Acute Neurocognitive Impairment during Cranial Radiation Therapy in Patients with Intracranial Tumors

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Background and Purpose: The objective of the current study was to evaluate the acute effects of cranial radiation therapy (CNS-RT) using different radiation doses (0, 1.8, 2, 3, ≥ 20 Gy) on cognitive function with special emphasis on memory. We assessed patients with and without intracranial tumors to distinguish between direct and indirect radiation effects on brain tissue.
Materials and Methods: Eighty-two patients were evaluated with neuropsychological testing before and acutely after radiotherapy (RT). Sixty-four patients received RT to the brain (55 with, 9 without intracranial tumor). Eighteen patients treated with RT to the breast served as controls.
Results: Patients with intracranial tumor demonstrated attention (19–38th percentile) and verbal memory scores (34–46th percentile) below the population average at baseline. The average Verbal Memory score was significantly different between patients with intracranial tumor and controls both at baseline (38th vs. 58th percentile) and after irradiation (27th vs. 52th percentile). Patients with preexisting peritumoral edema performed worse than patients without edema and controls. Radiation dose-related deficits were seen for working memory performance in patients with intracranial tumor.
Conclusion: Our data indicate no measurable impairment of cognitive functioning acutely after prophylactic cranial irradiation. Patients with intracranial tumor show a deterioration of almost all memory functions with a dose-dependent impairment in working memory. Patients with preexisting peritumoral brain edema show the strongest deterioration.

Key Words: Radiotherapy · Brain tumors · Neurocognition · Working memory

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Akute neurokognitive Beeinträchtigungen während Radiotherapie bei Patienten mit ZNS-Tumoren

Hintergrund und Ziel: Die vorliegende Arbeit untersucht Akuteffekte der kraniellen Strahlentherapie (ZNS-RT) nach unterschiedlichen Bestrahlungsdosen (0, 1.8, 2, 3, ≥ 20 Gy) auf die kognitive Funktion unter besonderer Berücksichtigung des verbalen Gedächtnisses. Wir haben Patienten mit und ohne Hirntumor untersucht, um zwischen direkten und indirekten Bestrahlungseffekten auf das Hirngewebe zu unterscheiden.
Patienten und Methodik: 82 Patienten wurden vor und unmittelbar nach Beginn der Radiotherapie (RT) neuropsychologisch untersucht. 64 Patienten wurden am ZNS bestrahlt (55 mit, 9 ohne Hirntumor). 18 Patientinnen, die an der Mamma bestrahlt wurden, dienten als Kontrollgruppe.
Ergebnisse: Vor RT-Beginn lagen Aufmerksamkeitsleistungen (Prozentränge von 19–38) und verbale Gedächtnisleistungen (Prozentränge von 34–46) der Patienten mit Hirntumor unterhalb des Mittelwertes für die Normalbevölkerung (Tabellen 4, 5). Die durchschnittliche verbale Gedächtnisleistung der Patienten mit Hirntumor unterschied sich vor (Prozentrang 38 vs. 58) und nach RT (Prozentrang 27 vs. 52) signifikant von der der Kontrollgruppe (Abbildung 1). Patienten mit einem peritumoralen Hirnödem vor ZNS-RT zeigen schlechtere Leistungen als Patienten ohne Hirnödem und Kontrollpatienten (Abbildung 3). Bestrahlungsdosisabhängige Effekte wurden für das Arbeitsgedächtnis bei Patienten mit ZNS-Tumor beobachtet (Abbildung 2).
Schlussfolgerung: Unsere Daten zeigen keine messbaren kognitiven Beeinträchtigungen unmittelbar nach Beginn einer prophylaktischen Ganzhirnbestrahlung. Patienten mit Hirntumor zeigen eine Verschlechterung der verbalen Gedächtnisfunktionen und eine dosisabhängige Beeinträchtigung im Arbeitsgedächtnis. Patienten mit einem peritumoralen Hirnödem vor ZNS-RT zeigen die größten Veränderungen.

Schlüsselwörter: Strahlentherapie · Hirntumoren · Neurokognition · Arbeitsgedächtnis

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Introduction

Therapeutic irradiation of the brain (CNS-RT) can induce a number of dose-related adverse effects in pediatric and adult patients, including cognitive impairment [6, 8, 12, 26, 30, 32, 35, 40, 46]. Most of research on cognitive effects of CNS-RT has concentrated on long-term neurocognitive sequelae. A deterioration of cognitive function in the acute phase after CNS-RT is not systematically described in the literature, and cognitive evaluations in that phase are rare. We have previously reported impaired performance in the verbal memory domain after the first fraction of fractionated stereotactic radiotherapy (FSRT) in patients with base of skull meningiomas [42]. In contrast, patients undergoing hyperfractionated total body irradiation (TBI) before autologous bone marrow/peripheral blood stem cell transplantation or patients undergoing radiosurgery for arteriovenous malformations (AVMs) showed no verbal memory impairment [43, 47–49].

The objective of the current study was to evaluate the acute effects of CNS-RT using different radiation doses (0, 1.8, 2, 3, ≥ 20 Gy) on cognitive functioning with special emphasis on memory in patients with and without intracranial tumors to distinguish between direct and indirect radiation effects, e.g., edema on brain tissue.

Materials and Methods

Demographics and Study Design

Eighty-two patients (median age 58 years, age range 26–79 yr) with different tumor types (breast, lung, meningioma and other) were tested twice, immediately before (day 0) and acutely (day 1) after RT. The baseline characteristics of the

Table 1. Patient characteristics.

Tabelle 1. Patientencharakteristik.

Characteristic	0 Gy n = 18	1.8 Gy n = 10	2 Gy[a] n = 9	2 Gy[b] n = 16	3 Gy[b] n = 25	≥ 20 Gy n = 4
Gender*						
Male	–	4	4	11	8	3
Female	18	6	5	5	17	1
Age (years)[d]	55±11	58±10	61±16	58±11	57±9	59±11
	(35–69)	(37–75)	(26–79)	(37–72)	(33–73)	(45–72)
Karnofsky performance status[d]*	87±6	86±7	83±14	81±10	78±9	80±8
	(80–100)	(80–100)	(60–100)	(60–90)	(60–90)	(70–90)
Pretreatment received						
Surgery (brain)*	–	6 (60)	–	11 (69)	6 (24)	–
Total resection (brain)*	–	1 (10)	–	8 (50)	5 (20)	–
Radiation therapy (brain)	–	1 (10)	–	–	–	–
Hormonal therapy*	7 (39)	–	–	1 (6)	4 (16)	–
Chemotherapy*	13 (72)	–	9 (100)	9 (56)	13 (52)	1 (25)
Brain lesion location[c]						
Frontal	–	1	–	6	11	2
Temporal	–	4	–	4	5	1
Parietal	–	0	–	8	11	1
Occipital	–	2	–	5	5	1
Infratentorial	–	4	–	1	8	–
Unknown	–	–	–	1	4	–
Preexisting peritumoral edema	–	–	–	5 (31)	18 (72)	2 (50)
Education						
Low education level	11 (61)	9 (90)	4 (44)	12 (75)	20 (80.0)	2 (50)
Middle education level	4 (22)	1 (10)	2 (22)	2 (12)	4 (16.0)	2 (50)
High education level	3 (17)	–	3 (33)	2 (12)	1 (4.0)	–
Dominance, right handed	16 (89)	9 (90)	7 (78)	15 (94)	23 (92)	4 (100)

Unless indicated otherwise, data presented as number of patients; data in parenthesis are percentages.

[a]Patients without brain tumor (PCI: prophylactic cranial irradiation).

[b]Patients with brain tumor (TCI: therapeutic cranial irradiation).

[c]Including multiple locations.

[d]Data presented as mean ± standard deviation; data in parenthesis are ranges.

*Indicates significant differences between groups, $p < .05$.

patients are listed in Table 1. Eighteen patients without cranial radiotherapy (control group) were compared to 64 patients with radiotherapy to the CNS (CNS-RT group). Ten patients received partial brain RT, and 50 patients received whole brain RT, 9 of them with prophylactic and 41 with therapeutic intent. Four patients were treated with radiosurgery for solitary brain metastasis. There was no change in corticosteroid dose from baseline in patients treated with fractionated RT. The patients treated with radiosurgery received 20 mg dexamethasone immediately before and 6 hours after radiosurgery. A peritumoral edema was present on CT or MRI scan in 25 brain tumor patients (45%).

Patient groups were not significantly different with respect to education, age, and handedness ($p > 0.05$), but they were different for gender and Karnofsky performance status (KPS). Subgroup analyses revealed a significantly lower mean KPS for patients in the 3 Gy single dose group compared to patients of the control group ($p < 0.01$).

Inclusion criteria were as follows: patient age ≥ 18 years, KPS ≥ 60, fluent in speaking German, no history of a psychiatric disorder or organic brain syndrome, and no chemotherapy at the time of RT. After complete description of the study to the patients, written informed consent was obtained. The institutional ethics committee reviewed and approved the protocol and the consent form.

Measures

Each patient underwent a neuropsychological examination just before (day 0) and after the beginning of irradiation (day 1). Each session lasted about 1 hour and was briefly interrupted if necessary. The neuropsychological test battery consisted of measures of verbal and visual memory, focused and divided attention, and alertness previously shown to be sensitive in detecting radiotherapy-associated impairment [1, 2, 9, 37, 42, 44]. In addition, premorbid intellectual functioning and emotional distress were assessed. Only standardized neuropsychological instruments (all with published normative data) were used (Table 2). The German version of the Hospital Anxiety and Depression Scale (HADS-D) [13] was used to measure levels of anxiety and depression at day 0.

Test results are given as IQ points (average normal population 100), percentile scores for attention and memory testing (average 50), and raw scores and sex-adjusted percentile scores for emotional distress. In addition, as previously published [42, 48], we computed three composite scores: Verbal Memory score, Visual Memory score, and General Attention score for each individual. These composite scores were defined as follows: Verbal Memory score = average of all verbal memory subtest scores; Visual Memory score = average of all visual memory subtest scores; General Attention score = average of all attention subtest scores.

Statistics

Data were analyzed using SPSS-13.0.1. Differences in demographic and baseline data were tested using the χ^2 test for categorical variables and the one-way analysis of variance (ANOVA) model for continuous variables. Subgroup analyses were evaluated with Mann-Whitney-U methods, comparing the control group with each of the five CNS-RT conditions. The significance level was set at $p < 0.01$ after Bonferroni correction. The primary analyses used to identify treatment effects were analyses of covariance (ANCOVAs), with baseline scores as covariates. An uncorrected value of $p < 0.05$ was used to determine statistical significance. Changes in neurocognitive functioning were estimated as adjusted mean change from baseline.

Results

Baseline Neurocognitive Performance and Emotional Functioning

Premorbid Intelligence and Emotional Distress

Patients with intracranial tumor had a significantly lower premorbid intelligence score than patients without intracranial tumor and controls group (Table 3). Compared to controls, patients treated with a 3 Gy single dose showed the lowest intelligence score (–12 points, $p = 0.002$), although still within the normal range. There were no significant differences on de-

Table 2. Neuropsychological test battery. AVLT: Auditory Verbal Learning Test; MCG: Medical College of Georgia Complex Figures; TAP: Test for Attentional Performance; MWT: Multiple-Choice Test of Vocabulary Knowledge.

Tabelle 2. Neuropsychologische Testbatterie. AVLT: Verbaler Lern- und Merkfähigkeitstest (VLMT); MCG: Medical College of Georgia Complex Figures Test; TAP: Testbatterie zur Aufmerksamkeitsprüfung; MWT: Mehrfachwahl-Wortschatz-Intelligenztest.

Tests and subtests		Specific cognitive function	Domain
AVLT [11]		Immediate supra-span	Memory (verbal)
		Learning	
		Interference	
		Immediate recall	
		Delayed recall	
		Recognition	
MCG [19, 25, 41]		Immediate recall	Memory (visual)
		Delayed recall	
TAP [50]	Alertness	Simple reaction time	Attention
		Phasic alertness	
	Divided attention	Divided attention	
	Go/No go	Selective attention	
MWT [18]		Vocabulary	Premorbid intelligence level

Table 3. Intelligence and emotional functioning (Day 0). SD: standard deviation; HADS-D: Hospital Anxiety and Depression Scale – German Version; n.s.: not significant.

Tabelle 3. Intelligenz und emotionales Befinden (Tag 0). SD: Standardabweichung; HADS-D: Hospital Anxiety and Depression Scale – Deutsche Version; n.s.: nicht signifikant.

	With tumor (n=55)	Without tumor (n=9)	Control group (n=18)	
	Mean (± SD)	Mean (± SD)	Mean (± SD)	p
Premorbid intelligence	97 (14)	112 (15)	106 (13)	0.003
Anxiety (HADS-D)	59 (34)	47 (38)	53 (32)	n.s.
Depression (HADS-D)	71 (30)	69 (32)	84 (16)	n.s.

IQ data presented as IQ points; emotional functioning data presented as sex-adjusted percentile scores.

Table 4. Attention scores (data presented as percentile scores). SD: Standard deviation; Md: median of reaction time; Sd: variance of reaction time; n.s.: not significant.

Tabelle 4. Aufmerksamkeitswerte (Angaben in Prozentrang). SD: Standardabweichung; Md: Mediane Reaktionszeit; Sd: Streuung der Reaktionszeiten; n.s.: nicht signifikant.

		With tumor (n=55)	Without tumor (n=9)	Control group (n=18)		
		Mean (± SD)	Mean (± SD)	Mean (± SD)	F_{Group} [a]	p
Alertness						
Simple reaction time						
Md	Day 0	30.2 (31.8)	22.0 (23.6)	16.3 (25.1)	1.36	n.s.
	Day 1	33.4 (33.0)	34.7 (31.0)	28.9 (25.6)	2.42	n.s.
Sd	Day 0	35.8 (32.3)	34.2 (30.9)	24.7 (31.0)	0.69	n.s.
	Day 1	38.7 (33.8)	49.7 (31.1)	53.0 (32.5)	5.14	0.008
Phasic alertness	Day 0	38.4 (31.4)	48.4 (39.0)	51.0 (38.3)	0.97	n.s.
	Day 1	39.0 (30.6)	50.7 (27.1)	44.7 (28.5)	0.32	n.s.
Divided attention						
Md	Day 0	18.8 (15.6)	28.6 (22.4)	25.3 (20.2)	1.41	n.s.
	Day 1	29.8 (24.4)	26.6 (30.3)	24.8 (22.0)	2.85	n.s.
Sd	Day 0	33.5 (25.2)	56.6 (24.8)	48.4 (22.3)	3.79	0.029
	Day 1	43.3 (27.9)	56.7 (27.8)	51.9 (31.3)	0.02	n.s.
Omission errors	Day 0	30.2 (25.7)	29.3 (20.5)	36.3 (23.4)	0.33	n.s.
	Day 1	28.0 (24.4)	33.7 (34.0)	47.0 (23.3)	2.73	n.s.
Go/No Go						
Md	Day 0	30.6 (28.8)	47.4 (31.3)	59.2 (36.8)	2.65	n.s.
	Day 1	31.4 (30.2)	42.2 (31.1)	60.0 (30.0)	0.31	n.s.
Sd	Day 0	30.3 (37.0)	36.8 (30.8)	29.2 (10.5)	0.09	n.s.
	Day 1	37.3 (33.1)	19.2 (16.6)	49.5 (40.8)	2.30	n.s.
Misses	Day 0	34.4 (18.9)	34.8 (22.5)	48.0 (2.2)	1.47	n.s.
	Day 1	37.3 (18.1)	39.0 (16.8)	46.7 (1.6)	0.04	n.s.

[a]F-statistic for treatment group as main effect. Day 0: results from analysis of variance (ANOVA).
Day 1: Results from analysis of covariance (ANCOVA) with day 0 score as covariate.

pression and anxiety scores between patients with or without intracranial tumor and controls (Table 3).

Cognitive functions

At baseline (day 0), patients with intracranial tumor performed below the average population on all attention (19–38th percentile) and all verbal memory (34–46th percentile) subtests (Tables 4 and 5). Compared to the control group, patients with and without intracranial tumors were impaired on almost all verbal memory tests. The Verbal Memory score in patients with and without intracranial tumors, and controls was 38, 43, and 58 percentile, respectively ($F = 4.67$, $p = 0.012$; Figure 1).

Treatment Effects

Attention

Most of the attention scores improved early after the beginning of CNS-RT, consistent with a previously reported practice effect [42, 43, 48]. Analysis of covariance with baseline score as covariate showed that attention functioning at day 1 was mainly attributable to differences in baseline score ($F = 59.9$, $p < 0.001$). Patients with intracranial tumor achieved a smaller improvement in the variance of simple reaction time as compared to patients without intracranial tumor and controls. Radiation dose-related deficits were not seen.

Memory

Patients with intracranial tumor scored significantly lower in the Verbal Memory score as compared to patients without intracranial tumor and controls (27, 45, and 52 percentile, respectively, $F = 12.09$, $p < 0.001$; Figure 1). Analyses of covariance demonstrated that verbal memory scores on day 1 were mainly attributable to differences in baseline score ($F > 8.0$, $p < 0.01$), but there was also an effect of treatment. Patients with intracranial tumor had a significantly poorer performance in 4 out of 6 verbal memory scores as compared to patients without intracranial tumor and controls (Table 5).

Additional analyses were performed to assess the acute effects of different radiation doses (0, 1.8, 2, 3, ≥ 20 Gy, Figure 1). There was a significant dose-related change in supra-span memory function ($F = 2.82$, $p = 0.022$, Figure 2). Patients treated with radiosurgery demonstrated the strongest decline, with a mean score below the 20th percentile. A second ANCOVA entering interference and attention scores as additional covariates showed that the treatment effect remained significant. The performance in supra-span

Table 5. Memory scores (data presented as percentile scores). SD: Standard deviation; Md: median of reaction time; n.s.: not significant.

Tabelle 5. Gedächtniswerte (Angaben in Prozentrang). SD: Standardabweichung; Md: Mediane Reaktionszeit; n.s.: nicht signifikant.

		With tumor (n=55)	Without tumor (n=9)	Control group (n=18)		
		Mean (± SD)	Mean (± SD)	Mean (± SD)	F_{Group} [a]	p
Verbal memory						
Supra-span	Day 0	45.9 (29.8)	56.3 (34.3)	63.8 (25.5)	2.67	n.s.
	Day 1	35.4 (24.6)	60.4 (33.9)	63.9 (33.0)	6.32	0.003
Learning	Day 0	36.8 (30.1)	39.8 (33.4)	64.3 (22.7)	6.12	0.003
	Day 1	25.5 (25.8)	41.9 (39.6)	58.5 (28.7)	4.17	0.019
Interference	Day 0	36.7 (32.1)	54.0 (42.5)	53.5 (31.0)	2.34	n.s.
	Day 1	39.2 (27.7)	46.4 (37.3)	65.3 (27.1)	3.84	0.026
Immediate recall	Day 0	33.6 (24.6)	28.4 (19.1)	46.6 (22.5)	2.38	n.s.
	Day 1	20.5 (20.8)	32.2 (28.2)	37.6 (24.2)	3.12	0.050
Delayed recall	Day 0	37.2 (27.5)	27.5 (30.1)	58.0 (21.8)	5.36	0.007
	Day 1	17.9 (18.6)	31.4 (25.8)	37.2 (24.7)	4.94	0.010
Recognition	Day 0	37.8 (30.6)	39.9 (24.1)	64.9 (21.5)	6.31	0.003
	Day 1	24.7 (25.0)	35.1 (35.2)	56.5 (21.8)	4.04	0.021
Visual memory						
Immediate recall	Day 0	56.4 (28.4)	58.9 (30.0)	63.6 (29.4)	0.40	n.s.
	Day 1	63.0 (28.8)	54.7 (16.1)	68.8 (25.1)	1.19	n.s.
Delayed recall	Day 0	61.0 (29.4)	65.4 (20.6)	64.6 (26.2)	0.17	n.s.
	Day 1	62.8 (28.6)	66.9 (18.6)	65.9 (25.0)	0.01	n.s.

[a]F-statistic for treatment group as main effect. Day 0: results from analysis of variance (ANOVA). Day 1: Results from analysis of covariance (ANCOVA) with day 0 score as covariate.

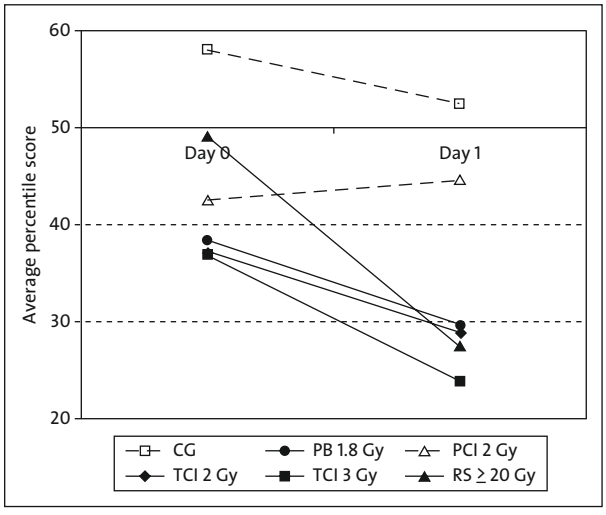

Figure 1. Verbal Memory performance before and acutely after irradiation. CG: Control group; PBI: Partial brain irradiation; PCI: Prophylactic cranial irradiation; TCI: Therapeutic cranial irradiation; RS: Radiosurgery; Day 0: before irradiation; Day 1: acutely after the beginning of irradiation.

Abbildung 1. Verbalgedächtnis vor und unmittelbar nach Bestrahlung. CG: Kontrollgruppe; PBI: Teilhirnbestrahlung; PCI: Prophylaktische Ganzhirnbestrahlung; TCI: Therapeutische Ganzhirnbestrahlung; RS: Radiochirurgie. Day 0: vor Bestrahlung; Day 1: umittelbar nach Bestrahlungsbeginn.

memory on day 1 was attributable to cognitive interference ($F = 36.82$, $p < 0.001$) and radiation dose ($F = 3.32$, $p = 0.009$), but not to differences in supra-span memory score on day 1 or attention scores. An impact of KPS, distress, intelligence or gender was not found.

Preexisting Peritumoral Edema

Day 1 cognitive performance of patients with preexisting peritumoral brain edema was below that of patients without edema and controls in 4 of 6 verbal memory subtests (learning, immediate recall, delayed recall, and recognition).

The patients were grouped according to the number of scores being 1 or 2 standard deviations (SDs) below baseline. Patients were considered as impaired when they were 2 SDs below baseline in at least one test score or 1 SD below baseline in at least three test scores. They were considered borderline impaired when two test scores were 1 SD below baseline on day 1. The remaining patients having no test scores 2 SDs and no more than one test score 1 SD below the baseline were classified as normal. According to this grading system, an impairment in verbal memory was found in 52% of patients with edema, compared with 41% of patients without edema and 11% of control patients (Figure 3).

Discussion

Severe cognitive impairments in the acute phase of CNS-RT are rare and thus have not been extensively investigated. Previously we observed no cognitive decline, but an improvement in attention functions after the first fraction of 1.2 Gy total body irradiation (TBI, no intracranial tumor) [48]. On the contrary, we observed a transient decline in most memory functions in patients with base of skull meningiomas after 1.8 Gy FSRT [42]. In the current study, we found an acute decline in cognitive functioning in patients with intracranial lesions and preexisting peritumoral edema, but also to a lesser extent in patients without edema, in line with previous reports of acute neurologic side effects after CNS-RT [24, 38].

The pathogenesis of these deficits remains unknown, but may involve a treatment-induced brain edema or an interruption of the blood-brain barrier. Capillaries and arterioles are the most radiosensitive component of the vasculature, and endothelial cells are regarded as the most radiosensitive cells of the vessel wall. A disturbed blood-brain barrier and a

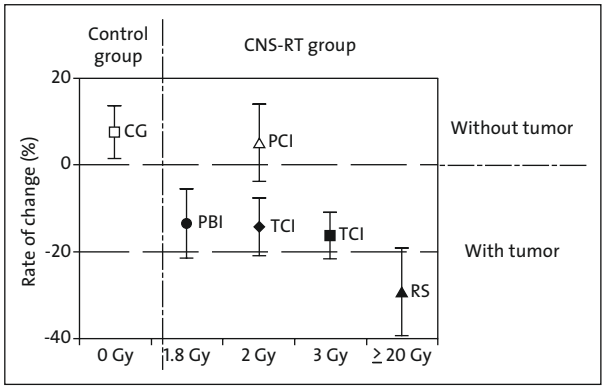

Figure 2. Effect of radiation dose on supra-span memory (adjusted mean rate of change from baseline ± standard error). CG: Control group; PBI: Partial brain irradiation; PCI: Prophylactic cranial irradiation; TCI: Therapeutic cranial irradiation; RS: Radiosurgery.

Abbildung 2. Einfluss der Bestrahlungsdosis auf das Arbeitsgedächtnis (Supraspanne; korrigierte, mittlere Veränderung gegenüber der Baseline ± Standardfehler). CG: Kontrollgruppe; PBI: Teilhirnbestrahlung; PCI: Prophylaktische Ganzhirnbestrahlung; TCI: Therapeutische Ganzhirnbestrahlung; RS: Radiochirurgie.

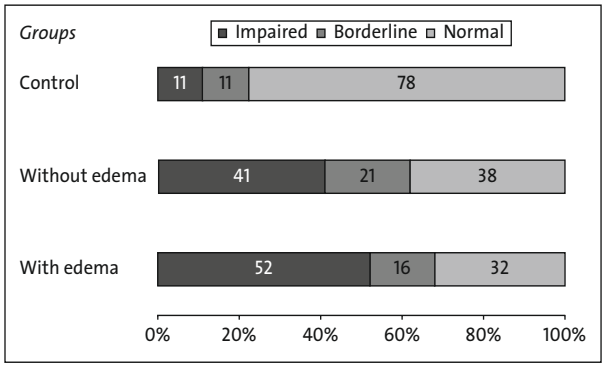

Figure 3. Verbal memory impairments in patients with intracranial tumor according to the presence of brain edema as compared to controls. Shown are the percentages of patients with impaired, borderline or normal verbal memory performance on day 1 as compared to baseline performance.

Abbildung 3. Verbale Gedächtnisbeeinträchtigungen bei Patienten mit ZNS-Tumor in Abhängigkeit vom Hirnödem im Vergleich zu den Kontrollpatienten. Dargestellt sind Patienten (%) mit beeinträchtigter, grenzwertiger oder normaler verbaler Gedächtnisleistung an Tag 1 im Vergleich zur Baseline.

higher vascularity are reported at an early phase after high-dose whole-brain irradiation in rodents [15, 17] and during CNS-RT in patients with gliomas [4] and meningeomas [10].

An alternative explanation for the acute cognitive deterioration after CNS-RT may be a radiation-induced reduction of neural stem and precursor cells in the subgranular zone (SGZ) of the hippocampus and in the subventricular zone (SVZ) of the lateral ventricles which are particularly sensitive to radiation-induced apoptosis [27, 28, 31, 34, 39]. In rodents, proliferating precursor cells and immature neurons show an acute dose-dependent reduction in cell number after exposure to X-rays [20, 27]. Both whole brain and localized irradiation block the formation of new neurons and impair hippocampal-dependent memory function [23, 34, 37].

There is evidence that increased glucocorticoid levels can influence cognitive performance [21]. In humans, acute high-dose administration of glucocorticoids induces a reversible impairment of hippocampal-dependent memory functions, whereas working memory and attention functions are unaffected [3, 5, 16, 29]. In our study, because no change in corticosteroid dose was made from baseline, we can exclude any relationship to neurocognitive impairment in our patients treated with fractionated RT. The patients treated with radiosurgery received 20 mg dexamethasone immediately before and 6 hours after radiosurgery. However, these patients were tested 2 hours before radiosurgery and 24 hours later, minimizing a major effect of dexamethasone, which shows a half-life of 3–6 hours. In addition, elderly patients are less sensitive to cognitive effects of short-term increases in cortisol levels than young patients, possibly due to an age-related downregulation of hippocampal glucocorticoid receptors [33].

Some studies in healthy adults show that acute mental stressors or the anticipation of stress can induce memory disturbances [5, 22], while other studies show no measurable effect on memory performance [14]. In the current study, the mean subscores for anxiety and depression and the rate of anxiety or depression scores in the pathological range were higher than those in the average population [13], indicating more psychological distress. However, preexisting anxiety or depression did not significantly interact with decreases in cognitive test performance.

In conclusion, our findings suggest no major impairment of cognitive functioning early after prophylactic cranial irradiation. Cognitive impairment was found only in patients with intracranial tumors and predominantly in verbal memory domains. The decline in working memory was dose-dependent. A stronger cognitive decline was found in patients with intracranial lesions and preexisting peritumoral edema, but also to a lesser extent in brain tumor patients without edema.

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