Hyperbaric Oxygen Therapy for Cognitive Disorders after Irradiation of the Brain

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Purpose: Analysis of the feasibility and effect of hyperbaric oxygen treatment (HBO) on cognitive functioning in patients with cognitive disorders after irradiation of the brain.

Patients and Method: Seven patients with cognitive impairment after brain irradiation, with an interval of at least 1.5 years after treatment, were treated with 30 sessions of HBO in a phase I–II study. A comprehensive neuropsychological test battery was performed before treatment, at 3 and 6 months thereafter. Patients were randomized into an immediate treatment group and a delayed treatment group. The delayed group had a second neurospychological test at 3 months without treatment in that period and started HBO thereafter.

Results: All eligible patients completed the HBO treatment and the extensive neuropsychological testing. One out of seven patients had a meaningful improvement in neuropsychological functioning. At 3 months there was a small, but not significant benefit in neuropsychological performance for the group with HBO compared to the group without HBO treatment. Six out of seven patients eventually showed improvement after HBO in one to nine (median 2.5) of the 31 tests, although without statistical significance.

Conclusion: HBO treatment was feasible and resulted in a meaningful improvement of cognitive functioning in one out of seven patients. Overall there was a small but not significant improvement.

Key Words: Hyperbaric oxygen therapy · Cognitive disorders · Brain irradiation · Late radiation effects

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Hyperbare Oxygenierung bei Patienten mit kognitiven Störungen nach Hirnbestrahlung

Hintergrund: Es wurden die Durchführbarkeit und Wirksamkeit der hyperbaren Oxygenierung (HBO) auf die Gehirnfunktion bei Patienten mit kognitiven Störungen nach Hirnbestrahlung untersucht.

Patientengut und Methode: In einer Phase-I/II-Studie wurden sieben Patienten mit kognitiven Störungen nach einem minimalen Intervall von 1,5 Jahren 30 HBO-Behandlungen unterzogen. Neuropsychologische Tests wurden vor HBO sowie 3 und 6 Monate nach Abschluss der Behandlung durchgeführt. Patienten wurden randomisiert in eine sofortige und eine späte Behandlungsgruppe. Die späte Behandlungsgruppe wurde nach 3 Monaten zum zweiten Mal neuropsychologisch getestet ohne zwischenzeitliche HBO-Behandlung. Nach diesem zweiten Test begann in dieser Gruppe die HBO.

Ergebnisse: Alle Patienten konnten die vorgeschriebene HBO-Therapie und das umfangreiche neuropsychologische Testprogramm abschließen. Einer von sieben Patienten zeigte eine bedeutsame Verbesserung der neuropsychologischen Funktion. Die HBO-Gruppe zeigte im Vergleich zu einer nicht mit HBO behandelten Kontrollgruppe nach 3 Monaten eine leichte, statistisch nicht signifikante Verbesserung. Bei sechs der insgesamt sieben HBO-Patienten waren Verbesserungen nachweisbar in einem bis neun (median 2,5) der 31 Tests, die statistisch jedoch nicht signifikant waren.

Schlussfolgerung: HBO ist bei Patienten nach Hirnbestrahlung durchführbar und erzielte bei einem von sieben Patienten eine bedeutsame Verbesserung der kognitiven Funktion. Insgesamt zeigte sich eine leichte, statistisch nicht signifikante Verbesserung der getesteten Hirnfunktionen.

Schlüsselwörter: Hyperbare Oxygenierung · Kognitive Störungen · Hirnbestrahlungen · Strahlenspätwirkungen

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Introduction

The risk of neuropsychological impairment after cerebral radiotherapy is well recognized, but the incidence is unknown [14]. Whereas several investigators did not demonstrate significant differences compared to surgery alone after fractionated, low-dose or limited-field irradiation [2, 23], minor to severe cognitive deficits have been reported [18] including necrosis and progressive dementia in 42% of patients [10]. Cognitive dysfunction is considered as irreversible and no recognized treatment is available at present, although hyperbaric oxygen treatment (HBO) for neurologic deficits has been suggested [15]. Microvascular failure, a well-described pathological effect of late radiation injury, is considered to be responsible for cognitive dysfunction after irradiation, especially if it occurs in the hippocampal area [1]. In irradiated tissue, stimulation of neo-angiogenesis by HBO has been proven in animal models [19] as well as in some clinical studies [3, 27]. Several clinical studies have reported positive effects of HBO in the treatment of delayed radiation injuries at sites like bladder, rectum and extremities [3, 12, 24, 27]. HBO studies for late radiation damage to the nervous system are rare, however. Feldmeier et al [11] demonstrated in an animal study a delay in the onset of myelitis with HBO applied as prophylaxis 6 weeks after irradiation, i.e. during the latent period. A comparable study however did not show a prophylactic action of HBO for late myelopathy [22]. Two small human studies with HBO treatment in three and ten patients with severe radiation-induced brain injury demonstrated either an improvement or stabilization of the Karnofsky performance status and radiological imaging [7, 13]. No neuropsychological testing was performed in both studies and no control group was available. The purpose of the current study is to analyze the feasibility and therapeutic effect of HBO by extensive neuropsychological testing in a group of adult patients with cognitive deficits after irradiation of the brain.

Patients and Methods

Patient accrual took place at the outpatient clinic of the radiotherapy department during the first half of 1999. Patients were selected on the presence of cognitive deficits as mentioned by the patient or partner during regular follow-up visits. They were asked whether they suffered from short-term memory loss, concentration problems or diminished speed of processing. The post-radiation period had to be at least 1.5 years, assuming that late effects are irreversible without intervention after such a period. However, it could not be assured that the cognitive impairment was due to irradiation damage as opposed to the initial tumor itself or tumor resection. Further inclusion criteria were radiation doses of at least 30 Gy in 3 weeks or biological equivalent, no signs of tumor recurrences on CT scan or MRI, age between 18 and 60 years, Karnofsky performance scale of 70 or more and informed consent. Exclusion criteria were concurrent severe neurological or vascular disease, uncontrollable epileptic fits, previous chemotherapy and a general condition impediment for HBO treatment. Ten patients provided initially informed consent for the study. Two patients refused HBO treatment during work-up period because of social reasons and one patient developed a tumor recurrence during the study period leaving seven evaluable patients for analysis. There were no changes in medication with CNS effects during the 6 months study period. Patient characteristics are summarized in Table 1. The level ofeducation was scored on a seven point scale, which ranges from elementary school to an university degree [23]. CT or MRI follow-up was not performed for study purposes.

Hyperbaric Oxygen

Hyperbaric oxygen was executed in a multiplace chamber. Thirty sessions, five to six times per week were administered at a pressure of 3 at with inhalation of 100% oxygen in the multiplace chamber. Treatment time was 125 minutes, including a compression and decompression time of 10–15 minutes. No air breaks were applied. A chamber monitor monitored patients during the HBO treatment.

Procedure

Patients were matched in pairs on age and education as closely as possible. To test for possible retest bias at neuropsychological examination (retest effects are improvements in test

Table 1. Patient characteristics.

Tabelle 1. Patientencharakteristik.

No.	Sex	Age	Education level	Histology	Tumor localization	Radiation field	Total dose/ Fraction dose	Follow-up after RT in months	Treatment group
1	F	49	5	Neuroblastoma	Ventricular	Craniospinal + boost	54 Gy/1.5	30	Delayed
2	F	56	4	Oligoastrocytoma	Frontotemporal	Focal	54 Gy/2 Gy	92	Delayed
3	F	47	5	Glioblastoma	Frontoparietal	Focal	28 Gy/7 Gy	91	Delayed
4	M	30	6	Ependymoma	Cerebellar	Craniospinal + boost	56 Gy/1.5 Gy	96	Immediate
5	F	47	4	Glioblastoma	Parietal	Focal	60 Gy/2 Gy	24	Immediate
6	F	54	4	Oligodendroglioma	Frontoparietal	Focal	54 Gy/2 Gy	17	Immediate
7	F	39	4	Medulloblastoma	Cerebellar	Craniospinal + boost	54 Gy/1.5 Gy	130	Immediate

performance, which are due to mere repetition of the testing), patients were randomly assigned to an experimental group who were treated immediate (immediate group) and a control group with delayed treatment (delayed group). The randomization was blinded and performed by an independent employee at the neurology department. The neuropsychological test battery was administered to both groups at 0 months (baseline), at 3 months and at 6 months. The immediate group started HBO treatment directly after the baseline test. The delayed group had their second examination at 3 months without treatment, and started HBO treatment thereafter. The immediate group consisted of four patients and the delayed group of three patients.

Neuropsychological Examination

A comprehensive neuropsychological test battery of about 3 hours duration was administered to all patients (Table 2 and Appendix). To minimize retest effects, parallel versions of different tests were used if available. Two trained undergraduate students supervised by a bound certified clinical neuropsychologist administered the tests. Time of day and place of examination were identical during the study. In the days before the examination the patient and a close relative (proxy rating) completed the MAC Questionnaire (from Memory Assessment Clinic) [9] and the DEX Questionnaire (from the Behavioral Assessment of Dysexecutive Syndrome) [26]. The MAC questionnaire contains two subscales measuring everyday memory abilities and the severity and frequency of amnestic symptoms. The DEX questionnaire is a rating scale of dysexecutive symptoms, such as distractibility, planning problems, apathy and lack of social awareness. The raw scores were used for analysis.

Statistics

Changes in the neuropsychological test results were analyzed using two different methods. First, the mean test scores before and after treatment were compared. Non-parametric tests (Wilcoxon signed-rank test and sign test) were used in view of the small sample size. The baseline data of the immediate group were pooled with the 3-month data of the delayed group (pre-HBO data); the same was done with the 3-month data of the immediate group and the 6-month data of the delayed group (post-HBO data). Second, we looked at score changes of each individual patient, because group comparisons of small samples may produce statistically non-significant results even if effect sizes are large and clinically meaningful [4]. This second analysis was done using the Reliable Change Index (RCI) [5]. The RCI is a function of the retest reliability and the standard deviation of the test scores. These were taken from the test manuals or published studies. The RCI does not correct for retest effects. Therefore we added the retest effect as an extra term to the formula. The retest effects of each test were taken from the test manuals or published studies. When the values were unknown, the observed retest effects of the delayed group in the present study were used (a table of the RCIs, retest effects and the change scores of each subject may be obtained from the first author). Negative retest effects were assumed to be chance fluctuations and set to zero. With this method the experimental group (immediate group) was compared to the control group (delayed group) at 3 months to control for a retest effect.

Results

The immediate group and the delayed group were not significant different (Mann-Whitney) in age, level of education and

Table 2. Overview of neuropsychological tests (for more detailed information see appendix).

Tabelle 2. Übersicht neuropsychologischer Tests (detaillierte Informationen im Anhang).

	Name of neuropsychological test	Type of measurement
1	Symbol Digit Modalities Test of the Wechsler Adult Intelligence Scale (WAIS)	Speed of information processing
2	Similarities of the WAIS	Ability to reason abstractly
3	Block Design of the WAIS	Visual-spatial insight and visuo-constructive skills
4	Boston Naming Test	Naming line drawings of objects and animals
5	Auditory Verbal Learning Test (AVLT)	Verbal memory
6	Letter Fluency of the Multilingual Aphasia Examination	General vocabulary memory
7	Category Fluency of the Groninger Intelligence Test (GIT)	Vocabulary memory related to animals and occupation
8	Logical Memory of the Rivermead Behavioural Memory Test	Memory for structured verbal material
9	Calculation of the GIT	Numerical ability
10	Warrington Recognition Memory Test Faces	Aspects of non-verbal memory
11	Trailmaking Test	Executive functioning, motor speed and attention
12	Stroop Color-Word Test	Selective attention, perceptual interference and response inhibition
13	Nelson's Modified Wisconsin Card Sorting Test (MWCST)	Cognitive flexibility
14	FEPSY	Reaction time and choice reaction time
15	Grooved Pegboard	Visual-motor and speed co-ordination

variables in relation to the radiotherapeutic treatment (see Table 1). All seven eligible patients completed the full period of 30 HBO sessions as well as the three neuropsychological tests. At baseline tests all patients showed cognitive impairment: five were scored as moderately, one severely and one as slightly impaired. Predominant impaired domains were mental slowness (all patients) and immediate recall (six patients).

In Tables 3 and 4 the means and standard deviations on each test of the immediate and the delayed group are presented. The first method of analysis, comparing the pre- and post-HBO results for all patients, showed no significant improvements on neuropsychological testing, except for the ability self rating scale of the MAC questionnaire (Wilcoxon signed-rank test $p = 0.016$). The patients scored their everyday memory abilities to be improved after treatment. This was not corroborated by the proxy ratings however.

The results of the second method of analysis can be seen in Table 5, which shows the total number of significant difference scores between baseline, 3 months and 6 months for each subject. At 3 months no significant difference was found between the immediate group and the delayed group. Although not significant, the sum of significant different scores after 3 months in the three untreated patients (delayed group) was +4, compared to +13 in the four treated patients (immediate group). Patient No. 5 in the immediate group showed the largest improvement. After treatment this patient had an increased mental speed and had better self and proxy ratings of memory and dysexecutive symptoms. Between 3 and 6 months this person showed a further improvement but the remaining three patients in the immediate group did not. In the delayed group two patients improved somewhat in the first 3 months (without treatment). Between baseline and 6 months, three out of four patients in the immediate group and all pa-

Table 3. Means and standard deviations of neuropsychological test scores of the immediate treatment group and the delayed treatment group at baseline, 3 months and 6 months. (T): T score; s: seconds; ms: milliseconds; dom: dominant hand; non dom: non dominant hand; rt: reaction time; SD: standard deviation.

Tabelle 3. Mittelwerte und Standardabweichungen der Punktwerte neuropsychologischer Tests für die „frühe“ und „späte“ Behandlungsgruppe vor Therapie sowie 3 und 6 Monate nach HBO. (T): T-Score; s: Sekunden; ms: Millisekunden; dom: dominante Hand; non dom: nicht dominante Hand; rt: Reaktionszeit; sd: Standardabweichung.

Test	Baseline immediate group Mean (SD)	Baseline delayed group Mean (SD)	3 Months immediate group Mean (SD)	3 Months delayed group Mean (SD)	6 Months immediate group Mean (SD)	6 Months delayed group Mean (SD)
GIT Calculation (T)	39.5 (11.1)	44.0 (2.0)	35.5 (8.7)	46.7 (12.1)	37.5 (11.8)	51.3 (10.1)
GIT Category fluency	49.3 (7.3)	48.7 (14.6)	50.5 (9.0)	50.0 (13.5)	44.5 (10.7)	44.3 (9.7)
Letter Fluency total	27.3 (21.4)	27.3 (9.9)	34.8 (23.8)	39.0 (13.0)	31.3 (19.6)	26.3 (13.1)
WAIS Similarities (T)	63.3 (7.3)	57.0 (8.0)	65.8 (11.4)	60.3 (12.7)	61.3 (13.2)	57.7 (7.0)
WAIS Symbol Digit (T)	45.8 (19.4)	55.0 (13.1)	50.3 (20.0)	56.7 (14.0)	53.3 (17.5)	58.7 (9.1)
WAIS Block Design (T)	52.5 (10.5)	52.7 (11.7)	53.8 (12.8)	56.7 (9.6)	54.5 (13.2)	58.5 (10.6)
Boston Naming Test	55.3 (2.3)	56.0 (3.0)	54.8 (4.6)	55.8 (4.6)	56.9 (0.8)	57.0 (2.6)
AVLT total	40.5 (5.8)	45.0 (4.0)	41.8 (6.3)	43.3 (2.9)	37.8 (7.1)	44.0 (2.6)
AVLT delayed recall	7.5 (3.3)	10.0 (1.7)	8.5 (2.4)	11.0 (2.6)	7.0 (1.4)	9.3 (0.6)
Logical Memory immediate	17.3 (3.9)	14.0 (2.0)	16.8 (6.0)	14.0 (3.8)	15.8 (4.9)	19.0 (4.8)
Logical Memory delayed recall	11.5 (3.8)	11.2 (3.8)	13.6 (5.9)	10.0 (4.8)	13.1 (3.0)	14.2 (4.1)
Trailmaking A s	61.0 (37.0)	38.3 (19.0)	47.8 (21.4)	39.3 (21.2)	55.8 (36.3)	38.7 (13.0)
Trailmaking B s	165.0 (103.7)	102.0 (29.3)	139.3 (103.6)	76.3 (23.0)	134.8 (68.2)	88.7 (27.8)
Stroop word s	51.0 (15.0)	50.7 (3.1)	50.0 (11.9)	49.3 (9.0)	49.5 (14.3)	43.3 (11.0)
Stroop color s	80.5 (36.5)	77.3 (16.3)	81.5 (42.4)	70.7 (3.1)	82.0 (41.5)	56.7 (11.4)
Stroop color-word s	157.0 (88.5)	114.7 (26.1)	148.5 (69.9)	105.3 (7.6)	138.5 (71.2)	103.3 (4.2)
MWCST errors	7.3 (3.1)	13.7 (4.0)	14.8 (7.0)	13.7 (13.2)	17.3 (15.2)	8.3 (3.5)
MWCST perseverations	1.3 (1.5)	4.7 (0.6)	3.5 (4.4)	5.0 (7.0)	5.5 (7.7)	2.0 (1.0)
MWCST categories	6.3 (0.6)	4.7 (1.5)	4.3 (1.5)	4.7 (2.1)	4.3 (2.5)	5.3 (0.6)
Warrington RMT Faces	36.8 (3.8)	38.0 (5.6)	40.8 (3.9)	42.0 (4.6)	42.5 (1.3)	43.7 (2.1)
Grooved Pegboard dom s	93.3 (35.0)	81.7 (10.0)	91.8 (30.3)	79.9 (12.1)	91.0 (30.6)	81.0 (6.6)
Grooved Pegboard non dom s	109.0 (31.2)	68.5 (7.8)	101.5 (28.9)	66.5 (7.8)	119.0 (38.8)	67.0 (1.4)
FEPSY simple rt dom ms	330.5 (75.1)	287.3 (16.3)	292.5 (9.1)	303.0 (47.6)	310.7 (17.0)	276.0 (26.9)
FEPSY simple rt non dom ms	282.8 (20.2)	311.0 (18.4)	304.8 (29.3)	304.0 (48.1)	307.0 (14.9)	284.0 (19.8)
FEPSY choice rt ms	372.3 (57.2)	427.0 (179.6)	321.5 (69.1)	386.0 (236.2)	350.0 (19.3)	386.5 (236.9)

tients in the delayed group showed some improvement (see Table 5).

26% of the significant improvements and deteriorations were on the MAC and DEX questionnaires. Other relative large improvements were on the Trailmaking Test (14%), Warrington RMT Faces (8%), FEPSY reaction rate (11%) and on Modified Wisconsin Card Sorting Test (9%). Other improvements were equally distributed over the remaining tests.

No seizures were observed during the HBO treatment or any other toxicity. One patient experienced absences and deterioration during the HBO treatment period. A CT scan showed a tumor recurrence and she was excluded from the study.

Discussion

The present study is the first study trying to assess the effect of HBO by neuropsychological testing in patients with cognitive disorders after brain irradiation. Looking at the neuropsychological score over time of each patient separately, no significant cognitive improvement was found after HBO. However, because of the low number, the power of this negative result is low. One out of 31 test variables (memory abilities) improved significantly at 3 months after start of HBO treatment for the total group. At 6 months, when all had their HBO treatment, there was an overall small improvement in six out of seven patients. One patient had a meaningful improvement. This finding, in combination with the lack of toxicity, which is in concordance with other HBO studies [24], is a basis for considering HBO treatment in an individual patient.

Two clinical studies have reported on HBO for progressive radiation-induced brain injury, mainly within 1 year after irradiation, showing improvement or stabilization of Karnofsky score or resolution of necrosis [7, 13]. In contrast to both studies, the present study reports on non-progressive patients with cognitive disorders for at least 1,5 years after radiotherapy, without necrosis on CT or MRI. These differences could suggest that HBO treatment is more effective against early-delayed progressive vascular damage and less effective for late damage in non-progressive patients without radiological signs of necrosis, indicating that timing of HBO treatment could be important.

Unfortunately no more than ten patients were initially eligible for the study despite the large number of patients receiving brain irradiation in our institute (about 40 per year). A statistical significant difference is therefore hard to attain. Several factors explain the low prevalence of cognitive disorders. First, 2-year survival of patients receiving high-dose radiotherapy for malignant glioma is very poor [16]. Second, the detrimental effects of modern, conformal and fractionated, moderate-dose radiotherapy are probably small [23]. Thus,

Table 4. Means and standard deviations of self and proxy rating scores in both groups at baseline, 3 months and 6 months (SD: standard deviation).

Tabelle 4. Mittelwerte und Standardabweichungen der Punktwerte bei Selbst- und Angehörigeneinschätzung in beiden Gruppen vor Therapie sowie 3 und 6 Monate nach HBO (SD: Standardabweichung).

Test	Baseline immediate group Mean (SD)	Baseline delayed group Mean (SD)	3 Months immediate group Mean (SD)	3 Months delayed group Mean (SD)	6 Months immediate group Mean (SD)	6 Months delayed group Mean (SD)
MAC ability scale self	57.0 (14.6)	74.3 (17.5)	66.0 (8.8)	69.7 (8.4)	61.3 (5.0)	72.2 (7.1)
MAC frequency scale self	67.5 (16.1)	73.0 (10.6)	76.8 (6.7)	78.7 (12.7)	77.0 (8.7)	82.7 (8.0)
MAC ability scale proxy	57.5 (14.3)	74.7 (20.1)	60.3 (7.9)	70.0 (7.2)	62.3 (6.7)	70.0 (12.5)
MAC frequency scale proxy	68.0 (15.3)	85.7 (7.6)	72.3 (11.6)	80.0 (2.0)	76.3 (16.7)	79.3 (9.1)
DEX self rating	30.0 (12.2)	27.7 (2.3)	21.5 (11.7)	35.0 (9.2)	13.3 (6.7)	24.7 (14.8)
DEX proxy rating	34.5 (15.2)	29.0 (20.7)	33.0 (17.8)	27.0 (19.7)	22.7 (21.5)	28.0 (26.9)

Table 5. Number of significant difference scores between baseline, 3 months and 6 months for each subject (ab: baseline 3 months scores; bc: 3 months – 6 months scores; ac: baseline – 6 months scores; No. 4–7: subjects from immediate group; No. 1*–3*: subjects from delayed group).

Tabelle 5. Anzahl der signifikanten Punktwertunterschiede zwischen Ausgangswert sowie 3 und 6 Monate nach HBO für jeden einzelnen Patienten (ab: basal – 3-Monats-Score; bc: 3 Monate – 6 Monate; ac: basal – 6 Monate; No. 4–7: Patienten aus der frühen Behandlungsgruppe; No. 1*–3*: Patienten aus der späten Behandlungsgruppe).

	No. 1*			No. 2*			No. 3*			No. 4			No. 5			No. 6			No. 7		
	ab	bc	ac	ab	bc	ac	ab	bc	ac	ab	bc	ac	ab	bc	ac	ab	bc	ac	ab	bc	ac
No. of tests improved	3	2	3	5	3	5	4	3	3	3	0	2	9	5	11	2	0	1	2	1	3
No. of tests declined	3	2	2	3	1	2	2	2	1	0	2	0	1	1	2	2	2	3	0	3	0
Improved – declined	0	0	1	2	2	3	2	1	2	3	-2	2	8	4	9	0	-2	-2	2	-2	3

randomized studies or even large prospective studies on this issue are difficult to attain.

There are still several questions to be answered considering the effect of HBO in irradiated brain tissue. The pathogenesis of radiation-induced brain damage is usually based on a dual focus, namely damage to the nerve fibers (demyelinization) and to the vasculature [6, 17, 20, 21]. A direct effect of HBO on the demyelinization component, once expressed, is not to be expected. Although an effect on revascularization of brain tissue can be expected from the role of HBO in several other organs, it has not been proven in brain tissue yet. Furthermore, neurocognitive deficits after irradiation have not been associated with specific histology. Both ischemic damages to the hippocampus (memory function) as diffuse white matter changes have been associated with diffuse cognitive disorders [1, 6, 8]. The current study suggests that HBO may have effects on radiation-induced cognitive functioning but questions on optimal timing of HBO, the domains of cognition which could improve and the extend of histologic changes after radiation which could be influenced by HBO, are still to be answered. Even the optimal number of sessions to gain significant improvements is not known. More than 30 sessions have been administered in several other organ sites [3, 12, 15]. The number of 30 sessions in this study was based on a few previous HBO studies in neurotoxicity [7, 11] as well as the amount of time spent for this particular patient group. Because of the slow progression of radiation damage to nervous tissue, including the slow breakdown of the endothelial cells [21], timing of HBO treatment could play a crucial role. Apart from the dose fractionation and volume-dependent severity of tissue injury, the time point of HBO during the latency period, when tissue damage is still at a subclinical, reversible but progressive level, may determine its success. This theory is the basis of a proceeding study, in which HBO will be administered within 6 months after brain irradiation, at the onset of cognitive symptoms. Results will be measured by late event-related components in the EG response to a visual odd-boll stimulus (visual odd-boll paradigm), finger tapping tests and sensory evoked potentials.

A striking finding in our study was that a considerable part of the observed improvements, per group and per patient, were due to subjective self ratings on the MAC (memory abilities) and DEX (desexecutive symptoms) questionnaires. This result is in concordance with verbally positive reports of the subjects, when they were asked for their well-being after treatment. This result may be explained by the known Hawthorne effect: the score changes due to the mere knowledge of being under observation.

Appendix

Description of Neuropsychological Tests

- *Symbol Digit Modalities Test of the Wechsler Adult Intelligence Scale (WAIS):* This test measures information processing speed. In 90 seconds the subject has to fill in as many numbers as possible beneath the corresponding signs. The number-sign pairs are listed on top of the test form. Raw scores are transformed into age-corrected T scores.
- *Similarities of the WAIS:* This test measures the ability to reason abstractly. The subject has to say what two objects or concepts have in common. For example: "In which way are an apple and a banana alike?" The similarity in this case is fruit. Raw scores are transformed into age-corrected T scores.
- *Block Design of the WAIS:* This test measures visual-spatial insight and visuo-constructive skills. With the use of colored blocks the subject has to copy several geometric patterns. Raw scores are transformed into age-corrected T scores.
- *Boston Naming Test:* This test measures naming problems. 60 line drawings of objects and animals of increasing difficulty must be named. The score is the raw number of correct responses.
- *Auditory Verbal Learning Test (AVLT):* This test measures verbal memory. The subject listens to five trials of 15 words. After every trial (immediate recall) and after 15 minutes (delayed recall) as many words as possible must be reproduced. Finally, a recognition trial is presented in which the subject has to discriminate between 15 target words and 15 new words. Parallel forms were used at follow-up. Raw scores are used.
- *Letter Fluency of the Multilingual Aphasia Examination:* The subject has to name as many words as possible that begin with a given letter during one minute. There are three trials with different letters. At follow-up parallel forms were used. The score is the raw number of correct responses.
- *Category Fluency of the Groninger Intelligence Test (GIT):* The subject has to name as many animals as possible during one minute. Next, the same procedure is repeated with occupations. Raw scores are transformed into age-corrected T scores.
- *Logical Memory of the Rivermead Behavioural Memory Test:* This test measures memory for structured verbal material. Two short newspaper articles are read to the subject. Immediately afterwards and after a 15 minute delay the subject has to remember as many elements of the articles as possible. The score is the number of elements recalled. Parallel forms were used at follow-up.
- *Calculation of the GIT:* This is a numerical ability test. Written additions have to be solved during one minute. Raw scores are transformed into age-corrected T scores.
- *Warrington Recognition Memory Test Faces:* This subtest measures an aspect of non-verbal memory. Fifty photographs of male faces are shown during 3 seconds each. Immediately afterwards the faces must be recognized out of 50 pairs of faces. The score is the raw number of correct responses.
- *Trailmaking Test:* This test measures executive functioning, motor speed and attention. In the first part the subject has to draw lines on a paper sheet between 25 numbered circles. In the second part the subject has to draw lines alternating between a number and a letter (1A2B3C etc.). In both parts the

subject is instructed to work as fast as possible. The score is time to completion in seconds.

- *Stroop Color-Word Test:* This test measures selective attention, perceptual interference and response inhibition. The subject has to read aloud a card with 100 black printed color names (red, blue, green and yellow). Next, the subject has to name 100 colored rectangles. Finally, the subject has to name the color of the ink in which 100 color names are printed. The words do not match with the color of the ink. For example the word "green" is printed in red. The subject is instructed to work as fast as possible. The score is time to completion in seconds.
- *Nelson's Modified Wisconsin Card Sorting Test (MWCST):* This test measures cognitive flexibility. The test consists of 48 cards with figures of different color, number and form. The task is to sort the cards according to one out of three possible sorting rules (color, number or form). The subject has to find out by himself what is the right sorting principle. The examiner gives feedback after each sort. After six correct sorts in a row the subjects is told to use a different sorting rule. Raw scores are used.
- *FEPSY:* This is a computerized test of simple and choice reaction time. In the simple reaction time test the subject has to press the space bar as fast as possible when a block appears in the middle of the screen. In the choice reaction time test the subject has to press a button on the right side of the keyboard with the right hand when a block appears on the right half of the screen and with the left hand at the left side of the keyboard when a block appears on the left side of the screen. The score is the median reaction time in milliseconds.
- *Grooved Pegboard:* This test measures visual-motor coordination and speed. In a pegboard with 25 keyholes the subject has to put the corresponding pegs as fast as possible. The score is time to completion in seconds.

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