Retrospective observational Clinical Study on Relapsed Malignant Gliomas Treated with Electro-hyperthermia

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Abstract

AIM: to evaluate the efficacy and tolerability of electro-hyperthermia (ET) for the treatment of relapsed malignant glioma.
Methods: this was a retrospective observational clinical study. Patients were included in the study if they had >18 years, informed consent signed, histological diagnosis of malignant glioma, failure of previous temozolamide-based chemotherapy and radiotherapy, indication for treatment with ET.
Hyperthermia was performed with short radiofrequency waves of 13.56 MHz using a capacitive coupling technique keeping the skin surface at 26 C°. The applied power ranged between 40-150 Watts and the calculated average equivalent temperature in the tumors was above 40 C° for more than 90% of the treatment duration (20-60 minutes gradually).
Results: 24 consecutive patients were enrolled in the study, 19 (79%) had glioblastoma multiforme (GBM) 13 were of grade 1-3 and 6 of rade 4, 5 (21%) ASTROCYTOMA.
Tumor response analysis two months after ET showed 2 (8%) complete remission (astrocytomas) and 5 (21%) partial remission (2 ASTROCYTOMA, and 3 glioblastomas), with a response rate of 29%. The median duration of response was 16 months (range 6-120).
The median survival of whole study population was 19.5 months (range 2-156), 55% survival rate at 1 year, and 15 % at two years. We observed 3 long survivors at 156, 60, 62 months in atrocitomas.
Conclusions: ET appears to have promising efficacy in adults with relapsed malignant glioma.

Keywords: relapsed malignant glioma, electro-hyperthermia, survival, tumor response

Introduction

The use of Hyperthermia has been known for long time, since it was found out that heat had the ability to kill cells. In the last decade, hyperthermia has been increasingly used as treatment choice for several types of cancer, because tumor cells are more sensible to heat than normal cells (1). Several methods of hypertermia for cancer treatment are currently available, such as magnetic nanoparticles (mNPs) inducing intracellular hyperthermia, external Radio-Frequency (RF), hyperthermic perfusion; frequency enhancers associated to magnetic field; catheter mediated hypertermia (2-4).

Hyperthermia can be used alone or in association with chemotherapy or radiotherapy in order to improve and prolong their benefit (5-7). The synergic effect of traditional hyperthermia (41–43°C) with chemo and radio-therapy is due to apoptosis induction, angiogenesis inhibition, chemo- and radio-sensitivity activation and high drug concentration induction inside the lesion. The heat, moreover, can induce the externalization of new antigens, thus increasing the tumor sensitivity to immunotherapy (8, 9).

Gliomas represent the majority (80%) of malignant brain cancers (10). According to the glioma grading system of the World Health Organization (WHO), the astrocytomas are classified by four grades (I, II, III, and IV); and oligodendrogliomas and oligoastrocytomas, by two grades (II and III). The most aggressive and common glioma is glioblastoma (a grade IV astrocytoma) (10). Glioblastoma multiforme (grade IV) (GBM) represent 65% of all gliomas (11). The prognosis is poor, especially for GBM patients, because of infiltration in surrounding brain tissues, and resistance to chemo- and radio-therapy (10). Anaplastic glioma (grade III) includes anaplastic astrocytoma, oligodendroglioma and oligoastrocytoma. It is less frequent and has a better prognosis than GBM (12). There are only few target therapy or biological drugs available for gliomas (13). The gold standard treatment consists of surgery followed by RT for high grade gliomas (HGG) (14). When surgey is not indicated radiation and chemotherapy in association with temozolomide (TMZ) is the most used choice for GBM (12-17).

The effectiveness of chemotherapy is not clear, but most indicated adjuvant therapy is the association of temozolomide to radiation, resulting in longer overall survival (16, 17).

However, most of HGG have disease recurrence. Median overall survival of recurrent HGG is 30-33 weeks, for this reason HGG therapy is very challenging. Treatment choices for recurrent HGG are surgical resection, re-irradiation (re-RT), chemotherapy, anti-angiogenic agents, and combination therapies of hypertermia with chemo- or radio-therapy (14). However, there is currently no standard treatment option, and surgery is indicated only for a limited group of patients with high performance status, small lesion, and young age (18). Radiofrequency (RF) and electro-hyperthermia can be applied intra- and extra-cranially and have efficacy of this treatment for brain-tumors (19, 20). As shown in randomized, controlled studies. (21). For this reason, the United States Food and Drug Administration approved brain-hyperthermia for HGG.

Reports on electro-hyperthermia for MG are few (22-26). One retrospective study shows only palliative results (22). Hager et al. (23) treated 35 patients with 13.56 MHz capacitive coupled device hyperthermia, reporting good tolerability for HGG with 11% of adverse events. He also reported improvement of survival and quality of life.

In our previous study, we treated with ET 12 patients with relapsed malignant gliomas and reported a response rate of 29% with a median duration of response of 10 months (range 4-32) (12, 9).

The purpose of this study was to extend our previous experiences to better evaluate the activity and toxicity of ET on relapsed malignant glioma patients. This article reports our

experiences to the recent advancements in ET treatment of patients with gliomas, in recurrent setting.

Materials and Methods

Patients selection

Patients were included in this study if had: >18 years old, informed consent signed, diagnosis of HGG relapsed, Eastern Cooperative Oncology Group (ECOG) performance status ≥2, normal hematological values and vital signs, previous temozolamide-based chemotherapy and radiotherapy. From April 2003 to January 2016, twenty-four patients with relapsed HGG were enrolled in the study.

Description of the device

EHT was administered with Oncotherm EHY-2000 device. This machine delivered a non-ionizing therapy that elevates the temperature of the tumour macro and micro-environments, in a controlled manner, to a therapeutic range of 40 –43°C (37-40). The device employs modulated electro-hyperthermia (mEHT) to achieve the controlled heating of a target anatomy (41,42) The device is a capacitive coupled impedance matching solid state electrical system that incorporates two electric capacitive plates (electrodes). One electrode is situated under the patient and is built into the treatment table, running the full length and width of the table platform. The second is a mobile electrode positioned over the patient's target anatomical area, as directed by the prescribing physician. The electrodes are coupled to the patient with electrically conductive temperature controlled water bolus to conduct and distribute electric current into tissue, as well as help cool the skin's surface. The capacitive system generates a 40-150-Watt radiofrequency (RF) carrier signal at 13.56 MHz, which is further modulated (amplitude modulation) for absorption by the tumour (41-44).

Electro-hyperthermia protocol

All patients received pre-procedural medications with a suspension of glycerol 18% and dexamethasone 12 mg before each ET session.

ET with short RF waves of 13.56 MHz was applied with capacitive coupling technique maintaining 26 C° at skin contact. ET was performed with an EHY 2000 device (CE0123, Oncotherm, Traisdorf, Germany). We used a power from 40 up to 150 Watt, resulting in an average equivalent temperature of >40 C° in the tumors, for more than 90% of the treatment duration (from 20 up to 60 minutes).

The targeted area was selectively treated using an electrode system cover, excluding the eye-area from the field. ET was performed in three sessions per week, increasing the power and time each session. First treatment was always at 40 Watt for 20 minutes. Time was gradually raised from 20 to 60 minutes and power from 40 up to 150 Watt in two weeks.

Hyperthermia was given with short radiofrequency waves of 13.56 MHz using a capacitive coupling technique keeping the skin surface at 22°C.

The applied power ranged between 40-150 Watts and the calculated average equivalent temperature in the tumors was above 40.5°C for more than 90% of the treatment duration. Duration treatment increases from 20 to 60 min. One treatment is: 3 session/wk for 4 weeks and recycle if evidence of clinical benefit or stable desease. Each patient received 24 sessions (range 12 – 64).

Outcome measures
The tumor responses were evaluated by MR or CT scan every two months. A complete remission (CR) was considered the complete disappearance of the tumor. A partial remission (PR) was considered the reduction of at least 20% in the two greatest diameters. A stable disease (SD) was considered when no tumor reduction or reduction <20% was observed. Progression was established when tumor size increased.
The ECOG performance status scale was used to evaluate the functional recovery.

Statistical Analysis
Descriptive statistical analysis was performed. Continuous date was reported as median and ranges. Proportions were reported as percentages.

Results

Sample characteristics
Twenty-four patients were enrolled in the study. Nineteen (79%) patients had glioblastoma multiforme (13 were of grade 1-3 and 6 of grade 4), 5 (21%) astrocytoma (table 1). Most patients 22 (92%) were pre-treated with surgery, and all patients were pre-treated with temozolomide associated to radiotherapy. Thirteen (54%) were females and 11 (46%) were males, median age was 60 (22-81). All patients were pre-treated with surgery (22/24), temozolomide and radiotherapy.

Tumor response and survival
Tumor response analysis two months after ET showed 2 (8%) complete remission (astrocytomas) and 5 (21%) partial remission (2 ASTROCYTOMA, and 3 glioblastomas), with a response rate of 29%. The median duration of response was 6 months 6 months (4-24) for gliomas, and 44 months for atrocitomas (14-156+). Stable disease was observed in 8 (33%) of patients and progression in 9 (38%) patiens.
The median survival of whole study population was 19.5 months (range 2-156), 55% survival rate at 1 year, and 15 % at two years. We observed 3 long survivors at 156, 60, 62 months in atrocitomas.
Ten patients had an objective clinical benefit as resulting from an increase of their ECOG from 3 to 1 in 4 (16%) patients and to 0 in 2 (8%) patients.

Five-year survival trends
Median overall survival was 14 months for gliomas and 61 months for astrocitomas (71% survival rate at 1 year, 50% at 2 and 29% at 3 years). Astrocytoma patients had longer survival: 60,60+,156+,62,60,63 months (fig. 1-4).
The 5-year survival data for the patients with the seven most commonly treated cancer types and stages was plotted on a Kaplan-Meier curve. This data was then compared to survival data for standard of care using the Surveillance, Epidemiology and End Results (SEER) database as a control for the evaluation of an integrative approach where LRHT was the primary variable being explored (fig.5). The graphs consist of survival probability on the vertical axis and Time from Diagnosis (in years) on the horizontal axis.

Tolerability
ET toxicity was mostly mild (G1). We observed one (4%) head pain, one (4%) scalp burn, five (21%) epilepsy that was resolved with a medication including diazepam 10 mg in 100 ml of saline and levetiracetam in tablets without any further attack.

Discussion

The first-line therapy for newly diagnosed HGG are several, including surgery, radiotherapy, chemotherapy with nitrosourea, temozolomide, bevacizumab, and irinotecan, alone or guided in combination and radiation alone or combined to temozolomide (27). There is currently no standard treatment for relapsed HGG, and several potentially active systemic drugs are not effective because of blood brain barrier blockade (28). Maintenance therapy and treatments for recurrent HGG widely vary according to physician, hospital and country and include surgery, re-radiation, second/third-line chemotherapies, biodegradable carmustine wafers, gene therapy and hyperthermia (28-32, 19-21).

The use of Electric Capacitive Transference hypertermia increases heat of brain tumor and is harmless for surrounding brain tissue that in no case reaches a temperature > 39.2°C (20). Most common side effects of hyperthermia are pain, burns or discomfort, but they are temporary and most of normal tissues are not damaged during the therapy.

Tumor cell are more sensible than normal cells to heat, and hypertermia inhibits the DNA repair system of tumor cells. For this reason, classic hyperthermia (42-43 °C) is often associated to chemotherapy or radiotherapy. This association is safe and well tolerated and increases the efficacy on overall survival and progression free survival (16, 18).

We previously reported the results of ET treatment of 12 recurrent HGG patients (14). We showed 1 CR and 2 PR with a response rate of 25% and a median duration of response of 10 months (12), without severe toxicity. The patient with CR is still alive with a progression free survival of 156 months.

In this paper we report our experiences in ET treatment of a larger number of 24 recurrent HGG patients. Tumor response analysis showed a similar response to that of our past paper with a response rate of 29 % two months after ET 2 (8%) complete remission (astrocytomas) and 5 (21%) partial remission (2 ASTROCYTOMA, and 3 glioblastomas). The median duration of response was longer 16 months (range 6-120) than our previous study 10 months (13). Tumor response was coupled to an improvement of performance status in 6 (24%) patients. Moran and colleagues reported a higher response rate 66%, however they observed only SD or PR and none CR (20). Tanaka et al. Had higher responses when treated 16 patients with brain cancers adopting hyperthermia with 13.56- MHz RF capacitive heating machine and showed a 50% of PR (19). However, the combination of hyperthermia with other methods did not allow to draw any conclusion about the efficacy of hyperthermia alone.

The median OS of whole study population was 19.5 months, 55% survival rate at 1 year, and 15 % at two years. Of particular interest we underline the presence of 3 long survivors at 156, 60, 62 months. OS was higher than that of magnetic hypertermia that resulted in survival ranging from 2.1 to 7.9 months (33).

OS was comparable to that reported by Sneed et al. 31% at the 2 years follow up (22)

Limitation of our study are the absence of an active comparator, non-randomization, and low number of patients. Further multicenter randomized studies with a larger number of patients are required to confirm our data.

Conclusions

ET hyperthermia therapy for recurrent HGG is feasible and may increase tumor response and survival. ET is a non-invasive method to treat HGG without severe toxicity

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Table 1) Chracteristics of the sample

ID	Sex	Age	Type of glioma	MGMT metilated	IDH1	Response	OS (months)
01	F	41	ASTROCYTOMA	YES	YES	PR	60
02	M	26	ASTROCYTOMA	NO	YES	RC	60
03	M	22	ASTROCYTOMA	YES	YES	RC	156
04	F	56	ASTROCYTOMA III	NO	NO	SD	62
05	M	63	ASTROCYTOMA/GBM	YES	NO	SD	60
06	M	58	GBM IV	NO	NO	SD	2
07	M	45	GBM IV	NO	NO	SD	14
08	F	67	GBM IV	NO	NO	PD	10
09	M	66	GBM IV	NO	NO	PD	9
10	M	54	GBM	ND	ND	PD	14
11	F	46	GBM	YES	YES	PR	24
12	M	65	GBM	ND	ND	PD	5
13	F	75	GBM	ND	ND	SD	8
14	F	76	GBM	ND	ND	PD	6
15	M	62	GBM IV	NO	NO	PD	14
16	M	74	GBM	NO	NO	SD	15
17	F	81	GBM	ND	ND	PD	8
18	M	53	GBM	ND	ND	SD	36
19	M	66	GBM	ND	ND	PR	25
20	F	66	GBM	ND	NF	SD	15
21	F	33	GBM	ND	ND	PD	32
22	F	49	GBM	ND	ND	PD	32
23	M	52	GBM IV	YES	ND	PR	24
24	F	66	ASTROCYTOMA III	ND	ND	PR	63
25	F	34	NOT DEFINED	ND	ND	PR	5

Figure 1) ASTROCYTOMA G III (G.E. 32 yrs) 1-Response

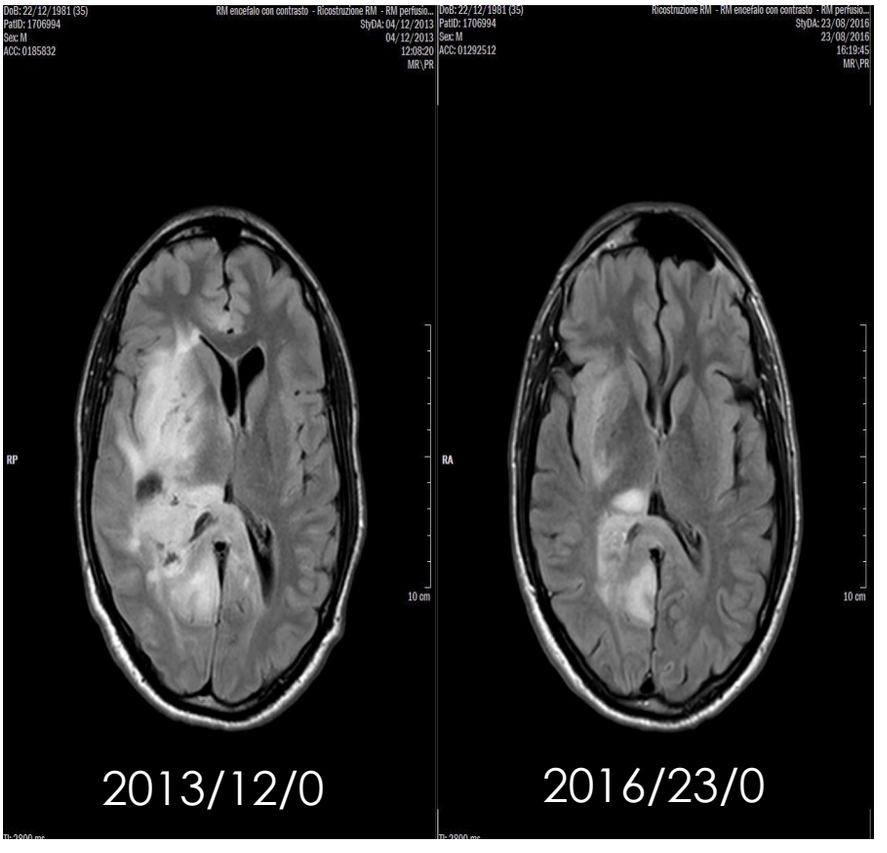

Figure 2) Astrocytoma GIII (g.e. 32 yrs) 2-response

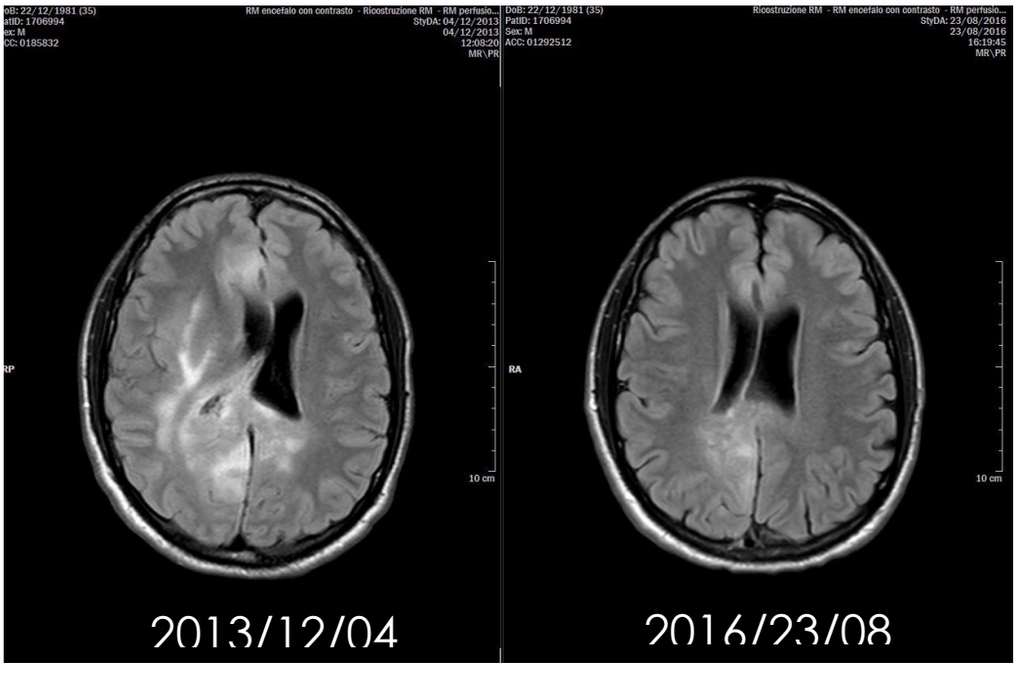

Figure 3) ASTROCYTOMA G III (G.E. 32 yrs)
3- Progression at 59 months later

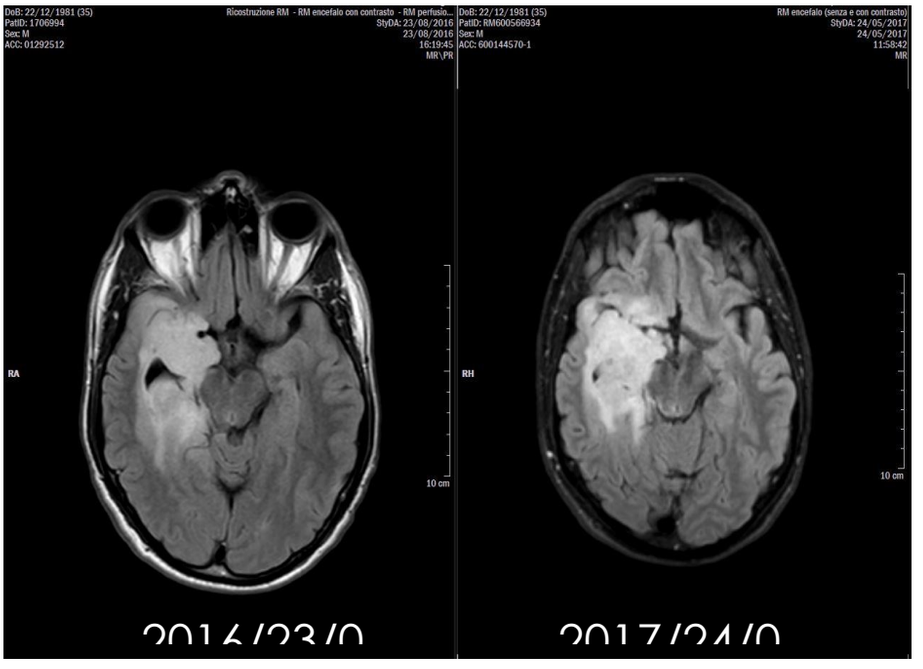

Figure 4) ASTROCYTOMA G III (G.E. 32 yrs)
3- Progression at 59 months later

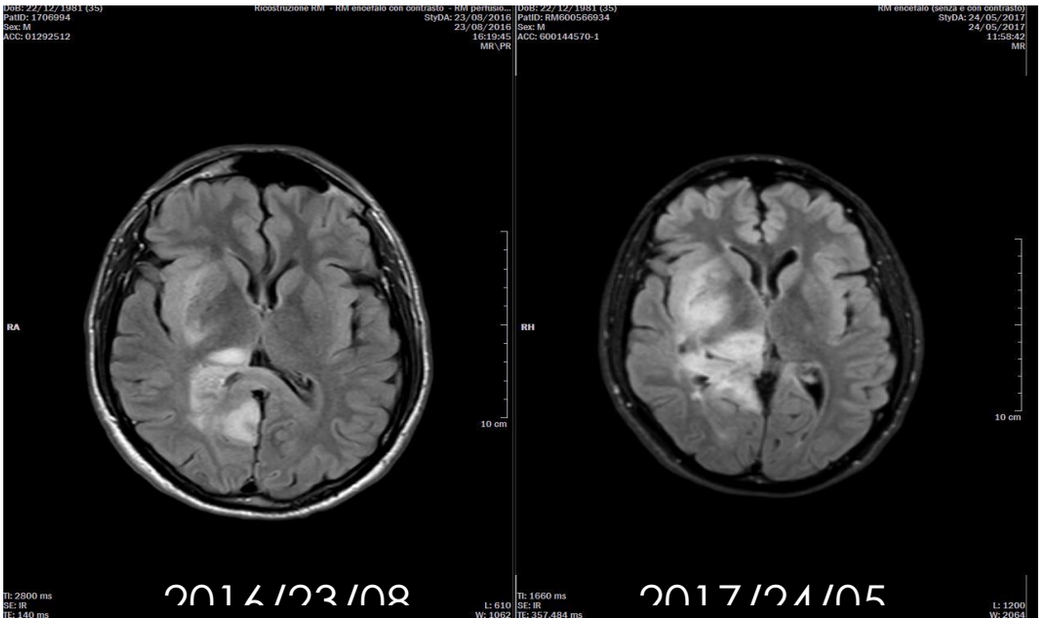

Figure 5) Survival data was compared to survival data for standard of care using the Surveillance, Epidemiology and End Results (SEER) database (in black) as a control for the evaluation of an integrative approach where EHT was the primary variable being explored