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ABSTRACT

Hyperthermia therapy (HT) of cancer is a well-known treatment approach. With the advent of new technologies, HT approaches are now important for the treatment of brain tumors. We review current clinical applications of HT in neuro-oncology and ongoing preclinical research aiming to advance HT approaches to clinical practice. Laser interstitial thermal therapy (LITT) is currently the most widely utilized thermal ablation approach in clinical practice mainly for the treatment of recurrent or deep-seated tumors in the brain. Magnetic hyperthermia therapy (MHT), which relies on the use of magnetic nanoparticles (MNPs) and alternating magnetic fields (AMFs), is a new quite promising HT treatment approach for brain tumors. Initial MHT clinical studies in combination with fractionated radiation therapy (RT) in patients have been completed in Europe with encouraging results. Another combination treatment with HT that warrants further investigation is immunotherapy. HT approaches for brain tumors will continue to a play an important role in neuro-oncology.

Introduction

Hyperthermia is a term derived from the Greek terms υπέρ/ypér, meaning 'above', 'more' or 'over' and θερμό ς/thermós meaning 'hot'. Hyperthermia therapy (HT) is most often used to describe the therapeutic technique of induced temperature increase through thermal energy delivery [1,2]. Extreme hyperthermia, also known as thermal ablation, refers to the local application of thermal energy resulting in very high tissue temperatures which induces irreversible injury [3]. Both hyperthermia and thermal ablation procedures have been used for the treatment of many different types of cancers including breast, melanoma, liver, kidney, lung, cervical, bone, lymph node metastasis, and head and neck tumors [3,4].

In this article, we review the literature on the different evolving thermal ablative procedures and HT modalities utilized for the treatment of brain tumors by discussing relevant preclinical and clinical data that have shaped the current state of HT in the field of neuro-oncology. We focus on the burgeoning clinical literature on thermal ablation laser interstitial therapy (LITT) and the rapidly growing literature on magnetic hyperthermia (MHT) and nanoparticle-mediated photothermal therapy (PTT). Finally, we review outcome data with other modes of HT utilizing microwaves, ultrasound, radiofrequency and light energy as well as novel HT devices employed in the clinical setting.

Physiological response to HT

HT is categorized into whole body HT (WHT), regional HT (RHT) and local HT (LHT) [1]. WHT or total body hyperthermia (39.5–42 °C) causes systemic vasodilation, endocrine and immune changes [5]. WHT leads to increased VEGF, IL1 and IL6 expression, neutrophil production and neutrophil tumor infiltration [6]. HT should be distinguished from fever, as during HT any core body temperature increase will not affect the hypothalamic temperature set point [4,7]. RHT is achieved through an external heating device and refers to the heating of a localized tumor and its healthy surrounding tissue [8]. RHT aims for a heterogeneous temperature distribution (39 − 43 °C) and leads to heat-dependent physiological changes implicating metabolic and tumor vasculature alterations [6]. Tumor tissue with lower perfusion compared to the surrounding normal tissue is more sensitive than healthy tissue to increased temperatures, potentially due to the reduced heat-dissipating ability of tumor tissue [9]. Moreover, the lower than normal pH of the interstitial space of tumors, renders tumor tissue more sensitive to HT when compared to healthy tissue leading to targeted tumor cell death. Nevertheless, to the best of our knowledge, data related to the underlying targeted cancer death have not been reported [9]. For the treatment of brain tumors, HT is utilized locally (LHT) and the temperature increase is mainly confined to the target lesion whereas the core body temperature and the temperature of the surrounding brain

parenchyma remain largely unchanged [10]. LHT can display antineoplastic effects after a local temperature increase to 40–44 °C [11].

Cellular response to HT

HT can lead to intracellular and extracellular heat related changes that may facilitate cell necrosis and/or apoptosis [3,12,13]. Specifically, HT results in distortion of the cell cytoskeleton components, disruption of cell membrane permeability and increase in intracellular sodium levels [11,14]. Increased temperatures induce a number of mitochondrial structural alterations consistent with mitochondrial injury [15,16]. Heat cell injury following HT, may result in a significant decrease of intra- and extracellular pH [14], and denaturation of histones, chromatin as well as intracellular enzymes implicated in the regulation of cell cycle and apoptosis [17,18]. Moreover, HT induces alterations on the expression level with irregular RNA synthesis and damage of the Golgi apparatus [9,11]. HT upregulates the expression of heat shock proteins (HSPs), a family of protein chaperons expressed in cancer cells and involved in the cellular DNA injury response [19,20]. Of note, HSPs seem to be involved in the resistance of cancer cells to therapies including HT. However, their specific role is yet to be unraveled [7,21].

HT and chemoradiosensitivity enhancement

Besides direct cellular injury, HT can lead to augmented antineoplastic effects by enhancing adjuvant therapies particularly radiation therapy (RT) and chemotherapy. A number of experimental studies have reported a synergistic interaction between HT, RT and chemotherapy [22–24]. HT can enhance the effect of chemotherapy through increased substrate delivery and by rendering malignant cells more sensitive to chemotherapy. Increased local delivery of the chemotherapeutic substrate can be achieved as heat may increase regional cerebral blood flow (rCBF), enable disruption of the blood brain barrier (BBB), facilitate accumulation of carriers conjugated with chemotherapy in the tumor and modulate drug-carrier detachment [25–31]. HT disrupts DNA repair mechanisms, damages ATP-binding cassette (ABC) transporters, increases intracellular drug metabolism and induces apoptotic pathways [23,24,32–36]. When HT is applied, in addition to DNA repair disruption, the AKT signaling pathway is disrupted leading to radiosensitization. Particularly, after HT, phosphorylated AKT and kinases involved in the AKT pathway such as p70 S6K, RSK1/2 and pS6 have been found significantly reduced [32,37–41].

HT and immunomodulation

HT elicits innate and adaptive immune responses which may enhance its treatment effects [3,42,43]. Studies have found that HT may increase the cytotoxic activity of natural killer (NK) and CD8+ T cells against tumor cells [44,45]. Preclinical studies have demonstrated that immunotherapy following HT may enhance antitumor immune responses [46–49].

Check point inhibitor administration following MHT has been shown to enhance CD3+ T-cell recruitment and local tumor control in a metastatic lung tumor rodent model [49]. The possibility of similar immune involvement in the central nervous system during HT has ignited an exciting new area of brain tumor research [50,51]. Initial preclinical data have shown that HT in combination with checkpoint inhibitors (anti-PD-L1 antibody) can enhance the antitumor effect against glioblastoma (GBM) [52].

Extreme HT/thermal ablation

LITT

Magnetic resonance imaging (MRI)-guided LITT is now a standard alternative to surgical resection for certain patients with primary and metastatic brain tumors [53]. Tumors that have recurred despite multiple therapies as well as radiation necrosis (RN) represent ideal candidates for LITT [54,55]. LITT was introduced in the late 1980s by Bown et al. [56] while the first results of the application of LITT in neurological surgery where reported a few years later in 1990 [57]. Early technologic constraints related to laser probe size and the inability to monitor and control thermal delivery limited the adaption of this technology for patients [58,59]. Recent technological advancements have led to the enthusiastic resurgence of LITT in the field of neurological surgery [60–62]. Stereotactic platforms, robotic arms, neuro-navigation and optimized laser probes have allowed precise targeting of the lesion [63–65]. In addition, thermal damage estimate (TDE) algorithms and models such as the Arrhenius model have successfully predicted the extent of ablation preoperatively [66]. Intraoperative magnetic resonance thermometry has enabled real-time tissue damage visualization permitting accurate delivery of the prescribed thermal doses [67,68]. Currently, LITT is the most widely reported thermal ablation mode utilized for the treatment of brain tumors.

LITT can offer a survival benefit comparable to that of open surgery with possibly lower surgery related complications rates and decreased hospital stay [69,70]. LITT has been implemented in an awake setting without the requirement of general anesthesia [71]. An initial stereotactic biopsy can be performed during the procedure for a tissue diagnosis. A number of studies have reported how safe and efficacious LITT is considered for both diagnosis and cytoreduction [54,72]. During LITT, a laser catheter probe is stereotactically inserted under image guidance into the tumor through a small burr hole (Figure 1) [70]. Light energy is then administered to the tip and converted to heat within the tumor achieving tumor cell death due to local thermal ablation and HT of the surrounding tissues [73,74]. Two of the most commonly used LITT platforms include the NeuroBlate System (Monteris Medical, Inc.) and the Visualase Thermal Therapy System (Medtronic, Inc.) [74–77]. The NeuroBlate platform utilizes a CO_2 gas-cooled laser catheter to deliver laser energy in a temperature-controlled manner [75]. The platform is connected to a MRI treatment planning software that provides real-time thermal data displaying the extent of thermal energy delivery as thermal-damage-threshold (TDT) lines
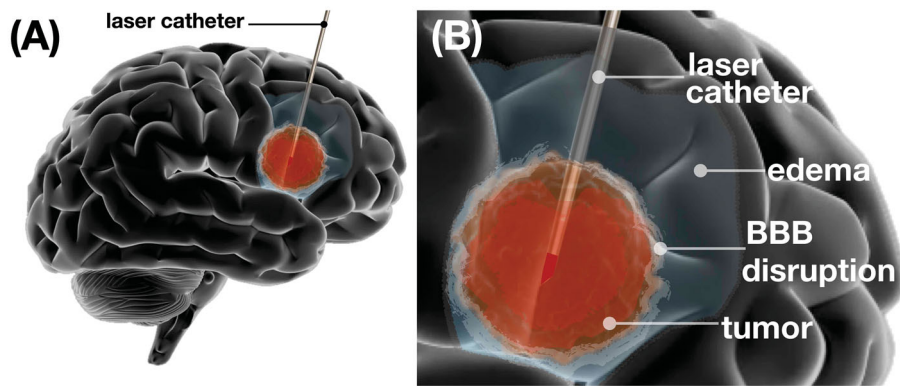
Figure 1. Brain tumor illustration demonstrating laser interstitial thermal therapy (LITT). (A) Schematic representation of intratumoral placement of laser catheter and brain tumor ablation. (B) Schematic representation of brain tumor ablation demonstrating post-LITT contrast enhancement consistent with LITT related blood brain barrier (BBB) disruption and LITT related perifocal edema.

[75]. The target volume is heated to an equivalent of 43 °C for at least 60 min and is considered to sustain coagulation necrosis. This time period has been selected according to empirical data proposing that the degree of tissue injury after exposure to 43 °C for 10 min is halfway between that at exposures of 2 and 60 min [78]. Tissue within this area may or may not undergo fatal thermal changes depending on a number of physiological factors [78]. Others have reported that this area is considered to have severe damage [74]. The outermost area corresponds to tissue exposed to 43 °C for at least 2 min, and is considered to have no permanent damage [75]. The Visualase system utilizes a laser catheter that is connected to a pump that circulates sterile saline to prevent overheating of the catheter tip and surrounding tissues [74]. Similar to the Neuroblate system, the Visualase platform is connected to MRI software displaying thermal data in real-time processed through Arrhenius model. Moreover, the platform has a safety temperature control system of automatic laser deactivation, based on predesignated temperature limits [76]. In the case of infiltrative tumors, the heat energy administered through LITT induces histologic changes which can be classified in three concentrically distinct areas consisting of a central area of necrosis-ablation zone (Zone 1), and two surrounding HT zones namely an area of granulation tissue surrounding the necrosis area (Zone 2), and an outmost area with the presence of viable tumor cells (Zone 3) [79]. Limitations of LITT include non-optimal treatment of tumors located adjacent to large blood vessels and/or cerebrospinal fluid (CSF) filled spaces such as ventricles or cisterns that may act as heat sinks [80].

LITT and BBB

LITT can increase the permeability of the BBB, in the area surrounding the ablation zone (HT zone) (Figure 1), providing a 4-week therapeutic window during which delivery of chemotherapeutic agents (CTAs) can be enhanced. Specifically, the highest permeability has been shown to take place within the first 2 weeks post-LITT while this effect wanes by weeks 4–6 [81,82]. It has been hypothesized that this LITT induced BBB disruption may facilitate immune cell migration through the BBB leading to an augmented immune response

against tumors. Based on this finding, multiple clinical trials have been launched to investigate the potential therapeutic benefit of checkpoint kinase inhibitors (CKIs) for the treatment of high grade gliomas (HGGs) when administered during the therapeutic window of BBB disruption following LITT [50,51].

Brain metastasis and RN

Currently, brain metastases and RN comprise the most common pathologies LITT is used for in neuro-oncology. A literature search which was limited to the last 10 years, identified 35 original studies reporting outcome data for 646 LITT-treated patients harboring brain metastases or RN [54,63,76,77,83–112]. LITT is most commonly employed for metastases that have recurred after surgical resection and RT. In one of the largest case series with LITT, brain metastases had the longest progression-free survival (PFS) compared to any other pathology (55.9 months) [54]. Recurrent and incompletely ablated brain metastases have been reported as the major predicting factors for post-LITT local recurrence [83]. Nevertheless, according to a recent systematic review, tumor control rates for recurrent brain metastases reach 80–100% at 3 months [113]. For lesions consistent with RN, LITT is commonly employed for patients that may not be good surgical candidates (e.g. deep-seated lesion location, advanced patient age, poor patient functional status) and have failed to respond to conservative treatments with corticosteroids [54,70,96,97]. Reported outcome data for these patients are promising with local control rates reaching 75% recurrence free [54].

Gliomas

LITT has been used for the treatment of HGGs in a number of studies [60,114–118]. A literature search over the last 10 years, identified 26 original studies reporting outcome data for 489 adult glioma patients treated with LITT [54,63,71,77–79,84,91,95,97–99,101,104,119–131]. The most commonly reported indications included recurrent GBM (e.g. multiple craniotomies, previous RT, high risk of wound dehiscence) [54,63,78,99,104,122,126,127,129,130] and newly

diagnosed GBM with unfavorable characteristics for surgical resection (e.g. deep seated, eloquent tumor location, advanced patient age, poor patient functional status) [54,63,99,104,119,120,124,125,127,129,130]. For recurrent GBM tumors, a large clinical series report a median overall survival of 12 months after LITT treatment [127,130] while in the newly diagnosed GBM patients the median overall survival ranges between 8 and 9 months [91,127,130]. Overall, the majority of the studies reporting data for recurrent GBM suggest that LITT is a safe treatment option which may provide a survival benefit with less operative morbidity and recovery time compared to conventional surgical resection [54,78,104,122,125–127,129,130]. In terms of newly diagnosed GBM, most of the studies report that LITT can increase overall survival in patients that would have otherwise only be eligible for biopsy and chemoradiation [54,63,99,104,119,120,124,125, 127,129,130]. Two available meta-analyses underscore the role of LITT for HGGs located in eloquent or deep-seated areas [132,133]. One meta-analysis compared LITT with surgical resection outcomes of patients with newly diagnosed and recurrent HGGs located in eloquent areas [132]. They reported that LITT-treated patients had increased cytoreduction rates and lower neurocognitive complication rates compared to patients who undergone surgical resection [132]. Another meta-analysis included only newly diagnosed HGGs patients in their study and reported overall survival 14.2 months indicating a comparable advantage among a subset of patients who would otherwise receive biopsy and chemoradiation without any cytoreduction. Nevertheless, both studies highlight the need of clinical trials to evaluate the role of LITT in HGGs. LITT has been also employed for low grade gliomas (LGGs) with promising results [63,97,119]. However, the lack of long-term follow-up data and controlled clinical trials precludes any assumptions regarding the role of LITT in this subset of patients.

Meningiomas

Similar to other recurrent brain tumors that have recurred despite multiple therapies, LITT has been described for patients with meningiomas that have failed surgery and RT [54]. Nine original studies have been published in the literature reporting data for 29 patients harboring meningiomas [54,63,71,77,84,98,131,134,135]. Although reported control rates are fairly promising for World Health Organization (WHO) grade I meningiomas, more aggressive (WHO grades II & III) meningiomas have higher recurrence rates [54,131,135]. However, all the studies reporting outcome data for patients with LITT-treated dural-based lesions are very small with a limited number of patients.

Pediatric tumors

LITT has also been advocated for newly diagnosed and recurrent pediatric brain tumors [136]. LITT-treated pathologies include: pilocytic astrocytomas [136–138], ependymomas [77,103,139], medulloblastomas [136,138], choroid plexus xanthogranulomas [136,138], subependymal giant cell astrocytomas [136,138,140–142], gangliogliomas [136,138,143], neuroectodermal tumors [77,103,144], gliosis [143], RN [143] and hypothalamic hamartomas [140]. Reported indications include deep-seated and recurrent, tumors [136,145]. The application of LITT for pediatric brain tumors has also shown promising outcomes, however, the number of patients treated and follow-up are limited. Futures studies are needed to further evaluate the role of LITT in pediatric neuro-oncology.

Hyperthermia modalities

MHT

MHT is a localized form of HT in which magnetic nanoparticles (MNPs) convert electromagnetic energy produced by an alternating magnetic field (AMF) into heat (Figure 2). This energy conversion is thought to occur through hysteresis losses and Brownian relaxation, a process in which frictional heating is generated by the physical rotation of the magnetic particles [146,147]. Even though the AMF is applied nonspecifically to the body, localized heating of the region of interest can be achieved by delivering MNPs directly to the tumor area [148]. This can be accomplished through targeted systemic delivery or by intratumoral administration. Newer modes of intratumoral delivery include the use of convection-enhanced delivery (CED) both in small and large animal models [149–154]. Notably, CED clinical trials have reported leakage of the infused substrate in off-target areas such as the subarachnoid space, ventricles and tumor resection cavities [155]. It has been shown that application of MNPs to different locations of the tumor may produce a more uniform temperature distribution across the lesion compared to laser catheter based treatment modalities such as LITT due to the distribution of MNPs which act as heat sources [156]. The heating capabilities of MNPs are largely determined by their size, shape, coating/composition, magnetic properties (e.g. saturation magnetization) and their specific absorption rate (SAR) (Table 1) [147,157]. In the context of MHT, SAR describes the power dissipation per unit of MNP in an applied AMF and largely defines their heating efficiency [158]. Magnetic iron-oxide nanoparticles (MIONPs) have been studied the most for MHT due to their superior biocompatibility and heating abilities with AMF [146,159–162]. Other MNPs synthesized from highly magnetic metals such as manganese, cobalt, iron or nickel have been described for MHT [163]. In addition to being excellent heating agents, multifunctional MIONPs also possess theranostic capabilities and can serve as contrast agents, drug-carriers and chemo-radiosensitizers [24,32,163–169]. There are many advantages to using MHT as a treatment for brain tumors and particularly GBM. First, the penetration depth of the AMF exceeds that of other activation modalities commonly used in HT (e.g. light or acoustic waves) allowing for the heating of deeply seated tumors without having to perform skin incisions or bone removal [163]. Coupled with the fact that MNPs have been shown to remain around the injection site for weeks, it is possible to perform multiple MHT sessions after single dosing [153,154,170]. In short, MNPs are a
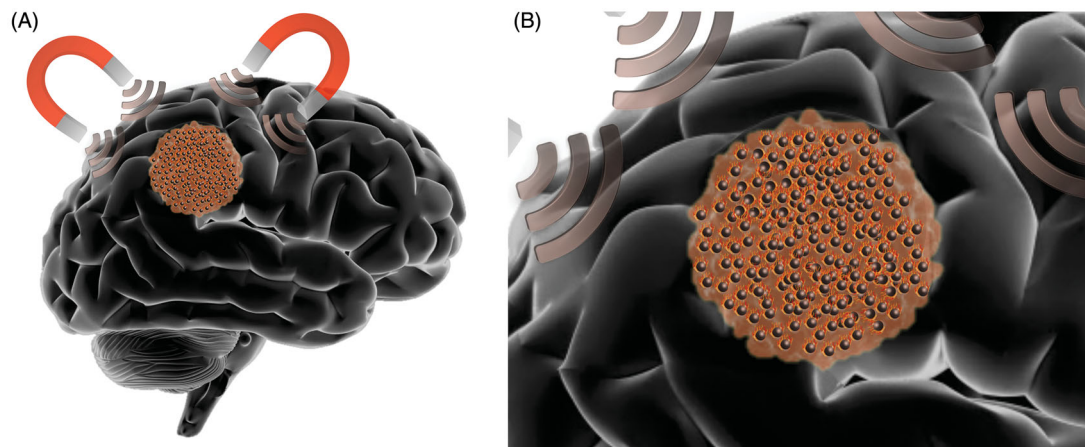
Figure 2. Schematic representation of magnetic hyperthermia therapy in the brain. (A) Alternating magnetic field is applied to the patient after local administration of magnetic nanoparticles (black spheres), generating highly localized hyperthermia. (B) Heat is produced *via* hysteresis losses and Brownian relaxation (a process in which frictional heating is generated by the physical rotation of the magnetic particle).

Table 1. Nanoparticle constructs utilized for magnetic hyperthermia therapy.

Study	Design	Brain tumor type	Nanoparticle construct
Adamiano et al. [184]	Preclinical	Human GBM (U87-MG + E297);	Superparamagnetic calcium phosphate nanocomposites (iron-doped hydroxyapatite and iron oxide nanoparticles coated with amorphous calcium phosphate)
Carvalho et al. [193]	Preclinical	Human GBM (U87-MG)	Magnetic iron oxide nanoparticles stabilized with carboxymethylcellulose
Fernandez et al. [183]	Preclinical	Human GBM (U87-MG)	Manganese-doped ferrite nanoparticles
Grauer et al. [204]	Clinical	GBM	Superparamagnetic iron oxide nanoparticles
Gupta et al. [172]	Preclinical	Rodent Glioma (C6)	Stevioside-coated iron oxide nanoparticles (STE-Fe$_3$O$_4$)
Pandey et al. [202]	Preclinical	Human GBM (U87-MG)	Iron Platinum alloy nanoparticles (FePt NP)
Rego et al. 2019 [171]	Preclinical	Rodent glioma (C6)	Aminosilane-coated superparamagnetic iron oxide nanoparticles
Shi et al. [190]	Preclinical	Human GBM (U87-MG); rodent glioma (C8-D1A)	Dual-functionalized liposomes (DOX@P1NS/TNC-FeLPs)
Tapeinos et al. [194]	Preclinical	Human GBM (U87-MG)	Lipid-based magnetic nanovectors (LMNVs)
Babincova et al. [195]	Preclinical	Human GBM (U87-MG)	Etoposide-carrying human serum albumin immobilized magnetic nanoparticles
Babincova et al. [191]	Preclinical	Rodent glioma (C6)	Thermosensitive magnetoliposomes containing SPIONs and doxorubicin
Jia et al. 2018 [189]	Preclinical	Human GBM (U251)	RGE-modified, SPION-, and Cur-loaded exosomes (RGE-Exo-SPION/Cur)
Lu et al. [188]	Preclinical	Human GBM (U251)	Cetuximab (C225)-encapsulated core-shell Fe$_3$O$_4$@Au magnetic nanoparticles
Nguyen et al. [173]	Preclinical	Human GBM (U87-MG)	Fluorescently labeled MPIC micelles (G1@Fe$_3$O$_4$)
Shirvalilou et al. [168]	Preclinical	Rodent glioma (C6)	5-Iodo-2-deoxyuridine (IUdR)-loaded magnetic nanoparticles (NGO/PLGA)
Zhou et al., 2018 [187]	Preclinical	Human GBM (U87-MG)	c(RGDyK) peptide PEGylated Fe@Fe$_3$O$_4$ nanoparticles (RGD-PEG-MNPs)
Alphandéry et al. [175,176]	Preclinical	Human GBM (U87-MG-Luc)	Magnetosomes (CM)
Hamdous et al. [177]	Preclinical	Rodent glioma (GL261 + RG2);	Chitosan (M-Chi), polyethyleneimine (M-PEI), and neridronate (M-Neri) coated nanoparticles
Le Fevre et al. [174]	Preclinical	Rodent glioma (GL261)	Magnetosomes-poly-L-lysine (M-PLL) and iron oxide nanoparticles
Ohtake et al. [196]	Preclinical	Human GBM (U87-MG + U251 + YKG)	Fe(Salen) nanoparticles
Zamora-Mora et al. [192]	Preclinical	Human GBM (A-172)	Chitosan nanoparticles (CSNPs)
Liu et al. [169]	Preclinical	Human GBM (U87-MG)	Ferromagnetic IMO nanoflowers (FIMO-NFs)
Shevstov et al. [185]	Preclinical	Rodent glioma (C6)	Superparamagnetic iron oxide nanoparticles conjugated with heat shock protein (Hsp70-SPIONs)
Pala et al. [186]	Preclinical	Human GBM (U87-MG)	Dextran-coated, aptamer-bound, aptamer-fluorescein magnetic NPs (NPAF)
Yi et al. [162]	Preclinical	Rodent glioma (C6)	Magnetic nano-iron
Jiang et al. [178]	Preclinical	Human GBM (U251)	Silver nanoparticles (AgNPs)
Meenach et al. [250]	Preclinical	Human GBM (M059K)	Magnetic PEG-based hydrogel nanocomposites
Zhao et al. [197]	Preclinical	Human GBM (U251)	Solar-planet structured magnetic nanocomposites (Amino silane coated magnetic nanoparticles)
Hua et al. [198]	Preclinical	Rodent glioma (C6)	Polymer poly[aniline-co-N-(1-one-butyric acid) aniline] (SPAnH) coated iron oxide nanoparticles
Liu et al. [179]	Preclinical	Human GBM (U251); Rodent glioma (C6)	Silver nanoparticles (AgNPs)
Liu et al. [156]	Preclinical	Rodent glioma (C6)	Magnetic nanoparticles
Maier-Hauff et al. [203]	Clinical	GBM	Iron-oxide (magnetite) nanoparticles

GBM: glioblastoma.

locally confined, remotely controllable tool for performing repeated HT.

Advanced MNPs

The surface coating of MNPs can increase the saturation magnetization of MNPs and enhance their heating capacity. For example, aminosilane coated MNPs were reported to display HT antitumor effects after a single MHT session using iron concentrations as low as 50 μg/10 μL [171]. Similarly, a stevioside coating can improve heating and enhance the antitumor effects when compared to noncoated MIONPs in vitro [172]. Instead of coating the NPs, one group encapsulated magnetite (Fe_3O_4) NPs within copolymer-based micelles as a way of increasing the colloidal stability and controlling the size and shape of the contained MIONPs. When used to perform MHT, these magnetic polyion complex micelles reduced cell viability in glioma cells at a concentration of iron 3 orders of magnitude lower than concentrations used in previous clinical trials [173]. Separately, a number of studies have used bacterial magnetosomes as an alternative for chemically synthesized MNPs. In comparison to conventional MIONPs, those studies report that bacterial magnetosomes can maintain tumor temperatures at 43–46 °C for longer, have higher antitumor efficacy in GBM cell lines, and require lower AMF amplitude to achieve target temperatures [174–177]. One potential issue MHT is facing is that high concentrations of MNPs are often required to reach the clinically needed thermal dose. Silver nanocrystals (AgNPs), though not MNPs themselves, have been shown to enhance the thermo-sensitivity, radio-sensitivity and apoptosis rate of glioma cells when administered in combination with MNPs due to silver's ability to cause reactive oxygen species (ROS) production and DNA damage. It has been proposed that using AgNPs and MNPs together may lower the concentration of MNPs necessary for effective MHT [178,179]. Another potential obstacle of MHT application is that internalization of MNPs has been reported to restrict Brownian motion and causes particle aggregation, both of which can lower the SAR and cause diminished heating [180–182]. To counteract this phenomenon, others have designed flower-like manganese-doped superparamagnetic iron-oxide nanoparticles (SPIONPs) functionalized with glioma specific $\alpha_v\beta_3$-integrin-ligands. Due to the unique shape and the doped-manganese, they were able to maximize SAR and induce significant intracellular heating and cell death mainly through non-apoptotic pathways [183]. However, other groups have reported that the cellular uptake of MNPs may be beneficial. In a recent study, MIONPs were conjugated with calcium phosphate and/or hydroxyapatite as a way of increasing their uptake by GBM cells. These internalized MIONPs reduced cell viability after MHT by a greater extent than their unconjugated counterparts that remained in the extracellular space [184].

Targeted delivery

Conjugated MNPs with cancer-specific moieties for targeted heating are currently being studied. MIONPs conjugated with HSP 70 were shown to selectively target CD40 receptors and decrease tumor mass in rat C6 glioma tumors when given intravenously [185]. Others have conjugated MNPs with anti-HER2 aptamers that required a 90-fold lower dose to achieve the same results as unconjugated NPs when performing MHT on HER-2 expressing cancer cells [186]. Multiple other MNPs conjugated with compounds specific for glioma targeting, such as c(RGDyK), cetuximab and neuropilin-1-targeted peptide were also shown to enhance MHT effects in vivo [154,187–189]. Loading of MNPs in vehicles that may cross the BBB may permit better targeting of tumors after systemic administration. MIONPs loaded onto targeted exosomes have been shown to cross the BBB and provide potent antitumor effects [189]. Others have demonstrated targeted delivery across the BBB by loading MIONPs into liposomes conjugated with the GBM specific cell-penetrating peptide, P1NS and the anti-GBM antibody, tenascin-C, to the liposomal surface [190].

Chemotherapy

HT has been proposed as a potential chemosensitizer in the brain due to HT-induced disruption of the BBB, increased blood flow and interference with DNA repair mechanisms [148]. The combination of MHT with chemotherapy may result in a more profound decrease in cell viability compared to chemotherapy or MHT monotherapy supporting the hypothesis of a synergistic effect between MHT and chemotherapy [191–197]. MNPs and CTAs can be delivered together using polymers [192,193,198], liposomes [190,191] or nanovectors made of both polymers and lipids [194] to minimize off-target toxicity, facilitate their cellular internalization and ensure their simultaneous delivery to the target site. Polymeric conjugates and carriers (often made from chitosan, carboxymethyl cellulose, polyethylene glycol (PEG) and polyaniline derivatives) are highly biocompatible, can stabilize MNPs in aqueous solutions, increase the solubility of CTAs, and have been used for the delivery of doxorubicin, 5-fluorouracil and carmustine [192,193,198–201]. Liposomal or lipid-based carriers can be designed to have phase transitions occur at specific temperatures (i.e. 43–46 °C) and have been used for heat-controlled release of doxorubicin or temozolomide (TMZ) [190,191,194].

Magneto-PTT

MNPs that can additionally convert light energy into heat have been utilized for the combination of PTT and MHT. This approach involves administration of MNPs followed by application of AMF and delivery of near infrared (NIR) light. Groups have developed MNPs capable of PTT to overcome the diminished heating of MNPs caused by cellular internalization. MNPs designed for both MHT and PTT were shown to decrease cell viability both in vitro and in vivo to a greater extent than those used for MHT or PTT alone [188]. In another study, novel FePt NPs were designed to perform magneto-PTT in combination with chemotherapy [202]. Chemo-magneto-PTT had a more pronounced antitumor

effect when compared to PTT monotherapy or PTT combined with chemotherapy.

Clinical studies

Two clinical trials within the past 10 years have evaluated the effects of MHT in combination with RT in humans. In the original study by Maier-Hauff et al. in 2011, 59 recurrent GBM patients underwent MHT in combination with fractionated RT [203]. Aminosilane coated MIONPs were injected intratumorally at an iron concentration of 112 mg/mL prior to MHT treatments. The median volume of magnetic fluid injected was 4.5 mL (range 0.5–11.6 mL), translating to a median dose of 0.28 mL of magnetic fluid per cm^3 of tumor volume. The thermotherapy generally consisted of six sessions with each session lasting 1 h. The median peak temperature measured within the tumor area during the sessions was 51.2 °C with a maximum of 82.0 °C. RT was performed immediately before or after thermotherapy and was fractionated (5×2 Gy per week) for a total dose of 30 Gy. As a first line therapy prior to MHT, 56/59 patients underwent surgical resection, 58/59 received RT and 51/59 chemotherapy. Patients were monitored at 3-month intervals with clinical follow up and CT scans (MRI was contraindicated due to the high concentration of MIONPs administered). The median overall survival (mOS) was 13.4 months for all patients suggesting that MHT in combination with fractionated stereotactic RT was clinically effective. Shortcomings reported in the study included the necessary removal of all metal implants within 40 cm of the treatment area (i.e. dental fillings) and the inability to use MRI for follow up due to MNP related artifacts.

In 2019, Grauer et al. reported on the effects of intracavitary MHT with RT on six recurrent GBM patients [204]. Similar to the study by Maier-Hauff et al., aminosilane coated MIONPs were used at an iron concentration of 112 mg/mL. Two to three layers of the MIONPs were applied onto the cavity wall following 5-aminolevulinic acid (5-ALA) fluorescence-guided resection of the tumor. After the administration of the MIONPs, six 1 h sessions of MHT were performed. The first thermotherapy session was performed 3 days before the start of RT after which both treatments were performed on the same day. All patients included in the study had previously been irradiated with a median interval of 8.1 months and a standard dose of 60 Gy. Four out of six patients were re-irradiated in the study at a fractionated rate of 1.8 Gy 5×/ week for a total dose of 39.6 Gy with two patients being excluded from re-irradiation due to maximum dose limitations. All patients had previously undergone surgical resection of their tumor. The mean follow-up time was 11.8 ± 9.3 months and the mOS and median PFS were 8.15 and 6.25 months, respectively. Patients treated at first recurrence had a mOS of 23.9 months whereas patients treated at second recurrence or later had a mOS of 7.1 months. One patient was still alive at the time of publication, 29 months after their last visit. However, 2–5 months post-MHT all patients experienced significant perifocal edema around the MNP deposits leading to clinical deterioration and prompting re-operation in four of the patients to remove NPs after

which their condition improved. Further immunohistochemical analysis revealed significant infiltration of CD3^{+}, CD8^{+} and CD68^{+} cells into the tumor sample after intracavitary thermotherapy. The reported survival benefits of MHT in combination with RT as well as the potential MHT-induced anti-tumor immune response are promising and warrant future investigation. The significant short-term cerebral edema related complications should be taken into consideration in the design of future trials, which should include closer monitoring and more comprehensive edema management.
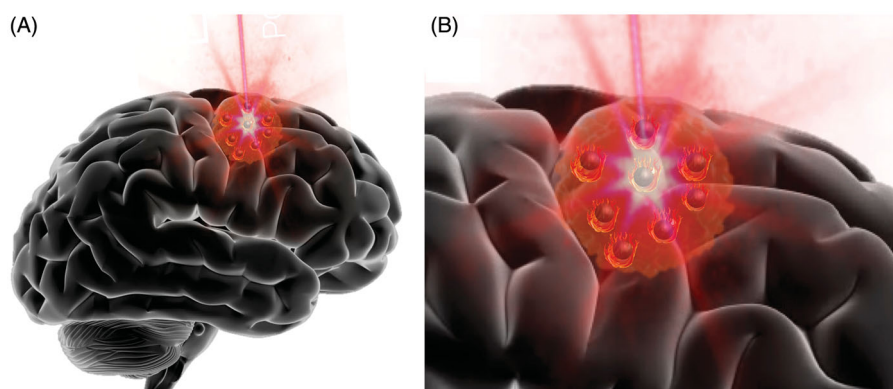
Nanoparticle-mediated PTT

Nanoparticle-mediated PTT is a rapidly evolving platform for HT applications which relies on the thermal properties of nano-scale photothermal agents (PTAs) that can act as local heat sources, and the penetrating properties of NIR radiation, which can reach the tumor and excite the PTAs (Figure 3) [205–207]. Nanoparticle-mediated PTT is a two-step therapy involving the local or systemic administration of PTAs followed by local application of light through NIR lasers. Light application to PTAs, results in localized surface plasmon resonance, through which PTAs absorb light at different wavelengths based on the oscillation of electrons on the surface and emit thermal energy increasing temperature in tumor tissue while preventing thermal damage to the surrounding normal brain [208,209]. PTT can be performed with pre-defined NIR light energy administration margins and temperature monitoring for further prevention of normal brain injury complications [210,211]. Different types of PTAs display different thermal properties according to their shapes, sizes and materials (Table 2). These characteristics reflect their heterogeneity on their electron number and configuration which in turn determine their light absorption and heat emission rates [208]. PTAs with high NIR absorbance rate that have displayed antineoplastic effects in GBM experimental models include carbon nanotubes [207,212–214], carbon nanodots [215], gold nanorods [209,216,217], gold nanoshells [217,218], gold nanospheres [219], gold nanostars [52,220], silk fibroin nanoparticles [221], silicon based nanoparticles [222] and iron-oxide carbon core-shell nanoparticles [210].

Targeted delivery of PTAs

In addition to their inherent heating properties, PTAs can be conjugated with antibodies, aptamers or other cell surface targeting compounds for their targeted delivery to the tumor [223]. Conjugation of PTAs with PEG chains and folate, has been shown to enhance their uptake by GBM cells and increase the therapeutic effects of PTT in vitro [224,225]. PEG has been also conjugated with peptide 22 polypeptide targeting the low-density lipoprotein receptor (LDLR). Peptide 22 polypeptide conjugation facilitated crossing of the BBB and delivery of the PTAs to the tumor in an orthotopic rodent glioma model [226]. CD133 monoclonal antibodies have been conjugated with carbon and gold PTAs for the

Figure 3. Illustration of brain tumor nanoparticle-mediated photothermal therapy (PTT). (A) Schematic representation of local NIR light application to a brain tumor after photothermal agents (PTAs) administration (black spheres). (B) Schematic illustration demonstrating NIR light excitation of PTAs within the brain tumor. PTAs absorb NIR light and emit thermal energy acting as local heat sources.

Table 2. Nanoparticle constructs utilized for photothermal therapy.

Study	Design	Brain tumor type	Nanoparticle construct
Casanova-Carvajal et al. [216]	Preclinical	Rodent glioma (CT-2A)	Gold nanorods biofunctionalized with CD133 antibody (B-GNRs)
Kwon et al. [165]	Preclinical	Human GBM (U87-MG)	Temozolomide/ICG-loaded iron oxide nanoparticles
Qian et al. [226]	Preclinical	Human GBM (U87-MG); rodent glioma (C6)	Pep22 linked polyethylene glycol (PEG) and oxidized nanocrystalline mesoporous carbon particles (OMCN)
Liu et al. [52]	Preclinical	Rodent glioma (CT-2A)	Gold nanostars
Shibata et al. [231]	Preclinical	Rodent glioma (9L gliosarcoma)	Phospholipid-conjugated indocyanine green (LP-iDOPE) nanoparticle
Zeng et al. [222]	Preclinical	Human GBM (NCH-421K); rodent glioma (C6)	TMZ-loaded porous silicon nanoparticles (TMZ/PSi NPs)
Han et al. [251]	Preclinical	Human GBM (U87-MG)	Two-dimensional Nb_2C MXenes
Lu et al. [188]	Preclinical	Human GBM (U251)	Cetuximab (C225)-encapsulated core-shell Fe_3O_4@Au magnetic nanoparticles
Qian et al. [215]	Preclinical	Human GBM (U87-MG)	Multicolor highly crystalline carbon nanodots (HCCDs)
Tsai et al. [235]	Preclinical	Rodent glioma (ALTS1C1)	Angiopep-2/cholesterol-conjugated poly(ethylene glycol) oleic acid-coated upconversion nanoparticles (ANG-IMNPs)
Wang et al. [210]	Preclinical	Rodent glioma (C6)	Iron oxide-carbon core-shell nanoparticles
Xu et al. [221]	Preclinical	Rodent glioma (C6)	Indocyanine green dyed silk fibroin nanoparticles (ICG-SFNPs)
Christie et al. [217]	Preclinical	Human GBM (ACBT); rodent glioma (P388-D1)	Macrophage loaded gold-silica nanoshells (AuNS) and gold nanorod (AuNR)
Yang et al. [252]	Preclinical	Human GBM (U87-MG)	Semiconducting poly (perylene diimide) (PPDI) and poly(ethylene glycol (PEG) tethered gold nanoparticles
Zhu et al. [253]	Preclinical	Human GBM (U87-MG)	Holo-Tf-indocyanine green (holo-Tf-ICG) nanoassemblies
Eldridge et al. [212]	Preclinical	Human GBM (U87-MG)	Short multi-walled carbon nanotubes (MWCNTs)
Kafa et al. [207]	Preclinical	Human GBM (primary astrocytoma type I)	Amino-functionalized multi-walled carbon nanotubes
Liu et al. [206]	Preclinical	Human GBM (U87-MG)	Novel Cs-based upconversion nanoparticles (UCNP-ICG-TOS-RGD)
Sheikh Mohamed et al. [224]	Preclinical	Human GBM (glioma)	Plasmonic fluorescent $CdSe/Cu_2S$ hybrid nanocrystals
Hao et al. [229]	Preclinical	Human GBM (U87-MG)	Docetaxel loaded ploy (lactide-co-glycolide) gold nanoparticles
Mohamed et al. [225]	Preclinical	Human GBM (glioma)	Ribotoxin-curin conjugated biogenic gold nanoparticles
Santos et al. [213]	Preclinical	Human GBM (U87-MG + U251 + LN229 + T98G)	Carbon nanotubes
Bidwell et al. [31]	Preclinical	Human GBM (U87-MG + D54); rodent glioma (C6)	Cell-penetrating peptides
Botella et al. [230]	Preclinical	Human GBM (42-MG-BA)	Mesoporous silica protected gold nanoclusters (Au@SiO_2)
Fernandez Cabada et al. [209]	Preclinical	Human astrocytoma (1321N1)	Gold nanorods
Day et al. [227]	Preclinical	Human astrocytoma (U-373 MG)	Polyethylene glycol-coated nanoshells and VEGF-coated nanoshells
Baek et al. [218]	Preclinical	Human GBM (ACBT)	PEGylated gold nanoshells
Wang et al. [214]	Preclinical	Human GBM (GBM-CD133$^+$; GBM-CD133$^-$ CSC)	Carbon nanotubes with CD133 monoclonal antibody
You et al. [219]	Preclinical	Human GBM (U87-MG)	Paclitaxel hollow gold nanospheres

GBM: glioblastoma; CSC: cancer stem-like cells.

targeting of CD133$^+$ glioma stem cells resulting in a profound decrease of tumor growth in both flank and orthotopic rodent glioma models [214,216]. Others have studied vascular endothelial growth factor (VEGF)-conjugated PTAs for targeting of the tumor vasculature in orthotopic GBM models [227]. VEGF targeting doubled the concentration of PTAs bound to tumor vessels and induced significant vascular injury [227]. Immune cells provide an additional method for the targeted delivery of PTAs. Monocytes and macrophages have been studied as potential vehicles, due to their capacity to phagocytize large doses of PTAs and their ability to cross the BBB and migrate toward tumor infiltrated tissues

[208,228]. Nevertheless, this method of targeted delivery has been only studied *in vitro* [217,218].

Chemo-PTT

The coadministration of CTAs and PTAs can be achieved *via* their conjugation or loading in nanoplatforms to implement combined chemotherapy and PTT. Moreover, NIR radiation and heat can modulate the release of the CTAs from these compounds increasing the drug bioavailability and enhancing therapeutic effects [219]. TMZ-loaded porous silicon nanoparticles (PSi NPs) have been studied in rodent GBM models [222]. TMZ has been also conjugated with MIONPs and studied *in vitro* where apoptosis was induced with GBM cells after application of NIR light [165]. Paclitaxel has been conjugated with gold nanospheres and studied *in vitro* and *in vivo* in GBM xenografts [219]. Application of NIR light triggered its release and augmented antitumor effects [219]. Curcin, a ribosome-inactivating protein has been conjugated with gold nanoparticles displaying high drug load capacity, pH-sensitive drug release and anti-proliferative effects in glioma cells lines *in vitro* [225]. Docetaxel has been loaded on gold nanoparticles and showed therapeutic effects against GBM cells *in vitro* and in a flank rodent GBM model *in vivo* [229]. Others have loaded campothecin (CPT), a topoisomerase inhibitor, on silica coated gold colloids which displayed cytotoxic effects in human glioma cells *in vitro* [230]. Finally, doxycycline (DOX) loaded in carbon nanoparticles showed therapeutic effects *in vivo*, in an orthotopic rodent glioma model [226].

Combined photodynamic/PTT

Photodynamic therapy (PDT) is a therapeutic approach involving the administration of a photosensitizer which upon the application of light, produces cytotoxic levels of ROS and triggers antitumor immune responses [148,231]. Most of the photosensitizers such as protoporphyrin IX (PpIX), 5,10,15,20-tetrakis(3-hydroxyphenyl) chlorin (mTHPC) and photofrin are excited with visible spectrum light which lacks the penetrating properties of NIR light [148,232,233]. Therefore, the laser optical fiber needs to be inserted into the target lesion for potent excitation of the photosensitizer. Upconversion nanoparticles (UCNP) have been employed to overcome this limitation as they emit visible spectrum light under NIR excitation and convert part of the administered light energy into heat [234]. Hence, UCNP act as both localized heaters and light sources enabling PTT and PDT effects [234]. UCNP have been utilized for PTT and PDT of GBM after NIR irradiation exhibiting pronounced antitumor effects *in vitro* and *in vivo* [206,235]. Moreover, some researchers have utilized indocyanine (ICG) conjugated liposomal and silk fibroin nanoparticles that do not possess any light emitting properties coupled with NIR spectrum light and have reported substantial PDT/PTT effects in rodent GBM models without the use of UCNP or visible light application [221,231].
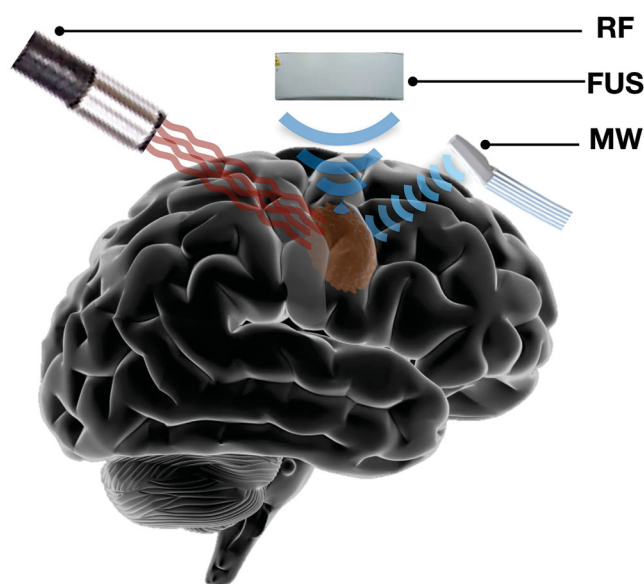
Figure 4. Schematic illustration summarizing some of the less common HT modalities that have been employed for brain tumor treatment. HT for brain tumors has been performed with ultrasound (US), radiofrequency (RF) and microwaves (MW).

Understudied HT modalities

HT has been performed with a variety of modalities utilizing ultrasound (US), radiofrequency (RF), microwaves (MW) as well as with novel devices using more traditional forms of energy to induce HT (Figure 4, Table 3). Focused US has been utilized for HT for brain tumors in the clinical setting as a potential minimally invasive alternative for brain tumors; however, complications rate were high and reported data were not sufficient to characterize its safety and efficacy [236–238]. Currently, US-based research paradigms are shifting toward bubble mediated US therapy or 5-ALA sonodynamic therapy (SDT) in which the effects of US ablation can be achieved with minimal temperature increases and thus prevent inadvertent thermal injury complications [239–242]. HT can be also utilized through RF generators, a technique also known as loco-regional electro-hyperthermia (EHT). RF EHT has been demonstrated in experimental glioma models enabling tumor temperature increases from 42 to 45 °C [14,243]. RF EHT has been employed in a canine model that studied the heat mediated local release of vehicle conjugated chemotherapy. RF after administration of temperature sensitive liposomes conjugated with doxorubicin demonstrated heat mediated local release of the chemotherapeutic substrate [244]. Furthermore, two studies have reported clinical EHT data. A Phase I clinical trial in patients with relapsed HGGs studied EHT with combined administration of nimustine. According to the reported data, the efficacy of EHT is not clear. Authors reported very high rates of edema related complications and thus suggested a phase II trial to further determine the effects of EHT [245]. The second study reporting clinical data was a retrospective study comparing a cohort of 54 patients with recurrent GBM who received EHT and TMZ with a cohort of patients who only received TMZ. Authors reported that the combination of EHT and TMZ significantly improved mOS [246]. HT has also been used with

Table 3. Understudied HT modalities for the treatment of brain tumors.

Study	Design	HT modality	Brain tumor type
Byun et al. [248]	Clinical	Novel hyperthermia device	BM
Schooneveldt et al. [247]	Clinical	M/W	PT
Bredlau et al. [244]	Preclinical	R/F	Canines with no tumors
Rozumenko et al. [249]	Clinical	LSTT	HGGs
Roussakow SV, 2017 [246]	Clinical	EHT	HGGs
Cha et al. [243]	Preclinical	EHT	Human GBM (U87-MG + A172)
Man et al. [32]	Preclinical	M/W	Human GBM (patient derived glioma stem cells specimens 3691 and 387)
Coluccia et al. [237]	Clinical	U/S	HGGs
James et al. [14]	Preclinical	R/F	Rodent glioma (9L gliosarcoma)
McDannold et al. [236]	Clinical	U/S	HGGs
Wismeth et al. [245]	Clinical	EHT	HGGs
Park et al. [238]	Clinical	U/S	HGGs

HT: hyperthermia; R/F: radio-frequency hyperthermia; EHT: electro-hyperthermia; U/S: ultrasound; M/W: microwave hyperthermia; LSTT: laser surface thermal therapy; BM: brain metastasis; HGGs: high grade gliomas; PT: pediatric tumor.

MW in combination with RT in an experimental rodent GBM model using patient-derived GBM cells showing a synergistic effect with an extended overall survival in animals [32]. Recently, a pediatric brain MW applicator has been developed along with models that aim to optimize MW administration. However, MW HT has not been implemented to the clinical setting [247].

Novel HT modalities in clinical settings

HT intracavitary devices have also been developed and reported in a phase I clinical trial [248]. This devise is comprised of a water pump that circulates hot water to a cavitated gold coated sphere. The sphere can be inserted in the tumor cavity intraoperatively after the tumor has been resected for HT of the cavity. Authors utilized this novel HT devise in patients with brain metastases, and reported a significantly lower local recurrence rate among the HT treatment group compared to the group that received tumor resection without subsequent HT. An alternative novel technique, termed laser surface thermal therapy (LSTT) has been used in patients with HGGs [249]. This technique involves thermal ablation of the post-resection tumor cavity through 808 and 1470 nm semiconductor lasers. The authors reported improved overall survival in HHG patients treated with LSTT in addition to microsurgical resection compared to patients who received only microsurgical resection. No LSTT-related adverse effects were reported.

Conclusion

HT is an important therapeutic modality for brain tumors that can be combined with other treatments. Multiple approaches exist for HT that include catheter implantation, MNPs and other agents. Currently, catheter-based LITT is the most common thermal ablation approach performed in brain tumor patients. LITT is a powerful, minimally invasive cytoreductive alternative that relies on MR imaging and real-time MR thermometry. The most rapidly evolving area in HT is the use of MNPs and AMF that can augment the effect of HT while sparing heat-related injury in the surrounding brain. More advanced MNPs with greater heating capacity and better tumor targeting schemes will provide the basis for future brain tumor treatments. Initial MHT clinical studies with early generation MNPs have been performed in Europe with encouraging results in combination with RT. The combination of thermal delivery with adjunct immunotherapeutic treatments is highly promising and warrants further investigation. Translational studies and carefully designed clinical trials are needed to continue the advancement of HT for treatment of brain tumors.

Disclosure statement

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