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CLINICAL INVESTIGATION **Brain**

MEMORY FUNCTION BEFORE AND AFTER WHOLE BRAIN RADIOTHERAPY IN PATIENTS WITH AND WITHOUT BRAIN METASTASES

Grit Welzel, M.Sc.,* Katharina Fleckenstein, M.D.,*† Jörg Schaefer, M.D.,* Brigitte Hermann, M.D.,* Uta Kraus-Tiefenbacher, M.D.,* Sabine K. Mai, M.D.,* and Frederik Wenz, M.D.*

*Department of Radiation Oncology, University Medical Center Mannheim, University of Heidelberg, Mannheim, Germany; and †Department of Radiation Oncology, Duke University Medical Center, Durham, NC

Purpose: To prospectively compare the effect of prophylactic and therapeutic whole brain radiotherapy (WBRT) on memory function in patients with and without brain metastases.

Methods and Materials: Adult patients with and without brain metastases ($n = 44$) were prospectively evaluated with serial cognitive testing, before RT (T0), after starting RT (T1), at the end of RT (T2), and 6–8 weeks (T3) after RT completion. Data were obtained from small-cell lung cancer patients treated with prophylactic cranial irradiation, patients with brain metastases treated with therapeutic cranial irradiation (TCI), and breast cancer patients treated with RT to the breast.

Results: Before therapy, prophylactic cranial irradiation patients performed worse than TCI patients or than controls on most test scores. During and after WBRT, verbal memory function was influenced by pretreatment cognitive status ($p < 0.001$) and to a lesser extent by WBRT. Acute (T1) radiation effects on verbal memory function were only observed in TCI patients ($p = 0.031$). Subacute (T3) radiation effects on verbal memory function were observed in both TCI and prophylactic cranial irradiation patients ($p = 0.006$). These effects were more pronounced in patients with above-average performance at baseline. Visual memory and attention were not influenced by WBRT.

Conclusions: The results of our study have shown that WBRT causes cognitive dysfunction immediately after the beginning of RT in patients with brain metastases only. At 6–8 weeks after the end of WBRT, cognitive dysfunction was seen in patients with and without brain metastases. Because cognitive dysfunction after WBRT is restricted to verbal memory, patients should not avoid WBRT because of a fear of neurocognitive side effects.

Brain metastases, Whole brain radiotherapy, Neurocognition, Memory, Early effects.

INTRODUCTION

Whole brain radiotherapy (WBRT) is the standard treatment for patients with brain metastases, especially with multiple lesions. It results in a median survival of 4–6 months and improves neurologic function in about one-half of the patients (1, 2). Prophylactic WBRT provides a survival benefit in patients with limited and extensive small-cell lung cancer (3, 4).

The acute side effects of WBRT can include alopecia, fatigue, and dermatitis; these are generally temporary. However, potential acute and subacute neurocognitive dysfunction in these patients has been widely discussed and is poorly understood. We have previously reported impaired performance in the verbal memory domain after the first fraction and 6–8 weeks after completion of fractionated stereotactic RT in patients with base of skull meningioma (5). In contrast, patients undergoing hyperfractionated total body irradiation before autologous bone marrow/peripheral blood stem cell transplantation showed no verbal memory impairment (6, 7).

The objective of the present study was to systematically evaluate the timing, intensity, and specificity of neurocognitive changes during and immediately after WBRT completion in patients with and without brain metastases, with special emphasis on verbal memory function. The results were compared with those from control patients undergoing RT to the breast.

Reprint requests to: Grit Welzel, M.Sc., Department of Radiation Oncology, University Medical Center Mannheim, Theodor-Kutzer Ufer 1–3, Mannheim 68167 Germany. Tel: (+49) 621-383-3530; Fax: (+49) 621-383-3493; E-mail: grit.welzel@radonk.ma.uni-heidelberg.de

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METHODS AND MATERIALS

Patients

A total of 44 patients were prospectively enrolled (Table 1 [8–12]), of whom 13 were small-cell lung cancer patients (prophylactic cranial irradiation [PCI] group). The therapeutic cranial irradiation (TCI) group (n = 16) consisted of 11 patients with non–small-cell lung cancer, 3 patients with breast cancer, and 2 patients with gastrointestinal cancer. The control group consisted of 15 patients with breast cancer.

The eligibility criteria included age ≥18 years, no previous cranial RT, a stable or decreasing steroid dose, Karnofsky performance score ≥60, life expectancy ≥3 months, and no significant mass effect on computed tomography or magnetic resonance imaging in patients with brain metastases. Patients were not included if they were <18 years old or had psychiatric illness, drug or alcohol abuse, mental retardation (*i.e.,* premorbid intelligence quotient of <70), or insufficient knowledge of the German language.

All patients gave written consent to participate in the study before enrollment. The ethics Committee for Clinical Research of the Medical Faculty at the University of Heidelberg, Germany approved the study, in accordance with the Declaration of Helsinki.

Study design and procedures

This was a prospective, longitudinal, single-center study. From all eligible patients, psychometric scores (anxiety, depression) and test results for cognitive function were obtained 1 day before RT (T0), at one to three fractions after beginning RT (T1), at RT completion (last day) (T2), and at 6–8 weeks after RT completion (T3).

The WBRT dose schedule was 40 Gy in 20 fractions within 4 weeks for the TCI group and 36 Gy in 18 fractions within 3.5–4 weeks in the PCI group. The control group received RT to the breast for 6 weeks.

Psychometric instruments

Table 1 lists the tests applied, as well as the specific cognitive functions and cognitive domains. To enable comparability and interpretation of the test results, the raw scores for each patient were transformed into intelligence quotient points (average normal population, 100) and percentile scores (average, 50). In addition, as previously published (5, 6), we computed three composite scores, the verbal memory score, visual memory score, and general attention score for each individual. These composite scores were defined as follows. The verbal memory score was the average of all verbal memory subtest scores; the visual memory score was the average of all visual memory subtest scores; and the general attention score was the average of all attention subtest scores. Depression and anxiety were assessed by the Hospital Anxiety and Depression Scale (German version) (13).

Definition of neuropsychological impairment

Twelve test parameters were included in the final analyses. At baseline, a percentile score of ≤8 was defined as a cutoff for cognitive impairment in a specific cognitive function (14). This cutoff corresponds to a z-score of z ≤1.4 standard deviation below the mean of 0. The reliable change index method was used to identify patients who improved, remained stable, or deteriorated across time (15, 16). A change was considered to be reliable if the individual reliable change index exceeded the 90% confidence interval.

Statistical analysis

The Statistical Package for Social Sciences software, version 14.0.1 (SPSS, Chicago, IL), was used for the analyses. The baseline characteristics among the patient groups were compared using analysis of variance and Bonferroni post hoc test for continuous measures, and the chi-square test for categorical variables. The exact significance of the paired differences between two time points was assessed using the Wilcoxon signed rank test. The test of treatment effect was based on the analysis of covariance (ANCOVA) model, with the baseline value as the covariate. All tests of significance were two tailed. A p value <0.05 was considered statistically significant. Because the verbal memory scores had already been reported to be impaired immediately after starting RT and at 6 weeks after RT completion (5), no Bonferroni correction was performed. Effect sizes were calculated using the Statistical Package for Social Sciences, version 14.0.1, partial eta squared (η^2) statistic (the proportion of variance associated with treatment effect, and baseline value, respectively) and Cohen's description of η^2 effect size as $\eta^2 > 0.0099$ (small), $\eta^2 > 0.059$ (medium), and $\eta^2 > 0.13$ (large) (17).

RESULTS

Study population

The demographic and treatment-related characteristics of the patient groups are listed in Tables 2 and 3. The three groups differed in age (F = 8.2, p = 0.001), Karnofsky

Table 1. Neuropsychological test battery

Tests	Subtests	Specific cognitive function	Domain
AVLT (8)		Immediate supraspan	Memory (verbal)
		Learning	
		Retroactive interference	
		Delayed recall	
		Recognition	
MCG (9)		Copy	Visuoconstruction
		Immediate recall	Memory (visual)
		Delayed recall	
TAP (10, 11)	Alertness	Simple reaction time	Attention
		Phasic alertness	
	Divided attention	Divided attention	
	Go/Nogo	Selective attention	
MWT (12)		Vocabulary	Premorbid intelligence level

Abbreviations: AVLT = Auditory Verbal Learning Test; MCG = Medical College of Georgia Complex Figures; TAP = Test for Attentional Performance; MWT = Multiple-choice Test of Vocabulary Knowledge.