular carcinoma to other liver malignancies.

Breast cancer

Breast cancer is another setting in which USMB-mediated radiosensitization has been investigated, with early-phase clinical data supported by preclinical evidence. In a prospective Phase I clinical trial, Moore-Palhares et al. evaluated USMB combined with radiotherapy in 21 patients with 23 breast or chest wall tumors. The treatment was well tolerated, with no severe adverse events attributed to microbubble administration, and observed toxicities were consistent with expected radiotherapy-related effects, primarily radiation dermatitis [26]. This expanded Phase I trial followed earlier feasibility work by Dasgupta et al. who reported USMB combined with radiotherapy in 8 patients with 9 breast tumors, demonstrating the technical feasibility and safety of this combined treatment approach [27].

Head and neck cancer

The first clinical evidence in head and neck squamous cell carcinoma (HNSCC) was provided by Moore-Palhares et al. in a phase 1 trial of 11 patients with newly diagnosed or recurrent HNSCC, in which focused ultrasound activation of intravenously administered microbubbles was performed before selected radiation fractions. Treatment was well tolerated, with no systemic or USMB-related toxicities. Among the 8 patients with response data at 3 months, the overall response rate was 87.5% (complete response 37.5%, partial response 50%). These results support feasibility of USMB integration into HNSCC radiotherapy but require confirmation in larger studies, given the small sample [28].

Prostate cancer

Evidence for USMB radiosensitization in prostate cancer is currently limited to preclinical models; no clinical trials have been published. Foundational work by Czarnota et al. demonstrated that ultrasound-stimulated microbubbles enhance radiation response through ASMase–ceramide–mediated vascular injury, increasing tumor cell death from ~4% with 2 Gy alone to ~40%

when combined with microbubble activation without dose escalation [15]. Sharma et al. subsequently confirmed this effect under clinically relevant fractionated conditions using daily 2 Gy fractions, with control tumors increasing in volume by 471% over four weeks, whereas the combined USMB + radiotherapy group showed tumor regression beginning at week three [29].

Treatment sequencing also influences efficacy. Klein et al. reported that maximal tumor response occurred when USMB and radiotherapy were separated by approximately a 6-hour interval, largely independent of treatment order [30]. Beyond antivascular strategies, Michon et al. explored a provascular approach in which ultrasound-targeted microbubble cavitation combined with sodium nitrite transiently increased tumor perfusion (approximately 1.9-fold) and improved tumor growth inhibition when 8 Gy radiotherapy was delivered within this reperfusion window. This approach is mechanistically distinct from oxygen-carrying microbubble strategies, acting through enhanced perfusion rather than direct oxygen delivery [31].

Larger-animal data are available from Petchiny et al., who reported substantial vascular disruption (approximately 80% reduction in microvessel density) in a rabbit PC-3 xenograft model, supporting feasibility in larger tumor volumes [32]. Despite this consistent preclinical signal, USMB radiosensitization in prostate cancer has not yet entered clinical investigation (Fig. 2).

Brain tumors

Most USMB studies in brain tumors have focused on transient BBB opening for drug delivery (see Drug Delivery — Brain). USMB radiosensitization in intracranial tumors has been explored in only a small number of preclinical studies, primarily in glioblastoma. In a rat F98 glioma model, Fletcher et al. reported that combining focused USMB with radiotherapy increased tumor apoptosis by up to ~396% and reduced tumor volume by 45-57% versus radiation alone, with concurrent increases in vessel-associated ceramide (~320-336%) consistent with the ASMase–ceramide pathway [33].

In a murine breast-cancer brain-metastasis model, Delaney et al. showed that ultrasound-triggered delivery of oxygen-loaded microbubbles before radiotherapy improved tumor response, extending the oxygen-delivery strategy from primary breast and head-and-neck tumors to intracranial disease [34].

A separate mechanistic study by He et al. demonstrated that UTMD enhances radiosensitivity in glioblastoma, partly through a tumor cell–intrinsic pathway involving the disruption of PGRMC1-mediated autophagy. Downregulation of PGRMC1 impaired autophagic flux and was associated with increased radiosensitivity, while its overexpression reduced this effect. This represents a mechanism distinct from the vascular and oxygenation-based effects of USMB [23].

Overall, USMB-mediated radiosensitization in brain tumors remains preclinical. The more advanced clinical work in this setting has focused on BBB opening for drug delivery, discussed in the next section.

Drug Delivery

Beyond radiosensitization, USMB has been investi-

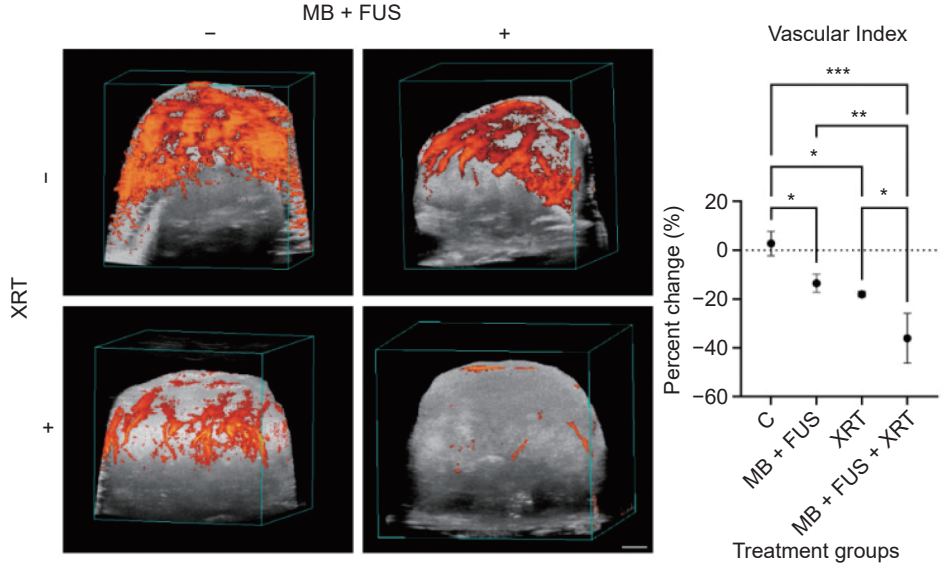


Figure 2 In vivo assessment of tumour perfusion using 3D Power Doppler (PD) ultrasound imaging. Left panel: Representative volumetric reconstructions of tumour vasculature (orange) are shown for each treatment group. Vascularity is visualized in a 3D overlay on B-mode grayscale anatomical images. Scale bar: 2 mm. Right panel: Average Vascular index (VI) across control (C), microbubble-enhanced focused ultrasound (MB + FUS), single-dose radiation therapy (XRT, 8 Gy), and MB + FUS + XRT treatment groups. Data are presented as mean ± SD. p-values ranging from $P < 0.05$ (*), $P < 0.01$ (**), $P < 0.001$ (***). (Reproduced from Petchiny et al32 under the Creative Commons CC-BY 4.0 license).

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gated as a platform for enhancing intratumoral drug delivery. A central limitation of systemic chemotherapy is the inability of many agents to reach therapeutic concentrations within solid tumors, owing to biological barriers including the blood–brain barrier in neuro-oncology, abnormal tumor vasculature, elevated interstitial pressure, and dense stromal architecture [35]. USMB provides a non-invasive, image-guided strategy to transiently modulate these barriers and enhance local drug deposition and retention without systemic dose escalation.

Mechanistically, USMB enhances drug delivery through cavitation-induced permeabilization of cellular and vascular structures. At the cellular level, microbubble oscillation generates transient pores in cell membranes, a process termed sonoporation, which facilitates direct intracellular drug uptake [36]. At the vascular level, cavitation can loosen endothelial tight junctions, increase transvascular flux, and transiently improve microvascular perfusion, thereby enhancing access of systemically administered agents to poorly perfused tumor regions [37]. Together, these effects modify the tumor microenvironment in a localized and reversible manner.

Brain tumors

The BBB is the principal physiological obstacle to systemic neuro-oncologic therapy, restricting central nervous system delivery of most small-molecule and essentially all large-molecule therapeutics. In this setting, USMB enables transient, localized, and reversible BBB disruption, facilitating drug penetration into peritumoral and infiltrative brain tissue. Two technological pathways have advanced clinically: implantable ultrasound devices for repeated BBB opening in recurrent glioma, and noninvasive transcranial focused ultrasound platforms that achieve image-guided BBB disruption without surgical implantation.

Implantable Systems Carpentier et al. provided first-in-human feasibility of implantable USMB BBB disruption using the single-emitter SonoCloud-1 device (CarThera, Paris, France) with carboplatin in 15 patients with recurrent glioblastoma; BBB opening was achieved with no dose-limiting toxicities or treatment-related serious adverse events [11]. In a subsequent SonoCloud-1 trial in patients with recurrent glioblastoma, Idbaih et al. divided their single-arm cohort into participants whose MRI showed clear BBB disruption after sonication and those with minimal or absent opening. The clear-opening subgroup had longer median progression-free survival (4.11 vs. 2.73 months) and overall survival (12.94 vs. 8.64 months) than the minimal-opening subgroup, suggesting that the extent of BBB disruption may influence therapeutic benefit [38].

The strongest clinical evidence for implantable USMB BBB disruption comes from the nine-emitter SonoCloud-9, which enables peri-tumoral BBB opening over a brain volume nine times larger than SonoCloud-1. Clinical studies across both single-center and multicenter settings have evaluated this platform. In a phase 1 trial by Sonabend et al., 17 patients with recurrent glioblastoma received SonoCloud-9 low-intensity pulsed ultrasound with microbubbles (LIPU/MB) and intravenous albumin-bound paclitaxel across 68 cycles, with one dose-limiting toxicity (grade 3 encephalopathy) observed at the highest paclitaxel dose level (260 mg/m^2) and BBB closure largely complete within one hour of sonication. To directly measure the pharmacokinetic effect of LIPU/MB, a substudy was performed in 7 trial participants whose tumor location permitted intraoperative biopsy of peri-tumoral brain tissue. In this substudy, sonication of peri-tumoral brain immediately followed by paclitaxel infusion and subsequent paired biopsy of sonicated and non-sonicated brain demonstrated a 3.7-fold increase in peri-tumoral paclitaxel concentration (0.14 vs. 0.04 μM; $P < 0.0001$). Histologic analysis showed tight-junction loosening, basement-membrane disruption, and endothelial transcriptional changes consistent with an active vascular response rather than passive permeability [39,40].

Carpentier et al. subsequently reported a multicenter phase 1/2 trial of SonoCloud-9 with carboplatin in 33 patients with recurrent glioblastoma across 90 sonications, demonstrating reproducible large-volume BBB opening (Fig. 3), acceptable safety, and MRI-based BBB closure kinetics with an estimated half-closure time of 1.3 hours (95% CI, 0.4-2.2). In the subgroup that received carboplatin immediately before sonication (n = 12), median overall survival was 14.0 months (95% CI 6.7-17.3) with a 1-year overall survival rate of 58%, compared with 11.8 months (95% CI, 8.0-13.2) and 47%, respectively in the subgroup that received carboplatin after sonication. These findings suggest that the timing of carboplatin administration relative to BBB opening may influence clinical outcomes [41].

Habashy et al. extended these findings with intracerebral microdialysis pharmacokinetic profiling in 4 patients with recurrent glioblastoma, showing a 3.1-fold increase in brain-to-plasma area-under-the-curve ratio for both carboplatin and fluorescein in sonicated versus non-sonicated brain. Notably, parenchymal carboplatin concentrations remained elevated above plasma levels for hours after BBB closure, indicating that BBB-impermeable drugs may be trapped in the brain following transient ultrasound-mediated opening. These findings support the importance of coordinating systemic drug

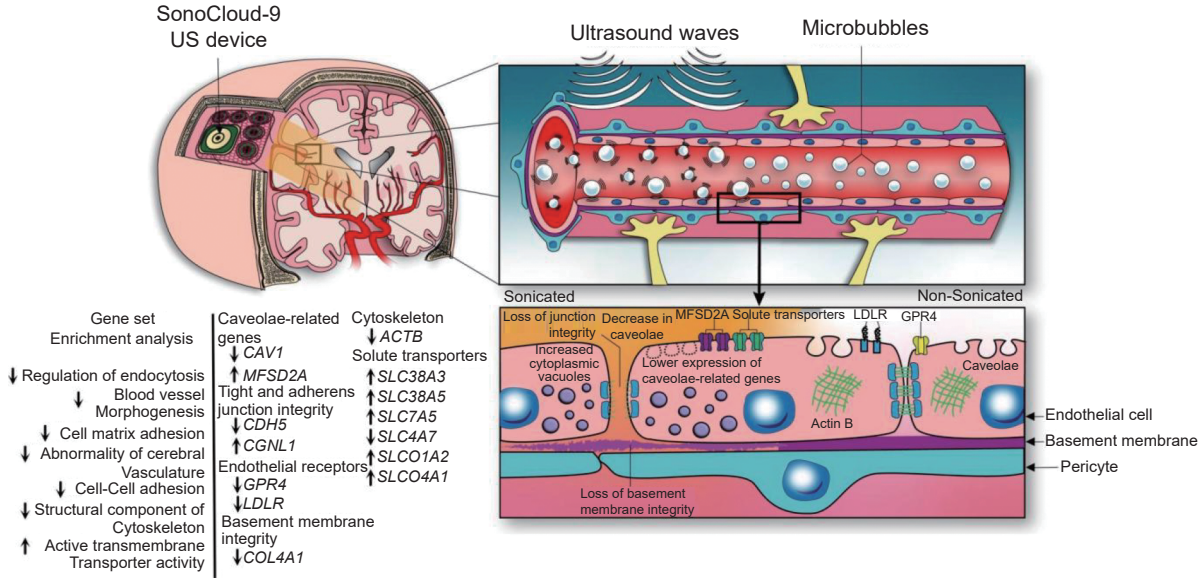


Figure 3 Schematic of intraoperative LIPU/MB procedure and time course of peritumoral brain biopsy. Photo from surgical microscope shows hyperfluorescent areas of dysfunctional BBB shortly after LIPU/MB and infusion of chemotherapy with fluorescein bolus as previously described (24). Blue arrows indicate sonicated peritumoral brain and pink arrows indicate nonsonicated peritumoral brain. Sonicated peritumoral brain biopsies were collected at early time points after LIPU/MB (within 15 minutes) and at later time points (at least 45 minutes after LIPU/MB). (Reproduced from Gould, A. et al.40 under the Creative Commons CC-BY 4.0 license).

administration with the transient BBB-opening window and selecting agents likely to benefit from sustained intraparenchymal exposure [42].

Noninvasive Approaches Mainprize et al. demonstrated transcranial MR-guided focused ultrasound with microbubbles before planned tumor resection in a phase 1 study; peri-tumoral targeting is clinically relevant because BBB disruption in malignant gliomas is heterogeneous, with infiltrative tumor cells often persisting in surrounding brain where the barrier remains intact. BBB opening was confirmed by a 15-50% increase in MRI contrast enhancement and resolved within approximately 24 hours, with no clinically significant USMB-related adverse events. Chemotherapy concentrations were higher in sonicated than unsonicated peri-tumoral samples, extending therapeutic reach beyond the more permeable tumor core [43].

One of the first noninvasive transcranial focused-ultrasound trial reporting an overall-survival signal was the multicenter phase 1/2 trial by Woodworth et al., in which microbubble-enhanced MR-guided focused ultrasound was combined with adjuvant temozolomide in 34 patients with newly diagnosed high-grade glioma. BBB opening was achieved in all treatment sessions and well tolerated, with a reported median progression-free survival of 13.5 months and overall survival of 31.3 months, exceeding typical outcomes expected with temozolomide alone. As a single-arm non-randomized study, these results require confirmation in a randomized trial but represent the first clinical signal that USMB-mediated BBB opening may translate into a survival benefit [44].

Pediatric translation has also begun. In a first-in-pediatrics feasibility study, Wu et al. reported neuronavigation-guided focused ultrasound with microbubbles and oral panobinostat in 3 children with relapsed diffuse midline glioma. BBB opening was achieved in all treated patients without sedation and as frequently as every 2 days. The trial was not powered to assess efficacy but established that repeated, spatially precise BBB opening is feasible in pediatric midline brain structures, including the brainstem [45].

Breast cancer

In breast cancer, heterogeneous vascularization and elevated interstitial pressure limit uniform chemotherapy penetration, motivating clinical evaluation of USMB to enhance intratumoral drug delivery [46,47].

Early clinical evidence comes from a small prospective non-randomized study by Zhou et al. in 26 patients with locally advanced HER2-negative invasive breast cancer (10 USMB + neoadjuvant chemotherapy; 16 chemotherapy alone). Ultrasound treatment was administered within 24 hours after each chemotherapy cycle using microbubbles and low-intensity diagnostic ultrasound. The combined treatment was well tolerated, with no serious adverse events, and a toxicity profile comparable to chemotherapy alone. Importantly, the USMB-treated group showed significantly smaller residual tumors (median diameter: 4.5 mm vs. 15.0 mm in the control group; P = 0.017). Pathologic complete response (pCR) was also improved, with 40% (4/10) of patients in the USMB group achieving pCR, compared with 0% (0/16) in the control group ($P = 0.014$) [48].

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A subsequent prospective study by Dong et al. evaluated 36 patients with invasive breast cancer (18 USMB-treated, 18 controls), in which ultrasound combined with microbubbles significantly expanded tumor perfusion area ($P < 0.001$) and improved perfusion within hypoperfused intratumoral regions, with increases in area under the curve ($P < 0.001$) and mean transit time ($P < 0.05$), further supporting the concept that USMB may improve vascular access and intratumoral delivery of systemic therapies in human breast tumors [49].

Pancreatic cancer

Pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal solid malignancies, with most patients presenting with unresectable or metastatic disease and systemic therapy offering only modest benefit. Dense desmoplastic stroma and a hypovascular microenvironment together create a major barrier to intratumoral chemotherapy penetration [50]. USMB has been investigated as a means of transiently increasing vascular and stromal permeability to enhance local chemotherapy delivery in this setting [51].

The first human therapeutic USMB trial was reported by Dimcevski et al., a phase 1 study of 10 patients with inoperable PDAC treated with gemcitabine plus USMB. Compared with a historical gemcitabine-only cohort ($n = 63$), USMB-treated patients tolerated significantly more chemotherapy cycles (13.8 ± 5.6 vs. 8.3 ± 6.0; $P = 0.008$) and achieved longer median overall survival (17.6 vs. 8.9 months; $P = 0.011$). Tumor size reduction was observed in 5 of 10 patients with no additional treatment-related toxicities. These findings provided the first clinical evidence that USMB can safely enhance chemotherapy delivery and may improve therapeutic response in pancreatic cancer [12].

A subsequent multicenter, open-label, randomized phase 2 trial by Han et al. evaluated 78 patients with inoperable pancreatic cancer (38 treated with sonochemotherapy; 40 with chemotherapy alone). The addition of USMB to systemic chemotherapy significantly improved median overall survival (9.10 vs. 6.10 months; $P = 0.037$) and disease control rate (73.7% vs. 42.5%; $P = 0.005$) without increasing serious adverse events, further supporting that USMB can enhance the effectiveness of systemic therapy in PDAC [52]. Building on these results, an ongoing multicenter Phase 2 randomized clinical trial (NCT04821284) led by Forsberg and colleagues is evaluating sonoporation combined with standard-of-care chemotherapy in patients with PDAC, with results pending.

Liver cancer

In colorectal liver metastases, USMB has been clinically evaluated as a strategy to enhance intratumoral chemotherapy delivery. In a first-in-human trial, Haram et al. enrolled 17 patients with histologically confirmed colorectal cancer and two or more liver metastases [53]. The study utilized an internal lesion randomization design in which two metastases within the same patient were randomized 1:1 to receive either systemic chemotherapy plus USMB (experimental lesion) or systemic chemotherapy with microbubbles only (control). While the primary endpoint of lesion volume reduction did not reach statistical significance due to marked inter-lesion variability, 12 of 17 patients (71%) demonstrated greater regression, or less progression, in the experimental metastases compared with paired intra-patient controls. These findings support early clinical feasibility and provide a signal of localized enhancement of chemotherapy delivery in metastatic liver disease [53].

Augmentation of Thermal Ablation

USMB has also been investigated as a means of enhancing focal tumor ablation. Thermal ablation techniques such as high-intensity focused ultrasound (HIFU) and radiofrequency ablation (RFA) destroy tumor tissue through localized coagulative necrosis, but their efficacy is limited by perfusion-mediated heat dissipation and incomplete treatment coverage. The "heat-sink" effect, in which blood flow within or adjacent to the tumor removes heat and reduces local temperature elevation, is a major contributor to incomplete ablation [4].

USMB enhances ablation through two mechanistically distinct effects. Microbubbles serve as exogenous nucleation sites for cavitation, concentrating acoustic energy and promoting tissue destruction through cavitation-induced mechanical stress [54]. This can reduce the acoustic power and treatment duration required to achieve effective ablation. In both HIFU and RFA, USMB-mediated microvascular disruption can also mitigate the heat-sink effect by transiently reducing perfusion within the ablation zone [55]. Compared with radiosensitization and drug delivery however, this application remains at an earlier stage of clinical translation, with published clinical evidence limited to a single small feasibility study in liver malignancies, and the broader evidence base largely preclinical.

Liver cancer

Liver malignancies are the most studied setting for microbubble-enhanced HIFU, with a small clinical feasibility literature supported by preclinical work. In a single-arm prospective feasibility study of 17 patients with advanced primary or metastatic liver malignancies, Zhou et al. evaluated microbubble-assisted HIFU [56]. Following a single intravenous bolus of microbubbles, rapid

grayscale changes were observed within seconds in most patients (15/17), consistent with intratumoral microbubble destruction. The mean tumor ablation rate was approximately 51.5%, and only mild elevations in liver enzymes were observed. While uncontrolled, the study demonstrated that microbubble administration could be incorporated into HIFU without added toxicity, supporting the feasibility and acute safety of microbubble-assisted HIFU in advanced liver malignancies [56]. Preclinical work has explored molecularly targeted microbubbles to improve ablation precision. In a murine HCC model, Xiong et al. used microbubbles bearing a ligand against B7-H3, an immune checkpoint expressed on tumor neovasculature. These targeted microbubbles produced a 4.6-fold higher contrast-ultrasound signal at the tumor than isotype controls. Microbubble-enhanced HIFU also achieved effective ablation at lower acoustic power, with significant coagulation at 70 W versus the 90 W required for HIFU alone. Adding B7-H3 targeting further improved outcomes: the targeted group showed the greatest tumor ablation, strongest growth suppression, and most pronounced $CD8^+$ T-cell infiltration of all groups, suggesting a path toward biologically targeted thermal ablation [57].

Prostate cancer

In prostate cancer, both HIFU and RFA have been investigated as focal thermal ablation strategies, with USMB explored preclinically as a means of mitigating perfusion-mediated heat loss and improving local energy deposition. Yang et al. provided early evidence in a PC-3 prostate-cancer xenograft model, in which mice received USMB pretreatment before RFA. The combination of USMB and RFA resulted in larger ablation volumes ($P = 0.002$ at Day 1 and $P = 0.022$ at Day 4) and higher ablation rates at all time points ($P < 0.001$), along with significant tumor growth suppression compared with RFA alone, in which tumor volumes continued to increase over time [58]. A subsequent optimization study from the same group further showed that the magnitude of this effect depends on ultrasound and microbubble parameters, with optimized conditions producing significant reductions in tumor perfusion and supporting microvascular disruption as the underlying mechanism by which USMB mitigates the heat-sink effect [59].

Molecularly targeted microbubbles have also been explored preclinically. Beyond non-targeted approaches, molecular targeting has been explored to improve the spatial precision of microbubble-assisted ablation. Zhou et al. developed BST-2–targeted microbubbles and combined them with HIFU in a murine prostate-cancer model. Compared with HIFU alone, the addition of targeted microbubbles produced larger ablation volumes, approximately 50% greater inhibition of residual tumor growth, and a survival rate of 70.3% (vs. ~35% with HIFU alone). Consistent with findings in liver tumor models, this approach was also associated with enhanced immune activation, including increased dendritic cell maturation (32.8% vs 9.67%) and $CD8^+$ T-cell infiltration (13.8% vs 5.35%), suggesting that targeted microbubble-assisted ablation may extend beyond physical tumor destruction to modulate the post-treatment tumor microenvironment [60]. The clinical trials of USMB in oncology discussed above are summarized in table 2 (Fig. 4).

Table 2 Clinical trials of ultrasound-stimulated microbubbles in oncology (by year).

First author, year	Application	Tumor	Phase/design	n	Microbubble agent	US delivery	Ref
Carpentier, 2016	Drug delivery	Recurrent GBM	Phase 1/2a, single-arm	15	SonoVue	SonoCloud-1 implantable + carboplatin	[9]
Dimcevski, 2016	Drug delivery	Inoperable PDAC	Phase 1, single-arm	10	SonoVue	External US + gemcitabine	[10]
Idbaih, 2019	Drug delivery	Recurrent GBM	Phase 1/2a, single-arm	21 enrolled/ 19 treated	SonoVue	SonoCloud-1 implantable + carboplatin	[36]
Mainprize, 2019	Drug delivery	Primary brain tumor	Phase 1, single-arm	5	Definity	Transcranial MR-guided FUS	[41]
Eisenbrey, 2021	Radiosensitization	HCC	Phase 1, randomized pilot	28	Optison	UTMD + 90Y-TARE	[15]
Zhou, 2022	Drug delivery	HER2-neg invasive breast	Prospective non-randomized	26 (10 USMB/16 ctrl)	SonoVue	Diagnostic US + neoadjuvant chemo	[46]
Dasgupta, 2023	Radiosensitization	Breast	Phase 1 feasibility	8 (9 tumors)	Definity	MR-guided FUS + RT	[25]
Haram, 2023	Drug delivery	CRC liver mets	First-in-human, lesion-randomized	17	SonoVue	External US + systemic chemo	[50]
Sonabend, 2023	Drug delivery	Recurrent GBM	Phase 1, single-arm	17	Definity	SonoCloud-9 + nab-paclitaxel	[37]
Han, 2024	Drug delivery	Inoperable pancreatic cancer	Multicenter, open-label, randomized phase 2	78 (38/40)	SonoVue	Diagnostic US + gemcitabine-based chemo	[49]

(To be continued on the next page)

(Continued)

First author, year	Application	Tumor	Phase/design	n	Microbubble agent	US delivery	Ref
Carpentier, 2024	Drug delivery	Recurrent GBM	Multicenter phase 1/2	33	Definity/ Luminity	SonoCloud-9 + carboplatin	[39]
Moore-Palhares, 2024 (Breast)	Radiosensitization	Breast/chest wall	Phase 1	21 enrolled (18 analyzed/20 tumors)	Definity	MR-guided FUS + RT	[24]
Moore-Palhares, 2024 (HNSCC)	Radiosensitization	HNSCC (newly dx + recurrent)	Phase 1	11 (8 with response data)	Definity	Focused US + RT	[26]
Zhou, 2024	Thermal ablation	Advanced primary/metastatic liver	Single-arm prospective feasibility	17	Sonazoid	HIFU + Sonazoid bolus	[53]
Habashy, 2025	Drug delivery	Recurrent GBM (PK substudy)	PK/microdialysis	4	Definity	SonoCloud-9 + carboplatin	[40]
Wessner, 2025 (HCC)	Radiosensitization	HCC	Single-center phase 2 randomized	98 (50/48)	Optison	2D UTMD + 90Y-TARE	[22]
Wessner, 2025 (ICC/MDL)	Radiosensitization	ICC + liver metastases	Single-center phase 2	30 (15/15 matched)	Optison	3D volumetric UTMD + 90Y-TARE	[23]
Wu, 2025	Drug delivery	Pediatric relapsed DMG	First-in-pediatrics feasibility	3	Definity	Neuronavigation-guided FUS + oral panobinostat	[43]
Woodworth, 2025	Drug delivery	High-grade glioma	Multicenter phase 1/2 (BT008), single-arm	34	Definity	MR-guided transcranial FUS + temozolomide	[42]
Dong, 2026	Perfusion (drug-delivery rationale)	Invasive breast	Prospective controlled, non-randomized	36 (18/18)	SonoVue	Diagnostic US + MB	[47]

Reference numbers correspond to the bibliography of the current manuscript. Abbreviations: BBB, blood-brain barrier; CRC, colorectal cancer; DMG, diffuse midline glioma; FUS, focused ultrasound; GBM, glioblastoma; HCC, hepatocellular carcinoma; HIFU, high-intensity focused ultrasound; HNSCC, head and neck squamous cell carcinoma; ICC, intrahepatic cholangiocarcinoma; MB, microbubble; MDL, metastatic disease to liver; PDAC, pancreatic ductal adenocarcinoma; PK, pharmacokinetics; RT, radiotherapy; TARE, transarterial radioembolization; US, ultrasound; USMB, ultrasound-stimulated microbubbles; UTMD, ultrasound-triggered microbubble destruction.

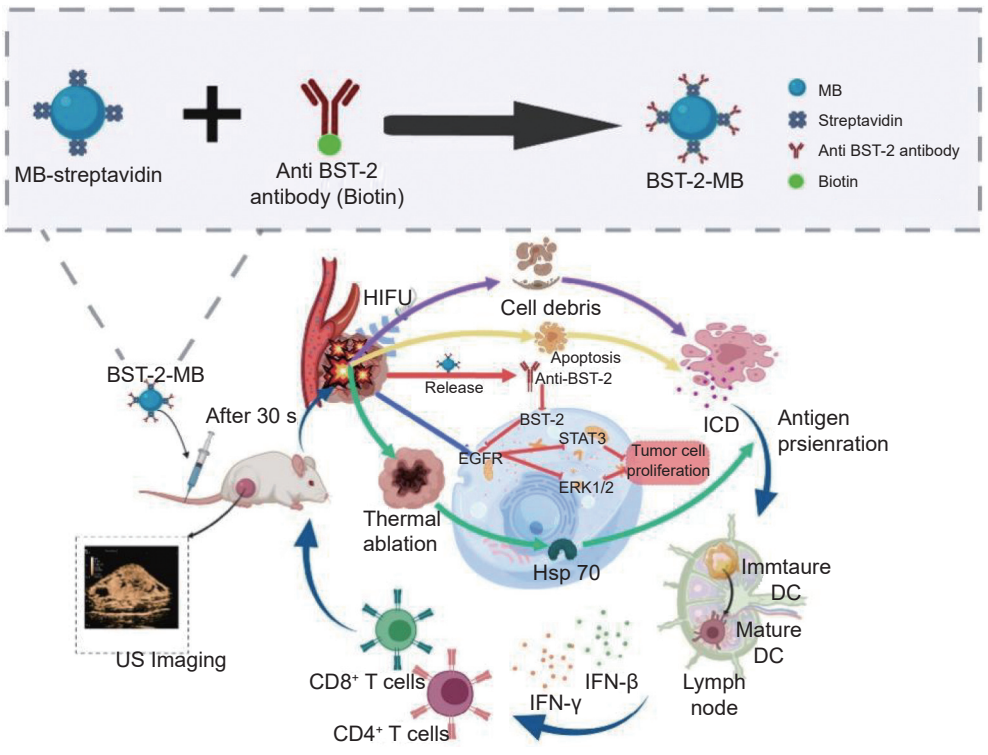


Figure 4 Schematic diagram of ultrasound combined with targeted microvesicle therapy for PCa. (red arrow: BST-2-EGFR-STAT3/ERK1/2 pathway inhibition; green arrow: HIFU thermal effect activates immunogenic cell death (ICD); purple arrow: HIFU cavitation effect generates cellular debris; yellow arrow: apoptosis due to multiple effects of HIFU; blue arrow: activation of immune pathways). (Reproduced from Zhou. et al60 under the Creative Commons CC-BY 4.0 license)

Limitations and Future Directions

Despite encouraging clinical and preclinical evidence, several limitations constrain the current USMB literature. Most clinical studies remain small, single-center phase 1 or 2 trials, with substantial heterogeneity in acoustic parameters, microbubble agents, and treatment timing across studies. No phase 3 trial has been completed in any indication**.** Translation has also been uneven across organ systems; for instance, prostate cancer has accumulated preclinical evidence for both radiosensitization and ablation, yet no clinical trials have been registered or completed in this setting. Tumor heterogeneity in vascular density, tumoral interstitial pressure, and stromal composition is also not consistently accounted for in current trials. Regulatory pathways are also undefined: none of the four clinically available microbubble agents currently holds approval for therapeutic use, meaning all clinical applications remain off-label. Standardized protocols and large multicenter randomized trials will be essential to confirm efficacy signals and define optimal treatment regimens.

Several directions are likely to shape the next phase of clinical development. Beyond the incidental immune effects observed in current radiosensitization and ablation studies, deliberate combinations of USMB with immune checkpoint inhibitors and other immunotherapies represent a particularly active area of investigation. This is supported by emerging evidence that cavitation can promote immunogenic cell death, dendritic cell maturation, and $CD8^+$ T-cell infiltration. Molecularly targeted microbubbles, exemplified by recent B7-H3- and BST-2-targeted agents, may further improve therapeutic precision and enable image-guided treatment. Sonodynamic therapy, in which ultrasound activates intratumoral sensitizers to generate cytotoxic reactive oxygen species, has also been investigated in combination with USMB, with early preclinical work suggesting both enhanced sensitizer delivery and induction of immunogenic cell death, representing a promising direction for future investigation [61,62]. Following early feasibility shown in pediatric diffuse midline glioma, expansion to broader pediatric oncology represents another important translational direction. Continued progress will depend on standardized clinical protocols, larger randomized trials, defined patient-selection criteria, and integration of USMB with broader oncologic therapeutic strategies.

Conclusion

Ultrasound-stimulated microbubbles have moved from a diagnostic imaging technology to an investigational therapeutic platform with growing clinical evidence across three principal applications. Radiosensitization is most clinically advanced in liver malignancies, with phase 2 randomized data in hepatocellular carcinoma and signal in intrahepatic cholangiocarcinoma; drug delivery is most clinically advanced in glioma, where multiple phase 1 and phase 1/2 trials of implantable and noninvasive systems have shown feasibility, pharmacokinetic enhancement, and a recent overall-survival signal; and pancreatic cancer has the strongest randomized evidence outside the liver and brain. Thermal-ablation enhancement remains predominantly preclinical. Larger randomized trials and standardized acoustic and microbubble protocols are the necessary next steps before USMB-based therapy can be incorporated into routine oncologic practice.

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Declarations

Conflict of interest

The authors decare that there is no conflict of interest relevant to this article.

Consent for publication

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