Retrospective clinical study of adjuvant electro-hyperthermia treatment for advanced brain-gliomas

Hüseyin Sahinbas[1],
Dietrich HW Grönemeyer[1],
Eckhard Böcher[2], Andras Szasz[3]

Summary

Malignant gliomas represent about 70 % of all brain tumors. Despite advances in standard therapy consisting of surgery, radiation therapy and chemotherapy, gliomas remain an essentially fatal disease, with a median survival time of 10 to 12 months and a 2-year survival rate of 8 % to 12 %. Electro-hyperthermia applied either alone or in combination with chemo- and/or radio-therapy is an advanced hyperthermia technique that has been used as adjuvant treatment for patients with malignant glioma. We present the results of a retrospective study of 140 patients with different stages of malignant glioma, which were treated/followed from January 2000 to February 2005. The endpoint was the overall survival and the survival from the 1st electro-hyperthermia treatment. The overall median survival time for patients with mostly advanced malignant glioma who received adjuvant electro-hyperthermia in this study was 20.4 months. The median survival time from the first electro-hyperthermia treatment was 6.6 months. Electro-hyperthermia was safe and well tolerated. The presented results show the feasibility of the treatment and suggest a benefit of the electro-hyperthermia treatment for patients with advanced malignant glioma.

Keywords
Malignant glioma, hyperthermia, chemotherapy, radiotherapy, survival rates

Introduction, objectives

Malignant gliomas represent about 70 % of all brain tumors [18]. Despite advances in standard therapy consisting of surgery, radiation therapy and chemotherapy, gliomas remain an essentially fatal disease, with a median survival time of 10 to 12 months and a 2-year survival rate of 8 % to 12 %. Without debulking surgery, survival time can be less than 6 months with a 2-year survival rate of 0 % [3, 6, 8, 14, 18]

Reasons for the lack of therapeutic success may be migrating tumor cells that spread into the surrounding healthy tissues, creating the basis for inevitable recurrences, and further disseminations as well as the insufficient chemoperfusion into the brain due to the brain-blood-barrier [1, 7]. Genetic alterations in glioblastoma multiforme, the most frequent histological type of glioma, are likely to affect cell proliferation and cell cycle control, as well as invasive metastatic growth [19]. Furthermore, disruption of cell death pathways also contributes to the pathogenesis of glioblastoma multiforme and may result in resistance to chemotherapy and radiation [22]. Therefore, innovative therapeutic strategies have been based on drugs targeting cellular proliferation [7], invasion and angiogenesis [4]. Local therapy may have a temporary effect, but to be curative, treatment must reach all the tumor cells and target various therapeutic approaches [12].

The limited therapeutic options for patients who fail to respond to standard therapy have resulted in the development of various adjuvant therapies that aim at the control of tumor growth while reducing the severity of side effects associated especially with systemic treatments.

Hyperthermia combined with radiation therapy and/or chemotherapy has been reported as a potential cancer treatment, although the underlying molecular mechanisms of this procedure are not well understood. A number of studies have shown that hyperthermia inhibits angiogenesis, enhances chemo- and radio-sensitivity and induces a high concentration of drugs in a tumor [11, 27].

The effect of hyperthermia on intracranial malignancies has been evaluated in a number of experimental and clinical studies using various technical approaches, e.g. microwave and laser devices [2, 5, 9, 10, 13, 16, 17, 20, 21, 23, 25, 29]. While many investigators point to potential benefits for patients who receive adjuvant hyperthermia, it should also be noted that the application of heat to the brain

1 University Witten-Herdecke, Institute of Microtherapy, Universitätstrasse 142, 44799-Bochum, Germany;
2 Clinic „Closter Paradise“, Im Stiftsfeld 1, 59494-Soest, Germany;
3 St. Istvan University, Biotechnics Department, Szent Istvan krt. 20., 1137-Budapest, Hungary

Table 1

	Diffuse Astrocytoma	Anaplastic Astrocytma	Glioblastoma multiforme	Total
Number of patients, n (%)	8 (5.7 %)	40 (28.6 %)	92 (65.7 %)	140 (100 %)
Mean age (years)	44.3	39.5	49	43.5

does bear the risk of edema formation and damage to the blood brain barrier [24]. Electro-hyperthermia is an advanced hyperthermia technique that has been applied either alone or in combination with radiation- and/or chemotherapy [10, 21]. Electro-hyperthermia is considered to be selective through the higher conductivity and higher permittivity of the extracellular matrix of the tumor tissue. This effect may be based on the higher ionic concentration in the more active cellular environments and different physiological conditions of malignant tissue. The technique potentially reduces the risk of edema formation and adverse effects on healthy tissue.

Temozoline is an orally administered cytotoxic alkalising chemo-agent that has demonstrated activity in the treatment of glioblastoma multiforme. Different therapy protocols of temozoline have been described and a number of reports show that repetitious, frequent, low dose, long duration administration of selected chemotherapeutic drugs, combined with anti-angiogenesis therapies, targets the tumor vasculature and may be more effective than other conventional episodic, bolus and/or high dose chemotherapy [15]. An in-vitro study showed that hyperthermia potentiates the effect of temozoline in tumor cells [19].

The purpose of this retrospective study was to evaluate the feasibility of electro-hyperthermia in patients with malignant glioma and its effect on survival times.

Description of the trial

This study was a retrospective evaluation of patients with malignant brain glioma, who were treated with electro-hyperthermia during a period of 56 months. All patients had inoperable, sub-totally resected or recurrent brain glioma and a Karnofsky Performance Score of > = 40 %.

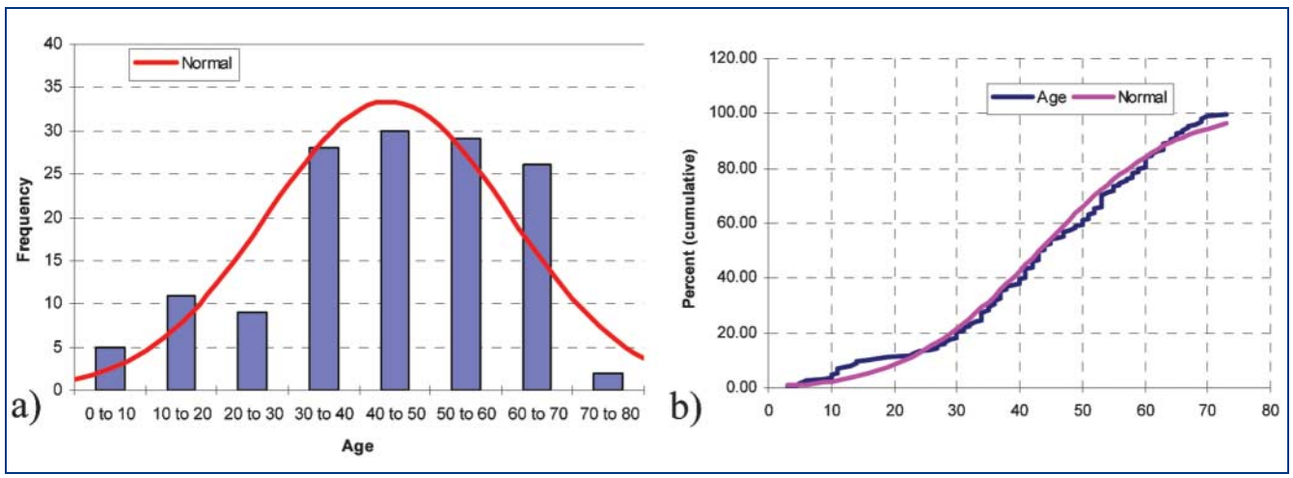

Fig. 1: Age-distribution (n = 140). a) Distribution by 10-year categories, b) probit cumulative.

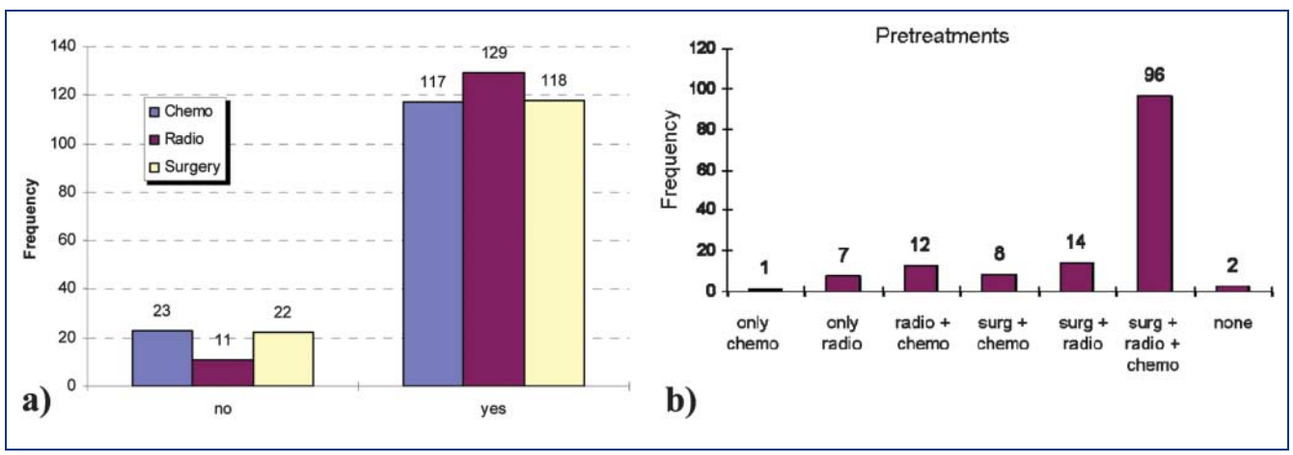

Fig. 2: Pretreatment overview by treatment (a) and combination (b).

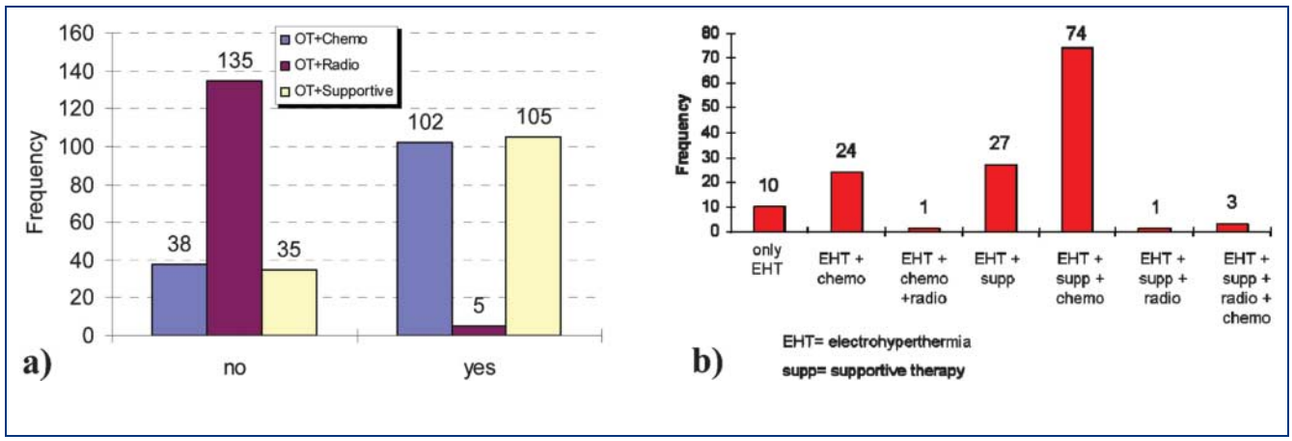

Fig. 3: Concomitant treatment overview by treatment (a) and combination (b).

Table 2: The applied supportive therapy.

Supportive therapy	Dose
Boswelia carterii	6 g/d, 3 ×/d
Mistletoe (e.g. Lectionol®)	15 ng, (3 ×/w), subcutaneously
Selenium	300 µg/d

The primary endpoints of the study were the median survival time and the median survival time from the first electro-hyperthermia treatment. The applied test was Kaplan-Meier log-rank. A total of 140 patients with malignant glioma were treated in the 56 month period. Demographic data and tumor diagnosis are summarized in Table 1.

As shown in Figure 1, the age-distribution was near to normal ($p < 0.001$, Chi-square test for discrete variables). There was a slight increase from the normal distribution in the range of 50–70 years. 15 patients (10.7 %) were below 18 years of age, and 8 patients (5.7 %) were over 68 years old. 50 patients (35.7 %) were female and 90 patients (64.3 %) were male.

All but 2 patients had received tumor treatment prior to electro-hyperthermia. Pretreatment included surgery (118 patients, 84 %), radiation therapy (129 patients, 92 %), and chemotherapy (117 patients, 84 %). Most patients had a combination of treatments as shown in Figure 2.

In most cases, electro-hyperthermia was applied as adjuvant therapy to standard treatment.

The distribution of concomitant treatments is shown in Figure 3. 102 patients (73 %) received concomitant chemotherapy, 5 patients (3.6 %) received radiation therapy, and 105 patients (75 %) received supportive therapy as described in table 2. If used, supportive therapy was started together with electrohyperthermia and was applied for 3 months. Patients who were not indicated to receive standard treatment were treated with electrohyperthermia only or in combination with supportive therapies.

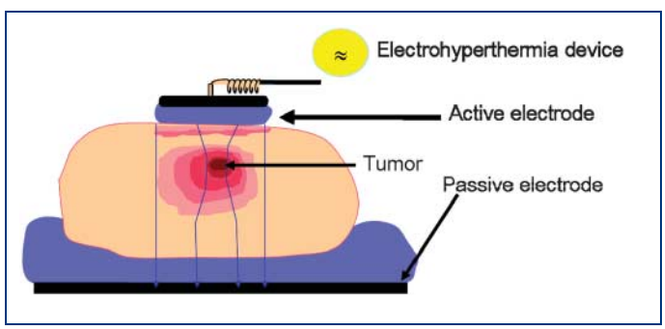

Fig. 4: Schematic display of loco-regional electro-hyperthermia.

The treatment method

Electro-hyperthermia was performed using the OncoTherm EHY 2000 (Oncotherm GmbH, Troisdorf, Germany). Short radiofrequency waves of 13.56 MHz were applied using a capacitive coupling technique keeping the skin surface at approximately 20 °C (Figure 4).

The applied power ranged between 40–150 W and the calculated average equivalent intra-tumoral temperature was above 40 °C more than 90 % of the treatment time. The electrode system was cautiously placed over the targeted area excluding the eye-area from the electrical field. Electro-hyperthermia was performed in two to three sessions per week. Applied power and application time and were gradually increased from 40 W for 20 minutes to 150 W for 60 minutes within the first two weeks.

Patients received a mean of 21.5 (range 2–108) electro-hyperthermia treatment sessions. The applied dose of electro-hyperthermia was regarded as low if it did not exceed the 8-times 60-minute load (dose-threshold). Such low doses were provided for 28 patients. The median time from diagnosis until the first electro-hyperthermia treatment was 11.3 months. The mean follow-up time after the last electro-hyperthermia treatment 6.6 months (Std.err = 0.8).

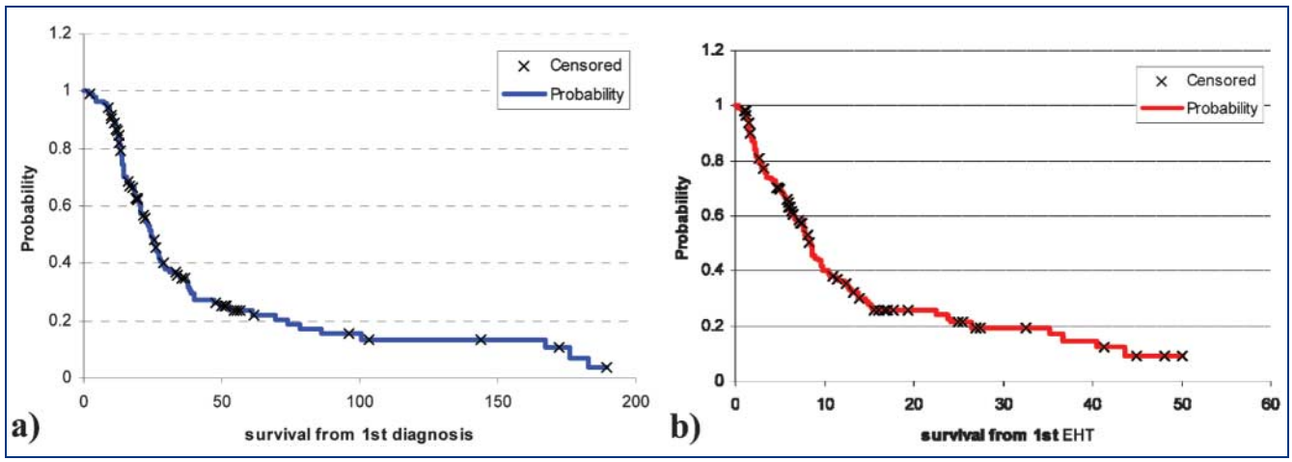

Fig. 5: Kaplan Meier Plots for median overall survival times.

Table 3: Mean and median survival time (months) by category

	Diffuse astrocytoma	Anaplastic astrocytma	Glioblastoma multiforme	Total
Number of patients, n (%)	8 (5.7 %)	40 (28.6 %)	92 (65.7 %)	140 (100 %)
Median survival time	56.1	26.1	16	20.4
Mean survival time	64.1	43	22.7	32.4
Median survival time from 1st EHT	8.9	9.1	6	6.6
Mean survival time from 1st EHT	12.3	13.2	7.7	9.9
Median time from diagnosis to 1st EHT	46.7	15.6	9.5	11.3
Mean time from diagnosis to 1st EHT	51.8	29.9	15	22.5

EHT: Electro-hyperthermia

Results and discussion

Overall, the median survival time was 20.4 months (range 1.4–190 months). The median survival time from the first electro-hyperthermia treatment was 6.6 months (range 0.3–50 months). The corresponding Kaplan-Meier plots are shown in Figure 5. As expected, the overall survival time was highest in patients with diffuse astrocytoma and lowest in the glioblastoma multiforme group. Categorized survival times are shown in Table 3.

Results of the subgroup analysis by age (< 50 years, > 50 years) are summarized in Table 4 and Table 5 and graphically displayed in Figure 6.

The analysis by age group greater and below 50 years of age shows a significantly higher median survival time for patients younger than 50 years in both time from first diagnosis ($p < 0.0003$) and time from first electro-hyperthermia ($p < 0.009$).

As shown in Figure 7, the relative dependency to dose-threshold (DT) was not significant for the overall median survival time ($p = 0.129$) and statistically significant for survival time from the first electro-hyperthermia treatment ($p < 0.01$).

No serious side effects related to electro-hyperthermia were reported (see Table 6). Patients tolerated the treatments well during the whole treatment period. During the treatment, most of the patients were relaxed, some even fell asleep. In subsequent MRI follow up examinations, no edema formation was observed (Figure 8).

Table 4: Mean and median survival time (months) for patients with diffuse or anaplastic astrocytoma by age group.

	< 50 years	> 50 years
Number of patients, n (%)	36 (25.7 %)	12 (8.6 %)
Median survival time	37.7	18.4
Mean survival time	56.7	23.3

Table 5: Mean and median survival time (months) for patients with glioblastoma multiforme by age group.

	< 50 years	> 50 years
Number of patients, n (%)	47 (33.6 %)	45 (32.1 %)
Median survival time	19	14.4
Mean survival time	28.7	17.1

Discussion

The overall median survival time for patients with mostly advanced malignant glioma who received adjuvant electro-hy-

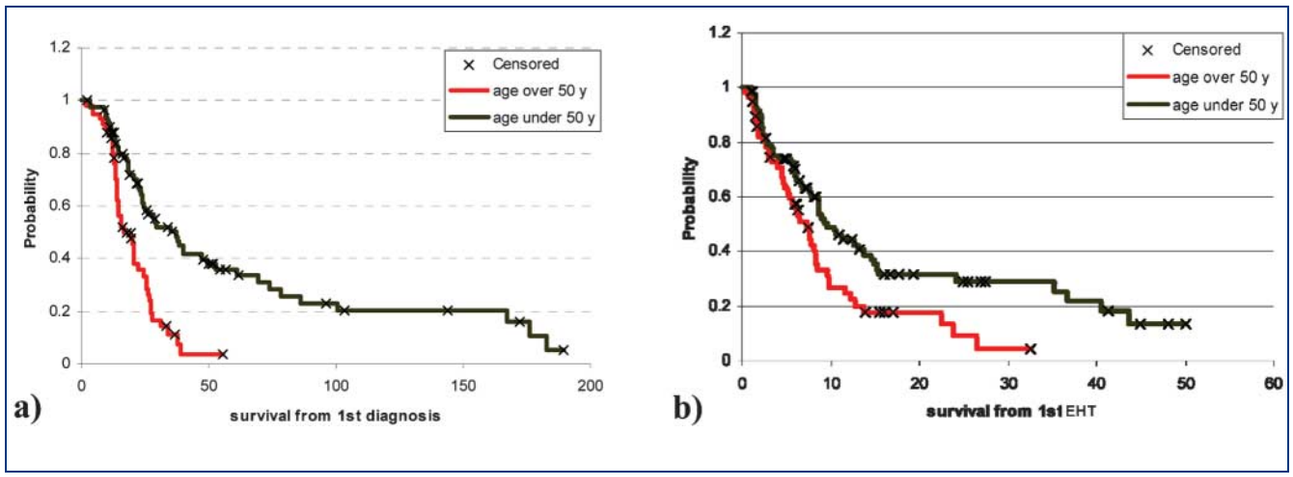

Fig. 6: Kaplan Meier Plots for median survival times by age groups.

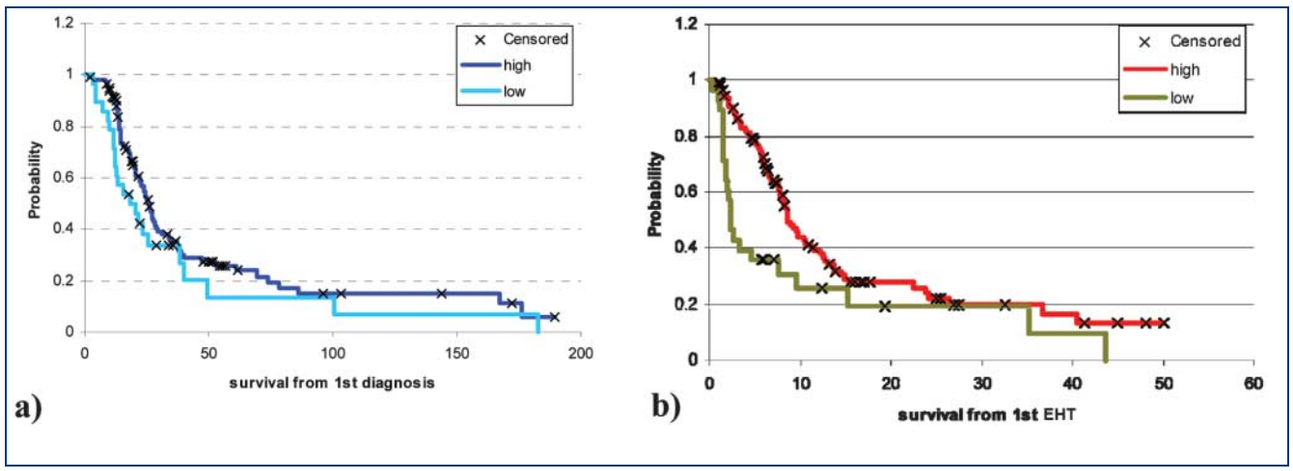

Fig. 7: Kaplan Meier Plots for dose dependence to dose threshold.

perthermia in this study was 20.4 months. The median survival time from the first electro-hyperthermia treatment was 6.6 months. Electro-hyperthermia was safe and well tolerated. Adding electro-hyperthermia to the overall treatment schedule was not considered as „extra load" by most patients.

When comparing the presented results with data from other studies it should be kept in mind that the design of this retrospective analysis and the low patient number, especially in the group of patients with diffuse astrocytoma, does not allow definite conclusions. In contrast to most prospectively designed study, who often focus on a selected population, the present study included all patients inoperable, subtotally resected or recurrent gliomas, in most cases with progression after radio- and/or chemotherapy.

Table 6: Overview of side effects.

Side effects	Rel. val.
Short term asthenia after treatment (< 2 h)	9 %
Local redness (rubor) of the skin	8 %
Subcutanous fibrosis of fatty tissue	1 %
Skin burn (diameter < 1.5 cm) Grade I–II	2 %
Headache and vomiting (< 2 h)	12 %

Stupp et al. [26] have treated a total of 573 patients with newly diagnosed glioblastoma with either radiotherapy alone or radiotherapy plus continuous daily temozolomide, followed by six cycles of adjuvant temozolomide. At a median follow-up of 28 months, the median survival was 14.6 months with radiotherapy plus temozolomide and 12.1 months with radiotherapy alone.

Data from the extensive U.S. National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program of cancer registries that collect clinical, demographic and cause of death information for persons with cancer show a median overall survival time of 42.7 months for patients with diffuse astrocytoma (n = 2749), 10.5 months for patients with anaplastic astrocytoma (n = 3273), and

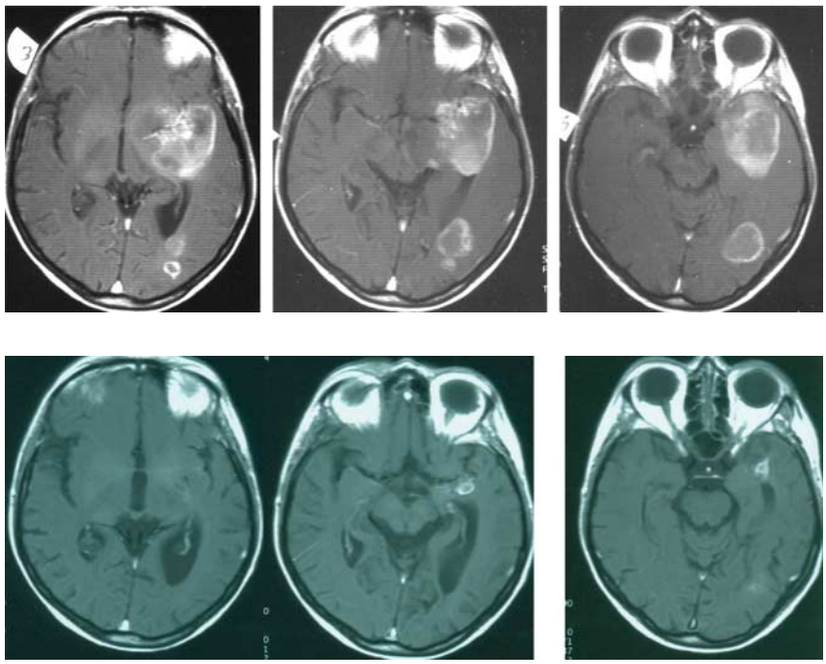

Fig. 8 a): MRI study of a 52-year-old female patient with a lesion of 6 × 5 × 4 cm in the left frontal region, and a mass in the left parietooccipital region measuring 4 × 3 × 3 cm diagnosed as glioblastoma multiforme in June 2002 (Pretreatment MRI, -T1, Gadolinium contrast).

10.2 months for patients with glioma multiforme (n = 5801) [28].

The presented results indicate that electro-hyperthermia either alone or in combination with radiation therapy or chemotherapy is feasible, well tolerated and safe in patients with advanced malignant gliomas. The clinical results and the results on survival time are encouraging, but must be confirmed by randomized, controlled clinical studies before more definite conclusions can be made.

Conclusions

The presented results show the feasibility of the treatment and suggest a benefit of the electro-hyperthermia treatment for the following reasons:

- Electro-hyperthermia was applied for brain tumors, showing a valid treatment potential.
- A transcranially applied, non-invasive electric field is able to perform the treatment.
- The treatment is safe and convenient to use.
- The survival time, as one of the most important parameters, was increased in patients with limited further treatment options.

References

[1] Begley DJ: ABC transporters and the blood-brain barrier. Current pharmaceutical design. 2004; 10: 1295–1312.

[2] Borok TL, Winter A, Laing J, et al: Microwave hyperthermia radiosensitized iridium-192 for recurrent brain malignancy. Med Dosim. 1988; 13: 29–36.

[3] Davis DL, Ahlbom A, Hoel D, Percy C: Is brain cancer mortality increasing in industrial countries? American Journal of Industrial Medicine. 1991; 19: 421–431.

[4] Eikesdal HP, Bjorkhaug ST, Dahl O: Hyperthermia exhibits anti-vascular activity in the s.c. BT4An rat glioma: lack of interaction with the angiogenesis inhibitor batimastat. Int J Hyperthermia. 2002; 18: 141–152.

[5] Fan M, Ascher PW, Schrottner O, et al: Interstitial 1.06 Nd:YAG laser thermotherapy for brain tumors under real-time monitoring of MRI: experimental study and phase I clinical trial. Journal of Clinical Laser Medicine & Surgery. 1992; 10: 355–361.

[6] Fisher PG, Buffler PA: Malignant gliomas in 2005: where to GO from here? JAMA. 2005; 293: 615–617.

[7] Friedlander DR, Zagzag D, Shiff B, et al: Migration of brain tumor cells on extracellular matrix proteins in vitro correlates with tumor type and grade and involves alphaV and beta1 integrins. Cancer Research. 1996; 56: 1939–1947.

[8] Greig NH, Ries LG, Yancik R, Rapoport SI: Increasing annual incidence of primary malignant brain tumors in the elderly. Journal of the National Cancer Institute. 1990; 82: 1621–1624.

[9] Guthkelch AN, Carter LP, Cassady JR, et al: Treatment of malignant brain tumors with focused ultrasound hyperthermia and radiation: results of a phase I trial. Journal of Neuro-oncology. 1991; 10: 271–284.

[10] Hager D, Dziambor H, App EM, et al. The treatment of patients with high-grade malignant gliomas with RF-hyperthermia. Proc Am Soc Clin Oncol. 22: 2003 (abstr 470).

[11] Hermisson M, Weller M: Hyperthermia enhanced chemosensitivity of human malignant glioma cells. Anticancer Research. 2000; 20: 1819–1823.

[12] Jendrossek V, Belka C, Bamberg M: Novel chemotherapeutic agents for the treatment of glioblastoma multiforme. Expert Opinion on Investigational Drugs. 2003; 12: 1899–1924.

[13] Kahn T, Harth T, Bettag M, et al: Preliminary experience with the application of gadolinium-DTPA before MR imaging-guided laser-induced interstitial thermotherapy of brain tumors. J Magn Reson Imaging. 1997; 7: 226–229.

[14] Kuratsu J, Ushio Y: Epidemiological study of primary intracranial tumours in elderly people. Journal of Neurology, Neurosurgery, and Psychiatry. 1997; 63: 116–118.

[15] Kurzen H, Schmitt S, Naher H, Mohler T: Inhibition of angiogenesis by non-toxic doses of temozolomide. Anticancer Drugs. 2003; 14: 515–522.

[16] Ley-Valle A. [Non invasive intracranial hyperthermia with Electric Capacitive Transference -ECT- Intratumoral and cerebral thermometry results]. Neurocirugia (Asturias, Spain). 2003; 14: 41–45.
[17] Moran CJ, Marchosky JA, Wippold FJ, 2nd, DeFord JA, Fearnot NE: Conductive interstitial hyperthermia in the treatment of intracranial metastatic disease. Journal of Neuro-oncology. 1995; 26: 53–63.
[18] Ohgaki H, Kleihues P: Epidemiology and etiology of gliomas. Acta neuropathologica. 2005; 109: 93–108.
[19] Pagani E, Falcinelli S, Pepponi R, et al: Combined effect of temozolomide and hyperthermia on human melanoma cell growth and O6-methylguanine-DNA methyltransferase activity. International Journal of Oncology. 2007; 30: 443–451.
[20] Pontiggia P, Duppone Curto F, Rotella G, et al: Hyperthermia in the treatment of brain metastases from lung cancer. Experience on 17 cases. Anticancer Research. 1995; 15: 597–601.
[21] Sahinbas H, Groenemeyer DHW, Boecher E, et al: Hyperthermia treatment of advanced relapsed glioma and astrocytoma (abstract). 9th ICHO, page 85; 2004.
[22] Sakaguchi Y, Stephens LC, Makino M, et al: Apoptosis in tumors and normal tissues induced by whole body hyperthermia in rats. Cancer Research. 1995; 55: 5459–5464.
[23] Selker RG, Eddy MS, Deutsch M, Arena VC, Burger P: On the development of an interstitial radiation protocol for a multicenter consortium. Experience with permanent low-dose rate and temporary high-dose rate 125I implants in failed and newly diagnosed glioblastoma patients: quality assurance methodology and a possible future adjuvant for therapeutic enhancement. Journal of Neuro-oncology. 1995; 26: 141–155.
[24] Sharma HS: Hyperthermia induced brain oedema: current status and future perspectives. The Indian Journal of Medical Research. 2006; 123: 629–652.
[25] Sneed PK, Stauffer PR, McDermott MW, et al: Survival benefit of hyperthermia in a prospective randomized trial of brachytherapy boost +/− hyperthermia for glioblastoma multiforme. International Journal of Radiation Oncology, Biology, Physics. 1998; 40: 287–295.
[26] Stupp R, Mason WP, van den Bent MJ, et al: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. The New England Journal of Medicine. 2005; 352: 987–996.
[27] Sumiyoshi K, Strebel FR, Rowe RW, Bull JM: The effect of whole-body hyperthermia combined with metronomic chemotherapy on rat mammary adenocarcinoma metastases. Int J Hyperthermia. 2003; 19: 103–118.
[28] Surveillance, Epidemiology, and End Results (SEER). National Cancer Institute; April 2000; www-seer.cancer.gov.
[29] Tanaka R, Kim CH, Yamada N, Saito Y: Radiofrequency hyperthermia for malignant brain tumors: preliminary results of clinical trials. Neurosurgery. 1987; 21: 478–483.

Correspondence to

Dr. med. Hüseyin Sahinbas
Universität Witten/Herdecke
Grönemeyer Institut
Universitätsstr. 140
44799 Bochum
E-Mail: sahinbas@microtherapy.de