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A review of sonodynamic therapy for brain tumors

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OBJECTIVE Sonodynamic therapy (SDT) is gaining attention as a promising new noninvasive brain tumor treatment that targets and selectively kills tumor cells, with limited side effects. This review examines the mechanisms of SDT and ongoing clinical trials looking at optimization of sonication parameters for potential treatment of glioblastoma (GBM) and diffuse intrinsic pontine glioma (DIPG). The results in the first patient with recurrent GBM treated at the Mayo Clinic are briefly discussed.

METHODS The authors of this literature review used electronic databases including PubMed, EMBASE, and OVID. Articles reporting relevant preclinical and clinical trials were identified by searching for text words/phrases and MeSH terms, including the following: "sonodynamic therapy," "SDT," "focused ultrasound," "5-ALA," "ALA," "brain tumors," "diffuse pontine glioma," "glioblastoma," and "high grade glioma."

RESULTS Preclinical and clinical trials investigating the specific use of SDT in brain tumors were reviewed. In preclinical models of high-grade glioma and GBM, SDT has shown evidence of targeted tumor cell death via the production of reactive oxygen species. Emerging clinical trial results within recurrent GBM and DIPG show evidence of successful treatment response, with minimal side effects experienced by recruited patients. So far, SDT has been shown to be a promising noninvasive cancer treatment that is well tolerated by patients. The authors present pilot data suggesting good radiological response of GBM to a single SDT treatment, with unpublished observation of a lack of off-target effects even after multiple (monthly) sonication outpatient treatments. The scope of the clinical trials of SDT is to investigate whether it can be the means by which the fatal diagnosis of GBM or DIPG is converted into that of a chronic, treatable disease.

CONCLUSIONS SDT is safe, repeatable, and better tolerated than both chemotherapy and radiotherapy. It has been shown to have an effect in human cancer therapy, but more clinical trials are needed to establish standardized protocols for sonosensitizer delivery, treatment parameters, and combination therapies. The most appropriate timing of treatment also remains to be determined—whether to prevent recurrence in the postoperative period, or as a salvage option in patients with recurrent GBM for which redo surgery is inappropriate. It is hoped that SDT will also be developed for a wider spectrum of clinical indications, such as metastases, meningioma, and low-grade glioma. Further clinical trials are in preparation.

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KEYWORDS sonodynamic therapy; recurrent glioblastoma; sonoluminescence; focused ultrasound

Sonodynamic therapy (SDT) is an emerging cancer therapy that uses focused ultrasound (FUS) waves guided by MRI (termed MR-guided FUS [MRgFUS]) to activate a chemical agent (termed a sonosensitizer) to produce reactive oxygen species (ROS) and trigger cancer cell death.[1–5] SDT has gained significant attention over recent years as a promising noninvasive treatment that targets and selectively kills tumor cells with limited side effects. The addition of MRI allows for real-time monitoring of temperature and thermal dose.

This review examines the mechanisms of SDT and ongoing clinical trials looking at optimization of sonication parameters for potential treatment of glioblastoma (GBM) and diffuse intrinsic pontine glioma (DIPG).[6–11]

Photodynamic Therapy

The concept of SDT has been developed from photodynamic therapy (PDT)—a phenomenon first reported more than 30 years ago. PDT is a phenomenon that features the

ABBREVIATIONS 5-ALA = 5-aminolevulinic acid; BBB = blood-brain barrier; DIPG = diffuse intrinsic pontine glioma; FUS = focused ultrasound; GBM = glioblastoma; IV = intravenous; MRgFUS = MR-guided FUS; PDT = photodynamic therapy; PpIX = protoporphyrin IX; rGBM = recurrent GBM; ROS = reactive oxygen species; SDT = sonodynamic therapy.

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use of a photosensitizing agent that, when activated by a light source, can induce cell death.[12–14] Since its discovery and the development of topical photosensitizers, PDT was first approved as a topical therapy to treat precancerous lesions in 1999, and has since been used in a variety of dermatological conditions such as skin cancer.[15]

On exposure to light of a specific wavelength, the photosensitizer is activated, and moves into its first singlet excited state. From this point, a chain of further electron transitions can occur, enabling the excited sensitizer to move into a longer-lived triplet state. In the absence of triplet state population, the excited photosensitizer returns to its ground state with the emission of light, known as fluorescence, and/or by means of radiationless transitions whereby energy is given to or taken up by another particle or system. Only when the excited photosensitizer returns to ground state from the triplet state will it release a sufficient quantity of ROS or singlet oxygen to initiate cell death through influencing mitochondrial dysfunction and enzymatic (including caspase) activation.[16] In addition to the activation of the caspase cascade, oxidation of specific proteins such as Bcl-2 further initiates apoptosis leading to cell death.[17] Photosensitizing agents are selectively absorbed by malignant cells, making their cytotoxic effects localized and tumor specific, with 5-aminolevulinic acid (5-ALA) having 96.5% sensitivity to high-grade glioma cells.[18]

PDT is effective but invasive—requiring craniotomy and direct exposure of the brain parenchyma. This is because light cannot penetrate deep enough through the skull to cause target tissue damage.[19] Additionally, potential side effects of PDT were reported by Lietke et al. Salvage interstitial PDT showed complications in 40% of patients—including transient worsening of neurological deficits, and malignant edema requiring emergency decompression in 1 patient.[20]

SDT works in a similar way by using the energy of ultrasound waves to activate sonosensitizing agents. However, the exact mechanism behind SDT-mediated cell death is not as well studied, and remains unclear. The main clinical benefit of SDT over PDT is that it has better tissue penetration depth, and does not require direct exposure of the tumor tissue for the FUS to cause tumor cell death—i.e., no requirement for incision and craniotomy.

Mechanisms of Cell Death in SDT

SDT has proven to be effective in both in vitro and in vivo settings, yet the mechanisms underlying sonoactivation have not been fully elucidated.[21] The current understanding posits that the biological consequences of SDT primarily arise from the acoustic cavitation phenomenon induced by the interaction between ultrasound and a chemical agent, involving the formation, growth, and collapse of bubbles in liquids.[13,22]

Cavitation comes in two forms: stable and inertial. In stable cavitation, bubbles steadily oscillate in a low-pressure sound field. Inertial cavitation, however, involves violent bubble oscillation and rapid growth, leading to a forceful collapse.

The exact mechanism of sonosensitizer activation is unclear. However, the first theory of sonosensitizer activation is through the direct influence of the FUS waves themselves—whereby microbubble collapse generates a high-pressure, high-temperature shock wave with sufficient energy to activate the sonosensitizer.[23] Microstreaming, a result of the oscillatory motion in stable cavitation, induces fluid movement, creating high shearing forces and leading to the production of ROS.

Another theory behind sonosensitizer activation is sonoluminescence. FUS induces microbubble formation and subsequent cavitation (induced by high-frequency sonication) around the surface of cancer cells. The energy provided by the collapse of the cavitating microbubbles initiates the release of a flash of blue light that in turn activates the sonosensitizer into its excited state.[24] In turn, as the activated sonosensitizer returns to the ground state, the released energy can be transferred to circumambient oxygen to produce a large amount of ROS including oxygen ions, peroxide, and singlet oxygen, which subsequently mediate the mitochondrial-dependent cell apoptosis through the damage of mitochondrial membrane, release of cytochrome-c, and activation of the caspase cascade. This mechanism holds promise for inducing transient damage to cell membranes, and presents a potential application for the treatment of cancer cells.[25,26]

Sonosensitizers

Sonosensitizers play a crucial role in the SDT process by converting acoustic energy into chemical energy through specialized chemical structures. This conversion generates ROS, an essential result of SDT that in turn elicits its cytotoxic effects. Hence, the effectiveness of SDT is heavily influenced by the performance of the sonosensitizer.[27] The two sonosensitizers that have been investigated for safety and efficacy in the treatment of brain tumors are oral or intravenous (IV) 5-ALA as well as a study investigating the potential use of fluorescein.[28]

5-ALA is a natural porphyrin precursor that has been widely demonstrated to have preferential uptake in brain tumor cells, including gliomas and multiple pediatric tumors.[29,30] It is currently approved for use in fluorescence-assisted resection of human gliomas. 5-ALA readily crosses the blood-brain barrier (BBB), and is preferentially metabolized by tumor cells (such as GBM) into a fluorescent photosensitizer called protoporphyrin IX (PpIX) via the heme pathway. On exposure to blue light, PpIX causes tumor cells to fluoresce pink. This allows for visual aid in the surgical theater—by better differentiation of tumor versus healthy brain cells.

Kennedy et al. first reported the PDT effect by showing that applying topical 5-ALA to superficial basal cell carcinomas resulted in sufficient PpIX accumulation to show significant fluorescence, and exert a therapeutic PDT effect by using red light from a slide projector—resulting in complete tumor response in 90% of the treated carcinomas.[31] Red light was first used in 5-ALA PDT studies because it has the deepest tissue penetration. However, PpIX shows the greatest absorption within the blue light spectrum—with red light being the least efficient wavelength for PpIX activation.[31]

TABLE 1. Comparison of FUS-mediated 5-ALA SDT to FUS-mediated BBB opening

	5-ALA SDT	BBB Opening
FUS machines tested	Insightec ExAblate 4000 Type 2.0 (200 kHz); NaviFUS (500 kHz); CV-01 Unfocused	Insightec ExAblate 4000 Type 2.0 (200 kHz); SonoCloud-1 & SonoCloud-9 (1.05 MHz)
Requires use of injected microbubbles	No	Yes
Selective only for tumor cells	Yes (due to 5-ALA metabolite PpIX accumulation)	No
Potential clinical indications being investigated	Newly diagnosed GBM; recurrent/progressive GBM; DIPG	Recurrent/progressive GBM; DIPG; AD; PD; ALS
Optimal sonication parameters determined (e.g., pulse repetition frequency, pressure, & duration; energy delivery)	No	Yes
Method of action	Photodynamic	Mechanical
Optimal no. of sonication sessions	Unknown	Unknown
Immunomodulatory effect	Yes	No
Side effects	No dose-limiting toxicities reported	Potential for (subclinical) hemorrhage, edema, & inflammation

AD = Alzheimer's disease; ALS = amyotrophic lateral sclerosis; PD = Parkinson's disease.

As previously mentioned, PpIX can also be activated by high-energy blue light to initiate immediate cell death, or programmed cell death (apoptosis) through the PDT effect as well as the SDT effect following exposure to FUS. 5-ALA SDT is not yet approved for clinical use. However, preclinical studies have shown that SDT-mediated PpIX activation can trigger ROS upregulation and apoptosis of tumor cells.[4]

SDT in Cancer

SDT has emerged as a promising and versatile approach in the treatment of cancers, showing the potential to overcome the limitations of conventional therapies. For solid tumors, SDT has shown efficacy in a variety of cancers, including glioma, pancreatic, breast, lung, prostate, and liver.[32–37]

The selective targeting of cancer cells and the noninvasive characteristics of SDT render it an appealing treatment choice for patients with glioma. GBM represents a category of primary malignant brain tumors characterized by their genetic heterogeneity, aggressive nature, and highly invasive behavior. Despite receiving optimal treatment involving surgery, cytotoxic chemotherapy, and radiotherapy, gliomas often recur locally, leading to a dismal prognosis.[38]

By targeting dividing tumor cells, regardless of their phenotype, SDT could potentially combat chemo- and immunoescape. This innovative approach holds potential for postponing tumor recurrences and addressing unresectable masses, given that the FUS waves can noninvasively penetrate deep into brain tissue. By specifically targeting glioma cells while sparing healthy tissue, SDT offers hope for preserving patients' quality of life by safeguarding vital brain functions.[39]

It is worth noting at this point that SDT is not to be confused with FUS-mediated opening of the BBB—see Table 1. The mechanism of FUS-mediated BBB opening relies on the injection of microbubbles intravenously that can act as substantial local amplifiers of acoustic energy and increase local cavitation when exposed to an acoustic pressure wave. The microbubbles expand and contract, creating a shear stress response to FUS—and when this oscillation occurs inside a blood vessel, it can temporarily and reversibly disrupt the integrity of the endothelium, to allow delivery of specific therapeutics into the brain across the vascular barrier.[40]

Preclinical Evidence of SDT Efficacy

Umemura et al. were the first to obtain in vitro evidence of SDT-induced cell death in a murine sarcoma cell line—using hematoporphyrin as a sonosensitizer.[41] The group showed FUS-induced cavitation to produce a sonoluminescence spectrum with the ability to activate hematoporphyrin, promote the release of singlet oxygen, and thereby enhance cellular damage.

Jeong et al. showed evidence of 5-ALA PDT-like effects of 5-ALA SDT on C6 rat glioma models exposed to high-intensity FUS applied via craniotomy directly to the brain surface.[1] No control rats survived past 14 days. However, within the subset of animals that survived to planned death, tumor size was significantly smaller in the 5-ALA SDT group compared to any of the other groups (FUS only, 5-ALA only, and FUS with Radachlorin) ($p < 0.05$).

Following this, Suehiro et al. confirmed the ability of 5-ALA SDT to induce a cytotoxic effect to an in vivo model of malignant glioma without a need for craniotomy, as well as illustrated this to occur in a tumor-specific manner.[2] 5-ALA SDT with high-intensity FUS greatly prolonged the survival of the tumor-bearing mice compared to that of the control group. Tumor cell necrosis was observed in the focus area, with apoptosis occurring in the perifocus area (i.e., the area surrounding the target of the FUS-irradiated field), with no damage to the surrounding (healthy) brain.

Yoshida et al. also investigated the efficacy of 5-ALA SDT on an F98 rat malignant glioma model. In comparison to control, FUS-only, and 5-ALA models, 5-ALA SDT suppressed tumor proliferation and invasion as well

as angiogenesis in vivo. The group also observed minimal damage to normal brain tissue.[4]

Wu et al. sought to optimize the ultrasound parameters of SDT, using a C6 rat glioma model.[3] MRgFUS at 1.06 MHz was delivered continuously at an in situ spatial-peak temporal-average intensity of 5.5 W/cm^2 for 20 minutes. The tumor growth responses were evaluated with weekly MRI following treatment. 5-ALA SDT (with either 32°C or 37°C as the starting core body temperature) significantly improved tumor growth inhibition and survival compared to 5-ALA alone and FUS alone—with neither of these therapies alone improving survival. Their promising results have shown that 5-ALA SDT with relatively low-power, continuous-wave FUS can produce an inhibitory effect on glioma growth in the absence of thermal dose.

The wide variety of sonication parameters used to obtain positive SDT results in preclinical studies adds support to a mechanism of action secondary to the pure precise mechanical effects of ultrasound (as occurs in BBB opening using microbubbles). This putatively adds support to a secondary phenomenon like sonoluminescence, which can be created with a large variety of frequencies and powers at low energy.

A preclinical study on DIPG cells exposed to exogenous 5-ALA showed that not only does 5-ALA accumulate in higher amounts in DIPG cells compared to C6 rat glioma tissue culture cells and human low-grade glioma cells, but also that diffuse midline glioma cells retain 5-ALA and produce PpIX for longer durations of time (more than 8 hours after removal of 5-ALA from the medium).[5] SDT has not been evaluated on animal models of DIPG; however, these results supported the initiation of a 5-ALA SDT trial in children diagnosed with DIPG.

Clinical Evidence of SDT Efficacy

SDT is a particularly attractive treatment option for brain tumors. MRgFUS allows for real-time anatomical and thermometric feedback. Because no general anesthetic is required for the procedure, there is allowance for awake patient feedback in addition. Clinical benefits include there being no requirement for craniotomy, and the procedure can be carried out in an outpatient setting.

The first SDT clinical trials for brain tumors including recurrent GBM (rGBM) and DIPG have thus far shown significant success—with clinical improvement, a lack of observed side effects, and the treatment was well tolerated by patients.

First In-Human Phase 0/1 SDT Clinical Trial

The first in-human phase 0/1 clinical trial of 5-ALA SDT investigated its feasibility, safety, and biological effects in patients with rGBM.[6] IV 5-ALA (SONALA-001; 10 mg/kg) was administered 6–7 hours prior to low-intensity FUS. In the dose-escalation arm, patients were assigned to one of three ascending acoustic energy doses of MRgFUS (200 J/400 J/800 J, measured at transducer surface), followed by a 4-day interval before planned tumor resection. IV 5-ALA avoids first-pass liver metabolism and gastrointestinal toxicities observed with oral 5-ALA (a higher oral dose is required to achieve the same tissue concentration observed with the IV 5-ALA).[42]

The first patient with rGBM treated with 5-ALA SDT showed significant tumor shrinkage after only 4 days of a single treatment, and SDT was well tolerated in all patients—with no patient experiencing drug- or device-related adverse events. Additionally, 5-ALA SDT demonstrated biomarker evidence of the PDT effect. Compared to internal control tissue, the apoptosis biomarker cleaved caspase-3 was elevated in all patients. The oxidative stress biomarkers 4-hydroxynonenal, glutathione, cysteine, and thiol were elevated in treated versus control tissues at all energy levels,[6] confirming for the first time in humans the same histological markers of cell death seen in the aforementioned animal studies of SDT for malignant glioma. All together, this study illustrated clinically, radiologically, and histologically that 5-ALA SDT is safe at 200 J and is likely to induce targeted cell death in patients with rGBM via oxidative stress.[6]

Phase 1/2 SDT Clinical Trial

Following this success, a phase 1/2 expansion study of SONALA-001 and MRgFUS for progressive or rGBM was commenced (SDT-202; NCT05370508).[7] The trial's main objectives were to evaluate safety, dose-limiting toxicities, and recommended phase 2 dose for the study's expansion portion. To determine optimal treatment parameters, the study had a Bayesian 3 + 3 design for escalating SONALA-001 (5 and 10 mg/kg) as well as increasing MRgFUS pulse pressure and energy levels (12, 24, and 28 J/subspot) during sonications. This protocol was amended to allow a maximum of 12 treatments delivered at monthly intervals. Unfortunately, recruitment for this study has paused due to a lack of funding. However, preliminary data from a compassionate use case has shown promising results. This patient had an *H3K27M*-mutant rGBM and was initially managed with surgical debulking of the tumor (Fig. 1). She subsequently received treatment with ONC201 (a dopamine receptor antagonist and a caseinolytic protease P agonist),[43] achieving a sustained partial response. However, the patient then displayed radiographic recurrence, as well as evidence of clinical deterioration. She later received treatment with laser interstitial thermal therapy (also known as stereotactic laser ablation).[44] She then received combined therapy of lomustine (an alkylating agent of the nitrosourea family) with bevacizumab (an anti–vascular endothelial growth factor antibody) (Fig. 1).

After this, she finally underwent SDT—52 mL, followed by 212 mL 1 month later. MR images show a regionally differential impact, with lesion regression caudally, despite progression rostrally (Fig. 2).

Another ongoing clinical trial investigating the safety and feasibility of 5-ALA SDT in patients with rGBM includes a phase 1 pilot study of the administration of 5-ALA SDT 1–3 weeks before surgery (NCT06039709).[8] There is also an ongoing phase 1 clinical trial in recurrent high-grade glioma being conducted by Alpheus Medical (NCT05362409). In this study, 5-ALA will be administered prior to CV01-delivered ultrasound, and will be repeated every 4 weeks.[9]

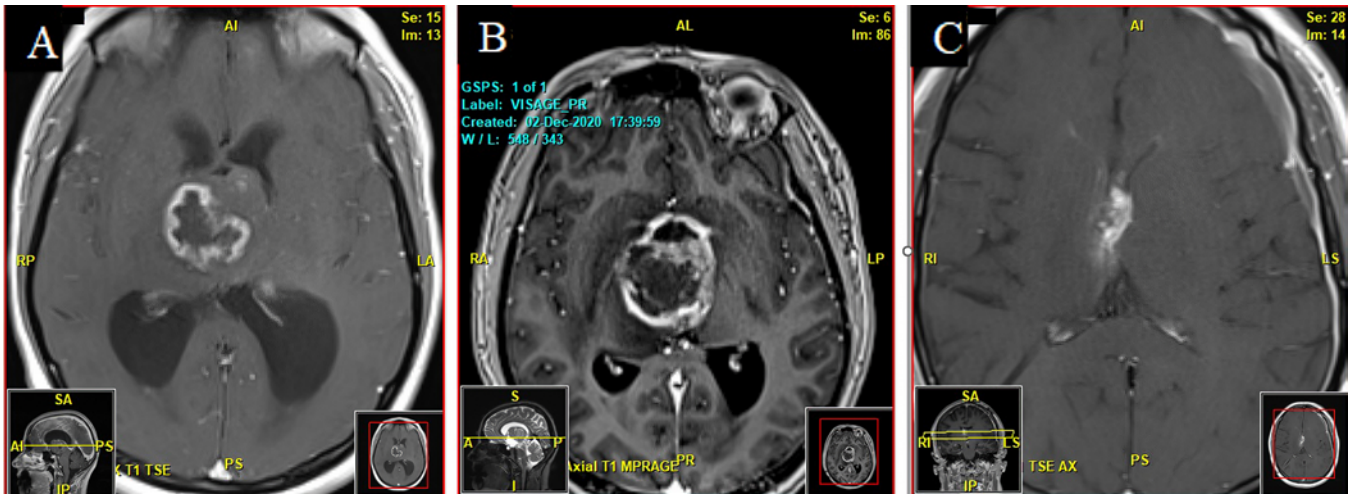

FIG. 1. A: Axial MRI section obtained at initial presentation. **B:** Axial MRI section showing radiographic deterioration following presentation. **C:** Axial MRI section obtained postdebulking.

There is also an interesting ongoing Italian phase 2 clinical trial looking at the role of 5-ALA SDT in newly diagnosed GBM (NCT04845919).[10] This is a prospective, nonrandomized, single-arm study to evaluate the safety and feasibility of 5-ALA SDT using the ExAblate Model 4000 Type 2. After SDT treatment, patients will undergo strict neuroradiological follow-up (minimum of 2 MRI sessions) and will undergo tumor resection 15–21 days after SDT, according to clinical and radiological status.

First In-Child SDT Clinical Trial for DIPG

DIPG is an aggressive pediatric brain tumor with a poor prognosis. The propensity of these tumors to infiltrate eloquent brainstem tissue means that surgery is not a feasible treatment option. This makes the search for other treatment options for these inoperable tumors a significant research target. Even with the current standard of care (fractionated radiotherapy [50.4–59.4 Gy in 28–33 fractions of 1.8 Gy daily over 6 weeks]), local recurrence is inevitable in most cases, and the mean survival for patients with DIPG remains approximately 9–12 months from diagnosis.[11,45]

A phase 1/2 multicenter, open-label study (NCT05123534) of 5-ALA SDT in patients with DIPG is currently underway.[11] The study aims to evaluate safety and tolerability of treatment with SDT in newly diagnosed patients with DIPG (following standard radiation therapy) to determine the maximum tolerated dose or recommended phase 2 dose of 5-ALA SDT. Up to 12 SDT sonications can be delivered during this trial. Thus far, the authors have described the first recruited patient as tolerating 5-ALA SDT well. The patient underwent SDT to the right side of the pons, with delayed SDT sonication to the left side (28 individual sonication targets per SDT

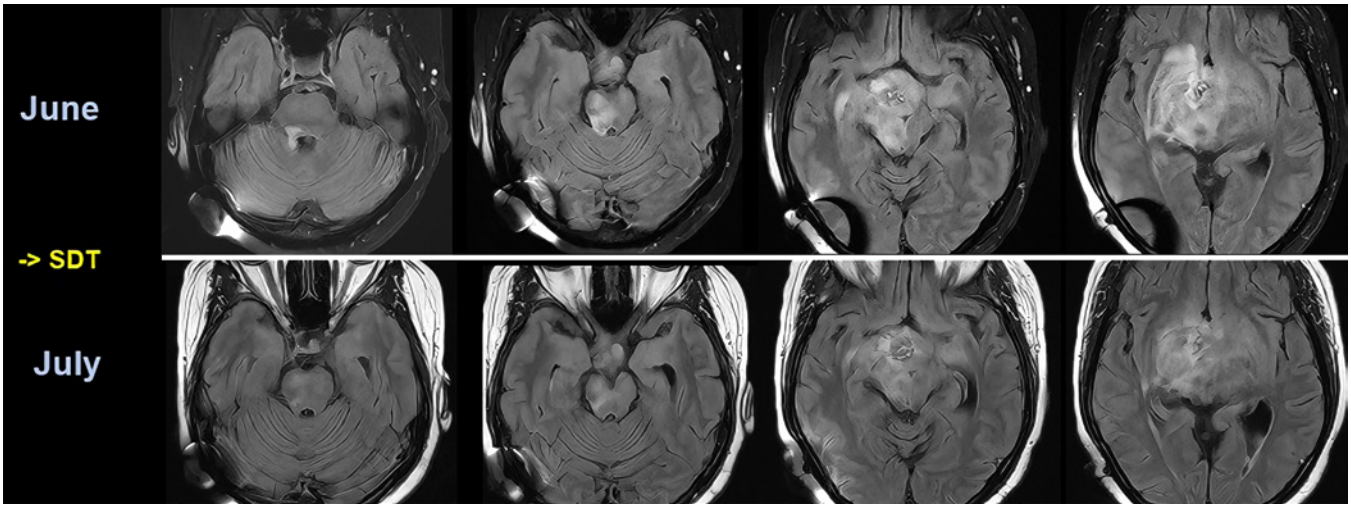

FIG. 2. Upper Row: Axial MRI sections obtained after combined therapy of lomustine and bevacizumab prior to SDT. **Lower Row:** Axial MRI sections obtained after the first round of SDT (52 mL), with each image in this row corresponding to the same-level axial slice from the row above. Imaging demonstrates reduction in FLAIR hyperintensity at the site of initial SDT sonication.

treatment; single time of sonication per focus at 50 W for a total energy of 200 J [total duration 100 seconds, pulse duration 2.4 msec, duty cycle 4%]) with no adverse effects, and clinical improvement of both walking and double vision. The results illustrate that SDT is safe at 200 J, and repeatable—with no adverse effects following repeated targeting of the pons. Unpublished data (S. Marcus, SonALAsense, Inc., 2024; data on file) from the first 10 patients enrolled have demonstrated that more than 70% of patients have lived beyond the median survival expected of DIPG.

Clinical Evidence of the Abscopal Effect of PDT and SDT

The abscopal effect is a phenomenon in which direct therapy (i.e., FUS) to the primary tumor can also promote regression of distant tumors. Preclinical data suggest that localized SDT has the potential to induce an abscopal effect through enhancing the body's overall immune recognition of tumor cells, and through promoting immune-mediated destruction of distant tumors.[46]

There is evidence to suggest an abscopal effect of PDT when used in the treatment of GBM, which is promising if SDT is to be developed as a form of cancer vaccine to treat GBM in humans. Stepp and Stummer treated deep-seated GBM with immunophotodynamic therapy and demonstrated that satellite lesions outside the treatment field significantly reduced in size after immunophotodynamic therapy, demonstrating an abscopal effect.[47] Similar distant tumor shrinkage has been observed in PDT-treated patients both with and without an immune checkpoint inhibitor.[48,49] The underlying immunological mechanisms still require further exploration.

The compelling preclinical efficacy of SDT against cancer has led to a number of clinical trials investigating its potential use against various tumors. However, given that the only published studies are in early phases, it is too soon to see any abscopal effects of SDT in a human population.

Conclusions

SDT is a promising noninvasive cancer treatment—with the scope to be the means by which we can convert the fatal diagnosis of GBM into that of a chronic, treatable disease.

SDT is safe, repeatable, and better tolerated than both chemotherapy and radiotherapy. It has been shown to have an effect in human cancer therapy, but more clinical trials are needed to establish standardized protocols for sonosensitizer delivery, treatment parameters, and combination therapies. The most appropriate timing of treatment also remains to be determined—whether it is used to prevent recurrence in the postoperative period, or as a salvage option in patients with rGBM for which redo surgery is inappropriate. It is hoped that SDT will also be developed for a wider spectrum of clinical indications, such as metastases, meningioma, and low-grade glioma (all of which have been demonstrated to uptake sonosensitizers to differing degrees). Further clinical trials will help us to define these parameters.

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Author Contributions

Conception and design: Hossain-Ibrahim. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: Hossain-Ibrahim, Hutton. Critically revising the article: Hossain-Ibrahim. Reviewed submitted version of manuscript: Hossain-Ibrahim. Approved the final version of the manuscript on behalf of all authors: Hossain-Ibrahim. Administrative/technical/material support: Hossain-Ibrahim. Study supervision: Hossain-Ibrahim.

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