Neurosurgical Applications of Magnetic Hyperthermia Therapy

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KEYWORDS

• Magnetic hyperthermia therapy • Magnetic fluid hyperthermia • Glioblastoma
• Magnetic particle imaging • Thermotherapy • Brain neoplasms • High-grade glioma

KEY POINTS

- Magnetic hyperthermia therapy is a highly localized and remotely controllable form of hyperthermia therapy that uses an alternating magnetic field to heat magnetic nanoparticles delivered to the tumor target.
- In addition to causing direct inhibitory and cytotoxic effects on tumor cells, magnetic hyperthermia therapy may enhance the effectiveness of standard radiotherapy and chemotherapy drugs used for high-grade gliomas through multiple mechanisms.
- Magnetic hyperthermia therapy is generally well tolerated and, when combined with radiation therapy, is associated with overall survival benefits in patients with malignant brain tumors; however, significant technical challenges limit its current clinical use in neurosurgery.
- As the nanoparticles may stay in position for weeks to months, multiple sessions of magnetic hyperthermia therapy can be performed over time, allowing for optimization of the timing of heat therapy with relation to radiotherapy and potential enhancement of the therapeutic ratio.
- Incorporating improved magnetic nanoparticle delivery methods, visualization of their distribution in the tissue, and noninvasive real-time thermometry into treatment planning is critical to advancing this treatment modality for patients.

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INTRODUCTION TO MAGNETIC HYPERTHERMIA THERAPY

Hyperthermia therapy (HT) is a treatment modality where the temperature of a region of the body or the whole body is elevated above baseline temperatures to treat the disease. Although HT can treat a variety of infections and diseases, the focus over the past half-century is to apply HT to treat various forms of cancer.[1–3] For HT to be effective, the temperature in approximately 90% of the target volume, referred to as T_{90}, must reach the minimum effective thermal dose.[4,5] Heating tumors to temperatures between 40°C and 45°C causes changes that are toxic to both tumor vasculature and the cancer cells themselves.[6–8] These changes include inducing apoptosis and protein damage, activating antitumor immune responses, and initiating vasodilation to enhance intratumoral blood flow that improves drug distribution and chemotherapy (CT) and increases tumor oxygenation for more effective radiation therapy (RT).[4,9–15] Heat-based therapies also transiently increase blood–brain barrier (BBB) and blood–tumor barrier (BTB) permeability, potentially allowing for lower dose CT to achieve therapeutic levels within brain tumors.[16,17] It is important to note that HT is distinct from fever in that HT, even when applied to the whole body, does not alter the hypothalamic temperature set point.[18] Although HT can be applied nonspecifically to the entire body, local hyperthermia produces fewer side effects.[19] Even still, optimal clinical implementation within the central nervous system (CNS) requires developing a practical means to appropriately target the delivery of heat and confirm the extent of temperature elevation with precise thermometry.

Magnetic nanoparticles (MNPs) represent a precision tool to perform highly localized HT known as magnetic hyperthermia therapy (MHT). After local delivery of the MNPs, an external alternating magnetic field (AMF) is applied to heat the MNPs Fig. 1. The potential mechanisms through which the MNPs convert the electromagnetic energy produced by the AMF into heat include magnetic hysteresis losses and Brownian relaxation, a process in which heat is generated by the physical rotation of the MNPs.[19,20] For spherical MNPs, the former mechanism dominates. The heating efficiency of MHT is largely determined by the size, shape, and composition of the MNPs, as well as the frequency and field amplitude of the AMF.[21] The specific loss power (SLP), or specific absorption rate (SAR), is a term used to characterize the heating efficiency of MNPs and is defined as the measured thermal loss normalized by mass or volume of magnetic material.[22,23] Though commonly used, SAR in this context is ambiguous and can lead to confusion. Heat absorbed by tissues exposed to electromagnetic fields is defined as SAR by the US Federal Communications Commission (FCC), which regulates electromagnetic radiation sources and their use.[24] Tissues exposed to the AMF during MHT will thus heat from two sources—directly from interactions with the AMF and indirectly from hysteresis heat produced by the MNPs. For clinical applications, we thus recommend the use of SLP when referring to MNP heat generation.

Common materials used to synthesize MNPs include manganese, cobalt, iron, and nickel. However, magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3) nanoparticles, collectively known as magnetic iron oxide nanoparticles (MIONPs), are the only MNPs approved for human use and have been extensively studied for MHT due to their heating capabilities and established record of biocompatibility and safety.[25–28] In addition to being excellent heating agents, MNPs possess additional therapeutic

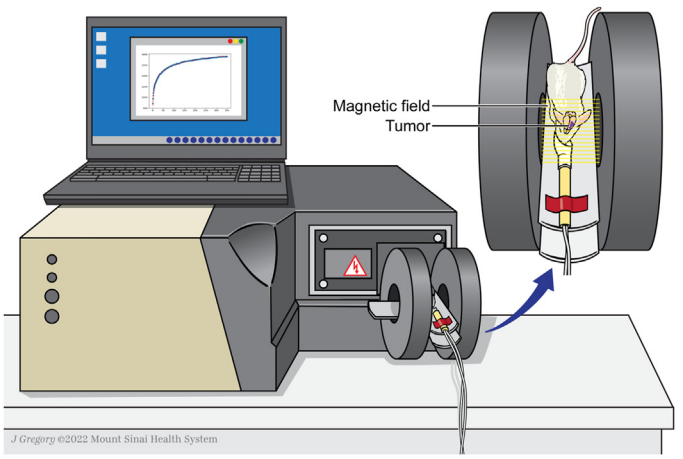

Fig. 1. Illustration of rodent MHT following intracranial MIONP delivery.

and diagnostic capabilities as contrast agents, drug-carriers and chemo-radiosensitizers.[29–37] Although MIONPs have significant therapeutic potential with an established safety record, toxicity is typically related to excessive or rapid iron release which depends on the nanoparticle coating, dose, and mode of administration.[38,39] The metabolic rate of the tissue into which they are deposited also plays a role in MNP-associated toxicity.[40–42] As the effectiveness of MHT is determined by the lowest thermal dose generated within the target region, it is important to design MNPs that generate significant heat at low concentrations to maximize therapeutic efficacy and minimize toxicity.[43]

Despite the non-specific application of the AMF to the body, localized MHT can be achieved by delivering the MNPs specifically to the tumor area, minimizing potentially harmful off-target heating. Local delivery of MNPs occurs either through targeted systemic delivery or direct intratumoral deposition, either by stereotactic injection or a technique known as convection-enhanced delivery (CED).[44–46] Targeted systemic delivery is most often accomplished by conjugating MNPs or MNP-encapsulating vesicles with cancer-specific moieties and administering them intravenously.[47–49] In addition, systemically delivered MNPs may be guided to the region of interest by applying an external static magnetic field to direct MNPs toward the tumor area.[50] Previous studies reported the use of a multi-trajectory installation of multiple MNP depots using neuro-navigation depending on the tumor location and geometry to obtain a more homogenous distribution.[51] CED is currently being studied as a method to deliver MNPs for MHT into the brain, as it bypasses the BBB and minimizes potentially toxic systemic effects.

Advantages of Magnetic Hyperthermia Therapy for the Treatment of Brain Cancer

In 1957, MHT was first explored as a treatment of cancer that had metastasized to the lymph nodes in a canine study.[52] Since then, MHT has been attempted *in vitro* and *in vivo* to treat a variety of cancers, including head and neck, pancreas, lung, prostate, breast, and brain.[4,53–61] In all cases, MHT can increase intratumoral temperatures, promote cancer cell death, and inhibit tumor growth.

In neurosurgery, MHT has been applied mainly to treat aggressive and therapy-resistant forms of brain cancer such as glioblastoma (GBM). As with other high-grade gliomas (HGGs), GBM is characterized by infiltrative growth into healthy surrounding brain tissue, as well as high levels of tumor cell heterogeneity.[62,63] Despite an intense standard of care therapeutic scheme consisting of maximal safe tumor resection followed by fractionated RT and concomitant and adjuvant temozolomide (TMZ) CT, prognosis remains poor for patients with GBM.[64–66] Recent FDA approval of 5-aminolevulinic acid (5-ALA) as an intraoperative imaging agent for fluorescence-guided surgery has significantly increased the average extent of tumor resection. However, due to its infiltrative nature and tendency to invade eloquent regions of the brain, total resection of GBM tumors remains unfeasible despite enhanced intraoperative tumor visualization.[65–72] Infiltrative tumor cells, including GBM stem-like cells (GSCs), that are left behind after tumor resection at the tumor margin and in the surrounding healthy brain often develop therapy resistance and are mediators of the invariable local and lethal recurrence that makes GBM refractory.[62,73,74] Despite decades of research, GBM remains one of the greatest challenges facing neurosurgical oncology due to limitations in drug delivery across the BBB and therapy resistance.[68–70]

Hyperthermia has been shown to enhance the cytotoxicity of RT to tumor cells. Since then, there have been numerous attempts to combine the two therapies and develop a feasible and effective approach in the clinical management of a variety of tumor types including GBM.[75] There are several distinct processes that may contribute to this biologic effect, although the dominant mechanism remains uncertain. HT initiates intracellular heat shock response(s) that disrupt the repair of radiation-induced double-strand DNA breaks.[76–80] HT also degrades or denatures the DNA repair pathway protein BRCA2.[81,82] Moderate HT, which increases perfusion, may also increase radiosensitivity by reducing the radioresistant hypoxic cell populations. More recently, HT has been investigated as a means to disrupt the BBB thereby enhancing drug delivery to brain tumors such that the effectiveness of DNA-damaging systemic drugs, such as TMZ and immune-oncologic agents, is improved.[83–86]

MHT has the potential to be highly relevant to future treatment of HGGs and was approved in Europe in 2012 as an adjuvant therapy for recurrent GBM in combination with RT.[87] In addition to providing all the advantages of HT (ie, opening of the BBB, induction of apoptosis, enhanced antitumor immune response), MHT additionally possesses unique features that overcome many limitations of other heat-based therapies commonly used to treat brain tumors. First, MIONPs radiosensitize GBM cells and induce

apoptosis in the GSCs thought to mediate local recurrence.[88,89] In addition, AMF penetration depth exceeds that of other activating modalities used in HT, such as light or acoustic waves.[25] Unlike other thermal therapies such as laser interstitial thermal therapy (LITT) which may only be performed intraoperatively, MHT can be performed after post-operative recovery and the initiation of RT in a minimally invasive manner through the application of an external AMF that reaches deep-seated tumors through skin and bone without incision.[25] Furthermore, MNPs can be administered at the time of surgical resection, sparing the patient an additional procedure to deliver the MNPs to the tumor site.[90] Moreover, MNPs remain in the brain around the delivery site for weeks to months, potentially allowing for multiple MHT sessions to be performed after a single delivery of MNPs.[89,91,92] Heating MNPs can also be precisely regulated by adjusting AMF parameters, and MHT produces a more uniform temperature distribution across brain lesions when compared with other thermal therapies such as LITT.[26,93] MHT provides a locally confined, remotely controllable, and easily reproducible form of HT.

PRECLINICAL APPLICATIONS OF MAGNETIC HYPERTHERMIA THERAPY IN NEUROSURGERY

Burton and colleagues[94] introduced the idea of applying a magnetic induction heating device to the brain using a ferromagnetic material. Since then, numerous preclinical studies have been conducted on brain cancer cell lines *in vitro* and *in vivo* primarily to (1) study efficacy, safety, and mechanism of action of MHT,[55,95–113] (2) develop and test new, more efficient and effective MHT nanoconstructs,[35,95–100,102,108–110,112,114–117] (3) assess MHT in combination with other therapies for brain cancer,[35,97,100,102,103,115,116,118] and (4) exploit the multifunctionality of MNPs for diagnostic and therapeutic applications.[35,47,97,100,103,115,116,119–122]

Although MHT is a highly localized form of HT, the nature of heat transfer makes spatial containment of energy deposition challenging, forcing further innovation. As a result, many researchers have focused on designing MNP constructs that heat well at non-toxic concentrations and target brain tumor cells for cancer-specific heating. One group showed that MIONPs encapsulated within positively charged liposomes had a high affinity for negatively charged glioma cells and generated intracellular hyperthermia *in vitro* that caused total cancer cell death after 40 min of MHT.[96] Another group used a calcium phosphate coating to increase MIONP internalization by GBM cell lines. They showed that allowing cancer cells to ingest the MIONPs for 24 h before AMF exposure significantly reduced cancer cell viability compared to when the AMF was applied immediately after MIONP administration but before internalization.[98] In addition, carboxymethyl-stevioside-modified magnetic dots demonstrating significant heating ability showed a profound anti-proliferative, anti-migratory, and anti-invasive effect on rodent glioma cells by inhibiting matrix metalloproteinase-2 and -9 expression, cell cycle arrest in the G0/G1 phase, and inducing oxidative stress upon re-exposure to an AMF.[95] These cancer cell-targeted applications of MNPs, and by extension MHT, may allow for lower concentrations of MNPs and lower power AMFs to be used for MHT. This is especially important when treating brain cancer due to the sensitivity of the brain and the potentially devastating effects that can occur from non-specific heating or MNP-related toxicity.

To further explore the clinical potential of MHT, several studies have focused on the possible synergism between MNPs/MHT and therapies currently used to treat HGGs. TMZ-loaded superparamagnetic NPs enhanced the cytotoxic effects of RT with a dose enhancement factor of 1.65.[103] In addition, this group showed that the combination of MHT, CT (TMZ), and RT caused enhanced anticancer efficacy compared to any monotherapy or two-modality combination therapy. Another group designed a temporary 2-5 cm balloon implant capable of being filled with MNPs and delivering high-dose rate brachytherapy for concurrent MHT and RT. They found that when using a human head phantom, they could heat tissue around the brain resection cavity at-risk for residual cancer cell presence between 40°C and 48°C and improve the uniformity of heating over previous multi-catheter interstitial approaches.[118] Many other groups have shown that MNPs can be effective drug carriers for CT and showed an added anti-tumor effect when giving MHT in combination with CT.[35,100,103,115,116] Finally, MHT in combination with photothermal therapy (PTT) was shown to be more effective than either monotherapy.[102] The therapies complement one another since although MHT is not limited by depth, it produces less heat per NP compared to PTT. On the contrary, PTT is limited by the depth penetration of the near-infrared light used to generate heat but can generate higher temperatures than MHT.[102]

Another interesting field of research is the use of bacteria-derived magnetosomes in lieu of chemically synthesized MNPs for MHT.[99,108–110] Magnetotactic bacteria naturally synthesize magnetic

iron oxide nanocrystals (magnetosomes) which, once purified and processed to remove harmful endotoxins, have excellent size, morphology, biocompatibility, and magnetic properties. Magnetosomes were shown to be more cytotoxic to cancer cells than healthy cells and had a higher antitumor efficacy than chemically synthesized MIONPs resulting in complete glioma tumor regression in some cases. This improved efficacy was likely because magnetosomes required lower AMF amplitude for effective MHT, displayed higher SLP, exhibited a less scattered distribution intratumorally, and were able to maintain tumor temperatures at 43-46°C for longer duration when compared to MIONPs at an equal iron concentration. Although magnetosomes offer several advantages over synthetic MNPs for MHT, their time-consuming and costly synthesis currently limits large-scale application.[123]

In addition to studying the ways in which various nanoconstructs can be applied for MHT, researchers have also focused on how MNPs may be used as dual therapeutic and diagnostic, or "theranostic," agents for brain cancer. Notably, MIONPs produce the highest relaxivity of magnetic resonance imaging (MRI) contrast agents known today, and numerous studies show that MNPs are effective MRI contrast agents when conjugated with cancer-specific moieties.[47,103,119] Similarly, one group found that systemically delivering MIONPs loaded into tumor-associated macrophages led to preferential accumulation of MIONPs at the tumor margin in rat gliomas, allowing for effective therapy and a clear delineation of the tumor border by multimodal imaging techniques.[122]

Optimal implementation of MHT requires verification of localization and persistence of the nanoparticles over time. Although MRI can be used for *in vivo* imaging of MIONPs, an emerging tomographic tracer imaging technique called magnetic particle imaging (MPI) offers many advantages over current MRI technology.[29] Briefly, MPI systems image MIONPs by generating strong magnetic field gradients. Within these gradients is a region of low magnetic field strength, known as the field-free point (FFP). As the FFP crosses a region containing MIONPs, the ensuing change in magnetization generates a signal that is used to create a high-resolution three-dimensional (3D) image by rastering the FFP through the sample volume, with no background signal from the tissue.[124–126] In a recent study, MPI showed higher sensitivity to detect MIONP-labeled cells than MRI and detected and quantified as few as 1×10^4 MIONP-labeled cancer cells dispersed throughout a mouse brain *ex vivo*.[120] Another advantage of MPI over MRI is that MPI can image MIONPs at concentrations typically used for MHT (50–100 mg of Fe per g of tissue). By contrast, when MIONPs exceed concentrations of 10^{-3} g Fe/g of tissue, they create a susceptibility artifact appearance on MRI that appears as a "black hole" that obscures tissue anatomy.[29] Further study of MPI is currently underway and has the potential to significantly advance the future clinical application of MHT.

CLINICAL APPLICATIONS OF MAGNETIC HYPERTHERMIA THERAPY IN NEUROSURGERY

Several clinical studies, both in the United States and internationally, have evaluated the use of MHT in human glioma patients. Characteristics of some are outlined in **Table 1**. Among the earliest was the study conducted by Iacono and colleagues,[127–129] which included a phase I clinical trial using adjuvant MHT in addition to RT in patients with either primary or recurrent HGGs (GBM or anaplastic astrocytoma). Twenty-eight patients received intratumoral nickel-4 wt.% silicon alloy ferromagnetic wire implants before 1 (11 patients) or 2 (17 patients) 60-min MHT sessions. The study found a median overall survival of 20.6 months, including 14.9-month overall survival for patients with GBM. Important to note in this safety trial were the three major complications found, including hydrocephalus secondary to edema from catheter implantation, pneumocephalus from failure to suture all scalp wounds after removal of the catheters, and intracranial hemorrhage at the time of catheter implantation. In addition, one patient died from treatment-related edema, who in retrospect was found to have too high of a ferromagnetic implant volume leading to a protocol change. In the cohort of 28 patients, 11 minor complications were observed, ranging from focal seizures to cerebral edema to neurological deficits. All minor complications were managed conservatively. The investigators were able to show a treatment response, with over 60% of temperature sensors in the tumor core, 35% of sensors at the tumor margin, and 3.5% of sensors in surrounding normal tissue exceeding 42°C. However, no significant difference was observed between the survival of patients in which tumor core temperatures exceeded 41.5°C and those in which lower temperatures were recorded. The authors concluded that although MHT in combination with RT may be an effective treatment option, significant morbidities were associated with this combination therapy. To better assess the effect of MHT, Stea and colleagues[130] conducted a

Table 1
Summarizing results from six clinical studies investigating magnetic hyperthermia therapy in combination with radiation therapy in high-grade gliomas patients with either primary or recurrent cancer.

Author (Year)	Journal (PMID)	Title	Primary Conclusion
Kobayashi et al,[131] 1991	J. Neurooncol. PMID: 1654402	Interstitial hyperthermia of malignant brain tumors by implant heating system: clinical experience	Safe and repeated MHT was possible in 23 out of 25 patients with malignant brain tumors with an overall response rate of 34.8%. No major side effects were observed. Degeneration of tumor cells, hemorrhage, vascular stasis, and thrombosis were seen in treated tumors adjacent to areas of coagulative necrosis around the ferromagnetic implant.
Stea et al,[128] 1992	Int. J. Radiat. Oncol. Biol. Phys PMID: 1429088	Treatment of malignant gliomas with interstitial irradiation and hyperthermia	Interstitial MHT of brain tumors with ferromagnetic implants is feasible and carries significant but acceptable morbidity given the extremely poor prognosis of this patient population. Preliminary survival analysis showed patients had a median survival of 20.6 months from diagnosis.
Stea et al,[130] 1994	Int. J. Radiat. Oncol. Biol. Phys PMID: 7928490	Interstitial irradiation versus interstitial thermoradiotherapy for supratentorial malignant gliomas: a comparative survival analysis	Multivariate analysis showed that MHT conferred a positive survival benefit as an adjuvant to RT. No difference was found in survival between 13 recurrent cancer patients treated with RT alone and 8 patients treated with MHT and RT.
Maier-Hauff et al,[51] 2007	J. Neurooncol. PMID: 16773216	Intracranial Thermotherapy using Magnetic Nanoparticles Combined with External Beam Radiotherapy: Results of a Feasibility Study on Patients with Glioblastoma Multiforme	MHT was generally well tolerated by all patients with minor or no side effects and signs of local tumor control were observed.
Maier-Hauff et al,[87] 2011	J. Neurooncol. PMID: 20845061	Efficacy and safety of intratumoral thermotherapy using magnetic iron-oxide nanoparticles combined with external beam radiotherapy on patients with recurrent glioblastoma multiforme	No serious complications were observed from thermotherapy using MNPs in combination with a reduced radiation dose. In 59 patients with recurrent GBM, MHT in combination with RT led to longer median overall survival following recurrence (mOS = 13.4 months, 95% CI: 10.6–16.2 months) compared with conventional therapies.

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Table 1
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Author (Year)	Journal (PMID)	Title	Primary Conclusion
Grauer et al,[90] 2019	J. Neurooncol. PMID: 30506500	Combined intracavitary thermotherapy with iron oxide nanoparticles and radiotherapy as a local treatment modality in recurrent glioblastoma patients	Intracavitary MHT combined with RT can induce a prominent inflammatory reaction around the resection cavity that might trigger potent antitumor immune responses.

follow-up study comparing MHT with RT to RT alone in patients with both primary and recurrent HGGs. In this study, multivariate analysis revealed that MHT conferred a positive survival benefit as an adjuvant to RT in patients with primary HGGs. However, in a subset of patients exhibiting recurrent tumors before treatment, the combination therapy provided no additional survival benefit compared to RT monotherapy.

Several international clinical studies were conducted over three decades to determine the effect of MHT, and to identify potential shortcomings of the intervention. In the early 1990s, Kobayashi and colleagues[131] performed between 10 and 46 sessions of MHT over a period of up to 23 weeks in 23 patients with malignant brain tumors. They found an overall response rate of 34.8% and reported nearly a doubling of response rate between untreated versus recurrent tumors (58.3% vs 30%). Patients tolerated the procedure well in this study, but the authors reported heterogenous temperature distribution and implant migration as potential limitations. In a smaller study of fourteen recurrent and two primary GBM patients, Maier-Hauff and colleagues[51] found that patients safely tolerated 4-10 (median 6) MHT sessions in combination with fractionated RT, and observed local tumor control. Rather than implanting ferromagnetic alloys through catheters (as had previously been performed by others), they directly implanted a high concentration (112 mg of Fe/mL) of aminosilane-coated MIONPs suspended in water into the tumor area. The same group conducted a larger trial of 59 patients with recurrent GBM in a two-center study in 2011 and reported a median overall survival from diagnosis of first tumor recurrence and from primary tumor diagnosis in the entire study population of 13.5 months (95% CI: 10.6–16.2) and 23.2 months (95% CI: 17.2–29.2), respectively.[87] Toxicity was relatively mild, and the most common symptoms observed during MHT were fever, headache, mild hypertension and tachycardia, and focal convulsions. Fourteen patients experienced transient worsening of their preexisting hemiparesis. Drawbacks of MHT reported from this study included the need to remove all metal from the treatment area (including metal dental implants), and indefinite exclusion of MRI for subsequent diagnosis of tumor progression. The results of this study led to European approval of MHT in 2012 as an adjuvant therapy for recurrent GBM in combination with RT.[87]

In a recent study, six patients diagnosed with recurrent GBM received intracavitary thermotherapy following 5-ALA-guided tumor resection. After resection, the cavity wall was coated with two to three layers of MIONPs using a hydroxycellulose mesh and fibrin glue that increased MNP stability and generated higher local MNP concentrations.[90] All patients received six semi-weekly sessions of MHT (60 min each) followed by RT in four out of six patients. Of the four patients who received combination therapy, two showed durable treatment responses of more than 23 months. Median progression-free survival was 6.25 months and median overall survival was 8.15 months. Histopathological analysis revealed sustained necrosis without tumor activity in areas adjacent to IONPs, as well as an immune response with macrophage infiltration and $CD3^+$ T cells. Patients experienced minor symptoms such as sweating and headaches. Edema was found in the surrounding MNP area in all cases (independent of RT), and all patients required postoperative dexamethasone, with four patients requiring MIONPs to be removed due to the significant nanoparticle-associated edema. The authors concluded that intracavitary MHT with RT induces a strong inflammatory response, including an antitumoral immune response, which may provide stabilization for recurrent GBM patients.

DISCUSSION

MHT has shown great promise in both preclinical and clinical studies for the treatment of HGGs. Preclinically, MHT can induce profound antitumor effects and synergism with CT and RT

when used to treat HGGs. Furthermore, MNPs have been used as multifunctional agents in applications such as cancer-targeting drug carriers, MRI contrast agents, and as mediators of MHT. With respect to clinical applications, six studies conducted between 1988 and 2019 highlight the various applications, advantages, and shortcomings of MHT over the course of its use in neurosurgery. Ni-Si ferromagnetic wires, aminosilane-coated MIONPs, and Fe-Pt alloy implant seeds have all been used to study MHT in combination with RT in a total of 157 malignant brain tumor patients diagnosed with primary or recurrent cancer. Although median temperatures achieved in the tumors ranged from 42°C to 53.2°C across five studies, temperatures in individual patients reached as high as 82°C, highlighting extreme variations in heating likely due to differences in MIONP properties, inhomogeneous distribution or migration of magnetic materials, and/or poorly regulated application of the AMF across the lesion. Overall, these studies reported that MHT was well tolerated, conferred a survival benefit, and potentially induced an MHT-mediated antitumor immune response.

Although MHT is reported as well-tolerated, it is important to consider therapy-related toxicities seen in previous clinical trials, as surgeons consider future clinical applications of MHT. In the study conducted by Grauer and colleagues,[90] all six patients suffered significant perifocal edema around the MIONP deposits 2 to 5 months following treatment, and four patients required follow-up surgery to remove the MIONPs after which their symptoms improved. Focal seizures were also reported as a common side effect in many of the studies, though they were generally resolved with conservative management.[87,127,128] Separately, others reported toxicity related to the implantation of the catheters which were used to administer the ferromagnetic material and for thermometry.[127–129] One patient in the early phase of one of these studies died due to treatment-related edema. Notably, this patient had the greatest number of catheters (n = 33) implanted and received the highest volume (119 cm^3) of Ni-4 wt.% Si alloy ferromagnetic wires. A separate finding reported by Stea and colleagues[127–129] was the sharp temperature decrease at the tumor margin compared with the significantly higher temperatures achieved in the tumor core. Moreover, the authors found that when the ferromagnetic wires were spaced apart by 1.3 cm or more, the number of temperature sensors measuring 42°C in the tumor decreased by approximately 30%. More comprehensive edema management, prophylactic antiepileptics, improved MNP delivery methods for a more homogeneous distribution of MNPs, and better AMF treatment planning to reduce off-target heating in the brain should be implemented in future clinical trials.

Although MHT has many advantages, for MHT to achieve its full clinical potential it is crucial to know the MNP distribution and to perform real-time 3D thermometry in the region of interest. At present, there is no effective way to simultaneously visualize MIONPs and noninvasively measure temperatures in the tumor during MHT. MRI is often used for noninvasive thermometry with other HT modalities (ie, PTT); however, the high static magnetic fields of MRI inhibit MNP rotation needed for heat generation in MHT.[132,133] Furthermore, the susceptibility caused by MNPs prevents their use for MR thermometry. Currently, conventional thermometry during MHT is typically achieved by invasively inserting radio frequency-resistant fiber-optic temperature probes into the tumor. These probes provide measures of local average temperature, and their misplacement or movement during treatment causes misleading readings.[92] Although heating during MHT can be estimated for a given field amplitude and frequency, SLP, and MNP concentration, large thermal gradients and unexpected variations in heating result from inhomogeneous MNP distribution within the tumor.[92] Infrared thermometry,[134] ultrasound thermometry[135,136] and luminescent nanothermometry[137] are examples of noninvasive techniques developed to measure temperatures during MHT. However, each technique has its own challenges ranging from limitations in-depth penetration to inaccuracies in thermometry caused by body movement. Additional research is needed to assess the clinical potential of these techniques.[138]

Combining MHT with MPI promises to overcome many of the obstacles facing the clinical application of MHT. In addition to enabling direct visualization of MIONPs, the underlying physics of MPI can be applied to provide real-time, noninvasive magnetic nanothermometry (MNT) during MHT.[29] Current research focuses on designing a device to simultaneously perform real-time MNT and MPI, and to inform and modulate AMF amplitude and frequency throughout the region of interest during MHT for regulated and reproducible delivery of a predetermined thermal dose. Recent studies have investigated systems capable of dual MPI-MHT,[139] as well as MPI systems fit for human use in the brain.[140,141] Future clinical success of MHT depends on developing an integrated MPI–MNT–MHT system. Such a system has the potential to minimize patient toxicity seen in previous clinical trials that is

possibly related to magnetic material migration and inhomogeneous heating.

FUTURE DIRECTIONS

The future of MHT as it relates to treating brain cancer is bright, although significant research is required for MHT to become a widely implemented clinical therapy in the treatment of HGGs. The reported survival benefits, general tolerability, and potential anti-tumor immune effect in response to MHT in combination with RT seen in clinical trials all warrant future investigation. It is important that future clinical studies account for variables that may affect clinical outcomes, such as ethnicity and preexisting comorbidities, as previous studies did not account for those variables. In addition, most clinical trials have assessed MHT in combination with RT, but few have fully explored MHT in combination with CT. Given the current standard of care for GBM, which consists of concomitant RT and TMZ CT, such studies are warranted. In addition, prior studies included small cohorts of patients, and future studies need to include larger patient populations, in addition to randomized controlled trials to compare MHT to current standard practices. Current clinical efforts include designing a phase-I study of recurrent GBM patients and assessing safety, tolerability, and clinical antitumor activity of MHT in 3 cohorts treated with predetermined thermal doses of 45°C, 50°C, and 55°C, respectively.[90]

Designing and studying biocompatible nanoconstructs made optimally for MHT, MPI, and MNT, as well as for synergism with current therapies for HGGs is a large field of research that needs further exploration. In addition, carefully designed translational and clinical studies are required to develop technology that enables concurrent MPI–MNT–MHT. These studies have the potential to dramatically improve what is already a highly localized and efficacious form of HT for the treatment of aggressive, therapy-resistant forms of brain cancer.

SUMMARY

In summary, MHT is a localized, repeatable, and remotely controllable form of HT that offers many benefits over current heat-based therapies used to treat brain cancer. Its use within neurosurgery spans decades and it has been implemented to treat HGGs in both preclinical and clinical studies. Although significant limitations remain for clinical applications of MHT, there is reason to be optimistic that future developments will overcome these shortcomings as MHT is reported to be generally tolerable and associated with overall survival benefits in glioma patients.[142] Maximizing the clinical potential of MHT requires integrating noninvasive thermometry, MNP imaging, and thermotherapy into a single platform such that volume and extent of heating can be confirmed. Overall, MHT has the potential to enhance current therapies used to treat HGGs as an adjuvant therapy and provide patients suffering from some of the most aggressive and therapy-resistant forms of cancer with improved quality of life and better outcomes.

CLINICS CARE POINTS

- Prophylactic antiepileptics, comprehensive edema management, and close monitoring/regulation of body temperature should be considered when administering magnetic hyperthermia therapy (MHT) to reduce side effects of focal convulsions, treatment-related edema, and generalized thermal stress.
- A multi-trajectory approach for the delivery of magnetic nanoparticles (MNPs) is imperative to promote the homogenous distribution of MNPs and heating throughout the lesion and tumor margin where infiltrating cancer cells reside.
- Real-time thermometry and magnetic particle imaging should be implemented during MHT to ensure that the appropriate thermal dose is being delivered to the region of interest.

CONFLICT OF INTERESTS

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