

Review

Fighting Fire with Fire: The Revival of Thermotherapy for Gliomas

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Abstract. *In 1891, an orthopedic surgeon in New York noted the disappearance of an inoperable sarcoma in a patient after a febrile illness. This observation resulted in experiments assessing the utility of heat therapy or thermotherapy for the treatment of cancer. While it initially fell from favor, thermotherapy has recently made a resurgence, sparking investigations into its anticancer properties. This therapy is especially attractive for glioblastoma multiforme (GBM) which is difficult to target due to the blood-brain barrier and recalcitrant to treatment. Here we briefly review the history of thermotherapy and then more methodically present the current literature as it relates to central nervous system malignancies. Recent developments show that heat is preferentially cytotoxic to tumor cells and induces cellular pathways which result in apoptotic and non-apoptotic death. Techniques to induce hyperthermia include regional hyperthermia by water bath, focused ultrasound, radiofrequency microwaves, laser-induced interstitial thermotherapy, and magnetic energy. The recent revival of these therapeutic approaches and their preliminary outcomes in the treatment of GBM is reviewed. From bacterial toxins to infusion of magnetic nanoparticles, hyperthermia has the potential to be an effective and easy-to-execute adjuvant therapy for GBM. Hyperthermia for GBM is a promising therapy as part of a growing armamentarium for malignant glioma treatment.*

“Those diseases that medicines do not cure are cured by the knife. Those that the knife does not cure are cured by fire. Those that fire does not cure, must be considered incurable” Hippocrates, 370 BC (36, 42).

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Fighting fire with fire, therapeutic hyperthermia to treat cancer has been attempted at various times throughout medical history but with limited success due to barriers related to delivery and limitations of available technology. We are however standing at an exciting frontier of the technological future with innovations in electromagnetic wave delivery, nanotechnology, and molecular and cellular biological understanding of cancer, which will translate into promising methods of using therapeutic hyperthermia. In this review, we describe the history of hyperthermia for the treatment of cancer, current hypotheses around its mechanism of action, and the application of modern technologies, including nanoparticles, to deliver thermotherapy for brain cancer, and review the current published clinical trials utilizing thermotherapy to treat brain tumors.

In 1891, Dr. William Coley, an orthopedic surgeon at New York Memorial Cancer Hospital, observed the complete disappearance of a recurrent inoperable sarcoma after the patient developed a febrile streptococcal infection (36). He then began experiments with systemic hyperthermia using “bacterial toxin therapy” for cancer and published the results of 10 patients in 1893 in the American Journal of Medical Science (18). Despite his reported success, others could not duplicate his work. Eventually, hyperthermia (fever toxin) for cancer was listed on the infamous unproven cancer treatment method list of the American Cancer Society [cited in (36)]. Therefore thermotherapy for cancer fell by the wayside with the discovery of radiation and chemotherapy.

During the past few decades, the rise of therapeutic options has resulted in an end to the nihilism associated with cancer, including glioblastoma multiforme (GBM). Due to the infiltrative nature of GBM and lack of a cure, traditionally these patients were sent home to die without any attempt to treatment. The use of surgical resection, steroids, radiation, and chemotherapy has resulted in improved survival and quality of life in many patients. Bolstered by these small improvements in survival, new enthusiasm has arisen to further investigate the pathogenesis of GBM and develop alternative therapies. This invigorated research effort

has led to re-discovery of hyperthermia therapy. Cavaliere *et al.* were to propose that cancer cells may have selective sensitivity to heat in 1967 (15). Recently, new technologies such as nanoparticles have revived thermotherapy for a wide variety of cancer types. This therapy is especially attractive for GBM which is recalcitrant to current treatment.

Methods

We performed a non-structure literature review of thermotherapy as it relates to the treatment of central nervous system tumors in general and gliomas specifically. First a targeted search was performed beginning with key articles known to the authors and a Web of Knowledge (Thomson Reuters) relevance search. Citations from these publications were assimilated as appropriate. Secondly a PubMed search was performed for "thermotherapy" and "glioma" in any search field. This resulted in 291 articles. All English, primary source material was included if the study used at least one form of thermotherapy and one *in vivo* or *in vitro* system relevant to the central nervous system or was a human clinical trial.

Mechanism of Action

How hot is hot enough? In the 1970s, research based on rodent work revealed elevated temperatures resulted in cancer cell death in culture (23). The degree of killing varied with only a 0.5°C change in temperature. Moreover, thermotherapy potentiated radiation effects on both normal and cancer cells *in vitro* (20, 62). Efficacy of heat for cancer was related to the cellular oxygen and pH of the microenvironment. Hypoxic cells and cells at a lower pH were found to be more sensitive to thermotherapy (6, 20, 61). These results implicated the cellular environment as the cause of increased sensitivity of tumor cells to heat compared to normal tissue. In laboratory studies, hyperthermia is preferentially cytotoxic to hypoxic glioma cells (77). Moreover, hyperthermia is attractive as part of multimodal treatment for GBM. When combined with mitomycin C or adriamycin, hyperthermia was synergistic in its effects (77).

Hyperthermia does not function indiscriminately though. A rodent sarcoma study examining hyperglycemia/hyperlactacidemia/hyperthermia effects on tumor growth found that treatment resulted in tumor remission in 50% of animals. Conversely, the animals that did not have remission had almost no effect at all (55). Subsequent research did show that human cancer cells had different temperature thresholds for killing using heat compared to rodent cells. Amour *et al.* found that human cancer cells *in vitro* had increased cell death, halt of proliferation and cell-cycle perturbations at 41°C, compared to rodent cells which responded to temperatures at 43°C or above (2).

The mechanism for the effect of hyperthermia on cell death is also unclear. In an attempt to elucidate the major pathways involved, Borkamo *et al.* performed microarray analysis of

rodent glioma tumors resected after treatment with a regional water-bath to 43°C. Total gene expression analysis revealed wide-ranging effects on genes involved in apoptosis, transcription, immune system, angiogenesis, metabolism/protein modifications, differentiation, cell signaling, response to stimulus, transport and cytoskeleton (8).

Inducing apoptosis. *In vitro* work has demonstrated hyperthermia to 41°C results in increased apoptosis when exposed to cytotoxic cytokines such as CD95L or APO2L (inducers of apoptosis *via* caspases and mitochondrial cytochrome *c*) (33). Fukami *et al.* investigated the relationship between apoptosis-inducing factor (AIF) and apoptosis under various thermal conditions (43, 45, and 47°C) using four p53 wild-type or -mutant human glioma cell lines (A172, T98G, U251MG, and YKG-1). They demonstrated that hyperthermia resulted in the AIF translocating from the mitochondria to the nucleus and AIF-positive cells and apoptotic cells increased in temperature-dependent manner. These findings support a role for AIF-induced apoptosis in hyperthermia (25).

In contrast, a different group found that temperatures up to 45°C did not independently induce apoptosis in human GBM cell lines, but resulted in transient growth arrest (46). The same group subsequently discovered that heat up to 43°C did potentiate adenoviral p53-overexpression-induced apoptosis in GBM cells *in vitro* (56). Regardless of its mechanism, these results support the notion that hyperthermia would be effective as adjuvant treatment for GBM. To this end it has been shown that water-bath emersion with hyperthermia to 43°C synergistically increased the toxicity of low-dose metronomic cyclophosphamide in a subcutaneous glioma model. More surprisingly in this study, 41% of treated animals had complete tumor regression (9).

Heat-shock proteins. Heating human glioma cells increases expression of certain heat-shock proteins such as HSP-27 and 72 (32). Heat-shock proteins have been shown to be cytotoxic to tumor cells in other cancer models. For example in a melanoma xenograft model, HSP-70 and inducible natural killer (NK) ligands synergistically promote activation of murine NK cells resulting in reduced tumor growth and prevention of metastases (21).

HSP-70 was also found to have an antitumor effect in the T-9 glioma rodent model. Following moderate hypothermia (43°C), HSP-70 resulted in growth inhibition for 24 h (39). These cells showed increased major histocompatibility complex (MHC) class I antigen presentation. *In vivo* these phenomena resulted in decreased tumor growth. In a later study, purified HSP-70 extracted from heated T-9 cells induced antitumor immunity in naïve T-9 rat glioma cells (40).

Some groups have attempted to take advantage of the role of HSP in hyperthermia. Treatment with NVP-HSP990, a

HSP-90 inhibitor, strongly sensitized U251 GBM cells to hyperthermia and ionizing radiation through augmentation of G₂/M arrest, mitotic catastrophe and associated apoptosis (53). Overall, HSPs use various pathways for their heat-induced effects on cancer cells. Moreover, HSPs are immunogenic and can be exploited for development of anti-tumor vaccines (10).

Improved drug delivery and targeting. Over the past 10 years, the majority of hyperthermia research has focused on targeted drug delivery. In its simplest form, hyperthermia can be used to disrupt the blood–brain barrier (BBB) and increase penetrance of a variety of molecules into tissues. Various tools are used to induce hyperthermia such as ultrasound. In one animal study, magnetic resonance imaging-monitored focused ultrasound (MRI-FUS) was used to transcranially disrupt the BBB in rat xenografts implanted with C6 glioma cells. The ultrasound treatment enhanced the penetration of *bis*-chloroethylnitrosourea (BCNU) in treatment animals up to 202%. Use of the focused ultrasound prior to BCNU administration reduced the volume of tumor burden and improved animal survival relative to untreated controls (47).

BBB disruption has also been used in conjunction with drug-carrying molecules to promote focused pharmacological delivery. In a mouse model of GBM, pulsed high-intensity FUS was used to disrupt the BBB and rupture intravenous microbubbles. Prior to each sonication, AP-1 liposomal doxorubicin was administered intravenously. This resulted in enhanced accumulation of the drug in tumor cells and significantly inhibited tumor growth compared with chemotherapy alone (82, 83). Similarly, Aoki *et al.* used hyperthermia to target thermosensitive liposomes in an *in vivo* rodent glioma model. Animals treated with hyperthermia and liposomes had a significantly longer overall survival time in comparison to controls (1). Later, adriamycin-encapsulated thermosensitive liposomes were used to target C6 glioma cells in a murine model. After intravenous systemic administration the heads of mice were heated in a water-bath at 42°C for 30 min. In the presence of hyperthermia, brain concentration of Adriamycin was 3.7-fold higher when using thermosensitive-liposomal adriamycin delivery than non-thermosensitive-liposomal adriamycin and 6.4-fold that of unconjugated adriamycin. Accordingly, the survival time of mice administered thermosensitive-liposomal adriamycin was longer than that in controls (27).

More recently, thermotherapy has also been used in conjunction with biopolymers. Elastin-like polypeptide (ELP) is a thermally-responsive biopolymer that forms aggregates above a specified temperature. Bidwell *et al.* modified ELP with cell-penetrating peptides to enhance delivery to brain tumors and mediate uptake across the tumor

cell plasma membranes and with a peptide inhibitor of c-Myc (H1). When combined with focused hyperthermia of intracerebral rat gliomas, the ELP-fused c-Myc inhibitor resulted in a 3-fold increase in tumor polypeptide levels and an 80% reduction in tumor volume, delayed onset of tumor-associated neurological deficits, and at least doubled median survival time including complete regression in 80% of animals (7).

Hyperthermia can also be used to temporally and spatial control transgene expression. Guilhon *et al.* in an *in vivo* subcutaneous glioma model showed selective local activation of green fluorescent protein under control of the HSP-70 promoter after MRI monitored focused ultrasound hyperthermia (28).

Hyperthermia Techniques

Early techniques to induce hyperthermia include crude methods such as whole-body hyperthermia and endotoxin-induced hyperthermia. Whole-body hyperthermia or limb hyperthermia are still undergoing testing and may be associated with significant risk (cardiac disorders, thrombocytopenia, permeability of capillary endothelia) (80). Modern applications of targeted hyperthermia include ultrasound waves, radiofrequency microwaves, laser, and magnetic energy.

Ultrasound. Hyperthermia with ultrasound can be achieved using non-invasive ultrasound but the attenuation and reflection from the skull has to be taken into consideration. This approach has not been described for hyperthermia in humans (3, 37, 38). Alternatively, a craniectomy allows for better ultrasound penetration and results in temperatures of at least 42°C in the tumor tissue (29, 60). This approach is obviously limited due to its need for invasive surgery to deliver thermotherapy. Most commonly focused ultrasound is combined with MRI thermomonitoring, referred to as MRI-FUS. This adds the ability to closely monitor the distribution and magnitude of thermal changes resulting from the ultrasound application. Other options include endovascular introduction of intravascular ultrasound (IVUS) to achieve hyperthermia in tumor tissue. IVUS for brain tumor hyperthermia has only been tested in feasibility studies (30, 31). A third method is the use of an echo-contrast agent. Levovist is an implantable ultrasound echo-contrast agent that can be administered either stereotactically or in the tumor cavity at the time of surgery to improve the accuracy of ultrasound for hyperthermia (52).

Multiple xenograft studies have been performed to demonstrate the efficacy of ultrasound-induced hyperthermia to reduce tumor burden or improve drug delivery in glioma models (71, 81, 84-86). This therapy is attractive because of widespread availability, low risk and the ability to combine

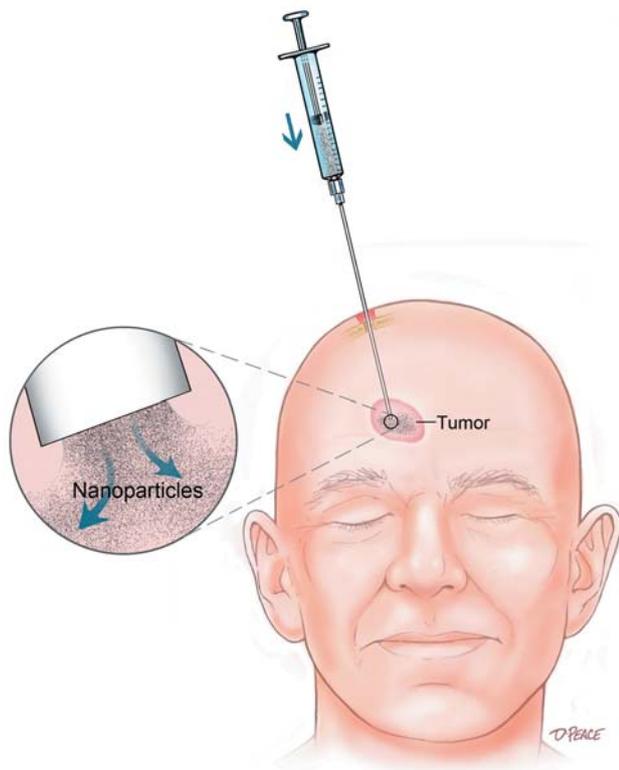


Figure 1. *Thermotherapy can be utilized by stereotactically injecting magnetically active substances such as iron oxide nanoparticles into the tumor parenchyma. These particles are then exposed to an alternating magnetic field to generate heat within the tumor.*

with other therapeutics. For example, animals with intracranial gliomas treated with ultrasound and 5-aminolevulinic acid (5-ALA) had lower mean tumor size compared to controls (58). Ultimately, human trials for ultrasound-induced hyperthermia will need to be conducted to determine safety and efficacy.

Microwave technology. Therapeutic hyperthermia from electromagnetic waves generated by radiofrequency or microwaves has also been described (68). In some studies this required stereotactic catheters to allow for interstitial brain tumor heating with helical coil microwave antennas (63, 67, 68). Other non-invasive methods include electro-hyperthermia with a transcranial capacitive-coupled radiofrequency heating device (Oncotherm) (79). In a study of 15 patients treated with Oncotherm, eight patients required reduction in dose (watts) due to overheating (79). Although attractive due to its non-invasive nature, this device is not Food and Drug Administration (FDA)-approved.

Several investigators have reported that a high concentration of drugs in a tumor can be achieved using local radiofrequency hyperthermia combined with intra-

arterial (IA) chemotherapy. Utilizing an isotransplanted intracranial C6 glioma model, Morita *et al.* infused either intra-arterial or intravenous adriamycin with or without interstitial hyperthermia using a homemade radiofrequency antenna that maintained the tumor temperature above 40°C. They found that the highest uptake of adriamycin occurred in animals receiving hyperthermia and intra-arterial injection, with these animals also showing increased survival time (54). Unfortunately, only one small feasibility study has been attempted in humans. This utilized concomitant radiofrequency hyperthermia and carotid injection of adriamycin, with limited toxicity, increased adriamycin concentrations, and promising therapeutic results(73).

Laser-induced Interstitial Thermotherapy (LITT). Lasers have also been described as a method for inducing brain hyperthermia (13). LITT uses high-powered lasers placed interstitially into the tumor. The lasers are MRI-compatible, allowing for image-guided treatment planning, targeting and monitoring (69). The laser treatment results in heat production and thermocoagulation. This option is both accurate and minimally-invasive, but needs further studies to establish safety and efficacy (14).

Early *in vivo* studies of LITT on transplanted glioma rodent models showed increased apoptosis restricted to residual neoplastic cells. However, marginal survival of tumor cells lead to a secondary outgrowth into the necrotic lesion adjacent to sprouting capillaries. The continued survival of neoplastic cells along the periphery of the laser's therapeutic range is a recurring problem with this modality (64).

As with the other hyperthermia therapies, LITT has also been used in combination with photoactivate photosensitizers. The essential feature this therapy is that *i.v.* administration of a photosensitizer selectively accumulates in neoplastic tissues, and, upon irradiation with light of a certain wavelength, produces particles toxic to this type of tissue. The first photosensitizer used *in vitro* to mediate photodynamic therapy and hyperthermia in human glioma and rat glioma spheroids was 5-ALA. LITT hyperthermia alone had no effect on spheroid survival at temperatures up to 49°C. When combined with 5-ALA, LITT had a synergistic effect at lower temperatures (40-46°C) (34). Photolon TM (Belmedpreparaty, Belarus) is a second-generation photosensitizer. After systemic administration of Photolon, irradiation of a specific area results in energy transfer from the excited photosensitizer molecule to molecular oxygen present in tissues. This process leads to production of singlet oxygen which interacts with lipids and other components of cell membranes thus leading to disruption of their integrity and, as a result, cell death. Using this photosensitizer Tserkovsky *et al.* recently showed that Photolon increased the cytotoxic effects of hyperthermia by 1.5- to 2.3-fold in C6-glioma cells *in vitro* (72).

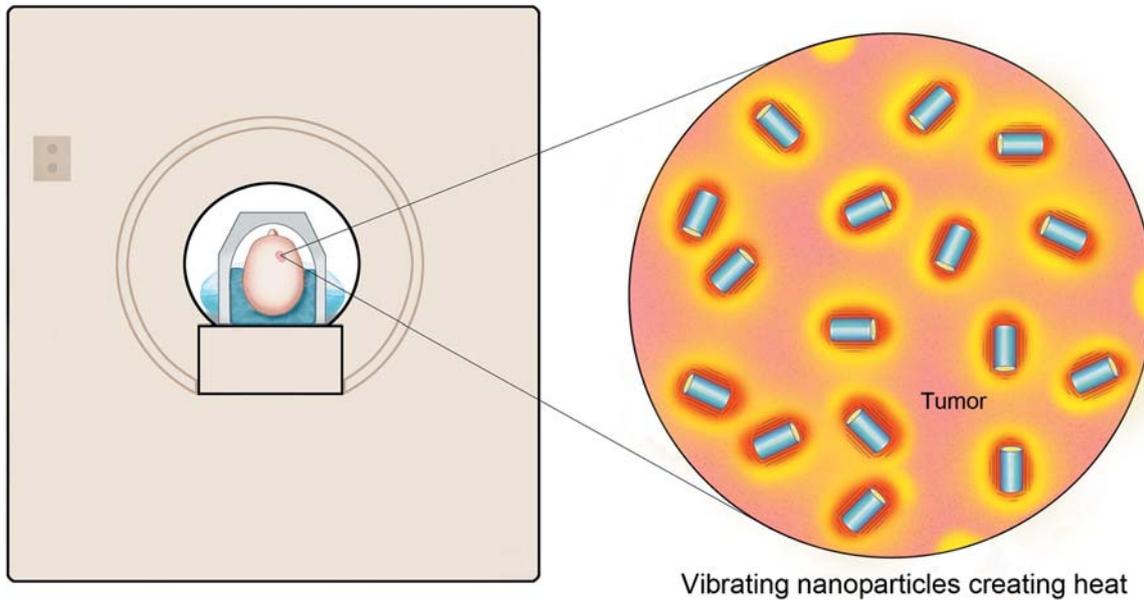


Figure 2. After implantation of iron oxide nanoparticles into the tumor, patients undergo regular MRI scans. This generates heat from the durable magnetically active nanoparticles, thereby treating the tumor.

Perhaps the most exciting use of LITT is for targeted drug release through nanotechnologies. Fernandez Cabada *et al.* irradiated gold nanorods with a continuous wave laser in glioma cells *in vitro* (22). Laser irradiation in the presence of gold nanorods induced a significant decrease in cell viability. Treatment compromised the integrity of the cell membrane instead of initiating the process of programmed cell death and resulted in increased death of malignant glioma cells. Similar work used macrophages as carriers for gold nanoshells and showed that macrophages could efficiently take up these nanoshells, infiltrate glioma spheres, and near-infrared irradiation resulted in almost complete growth inhibition of the glioma spheres (4). In an extension of this work, near-infrared-absorbing gold-silica nanoshells were antibody-tagged, so called immunonanoshells. These immunonanoshells exhibited *in vitro* activity against both medulloblastoma and high-grade glioma cell lines (5). Other work has used nanotechnology to thermally-ablate certain cell populations such as vascular endothelial growth factor-expressing cells (19) or CD133⁺ GBM cells (75). Furthermore the co-administration of nanoparticles and LITT has been facilitated by the development of fiberoptic microneedle devices (35).

Magnetic Nanoparticles (MNP). Magnetic hyperthermia consists of heat generated in a region of tumor through the application of MNPs subjected to an alternating magnetic field (Figure 1). The MNPs utilize several different mechanisms to convert the magnetic energy into heat energy. Some of the major heat-generating mechanisms include Neel and Brownian

relaxation and hysteresis loss (76) (Figure 2). Dedicated alternating magnetic field applicators are available outside of the US, including the MagForce unit in Germany and the Dai-Ichi unit in Japan (45). Temperatures are usually measured using fiber-optic thermometry probes placed in the tumor.

The goal of MNPs is a topographically-targeted therapy. Nanoparticle application can be *via* systemic delivery, magnetically-targeted, or convection-enhanced delivery. Systemic delivery is limited by the BBB, non-specific uptake of MNPs, and non-targeted distribution and systemic toxicity. The deposition and non-specific uptake of MNPs in the reticuloendothelial system after systemic intravenous administration can interfere with the delivery of MNPs to brain tumors (57, 59). Attachment of tumor-homing peptides to MNPs has recently been shown to permit better targeting of malignant brain tumors systemically in a rodent model (16). Magnetic responsiveness of the core of MNPs allows them to be guided by an external magnetic field. Interaction of locally administered MNPs with an applied external magnetic field can increase retention of MNPs at the tumor site. The magnetic targeting approach has been described in a rodent GBM model (16, 17).

One distinct advantage to MNPs is their stability over time, allowing multiple treatments without re-injection (43). In a recent post-mortem study evaluating the effects of hyperthermia using MNPs for GBM, the authors noted the nanoparticles were in areas of necrosis that were distinct from tumor necrosis (no pseudopallisading) and the nanoparticles were phagocytosed mostly by macrophages (74).

MNP-based hyperthermia has been evaluated for feasibility in animal models and human patients with malignant brain tumors. Dextran- or aminosilane-coated iron oxide nanoparticles have been used for thermotherapy in a rodent GBM model (43) and in a human clinical trial in patients with recurrent GBM (49, 50). Intratumoral injection of aminosilane-coated iron oxide MNPs and application of an alternating magnetic field before and after adjuvant fractionated radiation therapy significantly improved the survival of patients with recurrent GBM. However, a relatively high concentration of iron oxide MNPs, greater than 100 mg/ml, was required to achieve effective thermotherapy.

Outcomes from Human Hyperthermia Experiments

Hyperthermia has been tested for therapy of human brain tumors in some case reports, case series and in eight published trials. In 1994, a feasibility study tested hyperthermia *via* microwave antennas in 23 brain tumor patients (63). They found that four dipole antennas spaced 2 cm apart were capable of heating a volume of 5.9 cm × 2.8 cm × 2.8 cm to target temperatures 43°C or higher. In 1998, Sneed *et al.* published a phase II/III randomized trial of patients newly diagnosed with GBM treated with radiation therapy and hydroxyurea followed by brachytherapy alone or brachytherapy with hyperthermia (68). Hyperthermia was delivered using radiofrequency waves with microwave antennas implanted into the tumors. Sixty-eight patients were randomized and those in the hyperthermia group had significantly improved time-to-progression (33 *versus* 49 weeks) and overall survival (76 *versus* 80 weeks).

Fiorentini *et al.* performed a phase I trial of radiofrequency hyperthermia on 12 patients with biopsy-confirmed relapsed glioma. All patients were pre-treated with temozolamide-based chemotherapy and radiotherapy. Hyperthermia with short radiofrequency waves of 13.56 MHz was applied with a calculated average temperature in the tumors above 40°C for more than 90% of the treatment duration. One complete remission and but two partial remissions were achieved, with a response rate of 25%. The median survival of the entire patient population was nine months, with 25% survival rate at one year (24).

Wismeth *et al.* described a phase I study with 15 patients with malignant glioma treated with radiofrequency hyperthermia and nimustin (78). The hyperthermia was delivered using radiofrequency waves with microwave antennas implanted into the tumors. The median Karnofsky performance status was 80 at the start of the study and 60 at the end of the study. The trial was terminated due to progressive disease in 10 patients, non-dose-limiting toxicity in three patients, and other reasons in two other patients. Toxicities noted during treatment included local pain, increased hemiparesis, headache, fatigue, thrombocytopenia, leukopenia, vomiting and

confusion. Importantly, the authors identified several patients who had symptoms of increased intracranial pressure that were managed with steroids and mannitol.

Ram *et al.* published a phase I clinical study of MRI-FUS in the treatment of recurrent GBM. All patients underwent craniectomy to create an ultrasound window. Sonications were applied to induce thermocoagulation of the enhancing tumor mass and magnetic resonance imaging-generated thermal maps verified intratumoral temperature. MRI-FUS treatment resulted in immediate changes in contrast-enhanced T1-, T2-, and diffusion-weighted magnetic imaging and subsequent histological evidence of thermocoagulation. In one patient, heating of brain tissue in the sonication path resulted in a secondary focus outside the target causing neurological deficit. It was also noted that one distinct drawback of this method is its invasive nature, requiring creation of a bone window (60).

After a feasibility study in eight patients (44), Schwarzmaier *et al.* described LITT in 16 patients with recurrent GBM (65). All patients were treated with temozolamide concurrently with LITT. Using MRI guidance, a laser light fiber was placed in the tumor center. The tumor surrounding the fiber tip was heated to induce thermal necrosis of 2-3 cm radial diameter and heating of other tissue below the coagulation threshold. Laser irradiation was stopped when the temperature profile of the tissue reached a steady-state. The median survival after relapse of GBM was 9.4 months. After LITT, the median survival time was 6.9 months, but for the last six cases, survival was 11.2 months. The authors attribute this difference to a learning curve although the Karnofsky performance status scores and tumor volumes were worse for the first group of patients.

LITT was then used in combination with stereotaxis in 24 patients with recurrent glioma by Leonardi *et al.* (79, 80). The ablation procedure had to be stopped twice because of neurological deficit, and one major infection occurred. While there was no direct comparison to other therapies, survival times appeared comparable to historic controls. Due to the minimal invasive technique, these authors suggested that LITT might have a role in the treatment of small tumors, in eloquent deep-seated regions, as well as in older patients or patients with poor functional status. Another recent trial of stereotactically-guided LITT resulted in a continuous decline in metabolically active tumor volume within recurrent GBM, as assessed by serial positron emission tomography (26).

Carpentier *et al.* utilized LITT as a salvage therapy in four patients with GBM after total resection, chemotherapy and radiation therapy among patients who were not candidates for a second resection. Under stereotactic guidance, a fiberoptic applicator was inserted into the tumor and LITT was performed under continuous MRI. Adverse events included one transient supplementary motor area syndrome, one epileptic seizure, and one cerebrospinal fluid leakage. Post-procedure MRI showed a decrease in the size of all treated

tumors but recurrence was observed, with a median progression-free survival of 30 days. These authors offered LITT as an alternative in patients whom might desire a few additional weeks at the cost of a one-day procedure (11). This same group demonstrated local control of intracranial metastatic disease using similar methods (12).

Sloan *et al.* performed a phase I clinical trial of a LITT system in 10 patients with biopsy-confirmed recurrent GBM (66). LITT was delivered using a rigid, gas-cooled, side-firing laser probe and monitored using real-time MRI thermometry. Proprietary software, NeuroBlade, provided predictive thermal damage feedback and control of probe rotation and depth. The median survival was 316 (range=62-767) days. Three patients improved neurologically, six remained stable, and one worsened. Three out of 10 patients had a grade 3 adverse event at the highest dose. LITT has also been used for tumors other than glioma, with similarly mixed results (41, 48).

Interstitial brain tumor magnetic hyperthermia with implanted seeds was first described by Stea *et al.* (70). They treated 25 patients with malignant gliomas with surgery and radiation therapy followed by hyperthermia before and after brachytherapy. Hyperthermia was achieved by implanting ferromagnetic seeds. The only factors associated with survival were hyperthermia, patient age and histology (anaplastic astrocytoma *versus* GBM). They compared patient survival with a historic cohort treated similarly without hyperthermia and found that hazard of dying in the hyperthermia group was 0.53 [95% confidence interval (CI)=0.29-0.94].

Following a feasibility study (49), Maier-Hauff *et al.* published an efficacy and safety trial in 2011 of using nanoparticle-based hyperthermia for recurrent GBM (51). Fifty-nine patients with recurrent GBM underwent neuro-navigationally-controlled injection of iron oxide nanoparticles and subsequent heating with alternating magnetic field. This was combined with fractionated radiotherapy (30 Gy). After instillation of the particles, a head computer tomography evaluated the nanoparticle density to allow for calculating heat generation. The aim was to achieve no higher than 43°C beyond a 2 cm margin around the tumor. The median survival after recurrence was 13.4 months (95% CI=10.6-16.2 months) and from the time of initial diagnosis was 23.2 months. No serious complications were observed.

Overall, the application of thermotherapy for human brain tumors is still in its infancy. Serious side-effects (*e.g.* increased intracranial pressure and necrosis) have been described in human trials. Moreover, further translational studies need to be conducted to further elucidate the mechanism of action. The efficacy of thermotherapy which is a focal therapy for infiltrative tumors such as GBM is also still not understood. Realistically, thermotherapy has the potential for being a useful adjunct to other established therapies for brain tumors such as radiation therapy, chemotherapy and immunotherapy.

Conclusion

As hyperthermia therapy has evolved, this application has become an increasingly viable therapy for patients with brain tumors. From implanted catheters to infusion of magnetic nanoparticles, hyperthermia has the potential to be an effective and easy to execute adjuvant therapy for malignant glioma as the delivery techniques improve. With the establishment of safety, nanoparticles can now potentially be implanted at the time of initial resection, by passing the need for further surgery at the time of recurrence. Conversely, the enthusiasm for the improvement in delivery of heat must be tempered by the limited data in understanding the mechanism of action and efficacy of thermotherapy as a treatment modality for brain tumors. That being said, a substantial number of small human trials have demonstrated the relative efficacy of multiple hyperthermia modalities in the treatment of glioma. These studies suggest efficacy but have been limited in their scope and do report serious complications in some patients. While hyperthermia is not emerging as a stand-alone therapy, it does appear to have a role in non-operable disease or disease-refractory surgery, chemotherapy, and radiation. Further study of the efficacy of hyperthermia for GBM will be necessary.

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