

Retrospective clinical study for advanced brain-gliomas by adjuvant oncothermia (electro-hyperthermia) treatment

Sahinbas H, Baier JE, Groenemeyer DHW, Boecher E*, Szasz A**

University Witten-Herdecke, Institute of Microtherapy, Bochum, Germany;

(*) Clinic "Closter Paradise", Soest, Germany;

(**) St.Istvan University, Biotechnics Department, Budapest, Hungary

Abstract

Gliomas are one of the most common primary brain-tumors. Despite surgery and radiotherapy (RT) with or without adjuvant chemotherapy, malignant glioma remains an almost uniformly fatal disease characterized by a rapid and devastating clinical course. Oncologic hyperthermia (oncothermia or electro-hyperthermia = OT) applied either alone or in combination with chemo- and/or radio-therapy is a new modality of brain-glioma (BG) treatments. We present a retrospective study of 140 patients, which were treated/followed from February 2000 to June 2005. The endpoint was the overall survival and the survival from the 1st oncothermia treatment (survival from the relapse untreatable by other methods). The median/mean survival times were 19.8/31.7 month from 1st diagnosis and 6.7/10.0 months from 1st oncothermia, respectively. Results support the feasibility of oncothermia for advanced brain-glioma patients.

Key words: glioma, hyperthermia, oncothermia, survival-time

Introduction, objectives

Gliomas are common primary brain tumors in humans. Despite surgery and radiotherapy (RT) with or without adjuvant chemotherapy (CT), malignant glioma remains an almost uniformly aggressive fatal disease characterized by a rapid and devastating clinical course, [1]. The standard management of brain-gliomas (BG) involves cytoreduction through surgical resection, when feasible, followed by RT. RT may remarkably increase the median survival time (MST), while CT has no such robust effects. Unfortunately, the earlier well accepted PCV regimen (Procarbazine + CCNU(Lomustine) + Vincristine) was shown to be inefficient in a study with large numbers of patients (n=339 and n=335 in the control- and active-arms, respectively) [2]. Despite advances in therapy, BG remain essentially a fatal disease, with a median survival time of 10 to 12 months and 2-year survival of only 8% to 12% [3], [4], [5]. In a study where patients did not undergo debulking surgery, survival time was found to be less than 6 months and 2-year survival rate ended up at 0% [3]. The three studies of the Radiation Therapy Oncology Group (RTOG) retrospectively enrolled 1578 patients from 1974-1989, updated in 1991, show overall survival for anaplastic astrocytoma of 49.4 m for patients under the age of 50 years and 21.7 m for those being older. For glioblastoma multiforme 13.7 m and 9.7 m were obtained, respectively.

None of the established state-of-the-art treatments in malignant primary brain tumors, especially in GBM, could show effective or commonly accepted curative potential until today. One reason may be that tumor cells will migrate into the surrounding normal tissues, creating the basis for inevitable recurrences, and further disseminations. An other reason for the lack of success surely is the insufficient chemoperfusion into the brain in many patients due to the brain-blood-barrier, [6], [7]. In addition, it has been shown [8] that genetic alterations in GBM affect cell proliferation and cell cycle control, as well as invasive metastatic growth. And furthermore, disruption of cell death pathways also contributes to the pathogenesis of GBM and may result in resistance to chemotherapy and radiation [9]. Therefore, innovative therapeutic strategies have been based on drugs targeting cellular proliferation [10], invasion and angiogenesis [11]. Local therapy may have a temporary

effect, but for a cure, the treatment must reach all the tumor cells and target many therapeutic ways [12].

The present situation in the field of glioma-therapy is well summarized in one of the very recent editorial articles of JAMA [13]: “Where to GO from here?”.

Our present paper tries to indicate a possible alternative to go ahead: the brain oncothermia (OT) in combination with traditional tumor-treatment modalities like RT and CT.

Hyperthermia (HT) combined with RT and CT seems to be a promising method for cancer treatment, although many of the underlying molecular mechanisms of this combination treatment are not well understood until today. A number of studies showed that HT inhibits angiogenesis, enhances chemo- and radio-sensitivity and induces a high concentration of drugs within a tumor [14], [15].

Due to the limited effectiveness of established therapies, HT could be one of the important future methods to improve our treatment facilities. However, there are some restrictions to Hyperthermia in general, that hamper its use in cancer treatment., Namely, it could aggravate a preexisting edema and therefore increase the resulting pressure on the brain, which –finally- could be fatal. Despite those problems, a relatively high interest to study the effects of heat on brain-tumors is present [16], [17], [18]. Due to this reason, the proper localization of the incident energy is essential. Numerous well localized, mainly interstitial and invasive (ablative) techniques of HT are being applied in the treatment of gliomas [19], [20], [21], [22], [23], [24], [25], [26], [27], [28]. Some are also based on laser techniques [29], [30], others use implantable applications [31], [32].

Some other devices apply radiofrequency (RF) HT, with intra- and also extra-cranial approaches [33], [34], [35] Even ultrasound was tried for HT generation [36].

The electric capacitive coupling is introduced for transcranial applications by electro-hyperthermia [37] and later by by a similar method, (Electric Capacitive Transference, ECT) [38] was also applied. The clinical studies mentioned above , and in particular the controlled, randomized, double-armed study of Sneed et al. [39], indicated a surprisingly good efficacy of HT treatment for brain-tumors: The median survival had improved from 76 to 85 weeks, and the 2-year survival went up to 31% vs. 15%. In consequence, the FDA certified HT to the brain in its interstitial form.

One of the most advanced treatment modalities in this field of hyperthermia is called OncoThermia (OT). Usually it is applied in combination with chemo- and/or radiotherapy.

It is a new method in the treatment of brain gliomas with favourable toxicity profiles and show is promising preliminary results [40], [41], especially in combination with temozolomide (TMZ), which is an orally administered cytotoxic alkylating agent. TMZ has demonstrated its efficacy in the treatment of GBM [3]. Different therapy protocols with TMZ have been described [42]. A number of reports show that repetitious, frequent, daily-low dose but long duration administration of selected CT drugs can target tumor vessels and may be even more effective in some tumors than other, conventionally designed episodic, bolus and/or high dose CT schedules [42].

The rationale to achieve a potentiation effect on tumor cells by combining TMZ with HT was supported in an in-vitro study by Pagani et al. [43].

The technique behind oncothermia is currently one of the very rare methods in hyperthermia that can be applied to brain tissue. World wide experience with OT for BG is scarce, but the results in a variety of smaller studies show well its feasibility, [40], [44], [45], [46]. One of the retrospective OT-trials was presented at ASCO [41], showing markedly good results for n=35 cases: overall survival, progression free survival and survival from the first OT treatment are 106 (14-197) m, 47 (8-85) m 41 (0-92) m for WHO grade III and 20 (10-31) m, 15 (10-20) m, 8 (2-14) m, and grade IV, respectively.

Our objective in this article is to present a retrospective clinical study for 140 BG-patients, treated/followed from February 2000 to June 2005.

With this trial we would like to study the feasibility of OT for BG, and its effect on the survival times.

The treatment method

Electro-hyperthermia with short (RF) waves of 13.56 MHz was applied by capacitive coupling technique (oncothermia, OT), keeping the skin surface on 20 °C (OncoTherm EHY 2000 device, CE0123). For further details of the method we would like to refer to ([47], [48], [49]) where it has been explained in detail. The applied power ranged between 40-150 watts and the calculated average equivalent temperature in the tumors was above 40 °C in more than 90% of the treatment time. The targeted area was treated from the well covering electrode system, excluding the eye-area from the field. OT was performed in two/three sessions per week. Treatment time and power range per session were started with 40 W for 20 minutes, and (step by step) gradually and linearly raised up to 60 minutes, 150 W in two weeks.

Case-reports

In order to provide a comprehensive insight into the indications under which patients are being treated with Oncothermia we would like to present three representative cases

Case 1.

A 52-year-old female patient presented with the pre-history of raised lightheadness, headache and fatigue of two months' duration. Neurologic examination revealed central facial paralysis and homonymous hemianopsia. Laboratory evaluation was without significant pathologic findings. Magnetic resonance imaging (MRI) showed a lesion of 6x5x4 cm in the left frontal region, and a mass in the left parieto-occipital region measuring 4x3x3 cm (Fig. 1 /a.). Surgical intervention was not possible. She underwent stereotactic biopsy of the left frontal mass, where the histopathology was reported as GBM, WHO grade IV in May 2002. Treatment was started in June 2002 with fractionated RT (54 Gy total dose: 1.8 Gy x 5 d/wk for 6 weeks) from June 20th to August 20th in 2002. Her complaints were reduced though neurologic signs did not completely resolve. At September 24th it was decided to start an adjuvant therapy with local HT and temozolomide being administered concomitantly (TMZ) (100 mg/m²/d x 21 days, one week rest, for six cycles). Local hyperthermia was continued until December 17th 2002. The most recent MRI evaluation dating from April 28th 2004 showed a near complete remission (Fig. 1/b.). Her complaints disappeared and all the neurologic symptoms completely resolved. She has not required any further treatment from the time the adjuvant therapy was finished to date and appears for regular check-ups at our clinic. She is in good health and has an active quality of life.

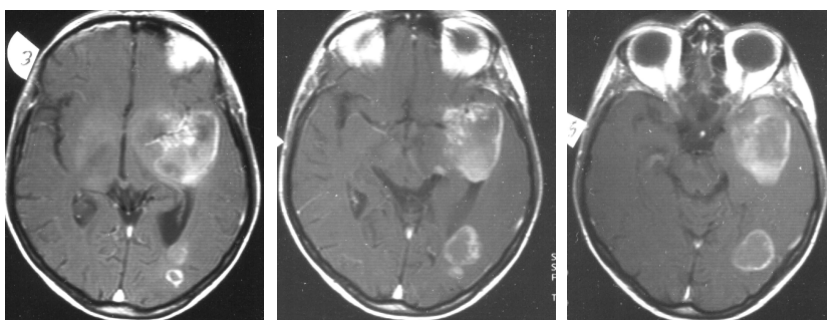


Fig. 1/a. Pretreatment imaging with MRI, -T1, (Gadolinium contrast, 12.06.2002)

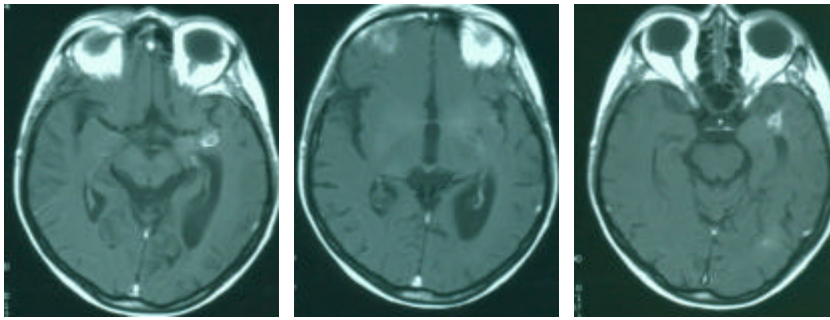


Fig. 1/b. Post treatment, imaging with MRI-T1, (Gadolinium contrast, 28.04.2004)

Case 2.

A 47-year-old male patient presented with the pre-history of Anaplastic Astrocytoma Neurologic examination revealed. Laboratory evaluation was without pathologic findings. Magnetic resonance imaging (MRI) showed a lesion of 8x6x5 cm in the temporal region. Staging classified the tumor as anaplastic astrocytoma grade WHO III at 17th of July.2001. The Patient underwent a partial resection in July 2001. RT (60 Gy total dose) was started at 15th in august2001, with partial overlapping of OT that started at 20th september2001 and finished at 14.12.01. In January 2002 the neurologic signs being observed before were not completely resolved. At 4th of march 2002 till april 19th 2002 a second OT cycle was started in combination with Temodal° (Temozolomide). The most recent MRI evaluation dated at June 16th 2005 showed a complete remission (CT) (Fig. 2.). His complaints disappeared and all the neurologic symptoms completely resolved. He has not required any further treatment from the time the adjuvant therapy was finished to date and appears for regular check-ups at our clinic. He is in normal health and has a good quality of life.

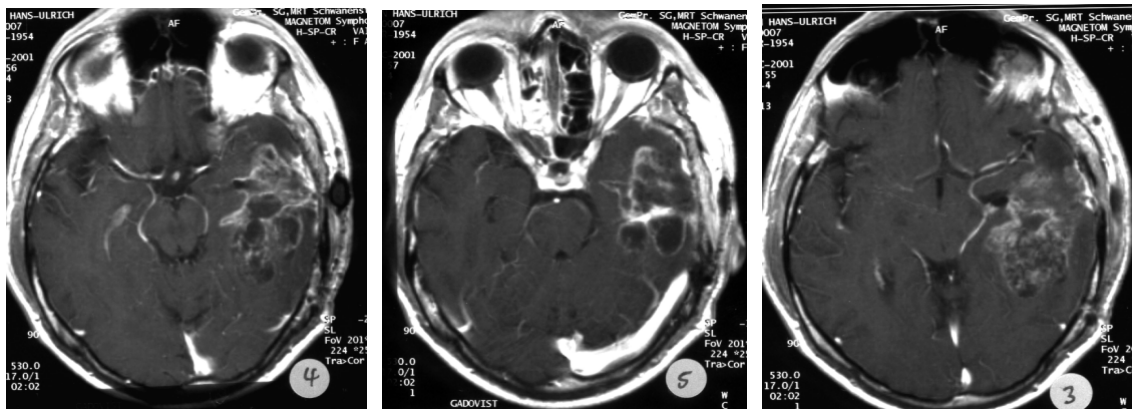


Fig. 2/a. Pretreatment imaging with MRI, -T1 12.12.2001

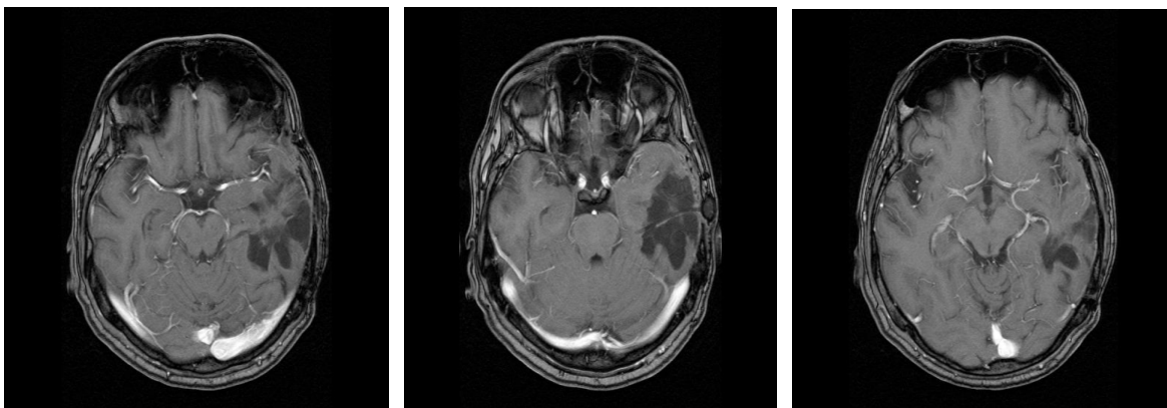


Fig. 2/b. Post treatment, imaging with MRI-T1 16.06.2005

Case 3.

A 30-year-old female patient presented with the pre-history of Anaplastic Astrocytoma. Neurologic examination revealed 01.03.2000 where the magnetic resonance imaging (MRI) showed a lesion of 5x4x3 cm in the left central brain region. It is staged as anaplastic astrocytoma grade WHO III. at 01st of march.2000. At the 22nd of march 2000 a metastatic lesion in the contra-lateral central region of 2x1 cm plus edema was observed. The patient underwent a partial resection in march 2000. Unfortunately shortly after that procedure the tumor relapsed and RT was started in March 2000 in combination with seed implantation in February 2001. OT monotherapy was applied from April 3rd 2001 until may 5th 2001 in combination with systemic chemotherapy using Temodal for 21 days at 100 mg/m² with 1week free interval. The MRI images after locoregional oncothermia showed a partial remission (Fig.3.). Her complaints disappeared and the neurologic symptoms decreased.

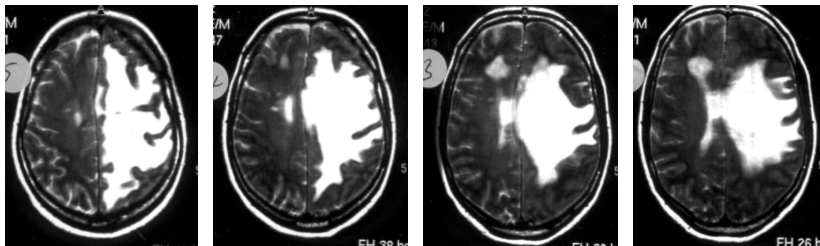


Fig. 3/a. Before OT (22.03.01)

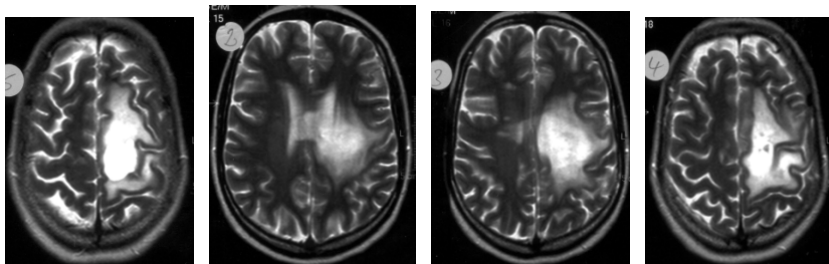


Fig. 3/b. After OT + Temodal (21.08.01)

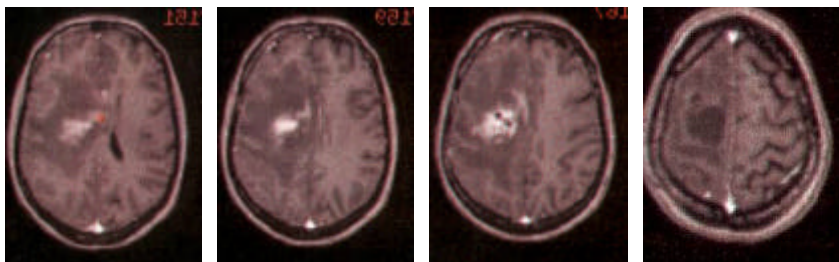


Fig. 3/c. After OT + Temodal (29.10.01)

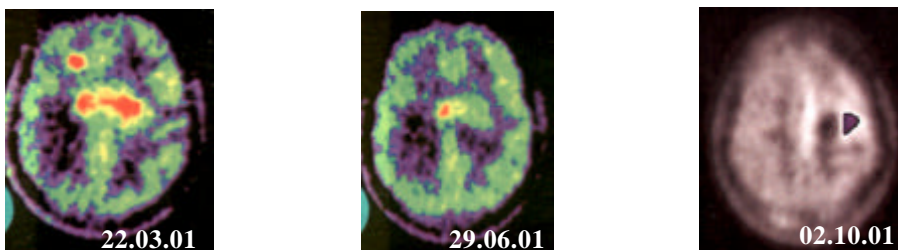


Fig. 3/d. Before OT(22.03.01) After RT+OT 29.06.01 OT+Temodal, (02.10.01)

Description of the trial

The study is an open-label, single arm, monocentric, retrospective study. The involved patients are being analyzed according to an intention-to-treat (ITT) schedule. Recruiting time was 56 months. The primary endpoints of the study were the overall survival time (OST) and the survival time from the first oncothermia treatment (TST). The applied test was Kaplan-Meier log-rank. Inclusion criteria were: (1) Inoperable or sub-totally resected or recurrent BG, (2) progression after radio- and/or chemo-therapy, (3) Karnofsky Performance Score (KPS) > 40%.

Distribution of the Brain Glioma (BG) patients by WHO-grade show mostly advanced cases: diffuse astrocytoma, (DA): 8, (5.7 %); anaplastic astrocytoma, (AA): 40, (28.6 %); glioblastoma multiforme, (GBM): 92, (65.7 %); (see Fig. 4.). Most of the patients failed to respond to the applied conventional therapies.

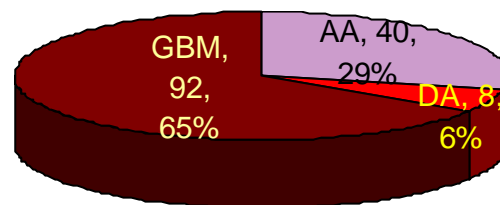


Fig. 4. Distribution of the 140 patients involved in the study.

The age-distribution is near to normal ($p < 0.001$ by Chi-square test for discrete variables), and no outliers ($p < 0.05$) were present. The median age was 43.5 y (3-73), the mean-age was 43.2 y (Std.err= 1.42), 15 (10.7 %) patients were below 18 y, and 8 (5.7 %) were over 68 y. The gender distribution was 50/90 female/male. In epidemiologic studies it is shown [50], [51], that BG is more frequent in an elderly population (in Japan BG-incidence is 2.40/100000/y over 70 y, while under 70 it is only 1.42/100000/y [52]). This did not appear in our case. A slight increase compared to the normal distribution could be observed in the range of 50-70 year ages, (Fig.5).

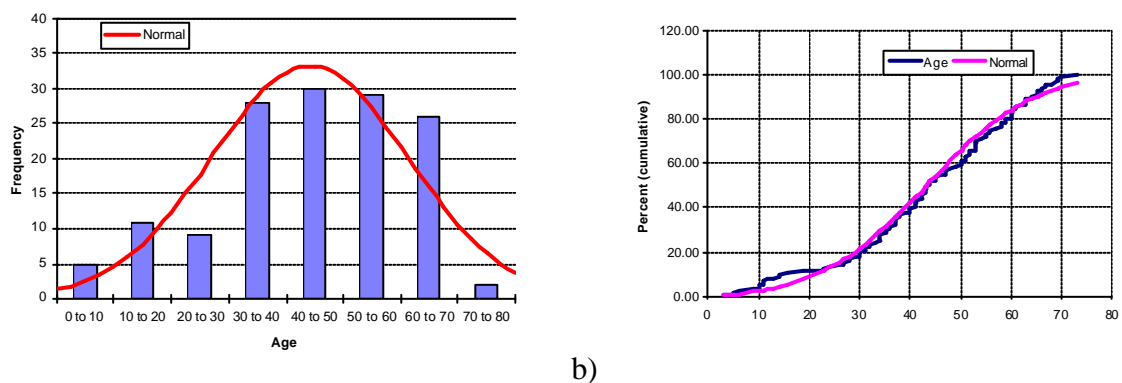


Fig.5. Age-distribution of BG patients (n=140). a) distribution by 10 y categories, b) probit cumulative

Pretreatments were applied in 364 cases (~2.6/patient), and its distribution by main categories is shown on Fig. 6. Chemotherapies were applied in 117 cases (84 %), radiation in 129 (92 %) and in 117 cases surgery (84 %) was done. (Two patients had not any pretreatments due to individual reasons.) In mean, 69% of all patients had all three therapy modalities.

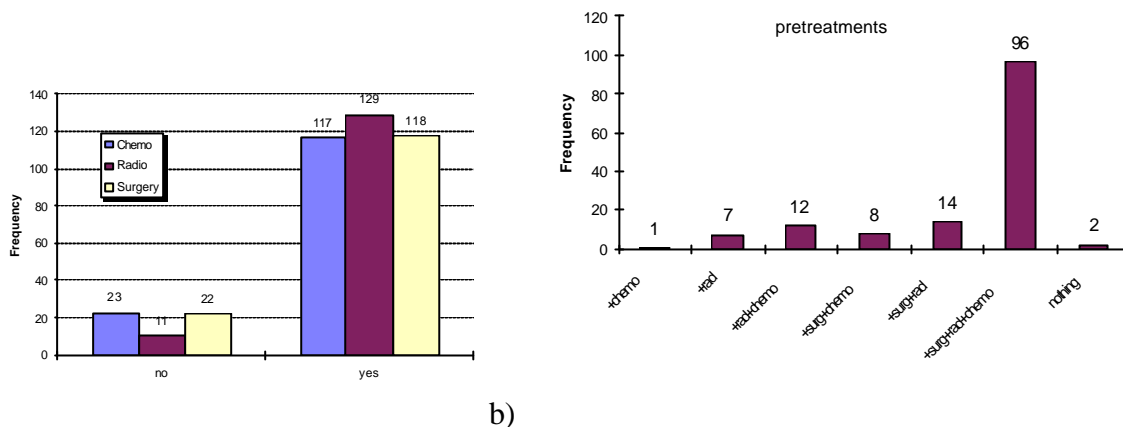


Fig. 6. The pretreatment distribution by its kind (a) and by its combinations (b).

Oncothermia was applied in most of the cases in an adjuvant setting. The distribution of adjuvant treatments is shown on Fig.7. Chemo therapies (in most of the cases TMZ) were given in 102 (73 %) cases and radiation was applied in 5 (3.6 %) cases. Just supportive therapy was administered to 105 (75 %) cases. Characterization of the applied supportive therapy is shown in Table 1. These therapies were started together with Oncothermia, which was applied between 3 and 6 months. Application of OT as a mono-therapy (2 cases (7 %)) or only combined with supportive therapies (27 cases, (19 %)) was done if no other modality was possible.

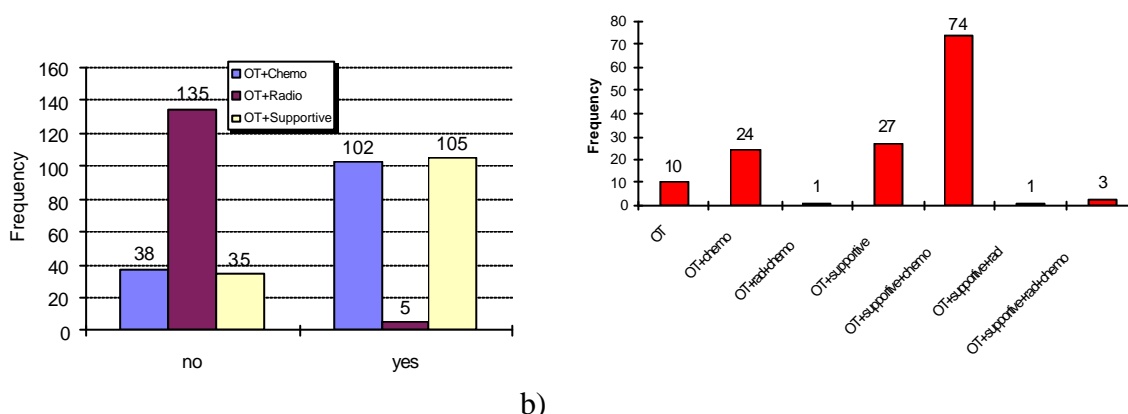


Fig. 7. The adjuvant/neo-adjuvant treatment distribution with OT by their kind (a) and by their combinations (b).

Supportive drug	Dose
Boswellia carterii (Weihrauch)	6 g/d. (3x/d)
Mistletoe (Mistel, Lectinol)	15 ng, (3x/w), subcutan
Selenium	300 µg/d

Table 1. The applied supportive therapy.

In average 1.8 (1-9) treatment cycles were given to a patient while the average treatment numbers were 21.5 (2-108). The median OT treatment number was 15. The applied dose of OT was regarded as low if it did not exceed 8-times 60 min load, (dose-threshold, DT). Such a low dose was provided in 28 patients. The median time of total duration of the OT treatment period was 1.7 m (1 d-36.4 m), in average 3.3 m (Std.err=0.4).

The median time elapsed from first diagnosis to first OT was 10.8 m (0.2-181) 21.7 m (std.err.=2.5) in average. The median follow-up time after the last OT was 3.4 m (1day-49.1 months) in average 6.6 m (Std.err=0.8).

Only very few toxicity or other problems were observed during the treatment. Mild headache could appear in a very few patients, which was clinically well controlled. We observed no increase in

oedema, especially. In most of the cases the oedema was reduced and the intracranial pressure also was decreasing. Not any surgical or other intervention was necessary during or after the OT treatments for anyone of the patients. All the patients showed very well tolerance of the treatment, and subjectively they reported better quality of life, but this was not objectively evaluated.

Treatment-Results

Median of OST (overall survival time) and of TST (treatment survival time) were 19.8 m (1.4-190) and 6.7 m (0.3-50), for all of the patients, respectively. The average (mean) of OST and TST were 31.7 (std.err=3.0) and 10.0 (std.err=0.9), respectively. The corresponding Kaplan-Meier (KM) plots are shown in Fig. 8. The same survivals categorized by their WHO-grade are shown in Table 2. and Figure 9.

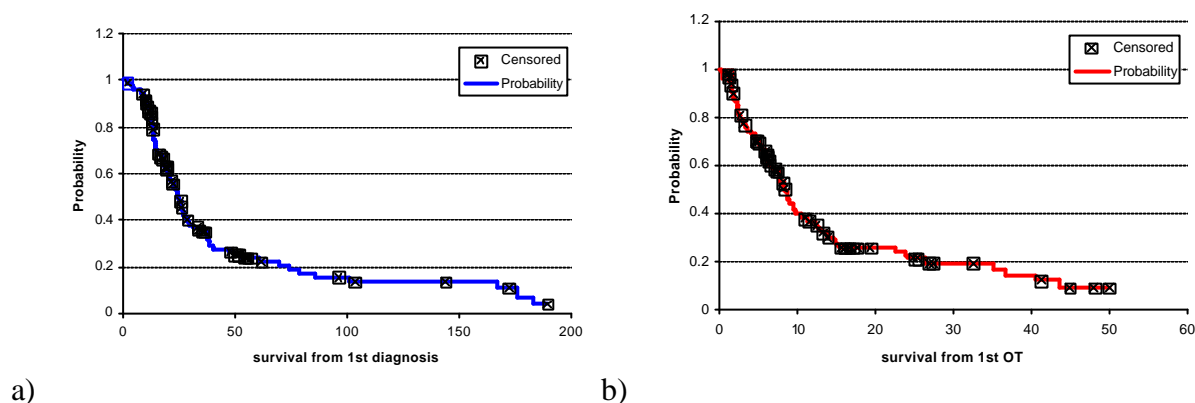


Fig.8. a) OST and b) TST KM-survival plots for all of the treated patients.

WHO grade	# Pts.	MST OST [m]	(min.-max.) [m]	MST TST [m]	(min.-max.) [m]	AST OST [m]	(Std.err.) [m]	AST TST [m]	(Std.err.) [m]
DA	8	59.2	22-190	11.6	1.1-41	73.6	18.8	15.6	5.2
AA	40	25.8	3.6-183	9.1	1.4-50	43.3	7.0	13.4	2.0
GBM	92	16.0	1.4-176	6.1	0.3-48	23.0	2.5	8.0	0.9

Table 2. Median and mean data of the survivals. (MST – median survival time, AST – average survival time)

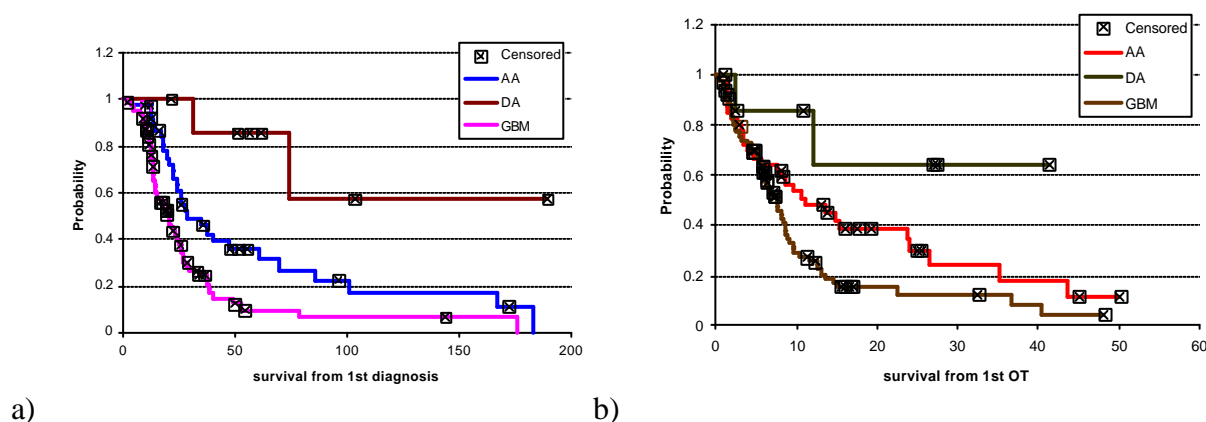


Fig.9. a) OST and b) TST KM-survivals for patients with DA, AA and GBM.

The dose analysis shows (Fig.10.) the relative dependence to DT not significant for OST ($p=0.129$) and significant for TST ($p<0.01$).

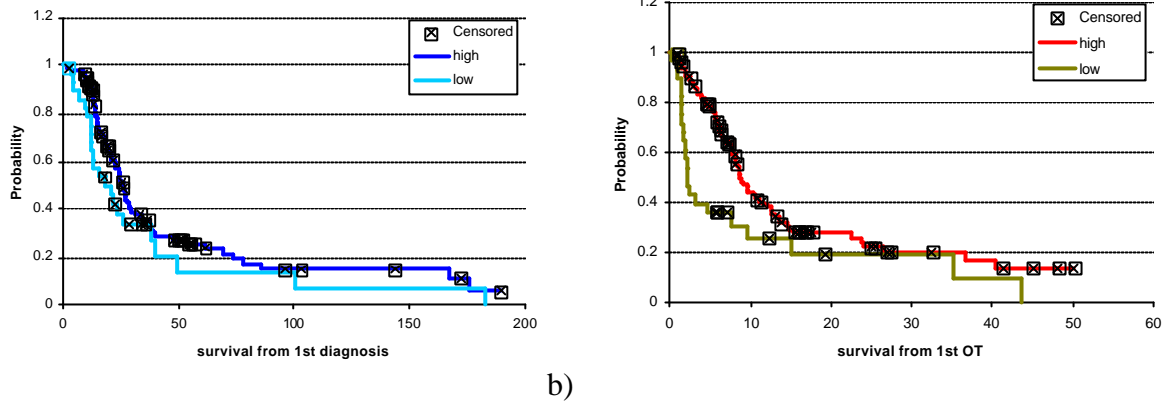


Fig. 10. a) Dose dependence to DT for OST ($p=0.129$) and b) for TST ($p=0.003$) survivals (KM survival plots).

The age-categories by young (<18 y, $n=15$) adult (between 18 y and 68 y) and elderly (>68 y, $n=10$), show no remarkable differences (Fig. 11.). The observed significant difference for elderly patients by the OST (at KM plot, Fig. 11/b.) could result from natural reasons. This assumption is supported by the results in TST KM-plot, were no difference can be seen (Fig. 11/d).

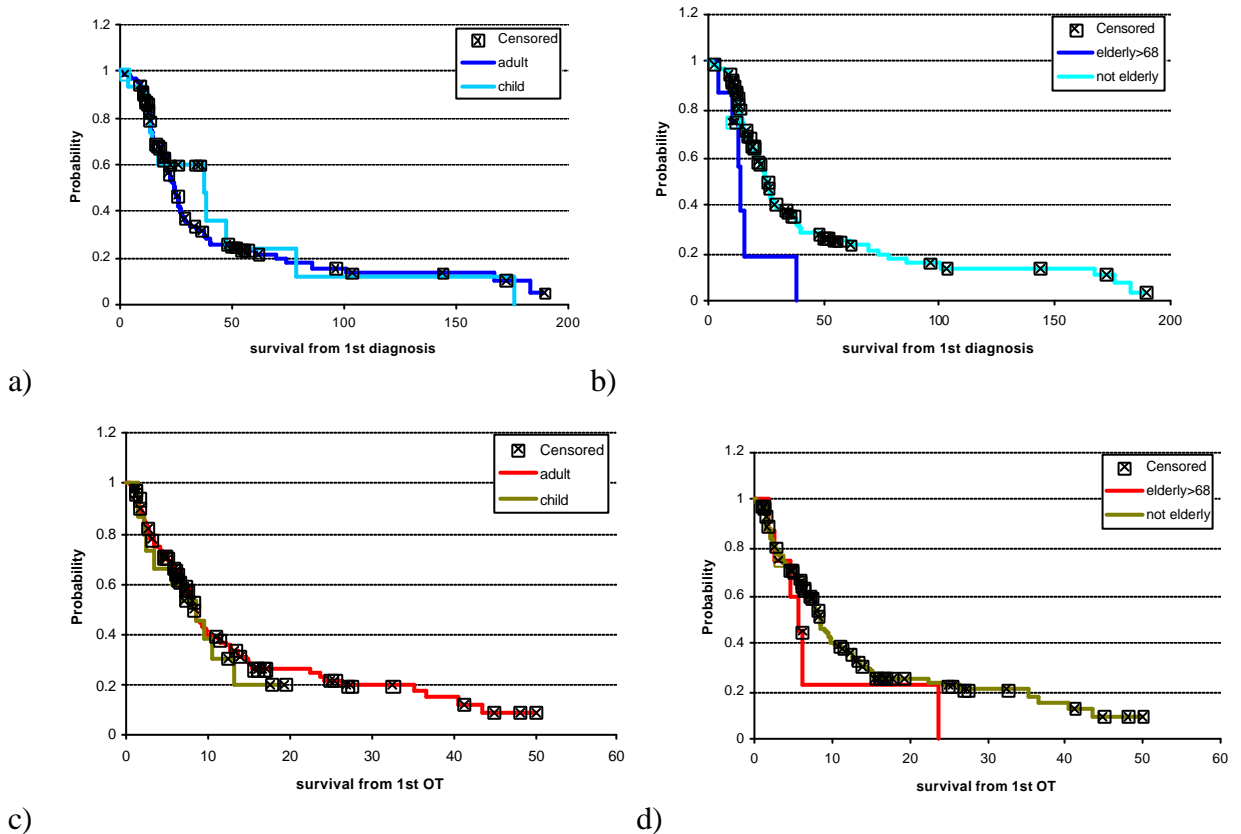


Fig. 11. Comparison of adults with young (<18 y) and elderly (>68 y) patients. a) OST for youngsters ($p=0.65$), b) OST for elderly ($p=0.016$), c) TST for youngsters ($p=0.66$), d) TST for elderly ($p=0.24$).

No serious side effects were observed (see Table 3.) Patients tolerated the treatments well during the whole treatment period. Most of the patients were well relaxed, some even felt asleep during the treatment. Patients reported better quality of life, but this information was not objectively measured.

Side effects	Rel. val.
1. Short term (< 2h) asthenia after the treatment	9%
2. Local redness (rubor) of the skin	8%
3. Complications	15%
Subcutan fibrosis of fat tissue	1%
Skin burn (diam.<1.5 cm) grade I-II	2%
Headache and vomiting (< 2h)	12%

Table 3. The observed side effects during the study.

Discussion

Median life Expectance of BG patients is over all as low as 11.3 month. In this study we observed 19.8 month in median survival time which would correspond to a gain of 75.2 %. According to the RTOG classifications [53], we divided the patients to two groups: age under- and over-50 years. The obtained patient's distribution is shown in Fig. 12. pie-diagram.

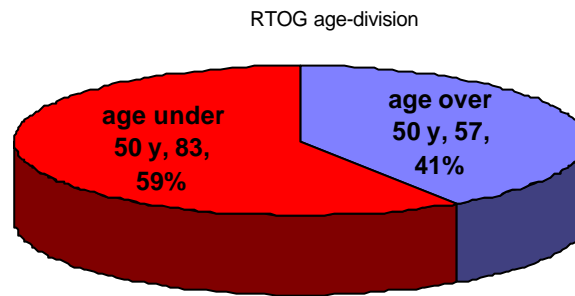


Fig. 12. Distribution of patients by 50 years age-threshold.

The OST and TST in general definitely differ highly significant by these categories, as the KM-plots show, Fig. 13.

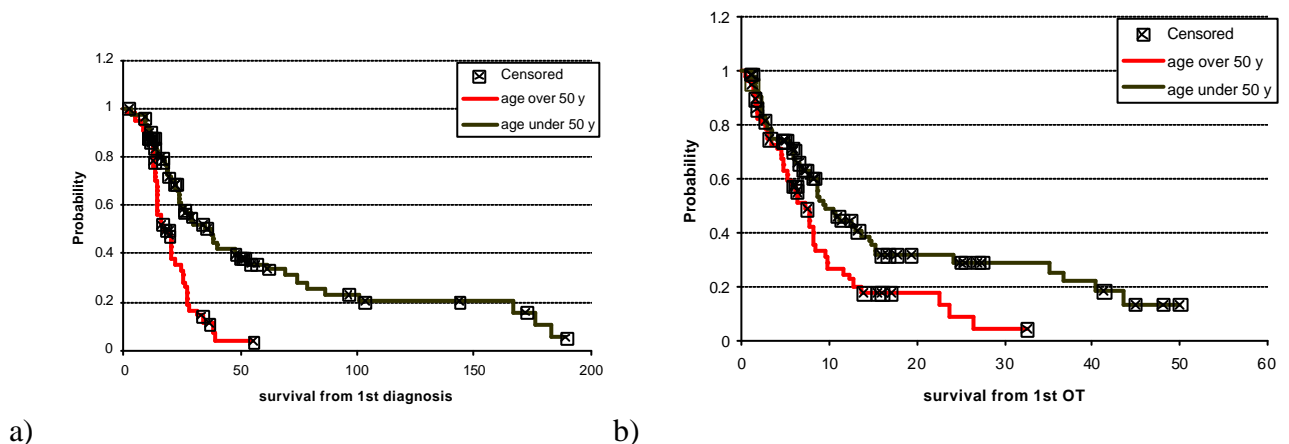


Fig. 13. KM plots by years threshold 50 year: for a) OST ($p < 0.0003$) and b) TST ($p < 0.009$).

By categories, the MST of OST was (except in one category) significantly higher (see Table 4) compared to what is to be expected for corresponding stage BG patients. The calculated relative gain for patients being under 50 years of age reaches a median of -28.5%, for those being older

24.0% in the group of DA+AA. In the group presenting with GBM numbers are 39.4% and 46.4%, respectively. The KM-plots show well the significant differences (Fig. 14.) with the exception of the DA+AA patients under 50 years of age that do not reach the level of significance. The reason of this discrepancy is not known. In a prospective trial this issue will need special consideration.

WHO grade	Patients no. (n)	MST OST [m]	(min.-max.) [m]	AST OST [m]	(Std.err.) [m]	MST RTOG [m]
DA+AA (<50y)	36	37.7	3.6-190	56.7	8.5	49.4
DA+AA (>50y)	12	18.4	9.9-56	23.3	3.8	21.7
GBM (<50y)	47	19.0	2.4-176	28.7	4.7	13.7
GBM (>50y)	45	14.4	1.4-39	17.1	1.3	9.7

Table 4. The main statistical characters by the RTOG division

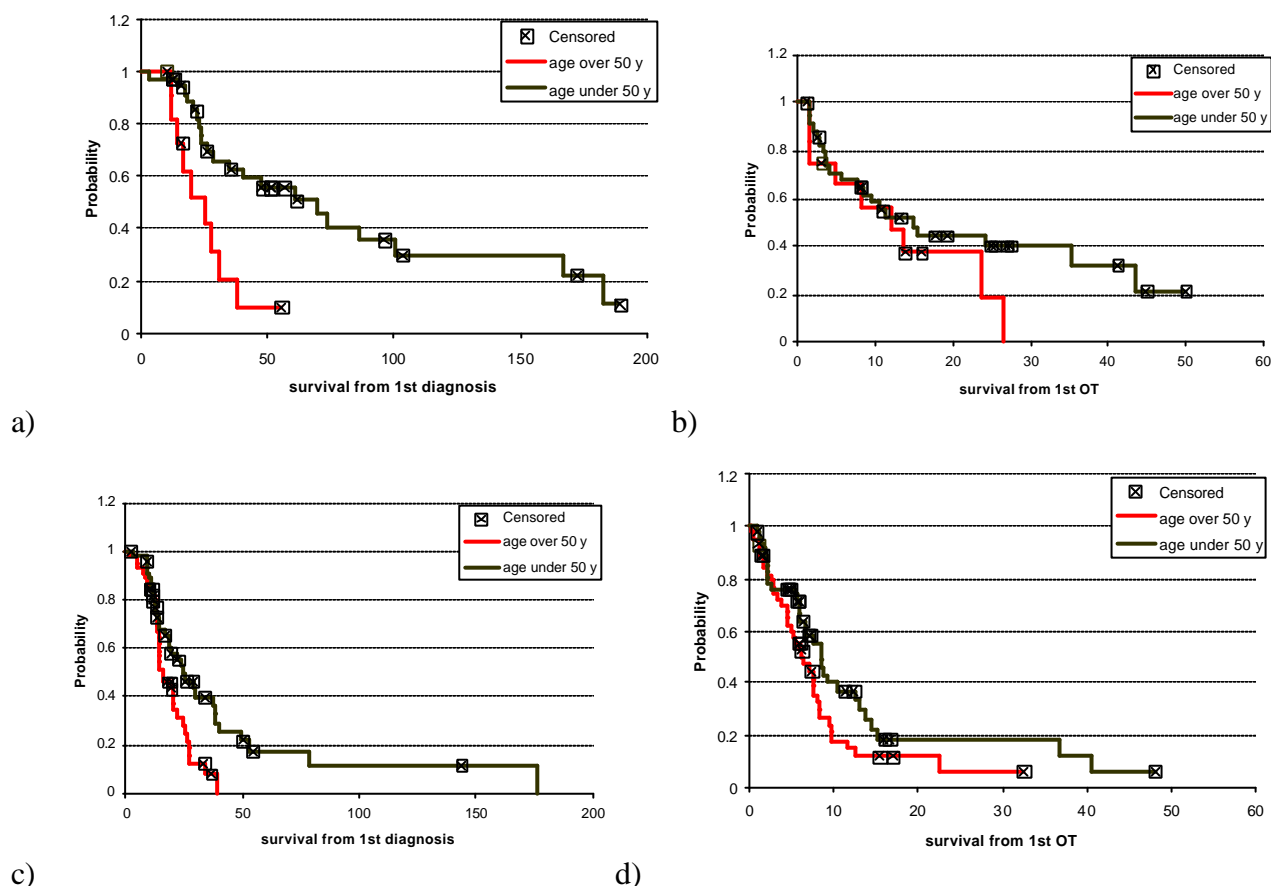


Fig. 14. The KM-plots of patients by RTOG categories. For AA+DA a) OST ($p < 0.003$) and b) TST ($p = 0.22$), as well as for GBM c) OST ($p < 0.009$) and d) TST ($p < 0.08$).

The results could be well compared to the available SEER [54] data. Comparison of the OST of our retrospective 140 patients and SEER retrospective 28.970 patients, as well as by grade categories, shown in Table 5. The gain of the MST OST in various categories is 38,6 %, 146% and 57.0 % for DA, AA and GBM patients, respectively.

WHO grade	Patient number (n) (present)	MST OST (present) [m]	MST OST (min. max.) [m]	Patient number (n) (SEER)	MST OST (SEER) [m]
DA	8	59.2	22-190	2749	42.7
AA	40	25.8	3.6-183	3273	10.5
GBM	92	16.0	1.4-176	5801	10.2

Table 5. Comparison of the data of SEER and our present study.

Survival time as a distribution by years is shown in Fig. 15.

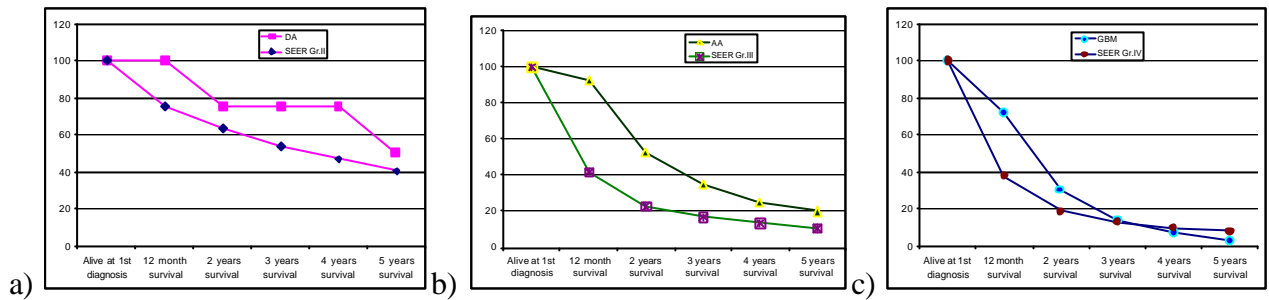


Fig. 15. The comparison of the results with SEER data by WHO grade categories: a) DA ($p < 0.015$), b) AA ($p < 0.045$) and c) GBM ($p = 0.33$).

In a recent publication [55], survival was 58% after one year and 31% after two years under administration of temozolomide. Compared to our results, the gain is also remarkable. 71.7 % (66/92) and 30.4 % (28/92) for 1 and 2 years survival, respectively. (The two-year survival for GBM in the RTOG study (no TMZ application) is only 17%, [53].) The most recent TMZ randomized clinical trial for GBM [56], summarizing the results of 573 patients from 85 cooperating centers shows a gain of MST from 12.1 m (without TMZ) to 14.6 m (with TMZ). In a former study TMZ results [57] were similar, having MST in the RT group (n=24) of 11.2 m, RT+CT (not TMZ) group (n=32) 12.7 m and for RT+TMZ group (n=23) 14.9 m. The two-year survival in the new study [56] increased from 10.4% (without TMZ) to 26.5% (with TMZ). In comparison, the evaluation of our present data shows superiority to many of the presently published results under administration of temozolomide.

A long term survival with GBM is a very rare occasion. Only 1.8% of the patients were alive after three years in a trial with 279 patients [58]. In our cases with 92 GBM patients 13 (14.1 %) had an OST being longer than 3 years, which is a remarkable gain.

Studying the MRI images, we have some indicative hints to suppose an extended apoptosis initialized by the oncothermia in a proportion of the patients. This could be in good correspondence with some theoretical considerations proposing a gain of the apoptotic processes by hyperthermia [59], as well as with some experimental facts showing the relevance of the enhanced apoptotic activity [60], [61], [62].

The presented results are well comparable with the oncothermia results published earlier on smaller cohorts of patients (n=35) [41], and (n=17) [63] by these other research groups.

Conclusion

The results are well indicating the feasibility and the benefit of the oncothermia treatment by numerous reasons:

1. Oncothermia was applied for brain tumours, showing a valid treatment potential and safe application.
2. A transcranially applied non-invasive electric field is able to perform the treatment.
3. No safety or mentionable toxicity problem has occurred. The development of an oedema, which was the general block of hyperthermia applications in the past, is not the case with oncothermia. There was not any eye-damage and/or vision-complication which were also a risk in the radiative hyperthermia methods. The treatment is safe and convenient to use.
4. We consider the survival time as one of the most important parameters measuring the efficacy of the method. The survival time was increased for the patients having no other treatment possibilities.

5. The quality of life of every patient who was treated with oncothermia was not worsened, even according to their subjective reports.

According to our present retrospective study on a relatively large number (n=140) of brain-glioma patients, the oncothermia is feasible to treat anaplastic astrocytoma and glioblastoma multiforme. Oncothermia is a potential way to escape from the present impasse situation to treat successfully brain gliomas. A comparison of the presently indicated data to the expected historical ones given from the large databases shows a remarkable increase in overall survival. Especially remarkable is a 3 years survival in 13 out of 92 patients with GBM. As well as the method is safe and stable; it is easy to use and well tolerated by the patients.

Our present data are only retrospective indications of the efficacy of the oncothermia method. A prospective, randomized, controlled double-arm clinical study is needed for an evidence-based evaluation.

References

- [1] Ries LAG, Eisner MP, Kosary CL, et al (eds): SEER Cancer Statistics, 1973-1998. Bethesda, MD, National Cancer Institute, 2001
- [2] Medical Research Council Brain Tumor Working Party: Randomized Trial of Procarbazine, Lomustine, and Vincristine in the Adjuvant treatment of High-grade Astrocytoma: A Medical Research Council Trial, *J. Clin. Oncol.* 19:509-518, 2001
- [3] Stupp R, Dietrich PY, Kraljevic SO, et al. Promising Survival for Patients With Newly Diagnosed Glioblastoma Multiforme Treated With Concomitant Radiation Plus Temozolomide Followed by Adjuvant Temozolomide. *JCO* 2002 ;20:5: 1375-1382
- [4] Walker MD, Alexander E Jr, Hunt WE, et al: Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas: A cooperative clinical trial. *J Neurosurg* 1978;49: 333-343
- [5] Kristiansen K, Hagen S, Kollevold T, et al: Combined modality therapy of operated astrocytomas grade III and IV: Confirmation of the value of postoperative irradiation and lack of potentiation of bleomycin on survival time; A prospective multicenter trial of the Scandinavian Glioblastoma Study Group. *Cancer* 1981;47: 649-652
- [6] 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 Res.* 1996 Apr 15;56(8):1939-47
- [7] Begley DJ. ABC transporters and the blood-brain barrier. *Curr Pharm Des.* 2004;10(12):1295-312
- [8] Pagani E, Falcinelli R, Repponi R et al. Combined effects of temozolamide- hyperthermia on cell growth and O6-Alkylguanine-DNA alkyltransferase (OGAT) activity of human melanoma cell lines. *Anticancer Research* 18:4807-5006, 1998
- [9] Sakaguchi Y, Stephens LC, Makino M, Kaneko T, Strebel FR, Danhauser LL, Jenkins GN, Bull JM: Apoptosis in tumors and normal tissues induced by whole body hyperthermia in rats. *Cancer Res* 57:5459-64, 1995
- [10] 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 Res.* 56:1939-47, 1996
- [11] 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.* 18(2):141-52, 2002
- [12] Jendrossek V, Belka C, Bamberg M. Novel chemotherapeutic agents for the treatment of glioblastoma multiforme. *Expert Opin Investig Drugs* 2003;12(12):1899-924
- [13] Fisher PG, Buffler PA: Malignant gliomas in 2005. Where to GO from here?, Editorials, *JAMA* 293:615-617, 2005.
- [14] Sumiyoshi K, Strebel FR, Rowe RW et al. The effect of whole-body hyperthermia combined with 'metronomic' chemotherapy on rat mammary adenocarcinoma metastases. *Int J Hyperthermia.* 2003;19(2):103-18
- [15] Hermisson M, Weller M. Hyperthermia enhanced chemosensitivity of human malignant glioma cells. *Anticancer Res.* 20(3A):1819-23, 2000
- [16] Siminia P, van der Zee J, Wondergem J, Haveman J: Effect of hyperthermia on the central nervous system: review, *Int. J. Hyperthermia,* 10:1-30, 1994
- [17] Matsumi N, Matsumoto K, Mishima N, Moriyama E, Furuta T, Nishimoto A, Taguchi K: Thermal damage threshold of brain tissue: Histological study of heated normal monkey brains, *Neurol. Med. Chir. (Tokyo),* 34:209-215, 1994
- [18] Haveman J, Siminia P, Wondergem J, van der Zee J, Hulshof MC: Effects of hyperthermia on the central nervous system: what was learnt from animal studies?, *Int. J. Hyperthermia,* 21:473-487, 2005

- [19] 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, *J Neurooncol.* 1995 Nov;26(2):141-55
- [20] Stea B, Rossman K, Kittelson J, Shetter A, Hamilton A, Cassady JR.: Interstitial irradiation versus interstitial thermoradiotherapy for supratentorial malignant gliomas: a comparative survival analysis, *Int J Radiat Oncol Biol Phys.* 1994 Oct 15;30(3):591-600
- [21] Nakajima T, Roberts DW, Ryan TP, Hoopes PJ, Coughlin CT, Trembly BS, Strohbehn JW.: Pattern of response to interstitial hyperthermia and brachytherapy for malignant intracranial tumour: a CT analysis, *Int J Hyperthermia.* 1993 Jul-Aug;9(4):491-502
- [22] Iacono RP, Stea B, Lulu BA, Cetas T, Cassady JR.: Template-guided stereotactic implantation of malignant brain tumors for interstitial thermoradiotherapy, *Stereotact Funct Neurosurg.* 1992;59(1-4):199-204
- [23] Sneed PK, Stauffer PR, Gutin PH, Phillips TL, Suen S, Weaver KA, Lamb SA, Ham B, Prados MD, Larson DA, et al.: Interstitial irradiation and hyperthermia for the treatment of recurrent malignant brain tumors, *Neurosurgery.* 1991 Feb;28(2):206-15
- [24] Edwards DK, Stupperich TK, Baumann CK, Zumwalt CB.: Volumetric interstitial hyperthermia: role of the critical care nurse, *Focus Crit Care.* 1991 Feb;18(1):35-9, 42, 45-50
- [25] Stea B, Cetas TC, Cassady JR, Guthkelch AN, Iacono R, Lulu B, Lutz W, Obbens E, Rossman K, Seeger J, et al.: Interstitial thermoradiotherapy of brain tumors: preliminary results of a phase I clinical trial, *Int J Radiat Oncol Biol Phys.* 1990 Dec;19(6):1463-71
- [26] Samaras M, GM. *J Neurooncol.*: Interstitial microwave hyperthermia for brain tumors. Results of a phase-I clinical trial, *Salcman* 1983;1(3):225-36
- [27] Sneed PK, Gutin PH, Stauffer PR, Phillips TL, Prados MD, Weaver KA, Suen S, Lamb SA, Ham B, Ahn DK, et al.: Thermoradiotherapy of recurrent malignant brain tumors, *Int J Radiat Oncol Biol Phys.* 1992;23(4):853-61
- [28] Stahl H, Wust P, Maier-Hauff K et al. The use of an early postoperative interstitial-hyperthermia combination therapy in malignant gliomas. *Strahlenther Onkol* 1995;171(9):510-24
- [29] Fan M, Ascher PW, Schrottner O, Ebner F, Germann RH, Kleinert R.: Interstitial 1.06 Nd:YA G laser thermotherapy for brain tumors under real-time monitoring of MRI: experimental study and phase I clinical trial, *J Clin Laser Med Surg.* 1992 Oct;10(5):355-61
- [30] Kahn T, Harth T, Bettag M, Schwabe B, Ulrich F, Schwarzmaier HJ, Modder U.: Preliminary experience with the application of gadolinium-DTPA before MR imaging-guided laser-induced interstitial thermotherapy of brain tumors, *J Magn Reson Imaging.* 1997 Jan-Feb;7(1):226-9
- [31] Borok TL, Winter A, Laing J, Paglione R, Sterzer F, Sinclair I, Plafker J.: Microwave hyperthermia radiosensitized iridium-192 for recurrent brain malignancy, *Med Dosim.* 1988 Mar;13(1):29-36
- [32] Moran CJ, Marchosky JA, Wippold FJ 2nd, DeFord JA, Fearnot NE.: Conductive interstitial hyperthermia in the treatment of intracranial metastatic disease, *J Neurooncol.* 1995 Oct;26(1):53-63
- [33] Pontiggia P, Duppone Curto F, Rotella G, Sabato A, Rizzo S, Butti G.: Hyperthermia in the treatment of brain metastases from lung cancer. Experience on 17 cases, *Anticancer Res.* Mar-Apr;15(2):597-601, 1995
- [34] Tanaka R. Gan To Kagaku Ryoho.: [Radiofrequency hyperthermia in malignant brain tumors: clinical trials] [Article in Japanese], 1988 Apr;15(4 Pt 2-2):1370-5
- [35] Tanaka R, Kim CH, Yamada N, Saito Y. *Neurosurgery.*: Radiofrequency hyperthermia for malignant brain tumors: preliminary results of clinical trials, 1987 Oct;21(4):478-83
- [36] Guthkelch AN, Carter LP, Cassady JR, Hynynen KH, Iacono RP, Johnson PC, Obbens EA, Roemer RB, Seeger JF, Shimm DS, et al.: Treatment of malignant brain tumors with focused ultrasound hyperthermia and radiation: results of a phase I trial, *J Neurooncol.* 1991 Jun;10(3):271-84
- [37] Hager D, (Biomed Clinic, Bad Bergzabern), Sahinbas H (Witten Herdecke University, Bochum) and Douwes (St.Georg Clinic, Bad Aibling) were pioneering this work starting in 1995. F
- [38] Ley-Valle A: .Non invasive intracranial hyperthermia with Electric Capacitive Transference -ECT- Intratumoral and cerebral thermometry results, *Neurocirugia (Astur).* 14(1):41-45, 2003
- [39] Sneed PK, Stauffer PR, McDermott MW, Diederich CJ, Lamborn KR, Prados MD, Chang S, Weaver KA, Spry L, Malec MK, Lamb SA, Voss B, Davis RL, Wara WM, Larson DA, Phillips TL, Gutin PH.: Survival benefit of hyperthermia in a prospective randomized trial of brachytherapy boost +/- hyperthermia for glioblastoma multiforme, *Int J Radiat Oncol Biol Phys.* 1998 Jan 15;40(2):287-95
- [40] Sahinbas H, Groenemeyer DHW, Boecher E, et al. Hyperthermia treatment of advanced relapsed glioma and astrocytoma. 9th ICHO 2004.page;85
- [41] D. Hager, H. Dziambor, E. M. App et al. The treatment of patients with high-grade malignant gliomas with RF-hyperthermia. 39th ASCO Annual Meeting. 2003 (*Abstract No. 470*)
- [42] Kurzen H, Schmitt S, Naher H et al. Inhibition of angiogenesis by non-toxic doses of temozolomide. *Anticancer Drugs*;14(7):515-22, 2003

-
- [43] Pagani E, Falcinelli R, Repponi R et al. Combined effects of temozolamide- hyperthermia on cell growth and O6-Alkylguanine-DNA alkyltransferase (OGAT) activity of human melanoma cell lines. *Anticancer Res* 1998;18 (237):4807-5006
- [44] D. Hager, H. Dziambor, E. M. App et al. The treatment of patients with high-grade malignant gliomas with RF-hyperthermia. 39th ASCO Annual Meeting. 2003 (Abstract No. 470).
- [45] A.Szasz, H.Sahinbas, A.Dani: Electro- hyperthermia for anaplastic astrocytoma and glioblastoma multiforme ICACT 2004, Paris, 9-12. February, 2004
- [46] Sahinbas H, Groenemeyer DHW, Boecher E, et al. Hyperthermia treatment of advanced relapsed glioma and astrocytoma. 9th ICHO 2004,page;85.
- [47] Szasz A, Szasz O, Szasz N: Electrohyperthermia: a new paradigm in cancer therapy, *Wissenschaft & Forschung, Deutsche Zeitschrift für Onkologie*, 2001; 33:91-99.
- [48] Szasz A, Szasz O, Szasz N Physical background and technical realization of hyperthermia, in: *Locoregional Radiofrequency-Perfusional- and Wholebody- Hyperthermia in Cancer Treatment: New clinical aspects*, (Eds: Baronzio GF, Hager ED), Springer Science Eureka.com, 2005
- [49] Szasz A, Vincze Gy, Szasz O, Szasz N: An energy analysis of extracellular hyperthermia, *Magneto- and electro-biology*, 22 (2003) 103-115
- [50] Davis DL, Ahlborn A, Hoel D, et al: Is brain cancer mortality increasing in industrial countries? *Am.J.Ind.Med.* 19:421-431, 1991
- [51] Greig NH, Ries LG, Yancik R , et al: *Natl. Canc. Inst.* 82:1621-1624, 1990
- [52] Karatsu J, Ushio Y: Epidemiological study of primary intracranial tumours in elderly people, *Journal of Neurology, Neurosurgery and Psychiatry*, 63:116-118, 1977
- [53] Scott CB, Scarantino C, Urtasun R, et al: Validation and predictive power of Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis classes for malignant glioma patients: A report using RTOG 90-06. *Int J Radiat Oncol Biol Phys* 40:51-55, 1998
- [54] Surveillance, Epidemiology, and End Results (SEER), National Cancer Institute, April 2000, www-seer.cancer.gov
- [55] Stupp R, Dietrich P-Y, Kraljevic SO, Pica A, Maillard I, Maeder P, Meuli R, Janzer R, Pizzolato G, Mirabell R, Porchet F, Regli L, deTribolet N, Miramanoff RO, Leyvraz S: Promising survival for patients with newly diagnosed glioblastoma multiforme treated with concomitant radiation plus temozolomide followed by adjuvant temozolomide, *J. Clin. Oncol.* 20:1375-1382, 2002
- [56] Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn, MJB, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E, Mirimanoff RO: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma, *The New England J. of Med.*, 352:987-996, 2005
- [57] Alba A, Brandes, Francesca Vastola, et.al.: A prospective study on glioblastoma in the elderly, *Am. Cancer Society*, Vol. 97:3 February 1, 2003
- [58] Scott JN, Newcastle NB, Brasher PMA, Fulton D, Hagen NA, MacKinnon JA, Sutherland G, Cairncross JG, Forsyth P: Long-term glioblastoma multiforme survivors: a population-based study, *Can. J. Neurol. Sci.* 25:197-201, 1998
- [59] Chen JW, Lin J, Madamanchi N, Trier TT, Campbell G: Apoptosis occurs in a new model of thermal brain injury, *J. Biomed. Sci.* 7:459-465, 2000
- [60] Fuse T, Yoon K-W, Kato T, Yamada K: Heat-induced apoptosis in human glioblastoma cell-line A172, *Neurosurgery* 42:843-849, 1998
- [61] Andocs G, Szasz A: Preliminary results of Oncothermia induced apoptosis in nude-mouse inoculated human-glioblastoma cells, Results of hyperthermia, Seminar, St. Istvan University, Aug. 24., 2005. (in Hungarian)
- [62] Vogel P, Dux E, Wiessner C: Evidence of apoptosis in primary neuronal cultures after heat shock, *Brain Res.* 764:205-213, 1997
- [63] Dani A, Varkonyi A: Electro-hyperthermia treatment of malignant brain tumors, Results of hyperthermia, Seminar, St. Istvan University, Aug. 26-27., 2003. (in Hungarian)