

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

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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/monitored 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

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Table 1

	Diffuse Astrocytoma	Anaplastic Astrocytoma	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 alkalisng 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 %.

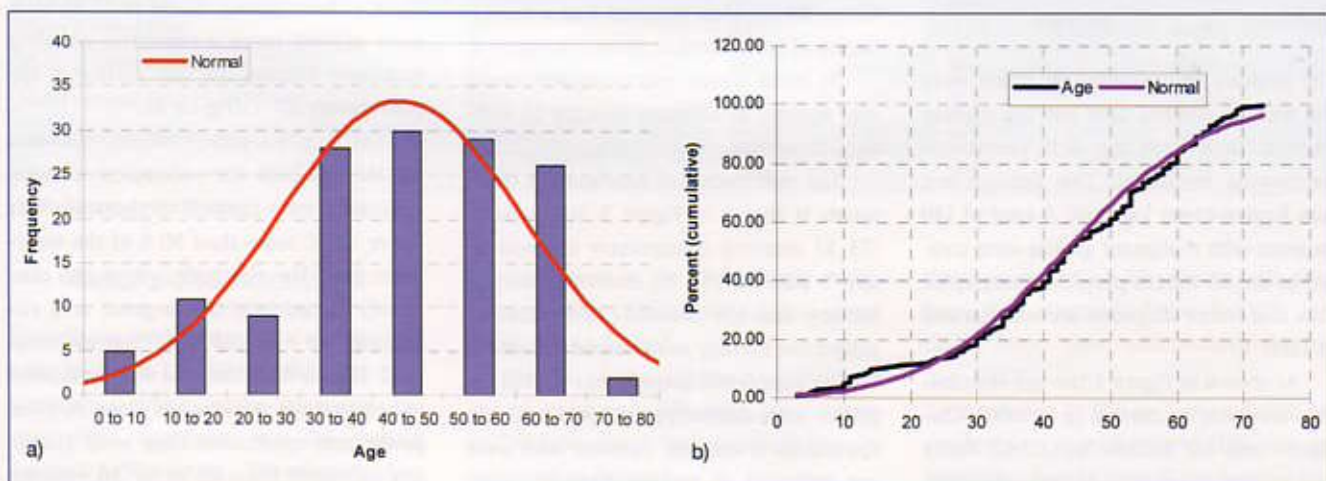


Fig. 1: Age-distribution (n = 140). a) Distribution by 10-year categories, b) probit cumulative.

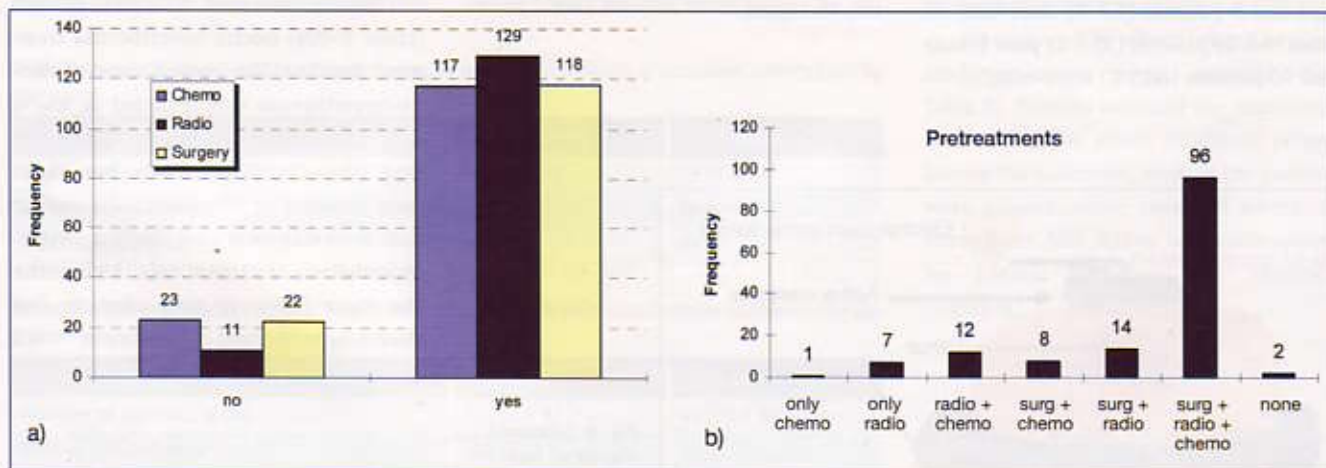


Fig. 2: Pretreatment overview by treatment (a) and combination (b).

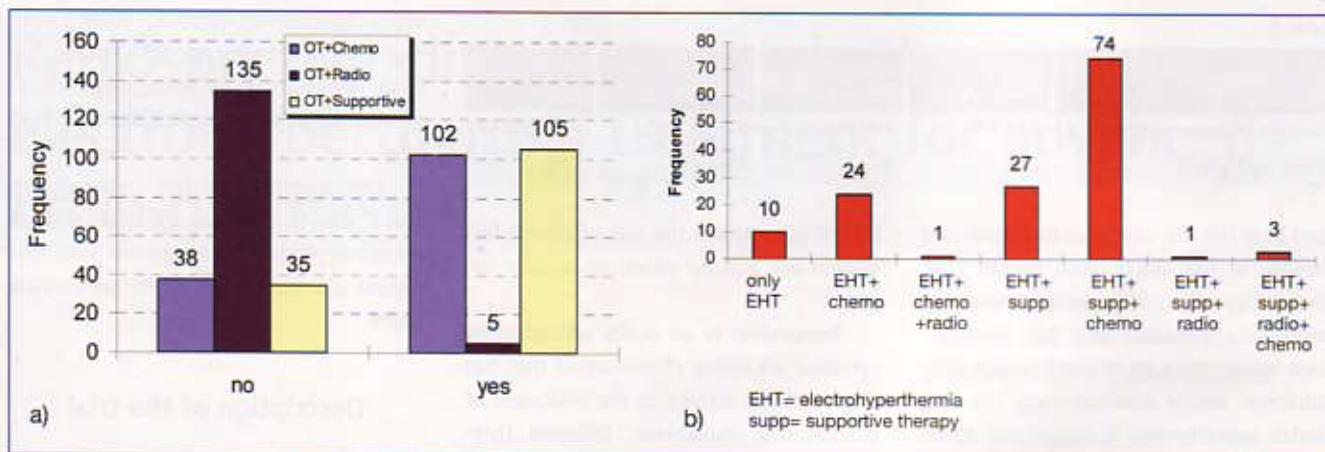


Fig. 3: Concomitant treatment overview by treatment (a) and combination (b).

Table 2: The applied supportive therapy.

Supportive therapy	Dose
Boswellia carterii	6 g/d, 3 x/d
Mistletoe (e.g. Lectionol®)	15 ng, (3 x/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.

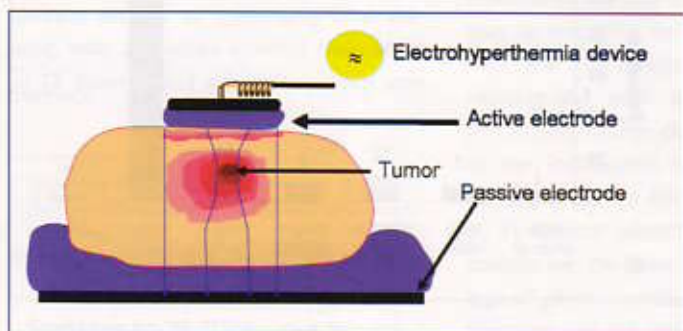


Fig. 4: Schematic display of loco-regional electro-hyperthermia.

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 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).

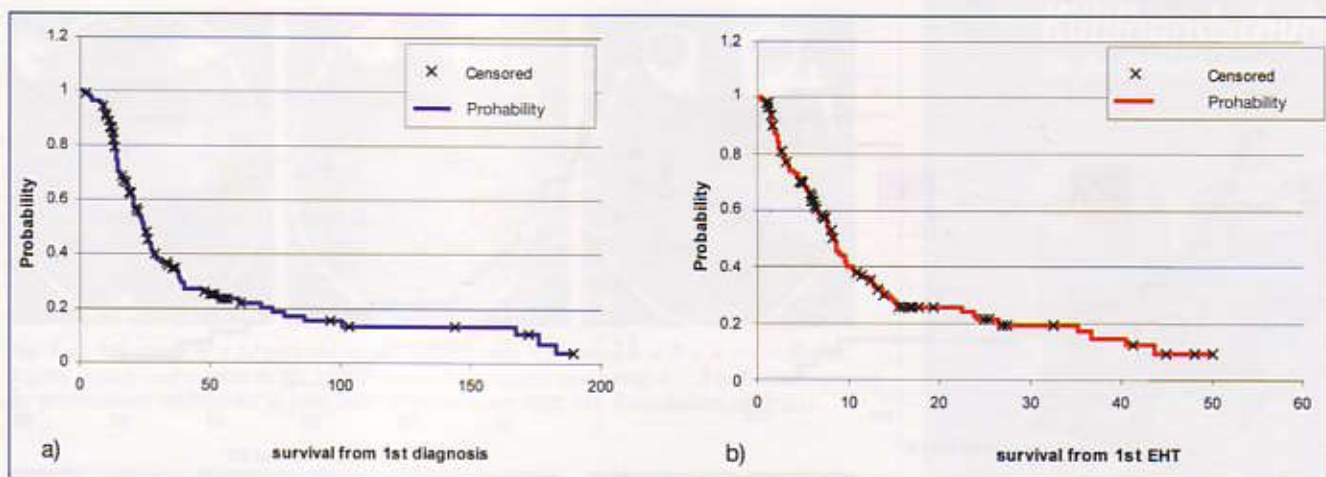


Fig. 5: Kaplan Meier Plots for median overall survival times.

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

	Diffuse astrocytoma	Anaplastic astrocytoma	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 1 st EHT	8.9	9.1	6	6.6
Mean survival time from 1 st EHT	12.3	13.2	7.7	9.9
Median time from diagnosis to 1 st EHT	46.7	15.6	9.5	11.3
Mean time from diagnosis to 1 st 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 astrocyto-

ma 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 pa-

tients 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).

Discussion

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

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

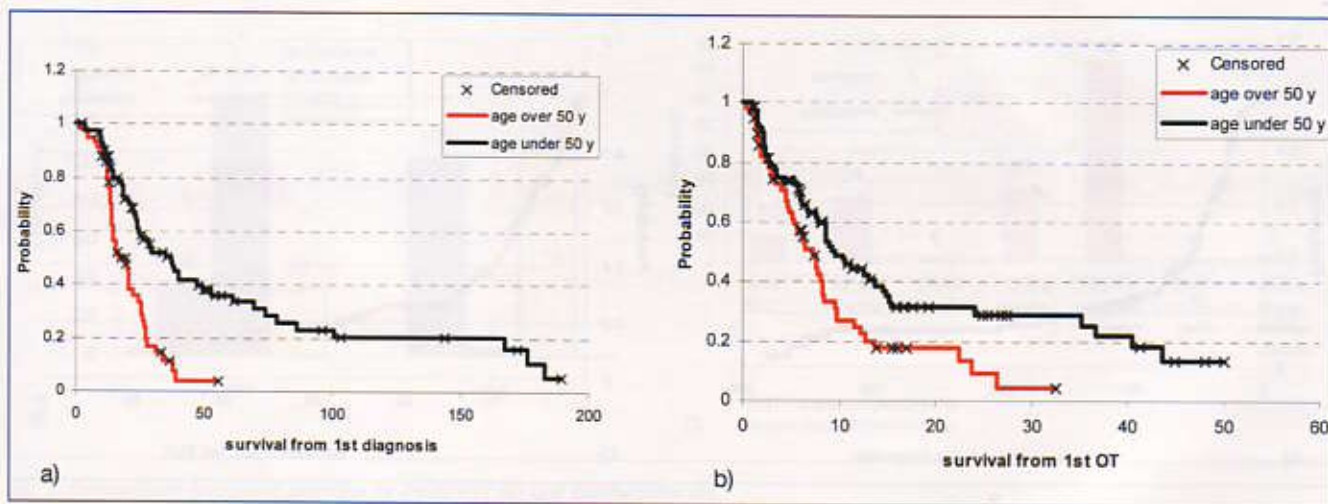


Fig. 6: Kaplan Meier Plots for median survival times by age groups.

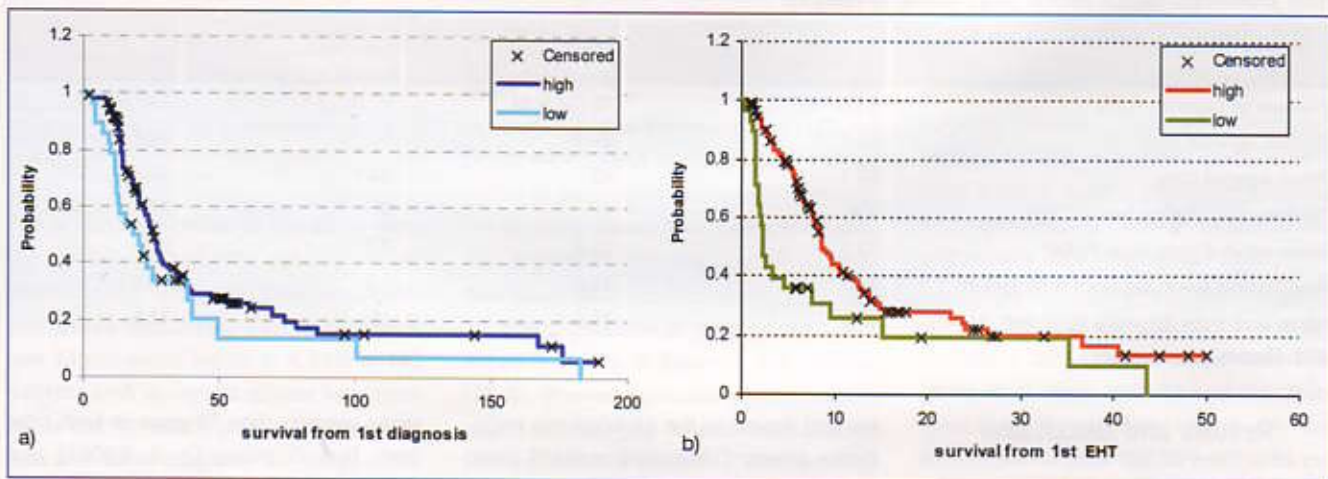


Fig. 7: Kaplan Meier Plots for dose dependence to dose threshold.

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 with inoperable, subtotally resected or recurrent gliomas, in most cases with progression after radio- and/or chemotherapy.

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

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 %
Subcutaneous fibrosis of fatty tissue	1 %
Skin burn (diameter < 1.5 cm) Grade I-II	2 %
Headache and vomiting (< 2 h)	12 %

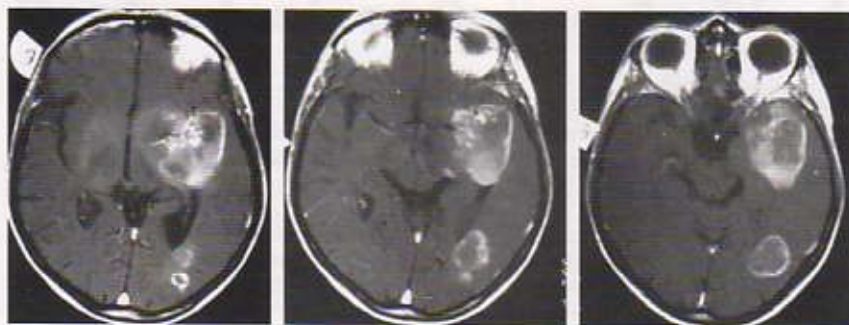


Fig. 8 a): MRI study of a 52-year-old female patient with a lesion of $6 \times 5 \times 4$ cm in the left frontal region, and a mass in the left parietooccipital region measuring $4 \times 3 \times 3$ cm diagnosed as glioblastoma multiforme in June 2002 (Pretreatment MRI, -T1, Gadolinium contrast).

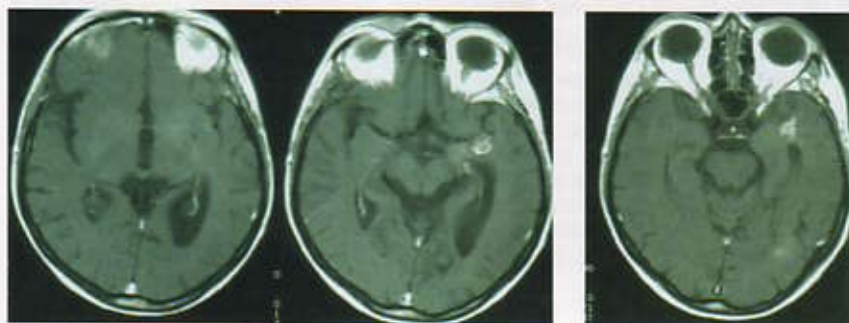


Fig. 8 b): MRI study from April 2004 showing clear remission of the tumor after fractionated radiotherapy (54 Gy total dose: $1.8 \text{ Gy} \times 5 \text{ d/wk}$ for 6 weeks) followed by adjuvant therapy of local electro-hyperthermia and concomitant temozolomide ($100 \text{ mg/m}^2/\text{d} \times 21$ days, one week rest, for six cycles) (Posttreatment 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.

Kühlhandschuhe für die Chemotherapie



Bei etwa 30% aller Patienten verursacht die Krebstherapie mit dem Wirkstoff Docetaxel zum Teil schmerzhaftes Nagel und Hautveränderungen. Dies kann zu einem vorzeitigen Abbruch der Behandlung führen.

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