The Long-term Effect of Gamma Knife Radiosurgery on Cognitive Functioning in Patients with Brain Metastases

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Abstract

Nowadays, most people with brain metastases live longer due to better treatment options, which makes it important to look at the long-term effects of treatment, and to reduce or prevent late cognitive side effects. Previous studies found improvements in cognitive functioning after radiosurgery, but didn't control for psychological variables. The current study investigated the effect of Gamma Knife Radiosurgery (GKRS) on cognitive functioning in patients with 1-10 brain metastases 12 months after treatment, controlling for psychological variables. Patients who were scheduled for GKRS at the Elisabeth-TweeSteden hospital were recruited. The morning before they underwent GKRS, they completed neuropsychological testing. Eventually, 92 patients (mean age = 62.4, 51.1% male) and 104 healthy controls (mean age = 60.3, 48.1% male) filled in all questionnaires (Hospital Anxiety and Depression Scale and Multidimensional Fatigue Inventory) and completed the neuropsychological test battery. From 30 patients (mean age = 63.2, 53.3% male) follow-up data after 12 months was obtained. ANOVAs showed that the patients had worse cognitive functioning than healthy controls at baseline. Besides, regression analyses showed effects of anxiety and depression on cognitive functioning, whereas fatigue didn't affect cognitive functioning. Repeated measures ANOVAs showed that the patients had no significant change in cognitive functioning 12 months after GKRS compared to baseline. This can be explained by the small sample and the fact that there wasn't controlled for the primary tumor and extracranial tumor progression. Further research is necessary to be able to make conclusions about this long-term effect and to investigate its course.

Keywords: GKRS, cognitive functioning, brain metastases, depression, anxiety

The Long-term Effect of Gamma Knife Radiosurgery on Cognitive Functioning in Patients with Brain Metastases

Brain metastases are secondary tumors that have spread from a primary cancer originating in another system (Bhangoo et al., 2011). The incidence of brain metastases is increasing. At the moment, approximately 20 percent of all patients with cancer will develop brain metastases (Achrol et al., 2019). The increasing percentage is due to the availability of improved imaging techniques that facilitate an earlier diagnosis, and due to effective systemic treatment regimens, which allow cancer to spread to the brain by prolonging life (Nayak et al., 2012). Brain metastases are the most common intracranial tumors and the prognosis of patients with brain metastases is poor (Tosoni et al., 2004). The median survival time varies widely among patients: it can range from a few months to a few years (Sperduto et al., 2020). The most common primary tumors to metastasize to the brain are lung, breast, and colorectal cancers, melanoma or renal cell carcinoma (Achrol et al., 2019; Gavrilovic & Posner, 2005; Nayak et al., 2012). In some cases, brain metastases can originate from an unknown primary tumor (Nayak et al., 2012). Headache is a common presenting symptom, but signs and symptoms depend on the location of the metastases (Tosoni et al., 2004). The fewer the brain metastases, the better the prognosis. Stark et al. (2004) found that a limited number of brain metastases (up to three) is a favorable prognostic factor.

In the treatment of brain metastases, Gamma Knife radiosurgery (GKRS) has had a large impact (Monaco et al., 2012). GKRS is a targeted therapy that minimizes unnecessary injury to healthy tissue (Suh, 2010). It delivers intersecting beams of radiation that converge on the target (Suh, 2010). GKRS can be repeated various times and can treat numerous metastases in a single treatment session (Monaco et al., 2012). Besides, it can treat tumors in locations that are not accessible by surgery (Monaco et al., 2012). If the treatment is effective, patients can have prolonged, good-quality survival (Kondziolka et al., 2005). For patients

with up to ten brain metastases, GKRS has been proven effective as the initial treatment option (Linskey et al., 2009; Schimmel et al., 2018; Suh, 2010). However, more recent studies indicate that volume is more important than the number of brain metastases (Yamamato et al., 2014). Before systemic treatments were used, the usual treatment for brain metastases was surgery and/-or whole-brain radiotherapy (WBRT) (Tabouret et al., 2012). Nowadays, GKRS is the initial treatment option, except in some specific cases, for example, in the treatment of large lesions (Lippitz et al., 2014; Suh, 2010). Contrary to GKRS, WBRT is more invasive and toxic (Monaco et al., 2012). WBRT is also associated with potential neurologic complications, for example headaches, nausea, fatigue, and memory loss. Besides, surgery is more invasive and has a longer recovery time than GKRS (Suh, 2010).

Because of the more spared healthy tissue due to the high level of precision of GKRS, fewer negative cognitive side effects can be expected after treatment (Lippitz et al., 2014; Schimmel et al., 2018). For people who want to preserve their cognitive functioning, GKRS is a preferred strategy (Brown et al., 2016; Schimmel et al., 2018). Cognitive function refers to mental processes that are involved in the acquisition of knowledge, manipulation of information, and reasoning (Kiely, 2014). The domains that are included in cognitive functions are perception, memory, learning, attention, decision-making, and language abilities (Kiely, 2014). Impaired cognitive functioning expresses itself through deficits in these domains, for example, difficulty with remembering things or with paying attention. Patients with brain metastases have impaired cognitive functioning compared with healthy controls (Schimmel et al., 2019). It is important to take into consideration that the underlying pathology of cognitive decline in those patients is multifactorial. Contributory factors are the cancer itself, the occurrence of brain metastases, medications, systemic chemotherapeutic agents, and whole-brain radiotherapies (Dye et al., 2015; Witgert & Meyers, 2011). Cognitive functioning can, in addition, be affected by psychological factors. Severe anxiety and

depressive symptoms are negatively associated with cognitive functioning (Bierman et al., 2005; de Vito et al., 2017). Besides, worrying has a negative impact on many aspects of neurocognitive performance (de Vito et al., 2017). Overall quality of sleep also has an impact on mood and cognition (Silva et al., 2020; Witgert & Meyers, 2011). These factors are important to control for when you are assessing cognitive functioning in patients with brain metastases, because they may experience sleep and mood disturbance and fatigue (Witgert & Meyers, 2011).

Looking at the existing literature about the effect of radiosurgery on cognitive functioning, a review by Schimmel et al. (2018) found evidence for (little) cognitive decline in the early phase after treatment with stereotactic radiosurgery (SRS), which was followed by a trend toward improvement or stability up to 12 months after SRS. The study by Aoyama et al. (2007) found higher scores on cognitive functioning after treatment than at baseline. They concluded that for most brain metastatic patients, control of the brain tumor is the most important factor for stabilizing neurocognitive function. Besides, Minniti et al. (2020) reported a high preservation of cognitive function after SRS. A contradictory finding was reported by Albers et al. (2022) who found a cognitive decline in 38% of the patients treated with GKRS at 3 months post-treatment and a decline in 23% of the patients at 6 months post-treatment. An explanation for this finding can be that this study looked at the individual differences at each time point, whereas Aoyama et al. (2007) and Minniti et al. (2020) studied group averages across different time points. However, Verhaak et al. (2021) found long-term improvements after GKRS in several domains of cognitive functioning on both individual and group levels.

There can be concluded that multiple studies have been done that looked at the effect of GKRS on cognitive functioning in patients with brain metastases. However, some information is missing in the literature. For example, the study of Verhaak et al. (2021) did

investigate the long-term effects of GKRS on cognitive functioning in patients with 1 to 10 brain metastases, but mainly focused on the outcomes 21 months post treatment. Minniti et al. (2020) studied the neurological outcome after stereotactic radiosurgery 12 months after treatment, but they used patients with 10 or more brain metastases for their research. In addition, the review of Schimmel et al. (2018) focused on the cognitive effects of SRS, but didn't control for psychological factors and included studies with participants who had more than 10 brain metastases. Next to this, Albers et al. (2022) only looked at the cognitive decline 3 and 6 months post-treatment. Because there has not yet been any research conducted that looks specifically at the effect of GKRS on cognitive functioning 12 months post-treatment in patients with 1-10 brain metastases, the current study investigates the effects at this time point. This can add knowledge to the existing literature. This study focuses on 12 months post-treatment instead of 21, because disease progression can lead to high rates of loss to follow-up, which will lead to insufficient statistical power and limited generalizability (Schimmel et al., 2018). Nowadays, most people with brain metastases live longer due to better treatment options, so it is important to look at the long-term effects of treatment (Nayak et al., 2012; Verhaak et al., 2021). It is important to have a full understanding of the cognitive side effects of radiotherapy, because cognitive functions are essential for our daily life and are related to therapy compliance (Schimmel et al., 2018). Alongside, psychological functioning can influence the scores on cognitive functioning, so it is important to control for these variables.

Taken together, the research question central to this study is the following: What is the long-term effect of Gamma-Knife radiosurgery on cognitive functioning in patients with 1-10 brain metastases? Firstly, patients with brain metastases are expected to score worse on cognitive functioning tests than healthy controls at baseline (*Hypothesis 1*). This expectancy is based on the study by Schimmel et al. (2019), which concluded that patients with brain

metastases have impaired cognitive functioning in comparison with healthy controls. In addition, there is expected that high levels of fatigue, depression, and anxiety have a negative effect on cognitive outcomes at baseline (*Hypothesis 2*). This expectancy is based on the findings that depression and anxiety have a negative association with cognitive functioning (Bierman et al., 2005; de Vito et al., 2017) and on the finding that overall quality of sleep has an impact on mood and cognition (Silva et al., 2020; Witgert & Meyers, 2011). Lastly, there is expected that patients have on average higher scores at 12 months post-treatment than at baseline on tests that measure cognitive functioning (*Hypothesis 3*). This expectancy is based on the findings of Aoyama et al. (2007) and Minitti et al. (2020), who found improvements in cognitive functioning after treatment with GKRS.

Method:

Participants and procedure:

The data of the current study are part of the prospective longitudinal observational Cognition and Radiation Study A (CAR-study A; ClinicalTrials.gov Identifier:

NCT02953756). This study was approved by the Medical Ethics Committee Brabant (File NL53472.028.15) and all patients signed for informed consent.

Adult patients with 1-10 brain metastases who were scheduled for GKRS at the Elisabeth-TweeSteden Hospital (ETZ; Tilburg, The Netherlands) were recruited. The morning before the patients underwent GKRS, they completed neuropsychological testing, which was administered by a trained test leader. In addition, data on demographic, medical/clinical history, and psychological variables were obtained. Follow-up was done 3, 6, 9, 12, 15, and 21 months after treatment. Every three months, an MRI scan was performed. The most important inclusion criteria were: 1-10 newly diagnosed brain metastases with a maximum of 3.5 cm for the largest lesion, Karnofsky Performance Status >/= 70, WHO performance status

</=2, and anticipated survival greater than 3 months. The most important exclusion criteria included Small Cell Lung Cancer (SCLC), lymphoma, leukemia, leptomeningeal disease, contraindications for MRI or gadolinium contrast, and progressive symptomatic systemic disease without treatment options, prior brain radiation or surgical resection of brain metastases. A full overview of the inclusion and exclusion criteria can be found in Table 1. Eventually, 92 patients with brain metastases participated in this study.

Besides the patient population, a normative group of adult non-cancer controls was recruited. They were selected to be comparable to the general population and our patient group. However, they were not allowed to have a history of cancer or severe cerebrovascular disease in the past year. The healthy controls completed the same tests as the patients, but they did this only once. Hundred four healthy controls participated in this study. For the analyses that make use of the data available at baseline and that include patients as well as healthy controls (*Hypotheses 1 and 2*), a total of 196 participants were included.

For the follow-up analysis (*Hypothesis 3*), only data from patients that participated until at least 12 months were included (N = 34). Four of them didn't complete the measures on cognitive functioning at T12 and were excluded. Finally, 30 patients were included.

Table 1

Inclusion- and Exclusion Criteria for this Study

Inclusion criteria
• Histologically proven malignant cancer, imaging and clinical presentation consistent with brain metastases • Contrast-enhanced volumetric MRI showing 1-10 newly diagnosed BM with a maximum diameter of 3.5 cm for the largest lesion and additional lesions not exceeding 3 cm in diameter • Lesion > 5 mm from brainstem or optic apparatus • Patient age >/= 18 years, • Karnofsky Performance Status >/= 70 • Who performance status </= 2 • Stable extracranial disease • Anticipated survival (independent of the brain metastases) greater than 3 months

- Patient informed consent obtained

Exclusion criteria

- No prior histologic confirmation of malignancy, primary brain tumor, melanoma, small cell lung cancer, lymphoma, leukemia, meningeal disease, progressive, symptomatic systemic disease without further treatment options
- No prior brain radiation
- No prior surgical resection of brain metastases
- No additional history of a significant neurological or psychiatric disorder
- No participation in a concurrent study in which neuropsychological testing and/or health-related QOL assessments are involved
- No contraindications to MRI or gadolinium contrast
- No underlying medical condition precluding adequate follow-up
- Lack of informed consent
- Patients unable to complete test battery and/or study questionnaires due to any of the following reasons: lack of basic proficiency in Dutch, IQ below 85, severe aphasia, or paralysis grade 0-3 according to MRC scale (Medical Research Council).

Instruments

GKRS

Treatment was performed with a Leksell Gamma Knife® Perfexion, Electa Instruments, AB (Gamma Knife Radiosurgery: GKRS). A dose of 18-25 Gy was prescribed with 99-100% coverage of the target, depending on the volume of the brain metastases.

Patient characteristics

Medical records were consulted to extract patient characteristics (Table 2).

Cognitive functioning

Cognitive functioning was measured with a neuropsychological test battery. The test battery was administered by a neuropsychologist and included six neuropsychological tests: Hopkins Verbal Learning Test-Revised, Trail Making Test, Controlled Oral Word Association, Wechsler Adult Intelligence Scale Digit Span, Wechsler Adult Intelligence Scale Digit Symbol, and Grooved Pegboard (for a short overview, see Table 3). Grooved Pegboard measures weren't used in the analyses for the current study. The level of cognitive functioning was established at multiple time points, but for the current study, only baseline and 12 months post-treatment measures were relevant.

The Hopkins Verbal Learning Test-Revised (HVLT-R; Benedict et al. 2013) is a verbal learning and memory test and includes a delayed recall trial, which follows after a 20-25 minute interval. The patient is asked to recall as many items of a 12-item word list as possible. Three different scores can be obtained from this test: a total recall score, the delayed recall score, and the retention score. Shapiro et al. (1999) concluded that the HVLT-R is a valid test of verbal learning and memory.

The Trail Making Test (TMT; Strauss et al., 2006) is a measure of attention, speed, and mental flexibility. The patient has to connect 25 numbers randomly arranged on a page in a proper order (Part A) and 25 numbers and letters in alternating order (Part B). The interference index is a better measure of the more complex divided attention, because it elucidates the added task requirements of part B (Strauss et al., 2006). The test-retest reliability of the TMT was found to be adequate for part A (.79) and high for part B (.89) (Strauss et al., 2006).

The Controlled Oral Word Association Test (COWA; Benton et al., 1983) is a verbal fluency test. It measures spontaneous production of words belonging to a certain category or beginning with a certain letter. The participant has to name words beginning with a letter for one minute, and has to repeat this for three different letters. By calculating the total number of acceptable words produced for all three letters, the performance of the participant is established. According to Ross et al. (2007), the interrater reliability of the cluster scoring system of the COWA appears to be excellent, but there seems to be very limited support for test-retest reliability.

The Wechsler Adult Intelligence Scale - III (WAIS; The Psychological Corporation, 1997) is a test battery that measures general intelligence. It consists of 14 subtests, and the Digit Span and Digit Symbol tasks are two of them. The Digit Span measures the attention and working memory of the patient. In the first trial, the patient has to repeat the numbers in

the same order as the administrator, whereas, in the second trial, the patient has to repeat the numbers in reversed order. The Digit Symbol measures processing speed. The patient has to copy the symbols that are paired with numbers within a 120 seconds limit. The WAIS was found to have substantial correlation with the WAIS-R (.80 and above; The Psychological Corporation, 1997).

Anxiety and depression

Symptoms of anxiety and depression were measured with the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983). The HADS is a self-assessment scale for detecting states of depression and anxiety in a hospital medical outpatient clinic setting. It consists of two subscales, one for anxiety and one for depression, that consist of seven questions. Each question is rated from 0 to 3. These subscales are also valid measures of the severity of the emotional disorder (Zigmond & Snaith, 1983). The higher the score on the HADS, the more symptoms the patient experiences. A score >/= 8 on each subscale is an indication of mild anxiety or depression. Regarding the reliability of this test, Bjelland et al. (2002) report a good intern consistency of the HADS with a mean Cronbach's alpha of .83 for the HADS-A and a mean Cronbach's alpha of .83 for the HADS-D. Symptoms of anxiety and depression were measured at multiple time points, but for the current study, only baseline and 12 months post-treatment measures were relevant.

Fatigue

Symptoms of fatigue were measured with the Multidimensional Fatigue Inventory (MFI; Smets et al., 1995). The MFI is a self-report measure that uses 20 items to evaluate five dimensions of fatigue: general fatigue, physical fatigue, reduced motivation, reduced activity, and mental fatigue. Each item is rated from 0 to 5, indicating to what extent the statement applied to him/her based on the preceding week. A higher score indicates more fatigue. The MFI was found to have good validity and good internal consistency, with an average

Cronbach's alpha of .84 (Smets et al., 1995). Symptoms of fatigue were measured at multiple time points, but for the current study, only baseline and 12 months post-treatment measures were relevant.

Table 2

Participant Characteristics

	Patients included at baseline	Controls included at baseline	Patients with complete follow-up (T12)
Participants included	92	104	30
Sex, male	47 (51.1%)	50 (48.1%)	16 (53.3%)
Age in years, mean (range)	62.4 (31 – 80)	60.3 (37 – 87)	63.2 (40 – 76)
Educational level			
Low	28 (30.4%)	25 (24.0%)	7 (23.3%)
Middle	37 (40.2%)	33 (31.7%)	15 (50.0%)
High	27 (29.3%)	46 (44.2%)	8 (26.7%)
KPS		NA	
70-80	33 (35.9%)		7 (23.3%)
90-100	59 (64.2%)		23 (76.7%)
RPA class		NA	
1	16 (17.4%)		4 (13.3%)
2	76 (82.6%)		26 (86.7%)
GPA		NA	
Class 2	15 (16.3%)		7 (23.3%)
Class 3	60 (65.2%)		18 (60.0%)
Class 4	17 (18.5%)		5 (16.7%)
Number of brain metastases		NA	
1	32 (34.8%)		14 (46.7%)
2-4	29 (31.5%)		6 (20.0%)
5-10	31 (33.7%)		10 (33.3%)
Total cumulative volume of brain metastases, median	8.2cm3	NA	3.6cm3
Primary tumor		NA	
Lung	55 (59.8%)		16 (53.3%)
Renal	15 (16.3%)		4 (13.3%)
Melanoma	12 (13.0%)		5 (16.7%)
Breast	6 (6.5%)		4 (13.3%)
Other	4 (4.4%)		5 (16.6%)
Systemic therapy		NA	
No	29 (31.5%)		11 (36.7%)
Yes	63 (68.5%)		19 (63.3%)

Noot. GPA, Graded Prognostic Assessment; KPS, Karnofsky Performance Status; NA, Not Applicable

Table 3

The Neuropsychological Tests that were used and the Cognitive Domains they assess

Neuropsychological test	Cognitive domain	Parallel versions
Hopkins Verbal Learning Test-Revised	Immediate and delayed verbal memory and recognition	Six
Trail Making Test	A: Psychomotor speed B: Cognitive flexibility	-
Controlled Oral Word Association	Word fluency	Two
WAIS Digit Span	Attention span and working memory	-
WAIS Digit Symbol	Information processing speed	-
Grooved Pegboard	Dominant and non-dominant hand dexterity	-

Noot. WAIS= Wechsler Adult Intelligence Scale

Statistical analyses

At first, the demographical variables were studied, and via an independent samples t-test and Chi-square tests was investigated whether there were significant differences in the age, education level, and sex of the patients and healthy controls. These variables were controlled for in further analyses. Besides, an independent samples t-test and Chi-square tests were used to investigate whether the patients who were not able to perform the follow-up at T12 and the patients who did perform the follow-up differed significantly in their age, education level, sex, and volume of brain metastases. Cognitive functioning consisted of five different variables: HVLT Delayed Recall T-score, TMT Interference Index T-score, COWA T-score, Digit Span Total Scaled Score, and Digit Symbol Total Scaled Score. Because there were no T-scores available for the Digit Span and Digit Symbol tests at T12, scaled scores were used.

For investigating hypothesis 1, five ANOVAs were performed to see if there was a significant difference in scores on cognitive functioning between patients with brain metastases and healthy controls. In these analyses, cognitive functioning was the dependent variable, and group (patient or control), sex, and education level were the fixed factors. Age was included as a covariate. A corrected alpha was used to reduce the false discovery rate due to multiple testing (Benjamini & Hochberg, 1995). These ANOVAs were tested for the baseline measures, because there was no data available from the healthy controls beyond baseline. Before performing the analyses, there was investigated whether the assumptions for performing an ANOVA weren't violated: independence of the observations, normal distribution of the dependent variable, and sphericity.

For investigating hypothesis 2, multiple regression analyses were performed to see if there was a significant effect of anxiety, depression, and fatigue on the different variables of cognitive functioning. Group (patient or control) was included as a control variable. A corrected alpha was used to reduce the false discovery rate due to multiple testing (Benjamini & Hochberg, 1995). These analyses were performed for the data at baseline. The scores on the domain of general fatigue were used to represent fatigue, the total score on the HADS anxiety scale to represent anxiety, and the total score on the HADS depression scale to represent depression. Before performing the analyses, there was investigated whether the assumptions for performing a multiple regression analysis weren't violated: there is a linear relationship between the outcome variable and the independent variables; residuals are normally distributed; no multicollinearity; homoscedasticity.

For investigating hypothesis 3, five repeated measures analyses were performed to see if there was a significant difference in scores on cognitive functioning between baseline and 12 months post-treatment. Sex and education level were included as between-subjects factors, time as a within-subjects factor, and age, difference score in volume of brain metastases,

anxiety, depression, and fatigue were included as covariates (the control variables are further explained under the text header 'Control variables'). The outcomes of the different tests that measure cognitive functioning were the dependent variables. A corrected alpha was used to reduce the false discovery rate due to multiple testing (Benjamini & Hochberg, 1995). These analyses were only performed on the patient population who completed all tests, both at baseline and 12 months post-treatment. Before performing the analyses, there was investigated whether the assumptions for performing a repeated measures ANOVA weren't violated: these are the same as the assumptions for the ANOVA (hypothesis 1).

All analyses were conducted using the program IBM SPSS Statistics (version 26) and a p-value of $p = 0.05$.

As the to-be-expected sample size was unknown, the desired sample size was computed for a medium ($\eta_p^2 = .06$) and a small effect size ($\eta_p^2 = .01$) using GPower3.1. For hypothesis 1: For a power of 0.80, the desired sample size was 125 participants for a medium effect size, and 779 participants for a small effect size. For hypothesis 2: For a power of 0.80, the desired sample size was 77 participants for a medium effect size, and 550 participants for a small effect size. For hypothesis 3: For a power of 0.80, the desired sample size was 34 participants for a medium effect size, and 198 participants for a small effect size.

Control variables

Based on earlier research about the long-term effect of GKRS on cognitive functioning in patients with brain metastases (Minitti et al., 2020; Verhaak et al. 2021), several control variables were included in the analyses.

Sex. Sex of the patient was obtained via medical records and was included as a categorical variable (coded as: 0 = 'male', 1 = 'female).

Age. Age of the patient was obtained via medical records and was included as a continuous variable.

Education level. Education level of the patient was obtained via medical records and was included as a categorical variable (coded as: 1 = ‘low educational level’, 2 = ‘middle educational level’, 3 = ‘high educational level’).

Difference score in volume of brain metastases. Volume of brain metastases was obtained via MRI scans and was included as a continuous variable. The volume of brain metastases at T0 was subtracted from the volume of brain metastases at T12. There was controlled for this variable, because neurocognitive test scores and global neurocognitive impairment have been found to be correlated with brain tumor volume (Habets et al., 2016; Meyers et al., 2004).

Results

At first, the mean scores and standard deviations of the participants on all tests and questionnaires were calculated (see Table 4). Because some participants had missing test scores on particular cognitive function measures, some analyses included fewer participants than others.

Table 4

Mean Scores on the Neuropsychological Measurements and Questionnaires

	Controls scores at baseline: Mean(SD)	Patient scores at baseline: Mean(SD)	Patient scores at T12: Mean(SD)
HVLT Delayed Recall T-score	45.0(11.7), *N* = 104	41.8(12.4), *N* = 92	41.5(14.2) *N* = 30
TMT Interference Index T-score	53.8(9.2), *N* = 103	44.6(12.5), *N* = 81	49.5(12.1), *N* = 27
COWA T-score	53.1(11.1), *N* = 104	46.1(12.7), *N* = 92	48.5(11.8), *N* = 22
Digit Span Total Scaled Score	10.7(2.9), *N* = 104	8.8(2.8), *N* = 91	10.4(3.2), *N* = 30
Digit Symbol Total Scaled Score	10.9(3.2), *N* = 104	7.5(3.6), *N* = 84	9.0(3.9), *N* = 26
HADS Anxiety Scale	4.4(2.8), *N* = 104	7.3(4.4), *N* = 92	5.1(3.7), *N* = 30

HADS Depression Scale	3.5(2.9), *N* = 104	5.7(4.1), *N* = 92	4.6(3.4), *N* = 30
MVI General Fatigue Z-Score	-0.2(1.2), *N* = 104	0.6(1.2), *N* = 92	0.9(1.3), *N* = 30

*Noot***.** HVLT, Hopkins Verbal Learning Test; TMT, Trail Making Test; COWA, Colour Word Association; HADS, Hospital Anxiety and Depression Scale; MVI, Multidimensional Fatigue Inventory

The independent samples t-test and Chi-square tests showed no significant differences in age ($t(193) = 1.521$, $p = .130$), education level ($\chi^2(2, N = 196) = 4.626$, $p = .099$), and sex (χ^2 $(1, N = 196) = 0.177$, $p = .674$) between the control group and the patients. However, there was still controlled for these variables in further analyses. The control group and patients had a significant difference in their scores for HADS anxiety ($t(196) = 5.359$, $p < .001$), HADS depression ($t(196) = 4.367$, $p<.001$), and MVI fatigue ($t(196) = 4.306$, $p<.001$).

The independent samples t-test and Chi-square tests showed no significant differences in age ($t(89) = .297$, $p = .558$), education level ($\chi^2(2, N = 92) = 1.906$, $p = .386$), sex ($\chi^2(1, N = 92) = .090$, $p = .764$), and volume of brain metastases ($\chi^2(2, N = 92) = 2.149$, $p = .342$) between the patients who were not able to perform follow-up at T12 and the patients who did perform follow-up.

To investigate hypothesis 1, five ANOVAs were performed to see whether there was a significant difference between the control group and the patients on cognitive functioning measures (see Table 5 for all p-values). Before testing the hypotheses, there was investigated whether the assumptions for performing an ANOVA were not violated: the dependent variables were at the ratio level; the patient and control group were independent from each other; there was homogeneity of variances in every group (all Levene's F-tests were above $p = .116$); the data were normally distributed for each dependent variable (checked by making histograms). On the HVLT, the patients and control group showed no significant differences

in their scores ($F(1,195) = 1.119$, $p = .275$) controlled for age, sex, and education level. The patients scored significantly lower than the control group on the TMT ($F(1,184) = 30.973$, $p < .001$), the COWA ($F(1,195) = 11.054$, $p = .001$), the Digit Span ($F(1,195) = 20.541$, $p < .001$) and on the Digit Symbol ($F(1,188) = 47.508$, $p < .001$), controlled for age, sex and education level. The given p-values are the values after correcting for multiple testing (Benjamini & Hochberg, 1995). Only a significant interaction effect between group and education level on the Digit Symbol was found ($F(2,188) = 8.306$, $p < .001$). Tukey post hoc tests, however, showed no significant differences in the education level between the groups on the Digit Symbol ($p = .440$). Main effects were found for education level on the HVLT ($F(2,188) = 16.273$, $p < .001$), on the TMT ($F(2,184) = 4.715$, $p = .010$), and on the COWA ($F(2,195) = 4.508$, $p = .012$). A main effect of sex was found on the HVLT ($F(1,195) = 7.187$, $p = .008$); and main effects of age were found on the Digit Span ($F(1,195) = 5.990$, $p = .015$) and on the Digit Symbol ($F(1,188) = 11.404$, $p = .001$).

Table 5

All P-values from the Five Different ANOVAS

Dependent variable	P-value
HVLT Delayed Recall T-score	
Age	.485
Group	.275
Sex	.008*
Education level	<.001*
Group * Sex	.322
Group * Education level	.625
Group * Sex * Education level	.188
TMT Interference Index Score	
Age	.916
Group	<.001*
Sex	.223
Education level	.010*
Group * Sex	.953
Group * Education level	.713
Sex * Education level	.078

Group * Sex * Education level	.557
COWA T-score	
Age	.814
Group	.001*
Sex	.141
Education level	.012*
Group * Sex	.660
Group * Education level	.797
Sex * Education level	.671
Group * Sex * Education level	.407
Digit Span Total Scaled Score	
Age	.015*
Group	<.001*
Sex	.511
Education Level	.443
Group * Sex	.623
Group * Education level	.102
Sex * Education level	.755
Group * Sex * Education level	.398
Digit Symbol Total Scaled Score	
Age	.001*
Group	<.001*
Sex	.237
Education level	.456
Group * Sex	.413
Group * Education level	<.001*
Sex * Education level	.339
Group * Sex * Education level	.697

*Noot***.** * indicates a statistically significant difference; HVLT, Hopkins Verbal Learning Test; TMT, Trail Making Test; COWA, Colour Word Association; HADS, Hospital Anxiety and Depression Scale; MVI, Multidimensional Fatigue Inventory

To investigate hypothesis 2, five multiple regression analyses were performed to see whether high levels of fatigue, depression, and anxiety have a negative effect on cognitive outcomes at baseline. Group was included as a control variable. Before testing hypothesis 2, there was investigated whether the assumptions for performing a multiple regression analysis were not violated: there was no multicollinearity or singularity (VIF = 1.789); outliers didn't have an influence on the results for the models (Cook's Distance </= 0.142); and the variables fulfilled the criteria of normality, linearity, homoscedasticity and independence of residuals (these were checked via Normal p-p plots and scatterplots). The model was not significant for

the HVLT (R^2 = .046, F(4,195) = 2.294, p = .061). The multiple regressions with TMT (R^2 = .170, F(4,183) = 9.151, p < .001), COWA (R^2 = .125, F(4,195) = 6.841, p < .001), the Digit Span (R^2 = .112, F(4,194) = 5.985, p < .001) and the Digit Symbol (R^2 = .204, F(4,187) = 11.700, p < .001) as dependent variables and depression, anxiety, fatigue, and group as independent variables were significant. The given p-values are the values after correcting for multiple testing (Benjamini & Hochberg, 1995). Depression had a significant negative impact on the HVLT (β = -.195; t(195) = -2.115, p = .036) and on the COWA (β = -.228; t(195) = -2.591, p = .010) when controlling for anxiety, fatigue, and group. Anxiety had a significant positive impact on the HVLT (β = .186; t(195) = 1.971, p = .050) when controlling for depression, fatigue, and group. Group had a significant impact on the TMT (β = .364; t(183) = 4.886, p < .001), the COWA (β = .257; t(195) = 3.468, p < .001), the DigitSpan (β = .320; t(194) = 4.272, p <.001), and on the DigitSymbol (β = .448; t(187) = 6.212, p <.001) when controlling for depression, anxiety, and fatigue. See Table 6 for all p-values.

Table 6

Coëfficients of the Multiple Regression Analyses: Estimates, Standard Errors, Confidence Intervals and P-Values

Dependent variable	Estimate (B)	SE	95% CI	*P*-value
HVLT Delayed Recall T-score				
HADS Anxiety Scale	0.580	.294	[0.000 ; 1.160]	.050*
HADS Depression Scale	-0.642	.303	[-1.240 ; -0.043]	.036*
MVI Algemene Vermoeidheid Z-score	-0.132	.773	[-1.657 ; 1.393]	.865
Group	1.119	.622	[-0.109 ; 2.346]	.074
TMT Interferention Index Score				
HADS Anxiety Scale	0.121	.273	[-0.418 ; 0.661]	.658
HADS Depression Scale	-0.481	.282	[-1.038 ; 0.076]	.090
MVI Algemene Vermoeidheid Z-score	0.077	.719	[-1.341 ; 1.496]	.914
Group	2.872	.579	[1.685 ; 3.969]	<.001*
COWA T-score				
HADS Anxiety Scale	0.013	.607	[-0.553 ; 0.579]	.965
HADS Depression Scale	-0.767	0.296	[-1.351 ; -0.183]	.010*
MVI Algemene Vermoeidheid Z-score	1.344	.754	[-0.144 ; 2.831]	.076

Group	2.105	.607	[0.908 ; 3.302]	.001*
DigitSpan Scaled Score				
HADS Anxiety Scale	-0.083	.071	[-0.223 ; 0.058]	.248
HADS Depression Scale	0.058	.073	[-0.087 ; 0.203]	.433
MVI Algemene Vermoeidheid Z-score	0.116	.187	[-0.253 ; 0.486]	.534
Group	0.643	.151	[0.346 ; 0.941]	<.001*
DigitSymbol Scaled Score				
HADS Anxiety Scale	-0.060	.086	[-0.230 ; 0.109]	.483
HADS Depression Scale	0.013	.089	[-0.162 ; 0.188]	.886
MVI Algemene Vermoeidheid Z-score	0.225	.226	[-0.221 ; 0.670]	.322
Group	1.130	.182	[0.771 ; 1.489]	<.001*

*Noot***.** * indicates a statistically significant difference; SE, Standard Error; CI, Confidence Interval; HVLT, Hopkins Verbal Learning Test; TMT, Trail Making Test; COWA, Colour Word Association; HADS, Hospital Anxiety and Depression Scale; MVI, Multidimensional Fatigue Inventory

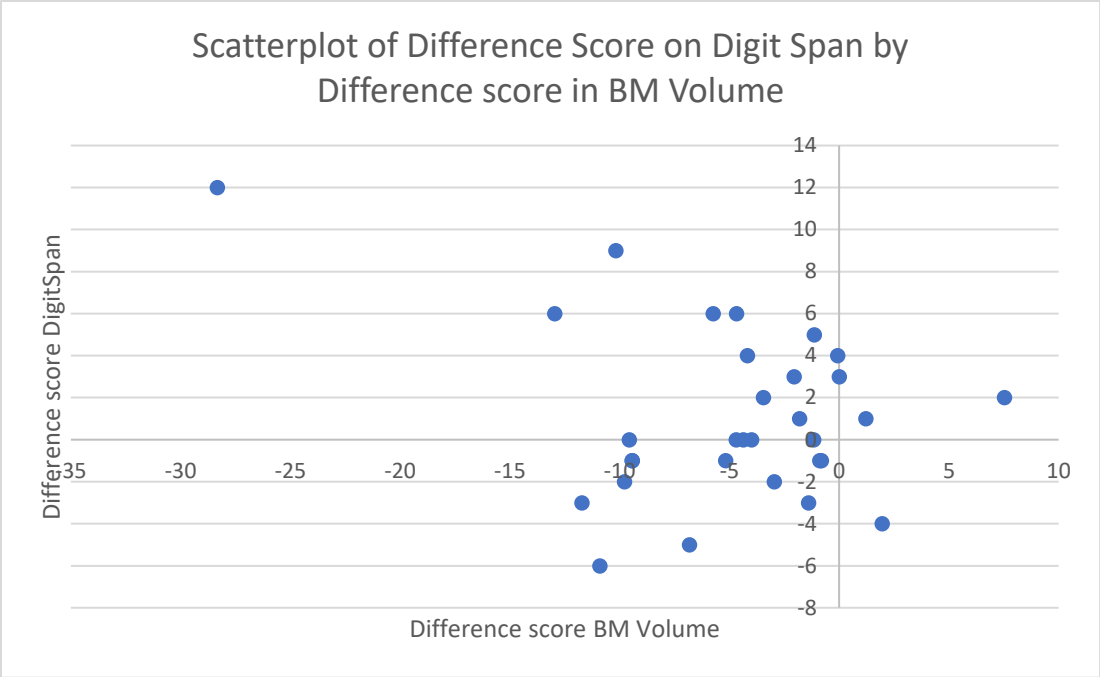
Because anxiety and depression had some significant effects on the cognitive function variables, there was decided that difference scores between T0 and T12 of these variables were included as covariates in the repeated measures analysis. Because fatigue didn't show any significant effects on the cognitive function variables, there was decided to not include this as a covariate.

To investigate hypothesis 3, five repeated measures ANOVAs were performed to see if there is a significant difference in the cognitive functioning scores of the patients between T0 and T12. Before testing hypothesis 3, there was investigated whether the assumptions for performing a repeated measures ANOVA weren't violated: the dependent variables were continuous; the same participants were measured twice; the dependent variables were normally distributed (checked by making histograms); sphericity (Box's Test of Equality of Covariance Matrices were all above $p = .301$). When comparing the scores of the patients at T0 and T12 for hypothesis 3, there were no significant effects. The patients didn't show a significant difference between T0 and T12 on the HVLT ($F(1,20) = 4.193$, $p = .208$), the TMT

($F(1,16) = 1.282$, $p = .343$), the COWA ($F(1,12) = .001$, $p = .978$), the DigitSpan ($F(1,20) = 1.597$, $p = .343$) and on the DigitSymbol ($F(1,13) = 3.527$, $p = .208$). The given p-values are the values after correcting for multiple testing (Benjamini & Hochberg, 1995). There was a significant effect of sex on the HVLT ($F(1,20) = 4.574$, $p = .045$) and a significant effect of age on the DigitSymbol ($F(1,13) = 7.895$, $p = .015$). All other main effects of the covariates and interactions with them were above $p = .056$. On the DigitSpan, there was a significant interaction effect between time and the difference score in volume of brain metastases ($F(1,20) = 5.295$, $p = .032$). To further investigate this interaction, an ANOVA with the difference score in digit span as dependent variable and the difference score in volume of brain metastases as a covariate was performed, and showed that there was a significant effect of the difference score in brain volume on the difference score of the digit span, controlled for depression, anxiety, age, and sex ($F(1,30) = 5.295$, $p = .032$). The plot showed that a reduction in brain volume is associated with better performance on the digit span on T0 compared to T12 (see Figure 1).

Figure 1

The Interaction between Time and the Difference Score in Volume of Brain Metastases on the Digit Span



Discussion

Because most people with brain metastases live longer nowadays due to better treatment options, it is important to look at the long-term effects of treatment (Nayak et al., 2012; Verhaak et al., 2021). Multiple studies found an improvement in cognitive functioning after radiosurgery, but none of them focused specifically on the effect of 12 months post-treatment, while also controlling for psychological variables. This study investigated the effect of Gamma Knife Radiosurgery (GRKS) on cognitive functioning in patients with 1-10 brain metastases 12 months after treatment. The patients were part of the Cognition and Radiation Study A and were scheduled for GKRS at the Elisabeth-TweeSteden Hospital. The current study found that patients with brain metastases scored worse on cognitive functioning measures than healthy controls at baseline, controlling for age, sex, and education level. Besides, effects of anxiety and depression on cognitive outcomes at baseline were found, controlling for fatigue and group (patient or healthy control). At last, the patients didn't show

an improvement in their cognitive functioning between baseline and 12 months after GKRS, controlling for age, sex, education level, anxiety, depression, and volume of brain metastases.

Regarding hypothesis 1, this study found that patients had on average worse cognitive functioning than healthy controls at baseline. This was the case for five out of six cognitive functioning variables, except for the HVLT (verbal memory). This is in line with the current literature, where multiple studies found lower neurocognitive function scores in patients with brain metastases than in healthy controls (Gerstenecker et al., 2014; Habets et al., 2016; Schimmel et al., 2019) and can be explained by multiple factors: the cancer itself or brain metastases lead to cognitive decline, and/or the effect of medication or side-effects of treatment lead to cognitive decline (Witgert & Meyers, 2011). However, other studies did find impairments in the verbal memory of the patients in relation to healthy controls (Gerstenecker et al., 2014; Schimmel et al., 2019). A possible explanation for this difference is that the current study only looked at delayed verbal memory, whereas earlier studies also included immediate memory and recognition. Further research is necessary to investigate memory functioning in patients with brain metastases.

When looking at hypothesis 2, fatigue, depression, anxiety, and group together caused worse cognitive functioning for all variables, except for the HVLT. This is attributable to the fact that ‘group’ had a significant effect on all variables, except for the HVLT (as mentioned above). However, when looking at the effects of the regression analyses separately, higher scores on depression led to worse cognitive functioning for two variables (HVLT and COWA), and higher scores on anxiety led to better cognitive functioning for one variable (HVLT). This corresponds with the study of Bierman et al. (2005), which found a negative association between depression and cognitive performance, and a curvilinear relationship between anxiety and cognitive performance. According to the DSM-V (American Psychiatric Association, 2013), symptoms of depression are the reduced ability to think, the loss of

concentration, and indecisiveness. These symptoms have a negative effect on the cognitive performance of the patient. In the current study, memory and verbal fluency seem to be the only cognitive functions that are negatively influenced by depression. This is supported by the study of Kizilbash et al. (2002) who found that depressive symptoms (without anxiety) have an adverse effect on immediate recall and the amount of acquisition. Besides, the study of Fossati et al. (2003) found that patients with depression performed worse than controls on a semantic fluency task. The patients scored higher than the control group on measures of depression, anxiety, and fatigue, but this didn't impact all cognitive function measures. According to Gerstenecker et al. (2014), depression may not be a primary contributor to cognitive dysfunction in patients with brain metastases. However, in the current study, the analyses were also performed for the healthy control group, and not only for patients with brain metastases. A lack of significant effects on the other cognitive domains (processing speed, attention, and working memory) can be attributed to the fact that the current study looked at depressive symptoms instead of a depression diagnosis. Therefore, depression scores will probably be lower in the current study, which will cause fewer cognitive impairments. Besides, hippocampal volume is reduced in patients with depression (Videbech & Ravnkilde, 2004), which can explain why depression had an influence on memory and not on cognitive flexibility, attention, and processing speed. Further research has to be done to investigate the effects of anxiety and depression on the different cognitive functioning domains. Higher fatigue didn't lead to worse cognitive functioning in the current study. This can be explained by the fact that the current study only looked at the general fatigue level of the patients, whereas the study of Silva et al. (2020) focused on the quality of sleep. Further research has to be done to examine the effect of fatigue on cognitive functioning in patients with brain metastases.

In contrast to the findings of Aoyama et al. (2007), Minniti et al. (2020), and Schimmel et al. (2018), the patients didn't show an improvement in their cognitive functioning between baseline and 12 months after GKRS. This can be explained by the small sample of the current research, which made it hard to find significant effects, even if they were present. The sample lacked participants for obtaining a power of 0.80. Besides, Aoyama et al. (2007), used a different cognitive functioning measure, namely the Mini Mental State Examination (MMSE). The MMSE is worldwide used as a screening test to assess the severity of cognitive impairment (Strauss et al., 2006; Tombaugh & McIntyre, 1992) and for follow-up of cognitive changes in patients suffering from dementia (Lancu & Olmer, 2006). Therefore, it is especially used for people with cognitive impairments, whereas the tests used in the current study can also be used for people without cognitive impairments. This can cause ceiling effects on the MMSE, and low sensitivity (Meyers & Wefel, 2003), which makes it easier to receive a higher cognitive function score. Their sample also consisted of more men than women and their study mainly focused on improvement of scores on the MMSE, instead of comparing the group averages. The study of Minniti et al. (2020) only looked at the changes in HVLT-scores, whereas the current study included several different tests to measure cognitive functioning. Their sample also consisted of patients with 10 or more brain metastases, whereas in the current study, the patients had 1-10 brain metastases. Besides, they didn't control for anxiety and depression scores, which could have contributed to the improvements that have been found.

The current study also found that a reduced volume of brain metastases led to better performance on the Digit Span. This finding corresponds to the studies of Habets et al. (2016) and Meyers et al. (2004), who found that neurocognitive test scores and global neurocognitive impairment are correlated with brain tumor volume. The other cognitive domains, except for attention/ working memory, weren't found to be affected by brain tumor volume in the current

study. Further research has to be conducted to investigate whether attention is more vulnerable to changes in brain metastases volume than other cognitive domains. The location of the brain metastases has to be further looked into, because symptoms depend on the location of the metastases (Tosoni et al., 2004). A possible explanation is that the brain metastases that had a reduction in their volume were mostly located in regions of the brain that are involved in attention, and weren't affecting other regions that are involved in other cognitive domains.

By controlling for multiple variables in the analysis, the current study contributes to the understanding of the possible impact that various factors can have on cognitive functioning, in this case, education level, age, anxiety, depression, and volume of brain metastases. Clinicians can implement this knowledge by offering the patients treatments that target the depressive symptoms, for example, Cognitive Behavioral Therapy (CBT; Beck, 2011) or Acceptance and Commitment Therapy (ACT; Hayes et al., 2006). Besides, appropriate management of psychiatric issues will allow the patient and family to more easily concentrate on treatment (Newton, 2007). Furthermore, this study confirmed that patients with brain metastases have worse cognitive functioning than healthy controls. This finding can be used by clinicians, who can set up cognitive training programs for patients with brain metastases. In comparison to the existing current research on the effect of GKRS on cognitive functioning, this study is scientifically relevant due to its use of multiple control variables and its longitudinal design, which makes use of both patients and healthy controls. This provides a broader perspective on the impact of brain metastases and GKRS and the implications for the patient's cognitive functioning.

Next to its longitudinal design, a strength of this study is that the healthy controls were matched with the patient sample so that their sex and age didn't differ significantly. Besides, the number of women and men in the sample was almost equal, which makes it possible to

generalize the findings to both sexes. Because cognitive functioning consists of multiple domains (Harvey, 2019), a strength of this study is that 'cognitive functioning' consisted of multiple different variables that measure these domains. The tests that were used to measure cognitive functioning are very well-known tests with good reliability and validity (Strauss et al., 2006). Furthermore, the questionnaires for measuring anxiety, depression, and fatigue also had good validity and internal consistency (Bjelland et al., 2002; Smets et al., 1995). Practice effects were minimalized by adding parallel versions of the HVLT and the COWA. Another strength is that this study controlled for multiple confounding factors that could have affected the cognitive functioning of the patient, for example, the volume of brain metastases, their psychological functioning, and their education level. This contributes to a reliable understanding of the long-term effect of GKRS on cognitive functioning.

Nevertheless, the limitations of the current study are important to take into account. An important limitation is the small sample at T12, which didn't meet the requirements for finding a small or medium effect using a power of 0.80. This made it hard to find a long-term effect in the current sample. Another limitation is that the different cognitive function variables didn't make use of the same test values; for example, some variables were t-scores and others were scaled scores. It would have been better if the test values were consistent across the entire study. Besides, this study made use of a non-probability sample; people could indicate themselves whether they were interested in participating. This can reflect different personality characteristics than non-participating patients, making it more difficult to generalize to the entire patient population. Another limitation is that the primary tumor varied between the patients. Different primary tumors can have different prognoses (Stelzer, 2013), which could have affected test performance. Lastly, extracranial tumor progression wasn't included as a covariate, whereas it can also lead to worse conditions. This could have contributed to the lack of improvements in cognitive functioning.

Because this study didn't find an improvement in cognitive functioning in the long term after GKRS, whereas other studies did find improvements, further research is needed to investigate the long-term effect of GKRS on cognitive functioning in patients with brain metastases. Future studies should consider the strengths and limitations that are discussed in the current study: A larger sample is needed, and multiple control variables need to be taken into account, for example, psychological functioning and extracranial tumor progression. It would be interesting to compare the cognitive function scores every three months, to see what the course is of cognitive functioning in the long term. This could give an indication for different interventions that could be applied in different stages of the treatment phase. When an improvement in cognitive functioning will be found in future studies, it would be interesting to compare the scores with healthy controls. By comparing, conclusions can be drawn as to whether cognitive functioning level will improve, so that the level is the same as the healthy controls, or whether their cognitive functioning is still worse. This could provide a direction to the extent of how much cognitive training will be necessary.

Since GKRS is increasingly used nowadays and people with brain metastases live longer due to better treatment options, it is important to look at the long-term effect of treatment (Nayak et al., 2012; Verhaak et al., 2021). Cognitive functions are essential for performing daily life activities, which makes it important to preserve them (Schimmel et al., 2018). The current study found no effects of GKRS on cognitive functioning 12 months after treatment. A larger sample at T12 and more control variables are needed in further research to investigate this long-term effect. This study found some evidence for negative effects of depression and a positive effect of anxiety on cognitive functioning, further research has to be done to make conclusions about these effects. The current study confirmed that patients with brain metastases have worse cognitive functioning than healthy controls. Cognitive training

programs and psychological interventions can be used by clinicians to improve the cognitive functioning of patients with brain metastases.

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