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TOPIC REVIEW

Magnetic Hyperthermia as an adjuvant cancer therapy in combination with radiotherapy versus radiotherapy alone for recurrent/progressive glioblastoma: a systematic review

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Abstract

Introduction Hyperthermia therapy (HT) is a recognized treatment modality, that can sensitize tumors to the effects of radiotherapy (RT) and chemotherapy by heating up tumor cells to 40–45 °C. The advantages of noninvasive inductive magnetic hyperthermia (MH) over RT or chemotherapy in the treatment of recurrent/progressive glioma have been confirmed by several clinical trials. Thus, here we have conducted a systematic review to provide a concise, albeit brief, account of the currently available literature regarding this topic.

Methods Five databases, PubMed/Medline, Embace, Ovid, WOS, and Scopus, were investigated to identify clinical studies comparing overall survival (OS) following RT/chemotherapy versus RT/chemotherapy + MH.

Results Eleven articles were selected for this systematic review, including reports on 227 glioma patients who met the study inclusion criteria. The papers included in this review comprised nine pilot clinical trials, one non-randomized clinical trial, and one retrospective investigation. As the clinical trials suggested, MH improved OS in primary glioblastoma (GBM), however, in the case of recurrent glioblastoma, no significant change in OS was reported. All 11 studies ascertained that no major side effects were observed during MH therapy.

Conclusion Our systematic review indicates that MH therapy as an adjuvant for RT could result in improved survival, compared to the therapeutic outcomes achieved with RT alone in GBM, especially by intratumoral injection of magnetic nanoparticles. However, heterogeneity in the methodology of the most well-known studies, and differences in the study design may significantly limit the extent to which conclusions can be drawn. Thus, further investigations are required to shed more light on the efficacy of MH therapy as an adjuvant treatment modality in GBM.

Keywords Magnetic hyperthermia · Glioma · Clinical Trial · Overall survival · Systematic Review

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Introduction

With a recorded number of 296,851 new cases globally, the year 2018 concluded with 241,037 deaths due to glioblastoma, indicating an annual mortality rate of 81.19% [1]. Encompassing 47.7% of all malignant brain tumors, glioblastoma is an insidious disease of poor prognosis, allowing roughly 5.6% of patients to meet their 5 year survival following diagnosis, according to the statistical report of the Central Brain Tumor Registry of the United States (CBTRUS) [2]. Nearly unchanged through the last few decades, the standard therapeutic approach to glioblastoma, based on the World Health Organization (WHO) guidelines, consists of surgical resection, radiation therapy (RT), and chemotherapy [3, 4].

A debilitating disease of the central nervous system with an aggressive behavior, glioblastoma has long been challenging mankind in terms of treatment [5]. Treatment is palliative and non-curative in most cases, providing only a short interval for patients, that usually does not exceed 24 months [6]. Due to the lack of a definitive treatment, alternative therapeutic modalities such as multimodal synergistic therapy have been developed [7, 8]. An effective combination of different conventional treatments, multimodal synergistic therapy integrates several modalities into an adjuvant therapy, such as hyperthermia, providing enhanced therapeutic effects compared to that of a singular treatment [9].

In hyperthermia, the therapeutic goal is to deliver the predetermined minimum effective dose to more than 90% of the target region [10]. The total thermal energy delivered to the site is measured with a well-recognized formula, in which the duration of exposure is normalized to the base effective temperature of 43 °C (CEM43) [11]. Magnetic hyperthermia therapy (MHT), a localized form of hyperthermia, adopts magnetic mediators or agents to convert the electromagnetic energy into heat, which is generated by an alternating magnetic field (AMF) in the first place [12]. The energy conversion is believed to be mediated through hysteresis losses, Brownian and Neel relaxation, a process in which frictional heating is produced by the physical rotation of magnetic particles [12]. To perform magnetic hyperthermia, a magnetic agent, along with a solenoid/head coil and thermocouples are required for generating an alternating magnetic field and measuring the temperature, respectively [13].

In spite of the non-specific regional application of AMF to the body, one can still achieve the localized heating of any desired region through delivering magnetic agents directly to the tumor site by means of targeted systemic delivery or intratumoral administration [12]. The recent development of different magnetic mediators, including millimeter and micrometer-scaled ferromagnetic alloy thermoseeds and metallic stents for interstitial implant-based hyperthermia, and magnetic nanoparticles (MNPs) for intracellular hyperthermia, has paved the way for clinical application of this technique [14]. Through the last few years, great steps have been taken in the development of MNPs [15]. Deeply-located magnetic agents inside tissues can be activated at organs by MHT at certain frequencies (f) and field (H) conditions, that are not harmful to the body ($H \times f \leq 5 \times 108$ A/ms) [16]. These agents release heat upon being exposed to an alternating magnetic field (AMF) of appropriate amplitude and frequency. The resulting heat leads to apoptotic or necrotic cell death in the tumor site, thus, decreasing the viability of tumor cells [9].

After demonstrating that magnetic particles could be selectively delivered to the tumor site and activated under an AMF to generate heat, Gilchrist et al. proposed the concept of magnetic hyperthermia (MH) for the first time in the 1960s [17]. Following three decades of exploration, the first clinical trial on MH through thermoseeds was conducted in Japan by Kida et al., who had investigated the treatment of brain cancer, and achieved promising therapeutic results [18]. Accordingly, one might expect the advent of high selectivity and enhanced heating homogeneity in the light of magnetic nanoparticle hyperthermia (MNH). In the meantime, the first clinical trial on MNP-based therapy against brain tumors, called NanoTherm®therapy (MagForce, Germany) [19], is in the second phase of clinical trial [20].

It is arguable that a well-evidenced combination of magnetic hyperthermia with the current conventional antitumor therapies could bring remarkable advantages to the treatment of glioblastoma. To our knowledge, there has never been a systematic review published on the effects of MH on the survival of patients with glioblastoma. Thus, we conducted a systematic review on the pertinent clinical trials in an attempt to summarize the evidence on the relationship between magnetic hyperthermia therapy and glioblastoma treatment (PICOS is detailed in Supplement 1).

Methods

The present study follows the PRISMA statement for transparent and comprehensive reporting of methodology and results [21].

Search strategy

We searched the following databases without restrictions on the language or date of publication, and humans were defined as the subject for this review:

PubMed/MEDLINE, Web of Science, Ovid, Excerpta Medica Database (Embase), and Scopus, updated as of June 2020. The PubMed search strategy is explained in Supplement 2.

Searching Other Resources:

We searched for the currently recruiting trials on the websites of Clinical Trials, World Health Organization (WHO), and International Clinical Trials Registry Platform (ICTRP).

Conference abstracts and proceedings from the last five years were looked for on the database of the American Society of Clinical Oncology (ASCO; supplements of Neuro-Oncology), and the International Psycho-Oncology Society (IPOS; The main journals in the field of neuro-oncology: Journal of Neuro-Oncology, Journal of Clinical Oncology, Thermal Medicine (Japanese Journal of Hyperthermic Oncology)). Publications from the last year that were not identified through the electronic search, were manually explored. We also manually sought relevant reference lists of important review articles, and that of the included articles. In addition, beyond major scientific databases, we also searched Google Scholar.

Protocol and registration code: PROSPERO 2020 CRD42020206990 [22].

Initial screening using eligibility criteria

The present study only included papers that met the following criteria: (1) clinical trials (CTs); (2) application of magnetic hyperthermia intervention as adjuvant therapy induced via radiofrequency coil; (3) inclusion of patients with primary or recurrent gliomas with or without prior history of surgery, radiotherapy or chemotherapy; (4) providing overall survival (OS) data until the death or last follow-up of patients; and (5) inclusion of an adult patient population ($\geq$ 18 years of age). Articles that represented over 50% of tumor types pertaining to the CNS were excluded. Editorials, letters, reviews, book series and non-human studies were also excluded. In addition, studies that had not published a full manuscript (such as conference presentations and abstract-only publications) were excluded, as well.

Candidate papers extracted from the earlier mentioned databases were reviewed for their relevance to the issue by means of Endnote (1095 papers). Duplicated articles were screened for and consolidated on initial review. Titles and abstracts of retrieved articles were first screened by two independent authors (S. Shievalilou and A.J. Esfahani). Afterwards, the same two authors read the full text of potentially suitable articles separately. Discrepancies were resolved by discussion (see Fig. 1 for PRISMA flow diagram of the present study).

Data extraction

We adopted a systematic data extraction tool for collection of the following:

Every paper considered for inclusion in this study was investigated for the following data: (1) general information: author name, year of publication, country of origin; (2) clinical data including: number of patients, age and gender, type of brain tumor, intervention details (summary of intervention and magnetic hyperthermia techniques used) and follow-up period; and (3) treatment outcomes including: median overall survival in months, side effects and mortality rates. The final verdict upon the inclusion of the selected papers was given by two reviewers (S. Shirvalilou and A.J. Esfahani). Both reviewers extracted data from each manuscript, while the third reviewer (S. Khoei) evaluated this data for accuracy and cohesiveness, independently.

A meta-analysis was not performed due to the heterogeneity in treatment regimens (e.g., monotherapy vs various combination regimens), the small sample size and study design (e.g., starting time-point for defining OS).

Risk of bias assessment

Risk of bias for every investigation included was assessed following the guidelines of Cochrane Collaboration Handbook [23]. Two authors (S. Shirvalilou and R. Sheervalilou) independently evaluated the risk of study bias. Any discrepancies in the results or the quality of studies were resolved in consensus with the third author (S. Khoei).

Results

Search strategy results

Following the search strategy described above, a total of 1080 records were identified, including 78 citations from PubMed, 445 from Embase, 251 from Ovid, 299 from Web of Science, 7 from Scopus, and 15 from other sources (e.g., international conferences). After the exclusion of duplicates, 902 records were screened. Initial assessment of titles and abstracts resulted in exclusion of 858 records, since they did not meet the inclusion criteria for our paper. Forty-four records were identified as potentially suitable for assessment through full-text reviewing. Of these, nine were excluded, as they did not report clinical trials, fourteen were excluded due to the unavailability of their full-text and lack of sufficient primary data, three were ruled out for being editorials and review articles, five clinical trials were put aside for not providing any relevant data on survival of patients, and two were eliminated for not reporting any findings regarding magnetic hyperthermia. Following this process, 11

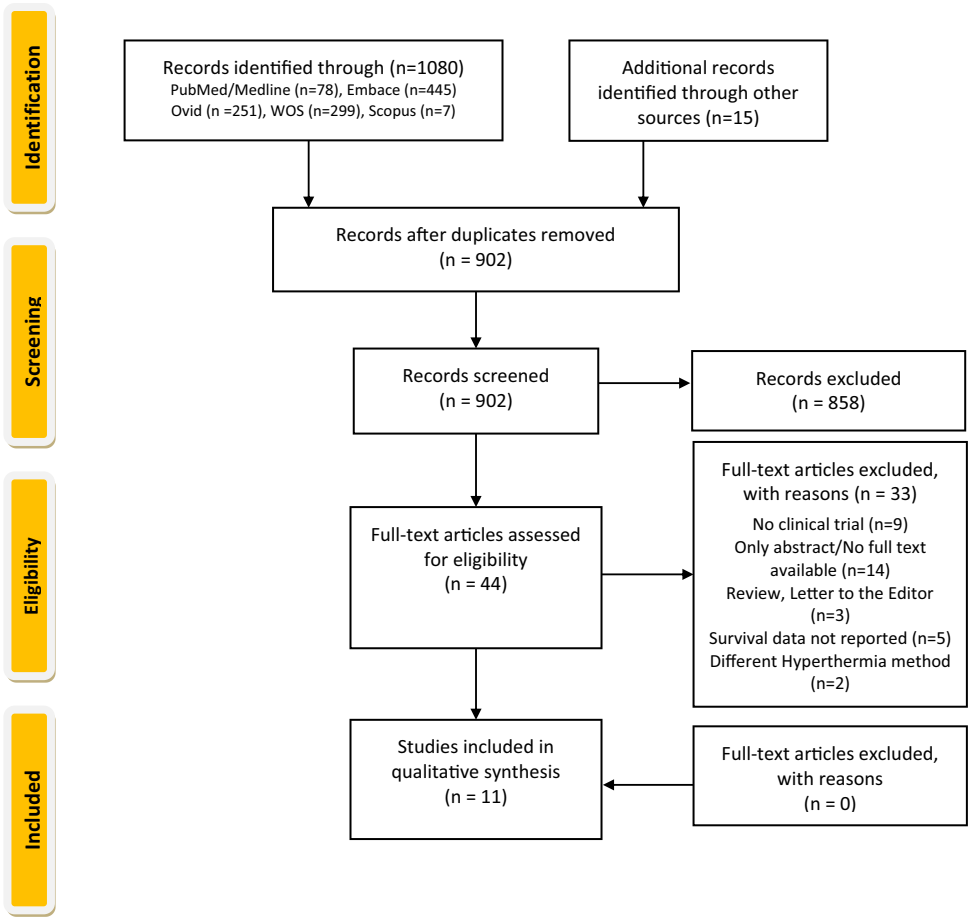

Fig. 1 Flow chart of publication search and selection

remaining papers were included into this systematic review. Ten articles were in English [19, 24–32], and one was in Japanese [33]. The search strategy is summarized in Fig. 1.

Included studies and participant details

Full details of 11 eligible studies are summarized in Table 1. Out of the 11 clinical trials assessed, 6 were phase I trials [19, 24–26, 29, 33], 3 were mixed phase I and phase II [27, 30, 31], and 2 were phase II trials [28, 32]. Most studies were prospectively designed. A total of five were conducted in the United States [25, 27, 29–31], four in Germany [19, 24, 28, 32], and two in Japan [26, 33]. Upon assessment of the papers, significant heterogeneity was detected in patient characteristics including tumor status, Karnofsky performance scale (KPS), pretreatment modalities, treatment protocol, and performance status. Based on the incorporation of magnetic hyperthermia, all studies included in this review can be divided into three subgroups; MH with catheter implantation (1990–1994) [25, 27, 29–31], MH with thermo-seed implantation (1991–1993) [26, 33], and MH with implantation of magnetic nanoparticles (2007–2019) [19, 24, 28, 32].

A total of 262 patients were investigated in the 11 studies included here. Of the 237 cases reported in 10 articles [19, 24, 26–33], the majority of patients were treated for recurrent disease (n = 122, 51.5%), while 105 patients (44.3%) received treatment for primary disease. Last but not least, 10 patients (4.2%) were treated for metastatic disease. A total of 202 patients were diagnosed with glioma (86.6% glioblastoma and 13.3% astrocytoma). The age or sex of the patients were not reported in 2 studies [25, 33]. Considering the available data (n = 20), the age range was 21–79, and 53% of patients were male.

Treatment characteristics

Most patients had already been extensively treated for their disease (surgery and radiotherapy with/without chemotherapy) on the areas in their body that were going to be treated with MH. During MH therapy, patients received a median external RT dose of 49.2 Gy (range 30–70) [24], brachytherapy (88.7 Gy, range 20.3–151 Gy) [27], external RT with brachytherapy (26–41 Gy) [25, 29, 31], external RT combined with chemotherapy [19, 26, 32, 33], or external RT (48.4 Gy, range 41–50.4 Gy) with brachytherapy

Table 1 Characteristics of the included studies

No	Author	Country	Total patients	Median age	Study population	MH device	Thermometry device	MH therapy Tumor temp(°C)/ Time (min)	Adjuvant therapy
1	Stea [29]	US	14 (10:4)	51 (21–69)	Primary (9)/ Recurrent (5) Glioblastoma (11)	80–100 kHz, 1500–2000 kA/m Ferromagnetic Nickel-silicon alloys	Thermocouple Copper constantan and Fiberoptic probe	42 °C to 45 °C 60 min	RT: 40 Gy Brachy: 32–40 Gy
2	Kida [33]	Japan	39	–		240 kHz, 1.65 kA/m Fe–Pt alloy implant	Thermocouple	38 °C to 42 °C 30–60 min	RT: 50 Gy Chemo: CDDP VP16, ACNU
3	Kobayashi [26]	Japan	25(11:14)	–	Primary (18)/ metastatic (7) Glioblastoma (10) Astrocytoma (3)	240 kHz, 1.65 kA/m Fe–Pt alloy implant	Thermocouple	44 °C to 46 °C 30–60 min	RT: 50 Gy Chemo: CDDP, ACNU
4	Iacono [25]	US	25	–		80–90 kHz, 1500 A/m Ferromagnetic wires of nickel-silicon	Fiberoptic probe	42 °C to 45 °C 60 min	RT: 40 Gy Brachy: 32–40 Gy
5	Stea [30]	US	28(12:16)	44(21–79)	Primary (23)/ recurrent (5) Glioblastoma (19)	80–100 kHz, 1500–2000 kA/m	Thermocouple Copper-constantan	42 °C to 45 °C 60 min	RT: 48.4 Gy Brachy: 13.9–50
					Astrocytoma (9)	Ferromagnetic Nickel-silicon alloys	and Fiberoptic probe		
6	Mack [27]	US	44(24:20)	(36–75)	Primary (19)/ recurrent (25) Glioblastoma (20)	80–100 kHz, 1500–2000 kA/m Ferromagnetic Nickel–silicon alloys	Thermocouple Manganin-constantan	38.7 °C to 43.7 °C 60 min	Brachy: 20.3–151
7	Stea [31]	US	33(15:18)	45(21–79)	Primary (25)/ recurrent (8) Glioblastoma (22)	80–100 kHz, 1500–2000 kA/m	Thermocouple Copper-constantan	42 °C to 45° 60 min	RT: 50 Gy Brachy: 26–41 Gy
					Astrocytoma (11)	Ferromagnetic Nickel-silicon alloys	and Fiberoptic probe		
8	Maier-Hauff [19]	Germany	14(5:9)	55(29–73)	Primary (2)/ recurrent (12) Glioblastoma (14)	100 kHz, 2.5–18 kA/m NanoTherm®therapy Magnetic fluid (112 mg/ml)	French catheter	42.4 °C to 49.5 60 min	RT: 70 Gy Chemo: TMZ
9	Van Landeghem [32]	Germany	3(0:3)	(41–67)	Primary (1)/ recurrent (2) Glioblastoma (3)	100 kHz, 2.5–18 kA/m NanoTherm®therapy Magnetic fluid (112 mg/ml)	Fiberoptic probe	49.5 °C to 65.6 60 min	RT: 30 Gy Chemo: TMZ

Table 1 (continued)

No	Author	Country	Total patients	Median age	Study population	MH device	Thermometry device	MH therapy Tumor temp(°C)/ Time (min)	Adjuvant therapy
10	Maier-Hauff [28]	Germany	59(27:32)	55(18–75)	Recurrent (59) Glioblastoma (59)	100 kHz, 2.5–18 kA/m NanoTherm®therapy Magnetic fluid (112 mg/ml)	French catheter	Median 51.2 °C 60 min	RT: 30 Gy
11	Grauer [24]	Germany	6(2:4)	60(42–75)	Recurrent (6) Glioblastoma (6)	100 kHz, 2–15 kA/m NanoTherm®therapy Magnetic fluid (20 mg/kg)	French catheter	Median 53.2 °C 60 min	RT: 39.6 Gy

(32.7 Gy, range 13.9–50 Gy) combined with chemotherapy [30] (Table 1).

For magnetic hyperthermia, plastic catheters were used for implantation of ferromagnetic nickel-silicon alloys into tumors in five multiple places studies [25, 27, 29–31], Fe-Pt alloy thermo-seeds in two studies [26, 33], magnetic fluid containing 112 mg/ml iron oxide nanoparticles in three studies [19, 28, 32], and 20 mg/kg magnetic fluid in one study [24]. After implanting magnetic particles, hyperthermia was induced with alternating magnetic coil. In all investigations, MT therapy had an average duration of 60 min. Temperature during MH therapy was measured with invasive methods in all studies. These investigations, however, failed to precisely report the type of thermometry equipment, and the number of temperature sensors (Table 1). The tumor temperature in the MH session was between 38 and 43.7 °C [27, 33], or 42 and 49 °C [19, 24–26, 28–31]. In one investigation, tumor temperature was reported 49.5 to 65.6 °C [32]. Hyperthermia was usually performed once or twice a week, however, two studies administered MH therapy two or three times a week [26, 33]. In most trials, the first course of MH was given 2 to 4 weeks following external RT (before brachytherapy), and a second course of MH followed immediately after disposing of the radioactive sources [25, 29–31]. In an investigation by Mack et al., 43 patients were treated with hyperthermia before the catheters were loaded with ^{92}Ir, and 17 patients received additional treatment after the radioactive sources were unloaded [27]. Certain trials adopted two treatments per week [19, 24, 26, 33]. In one study, stereotactic radiotherapy was initiated immediately before or after intratumoral thermotherapy [28]. One investigation failed to report the time interval between HT and RT [32] (Table 1).

Outcomes

Due to the heterogeneity and small sample sizes in these studies, we were not able to categorize them, and perform a statistical analysis on the available data. Thus, a brief description of each investigation is provided later in this manuscript. Accordingly, we considered two main outcomes: overall survival (OS) and mortality rate.

Overall survival

All 11 studies reported certain rates for OS. In this regard, the survival time here is given in months, starting from the day of re-treatment and diagnosis for patients with recurrent gliomas and primary untreated tumors, respectively. The majority of investigations were observational. One study reported hazard ratio (HR) as an index of patient mortality [31]. As for the measure of survival, two papers opted to report Kaplan Meier (KM) survival outcomes [28, 31]. One particular investigation indicated the survival advantage of a combination of IB (RT and brachytherapy) and IT (magnetic hyperthermia) over IB alone [31]. Stea et al., suggested that the median survival in patients with primary tumors (n = 25, 23.5 months) for the IT group was significantly longer than patients treated with IB (n = 37, 13.5 months, P = 0.013). As for the patients with recurrent tumors, the estimated 12-month survival probability was 0.23 for those treated with IT (n = 8, 95% CI = 0.0–0.46), that was not statistically different from the 0.25 value measured for patients treated with IB (n = 13, 95% CI = 0.0–0.55, P = 0.62) [31]. Maier-Hauff et al., used historical controls from previous investigations to compare their results. According to their study, the median survival for recurrent glioma patients treated with RT and chemotherapy (temozolomide) combined with MH was 13.4 months, compared to the 6.2 months in patients who had received RT and chemotherapy, indicating a significant difference [31]. Seven of the 11 studies reported positive effect of MH therapy on survival, however, they did not provide a direct comparison between therapeutic outcomes [19, 24–27, 29, 30].

Patient mortality was clearly defined in almost all of the studies. However, one paper did not clearly delineate the patient follow-up time. Though, even among the

investigations that reported the patient follow-up time, it varied majorly from 3 to 47 months. In 10 reported studies conducted on a total of 218 patients, 164 patients (75.2%) died after treatment with hyperthermia throughout the follow-up time (3 to 47 months) [19, 24–26, 28–33]. A comprehensive summary and analysis of each study is presented in Table 2.

Thermal toxicity

All 11 studies reported that no major side effects were observed during MH therapy. All patients who had developed major (e.g., seizures, cerebral edema) or minor adverse effects (e.g., sweating up to grade 1, fluctuations in blood pressure, motor disturbances and transient brain edema) recovered perfectly without long-term complications. In two cases of magnetic hyperthermia with catheter implantation, migration of the implant (n = 1) and massive hemorrhage at the site of the implant (n = 2) were reported [26, 33]. In three studies, tissue samples were collected from 11 patients after receiving MH treatment. Kida et al., reported that in all 11 cases, a clear microscopic necrosis at the periphery of the implanted thermo-seeds was confirmed. Tumor cells were detected in 3 cases within the necrotic area [33]. Two investigations revealed that the majority of the nanoparticles had aggregated in the peripheral areas of the localized necrosis within the tumor [24, 32].

Risk of bias of the included studies

The results drawn from the quality assessment of these clinical investigations are presented in Fig. 2. All components of the Cochrane Collaboration's tool were adopted for assessing the risk of bias [23]. Blinding of outcome assessment was not performed for any of the endpoints. Incomplete outcome data were separately assessed for survival (essential parameters), mortality and toxicity (non-essential parameters). A high risk of attrition bias was detected, that was attributed to the incomplete outcome assessment for survival in several papers. Since the study designs had not been closely controlled, we determined a high risk of bias due to the lack of blinding in all studies. The majority of bias types found in these studies lay within the inherent study design.

Table 2 Main results of the included studies

No.	Author	OS (months), median (range)	Mortality (%) in follow up time	Treatment-related complications
1	Stea [29]	Primary: (7–19)/recurrent: (1.5–9)	75.58	Transient neurologic complications (14) focal seizures (3), hydrocephalus (1), cerebral edema (2)
2	Kida [33]	Primary: (7 day–7 month) Metastatic: (2 day–7 month)	81.81	Massive hemorrhage (2)/vasodilation (9), swelling (1)
3	Kobayashi [26]	Primary: (1–21)/metastatic: (3–19)	60	Migration of the implant (1)/intratumoral hemorrhage (1)
4	Iacono [25]	12–39 month	88	Transient neurologic complications (5) Focal seizures (5), cerebral edema (1)
5	Stea [30]	Primary: 18.5 (2.25–43.61) Recurrent: 5.8 (28 day–15.15 month)	57.14	Transient neurologic complications (4) Focal seizures (6), hydrocephalus (1) Pneumoencephalos (1)
6	Mack [27]	8 (1–53)	–	–
7	Stea [31]	MH (primary): 23.5 Control (primary):13.5: (P = 0.013) MH (recurrent): 12 Control (recurrent):12: NS	81.81	Focal seizures (11), cerebral edema (11) Pulmonary embolus (2)
8	Maier-Hauff [19]	Primary: (3–8.4)/recurrent: 7.6 (4.1–28)	92.85	Fluctuations in blood pressure (1) Transient neurologic complications (1)
9	Van Landeghem [32]	Primary: 2.1/recurrent: 7.9	100	Transient neurologic complications (3)
10	Maier-Hauff [28]	Recurrent: 13.9 (10.9–16.8)	79.60	Transient neurologic complications (9), focal seizures (15) tachycardia (12), motor disturbances (14), headaches (9) fluctuations in blood pressure (10), sweating up to grade 1 (33)
11	Grauer [24]	Recurrent: 8.1 (2.8–29.1)	83.33	Transient neurologic complications (6) Sweating up to grade 1 (6)

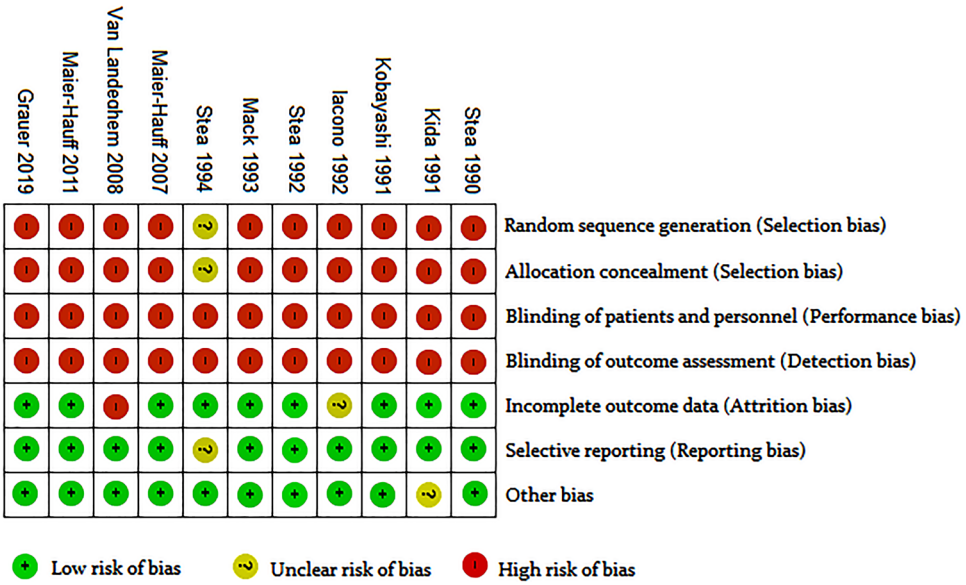

Fig. 2 Quality assessment of clinical studies was performed with use of the Cochrane Collaboration's tool for assessing risk of bias [24]. + low risk of bias; − high risk of bias; ? unclear risk of bias

Discussion

Combination of RT with hyperthermia, as some clinicians suggest, can be a promising modality for treatment of malignancies, with an emphasis on local and extracranial control of the ongoing disease, that may actually improve the OS. However, such strategy is not supported by solid evidence. The present work is the first rigorous systematic review to have assessed the effectiveness and toxicity of magnetic hyperthermia in combination with radiotherapy or chemotherapy in the treatment of gliomas. To our knowledge, no papers have been published on this issue to date. However, the articles included in this systematic review mostly had reported data from patients with primary/recurrent glioma from glioblastoma (86.6%) and astrocytoma (13.3%), therefore, these findings cannot be generalized to patients with other brain malignancies. Historically, the literature suggests the emergence of a trend toward favoring magnetic type of radiofrequency hyperthermia, which is being explored by an increasing number of investigations to improve survival in advanced cancers [13].

In our list, three devices in 11 trials were intended for clinical application. In studies conducted in the USA, magnetic field coils (80–100 kHz and 1500–2000 A/m) and nickel-silicon thermo-seeds [25, 27, 29–31] were used, whereas the Japanese opted for magnetic induction coil (240 kHz, 1.65 kA/m) and Fe-Pt alloy seeds [26, 33], and the German chose magnetic induction coil (100 kHz, 2.5–18 kA/m) and aminosilane coated superparamagnetic iron oxide nanoparticles (MagForce Nanotechnologies AG, Berlin, Germany) [19, 24, 28, 32]. In seven studies, toxicity due to catheter or thermo-seed implantation was attributed to migration of the implant or massive hemorrhage of the implant [25–27, 29–31, 33]. However, no such complications were reported in the other 4 investigations, that had used nanoparticle implants [19, 24, 28, 32].

The measured temperature during HT strongly depends on the type and extent of thermometry, and the tissue on which the technique is applied [34]. In all 11 studies, invasive thermometry was adopted to monitor the temperature of the tumor site during hyperthermia sessions. Thermocouple probes (Copper-constantan, Manganin-constantan, French catheter) [19, 24, 26–28, 33] and fiberoptic thermometry probes [25, 32] were used for thermometry. In 3 investigations, two methods were used simultaneously to control the temperature[29–31]. Optimal temperature, albeit rarely achieved, ranged from 41 to 43 °C, as mentioned in all papers. On the other hand, the maximum temperature achieved was often higher than the pre-specified allowed maximum limit, which ranged from 43 to 65.6 °C. This implicit heterogeneous temperature distribution resulted in a large variation between the maximum allowed temperatures attained by different institutes. The ESHO guidelines for superficial hyperthermia quality assurance, which has been published recently, might help to reduce such variation among institutes. According to these guidelines, one should aim for a $T90 > 40$ °C and $T50 > 41$ °C to locally maintain control over the tumor, with maximum temperatures of 43–45 °C [35]. Therefore, uniform temperature distribution and proper monitoring is one of the inherent limitation of this method.

Despite the direct effect of the temperature and thermal dose of HT in the ultimate quality of treatment, these studies often failed to report such parameters, and thus, did not point out any specific relationship between the thermal dose and therapeutic outcome. Only one study, led by Maier-Hauff, managed to report that no correlations were

found between tumor size, location, or treatment temperatures with either OS or side effects [28].

The treatment has been deemed safe for both newly-diagnosed patients and individuals with recurrent glioblastoma. Though, the clinical findings regarding the efficacy of this modality remains contentious. The greater proportion of the studies included in this review were observational, except for the investigation by Stea et al., where patients were classified prospectively into two exposure groups (RT vs RT and MH) [31]. Almost none of the patients in these studies were randomly assigned to different groups. These investigations also failed to match certain variables, e.g., ethnicity and comorbidities, between the groups, which might have led to remarkable differences in clinical outcomes reported for each group. Despite such limitations, we opted for an optimistic approach toward magnetic hyperthermia with nanoparticle implantation, as the majority of studies have suggested a positive association between OS and MH in glioma. However, in spite of this optimism, hyperthermia should be approached with caution, i.e., proper selection of patients, skillful application of intracranial injection techniques, and thermometry probes. It is highly imperative to minimize post-treatment neurological sequelae, that may counteract any potential benefits to the survival of patients. While further randomized clinical trials are underway, one ought to rely on available data and rational clinical reasoning for appropriate selection of patients who are most likely to benefit from magnetic hyperthermia as adjuvant therapy with RT in the management of gliomas.

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Data availability The data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Conflict of interest No potential conflict of interest was reported by the authors.

Ethical approval This study was approved by our institutional review board. No. 13899.

Consent for publication All authors have given consent for publication.

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