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REVIEW

Emerging Therapeutic Strategies for Brain Tumors

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Abstract
Nearly thirty thousand incidences of primary and 300 thousand incidences of metastatic brain cancer are diagnosed in the USA each year. It has a high mortality rate and is often unresponsive to the standard of care, which includes surgical resection, radiation, and chemotherapy. These treatment strategies are also hindered by their invasiveness and toxic effects on healthy cells and tissues. Furthermore, the blood–brain/tumor barrier severely limits delivery of anti-cancer therapeutics administered intravenously to brain tumors, resulting in poor tumor response to the treatment. There is a critical need to develop new approaches to brain cancer therapy that can overcome these limitations. Focused ultrasound has emerged as a modality that addresses many of these limitations and has the potential to alter the treatment paradigm for brain cancer. Ultrasound transmitted through the skull can be focused on tumors and used for targeted ablation or opening the vascular barriers for drug delivery. This review provides insight on the current status of these unique ultrasound techniques, different strategies of using this technique for brain cancer, experience in preclinical models, and potential for clinical translation. We also debate the safety perspective of these techniques and discuss potential avenues for future work in noninvasive planning, monitoring, and evaluation of the ultrasonic neurointervention.

Keywords Brain cancer · Transcranial focused ultrasound · Tumor ablation · BBB disruption · Passive cavitation detection · Passive cavitation imaging · MR thermometry

Introduction

Brain tumors have proven extremely difficult to treat and patients have a poor prognosis. The standard of care for brain cancer patients with newly diagnosed primary brain tumors consists of surgery, radiation, and chemotherapy. However, not all brain tumors are operable and the recurrence rate can be extremely high (Adib et al., 2019; Faustino et al., 2020). While radiation can be effective, the cumulative exposure dose is limited due to neurotoxic effects (Kim et al., 2008; Shaw et al., 1996; Smart, 2017). The effectiveness of anti-cancer agents administered systemically is hindered by the blood–brain/tumor barrier (BBB), which severely limits molecular transport into the brain (Abbott & Romero, 1996; Abbott et al., 2006, 2010; Arvanitis et al., 2020; Blumling Iii & Silva, 2012; van Vliet et al., 2014). Due to the high recurrence rate and the lack of treatment options, most patients diagnosed with primary brain tumors succumb to the disease within 2 years (Gilbert et al., 2013, 2014; Ostrom et al., 2017; Stupp et al., 2005, 2009). Thus, there is a critical need for novel methods that can effectively treat brain tumors and significantly reduce the mortality rate.

Focused ultrasound (FUS) has emerged as a treatment modality for brain cancer that may be leveraged to overcome the shortcomings that hinder conventional treatment options. For example, transcranial FUS can be used to thermally ablate brain tissue noninvasively with millimeter precision. A commercial MRI-guided transcranial FUS system has been approved by the FDA for treating essential tremor by thermally ablating the thalamus (Abrahao et al., 2019; Elias et al., 2016; Lipsman et al., 2013). Thermal ablation using MR-guided FUS can be used to debulk brain tumors without a craniotomy, thus reducing the risk of infection (McDannold et al., 2010). Additionally, transcranial FUS can be used to open the BBB reversibly, which could enable pharmaceutical intervention of various neurological conditions (Aryal et al., 2014; Meng et al., 2019). While the BBB

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in brain tumors is leaky, studies have shown that ultrasound-mediated BBB opening does improve the delivery and efficacy of chemotherapy (McDannold et al., 2019; Treat et al., 2012). Herein we review these emerging ultrasound-based treatment strategies for brain cancer in greater detail and discuss the technological and methodological advances needed for clinical translation.

Reversible BBB Opening

The BBB impedes the delivery of most drugs to the brain, thus inhibiting their effectiveness against serious neuropathologies. Scientists have explored different approaches to opening the vascular barrier temporarily, and the use of focused ultrasound combined with stabilized microbubbles has emerged as the most promising. FUS-mediated blood–brain barrier opening was pioneered by Prof. Kullervo Hynynen and his group in the early 2000s (Hynynen et al., 2001). This brain drug delivery method consists of three components: the low-intensity FUS, an intravenous administration of encapsulated microbubbles, and a drug of interest. The microbubbles that are used for BBB opening are currently FDA-approved as ultrasound contrast agents. These microbubbles are micrometer-sized particles that typically consist of a shell made of either lipid or protein, which encapsulates a gaseous core, typically perfluoropropane or sulfur hexafluoride. During the BBB opening process, FUS transmits acoustic waves through the skull, which oscillate circulating microbubbles in targeted regions of the brain as shown in Fig. 1A. The BBB is subjected to forces generated by the oscillating microbubbles, which can create defects in the endothelial cell layer and promote vesicle formation within the endothelial cells (Sheikov et al., 2004). As a result of these reversible cellular changes, the permeability of the BBB is increased temporarily. The extent and duration of FUS-mediated BBB opening have been explored using computational modeling as well as various imaging modalities, including magnetic resonance imaging, optical imaging, and positron emission tomography. It was reported that cavitating microbubbles open the BBB immediately and can reseal within four hours depending upon the FUS parameters (Cho et al., 2011; Marty et al., 2012; Park et al., 2012; Samiotaki et al., 2012; Ye et al., 2018a). The method has been utilized to enable the delivery of various molecules to the brain, including fluorescent dextrans (Alonso et al., 2013; Burgess et al., 2011; H. Chen & Konofagou, 2014; Kaushik et al., 2019; Liu et al., 2010; McDannold et al., 2012; Thévenot et al., 2012), nanoparticles, and biologics (peptides ~ 3 kDa, antibodies ~ 150 kDa, and viruses ~ 2 MDa) (Aryal et al., 2015a; Chen et al., 2010; Diaz et al., 2014; Etame et al., 2012; Fan et al., 2013a; Nance et al., 2014; Wang et al., 2012). The overwhelming evidence that FUS and microbubbles can open the BBB reversibly and selectively has motivated its use for improving the delivery of anticancer agents to brain tumors. The delivery and efficacy of temozolomide (TMZ) to glioblastoma tumors in mice have been improved by the FUS-mediated opening of the BBB (Liu et al., 2014; Wei et al., 2013). FUS-mediated BBB opening also has been used to facilitate the delivery of an O^6-methylguanine-DNA methyltransferase (MGMT) inhibitor to TMZ-resistant gliomas in mice (Papachristodoulou et al., 2019). Combining TMZ with FUS-mediated delivery of the liposomal MGMT inhibitor led to a reduction in tumor burden and prolonged animal survival significantly. FUS-mediated BBB opening has been used to increase the delivery of nanoparticles loaded with other anticancer agents, including doxorubicin (Aryal et al., 2013; Treat et al., 2012) and cisplatin (Coluccia et al., 2018; Timbie et al., 2017). Furthermore, a study reported that multiple sessions of chemotherapy combined with FUS-mediated BBB opening increased the volume of drug distribution in brain tumors and killed cancer cells completely in most of the treated animals (Aryal et al., 2013; Fan et al., 2013b; McDannold et al., 2019; Wei et al., 2013). Importantly, the safety of opening the BBB repeatedly with FUS has been demonstrated in preclinical models including non-human primates (Abrahao et al., 2019; Aryal, et al., 2015a, 2015b; Lipsman et al., 2018; McDannold et al., 2012; Rezai et al., 2020) and currently is being investigated clinically (Abrahao et al., 2019; Lipsman et al., 2018; Mainprize et al., 2019; Rezai et al., 2020). While transcranial ultrasound has been used predominantly for noninvasive disruption of the vascular barrier, an implantable ultrasound device has been developed to improve the spatial control of BBB opening (Goldwirt et al., 2016). The safety and effectiveness of the device are being investigated in clinical trials in Europe and the USA (Asquier et al., 2019; Beccaria et al., 2020; Idbaih et al., 2019; Zhang et al., 2020). To date, nineteen clinical trials are underway across the globe to explore the feasibility and safety of ultrasound-mediated BBB opening in brain cancer and other neurological diseases (Table 1).

For clinical translation, scientists recognize that a strategy by which the ultrasound output can be adjusted to ensure the safe and reliable opening of the BBB is critical. As mentioned previously, cavitating microbubbles are the primary mechanism for ultrasound-mediated BBB opening; therefore, methods to monitor and control the cavitation activity have been pursued. During ultrasound forced oscillations, the cavitating microbubbles emit acoustic signals that can be detected passively with single-element transducers, known as passive cavitation detection (PCD). Based on spectroscopic analysis of the PCD signal, researchers have determined that microbubbles that have sustained nonlinear oscillations characterized by strong harmonic and subharmonic signals are most effective at reversibly opening

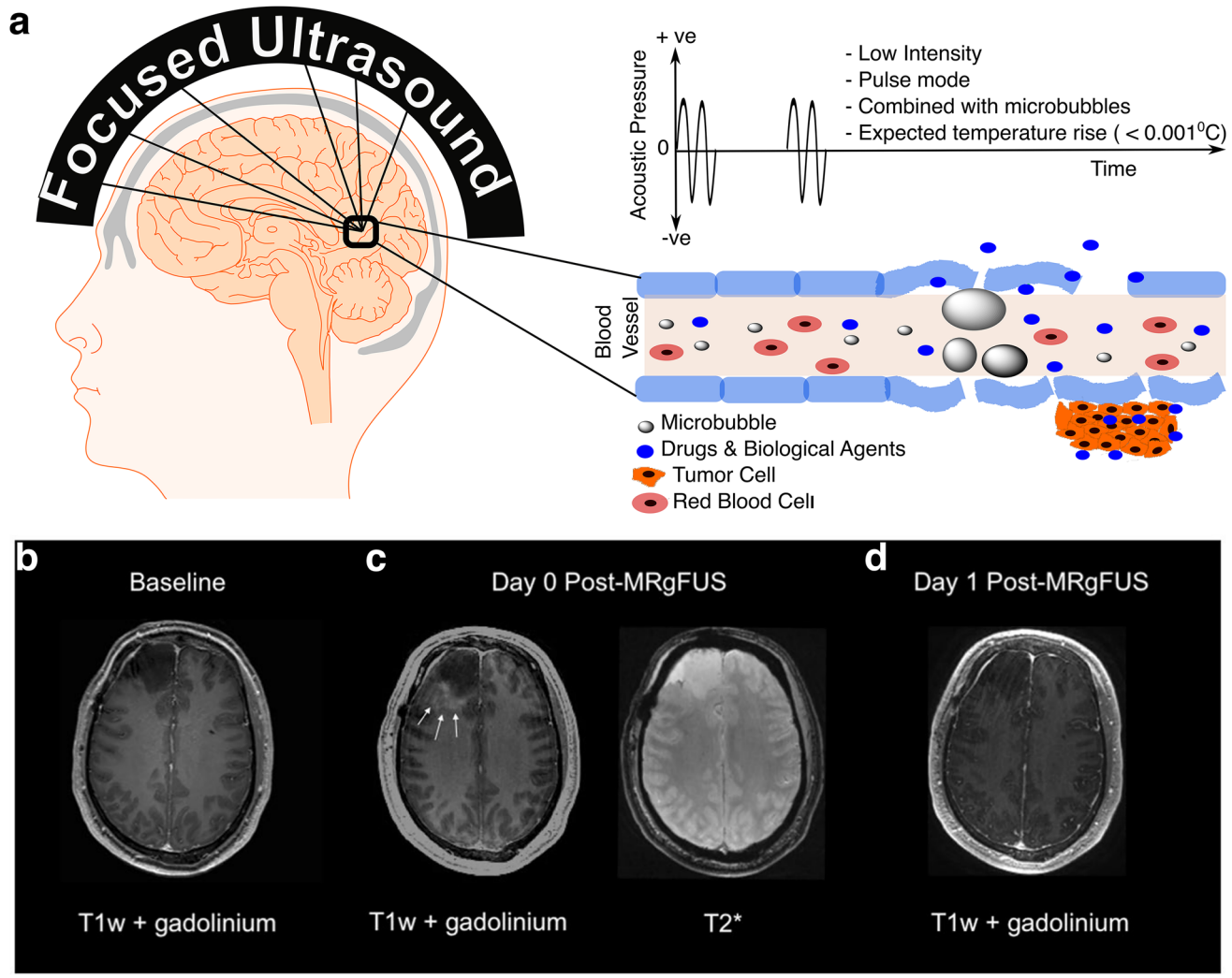

Fig. 1 Noninvasive, targeted, and transient opening of blood–brain/tumor barrier (BBB) in brain tumor patients using clinical MR-guided transcranial focused ultrasound system. The transient loosening of the vascular barrier allows drugs and biological agents from cerebral vasculature to extravasate into the brain tissue and helps to treat a wide range of neurological diseases and disorders. **A** Schematic of ultrasonic beam penetration through the skull to reach the desired region of the brain (left), characteristics of ultrasonic waves (low intensity in pulse mode (top-right)), and cavitation-induced opening of the BBB within the targeted zone after the low-intensity pulse (bottom-right). **B** Contrast-enhanced T1-weighted MR-images of brain tumor patient before ultrasound treatment. The tumor is visible within the hypointense zone. **C** Images after the ultrasonic intervention. White arrows in T1-weighted images show gadolinium leakage after BBB opening. T2*-weighted image indicates there is no microhemorrhage from the treatment. **D** T1-weighted images with gadolinium indicate that the opening of the BBB is resolved within a day (Mainprize et al., 2019). **B–D** Modified from Sci Rep. 2019; 9: 321.; Copyright © 2019, The Author(s)

Table 1 FUS-based BBB opening clinical trial for brain tumors, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis

Conditions	Brain tumor	Alzheimer's disease	Parkinson's disease	Amyotrophic lateral sclerosis
NCT Numbers	NCT04063514 NCT02343991 NCT03551249 NCT03616860 NCT03714243 NCT04440358 NCT04417088 NCT03712293 NCT03626896 NCT04446416	NCT04526262 NCT04118764 NCT02986932 NCT03739905 NCT03119961 NCT03671889	NCT04370665 NCT03608553	NCT03321487

the BBB (Arvanitis et al., 2012; McDannold et al., 2012; O'Reilly & Hynynen, 2012). This observation inspired the development of PCD-based feedback control strategies to adjust the ultrasound output and maintain nonlinear oscillations of cavitating microbubbles in a predefined range to achieve the safe and predictable opening of the BBB (O'Reilly & Hynynen, 2012; Sun et al., 2017). However, it was recognized that translating the feedback control strategy would require monitoring the cavitating bubbles in multiple dimensions, which was beyond the capability of single-element PCD systems. To meet this need, scientists have utilized multielement transducer arrays to detect and map cavitating bubbles in two dimensions, a process that is known as passive cavitation mapping or imaging (PCI) (Choi et al., 2014; Haworth et al., 2017; Salgaonkar et al., 2009). Innovative hemispherical transcranial ultrasound phased arrays that enable driving and imaging cavitation in multiple dimensions have been constructed for brain applications (Crake et al., 2018; Deng et al., 2016; O'Reilly et al., 2014). Briefly, a dual-mode hemispherical sparse array was constructed from 5×0.4 mm piezoceramic disc elements arranged in pseudorandom fashion on a low-profile laser-cut acrylic frame. The sparse array was designed to fit between the therapeutic elements of a 230-kHz clinical transcranial ultrasound transducer array (InSightec ExAblate 4000), within the bore of a 3 Tesla clinical MRI scanner. With the use of thickness and radial resonance modes of the piezo discs, the sparse array is capable of both B-mode imaging at 5 MHz for skull localization, as well as passive reception of acoustic emissions from cavitating (i.e., nonlinearly oscillating and collapsing) microbubbles. The transmit and receive zones for the sparse array can be steered throughout a volume of tissue, thus allowing for 3D B-mode imaging and volumetric passive cavitation mapping (O'Reilly et al., 2014). The hemispherical array was combined with contrast-enhanced MRI to guide cavitation-induced opening of the BBB in a volume of brain tissue (Jones et al., 2018). This achievement must not be overlooked as co-registration of the passive cavitation images and contrast-enhanced MR-images in multiple dimensions are not trivial. The next step will be incorporating closed-loop feedback control of cavitation activity into the hemispherical phased array system, which will bring ultrasound-mediated BBB opening closer to clinical translation for brain cancer therapy.

Thermal Therapy

Focused ultrasound waves can be absorbed by solid tumors and converted to heat, resulting in a local temperature rise that can be leveraged for thermal therapy as shown in **Fig. 2A**. Thermal therapy can be divided into two categories: thermal ablation and hyperthermia. Thermal ablation is achieved by raising the local temperature beyond the threshold for protein denaturation and thermal coagulation (> 56 °C), which results in lesion formation at the transducer focus within seconds (Guthkelch et al., 1991). Hyperthermia is characterized by lower temperatures than thermal ablation (i.e., 42–45 °C) and has been leveraged for localized drug delivery in brain tumors. The use of noninvasive methods for monitoring and mapping the local temperature changes, such as magnetic resonance thermometry, has made ultrasound-mediated thermal therapy a viable option for treating solid tumors. Focused ultrasound is showing a great promise to achieve these thermal therapies and becoming one of the cost-effective and less toxic treatment modalities as compared to others such as microwave, radiofrequency, and electroporation.

Thermal Ablation

While FUS-induced thermal ablation is being explored as a treatment strategy for brain cancer, numerous clinical trials have proven its effectiveness against other types of cancer, including cancer of the breast, liver, and kidney (Cheung et al., 2013; Furusawa et al., 2007; Guan & Xu, 2016; Hsiao et al., 2016; Nabi et al., 2010; Orsi et al., 2010; Wu et al., 2003; Zavaglia et al., 2013; Zhao & Wu, 2010). The method has been approved by the FDA for the treatment of uterine fibroids for many years and recently garnered approval for prostate cancer therapy (Hesley et al., 2008; Hu et al., 2016; Laughlin-Tommaso et al., 2019; Lyon et al., 2020; Macek et al., 2020; Machtinger et al., 2013; Stewart et al., 2006; Sundaram et al., 2017; Verpalen et al., 2020). Compared to the aforementioned cancers, ultrasound-mediated thermal ablation of brain tumors is challenging due to the effect of the skull on ultrasound wave propagation (Hynynen & McDannold, 2004; McDannold et al., 2010). In addition to absorbing energy from the transmitted wave, the skull distorts the beam resulting in a change in the location and shape of the focus (Fry & Barger, 1978; Martin & McElhaney, 1971; Pinton et al., 2012). Scientists have demonstrated that this beam distortion, known as phase aberration, can be resolved with the use of ultrasound phased arrays. A beam with a distorted wavefront is generated intentionally by the phased array, which is "corrected" by the skull to achieve the desired focal shape and location in the brain. Phased arrays also allow for steering the transducer focus electronically, which increases the accuracy of focal placement in the brain. The FDA has approved phased array technology and noninvasive thermal ablation of the thalamus (i.e., thalamotomy) for the treatment of essential tremors (Elias et al., 2016; Ghanouni et al., 2015; Lipsman et al., 2013). Technological advancements in magnetic resonance-guided transcranial focused ultrasound system with electronic beam

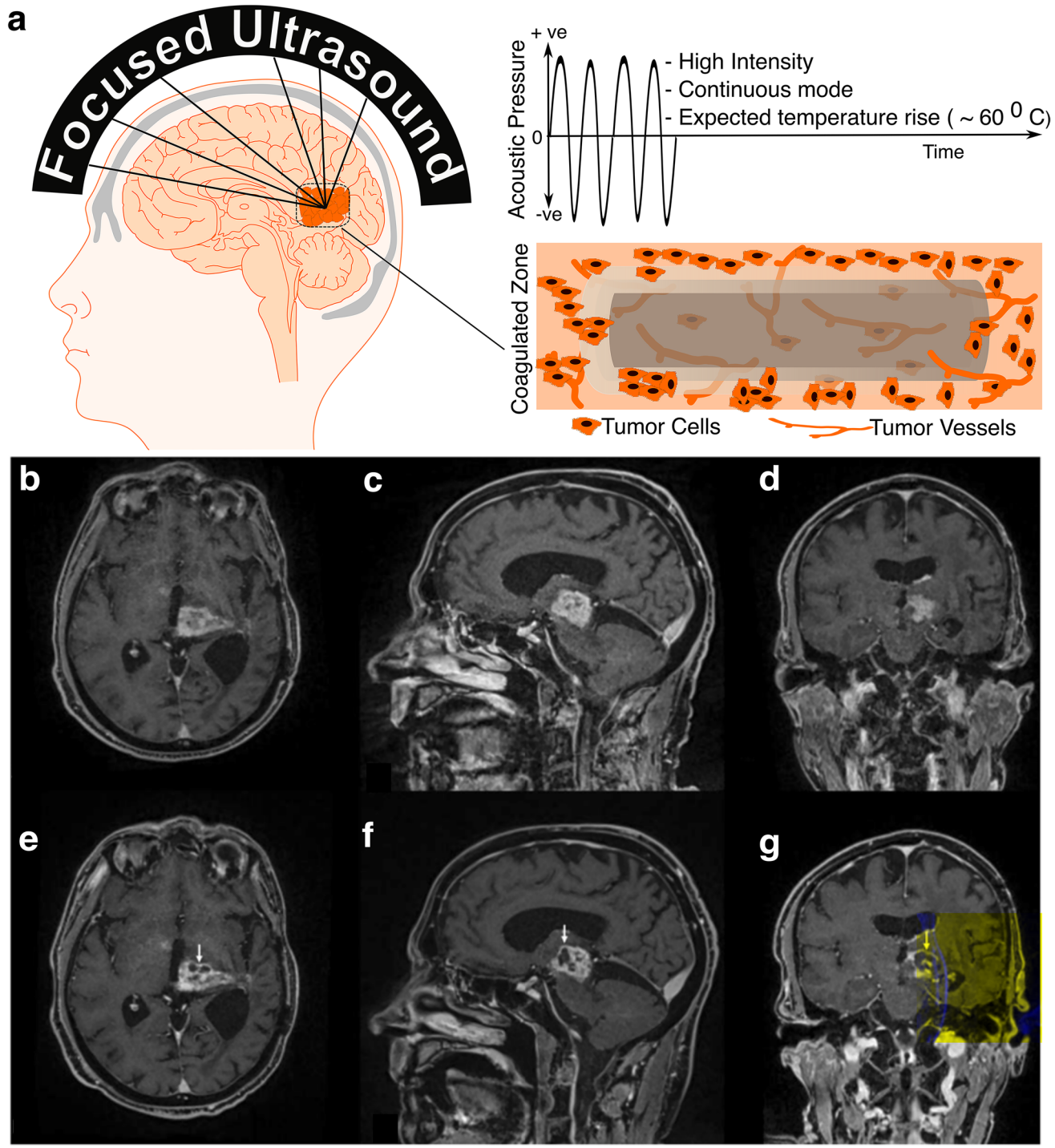

Fig. 2 Noninvasive thermal ablation in brain tumor patients using a clinical MR-guided focused ultrasound system. **A** Schematic of ultrasonic beam penetration through the skull to reach the desired region of the tumor (left), characteristics of the ultrasonic waves (high intensity in continuous mode) to achieve desire thermal dose (top-right), and expected tissue coagulation within the targeted tumor zone after the ultrasonic exposure (bottom-right). **B–F** Contrast-enhanced T1-weighted MR-images of brain tumor patients before (**B–D**) and after (**E–G**) ultrasound-mediated thermal ablation. A tumor (enhanced area in **B, C, D**) and the successful ablation of the peritumoral zone (arrow indicating in **E, F, G**) are visualized in all three different planes of MRI (Coluccia et al., 2014). **B–F** Modified from J Ther Ultrasound. 2014; 2: 17.; Copyright © 2015, Fandino et al.; licensee BioMed Central Ltd

steering capability helped to achieve tumor ablation without neurological deficits or adverse effects in a patient with recurrent glioblastoma for the first time (Coluccia et al., 2014), **Fig. 2B–F**. Currently, clinical trials evaluating the safety and feasibility of thermal ablation therapy in brain tumors are ongoing such as NCT01698437, NCT00147056, NCT01473485, and NCT03028246 (Table 2) but the results of these trials have yet to be released.

Hyperthermia

Ultrasound-mediated hyperthermia describes thermal therapy where the local temperature is raised within the range of 42–45 °C. Destroying solid tumors at these temperatures would require heating for tens of minutes, which is not ideal clinically. However, the temperature range is ideal for triggering drug release from temperature-sensitive liposomes, a biocompatible, biodegradable drug carrier. This approach for localized delivery of chemotherapeutic agents in solid tumors has been studied extensively in preclinical models (de Smet et al., 2010; Kneidl et al., 2014; Kong et al., 2000; Needham et al., 2000; Ta & Porter, 2013) and now has entered into the clinical trials for liver tumor (Amin et al., 2020; de Smet et al., 2011; Hynynen, 1991; Lyon et al., 2017; Santos et al., 2017; Staruch et al., 2015). In addition to triggering drug release, ultrasound-induced hyperthermia can promote relevant changes in the tumor micro-environment that could enhance tumor responsiveness to anti-cancer drugs. For example, hyperthermia can stimulate cancer cells to produce heat shock proteins, reduce the interstitial fluid pressure within solid tumors, increase tumor perfusion, change vessel permeability, and improve the delivery efficacy of anti-cancer agents in extracranial tumor models. Due to the effectiveness of the hyperthermia treatment in combination with temperature-sensitive liposomes, it is of interest for brain cancer. Recently, preclinical studies have reported that the hyperthermia-mediated delivery of an anti-cancer agent that was encapsulated within the temperature-sensitive carrier enhances the drug uptake within a targeted brain tumor model and holds a great promise for hyperthermia-mediated brain drug delivery (Arvanitis et al., 2019). Furthermore, hyperthermia can sensitize solid tumors to radiotherapy, thus reducing the cumulative radiation dose and mitigating radiotoxicity (Franckena et al., 2009; Prosnitz & Jones, 2002). Additional research is required to define the thermal dose needed for each of the aforementioned hyperthermia-induced bioeffects. This knowledge combined with MR thermometry for guidance could enable the use of ultrasound-mediated hyperthermia against brain cancer clinically.

Nonthermal Ablation: Mechanical Destruction of Tumor Tissue

The newest addition to the portfolio of ultrasound-based cancer treatment methods is non-thermal ablation. Whereas thermal ablation depends on tissue absorption of propagating ultrasound waves, non-thermal ablation results from damage caused by cavitation (i.e., oscillations and collapses of microbubbles driven by ultrasound). Several exogenous agents have been used to nucleate cavitation in vivo upon ultrasound exposure, including ultrasound contrast agents and liquid perfluorocarbon nanodroplets (McDannold et al., 2013, 2016; Peng et al., 2019; Sutton et al., 2015). The stresses generated by cavitation can disrupt blood flow within tumors, which can result in local ischemia and lesion formation (Peng et al., 2019). This treatment strategy is very appealing for clinical translation because it needs slightly higher pressure than the BBB opening threshold but lower than the acoustic intensity required for thermal ablation. Thus, there is less risk for skull heating and thermal damage, which reportedly can occur during thermal ablation of bulk brain tissue (McDannold et al., 2013, 2016). At much higher pressures, it is possible to drive intense cavitation activity and mechanically destroy target tissue, a process known as histotripsy (Cain et al., 2016; Kim et al., 2014; Sukovich et al., 2020; Tran et al., 2003). Preclinical data suggest that histotripsy with very short pulses (≤ 20 µs) transmitted through the skull can liquefy targeted brain tissue with

Table 2 FUS-based thermal ablation clinical trials for brain tumor treatment

Clinical Trials	Conditions	Locations
NCT01698437	Malignant Brain Tumors	MR-Center, University Children's Hospital Zurich, Switzerland
NCT00147056	Brain Tumor	Brigham and Women's Hospital Boston, Massachusetts, USA Swedish Medical Center Seattle, Washington, USA
NCT01473485	Glioma Metastatic Brain Cancer	Sunnybrook Health Sciences Centre Toronto, Ontario, Canada
NCT03028246	Benign Centrally Located Intracranial Tumors	Miami Children's Research Institute - Nicklaus Children's Hospital Miami, Florida, USA

minimal heat deposition within the intact skull. A non-thermal ablation is an attractive option for destroying brain tumors and warrants additional exploration particularly to evaluate tumor response to the treatment.

Technological Challenges for Clinical Translation of Ultrasound-Mediated Brain Cancer Therapy

The potential of emerging ultrasound-based methods for treating brain cancer has been demonstrated in numerous preclinical models. Clinical translation of these methods will require techniques to guide, monitor, and evaluate their effectiveness noninvasively. While MR thermometry can be used to quantify a thermal dose during ultrasound-mediated thermal therapy, methods to evaluate the outcome of the applied thermal dose are needed. For example, noninvasive techniques to assess tumor response to thermal ablation will facilitate clinical translation. Treatment strategies that depend on cavitation will benefit tremendously by the inclusion of methods to monitor and map the cavitation activity. Passive cavitation imaging is a breakthrough, but the technology needed to enable its use in brain applications is in its infancy. The sparse hemispherical phased arrays that are being developed significantly reduce the cost and complexity of the hardware needed for PCI in the brain. Combined with closed-loop feedback control algorithms, PCI and phased array technology will enable spatiotemporal control of cavitation with unprecedented accuracy. This can be leveraged for targeted BBB opening for enhanced delivery of anticancer agents or noninvasive debulking of brain tumors via mechanical ablation. Treatment evaluation involves confirmation of BBB opening; assessment of BBB opening volume; evaluation of any potential damage within treatment zone as well as along the ultrasonic beam path; quantification of drug transport from the vasculature into the brain parenchyma; and prediction of drug penetration, retention, distribution, and clearance. Different imaging modalities such as MRI, PET, and optical have been used to evaluate molecular transport through the BBB after ultrasound-mediated disruption (Burgess et al., 2014; Cho et al., 2011; Hynynen et al., 2001; Ye et al., 2018b; Zhu et al., 2018). Contrast-enhanced MRI does not require a craniotomy or radiolabeled tracers and thus is used most frequently for confirming ultrasound-mediated BBB opening as was noted in Fig. 1B–D. Dynamic contrast-enhanced MRI can be used to measure K_{trans}, the permeability transfer coefficient of molecules from blood plasma to the brain parenchyma, thus quantifying the change in BBB permeability. Furthermore, T2*-weighted MR-images can be used to assess the tissue damage. Numerous preclinical studies have demonstrated the utility of MRI-based imaging methods for evaluating changes in BBB permeability qualitatively and quantitatively, which has paved the way for clinical trials.

Conclusion

Thus far, different ultrasound-based approaches for brain cancer treatment have been investigated, including thermal ablation, hyperthermia, non-thermal ablation, and mechanical disruption of BBB for drug delivery. To date, BBB opening has entered into Phase 0/1 clinical trials for cancer treatments. Further studies are needed to determine the actual drug delivery efficacy, including the drug distribution, retention, pharmacokinetic, and clearance at tissue-levels, as well as its effects on tumor growth and patient prognosis in a personalized manner. The techniques hold great promise for the treatment of a wide range of neurological disorders. Advancements in technology and methodology for closed-loop feedback control of the ultrasound-induced bioeffects and evaluation of tumor response to treatment are on the horizon, which will bring these emerging treatment strategies closer to clinical translation.

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