Modulated Electro-Hyperthermia (mEHT) in Intergrative Cancer Treatment for Relapased Malignant Gliobastroma and Astrocytoma: a retrospective multicenter controlled study

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Modulated Electro-Hyperthermia (mEHT) in Intergrative Cancer Treatment for Relapased Malignant Gliobastroma and Astrocytoma: a retrospective multicenter controlled study

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Background

Brain tumor therapy with hyperthermia and with an electric field is approved by the United States Food and Drug Administration (FDA). There are interesting studies on glioma therapy with modulated electro- hyperthermia (mEHT), which combines the heat-therapy with an electric field. Clinical researchers had found the mEHT method feasible for not only palliative but reported also evidence of therapeutic response.

Purpose

To monitor the efficacy and safety of modulated electro-hyperthermia (mEHT) for the treatment of relapsed malignant glioma and astrocytoma.

Methods

We collected data retrospectively on 150 patients that were affected by malignant glioma and astrocytoma. Inclusion criteria were: informed consent signed, >18 years old, histological diagnosis of malignant glioma or astrocytoma, failure of previous temozolomide-based chemotherapy and radiotherapy, indication for treatment with mEHT as the palliative setting. mEHT was performed using a capacitive coupling technique keeping the skin surface at 26 C° and 40-42.5 C° inside the tumor for > 90% of treatment duration (20-60 minutes). The applied power was 40-150 Watts. Results of mEHT were compared to those of the best supportive care (BSC).

Results

150 consecutive patients were enrolled in the study, 111 (74%) had glioblastoma multiforme (GBM), and 39 (26%) had astrocytoma (AST). mEHT was performed to 28 (25%) of GBM and 25 (64%) of AST.

Tumor response analysis three months after mEHT was 29% for GBM and 48% for astrocytoma, whereas it was 4% for GBM and 10% for AST for the group that did not receive mEHT.

The median overall survival (OS) of the whole study population was 9 months (range 5-108) for GBM and 16 months (6-156) for AST group. We observed 3 long survivors at 156, 60, 62 months in AST group.

Modulated Electro-Hyperthermia (mEHT) in Integrative Cancer Treatment for Relapsed Malignant Glioblastoma and Astrocytoma: a retrospective multicenter controlled study

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Background

Malignant Gliomas Therapy (MGlioT) with an electric field is approved by the Food and Drug Administration (FDA).
Studies on MGlioT with mEHT, which combines the heat-therapy with an electric field, suggest a new way for research.

Experts had found the mEHT method is feasible for not only palliative but reported also evidence of therapeutic response.

Hypothesis: HT may be effective in HG gliomas (I)

•Radiofrequency hyperthermia is usefull for malignat brain tumors (Tanaka R, 1987)

•Thermotherapy of recurrent malignant brain tumors is usefull (Sneed 1992)

•Favourable effects of antineoplastic agents and hypertehrmia on cytoyoxicity toward chronically hypoxic glioma cells . (Watanabe M, 1992)

•Survival benefit of hyperthermia in a prospective randomized trial of brachytherapy boost +/-hyperthermia fot HG gliomas : improves mOS with p = 0.008; hazard ratio 0.51 (Sneed, 1998)

Hypothesis: HT may be effective in HG gliomas (II)

•Application of hyperthermia induced by superparamagnetic iron oxide nanoparticles in glioma treatment contribute toward establishing magnetic hyperthrrmia as a promising tool in the treatment of malignant gliomas (Silva AC, 2011).

•Treatment of malignant glioma using hyperthermia has beneficial effect s (Sun J, 2013)

•Concurrent hyperthermia and re-irradiation for recurrent high-grade gliomas suggested that is a safe and well-tolerated. (Heo J , Neoplasma, 2017)

•Hyperthermia induces traslocation of apoptosis-inducing factor (AIF) and apoptosis in human glioma cell lines (Fukami T, 2004)

•Improving efficiency of adriamycin crossing blood brain barrier by combination of thermosensitive liposomes and hypertehrmia (Gong W,2011)

•Efficacy and safety of intratumoral thermotherapy using magnetic iron-oxide nanoparticles combined with radiotherapy on patients with recurrent HG gliona (Mair-Hauff K, 2011)

Hypothesis: HT may be effective in HG gliomas (III)

•Treatment of malignant glioma using hyperthermia (Sun J, 2013)

•Thermotherapy-induced reduction in glioma invasiveness is mediated by tumor necrosis factor-alpha. (Qin LJ, 2015)

•Stereotactic Laser Interstitial Thermal Therapy for Recurrent High-Grade Gliomas. (Lee I, 2016).

•Enhanced Energy Localization in Hyperthermia Treatment Based on Hybrid Electromagnetic and Ultrasonic System: Proof of Concept with Numerical Simulations.(Nizam-Uddin N, 2017**).**

•Pulsed-wave low-dose ultrasound hyperthermia selectively enhances nanodrug delivery and improves antitumor efficacy for brain metastasis of breast cancer.(Wu SK, 2017)

Hypothesis: mEHT may be effective in HG gliomas

•Non invasive intracranial hyperthermia with capacitive transference ECT intratumoral and cerebral thermometry gives favourable results (Ley-Valle, 2003) .

• Regional EHT in combination with chemotherapy induces a mOS of 44,2 and 23,2 months in relapsed HG gliomas (Sahinbas, 2005) .

•Phase II clinical study on relapsed HG gliomas treated with EHT reported a RR of 25% (Fiorentini, 2006).

•EHT combined with alkylating drugs in relapsed HG gliomas reported that is tolerable and feasible (Wismeth ,2010).

•EHT inhibits glioma tumorigenicity through the induction of E2F1-mediated apoptosis. Int J Hyperthermia (Cha J, 2015).

Hypothesis: mEHT may be effective in HG gliomas

•Clinical and economic evaluation of modulated EHT concurrent to dose-dense temozolomide regimen in the treatment of recurrent glioblastoma: a retrospective analysis of a two-center German cohort trial with systematic comparison and effect-to-treatment analysis (Roussakov SV, 2017).

• Energy Absorption by the Membrane Rafts in the Modulated Electro-Hyperthermia (Papp E, 2017)

•Retrospective observational Clinical Study on Relapsed Malignant Gliomas Treated with Electro-Hyperthermia (Fiorentini, 2017)

Purpose

to study efficacy and safety of mEHT for the treatment of relapsed malignant glioma (GBM and AST) versus the best supportive care (BSC).

Methods 1

we collected data retrospectively on 149 patients affected by GBM and AST.

Inclusion criteria were: informed consent signed, >18 years old, histological diagnosis of malignant glioma, relapsed after surgery, adjuvant temozolomide-based chemotherapy and radiotherapy, indication for treatment with mEHT as the palliative setting.

Table 1. Description of AST patient's group

Parameters (AST)	#	%
Males	20	52.6
Females	18	47.4
mEHT treated	22	58
MGMT methylated	11	28.9
MGMT non methylated	11	28.9
MGMT ND	16	42.2
IDH1 mutated	13	34.2
IDH1 wild type	11	28.9
IDH1 ND	14	36.9
age (range)	22 - 80	-
survival (range)	3 - 156	-

Table 2. Description of GBM patient's group

Parameters (GBM)	#	%
Males	68	61.3
Females	43	38.7
mEHT treated	28	25.2
MGMT methylated	25	22.5
MGMT non methylated	27	24.3
MGMT ND	59	53.2
IDH1 mutated	13	11.7
IDH1 wild type	19	17.1
IDH1 ND	79	71.2
age (range)	27 - 86	-
survival (range)	2 - 108	-

Methods 2

mEHT was performed with capacitive coupling technique keeping the skin surface at 26 C° and 40-42.5 C° inside the tumor for > 90% of treatment duration (20-60 minutes). The applied power was 40-150 Watts step-up heating protocol. Results of mEHT were compared to those of the Best Supportive Care. BSC included further chemotherapy and radiotherapy, immunotheraphy, CBD and holistic therapy

Premedications of patients receiving mEHT on the Brain

Generally every patient received surgery and radiotherapy before mEHT, for this reason they had already an anti-seizures therapy.

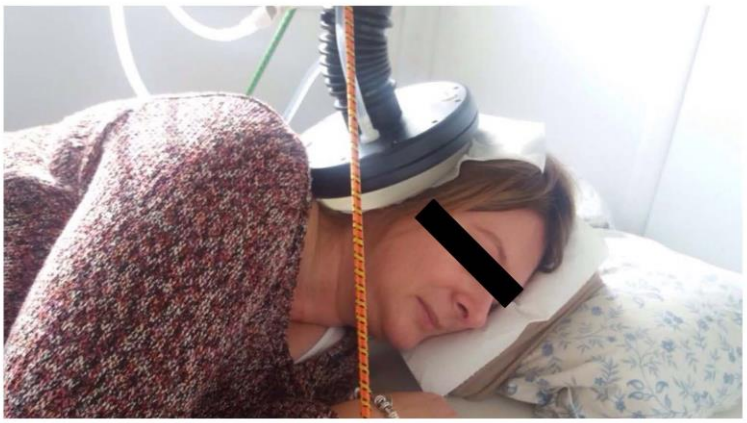
If the patient suffered from seizures, 250 ml of glicerol 18% solution was administered in 30 minutes before mEHT and also 12 mg of dexamethasone in drops were given to the patient.

Omeprazole (proton pump inhibitor) was administered for the whole cycle therapy at the dosage of 40mg/day.

Table 3. Treatment parameters

Practical parameters	value
step-up power (from-to [W])	40-150
average energy-dose (kJ)	540
Therapeutic temperature (°C)	40-42.5
treatment time /session	60
treatment frequency (weakly)	3
treatment cycle (weeks)	8
follow-up time (months)	16

ELECTRO HYPERTHERMIA



Treating area: **Brain tumor (Pons site)**

Invasivity: **NON-INVASIVE**

Results 1: 149 consecutive patients were enrolled, 111 (74%) had GBM and 38 (26%) had astrocytoma (AST). mEHT was performed to 28 (25%) of GBM and 24 (63%) of AST.

Tumor response was observed in 29% and 48% of GBM and astrocytoma in mEHT group respectively, whereas it was observed in 4% and 10% of GBM and AST in BSC group respectively, at the three months follow up.

Response rates of AST

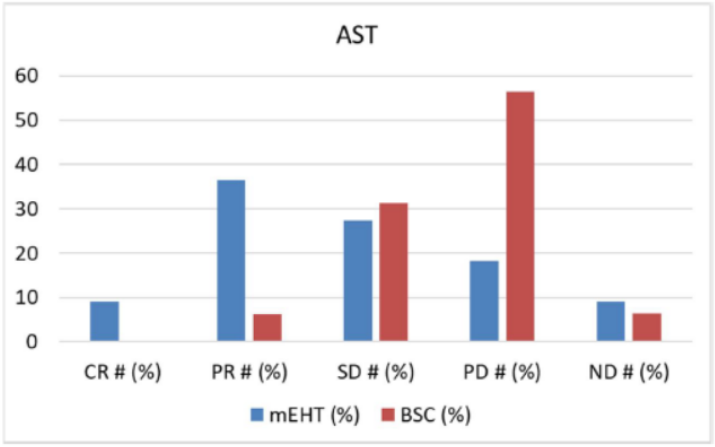


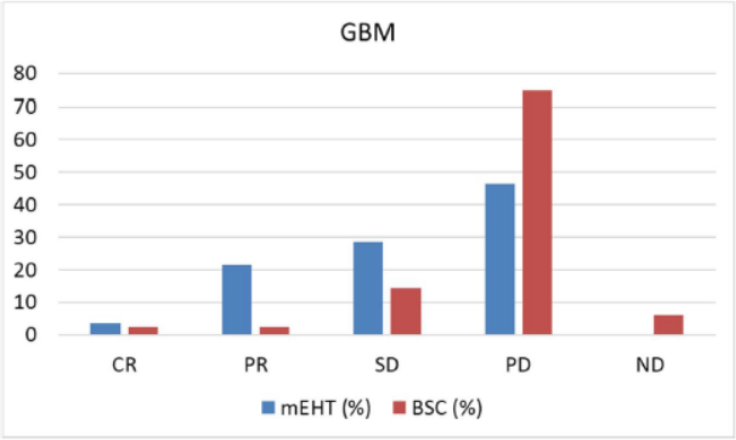
Table 4. Tumor response and survival of AST group

Results (AST)	mEHT (#)	mEHT (%)	BSC (#)	BSC (%)
CR # (%)	2	9	0	0
PR # (%)	8	36	1	6
SD # (%)	6	27	5	31
PD # (%)	4	18	9	56
ND # (%)	2	9	1	6
OS median [months] (range)	16	(3-156)	16.5	(3-120)

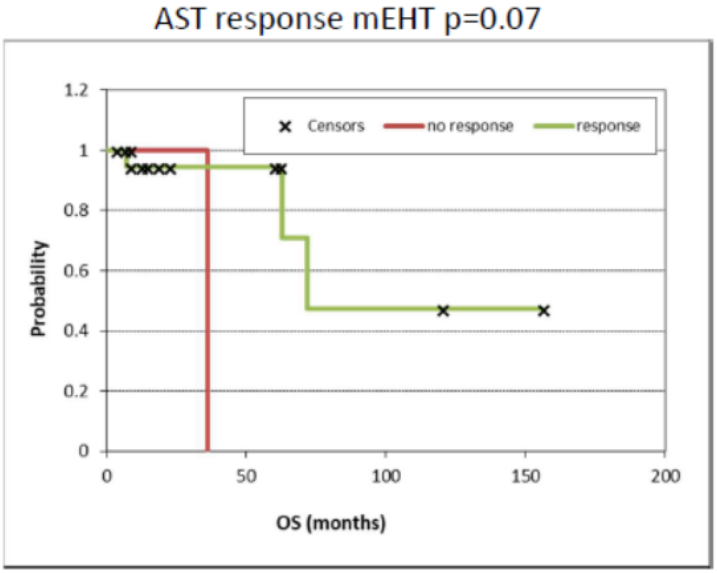
Table 5. Tumor response and survival of GBM group

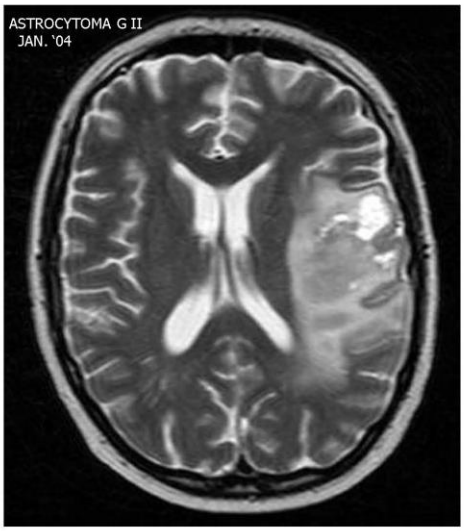
Results (GBM)	mEHT (#)	mEHT (%)	BSC (#)	BSC (%)
CR # (%)	1	4	2	2
PR # (%)	6	21	2	2
SD # (%)	8	29	12	14
PD # (%)	13	46	62	75
ND # (%)	0	0	5	6
OS median [months] (range)	14	(2-108)	9	(2-84)

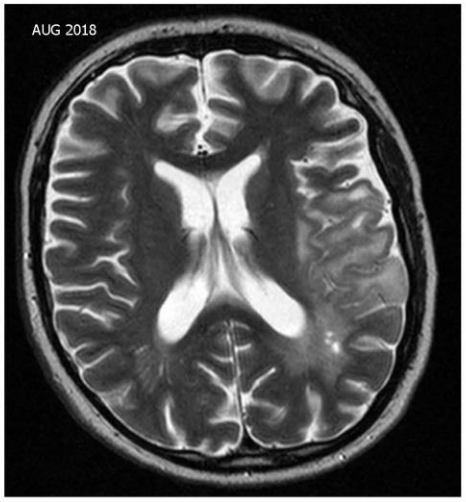
Response rates of GBM

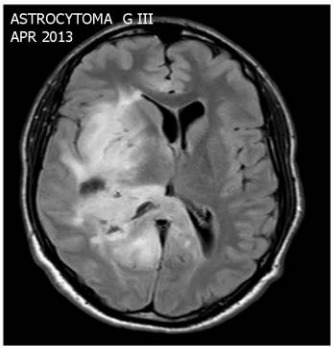


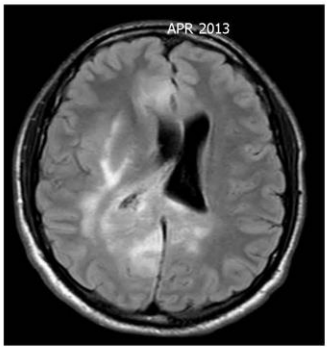
Results 2: Survival rate at 1st and 2nd year in the mEHT group was 77.3% and 40.9%, rispectively for AST. The 5-year OS of AST was 83% after mEHT vs. 25% after BSC.
The median overall survival (OS) was 10 months (2-108) for GBM and 16.5 months (3-156) for AST group. We observed 4 long survivors in AST and 2 in GBM group. Two of the long survivors in AST the one in GBM group were treated by mEHT.

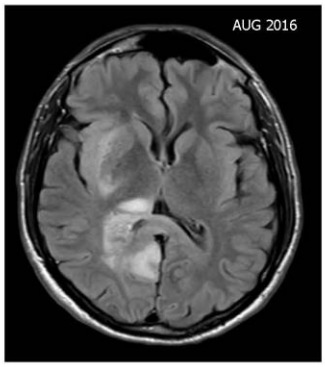


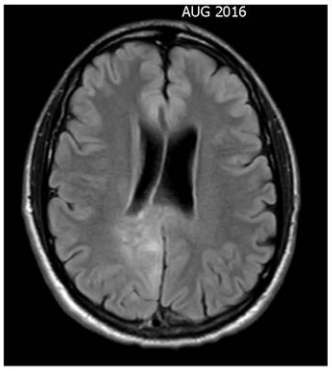

ASTROCYTOMA G II
JAN. '04


AUG 2018


ASTROCYTOMA G III
APR 2013


APR 2013


AUG 2016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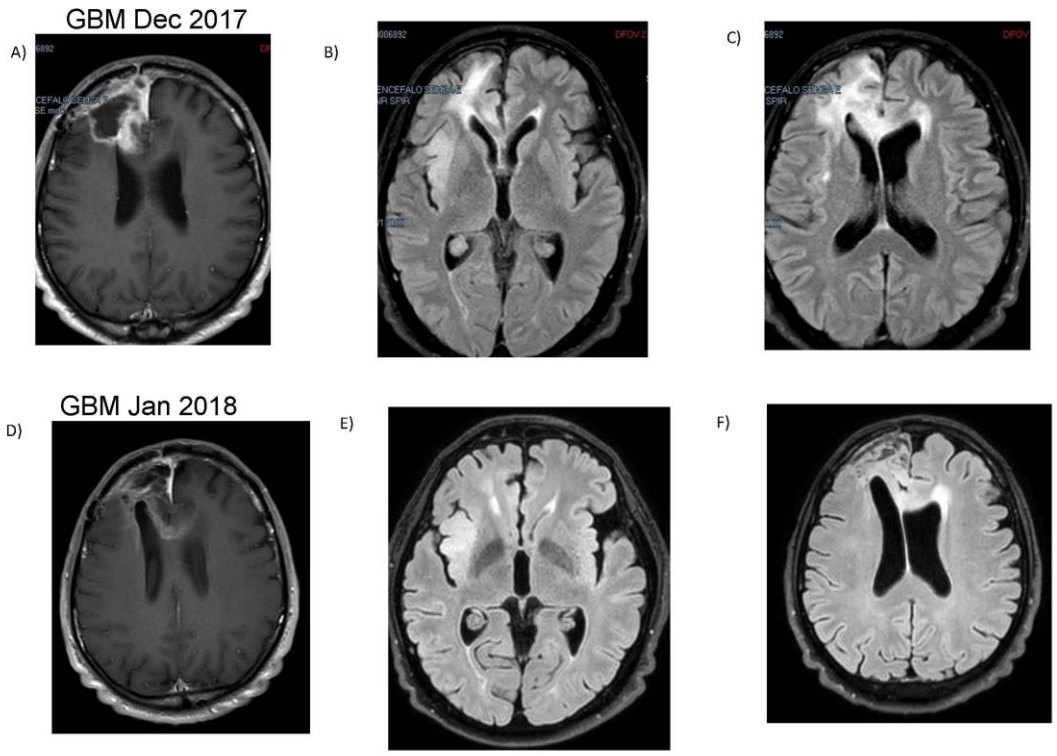
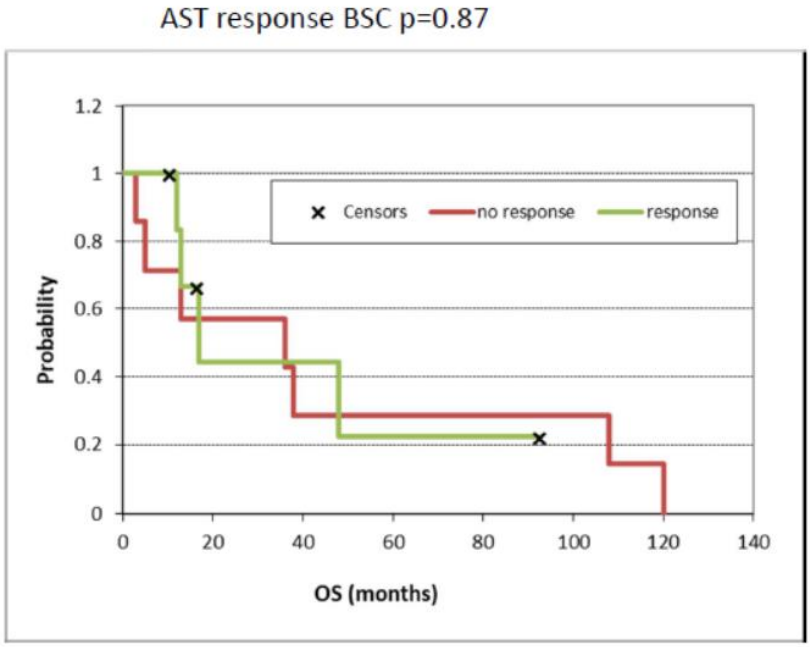
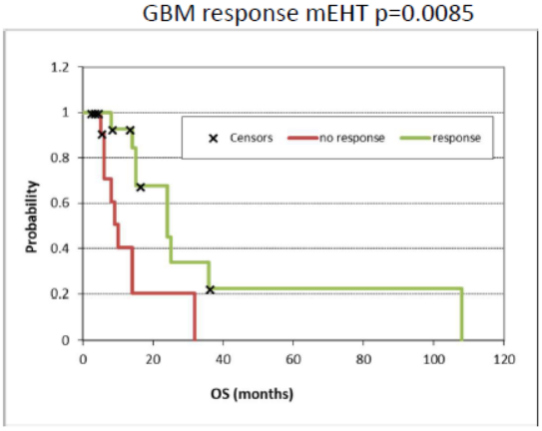
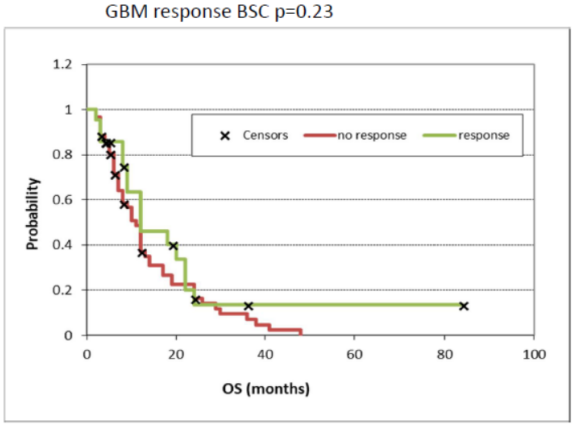

GBM Dec 2017
A)
B)
C)
GBM Jan 2018
D)
E)
F)


AST response BSC p=0.87
Censors
no response
response
Probability
OS (months)
0
0.2
0.4
0.6
0.8
1
1.2
0
20
40
60
80
100
120
140

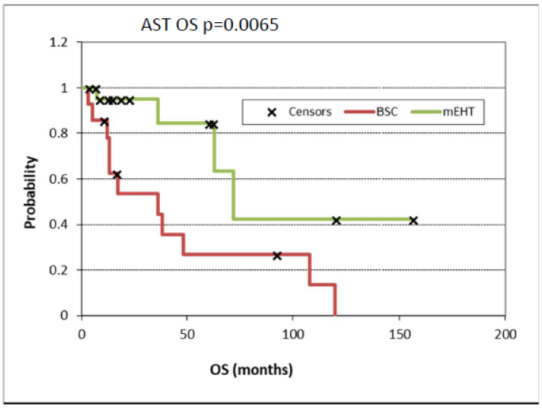
GBM response mEHT p=0.0085



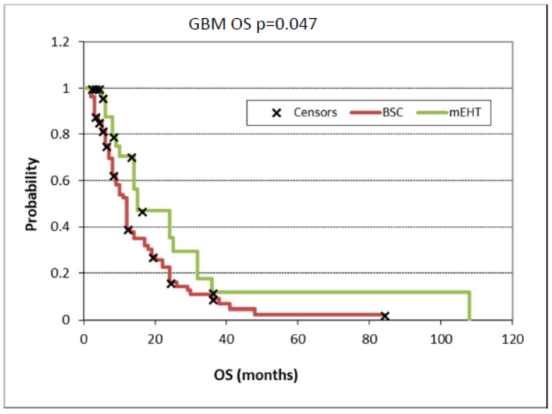
GBM response BSC p=0.23



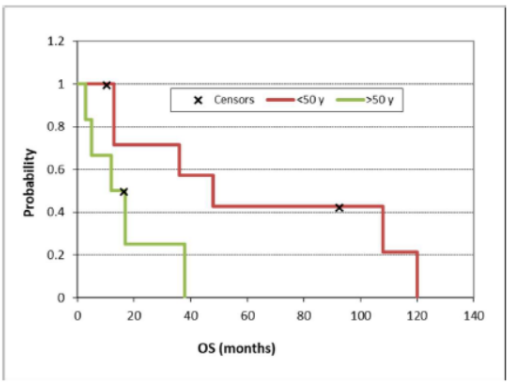
AST OS p=0.0065



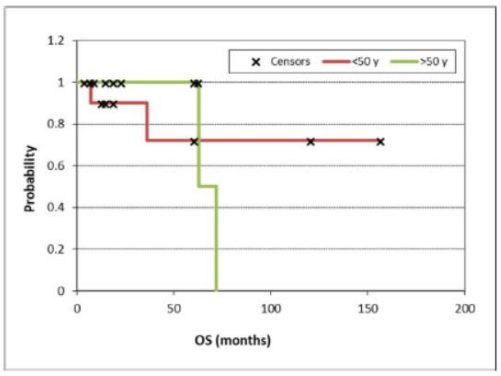
GBM OS p=0.047



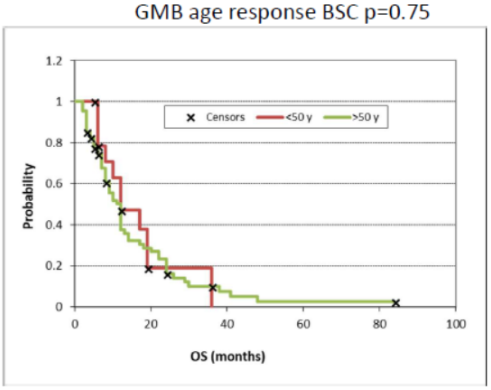
AST age response BSC p=0.04

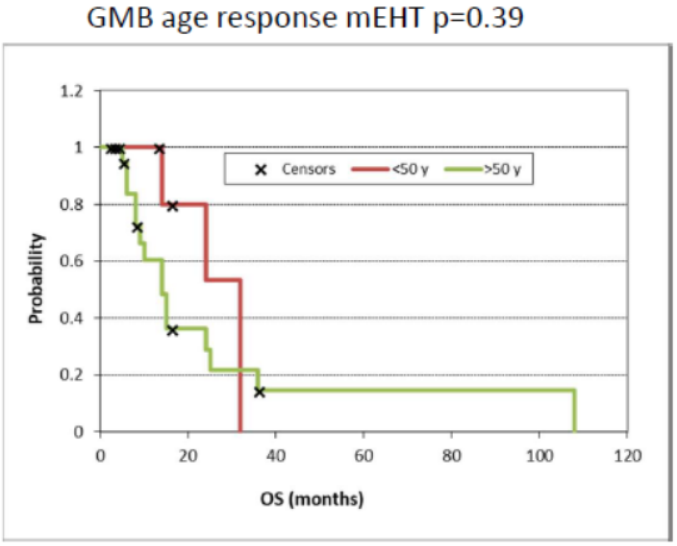


AST age response mEHT p=0.82



GMB age response BSC p=0.75





Conclusions: mEHT in integrative therapy may have promising efficacy for the treatment and palliation of relapsed GBM and AST.