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THE IMPACT OF RADIATION ON COGNITIVE FUNCTIONING IN PATIENTS WITH BRAIN METASTASES

A paradigm shift from whole brain radiation therapy to stereotactic radiosurgery

Proefschrift ter verkrijging van de graad van doctor aan Tilburg University

op gezag van de rector magnificus, prof. dr. W.B.H.J. van de Donk, in het openbaar te verdedigen ten overstaan van een door het college voor promoties aangewezen commissie in de Aula van de Universiteit op

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Wilhelmina Cornelia Maria Valk-Schimmel,

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Para ser grande, sê inteiro: nada

Para ser grande, sê inteiro: nada

Teu exagera ou exclui.

Sê todo em cada coisa. Põe quanto és

No mínimo qua fazes.

Assim em cada lago a lua toda

Brilha, porque alta vive.

14.2.1933

Odes de Ricardo Reis. **Fernando Pessoa**. Lisboa: Ática, 1946 (imp.1994), p. 148.

1ª publ. in **Presença** , nº 37. Coimbra: Fev. 1933.

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1

General introduction and outline of the dissertation

Cancer and brain metastases: epidemiology and burden

The global cancer burden continues to grow. Over 19 million new cancer cases and nearly ten million cancer deaths were reported in 2020. [1–3] The most common causes of cancer death were cancers of the lung, colon and rectum, and liver. [1] With a projected 40% increase in new cancer cases in 2040, the impact of cancer is expected to increase even further. [4] In the Netherlands, over a hundred thousand people were diagnosed with cancer and over forty-five thousand patients died of cancer in 2020 which makes cancer the most common cause of death in our country. By far the most frequent cause of cancer death, with 10 080 deaths, was lung cancer. [5]

Lung cancer is also one of the primary cancers with the highest propensity to spread to the brain, along with breast, colon and kidney, and melanoma cancer. [3] Together, these (primary) cancers account for more than two-thirds of all metastatic brain tumor cases. [6] Metastatic brain tumors or *brain metastases* are the most common type of brain tumors in adults. [7] Brain metastases are a frequent complication of systemic cancer and a significant cause of cancer mortality. [2,8,9] Depending on the type of the primary cancer, an estimated 10 to 30 percent of cancer patients develop brain metastases at some point during their disease. [10–12]

Brain metastases form when cancer cells spread from their original site (the primary tumor) and reach the brain via the bloodstream or via the lymph system. Cancer cells subsequently attach to endothelial cells and extravasate into the brain tissue where they survive and proliferate (e.g., by the induction of early angiogenesis and elevated expression of growth factors). This process is influenced by features of the tumor cells as well as the microenvironment, both at cellular and molecular level. [13–16] In the brain, the commonest sites for metastases are the cerebral cortex (80%), the cerebellum (15%), and the basal nuclei/brainstem (5-10%). [17]

The true incidence of brain metastases remains uncertain because of a lack of systematically collected, representative data. [8,18,19] In subgroups of patients with certain molecular subtypes of cancer (e.g., melanoma, lung, or breast cancer) the incidence may be as high as 50 percent. [17] The incidence of brain metastases is rising due to several factors including population aging which causes an overall increase in cancer incidence. [12,13,19] Moreover, cancer patients are living longer due to advancements in systemic/multimodal cancer treatments, which include a combination of (radio)surgery, radiotherapy, chemotherapy, immunotherapy, and targeted therapies, making it more likely for the primary tumor site to eventually spread to the brain. Additionally, increased screening with high-quality neuroimaging enables earlier detection of brain metastases. [3,12,19]

Sometimes brain metastases are the first presenting sign of a previously undiagnosed primary cancer (precocious brain metastases) and in other cases brain metastases are diagnosed within one to three months of the diagnosis of the primary cancer (synchronous brain metastases). However, in most patients (approximately 80%), the detection of brain metastases occurs from one to three months to even years after the initial diagnosis of the primary cancer (metachronous brain metastases of a known primary tumor). [18,20–23] Most patients are initially diagnosed with more than one brain metastasis. [24,25] A diagnosis of brain metastases can significantly affect a patient's clinical disease course (e.g., alterations in treatment plan and clinical trial eligibility) [26] and may cause significant emotional and physical distress to individual cancer patients, their families, and caregivers. [1,18]

Survival and prognosis

Although life expectancy of cancer patients is generally improving due to advancements in multimodal treatments and systemic therapies, many patients with brain metastases still face a poor prognosis. [3,27] Left untreated, median survival ranges between one and four months. The introduction of targeted therapies and immunotherapies have led to significant improvements in the survival of patients with brain metastases. [7,28–31] In subgroups of patients with brain metastases originating from non-small cell lung cancer (NSCLC), melanoma, or breast cancer for instance, specific genetic alterations (e.g., driver mutations in epidermal growth factor receptors (EGFR), BRAF mutations, and anaplastic lymphoma kinase (ALK) translocation) can affect the clinical prognosis. [31–33] Targeting these alterations with matched (targeted) therapy may lengthen overall survival with months, and in some cases even with years. [7,30,32,34] Survival varies widely by the specific histology and molecular diagnosis of the primary tumor, and by other prognostic factors such as the number and volume of the brain metastases and patient's age and performance status. [17,30,35] Survival is also determined by the extent and activity of the primary tumor as many patients with brain metastases die from uncontrolled extracranial disease independent of intracranial disease control. [17,36–38]

Prognostic scores

Different prognostic scores and tools have been developed and continue to be refined to individualize survival estimates. These scores can help clinicians and patients classify disease severity, guide treatment strategies, and evaluate clinical trial eligibility. [10,27,29,39] Historically, the recursive partitioning analysis (RPA) classified patients into three subsets based on the prognostic factors age, performance status, and extracranial disease status. [10,40] The graded prognostic analysis (GPA) was developed by adding the number of brain metastases as a prognostic factor. [41,42] Finally, the diagnosis-specific GPA (DS-

GPA) was developed for lung, melanoma, breast, renal cell, and gastrointestinal cancers, now including updates using molecular markers and newly identified prognostic factors for non-small cell lung cancer (NSCLC) and melanoma. [30,35,41]

Symptoms

At the time of diagnosis, brain metastases may be asymptomatic but, in most cases, they cause neurological symptoms. [10,22] These symptoms are mostly caused by the mass effect of the brain metastases and by edema which leads to direct compression of brain parenchyma. Steroid treatment for peritumoral edema and anticonvulsants to prevent recurrent seizures are usually indicated in these patients. [43] Symptoms may include headaches (sometimes with nausea or emesis), fatigue, seizures, focal deficits, personality changes, behavioral changes, and cognitive impairments, and are often related to the location and size of the brain metastases. [10,17,43] Many patients experience the additional psychosocial burden of recurrent cancer after diagnosis/treatment for the primary cancer. This in turn may cause emotional symptoms including anxiety, depression, and anger. [44] All of these symptoms, even with the slightest impairment, can significantly affect the quality of life of both patients and caregivers. [45–47] In the past, these problems have not always been adequately addressed due to the dismal prognosis and because the evaluation of treatment outcome was predominantly based on survival. [48,49] But as the number of patients with brain metastases increases, attention for the various challenges and the burden placed on patients and their caregivers is growing. [44,46]

Treatment

Traditionally, the (local) treatment options for brain metastases include neurosurgery, whole brain radiation therapy (WBRT) and stereotactic radiosurgery (SRS), or a combination of these. There have however been considerable changes over the past years in the clinical management of patients with brain metastases. [50] While surgery and radiation therapy (WBRT/SRS) remain the standard of treatment, new systemic treatment options, including immunotherapies and targeted therapies with intracranial activity/penetration, have become available. [16,26,29,51] Consequently, brain metastases can now also be treated with systemic therapy, either before, concomitantly, or after radiation therapy. [52–54]

Upfront surgical resection is indicated mainly for patients with a single (large) symptomatic metastasis (in an accessible location) and good performance status. [55,56] WBRT damages DNA and causes cancer cells to die. It has been the most widely used treatment since the 1950s, especially for patients with multiple brain metastases. [6,57,58]

Based on a more recent study, the QUARTZ trial, the use of WBRT may be limited in patients with poor performance status. This randomized clinical trial in patients with brain metastases from NSCLC, inoperable and unsuitable for SRS, reported no difference in survival or quality of life between patients who were randomized to best supportive care plus WBRT or best supportive care alone. [59–62]

The standard dose and fractionation schedule in Europe is 20 Gy in 5 fractions or 30Gy in 10 fractions of 3 Gy. WBRT has the capacity to treat both visible and occult micro-metastases which results in high intracranial control but carries an increased risk of cognitive decline due to radiation to the whole brain. [50,63] This decline is often progressive and has been reported in 50-90% of patients from months to years after WBRT. [58,64,65] These (late) effects are most pronounced for learning and memory, executive functioning, attention, processing speed and fine motor control. [57,64,66]

In contrast, SRS delivers a high radiation dose up to 25 Gy in one to five fractions to visible brain metastases with low radiation dose in the surrounding brain tissue. This results in high(er) local control and low(er) neurotoxicity. [27,29,63,67] Because of the higher risk of distant failure after SRS, routine surveillance imaging is recommended to identify any new distant brain metastases or recurrences at an early stage. Newly developed brain metastases and recurrences can be (re)treated with SRS when indicated. [67–69]

The concept of stereotactic radiosurgery was introduced by the Swedish neurosurgeon Lars Leksell in 1951 and ultimately in 1967, the first stereotactic Gamma Unit was installed in the Sophiahemmet Hospital in Stockholm. This unit was primarily intended for functional brain surgery. [70] Traditionally SRS has been delivered with a frame-based Gamma Knife platform but can now also be delivered using a frameless mask. [71] Since the 1980s, SRS can also be performed with linear or particle beam accelerators. [72,73] Because of concerns about the increased risk of cognitive decline after WBRT, treatment for patients with a limited number of brain metastases has now shifted from WBRT towards SRS. SRS has been accepted for one to four brain metastases and more recently for up to 10 brain metastases. [50,74–76] Although there is growing acceptance of SRS for multiple brain metastases, especially since the total volume rather than the number of brain metastases is being recognized as a more important eligibility criterion for SRS [77–80], the optimal local treatment for patients with more than 10 brain metastases remains a subject of debate [81–84] Both WBRT and SRS have proven to be effective for treating multiple brain metastases with similar overall survival. [75,76,85,86] However, while survival is considered the most objective health outcome, survival alone is not necessarily the most appropriate primary endpoint of clinical outcome in these patients. [87,88] Another clinically significant treatment goal is to prevent or

delay cognitive decline to maintain quality of life, especially considering the growing number of patients with longer expected survival. [57,89] The new ASCO-SNO-ASTRO guideline [50,90,91] on brain metastases, published in 2022 by three leading American organizations (American Society of Clinical Oncology; Society for Neuro-Oncology; American Society for Radiation Oncology), recommends as follows: SRS alone as opposed to WBRT or a combination of both should be offered to patients with one to four, and conditionally up to 10 [90,91] unresected brain metastases. For patients with more than four metastases and good performance status, SRS, WBRT, and the combination of SRS plus WBRT are all reasonable treatment options. SRS plus WBRT, as compared with SRS alone, may improve local and distant tumor control but data show worse cognitive functioning and quality of life and no survival difference. [60,67,92] SRS alone may be preferred for patients with better performance status or when systemic therapy with activity in the central nervous system (CNS) is available. The strength of the evidence for the latter recommendation was rated low because of a lack of randomized trials including patients with more than four brain metastases. Number, volume, and recurrence rate (or velocity [93]) of the brain metastases may be relevant factors in guiding radiation therapy for multiple brain metastases, but lack of evidence did not allow for recommendations on specific thresholds for these factors. In patients without hippocampal metastases who will receive WBRT, hippocampal avoidance (HA-WBRT) combined with memantine (a neuroprotectant) is strongly recommended. [50] In the Netherlands, the guideline on brain metastases has been updated in 2020. [94] SRS is now to be considered for patients with good performance status and up to 10 brain metastases (previously up to four). For patients with more than 10 brain metastases, conventional WBRT remains the treatment of choice in Europe. [81,95,96] Although the role of SRS in the treatment of multiple/extensive brain metastases (>10) remains controversial, in clinical practice, SRS alone has been frequently applied in these patients. [79,97] Already in 2000, a Japanese study on the efficacy of Gamma Knife radiosurgery (GKRS) alone in 24 patients with 10 up to 47 brain metastases (mean 20) was published. The authors concluded that GKRS can achieve acceptable tumor control, low morbidity, and good quality of life. [98] Since then, several retrospective studies have been published on the clinical outcomes after SRS alone (compared to WBRT [97,99]) in patients with 10 or more (and 20 or more [97]) brain metastases and good performance status. [38,97,99–107] In general, these (retrospective) studies showed that, rather than the number of treated lesions, the total tumor volume was a prognostic indicator for survival. SRS resulted in high local control, but distant recurrences occurred frequently after SRS (more frequently than after WBRT but with no survival differences [97,99]). In addition, survival in patients with more than 10 brain metastases was highly determined by the course of the extracranial disease. [38]

The current role of chemotherapy in the treatment of brain metastases is still limited and mostly restricted to experimental settings because of its reduced ability to cross the blood-brain and blood-tumor barrier at concentrations high enough to exert an antitumor effect. [32,108] By contrast, many recently approved targeted and immunotherapies (e.g., EGFR or ALK tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors including nivolumab and pembrolizumab) have been shown to have intracranial efficacy. This highlights the need for optimizing combinations of the available treatments (e.g., optimal timing and sequencing of SRS with targeted and immunotherapy). [26,32,71,85,109]

As current treatment strategies are usually multimodal, including (combinations of) systemic therapy, neurosurgery, WBRT, and (pre- or postoperative) SRS, multidisciplinary collaboration is required with contributions from neurosurgeons, medical/radiation oncologists, pulmonologists, neurologists, neuropsychologists, and specialist nurses. [21,26,85,110,111] Factors that play a role in the multidisciplinary management of brain metastases include performance status, histology, age, expected survival, prior treatment(s), extracranial diseases status, systemic treatment options, the size and location of brain metastases, and the cumulative volume and number of brain metastases, the availability of clinical trial participation, and the current (inter) national guidelines. [74,77]

Shared treatment decision-making

Balancing between (intracranial) tumor control and side-effects of cancer treatments can be quite challenging, especially because many patients already faced multiple lines of treatment for their primary cancer prior to treatment directed at the brain metastases. [112,113] The treatment decision between WBRT and SRS balances the competing risks of intracranial recurrence (higher in patients treated with SRS) and risk of cognitive side effects (higher in patients treated with WBRT). [68,114,115] Additional considerations include treatment duration and possible interruption of systemic therapy. WBRT is delivered in several sessions over 1 or 2 weeks and requires interruption of systemic therapy whereas SRS is generally delivered in a single session/day with shorter or no interruption of systemic therapy. [52,75,116,117] Because the treatment decision is sensitive to patients' own goals and preferences, shared-decision making is advocated [118–120] Ideally, patients are encouraged to actively participate in this process, and clinicians foster choice awareness in their patients. Together they evaluate and discuss patients' preferences and values regarding the (personal) benefits and harms of the available treatment options (including alternatives or abstaining from further treatment) and expected outcome of each treatment option. [118–120] Patients' decisional capacity and ability to engage in shared

treatment decision-making is, among other factors, highly influenced by the level of patients' cognitive impairment. [121–124] As many patients with brain metastases already suffer from cognitive impairments prior to treatment of brain metastases, screening for and monitoring of cognitive impairment in these patients is therefore of high importance. [48,122,124,125]

Assessment of cognitive functioning in patients with brain metastases

Cognitive skills and abilities, often called cognitive functions, are (high-level) cerebral functions we need to perform and to carry out tasks, from the simplest to the most complex. Cognitive skills or domains include the ability to learn and remember, to process (new) information and to acquire and apply knowledge, to analyze and reason, and to evaluate and decide. [126] These skills can be measured with objective (contrary to self-report measures) neuropsychological tests. Different tests are used per cognitive domain. However, no test is able to purely measure a single domain, as cognitive abilities rely on the integrity of several basic functions and higher-order functions. Basic functions include motor, sensory, and autonomic functions. Higher-order functions include learning and memory, and executive functions such as inhibition, planning and problem solving, attentional control. [127,128] Moreover, several brain structures are involved in higher-order functions working together in networks. [126,129]

In recent years cognitive functioning has been increasingly recognized as an outcome measure in clinical trials in patients with brain metastases. The methods of measuring cognitive performance in patients with brain metastases have changed as well: from the use of the Mini-Mental State Examination (MMSE) to standardized neuropsychological tests. The MMSE, which was developed as dementia screening instrument, proved to be insensitive to mild cognitive changes after radiotherapy and it has no parallel versions to minimize practice effects. [130,131] Neuropsychological tests, on the contrary, can provide more detailed information on cognitive functions and impairments per domain. In 2006 the International Cognition and Cancer Task Force (ICCTF) was founded. The ICCTF developed guidelines to increase the homogeneity of study methods. The ICCTF recommends the use of a standardized formal neuropsychological test battery to objectively measure cognitive change after treatment in patients with cancer. This test battery is also commonly used in patients with brain metastases. [132,133] The battery consists of six neuropsychological tests measuring the following cognitive domains: immediate and delayed verbal memory and recognition (Hopkins Verbal Learning Test-Revised with six parallel versions; HVLT-R), psychomotor speed (Trail Making Test; TMT-A), cognitive flexibility (TMT-B), word fluency (Controlled Oral Word Association with two parallel versions; COWA), attention span and working memory (Wechsler Adult Intelligence

Scale (WAIS) Digit Span), information processing speed (WAIS Digit Symbol), and dominant and nondominant hand dexterity (Grooved Pegboard). [132,133] In addition, the ICCTF provided guidelines on the use of appropriate control groups (both local controls and published normative data) to determine whether cognitive impairment is present and to correct for potential practice effects. [132,134]

Cognitive impairment prior to treatment

Pretreatment neuropsychological assessment is a prerequisite for the evaluation of cognitive changes after irradiation. [114] As abovementioned, prior to the treatment of their brain metastases, up to 80 or 90 percent of patients with brain metastases already have cognitive impairments, mostly in the domains of attention, memory, and executive functioning. [48,87,125,135–137] These impairments might be caused by direct effects of the primary tumor (e.g., due to increased systemic inflammation in response to cancer), the brain metastases themselves (due to neuroinflammation and increased pressure on surrounding brain tissue), epilepsy, medication, and/or by the side effects of (systemic) treatment or combination of treatments given for the primary cancer, or a combination of all of these. [48,138,139] In addition, there are substantial individual differences in the degree of impairment, mainly because of differences in volume and location of the brain metastases. [135,138] Moreover, symptoms of depression and anxiety, fatigue, sleep dysfunction, and pain may also contribute to cognitive impairment. [138,140] Advancing age, preexisting medical conditions such as diabetes and hypertension, and genetic factors (e.g., the Alzheimer's disease risk allele apolipoprotein E4 or APOE E4) are also known risk factors for cognitive impairment. [138,139,141,142] Cognitive reserve (individual differences in innate and developed cognitive capacity and flexibility/resilience to cope with brain damage) may be a protective factor that reduces the risk of cognitive impairment. [138,143]

Cognitive impairments may be self-reported during a consult or on a questionnaire. These are called subjective or perceived cognitive impairments. Objective cognitive impairments on the other hand are measured using formal neuropsychological tests. [144,145] Subjectively, and objectively measured cognitive impairments are only weakly associated or may even be unrelated. Subjective cognitive complaints are more strongly related to (psychological) factors such as anxiety, depression, and fatigue than to objective cognitive impairment. [138,141,144,146,147] Thorough assessment and understanding of objective as well as subjective cognitive impairments, such as slow processing of information, impairments in executive and self-regulatory functions and memory concerns, are of high relevance because both provide relevant insight into patients' functioning. Both may negatively affect patients' functional independence, participation in valued activities, relationships, ability to reason through (shared) medical treatment decisions, and ultimately patients' quality of life. [146,148,149]

Radiation injury and radiation-induced cognitive decline

After WBRT, both improvement and decline in cognitive functioning may be expected: Reduction in brain tumor load after treatment may alleviate cognitive deficits, while radiation may induce additional cognitive deficits that persist and may even increase over time. Traditionally, radiation injury is divided into three stages: acute, early delayed, and late delayed. [150,151] Acute and early delayed injury (after 1-6 months) are thought to be of a transient nature. Late delayed injury, including cognitive decline (after 4-24 months) on the other hand is usually considered more severe and irreversible. [150,152,153] The late delayed cognitive effects of conventional WBRT in patients with primary brain tumors as well as in patients with (resected) brain metastases, mostly from NSCLC, have been well documented, although insufficiently assessed in long-term survivors. Patients with late delayed injury after WBRT most often exhibit progressive impairments in learning and memory, processing speed, problem-solving ability, executive functioning (including cognitive flexibility), and attention, all of which can be very debilitating in daily life. [56,64,67,86,125,136,140,148,150,152,154–157] The extent of delayed cognitive impairment positively correlates with the total dose received and with the time-dose-fractionation scheme (and timing of chemotherapy). [49,152,158,159]

WBRT-induced cognitive impairment has also been studied in patients who received WBRT to prevent the development of brain metastases, called prophylactic WBRT or prophylactic cranial irradiation (PCI). [160] PCI is used in patients with highly aggressive cancers who are at increased risk of developing brain metastases. PCI has been the standard of care in patients with small cell lung cancer (SCLC) and is, to a lesser extent, also used in patients with advanced NSCLC. [158,161,162] PCI reduces the incidence of brain metastases and may improve survival in these patients but, as has been shown, often at the expense of cognitive decline. [160,163,164] Studies in patients with SCLC following PCI (after initial chemo/radiotherapy) have demonstrated declines in verbal memory (HVLT-R) [165], verbal fluency [166], and executive functioning. [167–169] Strategies to prevent cognitive decline after PCI, such as HA-PCI and the use of neuroprotectant drugs, are being investigated. Results from two recent trials in which patients with SCLC were randomized to either PCI or HA-PCI are conflicting. [164,168,170] One trial did not find a lower probability of cognitive decline after HA-PCI compared to PCI [164] whereas the other trial did find a significantly lower percentage of patients with cognitive decline after HA-PCI versus standard PCI (no differences in brain metastases incidence, overall survival, and quality of life). [171] The question whether the benefits of (HA-)PCI outweigh the risks of side-effects (including cognitive decline, fatigue, and decline in quality of life) remains unsettled. In addition, patients with SCLC are now being more closely monitored with MRI surveillance, and growing evidence (retrospective studies) suggests that SRS with MRI surveillance in combination with new immunotherapies

may be considered as a first treatment option in selected patients with SCLC (in line with the treatment of NSCLC brain metastases). [172–174]

Radiation-induced brain injury can result from direct toxic effects of radiation on the cells of the CNS, or indirectly through metabolic abnormalities, microvascular changes or inflammatory processes. [175,176] White matter changes are thought to be the most important cause of late delayed effects although these effects can also occur in the absence of evidence of demyelination or white matter necrosis. [58,138,177] Radiation therapy also damages the microenvironment surrounding progenitor cells near the hippocampus, disrupting hippocampal neurogenesis, which may, in turn, negatively affect (short-term) memory and learning functions and spatial processing (and in rare cases may escalate to dementia). [58,140,151,178] Additionally, radiation-induced cognitive impairment likely reflects damage to various regions and networks in the brain and these different regions and networks have different thresholds for radiation damage. [58,140,152,179] Radiation also has a negative effect on growth hormone secretion in the brain which may contribute to cognitive dysfunction. [180,181] Moreover, secondary reactive responses of the CNS to radiation-injury can initiate chronic oxidative stress and enhanced cytokine gene expression which ultimately contributes to long-term cognitive decline. [45,182]

Although research on SRS (alone or in combination with WBRT) in patients with brain metastases has been growing steadily, still relatively few studies have been published on cognitive outcomes after SRS. Previous studies mostly concerned patients with one up to four brain metastases. [67,92,183–187]. Three of these studies showed that cognitive performances remained stable after SRS. [183,185–187] Other studies showed evidence for small and mostly transient objective decline in learning and memory, motor dexterity, and executive functioning in the early phase after treatment [67,92,184], potentially followed by a trend toward improvement or stability up to 12 months after SRS. [184] Improvements in test performances were found in the domains of executive functioning, verbal fluency, visuoconstruction and motor dexterity. [184,187] The addition of WBRT after SRS however resulted in significantly more objective cognitive decline over time. Although higher intracranial tumor control rates were achieved with the addition of WBRT after SRS, no survival benefits were gained. [67,92]

Thus far, to our knowledge, results from only two prospective trials on cognitive outcome after SRS (versus WBRT) in patients with 10 or more brain metastases have been published: One full publication of a single arm trial by Minniti and colleagues [83], and one published abstract on a randomized trial by Li and colleagues. [75] In the single arm trial [83], cognitive functioning was assessed with the HVLT-R (only) in 40 patients

with 10-21 BM (median 13) at 3 (n=32), 6 (n=26), 12 months (n=21) after SRS. Percentages of decline for immediate and delayed verbal recall and recognition ranged between 4·7% and 18·7% across all follow-ups. The authors concluded that learning and memory performance is preserved in most patients with 10 or more brain metastases after SRS. Cognitive functioning was also assessed in 31 patients with 4-15 brain metastases who were randomized to either SRS or WBRT (a small majority of patients in the WBRT arm also received memantine). [75] Four months after treatment, mean immediate verbal recall scores (HVLT-R) significantly improved in the SRS arm but declined in the WBRT arm. A similar result, significant improvement after SRS and decline after WBRT, was found regarding a composite score including multiple cognitive domains (HVLT-R, COWA and TMT). There was no difference in median overall survival. The authors concluded that in patients with 4-15 brain metastases, SRS was associated with a reduced risk of cognitive decline compared to WBRT, without compromising OS.

The incidence of cognitive impairments after radiotherapy (WBRT/SRS) varies widely by study and is influenced by many factors, both clinical and methodological. Clinical factors include age, tumor histology, tumor progression, type of radiation therapy (WBRT or SRS), radiation dose, medication, chemotherapy, and other systemic therapies. Methodological factors include differences in study design, follow-up schedules, neuropsychological tests and norms, baseline cognitive performance, definition of cognitive decline, the use of methods (if any) to correct for practice effects beyond the use of parallel versions. [151] Practice effects are change in test performances over time due to familiarity with test items and procedures after repeated testing rather than true cognitive improvement. [132,134]

Cognitive impairment/changes were predominantly evaluated at group level while these analyses can mask individual cognitive impairment/changes. Furthermore, patient samples were (very) small at follow-up because of high loss to follow-up due to death, disability, and/or drop-out. These methodological differences and limitations hinder reliable conclusions on the cognitive side effects of radiotherapy. Additionally, studies did not directly compare SRS alone to WBRT alone (except for the abovementioned randomized trial by Li and colleagues in patients with 4-15 brain metastases [75]) or were terminated due to poor accrual. Studying cognitive change after radiotherapy remains challenging and requires longer-term follow-up while avoiding selective dropout (attrition bias) which may favor those with higher cognitive performances, and as a consequence decline may be underestimated. [86,151]

In all, as patients with brain metastases are living longer due to progress in systemic treatment, the incidence of brain metastases is increasing. Consequently, the number of patients with brain metastases that live long enough to experience radiation-induced cognitive decline is also increasing. These developments emphasize the importance of the preservation of cognitive functions and quality of prolonged life. [48,68,188] This is of particular importance for patients with longer expected survival. Neuropsychological assessment after WBRT or SRS may help to determine the true incidence and severity of cognitive impairment after treatment and eventually may help to improve cancer care, both in patients with up to 10 brain metastases as well as in patients with 10 or more brain metastases. To the best of our knowledge, there are no full-length publications of randomized trials yet that directly compare the effects of WBRT to SRS on cognitive function in patients with 10 or more brain metastases.

The CAR-Studies

The Elisabeth-TweeSteden Hospital (ETZ) in the Netherlands is a national center of expertise for the treatment of brain tumors (both primary brain tumors as well as brain metastases). The neurosurgical department is one of the largest neurosurgical practices in the Netherlands, with a total catchment area of approximately 2.3 million people. Nearly all treatment modalities for brain tumor patients are available, including SRS with Gamma Knife (Elekta Instruments AB, Stockholm, Sweden). Historically, the ETZ neurosurgical department has participated in clinical research and development of several innovative methods to improve treatment of patients with brain tumors, and with a strong focus on cognitive functioning and well-being. At the Gamma Knife Center Tilburg (ETZ, the Netherlands), it has been the policy since 2002 to treat patients with up to 10 brain metastases on the planning MRI-scan (triple-dose gadolinium-enhanced magnetic resonance imaging used for treatment planning). [189]

In 2015, we initiated the Cognition and Radiation (CAR) Studies A and B at the Gamma Knife Center Tilburg in close collaboration with the department of Cognitive Neuropsychology of Tilburg University. With the CAR-Studies we aimed to evaluate (long-term) cognitive changes in patients with brain metastases after WBRT or SRS, using a formal neuropsychological test battery.

We also included measures of depression and anxiety, health-related quality of life, and fatigue in our study designs as these are important psychological factors that may influence cognitive performance. In addition, we have chosen to use the reliable change index with correction for practice effects to establish reliable, cognitive improvement or decline on the individual patient level.

CAR-Study A (ClinicalTrials.gov identifier NCT02953756) is a single-arm prospective trial aimed to gain insight into the cognitive effects of GKRS over time. Previous studies mostly concerned patients with a limited number of brain metastases (1 up to 4) and did not correct for potential practice effects. The research question central to this study was the following: What are the effects of treatment with GKRS on cognition in patients with 1 up to 10 newly diagnosed brain metastases on the planning MRI-scan? Performance on measures of verbal learning and memory, executive function, attention, working memory, information processing speed, and fine motor dexterity was assessed using a comprehensive neuropsychological test battery, before (n=92), and every three months after GKRS, up to 21 months, in a relatively large sample. Our primary aim was to evaluate the (longitudinal) course of cognitive performances (stability, impairment or decline, or improvement) after standard care GKRS.

CAR-Study B (ClinicalTrials.gov identifier NCT02953717) is one of the first prospective randomized trials comparing cognitive outcomes after single fraction GKRS or (conventional) WBRT in patients with 11 to 20 newly diagnosed brain metastases on a high-resolution MRI-scan with triple dose gadolinium. The research question central to this study was as follows: Is there a difference in the cognitive side effects after treatment with WBRT versus GKRS in patients with newly diagnosed multiple BM? More specific: Is the proportion of patients with a clinically significant decline in verbal memory at 3 or 6 months significantly higher after treatment with WBRT in comparison with SRS? The same neuropsychological test battery was used, and assessments were scheduled before and at 3, 6, 9, 12, and 15 months after treatment.

Applied Bayesian stopping rules specified that during the trial, if the probability for a higher failure rate for memory decline after WBRT (versus GKRS) at 3 or 6 months would be greater than 0.975, then the trial would be halted/terminated early. A difference score of ≥5 points on the HVLT-R immediate memory score at 3 and 6 months was considered a failure.

Aim and outline of this dissertation

Cognitive impairments may hamper daily functioning and patients' ability to make shared treatment decisions. With the studies presented in this thesis, we aimed to evaluate long-term cognitive changes in patients with brain metastases after WBRT or SRS.

Ultimately, the purpose of this line of research is to allow patients and physicians to have an informed discussion about the potential benefits and (cognitive) risks of radiotherapy (SRS/WBRT) for brain metastases. Moreover, due to controversies and differences in local best practices and patient preferences, the results of these studies may help unify treatment-decision in this patient population.

First, we performed a literature review of the cognitive effects of radiosurgery (compared to WBRT) in patients with brain metastases (**Chapter 2**). We searched for prospective cohort studies and randomised trials on SRS alone or in combination with WBRT, including objective assessments of cognitive functioning.

In chapters 3 and 4 we present results from **CAR-Study A**. Baseline data of CAR-Study A was used to investigate the incidence and severity of cognitive impairments in patients with 1 to 10 brain metastases before GKRS (**Chapter 3**). Using multivariate analyses, both number and volume of BM were examined as potential predictors of baseline cognitive functioning. In addition, the role of other clinical factors (including KPS and DS-GPA) and psychological variables, such as fatigue and symptoms of anxiety and depression, known to impact cognitive test performance, were explored. For the study presented in **Chapter 4**, we evaluated change in cognitive performances following Gamma Knife radiosurgery of 92 patients with 1 to 10 brain metastases, up to nine months after treatment (n=41). In addition, potential baseline predictors of cognitive performance over time were explored using multivariable regression.

In **Chapter 5** we present the study protocol of **CAR-Study B**. In CAR-Study B patients with 11 to 20 brain metastases were randomized to either GKRS or WBRT. Neuropsychological tests were administered before and every 3 months after treatment up to 15 months. The primary objective was to determine the between-group difference in the percentages of patients with significant cognitive decline at three months after treatment as assessed with the HVLT-R. Interim monitoring was based on Bayesian statistics and early stopping rules specified that the trial would be terminated prematurely in case the probability/risk for verbal memory decline would be higher after WBRT than after GKRS (posterior probability >0.975) at three or six months after treatment. The results of an interim analysis that was performed after

the first 45 patients were enrolled in CAR-Study B are presented in **Chapter 6**. The primary aim of this interim analysis was to check whether the Bayesian stopping rules for cognitive failure were met. The secondary aim was to compare cognitive changes after treatment. Finally, **Chapter 7** provides a summary of, and a general discussion on the results of this thesis. Methodological limitations, translation of our findings into clinical practice and recommendations for future research are discussed.

References

1. World Health Organization. (n.d.). Cancer. Retrieved November 29, 2022, from https://www.who.int/health-topics/cancer.
2. Nayak L, Lee EQ, Wen PY. Epidemiology of brain metastases. Curr Oncol Rep 2012; 14: 48–54.
3. Achrol AS, Rennert RC, Anders C, et al. Brain metastases. Nat Rev Dis Primers 2019; 16: 1–26.
4. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. Ca Cancer J Clin 2021; 71: 209–49.
5. Central Bureau for Statistics. (2021, December 21). Overledenen; belangrijke doodsoorzaken (korte lijst), leeftijd, geslacht [Data file]. Retrieved November 29, 2022, from https://opendata.cbs.nl.
6. Amin S, Baine MJ, Meza JL, Lin C. Association of Immunotherapy With Survival Among Patients With Brain Metastases Whose Cancer Was Managed With Definitive Surgery of the Primary Tumor. JAMA Netw Open 2020; 3: e2015444.
7. Schroeder T, Bittrich P, Kuhne JF, et al. Mapping distribution of brain metastases: does the primary tumor matter? J Neuro-oncol 2020; 147: 229–35.
8. Cagney DN, Martin AM, Catalano PJ, et al. Incidence and prognosis of patients with brain metastases at diagnosis of systemic malignancy: a population-based study. Neuro-oncology 2017; 19: 1511–21.
9. Habbous S, Forster K, Darling G, et al. Incidence and real-world burden of brain metastases from solid tumors and hematologic malignancies in Ontario: a population-based study. Neuro-oncology Adv 2020; 3: 1–14.
10. Lamba N, Wen PY, Aizer AA. Epidemiology of brain metastases and leptomeningeal disease. Neuro-oncology 2021; 23: 1447–56.
11. Franchino F, Rudà R, Soffietti R. Mechanisms and Therapy for Cancer Metastasis to the Brain. Frontiers Oncol 2018; 8: 161.
12. Schouten LJ, Rutten J, Huveneers HAM, Twijnstra A. Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma. Cancer 2002; 94: 2698–705.
13. Linnert M, Iversen HK, Gehl J. Multiple brain metastases - current management and perspectives for treatment with electrochemotherapy. Radiol Oncol 2012; 46: 271–8.
14. Wrobel JK, Toborek M. Blood-brain Barrier Remodeling during Brain Metastasis Formation. Mol Med 2016; 22: 32–40.
15. Kienast Y, Baumgarten L von, Fuhrmann M, et al. Real-time imaging reveals the single steps of brain metastasis formation. Nat Med 2010; 16: 116–22.
16. Fidler IJ. The Biology of Brain Metastasis. Cancer J 2015; 21: 284–93.
17. McKay MJ. Brain metastases: increasingly precision medicine—a narrative review. Ann Transl Medicine 2021; 21: 1629.
18. Ostrom QT, Wright CH, Barnholtz-Sloan JS. Chapter 2 Brain metastases: epidemiology. Handb Clin Neurology 2018; 149: 27–42.
19. Singh R, Stoltzfus KC, Chen H, et al. Epidemiology of synchronous brain metastases. Neuro-oncology Adv 2020; 2: 1–10.
20. Shibahara I, Kanamori M, Watanabe T, et al. Clinical Features of Precocious, Synchronous, and Metachronous Brain Metastases and the Role of Tumor Resection. World Neurosurg 2018; 113: e1–9.
21. Jenkinson MD, Haylock B, Shenoy A, Husband D, Javadpour M. Management of cerebral metastasis: Evidence-based approach for surgery, stereotactic radiosurgery and radiotherapy. European Journal of Cancer 2011; 47: 649–55.
22. Füreder LM, Widhalm G, Gatterbauer B, et al. Brain metastases as first manifestation of advanced cancer: exploratory analysis of 459 patients at a tertiary care center. Clin Exp Metastas 2018; 35: 727–38.
23. Jünger ST, Schödel P, Ruess D, et al. Timing of Development of Symptomatic Brain Metastases from Non-Small Cell Lung Cancer: Impact on Symptoms, Treatment, and Survival in the Era of Molecular Treatments. Cancers 2020; 12: 3618.
24. Lu-Emerson C, Eichler AF. Brain Metastases. Continuum Lifelong Learn Neurology 2012; 18: 295–311.

25. Khuntia D, Brown P, Li J, Mehta MP. Whole-Brain Radiotherapy in the Management of Brain Metastasis. J Clin Oncol 2006; 24: 1295–304.
26. Tan AC, Boggs DH, Lee EQ, Kim MM, Mehta MP, Khasraw M. Clinical Trial Eligibility Criteria and Recently Approved Cancer Therapies for Patients With Brain Metastases. Frontiers Oncol 2022; 11: 780379.
27. Arvold ND, Lee EQ, Mehta MP, et al. Updates in the management of brain metastases. Neuro-oncology 2016; 18: 1043–65.
28. Kobets AJ, Backus R, Fluss R, Lee A, Lasala PA. Evaluating the natural growth rate of metastatic cancer to the brain. Surg Neurology Int 2020; 11: 254.
29. Lauko A, Rauf Y, Ahluwalia MS. Medical management of brain metastases. Neuro-oncology Adv 2020; 2: 1–14.
30. Sperduto PW, Mesko S, Li J, et al. Survival in Patients With Brain Metastases: Summary Report on the Updated Diagnosis-Specific Graded Prognostic Assessment and Definition of the Eligibility Quotient. J Clin Oncol 2020; 38: 3773–84.
31. Bander ED, Yuan M, Carnevale JA, et al. Melanoma brain metastasis presentation, treatment, and outcomes in the age of targeted and immunotherapies. Cancer 2021; 127: 2062–73.
32. Lee JS, Hong JH, Sun DS, et al. The impact of systemic treatment on brain metastasis in patients with non-small-cell lung cancer: A retrospective nationwide population-based cohort study. Sci Rep-uk 2019; 9: 18689.
33. Rabbie R, Ferguson P, Wong K, et al. The mutational landscape of melanoma brain metastases presenting as the first visceral site of recurrence. Brit J Cancer 2021; 124: 156–60.
34. Hansen AR, Bedard PL. Clinical application of high-throughput genomic technologies for treatment selection in breast cancer. Breast Cancer Res 2013; 15: R97.
35. Sperduto PW, Yang TJ, Beal K, et al. Estimating Survival in Patients With Lung Cancer and Brain Metastases: An Update of the Graded Prognostic Assessment for Lung Cancer Using Molecular Markers (Lung-molGPA). JAMA Oncol 2017; 3: 827–31.
36. Ahluwalia MS, Vogelbaum MV, Chao ST, Mehta MM. Brain metastasis and treatment. F1000prime Reports 2014; 6: 114.
37. Karlsson B, Hanssens P, Wolff R, Söderman M, Lindquist C, Beute G. Thirty years' experience with Gamma Knife surgery for metastases to the brain. J Neurosurg 2009; 111: 449–57.
38. Rogers SJ, Lomax N, Alonso S, Lazeroms T, Riesterer O. Radiosurgery for Five to Fifteen Brain Metastases: A Single Centre Experience and a Review of the Literature. Frontiers Oncol 2022; 12: 866542.
39. Johung KL, Yeh N, Desai NB, et al. Extended Survival and Prognostic Factors for Patients With ALK-Rearranged Non–Small-Cell Lung Cancer and Brain Metastasis. J Clin Oncol 2015; 34: 123–9.
40. Gaspar LE, Scott C, Murray K, Curran W. Validation of the RTOG recursive partitioning analysis (RPA) classification for brain metastases. Int J Radiat Oncol Biology Phys 2000; 47: 1001–6.
41. Moravan MJ, Fecci PE, Anders CK, et al. Current multidisciplinary management of brain metastases. Cancer 2020; 126: 1390–406.
42. Sperduto PW, Kased N, Roberge D, et al. Summary Report on the Graded Prognostic Assessment: An Accurate and Facile Diagnosis-Specific Tool to Estimate Survival for Patients With Brain Metastases. J Clin Oncol 2012; 30: 419–25.
43. Noh T, Walbert T. Brain metastasis: clinical manifestations, symptom management, and palliative care. Handb Clin Neurology 2018; 149: 75–88.
44. Cordes M-C, Scherwath A, Ahmad T, et al. Distress, anxiety and depression in patients with brain metastases before and after radiotherapy. BMC Cancer 2014; 14: 731.
45. Wilke C, Grosshans D, Duman J, Brown P, Li J. Radiation-induced cognitive toxicity: pathophysiology and interventions to reduce toxicity in adults. Neuro-oncology 2017; 20: 597–607.
46. Wu A, Colón GR, Lim M. Quality of Life and Role of Palliative and Supportive Care for Patients With Brain Metastases and Caregivers: A Review. Front Neurol 2022; 13: 806344.
47. Verhaak E, Gehring K, Hanssens PEJ, Sitskoorn MM. Health-related quality of life of patients with brain metastases selected for stereotactic radiosurgery. J Neurooncol 2019; 4: 289–10.

48. Parsons MW, Peters KB, Floyd SR, Brown P, Wefel JS. Preservation of neurocognitive function in the treatment of brain metastases. Neuro-oncology Adv 2021; 3: v96–107.
49. Gondi V, Meyer J, Shih HA. Advances in radiotherapy for brain metastases. Neuro-oncology Adv 2021; 3: v26–34.
50. Vogelbaum MA, Brown PD, Messersmith H, et al. Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline. J Clin Oncol 2022; 40: 492–516.
51. Vanneman M, Dranoff G. Combining immunotherapy and targeted therapies in cancer treatment. Nat Rev Cancer 2012; 12: 237–51.
52. Tonse R, Tom MC, Mehta MP, Ahluwalia MS, Kotecha R. Integration of Systemic Therapy and Stereotactic Radiosurgery for Brain Metastases. Cancers 2021; 13: 3682.
53. Borius P-Y, Régis J, Carpentier A, Kalamarides M, Valery CA, Latorzeff I. Safety of radiosurgery concurrent with systemic therapy (chemotherapy, targeted therapy, and/or immunotherapy) in brain metastases: a systematic review. Cancer Metast Rev 2021; 40: 341–54.
54. Liu L, Chen W, Zhang R, et al. Radiotherapy in combination with systemic therapies for brain metastases: current status and progress. Cancer Biology Medicine 2020; 17: 910–22.
55. Bailleux C, Eberst L, Bachelot T. Treatment strategies for breast cancer brain metastases. Brit J Cancer 2021; 124: 142–55.
56. Kirkpatrick JP. Answering the Big Clinical Questions in Brain Metastasis Management. Frontiers Oncol 2022; 11: 834122.
57. Brown PD, Ahluwalia MS, Khan OH, Asher AL, Wefel JS, Gondi V. Whole-Brain Radiotherapy for Brain Metastases: Evolution or Revolution? J Clin Oncol 2017; 36: 483-491.
58. Makale MT, McDonald CR, Hattangadi-Gluth JA, Kesari S. Mechanisms of radiotherapy-associated cognitive disability in patients with brain tumours. Nat Rev Neurol 2017; 13: 52–64.
59. Mulvenna P, Nankivell M, Barton R, et al. Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial. Lancet Lond Engl 2016; 388: 2004–14.
60. Tsao MN, Xu W, Wong RK, et al. Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. Cochrane Db Syst Rev 2018; 1: CD003869.
61. Nankivell M, Langley RE, Barton R, et al. How do the QUARTZ trial results inform future research for patients with brain metastases from non-small cell lung cancer? Transl Cancer Res 2017; 6: S446–7.
62. Tsao MN. Should optimal supportive care alone be the standard of care for brain metastases patients from non-small cell lung cancer, who are not eligible for radiosurgery or surgery? Transl Cancer Res 2016; 5: S1320–2.
63. Rubino S, Oliver DE, Tran ND, et al. Improving Brain Metastases Outcomes Through Therapeutic Synergy Between Stereotactic Radiosurgery and Targeted Cancer Therapies. Frontiers Oncol 2022; 12: 854402.
64. Tohidinezhad F, Perri DD, Zegers CML, et al. Prediction Models for Radiation-Induced Neurocognitive Decline in Adult Patients With Primary or Secondary Brain Tumors: A Systematic Review. Front Psychol 2022; 13: 853472.
65. Pazzaglia S, Briganti G, Mancuso M, Saran A. Neurocognitive Decline Following Radiotherapy: Mechanisms and Therapeutic Implications. Cancers 2020; 12: 146.
66. Constanzo J, Midavaine É, Fouquet J, et al. Brain irradiation leads to persistent neuroinflammation and long-term neurocognitive dysfunction in a region-specific manner. Prog Neuro-psychopharmacology Biological Psychiatry 2020; 102: 109954.
67. Brown PD, Jaeckle K, Ballman KV, et al. Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases: A Randomized Clinical Trial. JAMA 2016; 316: 401–9.
68. Pham A, Lo SS, Sahgal A, Chang EL. Neurocognition and quality-of-life in brain metastasis patients who have been irradiated focally or comprehensively. Expert Rev Qual Life Cancer Care 2016; 1: 45–60.

69. Khan M, Lin J, Liao G, et al. Comparison of WBRT alone, SRS alone, and their combination in the treatment of one or more brain metastases: Review and meta-analysis. Tumor Biol 2017; 39: 1–14.
70. Leksell L. Stereotactic radiosurgery. J Neurology Neurosurg Psychiatry 1983; 46: 797–803.
71. Wegner RE, Horne ZD, Liang Y, et al. Single Fraction Frameless Stereotactic Radiosurgery on the Gamma Knife Icon for Patients With Brain Metastases: Time to Abandon the Frame? Adv Radiat Oncol 2021; 6: 100736.
72. Park HS, Wang EH, Rutter CE, Corso CD, Chiang VL, Yu JB. Changing practice patterns of Gamma Knife versus linear accelerator-based stereotactic radiosurgery for brain metastases in the US. J Neurosurg 2015; 124: 1018–24.
73. Leksell L. The stereotaxic method and radiosurgery of the brain. Acta Chir Scand 1951; 102: 316–9.
74. Wegner RE, Abel S, D'Amico RS, Mehta GU, Sheehan J. Time from stereotactic radiosurgery to immunotherapy in patients with melanoma brain metastases and impact on outcome. J Neuro-oncol 2021; 152: 79–87.
75. Li J, Ludmir EB, Wang Y, et al. Stereotactic Radiosurgery versus Whole-brain Radiation Therapy for Patients with 4-15 Brain Metastases: A Phase III Randomized Controlled Trial. Int J Radiat Oncol Biology Phys 2020; 108: S21–2.
76. Robin TP, Rusthoven CG. Strategies to Preserve Cognition in Patients With Brain Metastases: A Review. Front Oncol 2018; 8: 415.
77. Nabors LB, Portnow J, Ammirati M, et al. Central nervous system cancers, version 2.2014. Featured updates to the NCCN Guidelines. J Natl Compr Canc Netw 2014; 12: 1517–23.
78. Niranjan A, Monaco E, Flickinger J, Lunsford LD. Guidelines for Multiple Brain Metastases Radiosurgery. Prog Neurol 2019; 34: 100–9.
79. Dahshan BA, Mattes MD, Bhatia S, et al. Efficacy of Stereotactic Radiosurgery in Patients with Multiple Metastases: Importance of Volume Rather Than Number of Lesions. Cureus 2017; 9: e1966.
80. Routman DM, Bian SX, Diao K, et al. The growing importance of lesion volume as a prognostic factor in patients with multiple brain metastases treated with stereotactic radiosurgery. Cancer Med-us 2018; 7: 757–64.
81. Kraft J, Mayinger M, Willmann J, et al. Management of multiple brain metastases: a patterns of care survey within the German Society for Radiation Oncology. J Neuro-oncol 2021; 152: 395–404.
82. Ferini G, Viola A, Valenti V, et al. Whole Brain Irradiation or Stereotactic RadioSurgery for five or more brain metastases (WHOBI-STER): A prospective comparative study of neurocognitive outcomes, level of autonomy in daily activities and quality of life. Clin Transl Radiat Oncol 2022; 32: 52–8.
83. Minniti G, Capone L, Nardiello B, et al. Neurological outcome and memory performance in patients with 10 or more brain metastases treated with frameless linear accelerator (LINAC)-based stereotactic radiosurgery. J Neuro-oncol 2020; 148: 47–55.
84. Kim GJ, Buckley ED, Herndon JE, et al. Outcomes in Patients With 4 to 10 Brain Metastases Treated With Dose-Adapted Single-Isocenter Multitarget Stereotactic Radiosurgery: A Prospective Study. Adv Radiat Oncol 2021; 6: 100760.
85. Ippolito E, Silipigni S, Matteucci P, et al. Radiotherapy for HER 2 Positive Brain Metastases: Urgent Need for a Paradigm Shift. Cancers 2022; 14: 1514.
86. McDuff SGR, Taich ZJ, Lawson JD, et al. Neurocognitive assessment following whole brain radiation therapy and radiosurgery for patients with cerebral metastases. J Neurol Neurosurg Psychiatry 2013; 84: 1384–91.
87. Lin NU, Lee EQ, Aoyama H, et al. Response assessment criteria for brain metastases: proposal from the RANO group. Lancet Oncol 2015; 16: e270-8.
88. Verhaak E, Schimmel WCM, Gehring K, Emons WHM, Hanssens PEJ, Sitskoorn MM. Health-related quality of life after Gamma Knife radiosurgery in patients with 1–10 brain metastases. J Cancer Res Clin 2021; 147: 1157–67.
89. Bragstad S, Flatebø M, Natvig GK, et al. Predictors of quality of life and survival following Gamma Knife surgery for lung cancer brain metastases: a prospective study. J Neurosurg 2018; 129: 71–83.
90. Schiff D, Messersmith H, Brastianos PK, et al. Radiation Therapy for Brain Metastases: ASCO Guideline Endorsement of ASTRO Guideline. J Clin Oncol 2022; 40: 2271-2276.

91. Gondi V, Bauman G, Bradfield L, et al. Radiation Therapy for Brain Metastases: An ASTRO Clinical Practice Guideline. Pract Radiat Oncol 2022; 12: 265-282.
92. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol 2009; 10: 1037–44.
93. Farris M, McTyre ER, Cramer CK, et al. Brain Metastasis Velocity: A Novel Prognostic Metric Predictive of Overall Survival and Freedom From Whole-Brain Radiation Therapy After Distant Brain Failure Following Upfront Radiosurgery Alone. Int J Radiat Oncol Biology Phys 2017; 98: 131–41.
94. Federatie Medisch Specialisten – Richtlijnendatabase. (2020, August 27). Hersenmetastasen. Retrieved April 29, 2022, from https://richtlijnendatabase.nl/richtlijn/hersenmetastasen.
95. Weiner JP. Neurocognitive Outcomes for Patients With Brain Metastasis in the Modern Era: Benefit of Treatment With Hippocampal Avoidance Whole-Brain Radiotherapy Plus Memantine. J Clin Oncol 2020; 38: 1003-1005.
96. Brown PD, Gondi V, Pugh S, et al. Hippocampal Avoidance During Whole-Brain Radiotherapy Plus Memantine for Patients With Brain Metastases: Phase III Trial NRG Oncology CC001. J Clin Oncol 2020; 38: 1019-1029.
97. Wei Z, Niranjan A, Abou-Al-Shaar H, Deng H, Albano L, Lunsford LD. A volume matched comparison of survival after radiosurgery in non-small cell lung cancer patients with one versus more than twenty brain metastases. J Neuro-oncol 2022; 157: 417–23.
98. Suzuki S, Omagari J, Nishio S, Nishiye E, Fukui M. Gamma knife radiosurgery for simultaneous multiple metastatic brain tumors. J Neurosurg 2000; 93 Suppl 3: 30–1.
99. Mizuno T, Takada K, Hasegawa T, et al. Comparison between stereotactic radiosurgery and whole-brain radiotherapy for 10-20 brain metastases from non-small cell lung cancer. Mol Clin Oncol 2019; 10: 560–6.
100. Chang WS, Kim HY, Chang JW, Park YG, Chang JH. Analysis of radiosurgical results in patients with brain metastases according to the number of brain lesions: is stereotactic radiosurgery effective for multiple brain metastases? J Neurosurg 2010; 113 Suppl: 73–8.
101. Yamamoto M, Kawabe T, Sato Y, et al. Stereotactic radiosurgery for patients with multiple brain metastases: a case-matched study comparing treatment results for patients with 2-9 versus 10 or more tumors. J Neurosurg 2014; 121 Suppl: 16–25.
102. Bhatnagar AK, Flickinger JC, Kondziolka D, Lunsford LD. Stereotactic radiosurgery for four or more intracranial metastases. Int J Radiat Oncol Biol Phys 2006; 64: 898–903.
103. Limon D, McSherry F, Herndon J, et al. Single fraction stereotactic radiosurgery for multiple brain metastases. Adv Radiat Oncol 2017; 2: 555–63.
104. Kim C-H, Im Y-S, Nam D-H, Park K, Kim JH, Lee J-I. Gamma knife radiosurgery for ten or more brain metastases. J Korean Neurosurg Soc 2008; 44: 358–63.
105. Susko MS, Garcia MA, Ma L, et al. Stereotactic Radiosurgery to More Than 10 Brain Metastases: Evidence to Support the Role of Radiosurgery for Ideal Hippocampal Sparing in the Treatment of Multiple Brain Metastases. World Neurosurg 2020; 135: e174–80.
106. Alongi F, Nicosia L, Figlia V, et al. Long-term disease outcome and volume-based decision strategy in a large cohort of multiple brain metastases treated with a mono-isocentric linac-based Stereotactic Radiosurgery technique. Clin Transl Oncol 2021; 23: 1561–70.
107. Hughes RT, Masters AH, McTyre ER, et al. Initial SRS for patients with 5-15 brain metastases: results of a multi-institutional experience. Int J Radiat Oncol Biol Phys 2019; 102: S141–2.
108. Jacus MO, Daryani VM, Harstead KE, Patel YT, Throm SL, Stewart CF. Pharmacokinetic Properties of Anticancer Agents for the Treatment of Central Nervous System Tumors: Update of the Literature. Clin Pharmacokinet 2016; 55: 297–311.
109. Berghoff AS, Venur VA, Preusser M, Ahluwalia MS. Immune Checkpoint Inhibitors in Brain Metastases: From Biology to Treatment. Am Soc Clin Oncol Educ Book 2016; 35: e116-e122.
110. Suh JH, Kotecha R, Chao ST, Ahluwalia MS, Sahgal A, Chang EL. Current approaches to the management of brain metastases. Nat Rev Clin Oncol 2020; 17: 279–99.

111. O'Halloran PJ, Gutierrez E, Kalyvas A, et al. Brain Metastases: A Modern Multidisciplinary Approach. Can J Neurological Sci J Can Des Sci Neurologiques 2021; 48: 189–97.
112. Wujanto C, Vellayappan B, Chang EL, Chao ST, Sahgal A, Lo SS. Radiotherapy to the brain: what are the consequences of this age-old treatment? Ann Palliat Medicine 2020; 0: 36–36.
113. Nieder C, Grosu AL, Gaspar LE. Stereotactic radiosurgery (SRS) for brain metastases: a systematic review. Radiat Oncol Lond Engl 2014; 9: 155–155.
114. Wefel JS, Parsons MW, Gondi V, Brown PD. Neurocognitive aspects of brain metastasis. Handb Clin Neurol 2018; 149: 155–65.
115. Lehrer EJ, Jones BM, Dickstein DR, et al. The Cognitive Effects of Radiotherapy for Brain Metastases. Frontiers Oncol 2022; 12: 893264.
116. Shen CJ, Kummerlowe MN, Redmond KJ, Rigamonti D, Lim MK, Kleinberg LR. Stereotactic Radiosurgery: Treatment of Brain Metastasis Without Interruption of Systemic Therapy. Int J Radiat Oncol Biology Phys 2016; 95: 735–42.
117. Zeng KL, Raman S, Sahgal A, et al. Patient preference for stereotactic radiosurgery plus or minus whole brain radiotherapy for the treatment of brain metastases. Ann Palliat Med 2017; 6: S155–60.
118. Stiggelbout AM, Pieterse AH, Haes JCJMD. Shared decision making: Concepts, evidence, and practice. Patient Educ Couns 2015; 98: 1172–9.
119. Gärtner FR, Portielje JE, Langendam M, et al. Role of patient preferences in clinical practice guidelines: a multiple methods study using guidelines from oncology as a case. BMJ Open 2019; 9: e032483.
120. Keirns CC, Goold SD. Patient-Centered Care and Preference-Sensitive Decision Making. JAMA 2009; 302: 1805–6.
121. Pace A, Koekkoek JAF, Bent MJ van den, et al. Determining medical decision-making capacity in brain tumor patients: why and how? Neuro-oncology Pract 2020; 7: 599–612.
122. Triebel KL, Gerstenecker A, Meneses K, et al. Capacity of patients with brain metastases to make treatment decisions. Psychooncology 2015; 24: 1448–55.
123. Gerstenecker A, Meneses K, Duff K, Fiveash JB, Marson DC, Triebel KL. Cognitive predictors of understanding treatment decisions in patients with newly diagnosed brain metastasis. Cancer 2015; 121: 2013–9.
124. Gerstenecker A, Duff K, Meneses K, Fiveash JB, Nabors LB, Triebel KL. Cognitive Predictors of Reasoning through Treatment Decisions in Patients with Newly Diagnosed Brain Metastases. J Int Neuropsychol Soc 2015; 21: 412–8.
125. Grinsven EE van, Nagtegaal SHJ, Verhoeff JJC, Zandvoort MJE van. The Impact of Stereotactic or Whole Brain Radiotherapy on Neurocognitive Functioning in Adult Patients with Brain Metastases: A Systematic Review and Meta-Analysis. Oncol Res Treat 2021; 44: 622–36.
126. Harvey PD. Domains of cognition and their assessment. Dialogues Clin Neurosci 2019; 21: 227–37.
127. Cristofori I, Cohen-Zimerman S, Grafman J. Chapter 11 Executive functions. Handb Clin Neurology 2019; 163: 197–219.
128. Lezak MD, Howieson DB, Loring DW, Fisher JS. Neuropsychological assessment. New York: Oxford University Press; 2004.
129. Kurashige H, Kaneko J, Yamashita Y, et al. Revealing Relationships Among Cognitive Functions Using Functional Connectivity and a Large-Scale Meta-Analysis Database. Front Hum Neurosci 2020; 13: 457.
130. Meyers CA, Wefel JS. The use of the mini-mental state examination to assess cognitive functioning in cancer trials: no ifs, ands, buts, or sensitivity. J Clin Oncol 2003; 21: 3557–8.
131. Bent MJ van den, Wefel JS, Schiff D, et al. Response assessment in neuro-oncology (a report of the RANO group): assessment of outcome in trials of diffuse low-grade gliomas. Lancet Oncol 2011; 12: 583–93.
132. Wefel JS, Vardy J, Ahles T, Schagen SB. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. Lancet Oncol 2011; 12: 703–8.
133. Witgert ME, Meyers CA. Neurocognitive and Quality of Life Measures in Patients with Metastatic Brain Disease. Neurosurgery Clinics of North America 2011; 22: 79–85.

134. Calamia M, Markon K, Tranel D. Scoring higher the second time around: meta-analyses of practice effects in neuropsychological assessment. Clin Neuropsychol 2012; 26: 543–70.
135. Pendergrass JC, Targum SD, Harrison JE. Cognitive Impairment Associated with Cancer: A Brief Review. Innovations Clin Neurosci 2018; 15: 36–44.
136. Meyers CA, Smith JA, Bezjak A, et al. Neurocognitive Function and Progression in Patients With Brain Metastases Treated With Whole-Brain Radiation and Motexafin Gadolinium: Results of a Randomized Phase III Trial. J Clin Oncol 2004; 22: 157–65.
137. Tucha O, Smely C, Preier M, Lange KW. Cognitive deficits before treatment among patients with brain tumors. Neurosurgery 2000; 47: 324–33; discussion 333-4.
138. Hardy SJ, Krull KR, Wefel JS, Janelsins M. Cognitive Changes in Cancer Survivors. Am Soc Clin Oncol Educ Book 2018; 38: 795-806.
139. Dyk KV, Ganz PA. Cancer-Related Cognitive Impairment in Patients With a History of Breast Cancer. JAMA 2021; 326: 1736–7.
140. Cramer CK, Cummings TL, Andrews RN, et al. Treatment of Radiation-Induced Cognitive Decline in Adult Brain Tumor Patients. Curr Treat Options Oncol 2019; 20: 42.
141. Schagen SB, Tsvetkov AS, Compter A, Wefel JS. Cognitive adverse effects of chemotherapy and immunotherapy: are interventions within reach? Nat Rev Neurol 2022; 18: 173–85.
142. Huntoon K, Anderson SK, Ballman KV, et al. Association of Circulating Markers with Cognitive Decline After Radiation Therapy for Brain Metastasis. Neuro-oncol 2022. Dec 6:noac262. Epub ahead of print.
143. Stern Y. Cognitive reserve. Neuropsychologia 2009; 47: 2015–28.
144. Gehring K, Taphoorn MJB, Sitskoorn MM, Aaronson NK. Predictors of subjective versus objective cognitive functioning in patients with stable grades II and III glioma. Neuro-oncology Pract 2015; 2: 20–31.
145. Országhová Z, Mego M, Chovanec M. Long-Term Cognitive Dysfunction in Cancer Survivors. Frontiers Mol Biosci 2021; 8: 770413.
146. Weijst L van der, Lievens Y, Surmont V, Schrauwen W. Neurocognitive functioning following lung cancer treatment: The PRO-Long Study. Tech Innovations Patient Support Radiat Oncol 2022; 21: 36–40.
147. Hutchinson AD, Hosking JR, Kichenadasse G, Mattiske JK, Wilson C. Objective and subjective cognitive impairment following chemotherapy for cancer: A systematic review. Cancer Treat Rev 2012; 38: 926–34.
148. Li J, Bentzen SM, Li J, Renschler M, Mehta MP. Relationship Between Neurocognitive Function and Quality of Life After Whole-Brain Radiotherapy in Patients With Brain Metastasis. Int J Radiat Oncol Biol Phys 2008; 71: 64–70.
149. Marotta D, Tucker Z, Hayward EN, et al. Relationship between cognitive functioning, mood, and other patient factors on quality of life in metastatic brain cancer. Psycho Oncol 2020; 29: 1174–84.
150. Greene-Schloesser D, Robbins ME. Radiation-induced cognitive impairment-from bench to bedside. Neuro-oncology 2012; 14 Suppl 4: iv37–44.
151. Turnquist C, Harris BT, Harris CC. Radiation-induced brain injury: current concepts and therapeutic strategies targeting neuroinflammation. Neuro-oncology Adv 2020; 2: vdaa057.
152. Greene-Schloesser D, Robbins ME, Peiffer AM, Shaw EG, Wheeler KT, Chan MD. Radiation-induced brain injury: A review. Front Oncol 2012; 2: 73.
153. Linskey ME, Andrews DW, Asher AL, et al. The role of stereotactic radiosurgery in the management of patients with newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol 2009; 96: 45–68.
154. Brown PD, Ballman KV, Cerhan JH, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC·3): a multicentre, randomised, controlled, phase 3 trial. Lancet Oncol 2017; 18: 1049–60.
155. Welzel G, Fleckenstein K, Schaefer J, et al. Memory function before and after whole brain radiotherapy in patients with and without brain metastases. Int J Radiat Oncol Biol Phys 2008; 72: 1311–8.

156. Johannesen TB, Lien HH, Hole KH, Lote K. Radiological and clinical assessment of long-term brain tumour survivors after radiotherapy. Radiother Oncol 2003; 69: 169–76.

157. Tallet AV, Azria D, Barlesi F, et al. Neurocognitive function impairment after whole brain radiotherapy for brain metastases: actual assessment. Radiat Oncol 2012; 7:77: 1–8.

158. Witlox WJA, Ramaekers BLT, Lacas B, et al. Association of different fractionation schedules for prophylactic cranial irradiation with toxicity and brain metastases-free survival in locally advanced non-small cell lung cancer: a pooled analysis of individual patient data from three randomized trials. Radiother Oncol 2021; 164: 163–6.

159. Crossen JR, Garwood D, Glatstein E, Neuwelt EA. Neurobehavioral sequelae of cranial irradiation in adults: a review of radiation-induced encephalopathy. J Clin Oncol 1994; 12: 627–42.

160. McTyre E, Scott J, Chinnaiyan P. Whole brain radiotherapy for brain metastasis. Surg Neurology Int 2013; 4: S236–44.

161. Zhang W, Jiang W, Luan L, Wang L, Zheng X, Wang G. Prophylactic cranial irradiation for patients with small-cell lung cancer: a systematic review of the literature with meta-analysis. BMC Cancer 2014; 14: 793.

162. Bovi JA. Prevention of Brain Metastases. Front Neurol 2018; 9: 758.

163. Ma X, Zhang Z, Chen X, et al. Prognostic factor analysis of patients with small cell lung cancer: Real□ world data from 988 patients. Thorac Cancer 2021; 12: 1841–50.

164. Belderbos JSA, Ruysscher DKMD, Jaeger KD, et al. Phase 3 Randomized Trial of Prophylactic Cranial Irradiation With or Without Hippocampus Avoidance in SCLC (NCT01780675). J Thorac Oncol 2021; 16: 840–9.

165. Gui C, Chintalapati N, Hales RK, et al. A prospective evaluation of whole brain volume loss and neurocognitive decline following hippocampal-sparing prophylactic cranial irradiation for limited-stage small-cell lung cancer. J Neuro-oncol 2019; 144: 351–8.

166. Simó M, Vaquero L, Ripollés P, et al. Longitudinal Brain Changes Associated with Prophylactic Cranial Irradiation in Lung Cancer. J Thorac Oncol 2016; 11: 475–86.

167. Niccolai LM, Rexer JL. Cognitive Impairment in Lung Cancer and Brain Metastases.Lung Cancer Rehabilitation. 2023; 177–84.

168. Maragkoudakis E, Kouloulias V, Grenzelia M, et al. Impact of Hippocampal Avoidance – Prophylactic Cranial Irradiation in Small Cell Lung Cancer Patients. Cancer Diagnosis Prognosis 2022; 2: 279–84.

169. Grosshans DR, Meyers CA, Allen PK, Davenport SD, Komaki R. Neurocognitive function in patients with small cell lung cancer. Cancer 2008; 112: 589–95.

170. Dios NR de, Couñago F, López JL, et al. Treatment Design And Rationale For A Randomized Trial Of Prophylactic Cranial Irradiation With Or Without Hippocampal Avoidance For SCLC: Premer-Trial On Behalf Of Goecp/Seor- Gicor. Clin Lung Cancer 2018; 19: e693–7.

171. Dios NR de, Couñago F, Murcia-Mejía M, et al. Randomized Phase III Trial of Prophylactic Cranial Irradiation With or Without Hippocampal Avoidance for Small-Cell Lung Cancer (PREMER): A GICOR-GOECP-SEOR Study. J Clin Oncol 2021; 39: 3118–27.

172. Pezzi TA, Fang P, Gjyshi O, et al. Rates of Overall Survival and Intracranial Control in the Magnetic Resonance Imaging Era for Patients With Limited-Stage Small Cell Lung Cancer With and Without Prophylactic Cranial Irradiation. JAMA Netw Open 2020; 3: e201929.

173. Takahashi T, Yamanaka T, Seto T, et al. Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2017; 18: 663–71.

174. Bernhardt D, Hommertgen A, Schmitt D, et al. Whole brain radiation therapy alone versus radiosurgery for patients with 1–10 brain metastases from small cell lung cancer (ENCEPHALON Trial): study protocol for a randomized controlled trial. Trials 2018; 19: 388.

175. Gondi V, Hermann BP, Mehta MP, Tomé WA. Hippocampal dosimetry predicts neurocognitive function impairment after fractionated stereotactic radiotherapy for benign or low-grade adult brain tumors. Int J Radiat Oncol Biol Phys 2012; 83: e487–93.

176. Gondi V, Pugh SL, Tome WA, et al. Preservation of Memory With Conformal Avoidance of the Hippocampal Neural Stem-Cell Compartment During Whole-Brain Radiotherapy for Brain Metastases (RTOG 0933): A Phase II Multi-Institutional Trial. J Clin Oncol 2014; 32: 3810–6.
177. Greene-Schloesser D, Moore E, Robbins ME. Molecular pathways: radiation-induced cognitive impairment. Clin Cancer Res 2013; 19: 2294–300.
178. Monje M, Dietrich J. Cognitive side effects of cancer therapy demonstrate a functional role for adult neurogenesis. Behavioural Brain Research 2012; 227: 376–9.
179. Peiffer AM, Leyrer CM, Greene-Schloesser DM, et al. Neuroanatomical target theory as a predictive model for radiation-induced cognitive decline. Neurology 2013; 80: 747–53.
180. Vatner RE, Niemierko A, Misra M, et al. Endocrine Deficiency As a Function of Radiation Dose to the Hypothalamus and Pituitary in Pediatric and Young Adult Patients With Brain Tumors. J Clin Oncol 2018; 36: 2854–62.
181. Mehta P, Fahlbusch FB, Rades D, Schmid SM, Gebauer J, Janssen S. Are hypothalamic- pituitary (HP) axis deficiencies after whole brain radiotherapy (WBRT) of relevance for adult cancer patients? – a systematic review of the literature. BMC Cancer 2019; 19: 1213.
182. Grigorieva EV. Radiation Effects on Brain Extracellular Matrix. Frontiers Oncol 2020; 10: 576701.
183. Habets EJJ, Dirven L, Wiggenraad RG, et al. Neurocognitive functioning and health-related quality of life in patients treated with stereotactic radiotherapy for brain metastases: a prospective study. Neuro-oncology 2016; 18: 435–44.
184. Chang EL, Wefel JS, Maor MH, et al. A pilot study of neurocognitive function in patients with one to three new brain metastases initially treated with stereotactic radiosurgery alone. Neurosurgery 2007; 60: 277–84.
185. Onodera S, Aoyama H, Tha KK, et al. The value of 4-month neurocognitive function as an endpoint in brain metastases trials. J Neurooncol 2014; 120: 311–9.
186. Kirkpatrick JP, Wang Z, Sampson JH, et al. Defining the Optimal Planning Target Volume in Image-Guided Stereotactic Radiosurgery of Brain Metastases: Results of a Randomized Trial. Int J Radiat Oncol Biology Phys 2015; 91: 100–8.
187. Meer PB van der, Habets EJJ, Wiggenraad RG, et al. Individual changes in neurocognitive functioning and health-related quality of life in patients with brain oligometastases treated with stereotactic radiotherapy. J Neurooncol 2018; 139: 359–68.
188. Marko NF, Weil RJ. Radiotherapy: Neurocognitive considerations in the treatment of brain metastases. Nat Rev Clin Oncol 2010; 7: 185–6.
189. Hanssens P, Karlsson B, Yeo TT, Chou N, Beute G. Detection of brain micrometastases by high-resolution stereotactic magnetic resonance imaging and its impact on the timing of and risk for distant recurrences. J Neurosurg 2011; 115: 499–504.

2

Cognitive effects of stereotactic radiosurgery in adult patients with brain metastases: A systematic review

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Abstract

Background Stereotactic radiosurgery (SRS) is increasingly applied in patients with brain metastases (BM) and is expected to have fewer adverse effects on cognitive functioning than whole brain radiation therapy (WBRT). Patients with BM are often confronted with a relatively short life expectancy, and the prevention or delay of cognitive decline to maintain quality of life is a clinically highly relevant treatment goal. This review systematically and specifically evaluates the current literature on the cognitive effects of SRS in patients with BM.

Methods Published trials on SRS alone or in combination with WBRT, including objective assessment of cognitive functioning, were identified through a systematic search of the PubMed database up to March 2018.

Results Of the 241 records screened, 14 studies matched the selection criteria: 2 pilot studies, 7 single-group/observational trials (1 study update) and 5 randomized trials (1 secondary analysis).

Conclusions In general, the results show little to no objective cognitive decline up to 4 months after SRS compared with WBRT. However, most trials suffered from methodological limitations that hindered reliable conclusions. Most importantly, few studies investigated the specific cognitive effects of SRS alone or versus WBRT. Furthermore, disentangling the cognitive effects of SRS from the effects of the disease itself and from the effects of other treatments remains very difficult. By presenting this comprehensive review, we aim to encourage researchers to probe deeper into this area and do so in a standardized and methodologically optimal manner. The ultimate objective of this line of research is to inform both doctors and patients more precisely about the cognitive effects they can expect from treatment. This study is expected to improve the quality of decision-making and maximize clinical outcomes for each individual patient.

Introduction

The incidence of brain metastases (BM) is increasing as a result of the growing elderly population, advances in detection with imaging techniques, and (systemic) cancer treatments that prolong life and allow BM to develop [1-3]. Consequently, the number of patients with BM who live long enough (>6 months) to experience radiation-induced brain injury, including cognitive deficits, is increasing rapidly. [4-7] These developments emphasize the importance of objective assessment of cognitive functioning in patients with BM. [6-10]

Concern about the potential late, progressive, and persistent adverse effects of whole brain radiation therapy (WBRT) on cognitive function has substantially changed the management of BM. [1,1,12] These late delayed effects have been well documented and are most pronounced for learning and memory, executive functioning, attention, processing speed, and fine motor control. [13,14] Stereotactic radiosurgery (SRS) allows precise and accurate radiation delivery to the target (BM) only, thereby aiming to prevent cognitive side effects of WBRT. [1,15-17] Although SRS as a sole modality is increasingly employed to treat BM, [1,18] relatively few studies have evaluated cognitive outcomes after SRS. The purpose of this study is to summarize and evaluate available information pertaining to the cognitive side effects of SRS in patients with BM. Published trials on SRS alone or in combination with WBRT, including objective assessment of cognitive functioning, were reviewed. We use the term “SRS” to refer to radiation therapy that is delivered via stereotactic guidance with approximately 1-mm targeting accuracy in 1 to 5 fractions using a linear accelerator, a Gamma Knife, or a particle beam accelerator. [19] Additionally, we will present an overview of ongoing trials in this area of research.

Because patients with BM are often confronted with a relatively short life expectancy, aiming to prevent or delay cognitive decline to maintain quality of life is a clinically highly relevant treatment goal.

Methods

Studies were identified by a systematic search of the PubMed database up to March 2018. Figure 1 is a Preferred Reporting Items for Systematic Reviews and Meta-Analyses [20] flow diagram that shows the number of records identified, included, and excluded and the reasons for exclusions. The search strategy is available in Appendix A. Eligible studies investigated SRS in one of the study arms. Studies on postoperative

SRS were excluded from this review because surgery itself may induce cognitive changes. In addition, surgery may carry the risk of postsurgical seeding. Only prospective, peer-reviewed trials, including a pretreatment neuropsychological assessment (i.e., screening instruments or neuropsychological tests that objectively evaluate cognitive functions) and in the English language were included. Additional literature was found by means of cross-references. Review articles and individual case reports were excluded from this review. In addition, ongoing studies on cognitive outcomes after SRS in patients with (multiple) BM were identified in March 2018 using the database of the U.S. National Institutes of Health (Clinicaltrials.gov) using similar search terms.

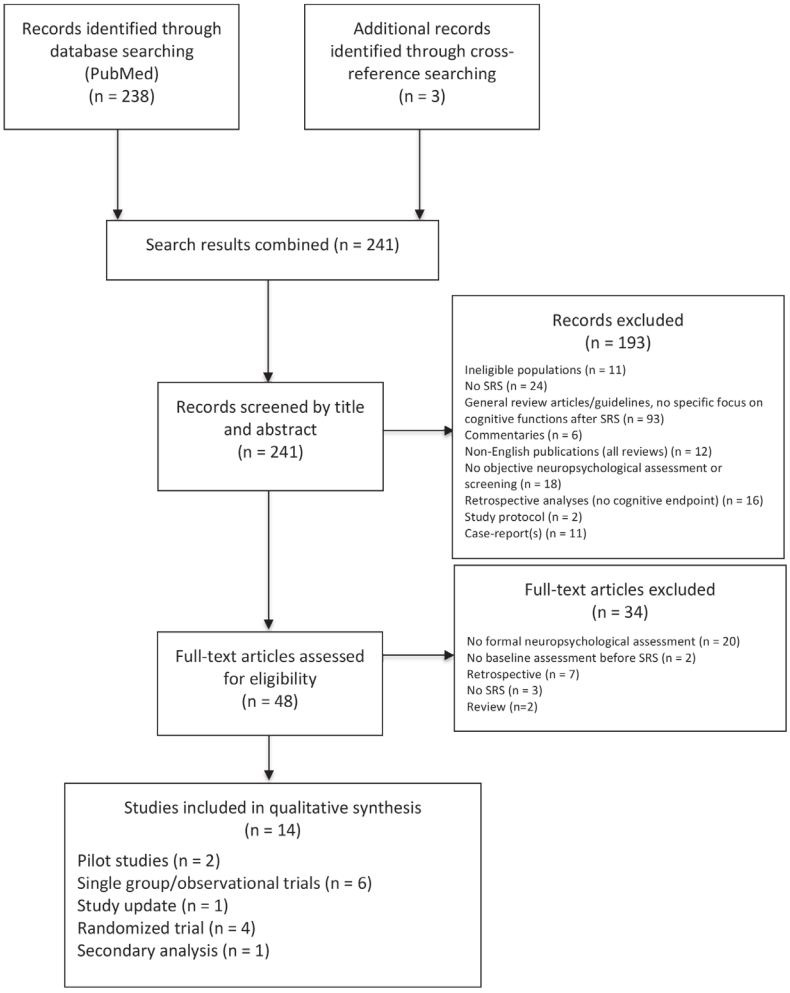

Figure 1. A PRISMA flow diagram illustrating the flow of information through the different phases of the systematic review

Results

The literature search yielded a total of 241 records. After initial screening by title and abstract, 48 articles were analyzed in full text, leaving 14 articles that matched the selection criteria: 2 pilot studies, 7 single-group/observational trials (1 study update), and 5 randomized trials (1 x secondary analyses) including SRS or a combination of WBRT and SRS as treatments under study. We discerned studies that examined the cognitive effects of SRS with formal neuropsychological testing (Table 1) and those that relied on the Mini-Mental State Examination (MMSE) solely (Table 2). In addition, 6 ongoing trials on cognitive outcome after SRS were identified via clinicaltrials.gov (Table 3).

Studies using formal neuropsychological assessment

In a prospective pilot study by Chang et al., fifteen patients with newly diagnosed BM (1-3; ≤4 cm) were treated with SRS only (14-21 Gy). [21] Various cognitive domains were assessed. A reliable change index was used to assess meaningful change in cognitive functioning. Within 1 month after SRS, all 13 patients with follow-up (100%) declined on ≥1 test, and 54% demonstrated decline on ≥2 tests. This was most common for the domains of learning and memory (54%) and motor dexterity (46%). Most improvements were noted in executive function (38%), verbal fluency (15%), motor dexterity (15%), and visual motor scanning (15%).

A second follow-up after 7 months was only possible for 5 longer-term survivors. Four out of five patients demonstrated stability or improvement in learning and memory, 3 patients showed stability or improvement in executive functioning, and 3 demonstrated the same for motor dexterity. These results must be interpreted cautiously because the number of participants and long-term survivors (15 and 5, respectively) was very low.

Following the earlier pilot study, a randomized trial to evaluate the effect of adding WBRT (30 Gy) to SRS (18-24 Gy) on cognitive function in patients with 1 to 3 BM was conducted by Chang et al. [22] Patients (n=58) were randomized into group 1 (SRS followed by WBRT within three weeks; n=28) and group 2 (SRS alone; n=30). The primary endpoint was a significant decline (5-point drop compared with baseline) in Hopkins Verbal Learning Test–Revised (HVLT-R) total recall at 4 months. A reliable change index was used to determine meaningful change.

The trial was halted prematurely because results showed significant Bayesian probability (with 96% confidence) of deterioration on the verbal learning and memory

test at 4 months in patients treated with both modalities, compared to patients treated with SRS only. At 4 months, 7 out of 11 patients (64%) in the SRS+WBRT group versus 4 out of 20 (20%) in the SRS group declined on memory (total recall). This significant difference persisted until 6 months. Patients assigned to SRS+WBRT also demonstrated greater decline in other measures of verbal memory than those in the SRS alone group. The chance of a significant worsening in executive function at 4 months was higher for SRS+WBRT than SRS alone, based on Bayesian probabilities, but this analysis was probably underpowered. After SRS only, despite higher overall survival (OS), patients were at higher risk of developing distant recurrences (DR) and received more subsequent treatment, compared to those treated with SRS+WBRT.

Correspondence in reaction to this trial included comments on the possible imbalance of the study groups. There was a higher disease volume (which negatively correlates to baseline cognitive function), and a tendency at baseline toward a lower cognitive performance in the combined treatment group. [36,37] Moreover, worse cognitive performance at 4 months in patients treated with SRS+WBRT (median OS: 5.7 months) might be explained by their terminal cancer. [36,37]

In a non-randomized pilot study by Onodera et al. patients were treated with either SRS or fractionated stereotactic radiation therapy (SRT; n=7 with 1 or 2 BM) or WBRT (n=20 with ≥3 BM and active systemic disease). [23] A brief neuropsychological test battery assessing memory, semantic fluency and executive functioning, also including the MMSE, was administered at baseline and 4, 8, and 12 months after treatment. No analyses to compare between-group differences of outcome were performed because the groups were not balanced for number of BM or baseline test performance (i.e., significantly better baseline performance in the SRS group). Follow-up neuropsychological test scores (at 4, 8, and 12 months) in the SRS group were available for 5, 4, and 4 patients respectively. There were no within-group changes in test performance over time. Patients in the WBRT group showed a significant decline in delayed memory at 4 months (n=17) and a significant improvement in immediate memory at 8 months (n=14). Long-term survivors in the WBRT group (n=9 with follow-up >12 months), demonstrated significant decline in list recognition at 4 and 12 months and executive functioning at 8 months. The secondary cognitive decline at 12 months, after improvement at 8 months, was attributed to the late adverse effect of WBRT as described in traditional radiation biology literature. [38,39] No significant changes over time were detected by the MMSE or semantic fluency task in either group. The intracranial tumor control rates at 8 months were comparable: 64.3% in the WBRT group and 60% in the SRS group. The results from this non-randomized (and imbalanced) study must be interpreted cautiously because the number of participants was very low.

Patients (n=49) with 1-3 BM (≤4 cm; 80 BM total) without prior intracranial radiation or surgery were eligible to participate in a trial by Kirkpatrick et al. in which individual lesions were randomized to either a 1- or 3- mm expansion of the gross tumor volume, as defined on contrast-enhanced magnetic resonance imaging (MRI; 40 BM in each group) to find an optimal balance between (local) control and toxicity after SRS (linear accelerator: 15-24 Gy). [24] The primary outcome was local recurrence (LR). Secondary outcome measures included cognitive functioning, proportion of radiation necrosis (RN), DR, and OS. LR, RN, and DR were judged based on biopsy test results. Cognitive functioning was measured with the MMSE and Trail Making Test at baseline and 3 months after SRS. There were no significant changes in any cognitive measure of the 24 patients for whom test scores were available. The 12-month local control (LC) rate did not differ significantly between groups. A nonsignificant higher risk of RN in the 3-mm expansion group compared with the 1-mm group was reported. The DR rate and median OS for all patients was 45.7% (median time of development: 9.7 months) and 10.6 months, respectively.

Habets et al. reported on the cognitive functioning of patients with 1 to 4 BM (n=97) measured before and at 3 and 6 months after SRT (18-24 Gy). [15] An extensive neuropsychological test battery was used. Changes in cognitive function over time were analyzed with linear mixed models. Test performance ≥1.5 standard deviation (SD) below the mean of healthy controls (education, age, and sex matched) was defined as cognitive impairment. Additional analyses were performed for 3 (sub)categories: (1) patients with high versus low Karnofsky performance status (KPS; <90 vs ≥90), (2) patients with a large (>12.6 cm3) versus medium (4.8-12.6 cm3) or small (<4.8cm3) total tumor volume, and (3) patients with active versus stable systemic disease status.

Baseline scores were available for 77 patients. At six-month follow-up (n=29), there were no significant changes in domain scores, and only verbal memory showed a trend toward improvement. Patients with lower KPS scores had worse information processing speed and executive functioning and a lower median OS (5.3 vs 11.1 months) than patients with higher KPS scores. Larger tumor volume was negatively associated with information processing speed. The presence of active systemic disease was unexpectedly positively associated with information processing speed and visuo-construction. Executive functioning was negatively associated with tumor progression. Use of steroids did not influence cognitive functioning over time. Intracranial progression occurred in 47 of 90 (52%) patients at follow-up and was attributed solely to DR in 27 patients. Total tumor volume after SRT decreased ≥50% in 25 of 90 (28%) patients. Salvage/subsequent therapy for progression was performed in 20 patients (WBRT: n=13, SRT: n=7).

In a randomized trial by Brown et al., SRS alone (n=111) was compared with SRS+WBRT (n=102) in patients with 1 to 3 BM (<3cm). [25] Cognitive functioning was assessed with a neuropsychological test battery at baseline; before random assignment to treatment; at week 6; and at months 3, 6, 9, 12. A total of 63 and 48 patients in the SRS and SRS+WBRT groups, respectively, completed 3-month assessments. The decline in cognitive functioning (≥1 SD from baseline on ≥1 test) at 3 months was more frequent after SRS+WBRT (91.7%) than after SRS alone (63.5%). The declines were most notable in the domains of immediate recall (SRS+WBRT: 30% vs SRS: 8%), delayed recall (51% vs 20%), and verbal fluency (19% vs 2%).

Such significant differences in decline were also found after 2 post hoc analyses that used 3 definitions of cognitive decline (1.5-SD decline in at least 2 tests, 2-SD or 3-SD decline in 1 test) and included patients who did not complete the 3-month assessment (treating those as experiencing cognitive decline at 3 months). The analyses of differences in mean change from baseline in normalized Z-scores showed a similar disadvantage for the combined group.

In a subgroup of long-term survivors (follow-up >12 months), more patients within the SRS+WBRT arm (n=19) had declined scores (1 SD on at least 1 test) at each subsequent assessment compared to patients in the SRS group (n=15). These differences were significant at 3 and 12 months and were most prominent in the domains of learning and memory, executive functioning, and motor dexterity (information retrieved from supplemental material).

Time to either LR or DR was significantly shorter after SRS compared with SRS+WBRT, and higher intracranial tumor control was achieved after SRS+WBRT at 3 (93.7% vs 75.3%), 6 (88.3% vs 66.1%) and 12 months (84.9% vs 50.5%), but there was no significant median OS difference (10.4 months for SRS vs 7.4 months for SRS+WBRT). Patients received significantly more subsequent treatments after SRS as compared with SRS+WBRT. A recent secondary OS analysis [26] confirmed the authors' initial recommendation of SRS alone with close monitoring for patients with 1 to 3 BM.

Table 1. Studies that evaluated cognitive effects of SRS with formal neuropsychological assessment

Study	Population (n)	Modality (n)	LC (1-yr) / Median OS Neurological death rate (%)	NP tests	Cognitive outcome
Chang et al., 2007 Single group (pilot) [21]	1-3 BM (≤4 cm) NSCLC (8); renal (3); melanoma (4) RPA class II	SRS (n=15) LINAC [¥]	70% / 7.2 mo NA	HVLT-R, COWA, TMT part A+B, WAIS Digit Span and Digit Symbol, GP	Cognitive decline at 1 mo (n=13): 100% on ≥1 test, 54% on ≥2 tests Declines vs Improvements: motor dexterity: 46% vs 15%, learning/mem: 54% vs 8%, EF: 15% vs 38%, visual motor scanning: 23% vs 15%, processing speed: 8% vs 8%, verbal fluency: 15% vs 15%, attention: 8% vs 8% In a subgroup (n=5) alive after 7 mo, 80% had stable/improved scores on memory, 60% on EF and motor dexterity
Chang et al., 2009 Randomized [22]	1-3 BM (≤4 cm) NSCLC (32); breast (8); other (18) RPA class I and II	SRS (n=30) LINAC [¥] SRS+WBRT (n=28) [§]	67% / 15.2 mo 28% 100% / 5.7 mo (*p*=.01) 40%	HVLT-R, COWA, TMT part A+B, WAIS Digit Span and Digit Symbol, GP	Trial halted prematurely: sig larger probability of decline on HVLT-R total recall at 4 mo: 7/11 (SRS + WBRT) vs 4/20 (SRS) Sig diff in posterior probabilities of decline (SRS vs SRS + WBRT): At 4 mo: total recall: 24% vs 52%, delayed recall: 6% vs 22%, delayed recognition: 0% vs 11%. At 6 mo: total recall: 8% vs 28%
Onodera et al., 2014 Pilot study (non-randomized) [23]	1-2 BM (SRS) ≥3 BM (WBRT) Lung (23); breast (1); other (3) RPA class I and II	SRS (n=7) LINAC [^] WBRT (n=20) [^]	60% (at 8 mo) / - (NA) NA 64% (at 8 mo) / - (NA) NA	RBANS list learning, RBANS semantic fluency, TMT A+B, MMSE	SRS group: no change in any test at any time point during FU (n=4 with FU >12 mo), WBRT group: sig decline of delayed mem at 4 mo (n=17), sig improvement in immediate mem at 8 mo (n=14) Sig decline in list recognition scores (at 4 and 12 mo), and TMT B scores (at 8 mo) in n=9 long-term survivors No sig change detected by MMSE in either group

Table 1. Continued

Study	Population (n)	Modality (n)	LC (1-yr) / Median OS Neurological death rate (%)	NP tests	Cognitive outcome
Kirkpatrick et al., 2015 Single group [24]	1-3 BM (<4 cm) NSCLC (25); melanoma (8); other (16) Median GPA: 2	SRS (n=49) LINAC [¥] Randomized per lesion: GTV +1 vs +3 mm	93% / 10.6 mo NA	TMT A+B, MMSE	No sig changes in TMT (A and B) and MMSE scores at 3 mo Median MMSE score at 3 mo: 30 (range 25-30; n=24)
Habets et al., 2016 Single group [15]	1-4 BM (≤4 cm) NSCLC (48); renal (12); other (37) Median KPS: 80	SRS (n=97) LINAC [°]	- (NA) / 7.7 mo (1 yr survival rate: 30%) NA	Auditory Verbal Learning, Rey Complex figure, Stroop, Letter digit modalities, Digit Span, Concept shifting, Word fluency, BADS	No sig changes in domain scores at 3 (n=39) and 6 mo (n=29) Non-sig trend toward improvement in verbal mem Use of steroids did not influence cognition
Brown et al., 2016 Randomized [25,26]	1-3 BM (< 3cm) NSCLC (146); breast (18); other (49) KPS ≥60	SRS (n=111) GK/ LINAC [#] SRS+WBRT (n=102) [#]	50.5% / 10.4 mo NA 84.9% (p<.001) / 7.4 mo (p=.92) NA	HVLT-R, COWA, TMT part A+B, GP	At 3 mo: sig more decline WBRT+SRS vs SRS (91.7% vs 63.5%) for immediate recall (30% vs 8%), delayed recall (51% vs 20%), verbal fluency (19% vs 2%) In a subgroup, alive after 1 yr (n=19 WBRT+SRS; n=15 SRS) more cognitive decline after WBRT+SRS vs SRS at each FU (sig at 3 and 12 mo), mostly in mem, EF, motor dexterity

BADS, Behavioral Assessment of the Dysexecutive Syndrome; BM, brain metastasis; COWA, Controlled Oral Word Association; diff, difference; EF, executive functioning; FU, follow-up; GK, Gamma Knife; GP, grooved pegboard; GPA, graded prognostic assessment; GTV, gross tumor volume; HVLT-R, Hopkins Verbal Learning Test-Revised; KPS, Karnofsky performance status; LC, local control; LINAC, linear accelerator; mem, memory; MMSE, Mini-Mental State Examination; NA, not available/ applicable; neg, negative; NP, neuropsychological; NSCLC, non-small cell lung cancer; OS, overall survival; PTV, planning target volume; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; RPA, recursive partitioning analysis; sig, significant; SRS, stereotactic radiation surgery; TMT, trail-making test; WAIS, Wechsler Adult Intelligence Scale; WBRT, whole brain radiation therapy

Dose and fractionation: [¥] Based on RTOG protocol 90-05 [72]: depending on the volume, a single fraction of 15-24 Gy to the 80% isodose line or higher, covering 99.5-100% of the target. [$] SRS+WBRT arm: WBRT 3 weeks after SRS. WBRT: 30 Gy (12 x 2.5 Gy). [^] SRS: based on largest diameter, a single fraction of 25 Gy for lesions ≤ 1.5 cm, and 28–35 Gy in 4 fractions for larger lesions. WBRT: 35 Gy (14 x 2.5 Gy). [°] PTV was defined as GTV + 2mm margin. The PTV received, depending on the volume and location, a single fraction of 18-21 Gy or 24 Gy in 3 fractions. [#] SRS: depending on the volume, a single fraction of 20-24 Gy to the 50-80% isodose line. SRS+WBRT: a single fraction of 18-22 Gy to the 50-80% isodose line. WBRT: 30 Gy (12 x 2.5 Gy, 2 weeks after SRS).

Studies using the Mini-Mental State Examination

In a randomized trial by Andrews et al., patients with BM (1-3; ≤4 cm) were assigned to WBRT (37.5 Gy) plus SRS boost (15-24 Gy within 1 week; n=164) or WBRT only (n=167). [27] OS was the primary outcome. After 6 months, in the combined treatment group (n=79; data missing for 29 patients [37%]), MMSE scores worsened in 27% of patients, improved in 25%, and remained unchanged in 11%. In the WBRT group (n=75; data missing for 15 patients [20%]), 32% of patients had a decline in MMSE scores, 32% showed improved scores, and 16% had stable scores. These differences were not significant. Significant higher response and LC rates were reported in the WBRT+SRS group. OS did not differ significantly between both groups. There was, however, an OS advantage for patients with a single BM in the SRS boost group.

In 2005, the feasibility of SRS alone (15-24 Gy; n=31) in patients with 1 to 3 BM was investigated in a prospective observational study by Manon et al. [28] The primary outcome was intracranial progression at 3 and 6 months (LR and/or DR). MMSE scores were available for 28 patients at baseline, 20 patients at 3 months, and 5 patients at 6 months. No significant changes in median MMSE scores over time were reported in the 5 patients with available MMSE scores. The median survival time was 8.3 months. The most important causes of death were extracranial (23%), intracranial (19%), and jointly occurring intra- and extracranial (19%) disease. The intracranial progression rates after SRS alone were high (48% at 6 months).

Table 2. Studies evaluating cognitive effects of SRS with the Mini-Mental State Examination *

Study	Population (n)	Modality (n)	LC (1-yr) / Median OS / Neurological death rate (%)	Cognitive outcome
Andrews et al., 2004 Randomized [27]	1-3 BM (≤4 cm) Lung: (211); breast: (34); other: (86) RPA class: I and II	WBRT (n=167) ¥ WBRT + SRS (n=164) LINAC ¥	71% / 6.5 mo / 31% 82% / 5.7 mo (*p*=.14) / 28%	No sig diff in change of MMSE scores at 6 mo: WBRT+SRS (n=79): decline (27%), improvement (25%), no change (11%) WBRT (n=75): decline (32%), improvement (32%), no change (16%)
Manon et al., 2005 Single group [28]	1-3 BM (≤4 cm) Renal: (14); melanoma: (14); sarcoma: (3) KPS ≥50	SRS (n=31) GK/ LINAC ‡	- (NA) / 8.3 mo / 19%	No sig changes in MMSE scores at 3 and 6 mo
Aoyama et al., 2007 Randomized [29,30]	1-4 BM (<3 cm) NSCLC: (88); colorectal: (11); other: (33) RPA class: I and II	SRS (n=67) GK/ LINAC § WBRT + SRS (n=65) §	72.5% / 8.0 mo / NA 88.7% / 7.5 mo (*p*=.42) / NA	No sig diff between groups (n=92): SRS: decline (26%), improvement (50%) WBRT+SRS: decline (39%), improvement (53%)
Aoyama et al., 2015 Secondary analysis of Aoyama et al., 2007 [31]	1-4 BM (<3 cm) NSCLC: (88) post-stratified on DS-GPA Unfavorable DS-GPA (0.5-2): n=41 Favorable DS-GPA (2.5-4): n=47	SRS (n=45) § WBRT + SRS (n=43) §	- (NA) / 8.6 mo / NA - (NA)/ 7.9 mo / NA	No sig diff in MMSE scores between treatment arms (SRS vs WBRT+SRS) in both prognostic groups classified by DS-GPA scores (favorable vs unfavorable prognosis)
Minniti et al., 2013 Single group [32]	1-4 BM (<3.5 cm); NSCLC: (58), breast: (18); other: (28); RPA class: II and III	SRS (n=102) LINAC #	90% / 13.2 mo / 24% 2-yr LC: 84%	At 6 mo (n=71): decline (7%), improvement (17%), no change (72%) At 1 yr (n=45): decline (24%), improvement (31%), no change (33%)
Nakazaki et al., 2013 Single group [33]	1-18 BM: 1-4 BM: (60); 5-10 BM: (8); >10 BM: (8) Lung: (45); colorectal: (8); other: (19) Median KPS: 85	SRS (n=76) GK Δ	- (NA) / 8.8 mo / NA	At 4.1 mo (n=76): decline (20%) At 3.8 mo (n=37 with BL MMSE ≤27): improvement (43%) 6 and 12 mo actuarial free rates of decline: 84% and 79%

Table 2. Continued

Study	Population (n)	Modality (n)	LC (1-yr) / Median OS / Neurological death rate (%)	Cognitive outcome
Yamamoto et al., 2014 Single group / non-randomized [34]	1-10 BM (<3 cm): 1 BM: (455); 2-4 BM: (531); 5-10 BM: (208); Lung: (912); Breast: (123); other: (159) RPA class: I, II and III	SRS (n=1194) GK ^	1 BM: 87.3 % / 13.9 mo 2-4 BM: 93% / 10.8 mo 5-10 BM: 93.5% / 10.8 mo 8%	FU scores available for: 66% (4mo); 69% (1 yr); 68% (2 yr); 92% (3 yr) of surviving patients Decline at 4 mo: 6% (n=662); 1 yr: 9% (n=366); 2 yr: 6% (n=128); 3 yr: 7% (n=30): No sig diff between 2-4 vs 5-10 BM
Yamamoto et al., 2017 Study update of Yamamoto et al., 2014 [35]	1-10 BM (<3 cm): 1 BM: (455); 2-4 BM: (531); 5-10 BM: (208); Lung: (912); Breast: (123); other: (159) RPA class: I, II and III	SRS (n=1194) GK ^	- (NA) / 12 mo / 9%	FU scores available for 66% (4mo); 62% (1 yr); 57% (2 yr); 50% (3 yr); 49% (4 yr) of surviving patients. Decline at 4 mo: 6% (42 of 662); 1 yr: 9% (32/366); 2 yr: 8% (15/185); 3 yr: 6% (6/100); 4 yr: 11% (4/38): No sig diff between 1 vs 2-4 vs 5-10 BM

BM, brain metastasis; diff, difference; FU, follow-up; GPA, graded prognostic assessment; GTV, gross tumor volume KPS, Karnofsky performance status; LC, local control; LINAC, linear accelerator; mem, memory; MMSE, Mini-Mental State Examination; NA, not available/applicable; neg, negative; NP, neuropsychologic; NSCLC, non-small cell lung cancer; OS, overall survival; PTV, planning target volume; RPA, recursive partitioning analysis; sig, significant; SRS, stereotactic radiation surgery; WBRT, whole brain radiation therapy.* Interpretation of MMSE scores: 25-30: No or decreased odds of cognitive impairment, 21-24: Mild cognitive impairment, 10-20: Moderate cognitive impairment, 0-9: Severe cognitive impairment. An increase or decrease of ≥3 points is generally defined as clinically meaningful change.

Dose and fractionation: ¥ Based on RTOG protocol 90-05 [72]: depending on the volume, a single fraction of 15-24 Gy to the 80% isodose line or higher, covering 99.5-100% of the target. SRS 1 week after WBRT. WBRT: 37.5 Gy (15 x 2.5 Gy). ǂ Based on RTOG protocol 90-05 [72]: depending on the volume, a single fraction of 15-24 Gy was prescribed to the isodose line, which encompasses the margin of the metastasis (50-90%, max 100%). $ SRS: depending on the volume, a single fraction of 18-25 Gy to the tumor margin. WBRT+SRS: SRS dose reduced by 30%. WBRT: 30 Gy (10 x 3 Gy). The isodose line nor the coverage was specified in the paper. # PTV = GTV + 1 mm margin. The PTV received, depending on the volume, a single fraction of 16-20 Gy to the 80-90% isodose line. Δ Depending on the volume, a single fraction of 14-24 Gy to that isodose line, covering 99-100% of the target. ^ Depending on the volume and the location, a single fraction of 16-22 Gy to that isodose line, covering 99-100% of the target.

Patients with 1 to 4 BM received treatment with SRS (18-25 Gy; n=67) or WBRT (30 Gy) followed by SRS (n=65) in a randomized trial by Aoyama et al. [29] A Japanese version of the MMSE was used as a primary outcome measure (administered at baseline, 1 and 3 months after treatment, and every 3 months thereafter). Baseline scores were available for 110 patients and did not differ between groups. Follow-up MMSEs were given to 92 patients with a median of 2.5 times. The number of patients in the MMSE analyses was variable because of the use of different criteria for these analyses, considering, for example, ceiling effects (i.e., a person performs at the near maximum level, in which case the MMSE may fail to measure improvement). After a median follow-up time of 5.3 months, 12 of 46 patients in the SRS group declined, and 11 of 22 patients improved. In the WBRT+SRS group, 14 of 36 patients declined, and 9 of 17 patients improved. These proportions did not differ significantly between groups. However, there was a trend for a difference in time until decline in MMSE scores (6.8 months in SRS group vs 13.6 months in WBRT+SRS group), presumably because of a significantly higher DR rate after SRS alone. In 7 patients treated with WBRT+SRS, MRI-determined leukoencephalopathy was observed, versus none in the SRS group. Of these 7 patients, 4 showed a significant deterioration ≥3 MMSE points. There was no significant difference in median OS and 1-year actuarial survival rate. [30] LC was not only found to be an important factor determining OS, but also an important determinant of cognitive stability.

A secondary analysis of the data was published in 2015. [31] Patients were post-stratified by their diagnosis-specific Graded Prognostic Assessment score (0.5-2 is unfavorable prognosis vs 2.5-4 more favorable prognosis). Only patients with non-small cell lung cancer (n=88) were included in this analysis. Patients with an unfavorable prognosis (n=36) had significantly lower baseline MMSE scores compared with patients with a more favorable prognosis (n=34). Separate analyses for these prognostic groups revealed no significant differences in MMSE scores between the 2 treatment arms (SRS vs WBRT+SRS), both at baseline and last follow-up (median duration until last follow-up: 3.6 months). However, for patients with more favorable prognosis, WBRT+SRS was associated with improved OS compared with SRS, presumably because of the preventative effect of WBRT on DR.

Minniti et al. assessed clinical outcomes in elderly patients (>70 years) with 1-4 BM after SRS (16-20 Gy; n=102; median age 77). [32] The MMSE was administered at baseline and at 6 and 12 months. At 6 months, 7% of 68 evaluable patients had worsened scores, 18% had improved scores, and 75% had unchanged scores. At 1 year (40 evaluable patients), 15% of patients showed declines in MMSE scores, 17% showed improvements, and 68% remained stable compared to baseline. In 9

patients, intracranial progression presumably caused the decline in MMSE scores; in 2 patients, the decline was attributed to RN. Severe neurological complications occurred in 7 patients. Because salvage/subsequent treatment with WBRT (n=28) and SRS (n=29) was performed in a substantial number of patients, results must be interpreted carefully.

Nakazaki et al. reported on MMSE scores of patients with multiple BM (1-18) after SRS (14-24 Gy; n=119). [33] Only patients with follow-up scores (n=76) were included in the analyses. Dropout and attrition resulted from systemic deterioration or death (median OS: 2.8 months). After SRS, at a median follow-up of 3.8 months, 43% of patients (16 of 37 patients with baseline MMSE ≤27) showed improvement of at least 3 MMSE points, and 20% of patients had worsened scores (15 of 76 patients; median follow-up: 4.1 months). The actuarial rates of patients free of decline ≥3 points in MMSE scores at 6 and 12 months were 84% and 79%, respectively. Lesion enlargement (n=4) and systemic deterioration (n=4) were the most likely causes of cognitive decline. DR occurred in 39 patients (51%) after treatment, only 2 of these patients (5%) showed a decline of ≥3 MMSE points. In the univariate and multivariate analyses, a larger volume of the largest metastasis (≥3 cm^3) was a significant prognostic factor for improvement of ≥3 points in MMSE scores.

The objective of the JLGK0901 study by Yamamoto et al., a large multi-institutional prospective longitudinal study, was to compare OS (primary endpoint) after SRS (18-24 Gy; n=1,194). [34] Patients were split into groups based on their number of BM (1 vs 2-4 vs 5-10). Except for cumulative tumor volumes (larger in patients with increased numbers of BM), the groups were well balanced at baseline. The percentages of patients who showed declines over time compared with baseline of at least 3 MMSE points at follow-up were 6% (of 662 available) at 4 months, 9% (of 366) at 1 year, 6% (of 128) at 2 years, and 7% (of 30) at 3 years. There were no significant differences between the groups based on number of BM. Most patients (92%) died from extracranial disease. Median OS was significantly longer in patients with a single brain metastasis (13.9 months) compared with patients with either 2 to 4 or 5 to 10 BM (10.8 months in both groups).

These results were recently updated and confirmed. [35] Follow-up was extended with 2 years. MMSE scores of the surviving patients remained stable until 4 years after SRS for 94% (of 100 available patients at 3 years) to 89% (of 38 available patients at 4 years). There were no differences between groups (1 vs 2-4 vs 5-10 BM) when using both complete-case and missing-data analyses. The lack of MMSE data was substantial and occurred in 34% of surviving patients at 4 months to 51% at 4 years

Table 3. Studies in progress evaluating cognitive effects of SRS in patients with brain metastases (identified via Clinicaltrials.gov, March 2018)

Principal Investigator **Trial Identifier**	**Design** **Primary outcome**	**Population**	**Intervention** **Target accrual (N)** **Modality**	**Estimated Primary Completion Date** **Recruitment status**	**NP tests, QOL questionnaires and PROs**
J.L. Li NCT01592968 US	Randomized LC (4 mo) Cognition (HVLT-R at 4 mo)	4-10 non-melanoma BM on dMRI (4-15 BM on pMRI) BM <3.5 cm	SRS (N=50) GK WBRT (N=50)	August 2019 *Recruiting*	NP test battery: HVLT-R, COWA, TMT part A and B, WAIS Digit Span and Digit Symbol, GP QOL/PROs: FACT-Br, Barthel ADL Index, MDASI-BT
P.E.J. Hanssens NCT02953756 The Netherlands	Single arm Cognition	1-10 BM (pMRI) Total tumor volume ≤30 cm^3	SRS (N=100) GK	March 2019 *Active, not recruiting*	NP test battery: HVLT-R, COWA, TMT part A and B, WAIS Digit Span and Digit Symbol, GP QOL/PROs: FACT-Br, HADS, MFI
P.E.J. Hanssens NCT02953717 The Netherlands	Randomized Cognition (HVLT-R at 3 mo)	11-20 BM (pMRI) Total tumor volume ≤30 cm^3	SRS (N=23) GK WBRT (N=23)	March 2019 *Recruiting*	NP test battery: HVLT-R, COWA, TMT part A and B, WAIS Digit Span and Digit Symbol, GP QOL/PROs: FACT-Br, HADS, MFI
P. Lambin NCT02353000 The Netherlands	Randomized QOL (EQ-5D-5L at 3 mo)	4-10 BM (pMRI) Total tumor volume ≤30 cm^3	SRS (N=115) LINAC WBRT (N=115)	April 2018 *Recruiting*	Verbal memory test: HVLT-R QOL/PROs: EQ-5D-5L, EORTC QLQ-C30 + BN20, Barthel ADL Index, QLQ-FA13
S. Rieken NCT03297788 Germany	Randomized Cognition (HVLT-R at 3 mo)	1-10 BM from SCLC	SRS (N=28) WBRT (N=28)	October 2019 *Not yet recruiting*	NP test battery: HVLT-R, CANTAB Test QOL: EORTC QLQ-BN20 +C15-PAL

Table 3. Continued

Principal Investigator Trial Identifier	Design Primary outcome	Population	Intervention Target accrual (N) Modality	Estimated Primary Completion Date Recruitment status	NP tests, QOL questionnaires and PROs
J. Debus NCT03303365 Germany	Randomized (SPACE vs. conventional sequence) New occurrence or progression of >10 BM (12 mo)	1-10 BM (pMRI)	SRS (N=100) SPACE SRS (N=100) CyberKnife	November 2019 *Not yet recruiting*	NP test battery: CANTAB Test QOL: QLQ-C30

ADL, activities of daily living; BM, brain metastasis; CANTAB, Cambridge Neuropsychological Test Automated Battery; COWA, Controlled Oral Word Association; d, diagnostic; diff, difference; EORTC QLQ-C30/BN20/C15-PAL/FA13, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire/Brain Neoplasm Module/Palliative/Cancer Related Fatigue module; EQ-5D-(5L), EuroQol Five Dimensions (Five Levels) Questionnaire; FACT-Br, Functional Assessment Cancer Therapy-Brain; FU, follow-up; GK, Gamma Knife; GP, grooved pegboard; GPA, graded prognostic assessment; GTV, gross tumor volume; HADS, Hospital Anxiety and Depression Scale; HVLT-R, Hopkins Verbal Learning Test-Revised; KPS, Karnofsky performance status; LC, local control; LINAC, linear accelerator; mem, memory; MDASI-BT, MD Anderson Symptom Inventory Brain Tumor Module; MFI, Multidimensional Fatigue Inventory; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; NA, not available/applicable; neg, negative; NP, neuropsychologic; NSCLC, non-small cell lung cancer; OS, overall survival; p, planning; PRO, patient-reported outcome; PTV, planning target volume; QOL, quality of life; RPA, recursive partitioning analysis; SCLC, small cell lung cancer; sig, significant; SPACE, Sampling Perfection with Application optimized Contrasts using different flip angle Evolution; SRS, stereotactic radiation surgery; TMT, trail-making test; WAIS, Wechsler Adult Intelligence Scale; WBRT, whole brain radiation therapy.

because they were treated elsewhere (e.g., hospice care). In 12 patients (1.1%), MRI-determined leukoencephalopathy was observed; 11 of these patients had undergone salvage/subsequent WBRT. For 8 out of these 12 patients, MMSE data were available and showed deterioration ≥3 MMSE points in 2 patients.

Table 4. Neuropsychological tests commonly used in clinical trials in patients with brain metastases (per the International Cancer and Cognition Task Force)

Neuropsychological test	Cognitive domain	Reference
Hopkins Verbal Learning Test - Revised (HVLT-R) Immediate recall Delayed recall Recognition	Verbal learning and memory	Benedict, R. H. B., Schretlen, D., Groninger, L., & Brandt, J. Hopkins verbal learning test - Revised: Normative data and analysis of inter-form and test-retest reliability. Clinical Neuropsychologist. 1998;12(1), 43-55.
Controlled Oral Word Association Test (COWA)	Verbal fluency (Aspect of executive functioning)	Benton AL. Neuropsychological assessment. Annual Review Psychology. 1994;45, 1–23.
Wechsler Adult Intelligence Scale (WAIS IV) Digit Span Digit Symbol-Coding	Working memory/ Attention Information processing speed	Wechsler D. Wechsler adult intelligence scale - Fourth Edition (WAIS–IV). San Antonio. 2008. Sherer M, Scott JG, Parsons OA, Adams RL. Relative sensitivity of the WAIS-R subtests and selected HRNB measures to the effects of brain damage. Arch Clinical Neuropsychology. 1994;9, 427e36.
Trail Making Test Part A Part B	Motor/processing speed Cognitive flexibility (Aspect of executive functioning)	Lezak MD. Neuropsychological Assessment. Oxford University Press, USA; 2004. Tombaugh TN. Trail Making Test A and B: normative data stratified by age and education. Arch Clinical Neuropsychology. Oxford University Press; 2004;19, 203e14.
Lafayette Grooved Pegboard (GP)	Fine motor dexterity	Bryden PJ, Roy EA. A new method of administering the Grooved Pegboard Test: performance as a function of handedness and sex. Brain and Cognition. 2005;58, 258e68.

Studies in progress

We identified 6 ongoing trials that specifically evaluate the cognitive effects of SRS in patients with BM (no prior radiation or surgery for BM, no concomitant targeted therapy): 2 trials of SRS as a sole modality and 4 randomized trials that directly compare (cognitive) outcomes of SRS versus WBRT (Table 3). All study designs included some measure of objective cognitive function as well as patient-reported outcomes such as health-related quality of life, anxiety, depression and fatigue. Three randomized trials by Li, Hanssens and Rieken, are specifically designed to compare changes in cognitive functioning after treatment with either SRS or WBRT in patients with *multiple* (up to 20) BM (with projected sample sizes of 100, 46 and 56 patients, respectively). Results of these trials could help diminish the controversy about the role of SRS alone versus WBRT in the treatment of multiple BM.

Discussion

Over the past decade, the management of patients with BM has changed substantially. [1,40] Concerns about the potential late adverse effects of WBRT on cognitive function has led to decreased use of (adjuvant) WBRT. In comparison with WBRT, SRS has a better ability to spare healthy tissue because of the high level of precision and quick dose fall-off. Therefore, few(er) negative cognitive side effects could be expected after treatment with SRS. [15,41] This review summarizes and evaluates the available evidence pertaining to the cognitive effects of SRS in patients with BM.

Studying cognitive effects of SRS in patients with brain metastases is challenging because, during the course of the disease, cognitive declines may be caused by multiple factors. To their credit, researchers have tried to challenge the numerous obstacles in this field of research. Still, many trials in this review suffered from one or more (methodological) limitations that hinder reliable conclusions about the cognitive effects of SRS. Most importantly, few direct studies have been published that investigate the specific cognitive effects of SRS alone. Neuropsychological limitations in interpretation of findings in this review included absence of or differences in the definition of cognitive change (improvement/decline); lack of control for practice effects (improved performance due to repeated testing over time), which may mask potential cognitive decline; imperfect test-retest reliability; little information about normative data used; and use of different neuropsychological tests. As mentioned, disentangling the cognitive effects of SRS from the effects of systemic disease and treatments [14,33], control of the BM, and the effects of other medications/treatments [42] is very difficult. This holds particularly true for the effects of chemotherapy; a growing

body of literature demonstrates cognitive impairments and associated neurobiological mechanisms resulting from this treatment. [43,44]

Not all studies have recorded or controlled for all these potential confounding factors that may contribute to cognitive decline alongside the effects of SRS, including number, volume, and location of BM; intra- (LR and DR) and extracranial disease progression; edema; systemic and targeted therapies; prior brain surgery or radiation; dose rates and radiation margins; salvage/subsequent therapies; epilepsy; prior neurologic disease; comorbidity; and medication use (e.g., anti-epileptic drugs and dexamethasone). Other (more psychological) factors may also affect cognitive performance (i.e., symptoms of fatigue, anxiety, or depression. Considering these limitations, the conclusions from the reviewed studies must be approached with caution.

In addition to these confounding effects, disease progression, as well as many other medical or psychological factors, may lead to high rates of loss to follow-up. This is reflected in the small number of patients with long-term assessments in the studies that have been reviewed. Limited follow-up and insufficient statistical power also affect our conclusions; as a result, the generalizability of some studies is limited as a result of small sample sizes and (very) small numbers of longer-term survivors (which is inevitable considering this patient population is still predominantly treated with palliative intent). Although the higher performance status of patients who are able and willing to take part in these long-term assessments may cause a bias toward better long-term cognitive functioning, it should be noted that these results are particularly relevant to and applicable for this small but increasing number of long-term survivors.

Despite these limitations, the studies that have been reviewed show evidence for (little) objective cognitive decline using a formal test battery (i.e., not MMSE) in the early phase after treatment with SRS, in learning and memory, motor dexterity, and executive functioning (at 1, 3, or 4 months after SRS depending on the follow-up schedule), potentially followed by a trend toward improvement or stability up to 12 months after SRS [21], although 3 of 6 studies found no changes in cognitive performance at up to 3 (n=24), 6 (n=29), or 12 months (n=4) of follow-up. [15,23,24] However, the addition of WBRT after SRS resulted in significantly more objective cognitive decline over time. [22,25]

Although higher intracranial tumor control rates were achieved with the addition of WBRT after SRS, no OS benefits were gained. [22,25] A recently published trial by Brown et al. also showed significantly more objective cognitive decline after WBRT than SRS in patients with *resected* brain metastases and no OS difference between the treatment groups (trial not reviewed because studies on postoperative SRS were excluded). [45]

Studies that used the MMSE instead of formal neuropsychological testing demonstrated that improvement or stability occurred more often than a decline in MMSE scores after treatment with SRS only. [28,29,32-34] The addition of SRS to WBRT in patients with 1 to 3 BM did not result in significant differences in change of MMSE scores (vs WBRT alone). [27] However, the MMSE is an insensitive an inaccurate measure for cognitive change after radiotherapy [46,47], and results are prone to a possible bias by ceiling effects. [48] To illustrate, the MMSE scores reported in the reviewed studies were already very high at baseline, which left little room for actual improvement. The study by Onodera et al., included both a formal neuropsychological battery and the MMSE and showed significant changes in neuropsychological test scores, including learning and memory impairment after WBRT, but this change was not detected by the MMSE (nor fluency task) in the study. [23]

The International Cancer and Cognition Task Force (ICCTF) recommends the use of a standardized neuropsychological test battery (Table 4). [49] These tests have demonstrated sensitivity to the neurotoxic effects of cancer treatment in other clinical trials. [21,22,25,50,51] The cognitive domains evaluated include memory, attention, executive functions (i.e., working memory and processing speed), motor dexterity, and psychomotor speed. The memory test (Hopkins Verbal Learning Test-Revised) has alternate forms to minimize the effects of repeated administration. Measures of motor and information processing speed are relatively resistant to the effects of practice. [52] Authorized translations are available in many languages and (American) normative data are available that take age into account, as well as education, sex, and handedness, where appropriate. [53,54]

Over recent years, major improvements have been made in the efficacy of systemic therapies, including molecularly/genetically targeted therapies (e.g., tyrosine kinase inhibitors) and immune checkpoint inhibitors. The combination of SRS and these targeted agents aim to improve (primary) tumor control and OS of patients with BM while minimizing cognitive impairment (limiting the use of WBRT). [1,5,55-57] The combination of SRS and immunotherapy is promising because radiation therapy may enhance both local and systemic anti-tumor immune responses. [58-60] However, the safety (neurotoxicity), dosage, and timing/scheduling of concurrent immunotherapy with SRS remains a topic of research [61,62] and prospective randomized trials including standardized neuropsychological assessments are needed to investigate the effects of these targeted therapies in combination with SRS on cognitive functions in patients with BM. [63,64]

Drugs that slow the cognitive decline of patients with BM and those that protect neurons during radiation treatment are a current topic of research. Radiation can result in a chronic inflammatory response that influences hippocampal cell proliferation, which has stimulated interest in trials using anti-inflammatory agents to prevent radiation injury. In addition, research has shown that damage to the hippocampus that is caused by radiation can lead to impairments in learning, (short-term) memory, and spatial processing. [65,66] By avoiding the hippocampal neural stem cells during WBRT, cognitive decline might be prevented or minimized. [67]

Effective treatment with the fewest negative cognitive side effects is increasingly becoming important because more patients with BM live longer after treatment, and persistent radiation-induced cognitive impairment particularly concerns longer-term survivors. To illustrate, approximately 20% of patients in the longer-term follow-up study by Yamamoto et al. survived for >3 years after SRS. [35] However, tumor progression (LR and DR) may negatively affect cognitive functions. Although there is a higher risk of DR after SRS compared with WBRT [22,25,28,29,68,69], the period of time during which WBRT can prevent the development of new BM is limited (approximately 6 to 8 months). [30,70] In addition, prophylactic WBRT results in worse cognitive outcomes than withholding WBRT (observation only) and experiencing a higher amount of intracranial progression (and no OS difference). [71] In the short term, patients with BM may benefit from the *preventive* effect of WBRT (lower DR rate); in the long term, surviving patients may experience the late adverse effect of WBRT on cognition. For patients to whom preservation of cognitive functioning is important, SRS with active surveillance and if necessary subsequent SRS for new BM might be the preferred management compared with WBRT. Neuropsychological assessment, especially assessment of longer-term functioning of patients treated for (multiple) brain metastases remains an important part of the evaluation of treatment success.

Most of the studies reviewed (12 of 14) were published within the last decade, which suggests a growing awareness of the possible cognitive (side) effects of radiation and the clinical significance of their impact on quality of life. With several trials underway, specifically designed to define the cognitive effects of SRS in patients with BM, our knowledge on cognitive outcome of SRS is progressing steadily. Ultimately, the purpose of this line of research is to inform individual patients with BM more precisely about the cognitive effects they can expect from treatment and to assist both doctors and patients in making (shared) individual treatment decisions.

Appendix A. Search strategy

Search carried out on March 1, 2018

PICO process

Patient/population:	Patients with brain metastases
Intervention:	Stereotactic radiosurgery (SRS)
Comparison/control:	Not applicable
Outcome:	Cognitive functioning

PubMed

((((((((("Brain neoplasms/secondary"[MeSH]) OR "Neoplasm Metastasis/radiotherapy"[Mesh]) OR "Neoplasm Metastasis/secondary"[MeSH]) OR "Neoplasm Metastasis/psychology"[MeSH]) OR "Neoplasm Metastasis/radiation effects"[MeSH]) OR "Infratentorial Neoplasms/secondary"[MeSH]) OR Brain metastas*[tiab])))

AND

((((((((((((((((((((("Radiosurgery"[MeSH]) OR Radiosurgery[tiab]) OR Stereotactic radiosurgery[tiab]) OR stereotactic[tiab]) OR SRS[tiab]) OR SRT[tiab]) OR Gamma Knife[tiab]) OR Gamma-Knife[tiab]) OR Gamma Knife Radiosurgery[tiab]) OR GKRS[tiab]) OR GK[tiab]) OR GKS[tiab]) OR CyberKnife radiosurgery[tiab]) OR Linear Accelerator radiosurgery[tiab]) OR Fractionated radiotherapy[tiab]) OR Advanced radiosurgery[tiab]) OR LINAC radiosurgery[tiab]) OR LINAC[tiab]) OR Linear Accelerator[tiab]) OR Tomo Therapy[tiab]) OR TomoTherapy[tiab]) OR Tomo[tiab])))

AND

((((((((((((((((((((((((((((((((((("Executive Function"[Mesh]) OR "Attention"[MESH]) OR "Memory"[MESH]) OR "Problem Solving"[MESH]) OR "Verbal Learning"[Mesh]) OR "Neuropsychology"[Mesh]) OR "psychological Tests"[Mesh]) OR "Word Association Tests"[Mesh]) OR "Neurologic Examination/psychology"[Mesh]) OR "Educational Measurement/psychology"[Mesh]) OR Neurocognit*[tiab]) OR Cognit*[tiab]) OR MMSE[tiab]) OR Minimental state examination[tiab]) OR Minimental state[tiab]) OR Mini mental status examination[tiab]) OR Mild Cognitive Impairment[tiab]) OR Executive Function[tiab]) OR Attention[tiab]) OR Memory[tiab]) OR Problem Solving[tiab]) OR Verbal Learning[tiab]) OR Neuropsycholog*[tiab]) OR Neuropsychological Tests[tiab]) OR Word Association Tests[tiab]) OR Neurologic Examination/psychology[tiab]) OR Educational Measurement/psychology[tiab]) OR Hopkins Verbal Learning Test[tiab]) OR HVLT[tiab]) OR Hopkins Verbal Learning Test Revised[tiab]) OR HVLT-R[tiab]) OR TMT[tiab]) OR Trail making test[tiab]) OR COWA[tiab]) OR Controlled oral word association[tiab]) OR Pegboard[tiab]) OR Digit span[tiab]) OR Digit symbol[tiab]) OR WAIS[tiab]) OR Weschler*[tiab] OR WMS[tiab]) OR Stroop[tiab]))

Additional searches

Reference lists of earlier reviews on SRS and/or WBRT. References of the included primary studies.

References

1. Arvold ND, Lee EQ, Mehta MP, et al. Updates in the management of brain metastases. Neuro Oncol. 2016;18:1043-1065.
2. Lippitz B, Lindquist C, Paddick I, Peterson D, O'Neill K, Beaney R. Stereotactic radiosurgery in the treatment of brain metastases: The current evidence. Cancer Treat Rev. 2014;40:48-59.
3. Tabouret E, Chinot O, Metellus P, Tallet A, Viens P, Gonçalves A. Recent trends in epidemiology of brain metastases: An overview. Anticancer Res. 2012;32:4655-4662.
4. Chao ST, Barnett GH, Liu SW, et al. Five-year survivors of brain metastases: A single-institution report of 32 patients. Int J Radiat Oncol Biol Phys. 2006;66:801-809.
5. Cochran DC, Chan MD, Aklilu M, et al. The effect of targeted agents on outcomes in patients with brain metastases from renal cell carcinoma treated with Gamma Knife surgery. J Neurosurg. 2012;116:978-983.
6. Greene-Schloesser D, Robbins ME. Radiation-induced cognitive impairment-from bench to bedside. Neuro Oncol. 2012;14:iv37-iv44.
7. Greene-Schloesser D, Robbins ME, Peiffer AM, Shaw EG, Wheeler KT, Chan MD. Radiation-induced brain injury: A review. Front Oncol. 2012;2:73.
8. Meyers CA, Rock EP, Fine HA. Refining endpoints in brain tumor clinical trials. J Neurooncol. 2012;108:227-230.
9. Suh JH. Stereotactic radiosurgery for the management of brain metastases. N Engl J Med. 2010;362:1119-1127.
10. Witgert ME, Meyers CA. Neurocognitive and quality of life measures in patients with metastatic brain disease. Neurosurg Clin N Am. 2011;22:79-85.
11. Dhakal S, Peterson CRI, Milano MT. Radiation therapy in the management of patients with limited brain metastases. Am J Clin Oncol. 2014;37:208-214.
12. McTyre E, Scott J, Chinnaiyan P. Whole brain radiotherapy for brain metastasis. Surg Neurol Int. 2013;4:S236-S244.
13. Ellis TL, Neal MT, Chan MD. The role of surgery, radiosurgery and whole brain radiation therapy in the management of patients with metastatic brain tumors. Int J Surg Oncol. 2012;2012:1-10.
14. Tallet AV, Azria D, Barlesi F, et al. Neurocognitive function impairment after whole brain radiotherapy for brain metastases: Actual assessment. Radiat Oncol. 2012;7:77.
15. Habets EJJ, Dirven L, Wiggenraad RG, et al. Neurocognitive functioning and health-related quality of life in patients treated with stereotactic radiotherapy for brain metastases: A prospective study. Neuro Oncol. 2016;18:435-444.
16. Platta CS, Khuntia D, Mehta MP, Suh JH. Current treatment strategies for brain metastasis and complications from therapeutic techniques. Am J Clin Oncol. 2010;33:398-407.
17. Tsao M, Xu W, Sahgal A. A meta-analysis evaluating stereotactic radiosurgery, whole-brain radiotherapy, or both for patients presenting with a limited number of brain metastases. Cancer. 2011; 118:2486-2493.
18. Lin X, DeAngelis LM. Treatment of brain metastases. J Clin Oncol. 2015;33:3475.
19. Barnett GH, Linskey ME, Adler JR, et al. Stereotactic radiosurgery – an organized neurosurgery - sanctioned definition. J Neurosurg. 2007;106:1-5.
20. Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. J Clin Epidemiol. 2009;62:1006-1012.
21. Chang EL, Wefel JS, Maor MH, et al. A pilot study of neuro-cognitive function in patients with one to three new brain metastases initially treated with stereotactic radiosurgery alone. Neurosurgery. 2007;60:277-283.
22. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: A randomised controlled trial. Lancet Oncol. 2009;10:1037-1044.

23. Onodera S, Aoyama H, Tha KK, et al. The value of 4-month neurocognitive function as an endpoint in brain metastases trials. J Neurooncol. 2014;120:311-319.
24. Kirkpatrick JP, Wang Z, Sampson JH, et al. Defining the optimal planning target volume in image-guided stereotactic radiosurgery of brain metastases: Results of a randomized trial. Int J Radiat Oncol Biol Phys. 2015;91:100-108.
25. Brown PD, Jaeckle K, Ballman KV, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases. JAMA. 2016;316:401-409.
26. Churilla TM, Ballman KV, Brown PD, et al. Stereotactic radiosurgery with or without whole-brain radiation therapy for limited brain metastases: A secondary analysis of the North Central Cancer Treatment Group N0574 (Alliance) randomized controlled trial. Int J Radiat Oncol Biol Phys. 2017;99:1173-1178.
27. Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: Phase III results of the RTOG 9508 randomised trial. Lancet. 2004;363:1665.
28. Manon R, O'Neill A, Knisely J, et al. Phase II trial of radiosurgery for one to three newly diagnosed brain metastases from renal cell carcinoma, melanoma, and sarcoma: An Eastern Cooperative Oncology Group study (E 6397). J Clin Oncol. 2005; 23:8870-8876.
29. Aoyama H, Tago M, Kato N, et al. Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. Int J Radiat Oncol Biol Phys. 2007;68:1388-1395.
30. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases. JAMA. 2006;295:2483-2491.
31. Aoyama H, Tago M, Shirato H. Stereotactic radiosurgery with or without whole-brain radiotherapy for brain metastases. JAMA Oncol. 2015;1:457-458.
32. Minniti G, Esposito V, Clarke E, et al. Stereotactic radiosurgery in elderly patients with brain metastases. J Neurooncol. 2013;111: 319-325.
33. Nakazaki K, Kano H. Evaluation of mini-mental status examination score after Gamma Knife radiosurgery as the first radiation treatment for brain metastases. J Neurooncol. 2013;112:421-425.
34. Yamamoto M, Serizawa T, Shuto T, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): A multi- institutional prospective observational study. Lancet Oncol. 2014; 15:387-395.
35. Yamamoto M, Serizawa T, Higuchi Y, et al. A multi-institutional prospective observational study of stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901 study update): Irradiation-related complications and long-term maintenance of Mini-Mental State Examination scores. Int J Radiat Oncol Biol Phys. 2017;99:31-40.
36. Mahmood U, Kwok Y, Regine WF, Patchell RA. Whole-brain irradiation for patients with brain metastases: still the standard of care. Lancet Oncol. 2010;11:221-222.
37. Weiss SE, Kelly PJ. Neurocognitive function after WBRT plus SRS or SRS alone. Lancet Oncol. 2010;11:220-221.
38. Dietrich J, Monje M, Wefel J, Meyers C. Clinical patterns and biological correlates of cognitive dysfunction associated with cancer therapy. Oncologist. 2008;13:1285-1295.
39. Soussain C, Ricard D, Fike JR, Mazeron JJ, Psimaras D, Delattre JY. CNS complications of radiotherapy and chemotherapy. Lancet. 2009;374:1639-1651.
40. Soliman H, Das S, Larson DA, Sahgal A. Stereotactic radiosurgery (SRS) in the modern management of patients with brain metastases. Oncotarget. 2016;7:12318-12330.
41. McDuff SGR, Taich ZJ, Lawson JD, et al. Neurocognitive assessment following whole brain radiation therapy and radiosurgery for patients with cerebral metastases. J Neurol Neurosurg Psychiatry. 2013;84:1384-1391.

42. Park HS, James BY, Knisely J, Chiang VL. Outcomes following gamma knife for metastases. In: Mathieu D, ed. Gamma Knife Radiosurgery. London, United Kingdom: InTech; 2011.
43. Monje M, Dietrich J. Cognitive side effects of cancer therapy demonstrate a functional role for adult neurogenesis. Behav Brain Res. 2012;227:376-379.
44. Wefel JS, Kesler SR, Noll KR, Schagen SB. Clinical characteristics, pathophysiology, and management of noncentral nervous system cancer-related cognitive impairment in adults. CA Cancer J Clin. 2015;65:123-138.
45. Brown PD, Ballman KV, Cerhan JH, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC$3): A multicentre, randomised, controlled, Phase 3 trial. Lancet Oncol. 2017;18:1049-1060.
46. Meyers CA, Wefel JS. The use of the mini-mental state examination to assess cognitive functioning in cancer trials: No ifs, ands, buts, or sensitivity. J Clin Oncol. 2003;21:3557-3558.
47. van den Bent MJ, Wefel JS, Schiff D, et al. Response assessment in neuro-oncology (a report of the RANO group): Assessment of outcome in trials of diffuse low-grade gliomas. Lancet Oncol. 2011; 12:583-593.
48. Franco-Marina F, García-González JJ, Wagner-Echeagaray F, et al. The Mini-mental State Examination revisited: Ceiling and floor effects after score adjustment for educational level in an aging Mexican population. Int Psychogeriatr. 2010;22:72-81.
49. Wefel JS, Vardy J, Ahles T, Schagen SB. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. Lancet Oncol. 2011;12:703-708.
50. Brown PD, Pugh S, Laack NN, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. Neuro Oncol. 2013;15:1429-1437.
51. Meyers CA, Smith JA, Bezjak A, et al. Neurocognitive function and progression in patients with brain metastases treated with whole brain radiation and motexafin gadolinium: Results of a randomized phase III trial. J Clin Oncol. 2004;22:157-165.
52. Benedict RH, Zgaljardic DJ. Practice effects during repeated administrations of memory tests with and without alternate forms. J Clin Exp Neuropsychol. 1998;20:339-352.
53. Benedict R, Schretlen D, Groninger L, Brandt J. Hopkins Verbal Learning Test Revised: Normative data and analysis of inter-form and test-retest reliability. Clin Neuropsychol. 1998;12:43-55.
54. Woods SP, Childers M, Ellis RJ, et al. A battery approach for measuring neuropsychological change. Arch Clin Neuropsychol. 2006;21:83-89.
55. Ahmed KA, Stallworth DG, Kim Y, et al. Clinical outcomes of melanoma brain metastases treated with stereotactic radiation and anti-PD-1 therapy. Ann Oncol. 2016;27:434-441.
56. Aly Z, Peereboom DM. Combination of radiotherapy and targeted agents in brain metastasis: An update. Curr Treat Options Neurol. 2016;18:32.
57. Magnuson WJ, Lester-Coll NH, Wu AJ, et al. Management of brain metastases in tyrosine kinase inhibitor-naïve epidermal growth factor receptor-mutant non-small-cell lung cancer: A retrospective multi-institutional analysis. J Clin Oncol. 2017;35. JCO 2016697144-1077.
58. Franceschini D, Franzese C, Navarria P, et al. Radiotherapy and immunotherapy: Can this combination change the prognosis of patients with melanoma brain metastases? Cancer Treat Rev. 2016; 50:1-8.
59. Kotecha R, Miller JA, Venur VA, et al. Melanoma brain metastasis: The impact of stereotactic radiosurgery, BRAFmutational status, and targeted and/or immune-based therapies on treatment outcome. J Neurosurg. 2017;33:1-10.
60. Sharabi AB, Tran PT, Lim M, Drake CG, Deweese TL. Stereotactic radiation therapy combined with immunotherapy: Augmenting the role of radiation in local and systemic treatment. Oncol N Y. 2015; 29:331-340.
61. Rahman R, Cortes A, Niemierko A, et al. The impact of timing of immunotherapy with cranial irradiation in melanoma patients with brain metastases: Intracranial progression, survival and toxicity. J Neurooncol. 2018;7:337-338.
62. Verduin M, Zindler JD, Martinussen HMA, et al. Use of systemic therapy concurrent with cranial radiotherapy for cerebral metastases of solid tumors. Oncologist. 2017;22:222-235.

63. Moraes FY, Taunk NK, Marta GN, Suh JH, Yamada Y. The rationale for targeted therapies and stereotactic radiosurgery in the treatment of brain metastases. Oncologist. 2016;21:244-251.

64. Tallet AV, Dhermain F, Le Rhun E, Noël G, Kirova YM. Combined irradiation and targeted therapy or immune checkpoint blockade in brain metastases: Toxicities and efficacy. Ann Oncol. 2017;28:2962-2976.

65. Correa DD. An update on cognitive functions in patients with brain tumors. Available at: http://www.asco.org. Accessed May 23, 2017.

66. Gondi V, Hermann BP, Mehta MP, Tomé WA. Hippocampal dosimetry predicts neurocognitive function impairment after fractionated stereotactic radiotherapy for benign or low-grade adult brain tumors. Radiat Oncol Biol. 2012;83:e487-e493.

67. Gondi V, Pugh SL, Tomé WA, et al. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): A phase II multi-institutional trial. J Clin Oncol. 2014;32:3810-3816.

68. Kocher M, Soffietti R, Abacioglu U, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: Results of the EORTC 22952-26001 study. J Clin Oncol. 2011;29:134-141.

69. Zindler JD, Slotman BJ, Lagerwaard FJ. Patterns of distant brain recurrences after radiosurgery alone for newly diagnosed brain metastases: Implications for salvage therapy. Radiother Oncol. 2014;112:212-216.

70. McPherson CM, Suki D, Feiz-Erfan I, et al. Adjuvant whole-brain radiation therapy after surgical resection of single brain metastases. Neuro Oncol. 2010;12:711-719.

71. Sun A, Bae K, Gore EM, et al. Phase III trial of prophylactic cranial irradiation compared with observation in patients with locally advanced non-small-cell lung cancer: Neurocognitive and quality- of-life analysis. J Clin Oncol. 2011;29:279-286.

72. Shaw E, Scott C, Souhami L, Dinapoli R, Kline R, Loeffler J, et al. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90-05. Radiation Oncology Biology. 2000;47: 291-298.

3

Cognitive functioning and predictors thereof in patients with 1 to 10 brain metastases selected for stereotactic radiosurgery

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Abstract

Background Information on predictive factors of cognitive functioning in patients with (multiple) brain metastases (BM) selected for radiosurgery may allow for more individual care and may play a role in predicting cognitive outcome after radiosurgery. The aim of this study was to evaluate cognitive performance, and predictors thereof, in patients with 1-10 BM before radiosurgery.

Methods Cognition was measured before radiosurgery using a standardized neuropsychological test battery in patients with 1-10 BM (expected survival >3 months; KPS ≥70; no prior BM treatment). Regression formulae were constructed to calculate sociodemographically corrected z scores. Group and individual cognitive functioning were analyzed. Multivariable regression was used to explore potential predictors.

Results Patients (N=92) performed significantly worse than controls (N=104) on all 11 test variables (medium-large effect sizes for 8 variables). Percentages of impairment were highest for information processing (55.3%), dexterity (43.2%) and cognitive flexibility (28.7%). 62% and 46% of patients had impairments in at least two, or three test variables, respectively. Models including combinations of clinical and psychological variables were predictive of verbal memory, psychomotor speed, information processing and dexterity. Neither number nor volume of metastases predicted patients' test performance.

Conclusions Already before radiosurgery, almost half of the patients suffered from severe cognitive deficits in at least three test variables. At group and individual level, information processing, cognitive flexibility, and dexterity were most affected. These cognitive impairments may impair daily functioning and patients' ability to make (shared) treatment decisions. Both clinical (symptomatic BM; timing of BM diagnosis) and psychological (mental fatigue) characteristics influenced cognitive performance.

Introduction

The incidence of brain metastases (BM) is increasing as a result of the growing elderly population, Stereotactic radiosurgery (SRS) is increasingly applied in patients with brain metastases (BM) as it is expected to cause less cognitive damage than whole brain radiation therapy (WBRT) because it allows precise radiation delivery to the BM only. Patients with newly diagnosed BM who are accepted for SRS alone represent a selective group of patients with a relatively good performance status (Karnofsky Performance Status ≥70) and an expected survival time of at least three months. [1] Nonetheless, before BM treatment, many patients experience cognitive impairments that may be caused by several factors, including the BM itself, medication use, the primary cancer, or side effects of systemic treatment. [2] Thorough assessment and understanding of these impairments is of high relevance because these impairments, e.g., slow processing of information, may negatively affect patients' ability to reason through (shared) medical treatment decisions, daily functioning and ultimately patients' quality of life. [3] In addition, pretreatment neuropsychological assessment is crucial for the evaluation of cognitive changes after SRS. [4]

There have been relatively few studies in patients with newly diagnosed BM who undergo SRS that evaluated (baseline) cognitive functions with objective neuropsychological tests, as opposed to insensitive measures for this purpose such as the Mini-Mental Status Examination (MMSE). [5] Moreover, in reports thereof, baseline test results were not the primary focus and were only (very) briefly discussed. The majority of patients (ranging from 53-67%) in these studies showed mild to severe impairments in at least one cognitive domain. Executive function, verbal learning and memory, dexterity, information processing, and visuoconstruction were the cognitive domains most frequently affected [6-10], which is in line with research in patients with BM in general. [11-15] Previous studies, however, concerned patients with a limited number of BM (1-4) whereas the use of SRS is expanding to patients with multiple (>4) BM. [16-18] More recently, total volume of BM, as opposed to their number, has gained interest as a predictor for outcomes of patients with BM (including overall survival, local control and distant progression of BM). [19-22] However, thus far, only a few studies have examined the relationship between number and volume of BM and (pretreatment) cognitive functioning in patients with BM. In univariate analyses, a larger total volume of BM was suggested to be associated with worse baseline cognitive performance in four studies, including two small pilot studies. [6,8,10,15] The number of BM was however not associated with cognitive performance in these studies, suggesting that cognitive functions are more affected by the total burden of BM than by the number of lesions. [15] To our knowledge only one previous

study explored potential predictors of pretreatment cognition in patients with BM in a multivariable manner. [15] This study showed that total volume of BM was a predictor for baseline cognitive impairment in patients that were randomly assigned to WBRT with or without motexafin gadolinium.

In the current study, we investigated the incidence and severity of cognitive impairments in patients with 1 to 10 BM before Gamma Knife radiosurgery (GKRS). Both number and volume of BM are examined as potential predictors of baseline cognitive functioning. In addition, the role of other clinical variables (including KPS and diagnosis-specific graded prognostic assessment (DS-GPA [23]) and psychological variables, such as fatigue and symptoms of anxiety and depression, known to impact cognitive test performance [24-26], were explored.

Methods

Baseline test data of patients from the ongoing prospective longitudinal observational Cognition and Radiation Study A (CAR-Study A; ClinicalTrials.gov Identifier: NCT02953756) were analyzed. In addition, non-cancer controls were recruited. This study was approved by the Medical Ethics Committee Brabant (file NL53472.028.15/P1515).

Patients

Adult patients were recruited at the Elisabeth-TweeSteden Hospital (ETZ; Tilburg, the Netherlands). Eligibility criteria were previously described by Verhaak et al. [27] Most important inclusion criteria included: 1-10 newly diagnosed BM on a diagnostic or referral MRI-scan from a histologically proven malignant cancer, KPS ≥70, total tumor volume ≤30 cm^3, and expected survival >3 months. Exclusion criteria included: active primary brain tumor, small cell lung cancer, leptomeningeal metastases, or progressive symptomatic systemic disease without further treatment options, prior treatment directed at the BM (e.g., radiation therapy or surgery). Patients were screened by the radiation-oncologist during the first consultation. Neuropsychological assessment (NPA) was performed by a trained neuropsychologist in the morning before treatment.

Non-cancer controls

A normative group of adult non-cancer controls, as previously described by Verhaak et al. [27], were recruited by convenience sampling from the general community and

were selected to be, as much as possible, comparable to the general population and our patient-group, except for the fact that they were not allowed to have (a history of) cancer or severe cerebrovascular disease in the past year. Eligible controls received a study information letter and a medical checklist. All patients and controls signed informed consent before the NPA.

Measures

Medical records were consulted to extract patient characteristics. BM diagnosed >30 days from the diagnosis of the primary tumor were considered metachronous (all other BM were considered synchronous). A well-established test battery [2,28] was used that consisted of six neuropsychological tests, generating 11 test variables. In addition, three questionnaires [29-31] were administered (Table 1). FACT-Br data was not evaluated in this study.

Table 1. Neuropsychological Test Battery Including Questionnaires

Neuropsychological test	Description/Cognitive domain
Hopkins Verbal Learning Test-Revised (HVLT-R)	Verbal memory test (12 target words, 6 parallel versions)
1. HVLT-R immediate recall	Short-term verbal memory span
2. HVLT-R delayed recall	Longer-term verbal memory
3. HVLT-R recognition	Delayed verbal recognition (correct responses minus semantically related and unrelated false-positive errors)
Trail Making Test (TMT)	Test of visual conceptual and visuomotor tracking
4. TMT A	Psychomotor speed
5. TMT B	Cognitive flexibility (aspect of executive functioning)
6. *Controlled Oral Word Association test* (COWA)	Speeded verbal fluency test (requires aspects of executive functioning; 2 parallel versions)
WAIS Digit Span	Forward and backward repetitions of series of digits
7. Digit Span forward	Immediate attention
8. Digit Span backward	Working memory
9. *WAIS Digit Symbol* (Digit Symbol)	Symbol substitution test of information processing speed (requires visuomotor coordination and sustained attention)
Lafayette Grooved Pegboard (GP)	A manipulative dexterity test
10. GP dominant hand	Motor dexterity dominant hand

Table 1. Continued

Neuropsychological test	Description/Cognitive domain
11. GP non-dominant hand	Motor dexterity non-dominant hand
Questionnaire	Description
Hospital and Anxiety and Depression Scale (HADS)	Symptoms of anxiety and depression
Multidimensional Fatigue Inventory (MFI)	Symptoms of General Fatigue, Physical Fatigue, Reduced Activation, Reduced Motivation and Mental Fatigue
Functional Assessment of Cancer Therapy-Brain (FACT-Br)	General quality of life (QOL) questionnaire that reflects symptoms or problems associated with brain malignancies across five scales
WAIS, Wechsler Adult Intelligence Scale.	

Statistical analyses

Descriptive and comparative (Chi-square test; independent samples t-test) analyses were performed with respect to characteristics of patients and controls.

By means of multiple linear regression analyses, that regressed raw cognitive test scores of the control sample on age, sex and educational level, normative formulae were generated. [32] Raw Trails B scores were adjusted for sex, age, educational level and the Trails A score to derive the interference index. Sociodemographically-adjusted z scores were derived: Patients' z score = patient's raw score minus the predicted score divided by the SD of the control sample's residuals. Higher z scores reflect better cognitive performance. To compare cognitive performance between patients and controls, one-tailed one-sample z tests were performed. Patients' mean z scores are equal to Glass' delta effect sizes ($Mean_{Patients}$ - $Mean_{Controls}$ / $SD_{Controls}$ [33]), where .2 = small, .5 = medium, and .8 = large effect. [34]

Impaired cognitive performance was defined as a z-score ≤-1.5. Percentages of patients with impaired performance per test variable, and on one, two or more tests were calculated.

Correlations were explored of patients' cognitive performances with clinical and psychological characteristics. A maximum of three additional predictors with the highest significant (p <.05) correlations were selected per test variable. Hierarchical multiple regression analyses were then performed to regress patients' z scores on the selected predictors. In all models, number (dummy-coded) and volume of BM were entered separately in Block 1. To reduce false discovery rate (FDR) due to multiple

testing, alpha's were corrected per hypothesis, according to the Benjamini-Hochberg method. [35] All statistical analyses were performed with SPSS Statistics 25.0.

Results

Participants' characteristics

In total, 92 patients and 104 controls were included. Patients and controls did not differ in terms of sex, age and education (Table 2). Forty percent of patients had more than three BM and the most common primary tumor was non-small cell lung cancer (NSCLC; 60%). Median total volume of BM was 5.64 cm^3. For 16 patients (17.4%) and 5 controls (4.8%) scores on one or more tests were missing due to: invalid assessment (HVLT-R recognition, TMT), unfamiliarity with the alphabet (TMT), visual problems (TMT, Digit Symbol, GP), and impairments in dexterity (TMT, Digit Symbol, GP).

Group-level cognitive performance

Patients performed significantly worse than non-cancer controls on all 11 test variables with medium to large effect sizes for 8 out of 11 variables (Table 3). Lowest performance was found on measures of psychomotor speed, cognitive flexibility, information processing, and dexterity of both dominant and non-dominant hand.

Individual cognitive performance

Percentages of impairment on all 11 test variables were higher in patients than in non-cancer controls. This difference was statistically significant, except for verbal recognition and attention (Table 3). These percentages were highest for information processing (55.3%), dexterity (43.2%; non-dominant hand) and cognitive flexibility (28.8%). Compared to controls, more patients showed cognitive impairments in more tests (Table 4). Significantly more patients (62% and 46%) than controls (18% and 3%) had an impairment in at least two or three test variables respectively.

Table 2. Characteristics of Patients and Controls

	No. of patients (%)	**No. of controls (%)**	**Test statistic**	***p*-value**
Number of participants	92	104		
Sex				
male	47 (51)	50 (48)	$\chi^2 = 0.18$ [A]	0.67
female	45 (49)	54 (52)		
Age in years, mean±SD (range)	62±10 (31-80)	59±11 (31-87)	$t = 1.53$ [B]	0.13
Educational level				
Low	28 (31)	25 (24)	$\chi^2 = 4.63$ [A]	0.10
Middle	37 (40)	33 (32)		
High	27 (29)	46 (44)		
KPS				
70-80	33 (36)	N/A		
90-100	59 (64)			
DS-GPA				
Class I (3.5-4 points)	8 (9)	N/A		
Class II (2.5-3 points)	33 (35)			
Class III (1.5-2 points)	44 (48)			
Class IV (0-1 points)	7 (8)			
Primary cancer				
Lung (NSCLC)	55 (60)	N/A		
Renal	15 (16)			
Melanoma	12 (13)			
Other	10 (11)			
Number of BM				
1	32 (35)	N/A		
2-4	29 (31)			
5-10	31 (34)			
BM volume by patient (cm^3), median (range)	5.64 (.02-31.15)	N/A		
Timing of BM diagnosis				
Synchronous	28 (30)			
Metachronous	64 (70)			
Extracranial metastases [a]				
Yes	66 (72)	N/A		
No	26 (28)			
BM Symptoms at diagnosis				
Symptomatic	64 (70)	N/A		
Asymptomatic	28 (30)			
Systemic therapy				
No	39 (42)	N/A		
Yes	53 (58)			
Chemotherapy [b]	37 (40)			

Table 2. Continued

	No. of patients (%)	No. of controls (%)	Test statistic	*p*-value
HADS scores [c], mean±SD				
Anxiety subscale	7.3±4.4	4.4±2.8	t = 5.36 [B]	<0.001
Depression subscale	5.7±4.1	3.5±2.9	t = 4.37 [B]	<0.001

Educational level according to Verhage (1964; 7 classes): low = 1-4, middle = 5, high = 6-7
N/A, not applicable; KPS, Karnofsky performance scale; DS-GPA, diagnosis-specific graded prognostic assessment; NSCLC, non-small cell lung cancer; BM, brain metastases [a] Including lymphatic metastases at baseline or before [b] Alone or in combination with other systemic therapies [c] Hospital Anxiety and Depression Scale with two 7-item subscales; range 0-21 points; higher scores indicate more symptoms of anxiety or depression [A] Chi-square test of homogeneity [B] Independent-samples T test.

Predictors of baseline cognitive performance

Supplementary Tables 1 and 2 present the results of the exploratory correlation analyses (Online Resource 1). A metachronous diagnosis of BM (compared to synchronous) was significantly associated with worse performance on 7 out of the 11 test variables. Chemotherapy was significantly negatively correlated with performance on 3 test variables (immediate and delayed memory and psychomotor speed). Mental fatigue was significantly negatively associated with psychomotor speed, information processing, and dexterity. Higher KPS was significantly associated with greater dexterity.

Four additional clinical (KPS; chemotherapy; symptomatic versus asymptomatic BM; timing of BM diagnosis) and four psychological predictors (Reduced Activation; Reduced Motivation; Mental Fatigue; symptoms of depression) were selected for the hierarchical multiple regression analyses. None of the initial regression models with only number and volume of the BM as predictors, nor the predictors themselves, were statistically significant (Table 5). The addition of the clinical and psychological predictors led to a statistically significant increase in explained variance in five models for measures of verbal memory, psychomotor speed, information processing and dexterity. In two models (delayed recognition and information processing), timing of BM diagnosis was the only significant predictor, whereby patients with metachronous BM performed worse. Post hoc descriptive analyses showed that of the patients with a metachronous diagnosis, 44% had NSCLC, 55% received (prior) chemotherapy and 53% had a high KPS of 90-100 (versus 96%, 7% and 89% in the synchronous group, respectively). For immediate verbal memory, symptomatic (versus asymptomatic) BM was a significant predictor, whereby patients with symptomatic BM performed worse. For psychomotor speed, mental fatigue was the only significant predictor in the model, with slower psychomotor speed in patients with more symptoms of mental fatigue. A final significant model did not yield any significant individual predictors (dexterity non-dominant hand).

Table 3. Cognitive performance at group and individual level

Test variables	Group level				Individual level			
	Mean Z Scores of patients versus controls [a]				Impaired performance per test variable [b]			
	z score [d]	z test	*p* value	Effect size [e]	Patients (%)	Controls (%)	χ^{2A}	*p* value
HVLT-R immediate recall	-.52	-4.95	<.001*	-0.52 (medium)	27.2%	4.9%	18.60	<0.001*
HVLT-R delayed recall	-.27	-2.59	.010*	-0.27 (small)	15.2%	4.8%	6.04	0.014*
HVLT-R recognition	-.21	-1.99	.047*	-0.21 (small)	14.3%	8.7%	1.54	0.215
TMT A	-.99	-9.21	<.001*	-0.99 (large)	25.3%	7.7%	11.08	0.001*
TMT B|A [c]	-1.49	-13.35	<.001*	-1.49 (large)	28.8%	5.8%	17.99	<0.001*
COWA	-.63	-6.06	<.001*	-0.63 (medium)	27.2%	7.7%	13.23	<0.001*
Digit Span forward	-.43	-4.10	<.001*	-0.43 (small)	10.9%	5.8%	1.64	0.200
Digit Span backward	-.78	-7.51	<.001*	-0.78 (medium)	22.8%	6.8%	10.15	0.001*
Digit Symbol	-1.49	-13.78	<.001*	-1.49 (large)	55.3%	6.7%	54.05	<0.001*
GP dominant hand	-1.43	-13.42	<.001*	-1.43 (large)	27.3%	6.9%	14.41	<0.001*
GP non-dominant hand	-1.63	-15.25	<.001*	-1.63 (large)	43.2%	5.9%	36.94	<0.001*

HVLT-R, Hopkins verbal learning test revised; TMT, trail making test; COWA, Controlled Oral Word Association; GP, Grooved Pegboard * $p \leq 0.05$ (group-level) and $p \leq 0.04$ (individual-level): alpha was corrected using the Benjamini-Hochberg method [35] [a] One-tailed one-sample z tests (*N controls* = 104; *M* = 0; *SD* = 1; *N patients* = 80-92) [b] Cognitive impairment was defined as a z score ≤ -1.5 (*N patients* = 80-92; *N controls* = 102-104) [c] TMT B|A: Trails B score adjusted for sex, age, educational level and the Trails A score [d] Higher z scores reflect better performance [e] Glass' delta: Interpretable as Cohen's *d* effect sizes: ≥ .20-.49 = small, ≥ .50-.79 = medium, ≥ .9 = large [34] [A] Chi-square test of homogeneity

Table 4. Cognitive performance at the individual level: impairment on one or more test variables [a]

No. of tests	Patients (%) (n=76)	Controls (%) (n=99)	χ^{2b}	*p* value
≥1 test	76.3	43.4	19.05	<.001 [c]
≥2 tests	61.8	18.2	35.10	<.001 [c]
≥3 tests	46.1	3.0	46.81	<.001 [c]
≥4 tests	36.8	3.0	33.72	<.001 [c]
≥5 tests	23.7	0	26.14	<.001 [c]
≥6 tests	14.5	0	15.29	<.001 [c]
≥7 tests	11.8	0	12.36	<.001 [c]
≥8 tests	6.6	0	6.71	0.010 [c]
≥9 tests	0	0	N/A	N/A
≥10 tests	0	0	N/A	N/A
11 tests	0	0	N/A	N/A

[a] Impaired performance (z score ≤-1.5) of patients with complete test scores on all tests. For 16 patients (17.4%) and 5 controls (4.8%) scores on one or more tests were missing due to: invalid assessment (HVLT-R recognition, TMT), unfamiliarity with the alphabet (TMT), visual problems (TMT, Digit Symbol, GP), and impairments in manual dexterity (TMT, Digit Symbol, GP) [b] Chi-square test of homogeneity [c] Statistical significance was considered as $p \leq 0.05$: alpha was corrected according to the Benjamini-Hochberg method [35]

Discussion

In this study we examined the incidence and severity of cognitive impairment, and clinical as well as psychological predictors thereof, in selected patients with 1-10 BM who were accepted for GKRS. Cognitive performance was measured with a well-established neuropsychological test battery. Previous studies on cognitive functioning were focused on patients with 1-4 BM or made use of an insensitive measure to assess cognitive test performance (the MMSE). [5] At group level, we found lowest cognitive test performance (large effect sizes; means that ranged between -1 and -1.6 SD below the normative mean) on measures of psychomotor speed, cognitive flexibility, information processing, and dexterity of both dominant and non-dominant hand. At the individual level, cognitive performance was most frequently impaired with respect to measures of short-term verbal memory span, cognitive flexibility, information processing, and dexterity of both dominant and non-dominant hand. Although at group level, patients performed significantly worse than controls (with small effect sizes) on measures of verbal recognition and immediate attention. At the individual level, however, there were no significant differences in the frequencies of impairment for these two measures. These results are largely in line with previous studies in patients with BM: cognitive impairment in one or more tests before treatment of BM ranged

between 53% and 80% (76% in our sample) and was most clearly demonstrated in the domains of executive functioning (including cognitive flexibility), verbal and visual memory, dexterity and psychomotor speed. [6,7,9,10,36,37]

We noted a degree of impairment in information processing in our study that is higher than in other studies. Some of these studies used different neuropsychological tests, however, both studies by Chang et al. [6,7] used the WAIS Digit Symbol test as well. At baseline, only 7% of their patients showed impaired performance in the pilot study [6] and baseline z scores in the larger randomized trial ranged between -0.1 and -0.4 [7] whereas in our sample, 55% of patients had impaired performance on this test and the mean z score was -1.5. This difference might be explained by differences in the study samples: compared to our study, their sample consisted of patients with fewer (1-3) BM, higher median KPS and lower median total BM volume BM. In addition, although having severe problems with dexterity was one of the exclusion criteria in our study, impairments in dexterity were (highly) prevalent in our patient sample: 27% of patients showed impaired dominant hand dexterity (the mean z score for this measure was -1.43 in our study versus -1.30 in the SRS-arm of Chang et al. 2009). These impairments may have influenced performance on the other measures with high dominant hand motor demands [38] and help explain the poor performance on information processing, psychomotor speed, and cognitive flexibility. The use of (additional) neuropsychological tests with minimal motor requirements should be considered in future trials in this patient population, as the assessment of speed (information processing or psychomotor) is aimed at understanding cognitive rather than physical function. [38]

Multivariable regression was used to examine whether number or volume of BM was predictive of pretreatment cognitive test performance. Neither number nor volume of BM were significant predictors in any of these initial models. Similarly, in previous studies based on univariate analyses, number of BM was not associated with cognitive performance. However, the same studies found negative associations uncorrected for multiple testing between total BM volume and measures of attention, verbal memory, information processing and executive functions. [6,8,10,15] We also found a significant negative univariate association between volume of BM and working memory but in multivariable analyses volume of BM was not a significant predictor of working memory.

Hierarchical multivariable models including clinical as well as psychological variables were predictive of performance on six measures of verbal memory, psychomotor speed, information processing, and dexterity. Timing of BM diagnosis was a significant individual predictor in two out of five significant regression models:

patients with a synchronous (versus metachronous) diagnosis of BM performed better on verbal recognition and had higher information processing (speed). This might be explained by the fact that these patients were still largely treatment-naïve and were in a better overall (higher KPS), and cognitive condition. Patients with a metachronous diagnosis of BM on the other hand, already received various types of systemic treatment, including chemotherapy, for their primary tumor, which may have contributed to the cognitive impairments [39,40] already before the diagnosis of the BM. These (cancer-related) cognitive impairments primarily involve the domains of memory, attention, executive functioning, and processing speed. [41]

Despite the fact that the patients in our study had significantly more symptoms of anxiety and depression than our controls we found no evidence for a direct effect of anxiety and depression on cognitive test performance in our prediction models. This is in line with a previous study in patients with BM and indicates that anxiety and depression may not be (primary) contributors to cognitive impairment in these patients. [37]

Table 5. Multiple hierarchical regression predicting patients' cognitive test performance

Test variable	Model	Predictor	B	*SE* B	p^*	*F(df)*	R^2	ΔR^2	$p^*(\Delta R^2)$
HVLT-R immediate recall	Model 1				0.220	1.50 (3,88)	0.049		
		Number of BM_{Single}	-0.635	0.363	0.084				
		Number of $BM_{5\text{-}10}$	0.023	0.366	0.949				
		Total volume of BM	0.002	0.020	0.922				
	Model 2				**0.011***	2.96 (6,85)	0.173	0.124	0.008*
		Number of BM_{Single}	-0.554	0.353	0.120				
		Number of $BM_{5\text{-}10}$	-0.081	0.352	0.818				
		Total volume of BM	0.014	0.020	0.474				
		Chemotherapy	-0.402	0.319	0.211				
		Symptomatic (y/n)	-0.743	0.318	**0.022***				
		Timing of BM diagnosis	-0.472	0.343	0.173				
HVLT-R delayed recall	Model 1				0.046	2.77 (3,88)	0.086		
		Number of BM_{Single}	-0.540	0.323	0.098				
		Number of $BM_{5\text{-}10}$	0.103	0.326	0.754				
		Total volume of BM	-0.029	0.017	0.102				
	Model 2				**0.013***	3.10 (5,86)	0.153	0.066	0.039*
		Number of BM_{Single}	-0.388	0.320	0.229				
		Number of $BM_{5\text{-}10}$	0.095	0.319	0.766				
		Total volume of BM	-0.030	0.017	0.079				
		Chemotherapy	-0.291	0.290	0.319				
		Timing of BM diagnosis	-0.533	0.308	0.087				
HVLT-R recognition	Model 1				0.426	0.94 (3,87)	0.031		
		Number of BM_{Single}	-0.166	0.356	0.642				
		Number of $BM_{5\text{-}10}$	0.071	0.359	0.844				
		Total volume of BM	-0.028	0.019	0.149				
	Model 2				**0.014***	3.04 (5,85)	0.151	0.120	0.004*
		Number of BM_{Single}	-0.049	0.345	0.888				
		Number of $BM_{5\text{-}10}$	-0.049	0.342	0.887				
		Total volume of BM	-0.019	0.019	0.313				
		Symptomatic (y/n)	-0.568	0.308	0.068				
		Timing of BM diagnosis	-0.790	0.300	**0.010***				

Table 5. Continued

Test variable	Model	Predictor	B	*SE* B	p^*	*F(df)*	R^2	ΔR^2	$p^*(\Delta R^2)$
TMT A	Model 1				0.135	1.91 (3,82)	0.065		
		Number of BM_{Single}	-0.425	.458	0.356				
		Number of BM_{5-10}	0.541	.459	0.242				
		Total volume of BM	-0.025	.025	0.302				
	Model 2				**0.005***0.695	3.42 (6,79)	0.206	0.141	0.005*
		Number of BM_{Single}	-0.172	0.438	0.249				
		Number of BM_{5-10}	0.504	0.433	0.389				
		Total volume of BM	-0.020	0.023	0.154				
		Chemotherapy	-0.572	0.398	0.492				
		Timing of BM diagnosis	-0.299	0.434	**0.021***				
		Mental Fatigue	-0.109	0.046					
TMT B|A	Model 1				0.683	0.501 (3,76)	0.019		
		Number of BM_{Single}	-0.567	0.723	0.435				
		Number of BM_{5-10}	-0.466	0.709	0.513				
		Total volume of BM	-0.028	0.038	0.455				
COWA	Model 1				0.289	1.27 (3,87)	0.042		
		Number of BM_{Single}	-0.515	0.315	0.106				
		Number of BM_{5-10}	-0.058	0.318	0.856				
		Total volume of BM	-0.006	0.017	0.708				
	Model 2				0.091	1.97 (5,85)	0.104	0.062	0.059
		Number of BM_{Single}	-0.419	0.312	0.183				
		Number of BM_{5-10}	-0.036	0.311	0.908				
		Total volume of BM	-0.010	0.017	0.562				
		Timing of BM diagnosis	-0.360	0.275	0.195				
		Reduced Motivation	-0.059	0.033	0.078				
Digit Span forward	Model 1				0.741	0.417 (3,88)	0.014		
		Number of BM_{Single}	0.015	0.240	0.950				
		Number of BM_{5-10}	0.069	0.242	0.777				
		Total volume of BM	-0.014	0.013	0.276				

Table 5. Continued

Test variable	**Model**	**Predictor**	**B**	***SE* B**	***p****	***F(df)***	***R²***	***ΔR²***	***p**(ΔR²)***
Test variable	Model	Predictor	B	*SE* B	*p**	F(*df*)	R^2	ΔR^2	*p**(ΔR^2)
Digit Span backward	Model 1				0.163	1.75 (3,88)	0.083		
		Number of BM_{Single}	-0.128	0.267	0.632				
		Number of $BM_{5\text{-}10}$	-0.144	0.269	0.594				
		Total volume of BM	-0.029	0.014	0.046				
	Model 2				0.108	1.96 (4,87)	0.083	0.026	0.118
		Number of BM_{Single}	-0.167	0.266	0.532				
		Number of $BM_{5\text{-}10}$	-0.188	0.268	0.486				
		Total volume of BM	-0.022	0.015	0.138				
		Symptomatic (y/n)	-0.379	0.240	0.118				
Digit Symbol	Model 1				0.518	0.764 (3,80)	0.028		
		Number of BM_{Single}	0.063	0.343	0.855				
		Number of $BM_{5\text{-}10}$	-0.033	0.353	0.925				
		Total volume of BM	-0.028	0.019	0.150				
	Model 2				**0.010***0.488	3.03 (6,77)	0.191	0.163	0.003*
		Number of BM_{Single}	0.226	0.324	0.859				
		Number of $BM_{5\text{-}10}$	-0.058	0.328	0.210				
		Total volume of BM	-0.023	0.018	**0.037***0.281				
		Timing of BM diagnosis	-0.625	0.295	0.072				
		Mental Fatigue	-0.041	0.038					
		Symptoms of depression	-0.068	0.037					
GP dominant hand	Model 1				0.511	0.78 (3,83)	0.027		
		Number of BM_{Single}	-0.720	0.771	0.353				
		Number of $BM_{5\text{-}10}$	-0.558	0.787	0.480				
		Total volume of BM	-0.038	0.041	0.361				
	Model 2				0.194	1.56 (4,82)	0.070	0.043	0.054
		Number of BM_{Single}	-0.602	0.761	0.431				
		Number of $BM_{5\text{-}10}$	-0.555	0.774	0.475				
		Total volume of BM	-0.030	0.041	0.466				
		Mental Fatigue	-0.152	0.078	0.054				

Table 5. Continued

Test variable	Model	Predictor	B	*SE* B	*p**	*F(df)*	R^2	ΔR^2	*p** (ΔR^2)
GP non-dominant hand	Model 1				0.977	0.07(3,84)	0.002		
		Number of BM_{Single}	-0.238	0.601	0.693				
		Number of $BM_{5\text{-}10}$	-0.238	0.609	0.697				
		Total volume of BM	-0.002	0.032	0.961				
	Model 2				**0.018***0.813	2.73(6, 81)	0.168	0.166	0.002*
		Number of BM_{Single}	-0.137	0.576	0.587				
		Number of $BM_{5\text{-}10}$	-0.312	0.571	0.949				
		Total volume of BM	-0.002	0.030	0.284				
		KPS	0.031	0.029	0.054				
		Timing of BM diagnosis	-01.03	0.526	0.062				
		Reduced Activity	-0.117	0.062					

HVLT-R, Hopkins verbal learning test revised; TMT, trail making test; COWA, Controlled Oral Word Association; GP, Grooved Pegboard; BM, brain metastases; KPS, Karnofsky Performance Index; B, unstandardized regression coefficient; *SE* B, standard error B; *df*,degrees of freedom Coding of predictors: single BM: Number of BM_{single} = 1; 2-4 BM: Number of BM_{single} = 0, Number of $BM_{5\text{-}10}$ = 0, 5-10 BM: Number of $BM_{5\text{-}10}$ = 1; Symptomatic: yes = 1, no/asymptomatic = 0; Timing of BM diagnosis: synchronous = 0, metachronous = 1 *Statistical significance was considered as $p \leq 0.005$ (models 1) and $p \leq 0.03$ (models 2), alpha was corrected according to the Benjamini-Hochberg method [35] and as $p \leq 0.05$ for the individual regression coefficients and change in R^2 per model (bold values indicate a statistically significant result)

Mental fatigue however was predictive of reduced psychomotor speed. Efforts should be continued to investigate specific patient- and tumor-specific factors that can predict cognitive test performance. Identification of these characteristics allow for more individually tailored care for patients. In addition, thorough assessment of cognitive impairment, and understanding of the predictors thereof, is crucial for the evaluation of cognitive changes after SRS. [4]

This study has some limitations to be considered. Our patients had BM originating from various primary tumor histologies. Since prognosis, systemic treatment, and timing of BM may vary with type of primary cancer [42], this might have affected cognitive test performance. However, as most BM originate from lung cancer, lung cancer patients represent the majority of patients with BM, both in clinical practice and in clinical trials (including this study). In addition, we did not examine or take into account the location(s) of the BM. Further study is required to examine the impact of BM location (e.g., supratentorial, cerebellar, brainstem and 'other') on cognitive test performance as cognitive impairment is related to the site of tumor growth. [43] Although we did not find a direct effect of number and volume of BM on cognitive test performance in our relatively large sample of patients with 1-10 BM, it is of interest to investigate whether change (reduction or progression) in number and volume influences change in cognitive test performances after SRS. Li et al. (2007) showed that greater volume reduction in total volume of BM was associated with a delay in cognitive decline after WBRT. [44]

Significant associations between cognitive test performance and daily functional independence have been found in brain tumor patients. [45] This study used mostly the same neuropsychological tests as the current study. Strongest associations were found for executive functioning (TMT B), language comprehension (COWA) and verbal learning and memory (HVLT-R). Patients with BM in our study showed significant impairments in all of these tests. These impairments may cause serious difficulties in day-to-day activities (e.g., daily chores, preparing dinner or communicating with family and friends). For example, patients may experience difficulties with the ability to plan ahead (related to impaired cognitive flexibility), slowness of comprehension and processing of information (related to impaired processing speed), and difficulties in learning and remembering new information (related to functions of memory), and difficulties in performing adequate movements appropriate to a certain task (related to impairments in dexterity and executive functioning). In addition, these difficulties in everyday living may increase the caregiver burden. [45]

Assessment of cognitive deficits is also crucial in understanding patients' ability in weighing the risks (cognitive impairment, distant recurrences, neurotoxicity) and benefits (cognitive preservation, local control, distant control) in coming to a treatment decision (e.g., WBRT, SRS or best supportive care). [46] A previous study indicated that over half of the patients with BM (prior to BM treatment) had a diminished ability to reason through medical treatment decisions [47], this was associated (same study sample) with worse verbal memory and information processing. [48,49] In our sample, 55% (information processing), 27% (immediate verbal memory and verbal fluency) and 23% (working memory) of patients had impairments in these cognitive domains, emphasizing the relevance of pretreatment neuropsychological assessment. Patients at risk may need additional (written) information and guidance through the process of understanding treatment choices. Early detection of these cognitive impairments may facilitate cognitive intervention planning. Intervention (e.g., cognitive rehabilitation programs [50]) at an early stage may benefit the quality of survival in these patients, which is of particular interest for the growing number of (subgroups of) patients with longer expected survival.

Supplementary tables

Supplementary Table 1. Correlations between clinical characteristics and patients' cognitive test performance [a]

	Number of BM	Total volume of BM	KPS	DS-GPA	Systemic therapy (y/n)	Chemo-therapy [c]	Symptomatic / Asymptomatic BM (0/1)	Synchronous / Metachronous dx of BM (0/1)	Epileptic seizures (y/n)	Time from primary cancer diagnosis to enrollment
HVLT-R immediate recall	0.096	-0.011	0.103	0.024	-0.128	**-0.234***	**-0.236***	**-0.284****	-0.155	-0.015
HVLT-R delayed recall	0.154	-0.189	0.067	-0.033	-0.089	**-0.233***	-0.187	**-0.271****	-0.084	-0.032
HVLT-R recognition	0.028	-0.160	0.068	-0.073	-0.132	-0.123	**-0.260***	**-0.299****	-0.052	-0.089
TMT A	0.180	-0.099	0.024	-0.186	-0.123	**-0.301****	0.067	**-0.260***	-0.026	-0.190
TMT B|A [b]	-0.087	-0.102	0.160	0.111	0.033	-0.024	-0.212	-0.195	0.141	0.049
COWA	0.121	-0.055	0.036	0.000	-0.090	-0.112	-0.096	**-0.213***	-0.063	-0.014
Digit Span forward	-0.028	-0.114	-0.005	-0.050	-0.046	-0.062	-0.137	-0.159	-0.080	-0.026
Digit Span backward	-0.064	**-0.230***	0.042	-0.153	0.054	-0.059	**-0.212***	-0.145	-0.185	0.094
Digit Symbol	0.006	-0.161	0.205	-0.089	-0.067	-0.196	-0.139	**-0.274***	-0.009	-0.039
GP dominant hand	0.036	-0.127	0.140	0.052	0.043	-0.059	-0.107	-0.160	-0.145	0.110
GP non-dominant hand	0.036	-0.007	**0.301****	0.177	-0.151	-0.104	-0.080	**-0.293****	0.074	0.084

* $p \leq 0.05$; ** $p \leq 0.01$. Bold values indicate a statistically significant result KPS, Karnofsky performance scale; BM, brain metastases; DS-GPA, diagnosis-specific graded prognostic assessment [a] Higher z scores reflect better performance [b]TMT B|A: Trails B adjusted for sex, age, educational level and Trails A [c] Alone or in combination with other systemic therapies

Supplementary Table 2. Correlations between psychological measures [a] and patients' cognitive test performance [b]

	General Fatigue	Physical Fatigue	Reduced Activity	Reduced Motivation	Mental Fatigue	Symptoms of Anxiety	Symptoms of Depression
HVLT-R immediate recall	-0.064	0.005	-0.005	-0.091	-0.025	0.111	0.022
HVLT-R delayed recall	-0.083	0.029	-0.035	-0.108	-0.108	0.104	0.004
HVLT-R recognition	0.131	0.186	0.163	0.091	-0.006	0.131	0.143
TMT A	-0.047	-0.034	-0.046	-0.093	**-0.346****	-0.093	-0.180
TMT B|A [c]	-0.009	0.046	0.107	0.172	0.035	0.042	-0.117
COWA	0.001	0.016	-0.002	**-0.213***	-0.191	-0.084	-0.198
Digit Span forward	-0.048	-0.002	0.079	0.047	-0.098	-0.130	-0.158
Digit Span backward	0.005	0.077	0.000	0.001	-0.203	-0.143	-0.115
Digit Symbol	-0.166	-0.096	**-0.222***	-0.189	**-0.288****	-0.211	**-0.318****
GP dominant hand	-0.102	-0.013	-0.150	-0.090	**-0.227***	-0.114	-0.179
GP non-dominant hand	-0.106	-0.035	**-0.29 t****	**-0.235***	**-0.266***	-0.124	-0.177

* $p \leq 0.05$; ** $p \leq 0.01$. Bold values indicate a statistically significant result [a] Raw subscale scores from the Multidimensional Fatigue Inventory (MFI) and the Hospital Anxiety and Depression Scale (HADS); higher scores indicate more symptoms [b] Higher z scores reflect better performance [c] TMT B|A: Trails B adjusted for sex, age, educational level and Trails A

References

1. Loeffler JS. Overview of the treatment of brain metastases. Wen PY, ed. UpToDate. Waltham, MA: UpToDate Inc. https://www.uptodate.com (Accessed on June 14, 2019).
2. Witgert ME, Meyers CA. Neurocognitive and Quality of Life Measures in Patients with Metastatic Brain Disease. Neurosurgery Clinics of North America. 2011 Jan;22(1):79–85.
3. Li J, Bentzen SM, Li J, Renschler M, Mehta MP. Relationship Between Neurocognitive Function and Quality of Life After Whole-Brain Radiotherapy in Patients with Brain Metastasis. International Journal of Radiation Oncology*Biology*Physics. 2008 May;71(1): 64–70.
4. Wefel JS, Parsons MW, Gondi V, Brown PD. Neurocognitive aspects of brain metastasis. Handb Clin Neurol. Elsevier; 2018;149:155–65.
5. Schimmel WCM, Gehring K, Eekers DBP, Hanssens PEJ, Sitskoorn MM. Cognitive effects of stereotactic radiosurgery in adult patients with brain metastases: A systematic review. Adv Radiat Oncol. 2018 Oct;3(4):568–81.
6. Chang EL, Wefel JS, Maor MH, Hassenbusch SJ, Mahajan A, Lang FF, et al. A pilot study of neurocognitive function in patients with one to three new brain metastases initially treated with stereotactic radiosurgery alone. Neurosurgery. 2007 Feb;60(2):277–83.
7. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol. 2009 Nov;10(11):1037–44.
8. Onodera S, Aoyama H, Tha KK, Hashimoto N, Toyomaki A, Terae S, et al. The value of 4-month neurocognitive function as an endpoint in brain metastases trials. J Neurooncol. 2014 Jul 19;120(2):311–9.
9. Brown PD, Jaeckle K, Ballman KV, Farace E, Cerhan JH, Anderson SK, et al. Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases. JAMA. 2016 Jul 26;316(4):401–9.
10. Habets EJJ, Dirven L, Wiggenraad RG, Verbeek-de Kanter A, Lycklama À Nijeholt GJ, Zwinkels H, et al. Neurocognitive functioning and health-related quality of life in patients treated with stereotactic radiotherapy for brain metastases: a prospective study. Neuro-oncology. Oxford University Press; 2016 Mar;18(3):435–44.
11. Mehta MP, Shapiro WR, Glantz MJ, Patchell RA, Weitzner MA, Meyers CA, et al. Lead-in phase to randomized trial of motexafin gadolinium and whole-brain radiation for patients with brain metastases: centralized assessment of magnetic resonance imaging, neurocognitive, and neurologic end points. J Clin Oncol. 2002 Aug 15;20(16):3445–53.
12. Brown PD, Ballman KV, Cerhan JH, Anderson SK, Carrero XW, Whitton AC, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC·3): a multicentre, randomised, controlled, phase 3 trial. Lancet Oncol. 2017 Aug;18(8):1049–60.
13. Berger A, Strauss I, Ben Moshe S, Corn BW, Limon D, Shtraus N, et al. Neurocognitive evaluation of brain metastases patients treated with post-resection stereotactic radiosurgery: a prospective single arm clinical trial. J Neurooncol. Springer US; 2018 Nov;140(2): 307–15.
14. Welzel G, Fleckenstein K, Schaefer J, Hermann B, Kraus-Tiefenbacher U, Mai SK, et al. Memory function before and after whole brain radiotherapy in patients with and without brain metastases. Int J Radiat Oncol Biol Phys. 2008 Dec 1;72(5):1311–8.
15. Meyers CA, Smith JA, Bezjak A, Mehta MP, Liebmann J, Illidge T, et al. Neurocognitive Function and Progression in Patients With Brain Metastases Treated With Whole-Brain Radiation and Motexafin Gadolinium: Results of a Randomized Phase III Trial. J Clin Oncol. 2004 Jan;22(1):157–65.
16. Hunter GK, Suh JH, Reuther AM, Vogelbaum MA, Barnett GH, Angelov L, et al. Treatment of five or more brain metastases with stereotactic radiosurgery. Int J Radiat Oncol Biol Phys. Elsevier Inc; 2012 Aug 1;83(5):1394–8.
17. Limon D, McSherry F, Herndon J, Sampson J, Fecci P, Adamson J, et al. Single fraction stereotactic radiosurgery for multiple brain metastases. Adv Radiat Oncol. 2017 Oct;2(4):555–63.

18. Lam T-C, Sahgal A, Chang EL, Lo SS. Stereotactic radiosurgery for multiple brain metastases. Expert Rev Anticancer Ther. 2014 Oct;14(10): 1153–72.
19. Baschnagel AM, Meyer KD, Chen PY, Krauss DJ, Olson RE, Pieper DR, et al. Tumor volume as a predictor of survival and local control in patients with brain metastases treated with Gamma Knife surgery. J Neurosurg. American Association of Neurological Surgeons; 2013 Nov;119(5):1139–44.
20. Emery A, Trifiletti DM, Romano KD, Patel N, Smolkin ME, Sheehan JP. More than Just the Number of Brain Metastases: Evaluating the Impact of Brain Metastasis Location and Relative Volume on Overall Survival After Stereotactic Radiosurgery. World Neurosurg. 2017 Mar;99:111–7.
21. Kotecha R, Miller JA, Chao ST, Mohammadi AM, Murphy ES, Suh JH, et al. What drives patient outcomes in brain metastases: Number, volume, or biology? Journal of Clinical Oncology. American Society of Clinical Oncology; 2017 May 30;35(15_suppl):2071–1.
22. Sharma M, Jia X, Ahluwalia M, Barnett GH, Vogelbaum MA, Chao ST, et al. Cumulative Intracranial Tumor Volume and Number of Brain Metastasis as Predictors of Developing New Lesions After Stereotactic Radiosurgery for Brain Metastasis. World Neurosurg. 2017 Oct;106:666–75.
23. Sperduto PW, Kased N, Roberge D, Xu Z, Shanley R, Luo X, et al. Summary Report on the Graded Prognostic Assessment: An Accurate and Facile Diagnosis-Specific Tool to Estimate Survival for Patients With Brain Metastases. J Clin Oncol. 2012 Jan 27;30(4):419–25.
24. Pulenzas N, Khan L, Tsao M, Zhang L, Lechner B, Thavarajah N, et al. Fatigue scores in patients with brain metastases receiving whole brain radiotherapy. Supportive Care in Cancer. Springer Berlin Heidelberg; 2014 Feb 9;22(7):1757–63.
25. Pendergrass JC, Targum SD, Harrison JE. Cognitive Impairment Associated with Cancer: A Brief Review. Innovations in Clinical Neuroscience. Matrix Medical Communications; 2018 Feb 1;15(1-2):36–44.
26. Thong MSY, Mols F, van de Poll-Franse LV, Sprangers MAG, van der Rijt CCD, Barsevick AM, et al. Identifying the subtypes of cancer-related fatigue: results from the population-based PROFILES registry. J Cancer Surviv. Springer US; 2018 Feb;12(1):38–46.
27. Verhaak E, Gehring K, Hanssens PEJ, Sitskoorn MM. Health-related quality of life of patients with brain metastases selected for stereotactic radiosurgery. J Neurooncol. 2nd ed. Springer US; 2019 May 9;4(5):289–10.
28. Wefel JS, Vardy J, Ahles T, Schagen SB. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. Lancet Oncol. Elsevier; 2011 Jul;12(7):703–8.
29. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983 Jun;67(6):361–70.
30. Smets EM, Garssen B, Cull A, De Haes JC. Application of the multidimensional fatigue inventory (MFI-20) in cancer patients receiving radiotherapy. Br J Cancer. 1996 Jan;73(2):241–5.
31. Weitzner MA, Meyers CA, Gelke CK, Byrne KS, Cella DF, Levin VA. The Functional Assessment of Cancer Therapy (FACT) scale. Development of a brain subscale and revalidation of the general version (FACT-G) in patients with primary brain tumors. Cancer. 1995 Mar 1;75(5):1151–61.
32. Oosterhuis HEM, van der Ark LA, Sijtsma K. Sample Size Requirements for Traditional and Regression-Based Norms. Assessment. 2nd ed. 2015 Jan 22;23(2):191–202.
33. Glass GV, McGaw B, Smith ML. Meta-analysis in social research. Sage Publications; 1981. 279 p.
34. Cohen J, 1988. Statistical power analysis for the behavioural sciences Hillsdale.
35. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. Journal of the Royal Statistical Society, Series B, Methodological. 57(1):289–300.
36. van der Meer PB, Habets EJJ, Wiggenraad RG, Verbeek-de Kanter A, Lycklama À Nijeholt GJ, Zwinkels H, et al. Individual changes in neurocognitive functioning and health-related quality of life in patients with brain oligometastases treated with stereotactic radiotherapy. J Neurooncol. Springer US; 2018 Apr 16;:1–10.

37. Gerstenecker A, Nabors LB, Meneses K, Fiveash JB, Marson DC, Cutter G, et al. Cognition in patients with newly diagnosed brain metastasis: profiles and implications. J Neurooncol. 6 ed. Springer US; 2014 Oct;120(1):179–85.

38. Low E, Crewther SG, Ong B, Perre D, Wijeratne T. Compromised Motor Dexterity Confounds Processing Speed Task Outcomes in Stroke Patients. Front Neurol. 2017;8:484.

39. Kesler SR, Blayney DW. Neurotoxic Effects of Anthracycline- vs Nonanthracycline-Based Chemotherapy on Cognition in Breast Cancer Survivors. JAMA Oncol. American Medical Association; 2016 Feb;2(2):185–92.

40. Schagen SB, Muller MJ, Boogerd W, Mellenbergh GJ, van Dam FSAM. Change in cognitive function after chemotherapy: a prospective longitudinal study in breast cancer patients. J Natl Cancer Inst. 2006 Dec 6;98(23):1742–5.

41. Wefel JS, Kesler SR, Noll KR, Schagen SB. Clinical characteristics, pathophysiology, and management of noncentral nervous system cancer-related cognitive impairment in adults. CA Cancer J Clin. 2015 Mar;65(2):123–38.

42. Stelzer KJ. Epidemiology and prognosis of brain metastases. Surg Neurol Int. 2013;4(Suppl 4):S192–202.

43. Dwan TM, Ownsworth T, Chambers S, Walker DG, Shum DHK. Neuropsychological assessment of individuals with brain tumor: comparison of approaches used in the classification of impairment. Front Oncol. 5 ed. Frontiers; 2015;5(6):56.

44. Li J, Bentzen SM, Renschler M, Mehta MP. Regression after whole-brain radiation therapy for brain metastases correlates with survival and improved neurocognitive function. Journal of Clinical Oncology. 2007 Apr 1;25(10):1260–6.

45. Noll KR, Bradshaw ME, Weinberg JS, Wefel JS. Neurocognitive functioning is associated with functional independence in newly diagnosed patients with temporal lobe glioma. Neurooncol Pract. 2nd ed. 2018 Aug;5(3):184–93.

46. Zeng KL, Raman S, Sahgal A, Soliman H, Tsao M, Wendzicki C, et al. Patient preference for stereotactic radiosurgery plus or minus whole brain radiotherapy for the treatment of brain metastases. Ann Palliat Med. 2017 Dec;6(Suppl 2):S155–60.

47. Triebel KL, Gerstenecker A, Meneses K, Fiveash JB, Meyers CA, Cutter G, et al. Capacity of patients with brain metastases to make treatment decisions. Psychooncology. 2nd ed. John Wiley & Sons, Ltd; 2015 Nov;24(11):1448–55.

48. Gerstenecker A, Duff K, Meneses K, Fiveash JB, Nabors LB, Triebel KL. Cognitive Predictors of Reasoning through Treatment Decisions in Patients with Newly Diagnosed Brain Metastases. J Int Neuropsychol Soc. Cambridge University Press; 2015 Jul;21(6):412–8.

49. Gerstenecker A, Meneses K, Duff K, Fiveash JB, Marson DC, Triebel KL. Cognitive predictors of understanding treatment decisions in patients with newly diagnosed brain metastasis. Cancer. 3rd ed. John Wiley & Sons, Ltd; 2015 Jun 15;121(12):2013–9.

50. Gehring K, Sitskoorn MM, Gundy CM, Sikkes SAM, Klein M, Postma TJ, et al. Cognitive rehabilitation in patients with gliomas: a randomized, controlled trial. Journal of Clinical Oncology. American Society of Clinical Oncology; 2009 Aug 1;27(22):3712–22.

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Group and individual change in cognitive functioning in patients with 1 to 10 brain metastases following Gamma Knife radiosurgery

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Abstract

Background Stereotactic radiosurgery is increasingly used to treat multiple (four or more) brain metastases. Preserving cognitive functions is a highly relevant treatment goal because cognitive deteriorations may negatively affect a patients' quality of life. The aim of this study was to assess cognitive change, at the group and individual level, in patients with 1 to 10 brain metastases up to 9 months after Gamma Knife radiosurgery (GKRS).

Methods Ninety-two patients with 1 to 10 newly diagnosed brain metastases, expected survival >3 months and Karnofsky Performance Status (KPS) ≥70 and 104 non-cancer controls were included. A neuropsychological test battery was administered before GKRS (n=92) and at 3 (n=66), 6 (n=52) and 9 (n=41) months after GKRS. The course of test performances, while taking into account practice effects, was analyzed using linear mixed models. Pre-GKRS predictors of cognitive trajectories were analyzed. To determine proportions of individuals with cognitive changes, reliable change indices, with correction for practice effects, were calculated.

Results At the group level, immediate memory, working memory and information processing speed significantly improved over 9 months after GKRS. There were no cognitive declines. Neither number nor volume of brain metastases influenced cognitive change over time. At the individual level, proportions of patients with stable, improved or declined performances were comparable with controls, except for information processing speed (more individuals with improvements in patients) and motor dexterity (more improvements and declines in patients).

Conclusions Cognitive functioning in patients with 1 to 10 brain metastases was preserved, or improved, up to 9 months after GKRS. Neither number nor volume of brain metastases influenced cognitive performance.

Introduction

Life expectancy in patients with brain metastases (BM) is increasing due to improvements in systemic treatments of the primary tumor. [1,2] Already before BM treatment, patients may suffer from cognitive impairments caused by an interplay of factors, including the BM themselves, the primary tumor and its treatments, and the patient's functional status. [3,4] These impairments often concern slow processing of information and memory problems and may negatively affect daily functioning and quality of life. [3]

A review on the cognitive effects after stereotactic radiosurgery (SRS) concluded that patients with BM experience little to no objective cognitive decline in the early phase after SRS, followed by a trend towards improvement or stabilization up to 12 months after SRS. [5] Furthermore, evaluation of *individual* cognitive changes after SRS showed that in most patients with BM, cognitive functions remained stable for at least 6 or 12 months after SRS. [6,7]

In recent years, the total volume of BM has become a more prominent eligibility criterion for SRS as opposed to the absolute number of BM. [8] Although the application of SRS is rapidly expanding to patients with multiple (>4) BM, previous studies on cognitive outcomes after SRS mostly included patients with a limited number of BM (1-4). These studies found no association, based on univariate analyses and uncorrected for multiple testing, between the number of BM and cognitive test performance, whereas higher total BM volume was significantly associated with worse attention, information processing and executive functions. [4,9]

Cognitive outcomes after SRS in patients with more than 4 BM, as measured with an objective neuropsychological test battery, have not been evaluated thus far. Only one recent study, which used the Hopkins Verbal Learning Test as a single neuropsychological test, reported on stable memory performance up to 12 months after SRS in most patients with multiple (>10) BM. [7]

Furthermore, none of the previous studies corrected for potential practice effects (i.e., improvements in performances due to familiarity with test items and test procedures [10,11]). Practice effects should be taken into account to avoid a potential underestimation of cognitive decline, even when using parallel/alternative versions of the same test. [10,11]

The aim of this study is to evaluate group and individual cognitive change, while taking into account practice effects, in patients with 1-10 BM up to 9 months after

Gamma Knife radiosurgery (GKRS). If cognitive functioning could be preserved at pre-treatment level, this would suggest that GKRS does not cause additional cognitive decline. In addition, potential predictors of cognitive performance over time were analyzed.

Methods

Cognition and Radiation-Study A (CAR-Study A; NCT02953756) is a prospective observational study and was approved by the Medical Ethics Committee Brabant (NL53472.028.15). We previously described baseline cognitive performances and health-related quality of life (HRQOL), and the course of fatigue in this patient group. [12-14]

Patients and procedures

Patients with 1 to 10 newly diagnosed BM (total volume ≤30 cm^3), Karnofsky Performance Status (KPS) ≥70 and expected survival >3 months were recruited. Additional eligibility criteria and procedures have previously been described. [12-14] A baseline neuropsychological assessment (NPA), including neuropsychological tests and questionnaires on symptoms of anxiety and depression, fatigue, and HRQOL, was carried out in the morning before GKRS. Follow-up assessments, combined with clinical follow-ups, were carried out 3, 6 and 9 months after GKRS. All patients gave written informed consent before the first NPA.

Non-cancer controls and procedures

For normative purposes, non-cancer controls [13,14] were recruited from the general community and the broad network of the research group. Controls were selected to be, as much as possible, comparable with the general population and our patient group (frequency matching). Exclusion criteria included a (history of) cancer diagnosis or severe cerebrovascular disease in the past 12 months. Follow-up assessments were carried out at 3 and 6 months after the first NPA.

Treatment

GKRS was carried out with a Leksell Gamma Knife® ICON™ (Elekta Instruments AB, Stockholm, Sweden). All patients received a dose of 18-25 Gy with 99- 100% coverage of the target. Given the high conformity and selectivity of GKRS, organs at risk (brainstem, optic nerves and chiasm) were only segmented and optimized in the GKRS planning workflow when relevant. Dose limits for these organs were 18 Gy for the brainstem and 8 Gy for the optic nerves and chiasm. No attempt was made to delineate the hippocampus nor was there a dose limit set for the hippocampus.

Measures

Sociodemographic and clinical characteristics were retrieved from patients' medical health records. Cognitive functioning was measured with a well-established battery including six neuropsychological tests: Hopkins Verbal Learning Test-Revised with six parallel versions (HVLT-R; immediate and delayed verbal memory and recognition), Trail Making Test (TMT-A; psychomotor speed and TMT-B; cognitive flexibility), Controlled Oral Word Association with two parallel versions (COWA; word fluency), Wechsler Adult Intelligence Scale (WAIS) Digit Span (attention span and working memory), WAIS Digit Symbol (information processing speed), and Grooved Pegboard (GP; dominant and non-dominant hand dexterity). [3,15]

The total volumetric sum of contrast-enhancing BM was determined at baseline and at 3, 6 and 9 months after GKRS, using T1-weighted, contrast-enhanced magnetic resonance imaging (MRI) scans (1.5 mm slice thickness). A complete response was defined as a disappearance of all BM (no longer visible). A partial response was defined as a ≥65% decrease in total tumor volume and no new BM. Intracranial progression was defined as a ≥73% increase in total tumor volume or new BM. Stable disease was defined as no complete response, no partial response, and no intracranial progression. [16]

Statistical analyses

Statistical analyses were carried out with SPSS version 25, except for the linear mixed models (LMMs) which were performed with R, version 3.6.1. [17]

Independent samples t-tests and chi-squared tests were carried out to compare characteristics of patients with and without at least one follow-up NPA. Kaplan-Meier curves were used to analyze overall survival. Cognitive changes were determined between baseline (pre-GKRS) and 9 months (T0-T9), and for three separate time intervals: baseline and 3 months (T0-T3), 3 and 6 months (T3-T6), and 6 and 9 months (T6-T9).

Raw cognitive test scores were converted into sociodemographically adjusted *z* scores based on data from our control group (including age, sex and education as covariates): *z* score = Yo - Yp / *SD*residual. Yo is the individual's raw test score, Yp is the predicted raw test score using regression-based formulae and *SD*residual is de standard deviationof the control group's residual. [18] For the TMT, the raw test score on TMT-A was entered as a fourth predictor variable to calculate the *z* score on TMT-B (the interference index TMT-B|A).

To correct for practice effects for the 3-, 6-, and 9-month follow-up data, patients' post-GKRS *z* scores were calculated using the controls' test scores at 3 months, as the

strongest practice effects occur within this time interval. [10,19] Except for the COWA, as each of the two parallel versions has a different set of letters, we used the controls' performance at 6 months to calculate post-GKRS *z* scores for patients at 6 months (a comparison with the same set of letters). An impaired test performance was defined as a *z* score ≤-1.50. [20] One-sample z-tests were used to compare mean cognitive function of patients with controls at baseline and at 9 months.

We used the *nlme* package [21] in R [17] to run 11 LMMs of the relationship between performance on each cognitive test and time. To estimate model parameters, the restricted maximum likelihood estimate (REML) method was used. The Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) were used to estimate model fit. As random effects, the intercepts for the effect of cognition were used. Random slopes were added for psychomotor speed only. The first-order autoregressive covariance structure (AR1) at level 1 and a scaled identity matrix at level 2 was used. Time was included as a categorical variable in subsequent models to examine changes in cognitive functioning for the separate time intervals. These LMMs were also used to examine the interaction effects between time and possible baseline predictors of cognition. The following predictors, based on results from previous studies [4,14], were analyzed: KPS (low 70-80 versus high 90-100), systemic treatment before or at time of GKRS (yes versus no), total volume of BM (small <4.8 cm^3, medium 4.8-12.6 cm^3, and large >12.6 cm^3), and number of BM (1-3 versus 4-10 BM).

Reliable change indices (RCIs), reflecting change at the individual level in the context of observed changes in the control group, correcting for measurement errors (including practice effects) were calculated according to formula 10 by Maassen et al. [22] A change in test score from baseline to follow-up was considered reliable if it fell outside of the 90% confidence interval, corresponding to RCI values above +1.645 (improved performance) or below -1.645 (declined performance). RCI values that did not exceed these values were defined as "stable" (no significant change). At the test level, numbers of patients with improved, stable, or declined cognitive performance were then counted for each test at each time interval.

Patients were categorized, based on the RCIs, into four categories: 1) "decline" (≥2 declines and ≤1 improvement on any of the 11 test variables); 2) "improvement" (≥2 improvements and ≤1 decline); 3) "both" (≥2 declines and ≥2 improvements); 4) "stable" (≤1 declines and ≤1 improvements). Chi-squared or Fisher exact tests were conducted to compare the proportions of participants in each category between patients and controls. For T0-T9 and T6-T9, the proportions of patients were compared with the proportions of controls between T0-T6 and T3-T6, respectively.

To control for the false discovery rate due to multiple testing, a corrected alpha, based on the procedure of Benjamini-Hochberg [23], was used per hypothesis.

Results

Characteristics and compliance

In total, 92 patients and 104 controls were included (Table 1). Patients and controls did not differ in sex, age, and education. Forty percent of patients had 4 to 10 BM. The 1-year survival rate was 48.9% and the median overall survival was 11.8 months. The cognitive tests were completed by 66 of 76 (86.8%), 52 of 68 (76.5%), and 41 of 57 (71.9%) patients alive at 3, 6, and 9 months, respectively. Reasons for dropout, apart from death (*n*=24), were: NPA was considered too burdensome (*n*=13), no follow-up MRI-scan as it was not clinically meaningful due to poor neurological/physical condition (*n*=12) and follow-up elsewhere (*n*=2). Of the 66 patients with at least one follow-up, 34 patients (51.5%) had intracranial progression (in 18 patients due to new lesions only; 52.9%), 15 patients (22.7%) had a partial or complete response, and 17 patients (25.8%) had stable disease between time of treatment and last follow-up. Clinical characteristics did not significantly differ between patients with or without follow-up. Patients without (*n*=26) versus patients with at least one follow-up NPA (*n*=66) had shorter survival (2.7 versus 17.1 months, $p < .001$).

Cognitive status at baseline and at 9 months - Group and Individual level

At baseline, patients performed significantly worse on all tests compared with controls ($p < .05$; range mean *z* scores: -0.21 to -1.63; supplementary Table 1 summarizes the mean *z* scores). The lowest mean scores were found for non-dominant hand dexterity, cognitive flexibility and information processing speed. At 9 months after GKRS, patients performed significantly worse than controls on seven of 11 tests, ($p < .03$; range mean *z* scores: -0.49 to -1.40). The lowest performances were found for dominant and non-dominant hand dexterity, information processing speed and psychomotor speed. Mean cognitive test performances were comparable for patients with or without intracranial progression at 3 (*n*=14 versus *n*=52), 6 (*n*=17 versus *n*=35) and 9 months (*n*=17 versus *n*=24) after GKRS (data not shown). At the individual level, significantly more patients had impaired performances than controls: at baseline for nine (15.2-55.3%) of 11 tests ($p \leq .04$), and at 9 months for seven (22.0-32.4%) of 11 tests ($p < .03$; supplementary Table 2 summarizes the percentages of impaired performances for patients and controls).

Table 1. Characteristics

	No. of patients included at baseline (%)	No. of controls included at baseline (%)	Patients with ≥1 follow-up NPA (%)	Patients without follow-up NPA (%)
Number of participants	92 (100)	104 (100)	66 (72)	26 (28)
Sex, male	47 (51)	50 (48)	31 (47)	16 (62)
Age in years, mean±SD (range)	62±10 (31-80)	60±10 (31-87)	62±9 (31-80)	61±11 (39-76)
Educational level [a]				
Low	28 (30)	25 (24)	16 (24)	12 (46)
Middle	37 (40)	33 (32)	30 (46)	7 (27)
High	27 (29)	46 (44)	20 (30)	7 (27)
KPS				
70-80	33 (36)	NA	21 (32)	12 (46)
90-100	59 (64)		45 (68)	14 (54)
GPA				
Class 2	15 (16)	NA	13 (20)	2 (8)
Class 3	60 (65)		41 (62)	19 (73)
Class 4	17 (19)		12 (18)	5 (19)
Number of BM				
1-3	55 (60)	NA	42 (64)	13 (50)
4-10	37 (40)		24 (36)	13 (50)
Total volume of BM, median (range) [b, c]	5.6 (.02-31.1)	NA	5.9 (.02-31.1)	5.3 (.04-31.0)
Small (<4.8 cm^3)	40 (44)		28 (42)	12 (46)
Middle (4.8-12.6 cm^3)	25 (27)		17 (26)	8 (31)
Large (>12.6 cm^3)	27 (29)		21 (32)	6 (23)
Primary tumor				
Lung	55 (60)	NA	40 (61)	15 (58)
Renal	15 (16)		11 (17)	4 (15)
Melanoma	12 (13)		7 (11)	5 (19)
Other	10 (11)		8 (12)	2 (8)
Systemic therapy [d]				
No	39 (42)	NA	28 (42)	15 (58)
Yes	53 (58)		38 (58)	11 (42)
Chemotherapy [e]	37 (40)		28 (42)	9 (35)
Median overall survival (months), (95% confidence interval)	11.8 (8.6 to 15.0) [f]	NA	17.1 (10.5 to 23.7) [g]	2.7 (1.7 to 3.7) [h]

BM, brain metastases; KPS, Karnofsky performance scale; GPA, graded prognostic assessment; NA, not applicable NPA, neuropsychological assessment; SD, standard deviation [a] Educational level (Verhage [31]; 7 levels): Low = 1-4, Middle = 5, High = 6-7 [b] Total volume of BM by patient (one patient had a total tumor volume of 31.3cm^3 on the planning MRI scan) [c] 19 of 92 (21%) of patients had a total BM volume >15cm^3 [d] Before or at time of GKRS [e] Alone only or in combination with other systemic therapies [f] 27 patients censored (29.3%) [g] 25 patients censored (37.9%) [h] 2 patients censored (7.7%) Percentages may not add up to 100% due to rounding

Change in cognitive performance – Group level

Over 9 months, cognitive performance remained stable, except for significant improvements in immediate memory, working memory and information processing speed. More specifically, working memory improved significantly between baseline and 3 months, and information processing speed improved significantly between 3 and 6 months. Although verbal recognition and verbal fluency did not change over 9 months, verbal recognition improved significantly between 3 and 6 months and decreased significantly between 6 and 9 months; the reverse was observed for verbal fluency (first decrease, and then improvement) (Table 2).

Table 2. Course of cognitive functioning in patients with brain metastases after GKRS

	Time Slope T0-T9			**Interval T0-T3**	**Interval T3-T6**	**Interval T6-T9**
	Beta (SE)	**F-value**	*p**	**Beta (SE)**	**Beta (SE)**	**Beta (SE)**
Immediate verbal memory	0.16 (0.1)	7.282	**.008**	0.28 (0.1)	0.09 (0.1)	0.08 (0.2)
Delayed verbal memory	-0.01 (0.0)	0.022	.883	0.09 (0.1)	-0.04 (0.1)	-0.09 (0.2)
Verbal recognition	0.09 (0.1)	3.224	.075	0.13 (0.1)	**0.52 (0.2)**	**-0.62 (0.2)**
Psychomotor speed	-0.04 (0.1)	0.202	.654	-0.38 (0.2)	0.14 (0.2)	0.17 (0.2)
Cognitive flexibility	0.23 (0.1)	3.358	.069	0.57 (0.3)	0.25 (0.3)	-0.27 (0.3)
Verbal fluency	-0.08 (0.0)	3.479	.064	-0.12 (0.1)	**-0.32 (0.1)**	**0.33 (0.1)**
Attention span	-0.04 (0.0)	1.590	.209	-0.14 (0.1)	0.09 (0.1)	-0.11 (0.1)
Working memory	0.22 (0.1)	19.295	**<.001**	**0.52 (0.1)**	0.08 (0.1)	0.03 (0.2)
Information processing speed	0.17 (0.0)	15.333	**<.001**	0.12 (0.1)	**0.33 (0.1)**	0.00 (0.1)
Dominant hand dexterity	0.06 (0.1)	0.277	.600	0.27 (0.2)	0.20 (0.3)	-0.42 (0.3)
Non-Dominant hand dexterity	0.04 (0.1)	0.230	.633	0.13 (0.2)	0.24 (0.2)	-0.38 (0.3)

GKRS, Gamma Knife radiosurgery; SE, standard error*Corrected alphas, using the Benjamini-Hochberg [23] procedure, were 0.014 for the overall models (time slope T0-T9), 0.033 for the time intervals of verbal recognition and verbal fluency, and 0.017 for the time intervals of the other cognitive tests. Bold type indicates statistical significance. T0 = baseline, T3, T6, T9 = 3, 6, 9 months.

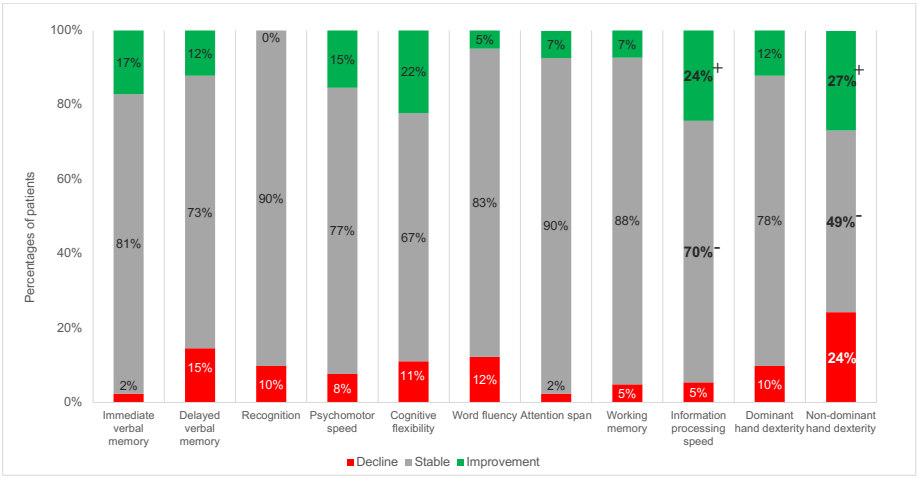

Figure 1. Individual cognitive changes at the test level over 9 months after GKRS (T0-T9; *n*=36-41)
Bold text indicates a statistically significant difference in the proportions of patients and controls with declined, stable or improved performance (+/- indicates that the percentage is significantly higher (+) or lower (-) in patients compared with controls)

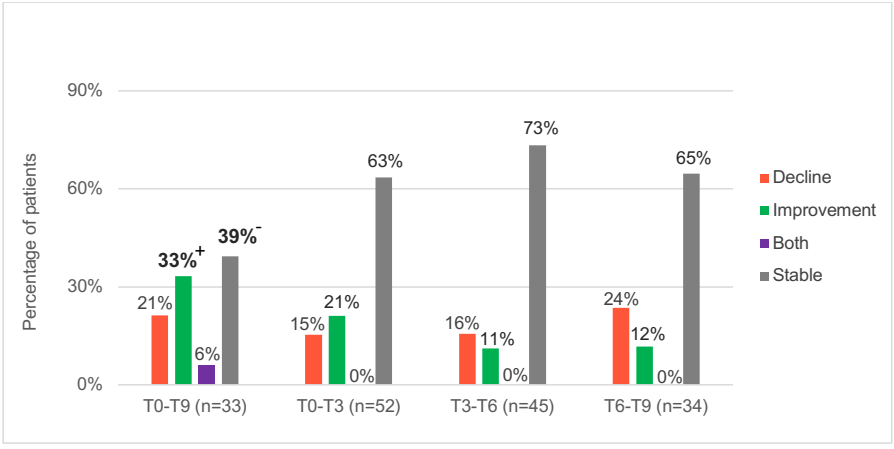

Figure 2. Reliable cognitive changes after GKRS at the individual patient level
Patient level categories: 1) "decline" (≥2 declines and ≤1 improvement on any of the 11 test variables); 2) "improvement" (≥2 improvements and ≤1 decline); 3) "both" (≥2 declines and ≥2 improvements); 4) "stable" (≤1 decline and ≤1 improvement). Bold text indicates a statistically significant difference in the proportions of patients and controls with declined, stable or improved performance (+/- indicates that the percentages were significantly higher (+) or lower (-) in patients compared to controls)

Predictors of cognitive performance over time – Group level

Patients with low (versus high) KPS had significantly more improvement over time in verbal recognition. No other significant predictors were found. Neither number nor volume of BM influenced cognitive performance over time (Supplementary Table 3 shows the LLM results for the baseline predictors of cognitive performances over time).

Individual change in cognitive performance – Test level

Although the proportions of patients with declined, stable or improved performance at test level fluctuated across the time intervals, there were no significant differences in proportions between patients and controls, except for information processing speed, and dominant and non-dominant hand dexterity (Figure 1 and Supplementary Tables 4 and 5, which summarize the individual cognitive changes in patients and controls, respectively). For information processing speed, over 9 months, and especially in the first 3 months post-GKRS, significantly more patients (versus controls) had improved performance (24.3% and 11.7%), and significantly fewer patients had stable scores (70.3% and 81.7%). For dominant hand dexterity, significantly more patients had declined (16.4%) or improved (18.0%) performance in the first 3 months only. For non-dominant hand dexterity, significantly more patients had declined (24.4%) or improved (26.8%) performance over 9 months.

Individual change in cognitive performance – Patient level

Over 9 months, test performance remained stable in 39.4% of patients and improved in 33.3% of patients; 21.2% of patients showed a decline and 6.1% of patients had both improvements and declines (Figure 2). Compared with controls, significantly fewer patients had stable performance (39.4% versus 77.0%) and more patients showed an improvement in test performance (33.3% versus 13.1%). Regarding the separate time intervals, 63.5-73.3% of the patients had stable test performances and 15.4-23.5% of patients had declined test performances. Improved performances were found in 11.1-21.2% of patients (no patients were categorized as ‘both’; Figure 2). There were no significant differences in the proportions of patients and controls with declined, stable or improved test performances (*p*-values >.14; data not shown).

Discussion

In this study, we evaluated group and individual level cognitive performance, corrected for practice effects, up to 9 months after GKRS in patients with up to 10 BM. Already at baseline, mean performances were worse in patients on all cognitive tests compared with controls, and at the individual level, percentages of impairment were significantly higher for most tests.

Over 9 months after GKRS, patients' performances improved for immediate verbal memory, working memory and information processing speed. Performances on all other measures remained stable. Previous studies showed little to no objective cognitive decline after SRS in patients with 1 up to 4 BM. [4,9,24] Compared with our study, these studies had shorter follow-up and/or smaller patient samples at follow-up. None of the previous studies on cognitive functioning in patients with BM after SRS took practice effects into account [5], which could have led to a potential underestimation of cognitive decline. [10,11] In our study, with correction for practice effects, still no decline in group performances over 9 months were found in patients with 1 to 10 BM. However, analyses of the separate time intervals showed both cognitive improvements and declines. This indicates that although the overall course remained stable up to 9 months after GKRS, fluctuations in test performances at group level do occur within the intervals.

Baseline KPS influenced change in test performance for one of 11 tests (more improvement over time in verbal recognition in patients with lower baseline KPS). In line with previous studies [4], the number of BM did not influence cognitive change over time in multivariate analyses. Neither did we find a statistically significant association between BM volume and change in cognitive performance. This is in contrast with previous studies based on univariate analyses that found significant negative associations between total BM volume and attention, information processing and executive functions. [4,9]

In accordance with the results at group level, and with van der Meer et al. [6], for most patients, both at the patient level and at the test level, cognitive functioning remained stable or improved over 9 months after GKRS, except for non-dominant hand dexterity. Performance on non-dominant hand dexterity, a measure that was not included in the study of van der Meer et al. [6], varied considerably at the individual level: there were significantly more improvements as well as more declines in patients as compared with controls. The individual variations in motor dexterity were not reflected in our group-level results. This underlines the importance of individual-level

analyses in addition to group-level analyses as the latter can mask individual cognitive changes. Regarding the separate time intervals, no significant differences were found between patients and controls in proportions of change except for information processing speed (more improvement in patients) and dominant hand dexterity (more improvement and decline in patients) during the first 3 months after GKRS.

At 9 months, performances on most tests, except for the memory tasks (including working memory), were still significantly below the normative mean of non-cancer controls. The lowest performances were found for psychomotor speed, information processing speed, and dominant and non-dominant hand dexterity. Also, frequencies of impairment were significantly higher in patients than in controls for most tests. These frequencies were highest for cognitive flexibility, information processing speed and dominant hand dexterity. This illustrates the persistent character of cognitive impairments that were already present before BM treatment. The impairments in dominant hand dexterity may have negatively influenced performance on the other cognitive tasks (such as the TMT and Digit Symbol) with high motor demands [25] and may partially explain the impaired performance on psychomotor speed, cognitive flexibility and information processing. In addition, chemotherapy and certain targeted therapies can cause peripheral neuropathy in some patients [26], which may also partially explain the impaired performance on these tasks with motor output.

Cognitive impairments may seriously worsen the ability to carry out everyday life activities and impair patients' quality of life. Patients may encounter difficulties with processing (new) information, switching between tasks, remembering new information, performing adequate movements appropriate to a certain task, and with the ability to reason through medical treatment decisions. [27] Additionally, patients may experience time pressure, and over-stimulation, which makes it harder to engage in, and enjoy, social interactions with others. These difficulties may also increase the caregiver burden. [28] Cognitive interventions, such as rehabilitation programs [29], may improve the quality of life/survival in these patients, especially for subgroups of patients with BM who have a longer life expectancy.

This study has limitations to consider. We included a heterogeneous study sample of patients with BM originating from different primary cancers. The study sample as a whole is, however, representative for the group of patients with BM that is generally treated with GKRS. Patients who were willing and able to participate in this study may have been more resilient compared with non-participating patients and consequently may have performed better than non- participating patients. Moreover, although mean differences in baseline test performances and clinical

characteristics between patients with and those without follow-up assessments were not statistically significant, it is likely that patients who completed the assessment at 9 months were the 'better performing' patients in terms of functional status and cognitive functioning. Additionally, the NPA was administered in the morning before treatment and at clinical follow-ups (including MRI scan and consult), during which patients may have experienced anxiety or depression. However, although patients had elevated levels of anxiety and depression, we found no evidence for a direct effect of anxiety and depression on cognitive test performance at baseline. [14] This is in line with a study by Gerstenecker et al. [30] in patients with BM and suggests that both anxiety and depression may not be primary contributors for cognitive impairment in these patients. [14,30] Furthermore, despite the correction for practice effects and the use of parallel versions, an additional practice effect may have occurred at 9 months because these patients may have been even more familiarized with the tests and the test procedures compared with the assessments at 3 or 6 months.

To conclude, up to 9 months after initial GKRS, both at the group and individual level, most patients with 1 to 10 BM showed preserved or improved cognitive functioning. This suggests that GKRS does not cause additional cognitive damage. Neither number nor volume of BM influenced cognitive performance.

Supplementary tableS

Supplementary Table 1. Mean cognitive functioning in patients with brain metastases

	Patients with BM Mean z scores (SD)				Patients with BM versus non-cancer controls					
					Baseline			9 months after GKRS		
	Baseline (n=80-92)	3 months (n=59-66)	6 months (n=47-52)	9 months (n=38-41)	z-value	p^*	Effect size [a]	z-value	p^*	Effect size [a]
Immediate verbal memory	-0.52 (1.4)	-0.23 (1.1)	-0.14 (1.2)	-0.06 (1.4)	-4.95	**<.001**	0.52	-0.36	.722	0.06
Delayed verbal memory	-0.27 (1.3)	-0.18 (1.1)	-0.20 (1.1)	-0.26 (1.2)	-2.59	**.010**	0.27	-1.64	.100	0.26
Verbal recognition	-0.21 (1.3)	-0.06 (1.0)	0.51 (0.8)	-0.11 (1.3)	-1.99	**.047**	0.21	-0.67	.501	0.11
Psychomotor speed	-0.99 (1.7)	-1.29 (1.7)	-1.28 (1.9)	-1.00 (2.0)	-9.21	**<.001**	0.99	-6.22	**<.001**	1.00
Cognitive flexibility	-1.50 (2.5)	-0.78 (2.4)	-0.51 (1.6)	-0.77 (2.0)	-13.40	**<.001**	1.50	-4.70	**<.001**	0.77
Verbal fluency [b]	-0.63 (1.2)	-0.68 (0.9)	-1.07 (1.1)	-0.73 (1.0)	-6.06	**<.001**	0.63	-4.67	**<.001**	0.73
Attention span	-0.43 (0.9)	-0.51 (0.9)	-0.41 (0.9)	-0.49 (1.0)	-4.10	**<.001**	0.43	-3.11	**.002**	0.49
Working memory	-0.78 (1.0)	-0.23 (1.1)	-0.15 (1.2)	-0.08 (1.2)	-7.51	**<.001**	0.78	-0.54	.591	0.08
Information processing speed	-1.49 (1.3)	-1.29 (1.2)	-1.04 (1.2)	-1.03 (1.4)	-13.78	**<.001**	1.49	-6.34	**<.001**	1.03
Dominant hand dexterity	-1.43 (2.8)	-1.18 (1.9)	-0.83 (1.6)	-1.28 (2.9)	-13.42	**<.001**	1.43	-8.17	**<.001**	1.28
Non-dominant hand dexterity	-1.63 (2.2)	-1.39 (2.3)	-1.01 (1.8)	-1.40 (2.5)	-15.25	**<.001**	1.63	-8.97	**<.001**	1.40

GKRS, Gamma Knife radiosurgery; SD, standard deviation *A corrected alpha of .05 (baseline) and .03 (9 months) was used (Benjamini-Hochberg, 1995) [a] Glass' delta effect size; ≤ 0.49 = small, from 0.50 to 0.79 = medium, and ≥ 0.80 = large (Glass et al., 1981) [b] Controls' performance at 6 months was used to calculate z scores for patients at 6 months (same set of letters) Bold type indicates statistical significance

Supplementary Table 2. Percentages of impaired cognitive performance for patients with brain metastases versus controls

	Baseline			3 months			6 months			9 months (controls 6 months)		
	Patients (%) n=80-92	Controls (%) n=102-104	p^*	Patients (%) n=59-66	Controls (%) n=75-77	p^*	Patients (%) n=47-52	Controls (%) n=67-69	p^*	Patients (%) n=37-41	Controls (%) n=67-69	p^*
Immediate verbal memory	27.2	4.9	**<.001**	13.6	6.5	.152	13.5	5.8	.203	19.5	5.8	.053
Delayed verbal memory	15.2	4.8	**.014**	13.6	7.8	.256	17.3	7.2	.087	22.0	7.2	**.025**
Verbal recognition	14.3	8.7	.215	10.6	7.8	.560	5.8	5.9	1.00	14.6	5.9	.172
Psychomotor speed	25.3	7.7	**.001**	33.9	6.5	**<.001**	38.8	8.7	**<.001**	25.6	8.7	**.017**
Cognitive flexibility	28.7	5.8	**<.001**	25.4	9.3	**.013**	25.5	9.0	**.017**	32.4	9.0	**.002**
Verbal fluency	27.2	7.7	**<.001**	19.7	5.2	**.008**	42.3	5.9	**<.001**	26.8	5.2 [a]	**.001**
Attention span	10.9	5.8	.200	13.6	3.9	**.036**	9.6	2.9	.138	9.8	2.9	.193
Working memory	22.8	6.8	**.001**	18.2	6.5	**.031**	15.4	2.9	**.019**	14.6	2.9	.050
Information processing speed	55.3	6.7	**<.001**	43.5	2.6	**<.001**	43.8	5.8	**<.001**	31.6	5.8	**<.001**
Dominant hand dexterity	27.3	6.9	**<.001**	32.3	6.6	**<.001**	22.9	7.4	**.017**	31.7	7.4	**.001**
Non-dominant hand dexterity	43.2	5.9	**<.001**	30.6	9.2	**.001**	26.5	6.0	**.002**	26.8	6.0	**.002**

GKRS, Gamma Knife radiosurgery *Acorrected alpha of .04 (T0 and T3) and.03 (T6 and T9) was used (Benjamini-Hochberg, 1995) [a] Percentages of impairment of patients at T9 were compared to percentages of impairment of controls at T3 (COWA T3 and T9: same set of letters) Cognitive impairment was defined as a z score ≤-1.5 Bold type indicates statistical significance

Supplementary Table 3. Course and predictors of cognitive functioning in patients with brain metastases over time after radiosurgery

		Immediate verbal memory	Delayed verbal memory	Verbal recognition	Psycho-motor speed	Cognitive flexibility	Verbal fluency	Attention span	Working memory	Information processing speed	Dominant hand dexterity	Non-dominant hand dexterity
Time slope												
Time slope T0-T9	*b(SE)*F-value	0.16 (0.1)	-0.01 (0.0)	0.09 (0.1)	-0.04 (0.1)	0.23 (0.1)	-0.08 (0.0)	-0.04 (0.0)	0.22 (0.1)	0.17 (0.0)	0.06 (0.1)	0.04 (0.1)
		7.282	0.022	3.224	0.202	3.358	3.479	1.590	19.295	15.333	0.277	0.230
	p value*	**.008**	.883	.075	.654	.069	.064	.209	**<.001**	**<.001**	.600	.633
Interaction effect with time												
Baseline KPS	*bSE*F-value	0.133	0.035	0.345	-0.324	0.053	-0.031	-0.124	0.047	-0.020	-0.286	-0.185
70 - 80 vs 90 - 100 (ref)	*p*-value*	0.15	0.12	0.13	0.21	0.31	0.10	0.07	0.12	0.11	0.27	0.20
		0.816	0.085	7.334	2.327	0.028	0.090	2.765	0.145	0.033	1.130	0.863
		.368	.770	**.008**	.129	.866	.764	.098	.704	.856	.290	.355
Systemic treatment	*bSE*F-value	-0.116	0.054	0.009	0.121	0.118	0.051	0.033	-0.19	0.024	0.290	0.256
Yes vs No (ref)	*p*-value*	0.14	0.11	0.12	0.19	0.29	0.09	0.07	0.11	0.10	0.24	0.18
		0.722	0.250	0.006	0.401	0.172	0.298	0.242	2.728	0.062	1.456	2.048
		.397	.618	.941	.528	.679	.586	.623	.101	.803	.230	.155
Baseline intracranial	*bSE*F-value	0.044	0.283	0.038	0.128	0.500	-0.104	0.070	0.078	0.299	-0.326	0.174
tumor volume	*p*-value*	0.17	0.13	0.14	0.23	0.34	0.12	0.08	0.14	0.12	0.29	0.22
Large vs Medium (ref)		0.069	4.469	0.071	0.306	2.174	0.804	0.705	0.308	6.033	1.243	0.614
		.794	.036	.790	.581	.143	.371	.402	.580	.015	.267	.435
Baseline intracranial	*bSE*F-value	0.009	-0.020	-0.001	-0.062	0.153	-0.220	-0.007	-0.084	0.077	-0.532	0.179
tumor volume	*p*-value*	0.16	0.12	0.13	0.21	0.31	0.11	0.08	0.13	0.11	0.27	0.20
Small vs Medium (ref)		0.003	0.027	0.000	0.085	0.239	4.237	0.009	0.410	0.502	3.785	0.775
		.956	.869	.993	.772	.626	.041	.923	.523	.480	.054	.380
Baseline number of	*bSE*F-value	0.032	-0.064	0.042	-0.135	-0.007	-0.122	-0.023	-0.023	-0.050	-0.355	-0.074
BM	*p*-value*	0.13	0.10	0.11	0.18	0.26	0.09	0.06	0.11	0.09	0.23	0.17
1-3 (ref) vs 4-10		0.060	0.380	0.141	0.571	0.001	1.842	0.123	0.042	0.299	2.439	0.185
		.807	.538	.708	.451	.979	.177	.726	.837	.586	.121	.668

Ref, reference category; vs, versus; T0 = baseline, T9 = 9 months *Acorrected alpha of .014 for the overall models (time slope T0-T9) and .010 for the predictors of each cognitive test was used (Benjamini & Hochberg, 1995) Total volume of BM was categorized into small (>4.8 cm^3), medium (4.8 - 12.6 cm^3), and large (>12.6 cm^3) Bold type indicates statistical significance

Supplementary Table 4. Individual cognitive changes after radiosurgery in patients with brain metastases [a]

	Over 9 months' time (T0-T9) n=36-41			**Interval 1 (T0-T3) n=56-66**			**Interval 2 (T3-T6) n=47-52**			**Interval 3 (T6-T9) n=37-41**		
	Declined (%)	**Stable (%)**	**Improved (%)**	**Declined (%)**	**Stable (%)**	**Improved (%)**	**Declined (%)**	**Stable (%)**	**Improved (%)**	**Declined (%)**	**Stable (%)**	**Improved (%)**
Immediate verbal memory	1 (2.4)	33 (80.5)	7 (17.1)	3 (4.5)	56 (84.8)	7 (10.6)	3 (5.8)	49 (94.2)	0 (0.0)	3 (7.3)	36 (87.8)	2 (4.9)
Delayed verbal memory	6 (14.6)	30 (73.2)	5 (12.2)	3 (4.5)	52 (78.8)	11 (16.7)	2 (3.8)	47 (90.4)	3 (5.8)	3 (7.3)	37 (90.2)	1 (2.4)
Verbal recognition	4 (9.8)	37 (90.2)	0 (0.0)	1 (1.5)	58 (89.2)	6 (9.2)	1 (1.9)	50 (96.2)	1 (1.9)	4 (9.8)	37 (90.2)	0 (0.0)
Psychomotor speed	3 (7.7)	30 (76.9)	6 (15.4)	6 (9.8)	46 (75.4)	9 (14.8)	5 (10.2)	41 (83.7)	3 (6.1)	4 (10.3)	32 (82.1)	3 (7.7)
Cognitive flexibility	4 (11.1)	24 (66.7)	8 (22.2)	6 (10.7)	40 (71.4)	10 (17.9)	6 (12.8)	35 (74.5)	6 (12.8)	4 (10.8)	29 (78.4)	4 (10.8)
Verbal fluency[n]	5 (12.2)	34 (82.9)	2 (4.9)	5 (7.6)	59 (89.4)	2 (3.0)	4 (7.7)	47 (90.4)	1 (1.9)	2 (4.9)	39 (95.1)	0 (0.0)
Attention span	1 (2.4)	37 (90.2)	3 (7.3)	0 (0.0)	66 (100.0)	0 (0.0)	0 (0.0)	51 (98.1)	1 (1.9)	0 (0.0)	39 (95.1)	2 (4.9)
Working memory	2 (4.9)	36 (87.8)	3 (7.3)	2 (3.0)	54 (81.8)	10 (15.2)	6 (11.5)	40 (76.9)	6 (11.5)	3 (7.3)	35 (85.4)	3 (7.3)
Information processing	2 (5.4)	**26 (70.3)** (-)	**9 (24.3)** (+)	4 (6.7)	**49 (81.7)** (-)	**7 (11.7)** (+)	0 (0.0)	45 (93.8)	3 (6.3)	2 (5.3)	36 (94.7)	0 (0.0)
Dominant hand dexterity	4 (9.8)	32 (78.0)	5 (12.2)	**10 (16.4)** (+)	**40 (65.6)** (-)	**11 (18.0)** (+)	4 (8.3)	40 (83.3)	4 (8.3)	7 (17.1)	33 (80.5)	1 (2.4)
Non-dom hand dexterity	**10 (24.4)** (+)	**20 (48.8)** (-)	**11 (26.8)** (+)	6 (9.7)	48 (77.4)	8 (12.9)	3 (6.1)	40 (81.6)	6 (12.2)	9 (22.5)	27 (67.5)	4 (10.0)

[a] Reliable cognitive change over time intervals based on the Reliable Change Index (RCI) using equation 10 of Maassen et al. 2009 RCI-values > +/- 1.645 indicate significant reliable improvement or decline (otherwise stability) Bold type indicates a statistically significant difference in proportions of change between patients and controls (+/- indicates that the percentage is higher/lower in patients compared to controls)

Supplementary Table 5. Individual cognitive changes in non-cancer controls [a]

	T0-T6 n=67-69			Interval 1 (T0-T3) n=75-77			Interval 2 (T3-T6) n=66-68		
Test variable	**Declined (%)**	**Stable (%)**	**Improved (%)**	**Declined (%)**	**Stable (%)**	**Improved (%)**	**Declined (%)**	**Stable (%)**	**Improved (%)**
Immediate verbal memory	4 (5.9)	59 (86.8)	5 (7.4)	6 (7.9)	68 (89.5)	2 (2.6)	4 (5.9)	62 (91.2)	2 (2.9)
Delayed verbal memory	5 (7.2)	61 (88.4)	3 (4.3)	4 (5.2)	69 (89.6)	4 (5.2)	3 (4.4)	63 (92.6)	2 (2.9)
Verbal recognition	3 (4.4)	60 (88.2)	5 (7.4)	3 (3.9)	65 (84.4)	9 (11.7)	3 (4.5)	62 (92.5)	2 (3.0)
Psychomotor speed	2 (2.9)	64 (92.8)	3 (4.3)	3 (3.9)	67 (87.0)	7 (9.1)	2 (2.9)	63 (92.6)	3 (4.4)
Cognitive flexibility	6 (9.0)	57 (85.1)	4 (6.0)	3 (4.0)	67 (89.3)	5 (6.7)	3 (4.5)	59 (89.4)	4 (6.1)
Verbal fluency	3 (3.9)	71 (92.2)	3 (3.9)	3 (3.9)	71 (92.2)	3 (3.9)	5 (7.5)	57 (85.1)	5 (7.5)
Attention span	4 (5.9)	61 (89.7)	3 (4.4)	1 (1.3)	73 (96.1)	2 (2.6)	3 (4.4)	63 (92.6)	2 (2.9)
Working memory	4 (5.9)	60 (88.2)	4 (5.9)	4 (5.3)	68 (89.5)	4 (5.3)	5 (7.4)	61 (89.7)	2 (2.9)
Information processing	5 (7.2)	62 (89.9)	2 (2.9)	4 (5.3)	72 (94.7)	0 (0.0)	2 (3.0)	60 (89.6)	5 (7.5)
Dominant hand dexterity	1 (1.5)	65 (95.6)	2 (2.9)	3 (3.9)	70 (92.1)	3 (3.9)	1 (1.5)	64 (95.5)	2 (3.0)
Non-dom hand dexterity	3 (4.5)	60 (89.6)	4 (6.0)	3 (3.9)	68 (89.5)	5 (6.6)	4 (6.1)	59 (89.4)	3 (4.5)

[a] Reliable cognitive change over time intervals b the Reliable based in the Reliable Change Index (RCI) using equation 10 of Maassen et al. 2009 RCI-values > +/- 1.645 indicate significant reliable improvement or decline (otherwise stability)

References

1. Jensen CA, Chan MD, McCoy TP, Bourland JD, DeGuzman AF, Ellis TL, et al. Cavity-directed radiosurgery as adjuvant therapy after resection of a brain metastasis. J Neurosurg. 2011;114(6):1585-91.
2. Nayak L, Lee EQ, Wen PY. Epidemiology of brain metastases. Current Oncology Reports. 2012;14(1):48-54.
3. Witgert ME, Meyers CA. Neurocognitive and quality of life measures in patients with metastatic brain disease. Neurosurgery Clinics of North America. 2011;22(1):79-85.
4. Habets EJ, Dirven L, Wiggenraad RG, Verbeek- de Kanter A, Lycklama à Nijeholt GJ, Zwinkels H, et al. Neurocognitive functioning and health- related quality of life in patients treated with stereotactic radiotherapy for brain metastases: a prospective study. Neuro-oncology. 2016;18(3):435-44.
5. Schimmel WC, Gehring K, Eekers DB, Hanssens PE, Sitskoorn MM. Cognitive effects of stereotactic radiosurgery in adult patients with brain metastases: A systematic review. Advances in Radiation Oncology. 2018;3(4):568-81.
6. van der Meer PB, Habets EJ, Wiggenraad RG, Verbeek-de Kanter A, à Nijeholt GJL, Zwinkels H, et al. Individual changes in neurocognitive functioning and health-related quality of life in patients with brain oligometastases treated with stereotactic radiotherapy. Journal of neuro-oncology. 2018:1-10.
7. Giuseppe M, Luca C, Barbara N, Giorgio R, Claudia S, Federico B, et al. Neurological outcome and memory performance in patients with 10 or more brain metastases treated with frameless linear accelerator (LINAC)-based stereotactic radiosurgery. Journal of Neuro- Oncology. 2020:1-9.
8. Nabors LB, Portnow J, Ammirati M, Brem H, Brown P, Butowski N, et al. Central nervous system cancers, version 2.2014. J Natl Compr Canc Netw. 2014;12(11):1517-23.
9. Chang EL, Wefel JS, Maor MH, Hassenbusch III SJ, Mahajan A, Lang FF, et al. A pilot study of neurocognitive function in patients with one to three new brain metastases initially treated with stereotactic radiosurgery alone. Neurosurgery. 2007;60(2):277-84.
10. Calamia M, Markon K, Tranel D. Scoring higher the second time around: meta-analyses of practice effects in neuropsychological assessment. The Clinical Neuropsychologist. 2012;26(4):543-70.
11. McCaffrey RJ, Duff K, Westervelt HJ. Practitioner's guide to evaluating change with neuropsychological assessment instruments: Springer Science & Business Media; 2000.
12. Verhaak E, Gehring K, Hanssens PEJ, Sitskoorn MM. Health-related quality of life of patients with brain metastases selected for stereotactic radiosurgery. J Neurooncol. 2019;143(3):537- 46.
13. Verhaak E, Schimmel WC, Sitskoorn MM, Bakker M, Hanssens PE, Gehring K. Multidimensional assessment of fatigue in patients with brain metastases before and after Gamma Knife radiosurgery. Journal of neuro- oncology. 2019;144(2):377-84.
14. Schimmel WC, Gehring K, Hanssens PE, Sitskoorn MM. Cognitive functioning and predictors thereof in patients with 1–10 brain metastases selected for stereotactic radiosurgery. Journal of neuro-oncology. 2019;145(2):265-76.
15. Wefel JS, Vardy J, Ahles T, Schagen SB. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. The lancet oncology. 2011;12(7):703-8.
16. Lin NU, Lee EQ, Aoyama H, Barani IJ, Barboriak DP, Baumert BG, et al. Response assessment criteria for brain metastases: proposal from the RANO group. The lancet oncology. 2015;16(6):e270-e8.
17. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, 2017. URL https://www.R-project.org.
18. Rijnen SJ, Meskal I, Emons WH, Campman CA, van der Linden SD, Gehring K, et al. Evaluation of normative data of a widely used computerized neuropsychological battery: applicability and effects of sociodemographic variables in a Dutch sample. Assessment. 2017:1073191117727346.
19. Bartels C, Wegrzyn M, Wiedl A, Ackermann V, Ehrenreich H. Practice effects in healthy adults: a longitudinal study on frequent repetitive cognitive testing. BMC neuroscience. 2010;11(1):118.
20. Lezak MD, Howieson DB, Loring DW, Fischer JS. Neuropsychological assessment: Oxford University Press, USA; 2004.

21. Pinheiro J, Bates D, DebRoy S, Sarkar D, R Core Team. nlme: Linear and Nonlinear Mixed Effects Models. R package version. 2018;3.1-137.
22. Maassen GH, Bossema E, Brand N. Reliable change and practice effects: Outcomes of various indices compared. J Clin Exp Neuropsychol. 2009;31(3):339-52.
23. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Series B Stat Methodol. 1995:289-300.
24. Brown PD, Jaeckle K, Ballman KV, Farace E, Cerhan JH, Anderson SK, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a ran-domized clinical trial. JAMA 2016;316:401e409.
25. Low E, Crewther SG, Ong B, Perre D, Wijeratne T. Compromised motor dexterity confounds processing speed task outcomes in stroke patients. Front Neurol. 2017;8:484.
26. Zaja ̨czkowska R, Kocot-Ke ̨pska M, Leppert W, Wrzosek A, Mika J, Wordliczek J. Mechanisms of chemotherapy-induced peripheral neuropathy. IJMS 2019;20:1451.
27. Gerstenecker A, Meneses K, Duff K, Fiveash JB, Marson DC, Triebel KL. Cognitive predictors of understanding treatment decisions in patients with newly diagnosed brain metastasis. Cancer. 2015;121(12):2013-9.
28. Noll KR, Bradshaw ME, Weinberg JS, Wefel JS. Neurocognitive functioning is associated with functional independence in newly diagnosed patients with temporal lobe glioma. Neuro- oncology practice. 2018;5(3):184-93.
29. Gehring K, Roukema JA, Sitskoorn MM. Review of recent studies on interventions for cognitive deficits in patients with cancer. Expert review of anticancer therapy. 2012;12(2):255-69.
30. Gerstenecker A, Nabors LB, Meneses K, Fiveash JB, Marson DC, Cutter G, et al. Cognition in patients with newly diagnosed brain metastasis: profiles and implications. J Neurooncol 2014; 120:179e185.
31. Verhage F. Intelligentie en leeftijd: onderzoek bij Nederlanders van twaalf tot zevenenzeventig jaar. Assen, The Netherlands: Van Gorcum; 1964.

5

A randomized trial to compare cognitive outcome after GKRS versus WBRT in patients with multiple brain metastases: research protocol CAR-study B

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Abstract

Background Gamma Knife radiosurgery (GKRS) is increasingly applied in patients with multiple brain metastases and is expected to have less adverse effects in cognitive functioning than whole brain radiation therapy (WBRT). Effective treatment with the least negative cognitive side effects is increasingly becoming important, as more patients with brain metastases live longer due to more and better systemic treatment options. There are no published randomized trials yet directly comparing GKRS to WBRT in patients with multiple brain metastases that include objective neuropsychological testing.

Methods CAR-Study B (ClinicalTrials.gov registration number NCT02953717; The Netherlands Trials Register number NTR5463) is a prospective randomised trial comparing cognitive outcome after GKRS or WBRT in adult patients with 11-20 newly diagnosed brain metastases on a contrast-enhanced MRI-scan, KPS ≥70 and life expectancy of at least 3 months. Randomisation by the method of minimization, is stratified by the cumulative tumor volume in the brain, systemic treatment, KPS, histology, baseline cognitive functioning and age. The primary endpoint is the between-group difference in the percentage of patients with significant memory decline at 3 months.

Secondary endpoints include overall survival, local control, development of new brain metastases, cognitive functioning over time, quality of life, depression, anxiety, and fatigue. Cognitive functioning is assessed by a standardized neuropsychological test battery.

Assessments (cognitive testing, questionnaires, and MRI-scans) are scheduled at baseline and at 3, 6, 9, 12 and 15 months after treatment.

Conclusions Knowledge gained from this trial may be used to inform individual patients with BM more precisely about the cognitive effects they can expect from treatment, and to assist both doctors and patients in making (shared) individual treatment decisions. This trial is currently recruiting. Target accrual: 23 patients at 3-months follow-up in both groups.

Introduction

Brain metastases (BM) are the most common tumors in the central nervous system, and account for 20% of cancer deaths each year. [1] Twenty to 40% of all cancer patients develop one or multiple BM during their illness. [2] If left untreated, these patients display a median survival of only one or two months. [3,4] Most BM originate from lung, breast, skin, kidney, gastrointestinal tract, lymphoma, and prostate. [1,5,6] The incidence of BM is thought to be rising as a result of the growing elderly population and advances in cancer treatments which prolong life, allowing for BM to develop. [2,7-10]

Most patients with BM already have cognitive deficits prior to BM treatment due to the BM itself, epilepsy or medication use (i.e., corticosteroids, anti-epileptic drugs, chemotherapy, other systemic therapies). [11-13] Whole brain radiation therapy (WBRT) has long been the mainstay of treatment for patients with BM. [14,15] However, its use has decreased in recent years due to advances in radiation technology and growing concerns regarding the often-persistent adverse effects after 6-24 months on cognitive function (e.g., memory, attention and concentration impairments as measured with objective neuropsychological tests). [9,16-18] Meanwhile, treatment has diversified, and stereotactic radiosurgery (SRS) is increasingly employed in the management of (multiple) BM to spare healthy tissue and thereby aiming to prevent cognitive side effects. [16,19,20]

Due to increased efficacy of systemic cancer treatments, there is a growing number of patients with BM that live long enough (i.e., >6 months) to experience radiation-induced brain injury, including cognitive decline. [21,22] Because cognitive functions are essential for our daily social, occupational and personal life, and are related to therapy compliance and quality of life in general, a full understanding of the cognitive side effects of radiotherapy is essential.

Traditionally, radiation-induced brain injury is divided into three categories: acute, early delayed, and late delayed. [23-25] Acute and early delayed injury (after 1-6 months) are thought to be of a transient nature. Late delayed injury (after 6-24 months) on the other hand is usually more severe and irreversible. Patients with late delayed effects most often exhibit progressive impairments in memory, visual motor processing, problem solving ability, and attention, all of which can be very debilitating in daily life. It has been demonstrated that the extent of delayed cognitive impairment correlates positively with the total dose received and with the time-dose-fractionation scheme. [12,16]

Radiation-induced brain injury can result from direct neurotoxic effects or indirectly through metabolic abnormalities, microvascular changes, enhanced cytokine gene

expression, persistent oxidative stress and inflammatory processes. [24,26,27] In addition, radiation therapy may, disrupt hippocampal neurogenesis, which may, in turn, negatively affect memory and learning functions. [28,29]

Among patients with 1-4 BM, the use of SRS has received widespread acceptance and is supported by prospective data. [19,30] In addition, SRS has been proven effective as the initial treatment option for patients with multiple BM: Mostly for patients with 5-10 BM, but also for patients with >10 BM and even for patients with >20 BM. [31-37] Yamamoto and colleagues conducted a case-matched study comparing treatment results after SRS for patients with 2-9 versus >10 BM. Approximately 90% of all patients died of extracranial disease, regardless of the number of BM. Survival times did not differ significantly between groups. It was concluded that these carefully selected patients with >10 BM (controlled primary cancer, no extracerebral BM, better KPS scores, and higher RPA class) might be favorable candidates for SRS alone. [33]

Additionally, according to the US guideline on BM there is growing evidence suggesting that the total tumor volume in the brain is a better selection criterion for SRS than the number of BM. [38] Accordingly, guidelines no longer specify an upper limit for the number of brain metastases. [38,39]

In comparison to WBRT, SRS has the better ability to spare healthy tissue because of the high level of precision and the quick dose fall-off. Therefore, treatment with SRS is expected to cause fewer cognitive side effects than WBRT. However, there are no published trials yet directly comparing SRS alone versus WBRT alone, that include objective neuropsychological testing. This prospective randomized study (CAR-Study B) will yield information on which treatment modality, Gamma Knife radiosurgery (a form of SRS) or WBRT, best preserves cognitive function in patients with 11-20 BM, as assessed with reliable and valid neuropsychological tests. These tests are recommended by the International Cognition and Cancer Taskforce (ICCTF). [40] Knowledge gained from this trial may possibly change clinical practice and international guidelines on BM.

This randomised trial is one of the two Cognition and Radiation studies (The CAR-Studies: CAR-Study A and B). CAR-Study A is a longitudinal trial assessing cognitive functions after Gamma Knife radiosurgery (GKRS) alone in patients with 1-10 BM (Clinicaltrials.gov identifier: NCT02953756).

Objectives

CAR-Study B aims to assess, in a randomised design, change in cognitive performance after treatment with either GKRS or WBRT in patients with multiple (11-20) BM.

The **primary objective** is to determine the between-group difference in the percentages of patients with significant cognitive decline at 3 months after treatment as assessed by the Hopkins Verbal Learning Test-Revised (a memory task). The primary hypothesis is that the percentage of patients with reliable cognitive decline at 3 months will be significantly higher after treatment with WBRT in comparison to GKRS, in patients with 11-20 newly diagnosed BM.

Secondary outcome measures

- Cognitive functioning over time (max 15 months)
- Overall survival
- Local control
- Development of new BM
- Patient Reported Outcomes (PROs)
    - Fatigue
    - Depression and anxiety
    - Quality of life

Methods

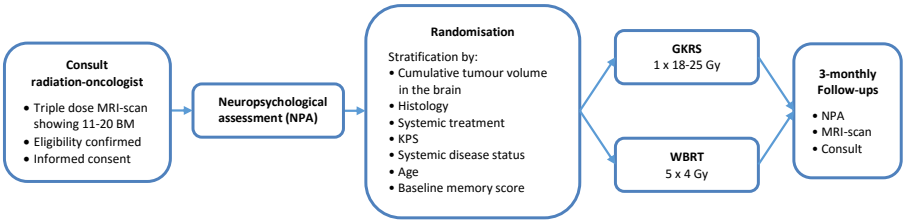
Trial Design

CAR-Study B is a two-arm randomised trial. Adult cancer patients (n=46), with 11-20 BM, Karnofsky Performance Status (KPS) ≥70 and a life expectancy of at least 3 months, are screened for inclusion and exclusion criteria (Table 1) by the radiation-oncologist. Eligible patients are invited for study participation at their first visit at the Gamma Knife Centre. During this first consultation, patients receive an information letter about the study and its procedures.

After signing a written informed consent statement, co-signed by the principal investigator or a formally delegated authorized person, a baseline neuropsychological assessment (NPA) is performed. Subsequently, patients are randomised by the method of minimization 1:1 to either GKRS (n=23) or WBRT (n=23). The trial schema and randomisation factors are shown in Figure 1. The trial has been approved by the local medical ethics review committee (METC Brabant, The Netherlands). Patients from both arms are followed up at 3, 6, 9, 12 and 15 months after treatment. High rates of attrition and noncompliance are very common in trials in patients with metastatic disease. [14,41] In an attempt to maximize patient comfort and convenience, the administration of the test battery and additional questionnaires is combined with usual care clinical visits on site (3-monthly contrast MRI-scans and consult with the radiation-oncologist).

In both groups, chemotherapy is administered at the discretion of the primary physician and recorded by the research team. Type and duration of systemic therapy, use of steroids and other medication are accurately monitored and registered. Treatment side effects for both arms are recorded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 4). Patients in both treatment arms may receive additional GKRS or WBRT, or salvage surgery when recurrences occur at any one of successive follow-ups; these additional treatments are recorded.

Figure 1. Trial Flow



Participants

Patients who meet the inclusion and exclusion criteria (Table 1) are eligible for the study. It is projected to include 46 patients.

Setting

Gamma Knife Centre Tilburg, Department of Neurosurgery, Elisabeth-TweeSteden hospital, The Netherlands.

Interventions

Gamma Knife Radiosurgery (GKRS)

GKRS is performed with a Leksell Gamma Knife® ICON, Elekta Instruments, AB. Depending upon the volume and location, a dose of 18-25 Gy is prescribed with 99-100% coverage of the target. Dose limits for organs at risk are as follows: brainstem: 18 Gy, optic chiasm, or optic nerves: 8-10 Gy.

Whole Brain Radiation Therapy (WBRT)

Dose and fractionation scheme will be at the discretion of the treating radiation oncologist (in a tertiary referral hospital dedicated to radiotherapeutic oncology), though most commonly used dose and fractionation schemes are 20 Gy in 5 fractions of 4 Gy (standard schedule in Europe) and 30 Gy in 10 fractions of 3 Gy (occasionally used schedule).

Table 1. Eligibility criteria

Inclusion criteria	Exclusion criteria

• Histologically proven malignant cancer
• Gadolinium-enhanced volumetric MRI-scan showing 11-20 newly diagnosed BM
• Cumulative tumour volume in the brain ≤30 cm^3
• Lesion >3 mm from the optic apparatus
• Patient age ≥18 years
• Karnofsky Performance Status ≥70
• Anticipated survival ≥3 months
• Patient informed consent obtained (verifying that patients are aware of the investigational nature of this study)
• Patients can be undergoing concurrent systemic therapy at the discretion of their treating oncologist
	• Primary brain tumor
	• A second active primary tumor
	• Small cell lung cancer, lymphoma, leukemia, meningeal disease
	• Prior brain treatment (radiation/surgery)
	• Upfront planned surgery after GKRS
	• History of a significant neurological or psychiatric disorder
	• Participation in a concurrent study in which neuropsychological or quality of life assessments are involved
	• Underlying medical condition precluding adequate follow-up
	• Patients unable to complete test battery due to any of the following reasons:
	  • Lack of basic proficiency in Dutch
	  • IQ <85
	  • Severe aphasia
	  • Paralysis grade 0-3 (MRC scale)
	  • Severe visual problems

Neuropsychological assessment and patient-reported outcomes

A reliable, valid neuropsychological test battery (Table 2) is used to assess cognitive functioning [40,42,43] and is administered by a trained neuropsychologist. In addition, measures of patient-reported outcomes (PROs) are used to assess anxiety and depression, quality of life and fatigue (Table 2). The total time for neuropsychological test administration, including assessment of PROs, ranges from approximately 60 to 90 minutes.

Assessment of outcome

Primary endpoint

The primary endpoint is the between-group difference in the percentages of patients with significant memory decline at 3 months after treatment. Memory decline is defined as a 5-point decrease from baseline in HVLT-R Total Recall score, based on a reliable change index (RCI). [44] This definition is based on the result reported by Chang et al. in 2009. [45]

Secondary endpoints

- Differences in percentages of patients with a ≥5-point decrease in HVLT-R total recall between treatment arms are evaluated at 6, 9, 12 and 15 months as is done for the primary endpoint at 3 months
- Group mean scores for all neuropsychological tests and questionnaires are determined for both treatment arms at baseline, 3, 6, 9, 12 and 15 months
- Percentages of patients with cognitive impairment are determined at baseline, 3, 6, 9, 12 and 15 months
- Overall survival is calculated as the time from the first day of treatment to date of death
- The RANO-BM criteria [46] (Response Assessment in Neuro-Oncology Brain Metastases) are used to determine local and distant tumour control

Randomisation

A software package (ALEA®) is used to support the online patient registration and randomisation, which is based on the **minimization method**. [47] Groups are balanced on various prognostic factors. This method has been proven to provide more balanced groups in smaller trials when compared with both restricted (stratified) and unrestricted (simple) randomisation and is able to incorporate more prognostic factors. [47-49] The Dutch Cancer Institute provides access to the online minimization program. [50] Eligible patients are assigned in 1:1 to either GKRS or WBRT. Prognostic factors included in the minimization algorithm are:

- Cumulative tumour volume in the brain (≤10 cm^3 vs. >10 cm^3)
- Histology (lung vs. other)
- Any systemic treatment (yes vs. no)
- Karnofsky Performance Status (70-80 vs. 90-100)
- Age (18-59 vs. 60 and over)
- Baseline HVLT-R (≤17 vs. 18-27 vs. ≥28, based on the trial by Chang et al., 2009)

Statistical Methods

The Bayesian power analysis and interim analyses are based on the randomised trial by Chang and colleagues. [45] An independent statistician will do interim monitoring of this trial using Bayesian statistical methods. [51,52] Each patient's HVLT-R total recall score recorded at 3 months is assigned a binary outcome: A decline in the total recall score of 5 points or greater compared with baseline will be considered a *failure* (0). A stable or improved score, or a decline of 4 points or less compared with baseline will be considered a *success* (1). The failure rate for treatment k is designated qk. The prior failure rates for both treatment groups will be modelled as Beta(2.09,

2.91)-distributions, with a mean of 0.42 for both groups (for details see Appendix A). During the trial, stopping rules specify that in the case of a probability greater than 0.975 for the event that the failure rate of one treatment group is higher than the failure rate of the other treatment group, we will stop randomising patients to that treatment-arm. In this case, the study is terminated prematurely, and the central research question will be answered. If the effect sizes are comparable to earlier accounts in the literature (following Chang et al. an effect size of 0.30 is expected), the early stopping rule will likely come into effect when 46 patients are enrolled (23 patients at 3-months follow-up in both groups; Appendix A).

Group analyses are carried out on an intent-to-treat principle. Raw cognitive test scores are compared with published normative values according to age (and, if available, to education) and converted into standardized scores. Cognitive impairment is defined as test performance at or below -1.5 SD from the normative mean. [6,53] Reliable change indices (RCI), reflecting change at the individual level in the context of observed changes based on published normative data, correcting for measurement errors are calculated, since group results may mask the variability in individual responses to the intervention. [44] Number of patients, who have improved versus the number of patients who remained stable, or declined, will be counted for all follow-up assessments. These will be compared over conditions with chi-squared tests.

Repeated measures analysis of variance with adjustment for potential confounders will be used, comparing subsequent follow-ups to baseline to assess cognitive change of group means over time and across treatment arms. These analyses are similar to those of the study of Chang et al. in which an identical cognitive endpoint was formulated. [45]

Missing data, if not too many, will be explicitly or implicitly (dependent on the statistical technique of choice) imputed to facilitate intention-to-treat analysis. Multiple imputation may be used for explicit imputation of missing values. Alternatively, we may use linear mixed models that implicitly deal with missing data under the assumption of missing at random.

Type and duration of systemic therapy and medication use will be taken into account if necessary.

Operational considerations

In case of new intracranial tumour activity, patients in both treatment arms may receive additional WBRT or GKRS at the discretion of the treating radiation-oncologist.

Table 2. Neuropsychological test battery and patient-reported outcomes

Cognitive Domain	**Cognitive Test**
Verbal memory	Hopkins Verbal Learning Test-Revised (HVLT-R)
Cognitive flexibility	Trail Making Test B (TMT B)
Word Fluency	Controlled Oral Word Association (COWA)
Working memory	Wechsler Adult Intelligence Scale - Digit Span
Processing speed	Wechsler Adult Intelligence Scale - Digit Symbol
Motor dexterity	Grooved Pegboard (GP)
Patient Reported Outcomes	**Questionnaire**
Quality of life	Functional Assessment of Cancer Therapy-Brain (FACT-Br) [a] • Physical well-being (PWB) • Functional well-being (FWB) • Social well-being (SWB) • Emotional well-being (EWB) • Brain Cancer Subscale (BRCS)
Fatigue	Multidimensional Fatigue Inventory (MFI)[a] • General fatigue • Reduced motivation • Physical fatigue • Mental fatigue • Reduced activity
Anxiety and depression	Hospital Anxiety and Depression Scale (HADS) [b] • Anxiety • Depression

[a]Published normative data of FACT-Br and MFI are used for the interpretation of quality of life and fatigue scores [55,56]

[b] A cut-off point ≥8 is used to indicate symptoms of depression or anxiety [57]

Discussion

Over the past decade, the management of patients with brain metastases has changed substantially. WBRT has long been the mainstay of treatment, especially in patients with more than 3 or 4 brain metastases. However, increasingly more patients with brain metastases are treated with SRS. SRS is well established in patients with a limited number of brain metastases (1-4) and research on SRS in patients with multiple (>4) brain metastases is growing steadily. According to the *American Society for Radiation Oncology* (ASTRO) and the *National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology* (NCCN) there now is growing evidence suggesting that the cumulative *volume* of the brain metastases, rather than the *number* of brain metastases, is a better selection criterion for SRS. Accordingly, the NCCN guideline no longer specifies an upper limit for the number of brain metastases. [38,39]

In addition, concerns about the potential late adverse effects of WBRT on cognitive function has led to decreased use of (adjuvant) WBRT. Compared to WBRT, SRS has

a better ability to spare healthy tissue because of the high level of precision and quick dose fall-off. Therefore, few(er) negative cognitive side-effects could be expected after treatment with SRS.

Cognitive functions are essential to our daily functioning and quality of life. Since more patients with brain metastases live longer after treatment, reducing or preventing (late) cognitive side effects is of great importance. CAR-Study B will yield information on which treatment modality, GKRS or WBRT, best preserves cognitive functions and quality of life of these patients. In addition to survival and tumour related outcomes, CAR-Study B measures relevant clinical outcomes, such as depression, anxiety and fatigue which are important psychological factors that may influence cognitive functioning. [54] Together with other trials, CAR-Study B may help diminish the controversy about the role of SRS versus WBRT in the management of multiple BM.

We chose the 3-months primary endpoint because *early* effects of radiation on cognition, albeit mostly transient, can negatively affect patients' quality of life. Moreover, at this point in time we will be able to assess cognitive function in as many of the patients enrolled, maintaining the highest possible statistical power.

The more persistent *late delayed* effects of radiation on cognitive functioning become apparent 6-12 months after treatment [22] and may be most disruptive for patients' quality of life. For this reason, we have also included long-term assessments in our design. Information on test performance in long-term survivors is essential for complete comprehension of the course of cognitive functions over time, even though many of the enrolled patients may have deceased at this point in the study.

This study may be highly relevant in clinical decision-making; knowledge gained from this trial may possibly change clinical practice and international guidelines on BM. For example, thus far in the Netherlands, the standard of care for patients with multiple brain metastases (>4) has remained WBRT. Ultimately, the purpose of CAR-Study B is to inform patients and doctors which treatment modality, GKRS or WBRT, best preserves cognitive functions and quality of life. This will enable patients and doctors to make shared treatment decisions grounded on scientific evidence and consequently maximize the clinical outcome of each individual patient.

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Appendix A.

For the Bayesian stopping rule, a weakly informative prior is employed with Beta(2.09,2.91)-distributions for both treatment groups. This prior contains the same amount of information as the prior of Chang et al. (2009). Furthermore, the prior mean is equal to 0.42 which is the sample average of the failure rates based on the results of Chang et al. The prior is displayed in Figure 2. The trial is terminated prematurely when the probability of the event that the failure rate of one treatment group, as computed under the Bayesian model, is higher than the failure rate of the other treatment group is greater than 0.975. Following Chang et al. an effect size of 0.30 is expected. A power analysis of the Bayesian stopping rule revealed the expected Bayesian probability as a function of the sample size n (Figure 3). The figure shows that for n=46 (23 patients in each group) and using a 0.3 effect size, it is expected that there is a 0.975 probability that the failure rate of WBRT treatment as found in the study is larger than the failure rate of GKRS treatment. Hence, we deem early stopping relatively likely if the effect sizes are comparable to earlier accounts in the literature.

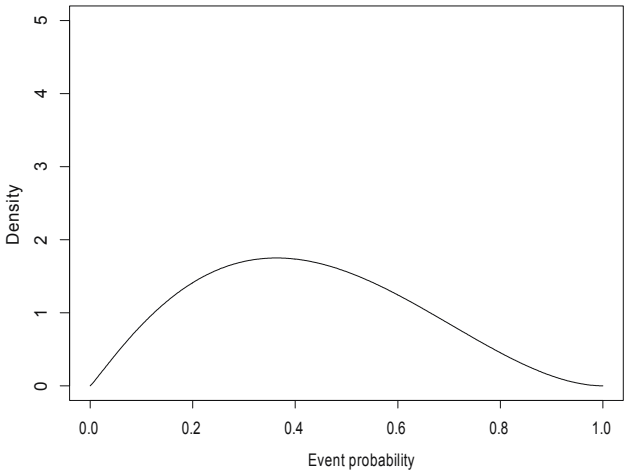

Figure 2. Prior distributions for failure rates of both groups, with prior mean 0.42.

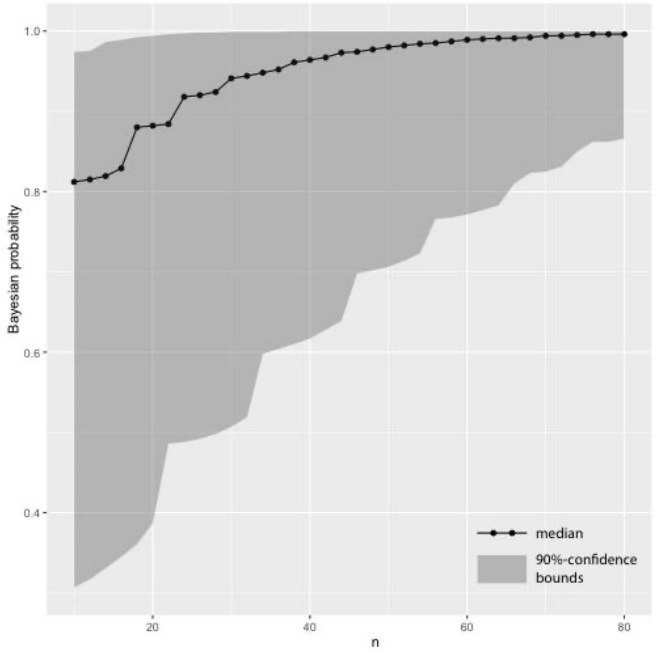

Figure 3. Bayesian power study

References

1. Kaal EC, Niël CG, Vecht CJ. Therapeutic management of brain metastasis. The Lancet Neurology. 2005;4:289–98.
2. Lippitz B, Lindquist C, Paddick I, Peterson D, O'Neill K, Beaney R. Stereotactic radiosurgery in the treatment of brain metastases: The current evidence. Cancer Treatment Reviews. Elsevier Ltd; 2014;40:48–59.
3. Khalsa SSS, Chinn M, Krucoff M, Sherman JH. The role of stereotactic radiosurgery for multiple brain metastases in stable systemic disease: a review of the literature. Acta Neurochir (Wien). 2013;155:1321–8.
4. Niranjan A, Lunsford LD, emerick RL. Stereotactic radiosurgery for patients with metastatic brain tumors: development of a consensus radiosurgery guideline recommendation. Basel: KARGER; 2012;25:123–38.
5. Rahmathulla G, Toms SA, Weil RJ. The Molecular Biology of Brain Metastasis. J Oncol. 2012;2012:1–16.
6. Chang EL, Wefel JS, Maor MH, Hassenbusch SJ, Mahajan A, Lang FF, et al. A pilot study of neurocognitive function in patients with one to three new brain metastases initially treated with stereotactic radiosurgery alone. Neurosurgery. 2007;60:277–83–discussion283–4.
7. Arvold ND, Lee EQ, Mehta MP, Margolin K, Alexander BM, Lin NU, et al. Updates in the management of brain metastases. Neuro-oncology. 2016;18:1043–65.
8. Elaimy AL, Mackay AR, Lamoreaux WT, Fairbanks RK, Demakas JJ, Cooke BS, et al. Clinical Outcomes of Stereotactic Radiosurgery in the Treatment of Patients with Metastatic Brain Tumors. World neurosurgery. 2011;75:673–83.
9. Ellis TL, Neal MT, Chan MD. The Role of Surgery, Radiosurgery and Whole Brain Radiation Therapy in the Management of Patients with Metastatic Brain Tumors. International Journal of Surgical Oncology. 2012;2012:1–10.
10. Perez-Larraya JG, Hildebrand J. In: Biller J, Ferro JM, editors. Handbook of Clinical Neurology. Elsevier; 2014. p. 1143–57.
11. Wefel JS, Parsons MW, Gondi V, Brown PD. Neurocognitive aspects of brain metastasis. Handb Clin Neurol. Amsterdam: Elsevier. 2018;149:155–65.
12. Platta CS, Khuntia D, Mehta MP, Suh JH. Current Treatment Strategies for Brain Metastasis and Complications from Therapeutic Techniques. American Journal of Clinical Oncology. 2010;33:398–407.
13. Mehta MP. Survival and Neurologic Outcomes in a Randomized Trial of Motexafin Gadolinium and Whole-Brain Radiation Therapy in Brain Metastases. Journal of Clinical Oncology. 2003;21:2529–36.
14. Barani IJ, Larson DA, Berger MS. Future directions in treatment of brain metastases. Surg Neurol Int. 2012;4:S220–30.
15. McTyre E, Scott J, Chinnaiyan P. Whole brain radiotherapy for brain metastasis. Surg Neurol Int. Medknow Publications; 2013;4:S236–44.
16. Abe E, Aoyama H. The Role of Whole Brain Radiation Therapy for the Management of Brain Metastases in the Era of Stereotactic Radiosurgery. Curr Oncol Rep. 2011;14:79–84.
17. Habets EJJ, Dirven L, Wiggenraad RG, Verbeek-de Kanter A, Lycklama À Nijeholt GJ, Zwinkels H, et al. Neurocognitive functioning and health-related quality of life in patients treated with stereotactic radiotherapy for brain metastases: a prospective study. Neuro-oncology. Oxford University Press; 2016;18:435–44.
18. Brown PD, Jaeckle K, Ballman KV, Farace E, Cerhan JH, Anderson SK, et al. Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases. JAMA. 2016;316:401–9.
19. Suh JH. Stereotactic radiosurgery for the management of brain metastases. N. Engl. J. Med. 2010;362:1119–27.
20. Tsao MN. Brain metastases: advances over the decades. Ann Palliat Med. 2015;4:225–32.

21. Cochran DC, Chan MD, Aklilu M, Lovato JF, Alphonse NK, Bourland JD, et al. The effect of targeted agents on outcomes in patients with brain metastases from renal cell carcinoma treated with Gamma Knife surgery. J Neurosurg. 2012;116:978–83.
22. Greene-Schloesser D, Robbins ME, Peiffer AM, Shaw EG, Wheeler KT, Chan MD. Radiation-induced brain injury: A review. Front Oncol. 2012;2:73.
23. Baschnagel A, Wolters PL, Camphausen K. Neuropsychological testing and biomarkers in the management of brain metastases. Radiat Oncol. BioMed Central Ltd. 2008;3:1–12.
24. Dietrich J, Monje M, Wefel J, Meyers C. Clinical Patterns and Biological Correlates of Cognitive Dysfunction Associated with Cancer Therapy. The Oncologist. 2008;13:1285–95.
25. Soussain C, Ricard D, Fike JR, Mazeron J-J, Psimaras D, Delattre J-Y. CNS complications of radiotherapy and chemotherapy. Lancet. 2009;374:1639–51.
26. Greene-Schloesser D, Moore E, Robbins ME. Molecular pathways: radiation-induced cognitive impairment. Clin. Cancer Res. American Association for Cancer Research; 2013;19:2294–300.
27. Tofilon PJ, Fike JR. The radioresponse of the central nervous system: a dynamic process. Radiat. Res. 2000;153:357–70.
28. Suh JH. Hippocampal-avoidance whole-brain radiation therapy: a new standard for patients with brain metastases? Journal of Clinical Oncology. American Society of Clinical Oncology; 2014;32:3789–91.
29. Gondi V, Hermann BP, Mehta MP, Tomé WA. Hippocampal dosimetry predicts neurocognitive function impairment after fractionated stereotactic radiotherapy for benign or low-grade adult brain tumors. Radiation Oncology Biology. 2012;83:e487–93.
30. Linskey ME, Andrews DW, Asher AL, Burri SH, Kondziolka D, Robinson PD, et al. The role of stereotactic radiosurgery in the management of patients with newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol. 2009;96:45–68.
31. Douglas J, Goodkin R. A simple treatment planning strategy for patients with multiple metastases treated with Gamma Knife surgery. 2006;105 Suppl:2–4.
32. Park S-H, Hwang S-K, Kang D-H, Lee S-H, Park J, Hwang J-H, et al. Gamma knife radiosurgery for multiple brain metastases from lung cancer. 2008;16:626–9.
33. Yamamoto M, Kawabe T, Sato Y, Higuchi Y, Nariai T, Watanabe S, et al. Stereotactic radiosurgery for patients with multiple brain metastases: a case-matched study comparing treatment results for patients with 2-9 versus 10 or more tumors. J Neurosurg. 2014;121 Suppl:16–25.
34. Ojerholm E, Lee JYK, Kolker J, Lustig R, Dorsey JF, Alonso-Basanta M. Gamma Knife radiosurgery to four or more brain metastases in patients without prior intracranial radiation or surgery. Cancer Med. 2014;3:565–71.
35. Kim C-H, Im Y-S, Nam D-H, Park K, Kim JH, Lee J-I. Gamma knife radiosurgery for ten or more brain metastases. J Korean Neurosurg Soc. 2008;44:358–63.
36. Hunter GK, Suh JH, Reuther AM, Vogelbaum MA, Barnett GH, Angelov L, et al. Treatment of five or more brain metastases with stereotactic radiosurgery. Int. J. Radiat. Oncol. Biol. Phys. Elsevier Inc; 2012;83:1394–8.
37. Suh JH, Chao ST, Angelov L, Vogelbaum MA, Barnett GH. Role of stereotactic radiosurgery for multiple (> 4) brain metastases. 2011;1:31–40.
38. Nabors LB, Portnow J, Ammirati M, Brem H, Brown P, Butowski N, et al. Central nervous system cancers, version 2.2014. Featured updates to the NCCN Guidelines. J Natl Compr Canc Netw. 2014;12:1517–23.
39. Soliman H, Das S, Larson DA, Sahgal A. Stereotactic radiosurgery (SRS) in the modern management of patients with brain metastases. Oncotarget. 2016;7:12318–30.
40. Wefel JS, Vardy J, Ahles T, Schagen SB. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. Lancet Oncol. Elsevier; 2011;12:703–8.

41. Rades D, Dziggel L, Segedin B, Oblak I, Nagy V, Marita A, et al. A new survival score for patients with brain metastases from non-small cell lung cancer. Strahlenther Onkol. 2013;189:777–81.
42. Witgert ME, Meyers CA. Neurocognitive and Quality of Life Measures in Patients with Metastatic Brain Disease. Neurosurgery Clinics of North America. 2011;22:79–85.
43. Meyers CA, Brown PD. Role and relevance of neurocognitive assessment in clinical trials of patients with CNS tumors. Journal of Clinical Oncology. 2006;24:1305–9.
44. Maassen GH, Bossema E, Brand N. Reliable change and practice effects: outcomes of various indices compared. J Clin Exp Neuropsychol. 3rd ed. Taylor & Francis Group; 2009;31:339–52.
45. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol. 2009;10:1037–44.
46. Lin NU, Lee EQ, Aoyama H, Barani IJ, Barboriak DP, Baumert BG, et al. Response assessment criteria for brain metastases: proposal from the RANO group. Lancet Oncol. 2015;16:e270–8.
47. Scott NW, McPherson GC, Ramsay CR, Campbell MK. The method of minimization for allocation to clinical trials. a review. Control Clin Trials. 2002;23:662–74.
48. O'Callaghan CA. OxMaR: Open Source Free Software for Online Minimization and Randomization for Clinical Trials. Añel JA, editor. PLoS ONE. 2014;9:e110761–10.
49. McPherson GC, Campbell MK, Elbourne DR. Use of randomisation in clinical trials: a survey of UK practice. Trials. BioMed Central; 2011;13:198–8.
50. ALEA online randomisation software. https://prod.tenalea.net/avl/dm/ Accessed 14 Feb 2018.
51. Thall PF, Simon R. Practical Bayesian guidelines for phase IIB clinical trials. Biometrics. 1994;50:337–49.
52. Saville BR, Connor JT, Ayers GD, Alvarez J. The utility of Bayesian predictive probabilities for interim monitoring of clinical trials. Clin Trials. SAGE Publications; 2014;11:485–93.
53. Lezak MD. Neuropsychological Assessment. Oxford University Press, USA; 2004.
54. Dirven L, Armstrong TS, Taphoorn MJB. Health-related quality of life and other clinical outcome assessments in brain tumor patients: challenges in the design, conduct and interpretation of clinical trials. Neurooncol Pract. 2015;2:2–5.
55. Smets EM, Garssen B, Bonke B, De Haes JC. The multidimensional fatigue inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res. 1995;39:315–25.
56. Weitzner MA, Meyers CA, Gelke CK, Byrne KS, Cella DF, Levin VA. The functional assessment of cancer therapy (FACT) scale. Development of a brain subscale and revalidation of the general version (FACT-G) in patients with primary brain tumors. Cancer. 1995;75:1151–61.
57. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the hospital anxiety and depression scale. An updated literature review. J Psychosom Res. 2002;52:69-77.

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Interim results from CAR-Study B: An ongoing randomized trial on the effect of SRS or WBRT on cognitive performance in patients with 11-20 brain metastases

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Abstract

Background Both stereotactic radiosurgery (SRS) and whole brain radiation therapy (WBRT) have proven to be effective treatments for multiple brain metastases (BM) with similar overall survival. Cognition and Radiation (CAR) Study B is a randomized trial on the effect of Gamma Knife radiosurgery (GKRS) or WBRT on cognitive performance in patients with 11-20 BM. The primary and secondary aim of this interim analysis were to check whether Bayesian stopping rules for cognitive failure were met, and to compare cognitive changes after treatment respectively, for the first 45 patients enrolled.

Methods Patients with 11-20 newly diagnosed BM on a triple-dose contrast-enhanced MRI-scan, expected survival >3 months and Karnofsky Performance Status (KPS) ≥70, were stratified by age, histology, total BM volume, systemic treatment, KPS, and baseline Hopkins Verbal Learning total recall (HVLT-R TR) score, and randomized 1:1 (minimization) to GKRS or WBRT. Neuropsychological tests were administered before (T0) treatment (n=21 vs n=20), and at 3 (T3; n=16 vs n=14) and 6 (T6; n=9 vs n=9) months thereafter. A decline of ≥5 points in HVLT-R TR score was considered a cognitive failure. The trial would be halted if the posterior probability for a higher cognitive failure rate in one group versus the other was >0.975 at T3 or T6 according to the employed beta (2.09,2.91) prior (prior mean of 42%), based on the average failure rates at 4 months reported by Chang et al. (2009). Between-group differences in changes of test performances over 6 months were analyzed using mixed ANOVAs. Proportions of cognitive changes (T0-T6) at the individual level based on reliable change indices correcting for practice effects, were determined.

Results HVLT-R TR failure rates in the GKRS versus WBRT group were 31% versus 29% at T3, and 0% versus 33% at T6. The observed failure rates after WBRT at T3 and T6 were lower than the average failure rates of Chang et al. (2009). Posterior probabilities were 0.451 at T3 and 0.918 at T6. Over 6 months, changes in performance on tests of immediate (p=.003) and delayed recall (p=.024), and information processing speed (p=.003) were significantly different between groups (large effect sizes), with significant declines after WBRT, but not after GKRS. Over 6 months, at the individual patient level, there were no declines in performances across all tests in the GKRS group (n=8) while performances declined in 4 out of 8 patients in the WBRT group.

Conclusions The stopping rules were not met since the posterior probabilities did not cross the threshold. Other preliminary findings in this small sample suggest that cognitive decline, both at group and individual level, is more pronounced after WBRT compared to GKRS. Accrual is continued (NCT02953717; ZonMw 842003006).

Introduction

Due to increased screening and improved systemic disease control, the incidence of brain metastases (BM), and particularly of multiple BM, is rising. [1,2] Radiotherapy remains the mainstay of treatment. Concern about the negative cognitive side-effects of whole brain radiation therapy (WBRT) has led to an increased use of stereotactic radiosurgery (SRS) as initial treatment for patients with up to 10 BM. [3–5] The optimal local treatment for patients with multiple (>10) BM, however, remains a topic of debate. [6–8] In the shared treatment decision-making process, patient and physician together evaluate and discuss the patient's preference and values regarding the benefits and risks of the available treatment options. The treatment decision is influenced by a manifold of prognostic and clinical factors including age, expected survival, performance status, prior treatment(s), histology, extracranial diseases status, the size, location, and number of BM, and the current (inter)national guidelines. [9]

Both SRS and WBRT have proven to be effective treatments for multiple BM with similar overall survival. [10] Adjuvant WBRT after SRS has been shown to improve local control and prevent recurrences but carries an increased risk of cognitive decline and does not improve survival compared to SRS with surveillance (salvage treatment). [11]

The US guideline on BM no longer specifies an upper limit for the number of BM, as emerging evidence supports the hypothesis that the total volume rather than the number of BM is a better eligibility criterion. [12] Hence, the application of SRS is now rapidly expanding to patients with multiple BM.

Although technological improvements now allow for hippocampal avoidance with WBRT (HA-WBRT), or HA-WBRT with a simultaneous integrated boost dose to the BM (HA-SIB-WBRT), to better preserve cognitive functions [13–15], conventional WBRT remains the standard of treatment for patients with >10 BM in Europe. [1] The long-term cognitive effects of HA-WBRT are yet to be evaluated. [16]

Cognition and Radiation Study B (CAR-Study B), to our knowledge one of the first randomized trials that directly compares (conventional) WBRT to SRS, evaluates cognitive change up to 15 months after single fraction GKRS or WBRT in patients with 11-20 BM using a comprehensive neuropsychological test battery including the Hopkins Verbal Learning Test-Revised (HVLT-R). [17]

The current paper presents interim results of CAR-Study B that concern the primary outcome measure (failure rates for decline on HVLT-R total recall), and secondary

outcome measures (change in cognitive test performances) from baseline to three (T0-T3) and six months (T0-T6) after treatment of the first 41 eligible patients. We especially focused on the second interval because potential, often persistent, late delayed effects of radiation on cognitive functioning become apparent about 6 months after treatment [14,18], and because these effects may be most disruptive for patients' quality of life. [19] Changes in test performance are assessed at group and individual patient level. In addition, test performances of longer-term survivors up until 15 months after treatment are described (T0-T15).

Given the paucity of evidence on this topic we deem it important to communicate these interim results of this ongoing trial. We believe this preliminary information is of interest to patients with >10 BM and their doctors as it can be used in the shared decision-making process.

Methods

Design

This paper presents preliminary interim results from the ongoing randomized trial CAR-Study B (45 patients enrolled). CAR-Study B (Clinical trials ID NCT02953717) was approved by the Medical Ethics Committee Brabant (MEC file NL53447.028.15). The full study protocol has been published in 2018 and includes a detailed description of the eligibility criteria, randomization method, tests, and questionnaires, and stopping rules. [17] The updated study protocol, with an additional stopping rule at T6, equal to the one at T3, has been approved by the MEC in 2019. In short, adult cancer patients with 11 to 20 BM on a triple-dose contrast-enhanced MRI-scan, a total BM volume ≤ 30 cm^3, a Karnofsky Performance Status (KPS) ≥ 70 were recruited at the Gamma Knife Center, Elisabeth-TweeSteden hospital (Tilburg, the Netherlands).

Randomisation

Patients were assigned 1:1, using a software package (ALEA□) which is based on the minimization method[20], to either GKRS or WBRT. Factors that were included in the minimization algorithm were: total volume of BM (≤ or >10 cm^3), histology (lung or other), systemic treatment for primary cancer (yes or no), KPS (70-80 or 90-100), age (<or ≥60) and baseline Hopkins Verbal Learning Test-Revised (HVLT-R) raw test score (≤17 or 18-27 or ≥28).

Procedure

During the first consultation visit, the radiation-oncologist screened for study eligibility, after which eligible patients, received study information. Patients provided written informed consent prior to enrollment and randomization. The neuropsychological assessments (NPAs) were scheduled after the first consultation (baseline; T0) and were repeated at 3 (T3), 6 (T6), 9 (T9), 12 (T12) and 15 (T15) months after treatment. In case of local recurrences and/or new BM, patients in both arms received salvage treatment (GKRS, WBRT or surgery) as long as it was considered clinically meaningful.

Study treatments

GKRS was performed with a Leksell Gamma Knife® ICON, Elekta Instruments AB (Stockholm, Sweden). Depending upon the volume and location, a GKRS dose of 18-25 Gy was delivered to the target with 99-100% coverage. Dose limits for organs at risk were 18Gy for the brainstem and 8Gy for the optic nerves (there was no dose limit set for the hippocampus).

Patients randomly assigned to (conventional) WBRT received 20 Gy in five fractions of 4 Gy (or 30 Gy in 10 fractions of 3 Gy), delivered 5 days a week.

Clinical outcomes

Patient characteristics were retrieved from patients' medical records. Baseline total volume of BM was determined using triple-dose contrast-enhanced T1-weighted images (1.5-mm slices). Overall survival (OS) was defined as the interval between date of enrollment and date of death from all causes, or date of last follow-up for survivors. Causes of death were assessed by the radiation-oncologist, based on imaging and clinical evaluation. The cause of death was classified as: *intracranial* in case of stable systemic disease and evidence of progression of the treated BM, development of new BM, intracranial bleeding, complications of seizures, or leptomeningeal disease; *extracranial* in case of extracranial (systemic) progression and stable intracranial disease; *both* in case of documented intra and extracranial progression; *intercurrent* in case the cause of death was not related to the tumor; or *unknown*.

Neuropsychological assessment

Cognitive functioning was measured with a well-established battery [21,22], including six neuropsychological tests, generating 11 test variables (duration approximately 60 minutes): The HVLT-R, a verbal memory test, with six parallel versions (immediate and delayed verbal recall, and recognition), Trail Making Test (TMT-A; psychomotor speed and TMT-B; cognitive flexibility), Controlled Oral Word Association with two parallel

versions (COWA; word fluency), Wechsler Adult Intelligence Scale (WAIS) Digit Span (attention span and working memory), WAIS Digit Symbol (information processing speed) and Grooved Pegboard (GP; dominant and non-dominant hand dexterity).

Statistical Analyses

To compare patient characteristics between groups at T0, T3 and T6, independent samples t-tests, and chi-square/Fisher Exact tests were performed. To analyze overall survival (OS), Kaplan-Meier curves were used. OS was compared between groups using log-rank tests. Logit transformation was employed as a method for estimation of the confidence intervals to address skewed data.

The applied Bayesian interim analysis focused on dichotomized change scores of the HVLT-R total recall score at T3 and T6. These change scores were considered a failure (≥5 points decline) or a success (stable/improved/≤4 points decline). Failure rates at T3 and T6 were calculated. The prior failure rates for both treatment groups were modelled as Beta(2.09, 2.91)-distributions, with a prior mean of 42%, based on the randomized trial by Chang et al.[23] The trial would be terminated early if the posterior probability for a higher failure rate in one group compared to the other is >0.975 at 3 or 6 months.

For normative purposes, raw cognitive test scores were converted into socio-demographically adjusted z scores, based on data from our control group including age, sex and education as covariates. [24,25] Follow-up z scores were also corrected for practice effects. [26]

To test for between-group differences in mean cognitive performances at T0 and T6, independent samples t-tests were used. To examine whether mean test performances followed a different trajectory over time after GKRS or WBRT, mixed ANOVAs with between-subjects factor *group* (GKRS vs WBRT) and within-subjects factor *time* (T0, T3, T6) were performed for each test variable. Post-hoc pairwise comparisons with Bonferroni adjustments were conducted when appropriate. In case of statistical significance, test performances for these measures were further explored at the individual level in a small group of long-term survivors (T0-T15).

Reliable change indices (RCIs) were calculated using formula 10 as proposed by Maassen et al. [27], for each individual patient for T0-T3, T0-T6 and T0-T15. RCIs reflect change in test performance in *individual* patients in the context of observed changes in the control group and allow for correcting for measurement error including practice effects. [27] RCI values ≥1.645 and ≤-1.645 were defined as reliable improvement and decline (otherwise ‘stable’/no change).

At the individual patient level, patients were categorized based on their RCI values into four patient-level categories (visualized by histograms): (i) 'decline' (≥2 declines and ≤1 improvement on any of the 11 test variables); (ii) 'improvement' (≥2 improvements and ≤1 decline); (iii) 'both' (≥2 declines and ≥2 improvements); (iv) 'stable' (≤1 decline and ≤1 improvement).

All statistical analyses were performed with SPSS Statistics 28.0, except for the evaluation of the stopping rule and the survival analysis, which were performed with R, version 3.6.1 (R Core Team 2019). [28,29]

Results

The literature Between October 13, 2016, and August 26, 2019, 45 patients were enrolled and randomized. Four patients were excluded after randomization (Figure 1). Eventually, 41 patients were treated with GKRS (n=21) or WBRT (n=20). Median time-to-treatment initiation was 3 days (range 1-12) in the GKRS group versus 8 days (2-25) in the WBRT group (one patient in this group received 10 fractions of 3 Gy). Most patients had primary lung cancer and the median number of BM was 12 (IQR 11-15) and 12.5 (IQR 12-17.5) in the GKRS and WBRT group, respectively. Patient characteristics (Table 1), including the variables used in the minimization algorithm, did not significantly differ between groups at T0, T3 or T6, except for the use of dexamethasone at T0 (p=.0307): more patients used dexamethasone in the GKRS group compared to the WBRT group.

Median OS did not significantly differ between groups ($\chi^2(1) = .002$, p=.9650): 5.3 months (95% CI 3.5–15.0; 2 out of 21 patients were censored) for the GKRS group and 6.9 months for the WBRT group (95% CI 5.8–14.9; 2 out of 20 censored).

The cause of death in the GKRS versus WBRT group was classified as intracranial (n=5 versus n=2), extracranial (n=10 versus n= 8), both (n=3 versus n=7), intercurrent (n=0 versus n=0), or unknown (n=1 versus n= 1).

Applied Bayesian stopping rules

In January 2020, after 45 patients were enrolled and randomized, the Bayesian interim analysis was performed at T3 (n=30) and T6 (n=18). Failure rates after GKRS versus WBRT were as follows: 31% (5/16) versus 29% (4/14) at T3, and 0% (0/9) versus 33% (3/9) at T6. The posterior probabilities of 0.451 (T3) and 0.9175 (T6) for the event that the failure rate for decline in the HVLT-R total recall score after WBRT was

higher than after GKRS, did not cross the threshold of 0.975 at T3 nor at T6. Hence, accrual was continued.

Cognitive Status at Baseline and at 3 and 6 Months after GKRS or WBRT

Most of the patients' mean baseline test scores were below the normative mean with group mean deviations up to -2.2 SD. At baseline, patients assigned to GKRS (versus WBRT) performed somewhat worse on most test variables but there were no statistical differences in any of the mean test performances at this time-point, nor at six months after treatment (independent samples t-tests, p-values >.1000). In both groups, we observed that mean z scores for performances on almost all test variables remained negative at T3 and T6 (Supplemental Table 1).

Change in Cognitive Performance at Group Level

Figure 2 visualizes the course of test performances (n=9 in both groups) over the first six months after treatment. There was a statistically significant (cross-over) interaction with large effect size between treatment and time for immediate verbal recall (p=.0034, η^2p=.30), delayed verbal recall (p=.0235, η^2p=.21), and information processing speed (p=.0028, η^2p=.31), indicating that, mean test performances changed differently after GKRS (showing minimal change) as compared to WBRT (showing significant decline). Post-hoc comparisons showed that *within* the WBRT group significant decline in performances (mean difference in z scores; *MD*) for immediate verbal recall and information processing speed occurred from both baseline to T3 (p=.0361, *MD* = .9, 95% CI .05–1.7 and p=.0057, *MD* = .9, 95% CI .3–1.6) and from baseline to T6 (p=.0106, *MD* = .9, 95% CI .2–1.6 and p=.0338, *MD* = .8, 95% CI .1–1.5); for delayed verbal recall decline occurred from baseline to T6 (p=.0080, *MD* = 1.4, 95% CI .3–2.4).

Table 1. Patient characteristics

Baseline characteristics [a]	**Baseline**		**3 months**		**6 months**	
	GKRS	**WBRT**	**GKRS**	**WBRT**	**GKRS**	**WBRT**
Number of patients (n, %)	**21**	**20**	**16**	**14**	**9**	**9**
Sex, male	12 (57)	8 (40)	8 (50)	7 (50)	4 (44)	4 (44)
*Age (yr), median (range)	64 (41-85)	60 (34-74)	59 (41-85)	60 (34-71)	58 (43-75)	60 (52-71)
Educational level [b]						
Low	12 (57)	10 (50)	7 (44)	7 (50)	5 (56)	6 (67)
Middle	3 (14)	7 (35)	3 (19)	6 (43)	1 (11)	2 (22)
High	6 (29)	3 (15)	6 (38)	1 (7)	3 (33)	1 (11)
*KPS, median (range)	90 (70-100)	90 (80-100)	90 (70-100)	90 (80-100)	100 (70-100)	90 (90-100)
70-80	5 (24)	4 (20)	3 (19)	1 (7)	1 (11)	0 (0)
90-100	16 (76)	16 (80)	13 (81)	13 (93)	8 (89)	9 (100)
RPA: Class 1 (favorable)	11 (52)	7 (35)	10 (63)	6 (43)	5 (56)	5 (56)
Class 2	10 (48)	13 (65)	6 (38)	8 (57)	4 (44)	4 (44)
DS-GPA:						
Class 1 (favorable)	1 (5)	2 (10)	1 (6)	2 (14)	0 (0)	2 (22)
Class 2	8 (38)	5 (25)	7 (44)	4 (29)	5 (56)	3 (33)
Class 3	11 (52)	12 (60)	7 (44)	8 (57)	4 (44)	4 (44)
Class 4	1 (5)	1 (5)	1 (6)	0 (0)	0 (0)	0 (0)
Number of BM, median (IQR)	12 (11-15.0)	12.5 (12-17.5)	12 (11-14.8)	12.5 (12-16.5)	12 (11-15.5)	13 (11.5-16.5)
*Volume of BM cm^3, median (IQR)	10.2 (4.7-16.7)	9.1 (3.1-18.4)	7.4 (4.3-14.7)	8.4 (2.5-21.9)	6.1 (4.7-11.3)	4.6 (1.6-22.1)
*Histology						
Lung	15 (71)	14 (70)	11 (69)	11 (79)	6 (67)	7 (78)
Breast	2 (9)	2 (10)	2 (13)	1 (7)	1 (11)	1 (11)
Melanoma	0 (0)	3 (15)	0 (0)	2 (14)	0 (0)	1 (11)
Renal	1 (5)	1 (5)	1 (6)	0 (0)	1 (11)	0 (0)
Other	3 (15)	0 (0)	2 (13)	0 (0)	1 (11)	0 (0)
*Systemic therapy(yes) [c]	9 (43)	9 (45)	8 (50)	7 (50)	6 (67)	3 (33)
Chemotherapy [d]	9 (43)	4 (20)	8 (50)	3 (21)	6 (67)	2 (22)
Synchronous BM	9 (43)	9 (45)	7 (44)	6 (43)	3 (33)	4 (44)
Extracranial hematogenous metastases (yes)	7 (33)	10 (50)	5 (31)	6 (43)	3 (33)	3 (33)
Symptomatic BM (yes)	13 (62)	13 (65)	10 (63)	8 (57)	6 (67)	4 (44)
Use of anti-epileptic drugs (yes)	3 (14)	3 (15)	2 (13)	3 (21)	2 (22)	1 (11)
Use of dexamethasone (yes)	18 (86)	11 (55)	13 (81)	7 (50)	7 (78)	3 (33)
HVLT-R Total recall						
*Raw score, mean (SD)	23 (5.1)	24 (5.1)	24 (5.0)	25 (4.8)	23 (5.2)	25 (4.5)
Z score, mean (SD)	-0.3 (1.0)	-0.1 (1.1)	-0.2 (1.1)	0.4 (0.9)	-0.6 (-1.1)	0.2 (0.7)

GKRS, Gamma Knife radiosurgery; WBRT, whole brain radiation therapy; BM, brain metastases; KPS, Karnofsky performance status; RPA, recursive partitioning analysis; DS-GPA, diagnosis-specific graded prognostic assessment; IQR, interquartile range; HVLT-R, Hopkins verbal learning test - revised; CI95 95% confidence interval [a] Percentages may not total 100 due to rounding [b] Educational level (Verhage, 1964; 7 levels): Low = 1-4, Middle = 5, High = 6-7 [c] Before or at time of GKRS or WBRT [d] Alone only or in combination with other systemic therapies * (Prognostic) factors that were included in the minimization algorithm

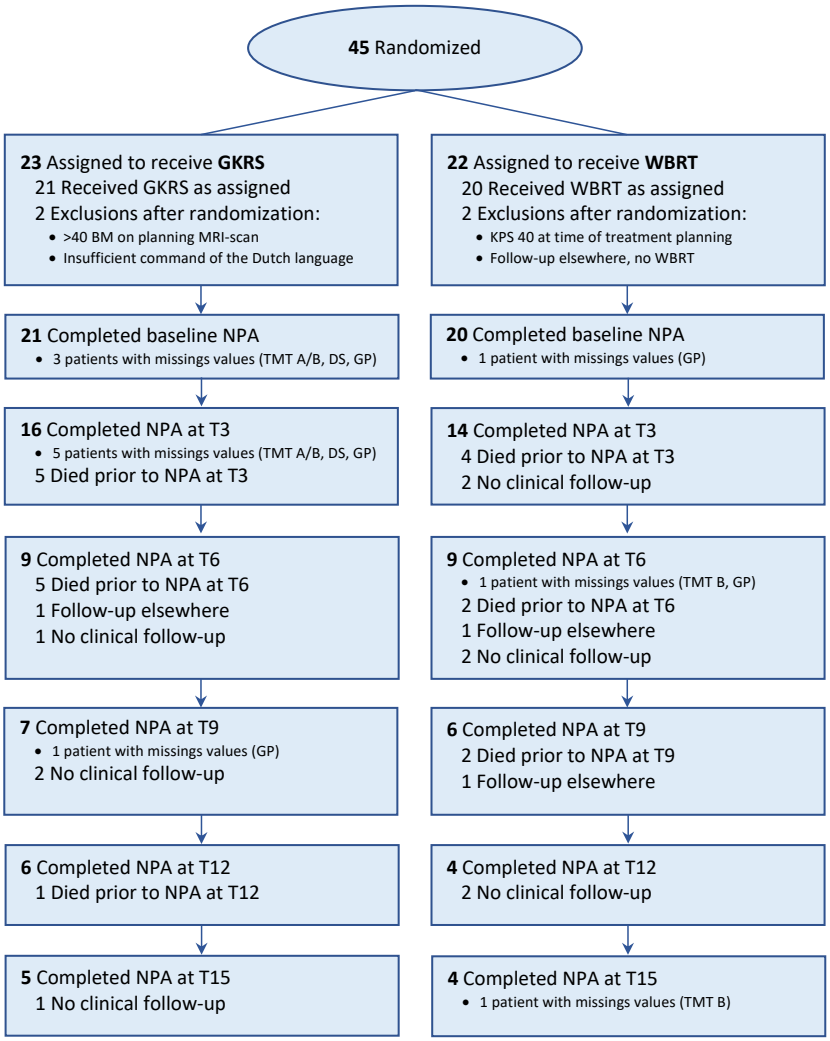
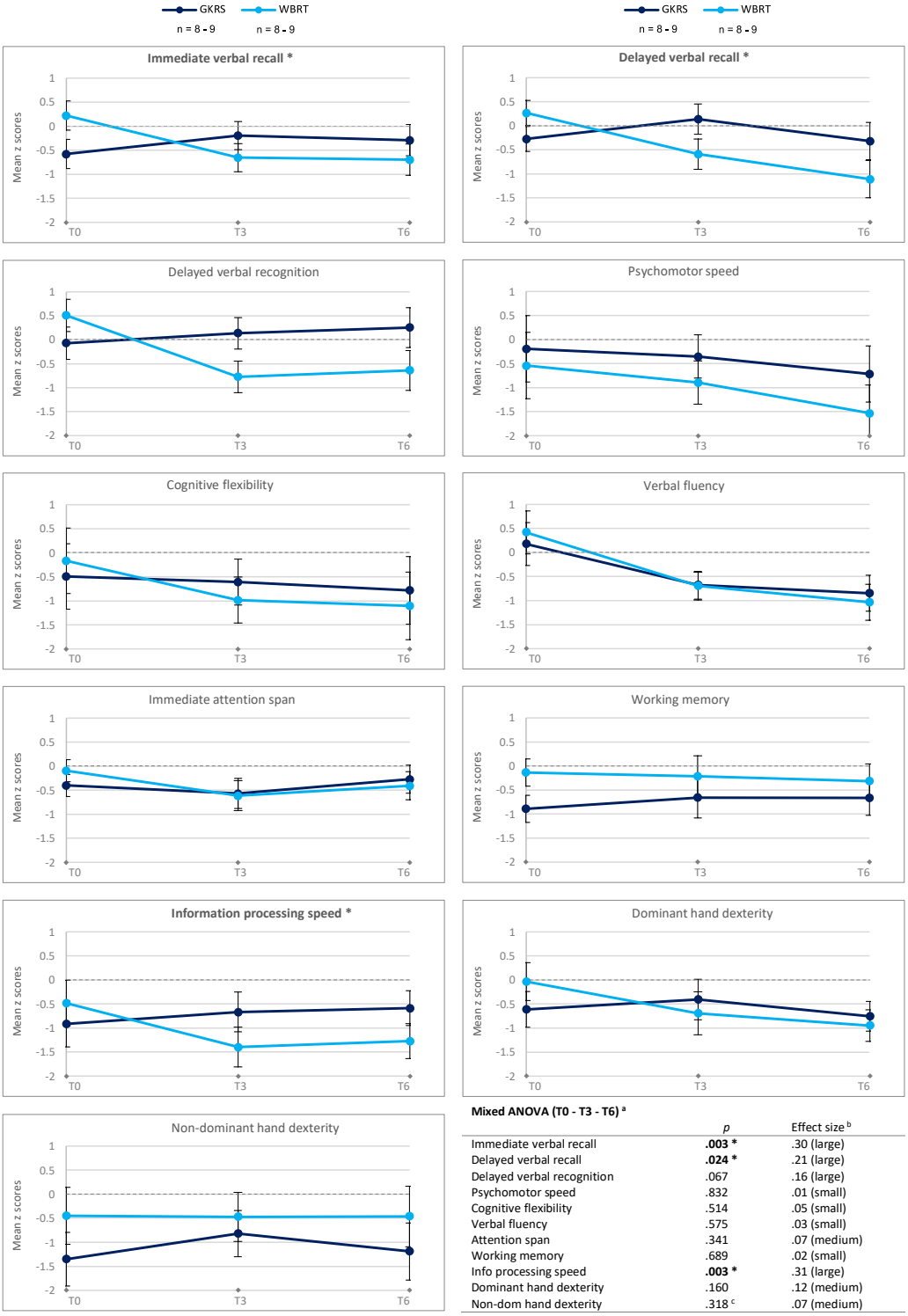


Figure 1. Patient flow of the first 45 patients in CAR-Study B

GKRS, Gamma Knife radiosurgery; WBRT, whole brain radiation therapy; BM, brain metastases; KPS, Karnofsky performance status; NPA, neuropsychological assessment; TMT, Trail Making Test (A and B); DS, Digit Symbol; GP, Grooved Pegboard; T0, baseline; T3, T6, T9, T12, T15, 6-, 9-, 12-, and 15-months follow-up. In total and over time, for 10 patients (24%) scores on one to three tests were missing due to: unfamiliarity with the alphabet (TMT), inability to complete the test (TMT), patient's explicit wish to stop (TMT), visual problems (TMT, DS, GP), invalid assessment (GP), impairments in dexterity (DS, GP), and tiredness (GP)

> **Figure 2**. Mean performances ± standard error

T0, baseline; T3, T6, 3- and 6-months follow-up; GKRS, Gamma Knife radiosurgery; WBRT, whole brain radiation therapy. Lower z scores indicate worse performance. The dashed line represents the normative mean (M = 0) * Indicates a significant interaction effect between group and time [a] Mixed ANOVA with between-subjects factor group and within-subject factor time [b] Partial eta squared: small (η2p = .01), medium (η2p = .06), and large (η2p = .14) effects c Greenhouse-Geisser correction



Mixed ANOVA (T0 - T3 - T6) [a]

	p	Effect size [b]
Immediate verbal recall	**.003** *	.30 (large)
Delayed verbal recall	**.024** *	.21 (large)
Delayed verbal recognition	.067	.16 (large)
Psychomotor speed	.832	.01 (small)
Cognitive flexibility	.514	.05 (small)
Verbal fluency	.575	.03 (small)
Attention span	.341	.07 (medium)
Working memory	.689	.02 (small)
Info processing speed	**.003** *	.31 (large)
Dominant hand dexterity	.160	.12 (medium)
Non-dom hand dexterity	.318 [c]	.07 (medium)

Verbal Memory Performance and Information Processing Speed in Long-term Survivors at the Individual Level

At the individual level, the course of test performance on immediate recall, delayed recall and information processing speed remained stable *up to 15 month*s in three out of the five long-term survivors in the GKRS group (Figure 3). The two other long-term survivors showed reliable improvement in delayed verbal recall and information processing speed, or in delayed verbal recall only. In the WBRT group, test performances on these measures remained stable over 15 months in two out of the four long-term survivors and declined in the other two patients (one patient declined on all three tests and one patient declined on information processing speed only).

Change in Cognitive Performance across tests for each individual patient

Over six months, we observed that test performances remained stable in 6 out of 8 patients in the GKRS group, while 2 improved. Test performances declined in 4 out of 8 patients in the WBRT group (Figure 4), remained stable for 3, and improved for 1 patient.

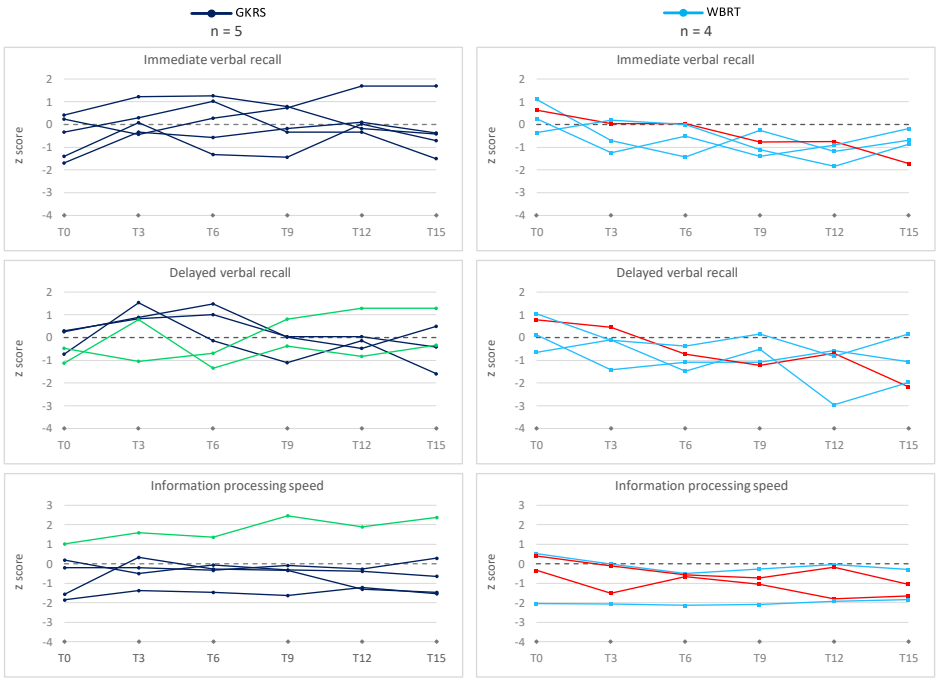


Figure 3. Individual z-scores from baseline to 15-months after GKRS or WBRT

GKRS, Gamma Knife radiosurgery; WBRT, whole brain radiation therapy. A higher score means better performance. The red and green lines indicate a reliable cognitive decline (red) or improvement (green) over time from baseline to 15-months follow-up, based on the RCI (cut-off value +/- 1.645). Lower z scores indicate worse performance. The dashed line represents the normative mean (M = 0)

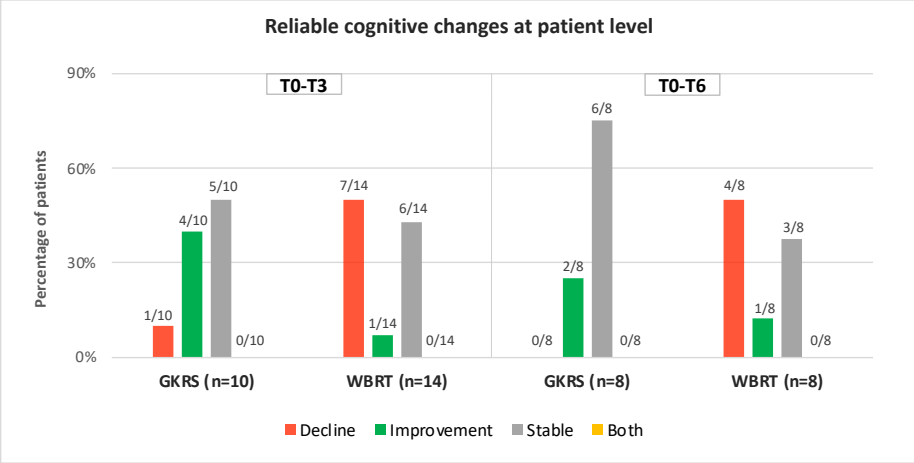


Figure 4. Reliable cognitive changes after GKRS or WBRT at the individual patient level

T0, baseline; T3, T6, 3- and 6-months follow-up; GKRS, Gamma Knife radiosurgery; WBRT, whole brain radiation therapy. Patient-level categories: (i) 'decline' (≥2 declines and ≤1 improvement on any of the 11 test variables); (ii) 'improvement' (≥2 improvements and ≤1 decline); (iii) 'both' (≥2 declines and ≥2 improvements); (iv) 'stable' (≤1 decline and ≤1 improvement). Note. None of the patients were categorized as 'Both'

Discussion

Both SRS and WBRT have proven to be effective treatments for multiple BM with similar overall survival. [10] The question, which treatment modality, GKRS or WBRT, best preserves cognitive functioning in patients with more than 10 BM, addresses a highly relevant and important research topic. CAR-Study B is one of the first randomized trials to assess change in cognitive test performance in patients with 11-20 newly diagnosed brain metastases up to 15 months after randomization to either GKRS or WBRT using a comprehensive neuropsychological test battery. The current paper presents interim results of CAR-Study B that provide gained insights into cognitive test performances over time of the first 41 patients as well as an evaluation of the pre-specified stopping rules.

The early data showed insufficient support to justify early termination of the trial since the posterior probabilities, for the event that failure rates for verbal memory (decline) were higher in the WBRT versus the GKRS group, did not cross the threshold at 3 or 6 months after treatment. Hence, accrual was continued. The observed failure rates after WBRT at 3 and 6 months, were lower than the expected failure rate according to the employed beta (2.09,2.91) prior (having a prior mean of 42%), which was based on the average failure rates reported by Chang et al. at 4 months. [23]

Our other findings, both at group and individual level, suggest that cognitive decline was more pronounced after WBRT compared to GKRS. Changes in mean cognitive performances differed significantly between groups over a period of six months (n=9 in both groups). There were significant declines in immediate and delayed verbal recall and information processing speed after WBRT but there were no significant changes after GKRS. Performance on these measures also remained stable (or improved) in the five long-term survivors in the GKRS group, while in the WBRT group we observed declined performance on these measures in two out of the four long-term survivors. At the individual *patient* level, we observed more patients with declined performance in the WBRT group compared to the GKRS group over six months after treatment.

Given the paucity of evidence on this topic, we believe that it is important to communicate the first interim results of this ongoing trial, and that these interim results are of interest to patients with >10 BM and their doctors as this information can (cautiously) be used in the shared decision-making process. The preliminary results presented here should be interpreted with caution as sample sizes are still small, and we are awaiting more robust findings from the ongoing trial.

However, our findings are in line with a recently published abstract on a randomized trial by Li and colleagues. [30] By using the HVLT-R, COWA and TMT, cognitive functioning was assessed in patients with 4-15 BM who were randomized to either SRS or WBRT (a small majority of patients in the WBRT arm also received the neuroprotective agent memantine). Four months after treatment (total n=31) mean immediate verbal recall scores significantly improved in the SRS arm but declined in the WBRT arm. A similar result, significant improvement after SRS and decline after WBRT, was found regarding a composite score including HVLT-R, COWA and TMT. Median OS appeared higher (10.4 versus 8.4 months in the SRS and WBRT group; non-significant) than in our study (5.3 versus 6.9 months; non-significant). An explanation for this may be the fact that patients with 1-3 BM who were previously treated with SRS were also allowed on their trial. These patients might represent a patient group with more favorable prognosis, despite the subsequent development of multiple BM after the initial treatment with SRS. In addition, their study included patients with a lower median number of BM at enrollment: 8 versus 12 in our trial. Unfortunately, we were not able to compare additional patient characteristics (such as the number and, in particular total volume of BM, age, functional/performance status, etc.) as the results have only been published in an abstract. The authors conclude that in patients with 4-15 BM SRS was associated with a reduced risk of cognitive decline compared to WBRT, without compromising OS.

Additionally, in a single arm trial by Minniti and colleagues [7], cognitive functioning was assessed with the HVLT-R (only) in 40 patients with 10-21 BM (median 13) and total volume of BM <15cm^3 at 3 (n=32), 6 (n=26), 12 months (n=21) after SRS. Percentages of decline for immediate and delayed recall and recognition ranged between 4.7% and 18.7% across all follow-ups (based on an RCI). The higher median OS (14.1 versus 5.3 months in our GKRS study arm) may, in part, be explained by the younger age of their patients (median age 57 versus 64 years) and the lower total volume of the BM (4.7cm^3 versus 10.2cm^3). The authors concluded that learning and memory performance is preserved in most patients with >10 BM after SRS.

The findings of these studies emphasize the importance of the continuation of CAR-Study B, generating additional data that will allow for more reliable conclusions.

There are limitations to consider. As mentioned, the current evaluation is based on a small number of patients and there was a relatively high dropout rate (which is inherent to this patient population). The most common reason for dropout was death, due to either intra- or extracranial disease progression. Moreover, there were five patients at T3 in the GKRS group (versus none in the WBRT group) with missing values. The missing values did not concern the primary outcome (failure rates for decline in *verbal* memory). In addition, test performances were also analyzed at the individual patient level, including patients with complete scores on all measures only. However, these missing values concerned tests with high motor demands such as the TMT (4 missings), Digit Symbol (2 missings) and GP (4 missings). This may have caused a bias towards better mean performance in the GKRS group. In addition, measuring change in mean test performance in a terminal stage may cause a bias toward better long-term cognitive performance, as 'decliners' may dropout after which mean scores may increase or show less decline. It should however be noted that dropout rates were comparable between both groups, and analyses were also performed at the individual patient level. Finally, it is very difficult to disentangle the cognitive effects of radiation therapy (GKRS/WBRT) from the effects of the intracranial and extracranial disease status, systemic treatments, salvage treatments, additional medications or treatments, and time to radiation and systemic treatment initiation. Eventually, with increased power (larger sample size) CAR-Study B will be able to provide more definite answers and examine and report on the influence of some of these confounding factors.

Notwithstanding these limitations, the interim results suggest that cognitive decline is more pronounced after WBRT compared to GKRS. Aiming to prevent or delay cognitive decline to maintain quality of life is a clinically significant treatment goal

for patient with multiple BM who have a relatively short life expectancy. Ultimately, CAR-Study B aims to assist doctors and individual patients in making shared treatment decisions to maximize the clinical outcome and quality of life of patients.

Supplementary tables

Supplemental Table 1. Cognitive Performance at group level

	Mean z score (SD)				Mean z score (SD)		Mean z score (SD)			
	GKRS vs WBRT at T0				T3		GKRS vs WBRT at T6 [a]			
	GKRS (n=19-21)	WBRT (n=19-20)	*p*	Effect size [b]	GKRS (n=13-16)	WBRT (n=14)	GKRS (n=9)	WBRT (n=8-9)	*p*	Effect size [b]
Immediate verbal recall	-0.33 (1.02)	-0.07 (1.12)	0.45	-0.23	-0.39 (1.11)	-0.39 (1.13)	-0.29 (1.15)	-0.70 (0.76)	0.39	0.40
Delayed verbal recall	-0.27 (0.88)	0.04 (1.01)	0.30	-0.32	-0.25 (1.34)	-0.51 (1.10)	-0.32 (1.11)	-1.11 (1.22)	0.17	0.65
Delayed verbal recognition	-0.44 (1.58)	0.12 (1.09)	0.19	-0.41	-0.04 (0.88)	-0.62 (1.20)	0.25 (0.73)	-0.64 (1.61)	0.15	0.68
Psychomotor speed	-0.08 (1.13)	-1.09 (2.37)	0.10	0.54	-1.27 (2.60)	-0.97 (1.36)	-0.72 (1.39)	-1.53 (2.05)	0.34	0.44
Cognitive flexibility	-0.57 (1.49)	-0.96 (1.99)	0.50	0.21	-1.24 (1.78)	-1.41 (2.40)	-0.93 (2.05)	-1.11 (1.82)	0.85	0.09
Verbal fluency	0.26 (1.52)	-0.05 (0.98)	0.44	0.24	-0.75 (1.02)	-0.72 (0.82)	-0.85 (1.20)	-1.03 (1.04)	0.73	0.16
Attention span	-0.13 (1.01)	-0.12 (0.67)	0.99	-0.01	-0.51 (0.87)	-0.50 (0.87)	-0.27 (0.96)	-0.41 (0.78)	0.75	0.15
Working memory	-0.35 (0.95)	-0.30 (0.89)	0.88	-0.05	-0.57 (1.19)	0.03 (1.37)	-0.67 (0.96)	-0.32 (1.18)	0.50	-0.31
Info processing speed	-1.00 (1.00)	-0.87 (1.27)	0.72	-0.11	-1.64 (1.87)	-1.47 (1.05)	-0.59 (1.08)	-1.27 (1.10)	0.20	0.60
Dominant hand dexterity	-1.26 (2.13)	-0.67 (1.58)	0.33	-0.31	-0.81 (1.43)	-0.80 (1.10)	-0.75 (1.12)	-0.95 (0.64)	0.67	0.20
Non-dom hand dexterity	-2.21 (2.64)	-1.50 (3.08)	0.45	-0.25	-1.13 (1.65)	-0.82 (1.17)	-1.19 (2.28)	-0.46 (0.91)	0.41	-0.39

T0, baseline; T3, T6, 3- and 6-months follow-up; GKRS, Gamma Knife radiosurgery; WBRT, whole brain radiation therapy; diff, difference; SD, standard deviation [a] Independent samples t tests [b] Hedges' correction: Interpretable as Cohen's d effect sizes: small (d = .2), medium (d = .5), and large (d = .9) effects. Lower z scores indicate worse performance

References

1. Kraft J, Mayinger M, Willmann J, *et al.* Management of multiple brain metastases: a patterns of care survey within the German Society for Radiation Oncology. *J Neuro-oncol* 2021; **152**: 395–404.
2. Tabouret E, Chinot O, Metellus P, Tallet A, Viens P, Gonçalves A. Recent trends in epidemiology of brain metastases: an overview. *Anticancer Res* 2012; **32**: 4655–62.
3. Grinsven EE van, Nagtegaal SHJ, Verhoeff JJC, Zandvoort MJE van. The Impact of Stereotactic or Whole Brain Radiotherapy on Neurocognitive Functioning in Adult Patients with Brain Metastases: A Systematic Review and Meta-Analysis. *Oncol Res Treat* 2021; **44**: 622–36.
4. Achrol AS, Rennert RC, Anders C, *et al.* Brain metastases. *Nat Rev Dis Primers* 2019; **16**: 1–26.
5. Moravan MJ, Fecci PE, Anders CK, *et al.* Current multidisciplinary management of brain metastases. *Cancer* 2020; **126**: 1390–406.
6. Chaung KV, Sloan AE, Choi S. Limited brain metastases: a narrative review. *Ann Palliat Medicine* 2021; **10**: 6016–27.
7. Minniti G, Capone L, Nardiello B, *et al.* Neurological outcome and memory performance in patients with 10 or more brain metastases treated with frameless linear accelerator (LINAC)-based stereotactic radiosurgery. *J Neuro-oncol* 2020; **148**: 47–55.
8. Ferini G, Viola A, Valenti V, *et al.* Whole Brain Irradiation or Stereotactic RadioSurgery for five or more brain metastases (WHOBI-STER): A prospective comparative study of neurocognitive outcomes, level of autonomy in daily activities and quality of life. *Clin Transl Radiat Oncol* 2022; **32**: 52–8.
9. Mehta MP, Ahluwalia MS. Whole-brain radiotherapy and stereotactic radiosurgery in brain metastases: what is the evidence? *American Society of Clinical Oncology Educational Book* 2015; **35**: e99-e104.
10. Wefel JS, Parsons MW, Gondi V, Brown PD. Neurocognitive aspects of brain metastasis. *Handb Clin Neurol* 2018; **149**: 155–65.
11. Kocher M, Wittig A, Piroth MD, *et al.* Stereotactic radiosurgery for treatment of brain metastases: A report of the DEGRO Working Group on Stereotactic Radiotherapy. *Strahlenther Onkol* 2014; **190**: 521–32.
12. Nabors LB, Portnow J, Ammirati M, *et al.* Central nervous system cancers, version 2.2014. Featured updates to the NCCN Guidelines. *J Natl Compr Canc Netw* 2014; **12**: 1517–23.
13. Chia BSH, Leong JY, Ong ALK, *et al.* Randomised prospective phase II trial in multiple brain metastases comparing outcomes between hippocampal avoidance whole brain radiotherapy with or without simultaneous integrated boost: HA-SIB-WBRT study protocol. *Bmc Cancer* 2020; **20**: 1045.
14. Gondi V, Pugh SL, Tome WA, *et al.* Preservation of Memory With Conformal Avoidance of the Hippocampal Neural Stem-Cell Compartment During Whole-Brain Radiotherapy for Brain Metastases (RTOG 0933): A Phase II Multi-Institutional Trial. *J Clin Oncol* 2014; **32**: 3810–6.
15. Brown PD, Gondi V, Pugh S, *et al.* Hippocampal Avoidance During Whole-Brain Radiotherapy Plus Memantine for Patients With Brain Metastases: Phase III Trial NRG Oncology CC001. *Journal of Clinical Oncology* 2020; **38**: JCO1902767.
16. Andratschke N, Belderbos J, Mayinger M, Schagen SB, Ruysscher DD. Hippocampal Avoidance and Memantine for Whole-Brain Radiotherapy: Long-Term Follow-Up Warranted. *J Clin Oncol* 2020; **38**: 3454–5.
17. Schimmel WCM, Verhaak E, Hanssens PEJ, Gehring K, Sitskoorn MM. A randomised trial to compare cognitive outcome after gamma knife radiosurgery versus whole brain radiation therapy in patients with multiple brain metastases: research protocol CAR-study B. *BMC Cancer* 2018; **18**: 218.
18. Tallet AV, Azria D, Barlesi F, *et al.* Neurocognitive function impairment after whole brain radiotherapy for brain metastases: actual assessment. *Radiat Oncol* 2012; **7**: 1–8.
19. Greene-Schloesser D, Robbins ME, Peiffer AM, Shaw EG, Wheeler KT, Chan MD. Radiation-induced brain injury: A review. *Front Oncol* 2012; **2**: 73.
20. Scott NW, McPherson GC, Ramsay CR, Campbell MK. The method of minimization for allocation to clinical trials. a review. *Control Clin Trials* 2002; **23**: 662–74.

21. Witgert ME, Meyers CA. Neurocognitive and Quality of Life Measures in Patients with Metastatic Brain Disease. *Neurosurgery Clinics of North America* 2011; **22**: 79–85.
22. Wefel JS, Vardy J, Ahles T, Schagen SB. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. *Lancet Oncol* 2011; **12**: 703–8.
23. Chang EL, Wefel JS, Hess KR, *et al.* Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol* 2009; **10**: 1037–44.
24. Rijnen SJM, Meskal I, Emons WHM, *et al.* Evaluation of Normative Data of a Widely Used Computerized Neuropsychological Battery: Applicability and Effects of Sociodemographic Variables in a Dutch Sample. *Assessment* 2020; **27**: 373–83.
25. Schimmel WCM, Gehring K, Hanssens PEJ, Sitskoorn MM. Cognitive functioning and predictors thereof in patients with 1-10 brain metastases selected for stereotactic radiosurgery. *J Neurooncol* 2019; **22**: 1–12.
26. Schimmel WCM, Verhaak E, Bakker M, Hanssens PEJ, Sitskoorn MM, Gehring K. Group and Individual Change in Cognitive Functioning in Patients With 1 to 10 Brain Metastases Following Gamma Knife Radiosurgery. *Clin Oncol* 2021; **33**: 314–21.
27. Maassen GH, Bossema E, Brand N. Reliable change and practice effects: outcomes of various indices compared. *J Clin Exp Neuropsychol* 2009; **31**: 339–52.
28. R Core Team. R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2019, https://www.R-project.org/.
29. Therneau T (2021). *A Package for Survival Analysis in R*. R package version 3.2-13, https://CRAN.R-project.org/package=survival.
30. Li J, Ludmir EB, Wang Y, *et al.* Stereotactic Radiosurgery versus Whole-brain Radiation Therapy for Patients with 4-15 Brain Metastases: A Phase III Randomized Controlled Trial. *Int J Radiat Oncol Biology Phys* 2020; **108** (suppl): 21–2 (abstr).

7

General discussion and directions for future research

Summary, general discussion and future directions

General objective

Diagnostic and therapeutic progress has led to longer survival in cancer patients with rising incidence of brain metastases. [1] Many patients present with multiple brain metastases at initial diagnosis. [2–4] Over the years, the clinical management of brain metastases has evolved considerably. Historically, radiation to the whole brain (whole brain radiation therapy; WBRT) has been the cornerstone of treatment. In contrast to WBRT, stereotactic radiosurgery (SRS) delivers a high radiation dose to visible brain metastases only with low radiation dose to the surrounding brain tissue. Both SRS and WBRT have proven to be effective treatments for brain metastases with similar overall survival. [5–8] As the survival of cancer patients is increasing, the prevention or delay of radiation-induced cognitive decline to maintain quality of life has become a highly relevant treatment goal for patients with brain metastases. [9]

Cognition and Radiation (CAR) Studies A and B

In this doctoral dissertation we examined the impact of SRS versus WBRT on cognitive functioning in adult patients with up to 20 brain metastases. Firstly, we performed a systematic literature review to summarize and evaluate the available information pertaining to the cognitive side effects of SRS, alone or in combination with WBRT, in patients with brain metastases (**Chapter 2**). Secondly, we designed two clinical trials assessing cognitive functioning in patients with up to 10 brain metastases (Cognition and Radiation Study A; CAR-Study A) and 11 to 20 brain metastases (CAR-Study B), respectively.

CAR-Study A is a prospective single-center, single-arm longitudinal trial. Cognitive functioning was assessed before Gamma Knife radiosurgery (GKRS) and every three months thereafter, up to 21 months. For this dissertation, CAR-Study A data up until the follow-up assessment at nine months (T9; n=41), was used (**Chapters 3 and 4**).

CAR-Study B is a prospective randomized (multicenter) trial that compares cognitive effects up to 15 months after either GKRS or WBRT (**Chapter 5**). An interim analysis was performed after the first 41 eligible patients were enrolled (all recruited at the Gamma Knife Center Tilburg, ETZ; **Chapter 6**).

Both CAR-Studies were initiated at the Gamma Knife Center Tilburg, department of Neurosurgery, Elisabeth-TweeSteden Hospital (ETZ), in close collaboration with the department of Cognitive Neuropsychology of Tilburg University. The trial proposals were awarded with research grants from the Dutch organization for health research and

development (ZonMw) for a period of four years: from 2015 to 2019 for CAR-Study A and from 2016 to 2020 for CAR-Study B. Subsequently, research ethics committee approval for both studies was obtained in June 2015 (CAR-Study A) and October 2016 (CAR-Study B). In October 2017, CAR-Study B, originally a single-center trial, also received research ethics committee approval for a second collaborative research site, the Antoni van Leeuwenhoek hospital (AvL) in Amsterdam. In March 2020, additional funding from Elekta Instrument AB (Sweden) was granted for the (prolonged) continuation and completion of CAR-Study B.

Neuropsychological tests and additional questionnaires

Cognitive functioning was measured using a formal neuropsychological test battery measuring several cognitive domains, including verbal learning and memory, cognitive flexibility, word fluency, information processing speed, and hand dexterity. In addition, three questionnaires, measuring fatigue, health-related quality of life, and symptoms of anxiety and depression were administered. For normative purposes, we recruited a control group consisting of 104 adults without cancer. The control group was assessed at 3 and 6 months after the first assessment. This allowed us to correct for practice effects. Both patients and controls signed for informed consent before the start of the studies, and all completed the same tests and questionnaires.

This section provides a summary and general discussion of the results of this thesis. Methodological challenges and limitations, translation of our findings into clinical practice, and recommendations for future research are discussed.

Summary and discussion of the main research findings

The systematic literature search (**Chapter 2**) showed that, prior to the start of the CAR-Studies, little research had been conducted in this field. Moreover, only few studies used objective neuropsychological tests to assess cognitive functioning after SRS (versus WBRT) in patients with brain metastases. Six out of the 12 clinical trials (mostly patients with up to 4 brain metastases) that were identified, relied on the Mini-Mental State Examination (MMSE), a screening tool for dementia, solely to assess cognitive functioning. However, the MMSE is known to be rather insensitive to cognitive changes after radiotherapy. [10] Moreover, none of the studies corrected for potential practice effects due to repeated neuropsychological testing over time (e.g., improvements in test performances due to familiarity with the test and the test procedures). Additionally, differences in study designs and neuropsychological tests, but also variations in the definition and calculation of cognitive change, made it difficult to compare results.

Nonetheless, in general, the studies we reviewed suggest that patients with brain metastases show little to no objective cognitive decline in the early phase after SRS, followed by a trend towards improvement or stabilization up to 12 months after SRS. Because these studies did not correct for practice effects, cognitive decline may have been masked or cognitive improvements may have been overestimated. Although higher intracranial tumor control rates were achieved with the addition of WBRT to SRS, no survival benefit was observed. However, the combination of WBRT and SRS resulted in significantly more cognitive decline over time.

At the time of publication, the systematic literature search revealed no evidence of published randomized trials that directly compared cognitive outcomes after stereotactic SRS or WBRT in patients with more than 10 brain metastases.

CAR-Study A

Further to our review, we assessed the incidence and severity of cognitive impairments at baseline (prior to GKRS), at the group and individual level, in 92 patients with up to 10 brain metastases (**Chapter 3**). We showed that patients already suffer from cognitive impairments prior to treatment of brain metastases, which is in line with previous research. [11–16] At group level, patients performed significantly worse than controls on all 11 tests (mostly with large effect sizes). At the individual level, significantly more patients (62% and 46%) than controls (18% and 3%) suffered from severe cognitive deficits in at least two or three cognitive domains, respectively. Both at group and individual level, information processing, cognitive flexibility, and hand dexterity were affected most. Number and volume of brain metastases were not found to be predictive of pretreatment cognitive test performance.

As a next step, we evaluated group and individual cognitive changes over time in 41 patients with nine months follow-up after GKRS (**Chapter 4**). Our main finding, based on group-level linear mixed model analyses (LMMs), was that cognitive performances had not significantly changed over 9 months, except for significant improvements on immediate memory, working memory and information processing speed. There were no significant cognitive declines during this interval. Group analyses of three separate time intervals (of three months each) however, showed both cognitive improvements and declines after correction for practice effects. This indicates that although the overall course of performances remained stable up to nine months after GKRS, fluctuations in test performances at the group level do occur within the time intervals. Neither number nor volume of brain metastases influenced cognitive performances over time.

Evaluation of individual cognitive changes (per individual patient as well as per individual test and with correction for practice effects) also showed stable or improved cognitive performances in most patients (73%) up to nine months after GKRS, except for performances on nondominant hand dexterity. For this measure, there were significantly more improvements (27%) as well as declines (24%) in patients compared with our controls. The group-level results did not reflect these individual variations in hand dexterity. This stresses the importance of individual-level analyses, both at patient and at test level, in addition to group-level analyses as the latter can mask individual cognitive changes.

At nine months after treatment, patients still performed worse on most tests as compared with controls which illustrates the persistent character of the cognitive impairments. These findings were confirmed in another study of our research group in which we analyzed the course of cognitive test performances of long-term survivors in the same CAR-Study A cohort, up to 21 months after GKRS. [17] Herein, 38 long-term survivors who at least completed the follow-up neuropsychological assessment at 12 months after initial GKRS were included, of whom 21 completed the final assessment after 21 months. Cognitive performance was preserved or improved up to 21 months after GKRS, both at group and individual level and after correction for practice effects. In all, our findings at group-level in patients with up to 10 brain metastases are in line with the previous studies that were described in our systematic review. [11–13,15,16,18–20]

After publication of our review, three studies, including a secondary/additional analysis, have been published that also report on cognitive changes after SRS for (limited number of) brain metastases at the individual level. In accordance with our results, cognitive performances of most patients were preserved for at least six to twelve months after SRS. [19,21,22] However, the authors from the most recent study [22] stated that their results were not in line with our publication [23] (**Chapter 4**). Their main conclusion was that a considerable proportion of patients with brain metastases experience cognitive decline after SRS. This (non-randomized) study examined individual cognitive declines over three and six months after SRS using an RCI with correction for practice effects. SRS was delivered with a Gamma Knife (GKRS group; n=40) or a linear accelerator (LINAC group; n=29). [22] These groups were analyzed separately. In both groups, most patients had one to four brain metastases (like in our study) but there were significant differences between groups (GKRS versus LINAC) regarding the number of patients with >4 brain metastases (38% versus 7%; p = 0.001) and the mean total volume (standard deviation) of brain metastases (4.1 (4.8) versus 6.2 (10.4); p = 0.013). The upper limit of the number of brain metastases in both groups was not reported. To match these significantly different patient

characteristics, patients with six or more brain metastases from both groups were excluded for additional analyses. The same core test battery as in the CAR-Studies was used, except theirs did not include the Digit Symbol (a measure of information processing speed) and ours did not include the Boston Naming Test (assessing naming abilities/language). The definition of decline at test level (RCI values below −1.645) was similar between both studies but a different definition of decline at patient level was used: "≥2 declines on any of the 10 test variables" in their study as compared to "≥2 declines and ≤1 improvement on any of the 11 test variables" in our study. The authors argued that in our study, patients could 'overcompensate' for decline by improvements on other test variables. Firstly, this argument is only applicable to the analysis at the individual patient level, not to the individual test level. Secondly, in our study we used an additional category 'both', defined as "≥2 declines and ≥2 improvements". We considered a patient with decline on only one single test variable and improvement on one other single test variable as 'stable' because of the many (11) test variables. In case a patient would decline on two or more tests and improve on two or more of the other tests, this patient would have been classified as 'both' (not as 'stable' or 'improved') which would have been the case if we indeed allowed patients to overcompensate. Also, only two of 33 patients in our study were classified as 'both' for the 9-month interval (none of the patients were classified as such regarding the separate time intervals), indicating that only very few patients "compensated" for declines on two or more tests by improving on two or more of the other tests. The authors also stated that the statistical testing for differences between proportions of patients and controls in each category of cognitive change (decline, improvement, both or stable) in our study could be viewed as an overcorrection as these categories of cognitive change were already defined based on reliable change intervals in our control group. We recognize this might be a topic of discussion. In our control group (based on the same RCI formula) performances of a subgroup of controls had also changed over six months' time (2% to 9% decline and 3% to 7% improvement at test level) indicating that, to some degree, cognitive change 'normally' occurs in non-cancer controls. We chose to not to ignore this and to take these 'normal' fluctuations into consideration.

More importantly, percentages of decline and improvement were comparable between both studies, both at the individual test and patient level, even though the results were interpreted somewhat differently. At test level, performances declined in 3% to 13% of patients in their GKRS group and in 0% to 24% in their LINAC group over six months. In our study, performances of 2% to 24% of patients declined over nine months after GKRS. Stability or improvement at test level occurred in 87% to 97% of patients after GKRS and in 76% to 100% of patients after LINAC based SRS

(compared to 76% to 98% in our study). At the individual patient level, cognitive performances on at least two tests declined in 23% (GKRS) and 24% (LINAC) of patients, compared to 21% of patients in our study. Percentages of improvement on at least two tests were also comparable between studies: 25% (GKRS group) and 24% (LINAC group; supplemental information) compared to 33% in our patients. The authors underline the fact that considerable proportions of individual patients (patient level) suffered from cognitive declines after SRS.

Considering our work and all acquired evidence to date, the general conclusion of CAR-Study A is that at group level, GKRS does not cause additional cognitive decline in patients with up to 10 brain metastases. Furthermore, at the individual level, performances remain stable in most patients although cognitive fluctuations (declines as well as improvements) may occur in a subset of patients.

CAR-Study B

In **Chapter 5**,we presented the study protocol of CAR-Study B. Patients with 11 to 20 brain metastases were randomized to either GKRS or WBRT using the minimization method. Stratification factors included patients' age, histology, cumulative volume of the brain metastases, systemic treatment, Karnofsky Performance Score (KPS), and baseline Hopkins Verbal Learning Test - Revised (HVLT-R) score. The primary objective was to determine the between-group difference in the percentages of patients with significant decline in immediate verbal recall at three and six months after treatment as assessed with the HVLT-R. Interim monitoring was based on Bayesian statistics. Early stopping rules specified that the trial would be terminated prematurely in case the risk of verbal memory decline would be higher after WBRT than after GKRS at three or six months after treatment (posterior probability >0.975). The interim analysis was performed in January 2020 after 41 eligible patients were enrolled and randomly assigned to receive GKRS (n=20) or WBRT (n=21). The primary aim of the interim analysis (**Chapter 6**) was to check whether the Bayesian stopping rules for cognitive failure were met. The secondary aim was to compare cognitive changes after treatment between groups. The early data showed insufficient support to justify early termination of the trial because the stopping rules were not met at that time. Hence, the accrual was continued.

Our preliminary findings suggested that patients in the GKRS group experienced less cognitive decline over time compared to those in the WBRT group, both at group and individual level and after correction for practice effects. At group level, changes in cognitive performances differed significantly between groups over a period of six months (n=9 in both groups). There were statistically significant declines in mean

immediate and delayed verbal recall and information processing speed after WBRT but there were no significant changes after GKRS. The five long-term survivors (patients who completed the 15 months follow-up) in the GKRS group demonstrated stable (or improved; n=2) performance on these measures while we observed a decline in performances on these measures in two out of the four long-term survivors in the WBRT group. At the individual patient level, we observed more patients with declined performance in the WBRT group compared to the GKRS group over the period of six months after treatment.

In our literature review we already concluded that the addition of WBRT to SRS in patients with one to three brain metastases resulted in significantly more objective cognitive decline over time, based on two trials that randomized between either SRS or SRS plus WBRT. [12,15,20] Our preliminary findings that cognitive decline is more pronounced after WBRT compared to GKRS was supported by a more recent published abstract on a randomized trial by Li and colleagues. [5] In this study, cognitive functioning was assessed in 72 patients with four to 15 brain metastases who were randomized to either SRS or WBRT (a small majority of patients in the WBRT arm also received memantine). Four months after treatment, verbal memory as measured with the HVLT-R (n=31), significantly improved in patients in the SRS group but declined in patients who were treated with WBRT. A similar significant improvement after SRS and decline after WBRT was found for the composite cognitive score including multiple cognitive domains (HVLT-R, COWA and TMT). The authors concluded that SRS was associated with a reduced risk of cognitive decline compared to WBRT (even despite a small subgroup receiving memantine), without compromising survival.

In another recent, prospective single arm trial by Minniti and colleagues, verbal memory was assessed with the HVLT-R in 40 patients with 10 to 21 brain metastases up to 12 months after SRS (n=21). [21] Verbal memory remained stable in the majority of patients: 95%, 91% and 86% for immediate recall, delayed recognition, and delayed recall, respectively (compared to 98%, 90% and 85% up to nine months in our study). The authors concluded that SRS is a safe treatment for patients with 10 or more brain metastases, with a small risk of decline in immediate (4.7%) and delayed (14.2%) verbal memory, and delayed recognition (9.5%) at 12 months, comparable to the findings reported in patients with one to four brain metastases. Nevertheless, the interim results from CAR-Study B need to be interpreted carefully because the results are preliminary, and the study still needs to be finalized.

A second interim analysis was performed in April 2022 after 81 patients were enrolled. This time the data did show sufficient support to justify early termination of the trial as the prespecified stopping rule came into effect: The chance of verbal memory decline at six months was greater after WBRT than after GKRS. Consequently, CAR-Study B was halted. This suggests confirmation of our previous preliminary conclusions. Results from the second interim analysis were not discussed in this dissertation because the available data is currently being processed and analyzed. All (longer term) follow-up assessments were completed in January 2023. Before we will be able to answer the central research question, important variables need to be considered that may have influenced cognitive change after WBRT versus GKRS. These include, among others, the extracranial disease status, systemic therapies, intracranial tumor status, and location of the brain metastases. For the latter two, all baseline and follow-up metastases on MRI-scans are being (manually) segmented. [24] We are currently also exploring the possibilities of deep learning models for (fully) automated tracking and segmentation of brain metastases and peritumoral edema. [25–29]

Predictors of baseline cognitive functioning (prior to GKRS)

We examined potential predictors of baseline cognitive functioning in the CAR-Study A cohort (**Chapter 3**), using multivariable regression with correction for multiple statistical testing. We found that both clinical and psychological factors influenced pretreatment cognitive test performance. Mental fatigue was predictive of slower psychomotor speed. Symptomatic brain metastases, as opposed to asymptomatic, were predictive of declined immediate verbal memory. Patients with a metachronous (versus synchronous) diagnosis of brain metastases performed worse on delayed recognition and information processing speed. Posthoc analysis showed that patients with metachronous brain metastases had a lower Karnofsky performance status at baseline and had already received systemic treatment(s) for their primary tumor (mostly chemotherapy), whereas patients with synchronous brain metastases were almost all treatment naïve prior to enrollment. The primary tumor itself as well as the systemic therapies including chemotherapy may have contributed to the cognitive impairments that were already present before diagnosis of the brain metastases. [30–33] Previous studies showed that these (cancer-related) cognitive impairments primarily involve the domains of memory, attention, processing speed and executive functioning. [34,35]

The patients in CAR-Study A our study reported significantly more symptoms of anxiety and depression than our controls. We did not find a direct effect of anxiety and depression on cognitive test performance, in accordance with a previous study in patients with BM. This suggests that anxiety and depression may not be (primary) contributors to cognitive impairment in these patients. [36] Regarding the number and

the total volume of brain metastases, we found that neither of these factors were predictive of test performances on the 11 cognitive measures at baseline. Accordingly, the number of brain metastases was not associated with baseline cognitive functioning in previous studies (including two pilot studies). [11,13,14,16] The same studies did however find negative associations between total volume of brain metastases and baseline performance on measures of attention, verbal memory, information processing and executive functions. [11,13,14,16] . These findings were uncorrected for multiple testing and based on univariate analyses.

Predictors of cognitive change after radiotherapy for brain metastases

Specific patient- and tumor-specific factors can predict cognitive outcomes over time. Identification of these characteristics may allow for timely, more individually tailored care for patients. In our CAR-Study A cohort, performance status (KPS) at baseline influenced change in only one out of the 11 measures (multivariate analyses): patients with lower baseline KPS showed more improvement in verbal recognition over time (**Chapter 4**). In a previous study higher age was found to be predictive of cognitive decline over six months after SRS in patients with brain metastases. [22] We did not include age in our prediction models as the number of potential predictors that were allowed to be included was limited, given our sample size of 92 patients (CAR-Study A). In accordance with previous research, the number of brain metastases was not predictive of cognitive change after GKRS (in multivariate analyses). [16,22] Neither did we find any association between the total volume of brain metastases at baseline and change in cognitive test performances over time. In contrast, Habets and colleagues [16] found a univariate association between larger initial tumor volume (> 12.6 cm^3) and worse information processing speed over a period of six months after SRS. Performances on most measures however did not differ between patients with larger or smaller initial total tumor volumes. [16] Although we used the same definition of 'large', 'medium' and 'small' total volumes, the median total volume and its range differed between studies: 7.8cm^3 (range 0.12 – 63.9cm^3) in the study by Habets et al. (2016) and 5.6cm^3 (range 0.02 – 31.1cm^3) in the CAR-Study A cohort. Moreover, the study by Habets et al. included patients with up to 4 brain metastases whereas the patients included into CAR-Study A had up to 10 brain metastases. The total tumor volume in the brain is defined as the sum of all individual lesion volumes. These individual volumes (and their locations) may vary greatly by patient. To illustrate, one or two (very) large metastases and other smaller ones, or many microscopic and other small/medium sized metastases can both sum up to a large total tumor volume. Large metastases, where mass effect is of concern, tend to cause more neurologic symptoms, including cognitive deficits as compared to (multiple) small(er) brain metastases. The fact that Habets et al. (2016) included patients with limited brain metastases but with

a relatively high median total tumor volume, might therefore explain why they did find total tumor volume and information processing speed to be negatively associated in univariate analyses.

Next to the individual lesion volume and total volume, it is vital to assess intracranial tumor control (i.e., the change in volume of individual lesions and the development of new lesions after treatment) and its association with cognitive performance as intracranial progression can be associated with cognitive decline. [14,37–39] In CAR-Study A, we found no differences in mean test performances between patients with or without intracranial progression at 3, 6 and 9 months after GKRS (**Chapter 4**). Habets et al. (2016) found that patients with intracranial progression declined on executive functioning while patients with a partial response improved over six months after SRS. There were no differences between patients with or without intracranial progression regarding the other six cognitive domains.

Confounding factors

As described in chapters 2 and 3, there are many factors that may influence/predict cognitive change after SRS or WBRT. These include the effects of the brain metastases itself, intracranial tumor control, location, and volume of the brain metastases, peritumoral edema [13], other (systemic) treatments and medication, as well as (cancer-related) symptoms as fatigue, anxiety, and depression. Because of this, it is very difficult to entangle the cognitive effects of SRS or WBRT from all these other (confounding) factors. Multivariate/multivariable analyses in much larger samples are required to address this problem. Prediction analyses of individual cognitive changes also require large(r) patient samples. Single institutions may encounter difficulties in accruing such large samples especially for robust trials possessing enough statistical power to make comparisons between treatment modalities. [40] (Inter) National cooperation between treatment centers and the pooling of prospectively uniformly managed/gathered data could be a solution to this problem. [40]

The challenges of CAR-Study B

The implementation of CAR-Study B was a challenge despite our extensive experience with the logistical planning of large longitudinal trials of our collaborative Elisabeth TweeSteden Hospital / Tilburg University research team. At the start of CAR-Study B, the recruitment and inclusion was rather slow. Firstly, the ethics approval took much longer than expected because the medical ethics committee initially regarded GKRS in patients with more than 10 brain metastases highly experimental. Our research team had to submit additional scientific evidence and a rationale on the feasibility and efficacy of GKRS in these patients. Secondly, we experienced an initial hesitation

among the physicians to refer patients with multiple brain metastases for possible treatment with GKRS. In addition, about two years later, patients were sometimes no longer referred to participate in CAR-Study B because patients or their doctors now preferred treatment with GKRS and did not want to be randomized and possibly be treated with WBRT.

As inherent to this patient population, also CAR-Study B suffered from a relatively high drop-out rate. Either because patients died before their first follow-up appointment, or because their appointment was canceled due to deterioration of the condition of the patient. Like in other studies, the most common reason for dropout was death, due to either intra- or extracranial disease progression. [20,22] Finally, because of the long-term follow-up of 15 months, it took a significant amount of time to collect all neuropsychological data.

Dutch guideline on brain metastases

Historically, patients were primarily being referred for SRS based on the number of brain metastases. However, previous research [41,42] showed that the cumulative volume rather than the actual number of brain metastases is important for survival. At the beginning of the CAR-Studies, the then applicable Dutch guideline (2011) recommended that SRS was to be restricted to patients with good performance status and up to 3 brain metastases. The updated Dutch guideline (2020) [43] reflects the results of our work and shows a paradigm shift in the treatment of brain metastases. The guideline now recommends considering SRS as a treatment option for patients with good performance status and up to 10 brain metastases, and even in selected patients with more than 10 brain metastases, with a total cumulative volume of the brain metastases of less than 30cm^3.

Quality of life and fatigue

Fatigue is one of the most prevalent and distressing symptoms experienced by cancer patients. Persistent feelings of fatigue may negatively influence patients' functioning in daily life and quality of life in general. [44–46] Our research group has previously published on changes in different aspects of quality of life (FACT-Br) and fatigue (MVI) of patients in the CAR-Study A cohort. Already at baseline, most patients (64%) reported clinically meaningful low health-related quality of life (HRQOL) on at least one subscale compared to the general population. [47] Most (58%) patients reported problems with emotional well-being. Also, at group mean level, patients reported statistically significant and clinically meaningful lower emotional well-being compared to the general population and a normative adult cancer sample. However, patients reported significantly, and clinically meaningful, higher social well-being.

An explanation for this could be that patients may have experienced increased support just before the upcoming treatment. Higher levels of anxiety and depression as well as physical and mental fatigue were predictive of lower baseline HRQOL. Over a period of nine months after GKRS, aspects of HRQOL remained stable, except for an improvement in emotional well-being and a decline in physical well-being. Similar to our results on cognitive performances, HRQOL scores did vary considerably at the individual patient level. [48]

Patients (compared to controls) also experienced significantly higher levels of fatigue on all five subscales before GKRS (both at group and individual level), especially on reduced activity and mental fatigue. [49] Over six months after GRKS, different patterns were found for the various aspects of fatigue: general and physical fatigue increased significantly, whereas mental fatigue decreased significantly. Our findings showed that fatigue is not only a prevalent, but also a severe and persistent problem in patients with brain metastases.

Daily life problems and treatment decision-making

In daily living, patients with brain metastases often suffer from a combination of different symptoms and problems that all have their influence on daily life functioning and on the appraisal of quality of life. Cognitive impairments such as memory loss and slowed processing of information, combined with emotional and physical symptoms such as anxiety, depression, mood changes, pain, headaches, sleep disturbances and fatigue may seriously interfere with the ability to carry out tasks in daily life. For example, patients may find themselves struggling to follow a conversation, or to concentrate on or switch between certain tasks (e.g., financial management or administration or household chores). Patients with brain metastases may find it difficult to engage in and enjoy social interactions with others. This in turn may increase the caregiver burden ascaregivers often have a variety of responsibilities/ caregiving tasks that can become stressful and overwhelming. [58]

Patients may experience difficulties with processing and remembering (new) information which may interfere with the ability to reason through medical treatment decisions. Patients at risk for cognitive dysfunction may need additional guidance through this process. For example, by also providing information in writing that is clear and understandable for all patients (regardless of their educational level), using decision aids, engage family and caregivers, and actively trying to listen to and understand patients' goals in life and health. In a study by Zeng et al. (2017), patients with up to four brain metastases were asked to participate in the decision-making process by taking either an active or passive role. [50] All patients (n=23) actively

engaged in treatment decision-making (SRS or SRS plus WBRT). Most important factors influencing treatment preference were quality of life, functional independence, and survival.

Limitations and methodological considerations The studies regarding the CAR-Study A and B, as described in this dissertation have limitations to consider. One of these limitations is the high dropout, as patients with brain metastases are a very vulnerable population (as discussed earlier). Moreover, the patients that lived long enough, and were willing, to complete the follow-up measurements at six and nine months (or even at 15 or 21 months) might have been the better performing patients in terms of functional status and cognitive functioning. Information on longer term cognitive functioning after radiotherapy is however of high relevance for the growing number of such patients with better prognosis. Also, we included a heterogeneous sample of patients with different primary histologies. These different histologies and consequently different systemic therapies, may have influenced cognitive performances differently. Our study samples of patients with up to 10 (CAR-Study A) and up to 20 brain metastases (CAR-Study B) do represent the groups of patients that are treated in our daily clinical practice. Additionally, the baseline and follow-up neuropsychological assessments were scheduled just before treatment or follow-up consultations with the radiation-oncologist to minimize patient burden and attrition. The upcoming treatment and/or consultations may have caused worrying/anxiety or disturbed sleep during the nights prior to the assessments, which may in turn have caused depressive feelings. These potentially elevated levels of anxiety/stress and depression may have had their influence on patients' performance during the assessments, although we did not find evidence for a direct effect of anxiety or depression on patients' test performances at baseline. Finally, the neuropsychological test battery includes some tests that highly rely on motor dexterity, such as the Trail Making and Digit Symbol test. Many of our patients had impairments in motor dexterity, which may have confounded the outcomes on information processing speed and cognitive flexibility. [52] As impairments in dexterity are (highly) prevalent in this patient population, additional neuropsychological tests with minimal motor requirements should be considered. For example, an oral version of the Digit Symbol test, which doesn't require a psychomotor response, might capture 'cognitive' information processing speed more accurately. This version of the Symbol Digit Modalities Test for example, has been shown particularly sensitive to slowed information processing in patients with multiple sclerosis and stroke. [53,54]

Future directions and recommendations

Whole brain radiation therapy with hippocampal avoidance and/or memantine

Radiation to the hippocampus may induce impairments in learning, (short-term) memory, and spatial processing. By avoiding the hippocampus during WBRT (HA-WBRT), these impairments may be prevented or minimized. [55] However, cognitive functioning also includes several other functions such as attention, decision making, planning and language abilities that are associated with multiple other structures in the brain at the network level. HA-WBRT may preserve certain cognitive functions but does not prevent the potential cognitive impairment caused by radiation damage to the rest of the healthy brain. Another option to minimize the cognitive effects of WBRT is to use neuroprotectants, such as memantine. [56] To determine which treatment approach provides the most benefit, in terms of multiple aspects of cognitive functioning as well as intracranial tumor control, patients should be recruited in prospective trials that compare different radiation modalities (i.e., WBRT, HA-WBRT, SRS) and the value of the use of neuroprotectants. [57–59]

Multimodality treatment of brain metastases

New systemic treatments with potential intracranial efficacy have become available. [60,61] This has influenced the management of brain metastases. Current treatment strategies are now usually multimodal including molecular targeted therapies and immune checkpoint inhibitors whether or not combined with radiation therapy. [9,62] Such novel combinations should ideally result in radio-sensitization of the brain metastases and/or provide normal tissue protection to reduce side-effects. [7,57,63,64] Current research concerns the safety and intracranial efficacy as well as the optimal timing, sequencing, and combination of these targeted therapies along with SRS for brain metastases. [57,63] Future trials addressing this topic should routinely incorporate objective cognitive outcome measures to assess and monitor the potential ‘collateral damage’ of these novel drug-radiotherapy combinations, and to determine whether normal brain tissue is indeed protected, and cognitive functioning is preserved.

Early screening and cognitive interventions

As has been described in chapters 3 and 4, most patients with brain metastases already suffer from (severe) cognitive impairments prior to treatment. These impairments may also be predictive of longer-term cognitive impairment. Identification of cognitive impairment at an early stage may enable timely interventional rehabilitation programs aimed at teaching compensatory strategies to promote neuroplasticity. This may help to ameliorate or delay further cognitive decline and to minimize the effect

of cognitive impairment on daily life. Eventually, this can improve overall quality of life by making patients more functionally independent. Research into these cognitive rehabilitation programs in patients with brain metastases is still scarce, most likely due to the historically dismal prognosis for many patients. [37] However, as the number of patients with longer survival is increasing, more patients may benefit from early cognitive rehabilitation. In turn, this may positively influence patients' therapy adherence and their shared decision-making capacity.

Harmonization of instruments

There are many validated neuropsychological tests and questionnaires on patient-reported measures and/or experiences (PRMs) available. This causes a large heterogeneity across studies. [9] Already in 2011, the ICCTF published recommendations to harmonize studies of cognitive function in patients with cancer by using a standardized neuropsychological test battery. [40] The ICCTF provided guidelines on the use of appropriate control groups to determine whether cognitive impairment is present and to correct for potential practice effects. Although several clinical trials in patients with brain metastases trials have made use of the test battery as recommended by the ICCTF [5,11,12,15,21,22], still many different tests and especially different questionnaires are being used. [16,19,65] In addition, differences in the definitions of impairment and change, as well as differences in normative data and statistical methods, may also hamper the comparison between studies.

PRM questionnaires cover topics such as quality of life, subjective cognitive functioning, fatigue, symptoms experience, adequate involvement in and explanation of care, trust and communication and shared decision-making with clinicians, and dignity and respect. PRMs are becoming increasingly important in the context of individual patient management. [66,67] To be able to compare and pool results, preferably in open databases, there is an urgent need to also harmonize these instruments and (statistical) methods. [9]

Conclusions

With the studies presented in this thesis, we aimed to evaluate the cognitive performances before and changes after WBRT or SRS in patients with up to 20 brain metastases, using a formal, internationally recommended neuropsychological test battery, correcting for practice effects. [40] In line with previous research, we showed that most patients with brain metastases already suffer from cognitive impairment prior to treatment. GKRS did not cause additional cognitive decline in the **CAR-Study A** cohort (patients with up to 10 brain metastases) as cognitive functions remained stable at the pretreatment level or improved over nine months after treatment. Individual cognitive changes occurred in a minority of patients. Neither number nor cumulative

volume of brain metastases influenced cognitive performances over time. In terms of preservation of cognitive functioning, GKRS can be safely applied in patients with up to 10 brain metastases. The revised and current Dutch guideline now also reflects the results of our work and the paradigm shift from WBRT to SRS for selected patients with up to 10 brain metastases.

CAR-Study B is one of the first randomized trials that directly compares cognitive functioning after WBRT or SRS in patients with 11 to 20 brain metastases. Patients underwent neuropsychological evaluation before, and up to 15 months after treatment. The preliminary findings from the first interim analysis suggested that cognitive decline is more pronounced after WBRT compared to GKRS. After a second interim analysis, CAR-Study B was halted as the stopping rule came into effect: The chance of verbal memory decline at six months was greater after WBRT than after GKRS. This confirms our preliminary conclusion. Potentially confounding factors, such as the intracranial tumor status have not yet been accounted for. Final results from CAR-Study B are forthcoming and may provide additional guidance for clinicians, patients, family or other caregivers in shared decision-making. CAR-Study B already created awareness among referring clinicians of the paradigm shift in brain metastasis treatment: SRS should also be considered as one of the treatment options for selected patients with more than 10 brain metastases. Eventually, CAR-Study B has the potential to impact and improve the standard of care for patients with multiple brain metastases by minimizing cognitive impairment and optimizing patients' quality of life.

With the emergence of novel, targeted and immunologic therapies, the future role of radiotherapy for brain metastases is evolving. Preservation of cognitive functioning and quality of life will remain a key treatment outcome in future trials. Ultimately, the purpose is to facilitate patients, their caregivers, and treating physicians to have a well-informed discussion about the potential risks and benefits of the different treatment options for brain metastases.

References

1. Singh R, Stoltzfus KC, Chen H, *et al.* Epidemiology of synchronous brain metastases. *Neuro-oncology Adv* 2020; 2: 1–10.
2. Goyal S, Silk AW, Tian S, *et al.* Clinical Management of Multiple Melanoma Brain Metastases: A Systematic Review. *JAMA Oncol* 2015; 1: 668–76.
3. Enrique G-V, Irving S-R, Ricardo B-I, *et al.* Diagnosis and management of brain metastases: an updated review from a radiation oncology perspective. *J Cancer Metastasis Treat* 2019; 5: 54.
4. Schellinger PD, Meinck HM, Thron A. Diagnostic Accuracy of MRI Compared to CCT in Patients with Brain Metastases. *J Neuro-oncol* 1999; 44: 275–81.
5. Li J, Ludmir EB, Wang Y, *et al.* Stereotactic Radiosurgery versus Whole-brain Radiation Therapy for Patients with 4-15 Brain Metastases: A Phase III Randomized Controlled Trial. *Int J Radiat Oncol Biology Phys* 2020; 108: S21–2.
6. Robin TP, Rusthoven CG. Strategies to Preserve Cognition in Patients With Brain Metastases: A Review. *Front Oncol* 2018; 8: 415.
7. Ippolito E, Silipigni S, Matteucci P, *et al.* Radiotherapy for HER 2 Positive Brain Metastases: Urgent Need for a Paradigm Shift. *Cancers* 2022; 14: 1514.
8. McDuff SGR, Taich ZJ, Lawson JD, *et al.* Neurocognitive assessment following whole brain radiation therapy and radiosurgery for patients with cerebral metastases. *J Neurol Neurosurg Psychiatry* 2013; 84: 1384–91.
9. Matsui JK, Perlow HK, Baiyee C, *et al.* Quality of Life and Cognitive Function Evaluations and Interventions for Patients with Brain Metastases in the Radiation Oncology Clinic. *Cancers* 2022; 14: 4301.
10. Meyers CA, Wefel JS. The use of the mini-mental state examination to assess cognitive functioning in cancer trials: no ifs, ands, buts, or sensitivity. *J Clin Oncol* 2003; 21: 3557–8.
11. Chang EL, Wefel JS, Maor MH, *et al.* A pilot study of neurocognitive function in patients with one to three new brain metastases initially treated with stereotactic radiosurgery alone. *Neurosurgery* 2007; 60: 277–84.
12. Chang EL, Wefel JS, Hess KR, *et al.* Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol* 2009; 10: 1037–44.
13. Onodera S, Aoyama H, Tha KK, *et al.* The value of 4-month neurocognitive function as an endpoint in brain metastases trials. *J Neurooncol* 2014; 120: 311–9.
14. Meyers CA, Smith JA, Bezjak A, *et al.* Neurocognitive Function and Progression in Patients With Brain Metastases Treated With Whole-Brain Radiation and Motexafin Gadolinium: Results of a Randomized Phase III Trial. *J Clin Oncol* 2004; 22: 157–65.
15. Brown PD, Jaeckle K, Ballman KV, *et al.* Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases: A Randomized Clinical Trial. *JAMA* 2016; 316: 401–9.
16. Habets EJJ, Dirven L, Wiggenraad RG, *et al.* Neurocognitive functioning and health-related quality of life in patients treated with stereotactic radiotherapy for brain metastases: a prospective study. *Neuro-oncology* 2016; 18: 435–44.
17. Verhaak E, Schimmel WCM, Gehring K, Hanssens PEJ, Sitskoorn MM. Cognitive Functioning and Health-Related Quality of Life of Long-Term Survivors With Brain Metastases Up to 21 Months After Gamma Knife Radiosurgery. *Neurosurgery* 2021; 88: E396–405.
18. Kirkpatrick JP, Wang Z, Sampson JH, *et al.* Defining the Optimal Planning Target Volume in Image-Guided Stereotactic Radiosurgery of Brain Metastases: Results of a Randomized Trial. *Int J Radiat Oncol Biology Phys* 2015; 91: 100–8.
19. Meer PB van der, Habets EJJ, Wiggenraad RG, *et al.* Individual changes in neurocognitive functioning and health-related quality of life in patients with brain oligometastases treated with stereotactic radiotherapy. *J Neurooncol* 2018; 139: 359–68.

20. Schimmel WCM, Gehring K, Eekers DBP, Hanssens PEJ, Sitskoorn MM. Cognitive effects of stereotactic radiosurgery in adult patients with brain metastases: A systematic review. *Adv Radiat Oncol* 2018; 3: 568–81.
21. Minniti G, Capone L, Nardiello B, *et al.* Neurological outcome and memory performance in patients with 10 or more brain metastases treated with frameless linear accelerator (LINAC)-based stereotactic radiosurgery. *J Neuro-oncol* 2020; 148: 47–55.
22. Albers EAC, Ruiter MB de, Poll-Franse LV van de, Merckel LG, Compter A, Schagen SB. Neurocognitive functioning after Gamma Knife and LINAC stereotactic radiosurgery in patients with brain metastases. *J Neuro-oncol* 2022; 160: 649–58.
23. Schimmel WCM, Verhaak E, Bakker M, Hanssens PEJ, Sitskoorn MM, Gehring K. Group and Individual Change in Cognitive Functioning in Patients With 1 to 10 Brain Metastases Following Gamma Knife Radiosurgery. *Clin Oncol* 2021; 33: 314–21.
24. Lu S-L, Xiao F-R, Cheng JC-H, *et al.* Randomized multi-reader evaluation of automated detection and segmentation of brain tumors in stereotactic radiosurgery with deep neural networks. *Neuro-oncology* 2021; 23: 1560–8.
25. Jünger ST, Hoyer UCI, Schaufler D, *et al.* Fully Automated MR Detection and Segmentation of Brain Metastases in Non□small Cell Lung Cancer Using Deep Learning. *J Magn Reson Imaging* 2021; 54: 1608–22.
26. Kaur M, Petersen GC, Reppert M von, *et al.* NIMG-04. Longitudinal tracking of peritumoral edema volume using PACS-integrated tools provides critical information in treatment assessment of NSCLC brain metastases after radiosurgery. *Neuro-oncology* 2022; 24: vii162.
27. Jekel L, Bousabarah K, Lin M, *et al.* NIMG-02. PACS-integrated auto-segmentation workflow for brain metastases using NNU-NET. *Neuro-oncology* 2022; 24: vii162.
28. Petersen GC, Bousabarah K, Verma T, *et al.* Real-time PACS-integrated longitudinal brain metastasis tracking tool provides comprehensive assessment of treatment response to radiosurgery. *Neuro-oncology Adv* 2022; 4: vdac116.
29. Jalalifar SA, Soliman H, Sahgal A, Sadeghi□Naini A. Predicting the outcome of radiotherapy in brain metastasis by integrating the clinical and MRI□based deep learning features. *Med Phys* 2022; 49: 1–12.
30. Kesler SR, Blayney DW. Neurotoxic Effects of Anthracycline- vs Nonanthracycline-Based Chemotherapy on Cognition in Breast Cancer Survivors. *JAMA Oncol* 2016; 2: 185–92.
31. Schagen SB, Muller MJ, Boogerd W, Mellenbergh GJ, Dam FSAM van. Change in cognitive function after chemotherapy: a prospective longitudinal study in breast cancer patients. *J Natl Cancer Inst* 2006; 98: 1742–5.
32. Das A, Ranadive N, Kinra M, Nampoothiri M, Arora D, Mudgal J. An Overview on Chemotherapy-induced Cognitive Impairment and Potential Role of Antidepressants. *Curr Neuropharmacol* 2020; 18: 838–51.
33. Mounier NM, Abdel-Maged AE-S, Wahdan SA, Gad AM, Azab SS. Chemotherapy-induced cognitive impairment (CICI): An overview of etiology and pathogenesis. *Life Sci* 2020; 258: 118071.
34. Wefel JS, Kesler SR, Noll KR, Schagen SB. Clinical characteristics, pathophysiology, and management of noncentral nervous system cancer-related cognitive impairment in adults. *CA Cancer J Clin* 2015; 65: 123–38.
35. Janelsins MC, Kesler SR, Ahles TA, Morrow GR. Prevalence, mechanisms, and management of cancer-related cognitive impairment. *Int Rev Psychiatr* 2014; 26: 102–13.
36. Gerstenecker A, Nabors LB, Meneses K, *et al.* Cognition in patients with newly diagnosed brain metastasis: profiles and implications. *J Neurooncol* 2014; 120: 179–85.
37. Parsons MW, Peters KB, Floyd SR, Brown P, Wefel JS. Preservation of neurocognitive function in the treatment of brain metastases. *Neuro-oncology Adv* 2021; 3: v96–107.
38. Li J, Bentzen SM, Renschler M, Mehta MP. Regression after whole-brain radiation therapy for brain metastases correlates with survival and improved neurocognitive function. *Journal of Clinical Oncology* 2007; 25: 1260–6.

39. Devisetty K, Pugh S, Brown P, *et al.* NCOG-03. Impact of the rate of radiographic response (RR) of brain metastases (BM) to Whole Brain Radiation Therapy (WBRT) on neurocognitive function (NCF) on NRG-CC001. *Neuro-oncology* 2022; 24: vii197.
40. Wefel JS, Vardy J, Ahles T, Schagen SB. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. *Lancet Oncol* 2011; 12: 703–8.
41. Likhacheva A, Pinnix CC, Parikh NR, *et al.* Predictors of survival in contemporary practice after initial radiosurgery for brain metastases. *Int J Radiat Oncol Biol Phys* 2013; 85: 656–61.
42. Nabors LB, Portnow J, Ammirati M, *et al.* Central nervous system cancers, version 2.2014. Featured updates to the NCCN Guidelines. *J Natl Compr Canc Netw* 2014; 12: 1517–23.
43. Federatie Medisch Specialisten – Richtlijnendatabase. (2020, August 27). Hersenmetastasen. Retrieved January 18, 2023, from https://richtlijnendatabase.nl/ richtlijn/hersenmetastasen.
44. Ahlberg K, Ekman T, Gaston-Johansson F, Mock V. Assessment and management of cancer-related fatigue in adults. *Lancet* 2003; 362: 640–50.
45. Noh T, Walbert T. Brain metastasis: clinical manifestations, symptom management, and palliative care. *Handb Clin Neurology* 2018; 149: 75–88.
46. Stone PC, Minton O. Cancer-related fatigue. *Eur J Cancer* 2008; 44: 1097–104.
47. Verhaak E, Gehring K, Hanssens PEJ, Sitskoorn MM. Health-related quality of life of patients with brain metastases selected for stereotactic radiosurgery. *J Neurooncol* 2019; 4: 289–10.
48. Verhaak E, Schimmel WCM, Gehring K, Emons WHM, Hanssens PEJ, Sitskoorn MM. Health-related quality of life after Gamma Knife radiosurgery in patients with 1–10 brain metastases. *J Cancer Res Clin* 2021; 147: 1157–67.
49. Verhaak E, Schimmel WCM, Sitskoorn MM, Bakker M, Hanssens PEJ, Gehring K. Multidimensional assessment of fatigue in patients with brain metastases before and after Gamma Knife radiosurgery. *J Neurooncol* 2019; 4: 289–8.
50. Zeng KL, Raman S, Sahgal A, *et al.* Patient preference for stereotactic radiosurgery plus or minus whole brain radiotherapy for the treatment of brain metastases. *Ann Palliat Med* 2017; 6: S155–60.
51. Bakker EM, Witkamp FE, Luu KLN, *et al.* Caregiver activation of relatives of patients with advanced cancer. *Eur J Cancer Care* 2022; 31: e13656.
52. Low E, Crewther SG, Ong B, Perre D, Wijeratne T. Compromised Motor Dexterity Confounds Processing Speed Task Outcomes in Stroke Patients. *Front Neurol* 2017; 8: 484.
53. Koh C-L, Lu W-S, Chen H-C, Hsueh I-P, Hsieh J-J, Hsieh C-L. Test–Retest Reliability and Practice Effect of the Oral-format Symbol Digit Modalities Test in Patients with Stroke. *Arch Clin Neuropsych* 2011; 26: 356–63.
54. Benedict RH, DeLuca J, Phillips G, *et al.* Validity of the Symbol Digit Modalities Test as a cognition performance outcome measure for multiple sclerosis. *Mult Scler J* 2016; 23: 721–33.
55. Brown PD, Gondi V, Pugh S, *et al.* Hippocampal Avoidance During Whole-Brain Radiotherapy Plus Memantine for Patients With Brain Metastases: Phase III Trial NRG Oncology CC001. *J Clin Oncol* 2020; 38: 1019–29.
56. Suh JH. Hippocampal-avoidance whole-brain radiation therapy: a new standard for patients with brain metastases? *Journal of Clinical Oncology* 2014; 32: 3789–91.
57. Berghoff AS, Preusser M. New developments in brain metastases. *Ther Adv Neurol Diso* 2018; 11: 1–14.
58. Shinde A, Akhavan D, Sedrak M, Glaser S, Amini A. Shifting paradigms: whole brain radiation therapy versus stereotactic radiosurgery for brain metastases. *CNS Oncol* 2019; 8: CNS27.
59. Tsai P-F, Yang C-C, Chuang C-C, *et al.* Hippocampal dosimetry correlates with the change in neurocognitive function after hippocampal sparing during whole brain radiotherapy: a prospective study. *Radiat Oncol Lond Engl* 2015; 10: 253.
60. Lauko A, Rauf Y, Ahluwalia MS. Medical management of brain metastases. *Neuro-oncology Adv* 2020; 2: 1–14.

61. Tan AC, Boggs DH, Lee EQ, Kim MM, Mehta MP, Khasraw M. Clinical Trial Eligibility Criteria and Recently Approved Cancer Therapies for Patients With Brain Metastases. *Frontiers Oncol* 2022; 11: 780379.
62. Palmer JD, Trifiletti DM, Gondi V, *et al.* Multidisciplinary patient-centered management of brain metastases and future directions. *Neuro-oncology Adv* 2020; 2: vdaa034.
63. Tonse R, Tom MC, Mehta MP, Ahluwalia MS, Kotecha R. Integration of Systemic Therapy and Stereotactic Radiosurgery for Brain Metastases. *Cancers* 2021; 13: 3682.
64. Rivera S, Vens C, Maingon P, *et al.* Abstract C220: Combining novel targeted therapies and radiotherapy: A challenge to overcome. *Mol Cancer Ther* 2013; 12: C220.
65. Leemans K, Ridder MD. Cognition: development of a cognitive testing battery on the iPad for the evaluation of patients with brain Mets. *Acta Neurol Belg* 2022; 122: 145–52.
66. Brunelli C, Borreani C, Caraceni A, *et al.* PATIENT VOICES, a project for the integration of the systematic assessment of patient reported outcomes and experiences within a comprehensive cancer center: a protocol for a mixed method feasibility study. *Health Qual Life Out* 2020; 18: 252.
67. Albers EAC, Fraterman I, Walraven I, *et al.* Visualization formats of patient-reported outcome measures in clinical practice: a systematic review about preferences and interpretation accuracy. *J Patient-reported Outcomes* 2022; 6: 18.

A

Appendix

Nederlandse samenvatting

Achtergrond

Hersenmetastasen zijn uitzaaiingen in de hersenen afkomstig van een tumor elders in het lichaam.

Het percentage kankerpatiënten bij wie hersenmetastasen ontstaan, varieert afhankelijk van het type en stadium van de kanker. Kankersoorten zoals longkanker, borstkanker, huidkanker (melanoom) en nierkanker hebben een hoger risico om (via de bloedbaan of het lymfestelsel) uit te zaaien naar de hersenen. Naar schatting ontwikkelt ergens tussen de 15 en 30 procent van alle kankerpatiënten hersenmetastasen gedurende het ziekteverloop.

Vanwege de vooruitgang in diagnostiek (vroeger opsporen van hersenmetastasen met verbeterde beeldvormingstechniek) en de toegenomen overleving van kankerpatiënten (meer systemische behandelopties) worden steeds vaker hersenmetastasen gediagnosticeerd. Bovendien worden bij de eerste vaststelling/diagnose vaak meerdere hersenmetastasen gevonden.

Er zijn verschillende behandelingen voor hersenmetastasen, waaronder operatie (neurochirurgie), radiotherapie (bestraling) en soms chemotherapie. Ook een combinatie van behandelingen is mogelijk. Nieuwere systemische behandelingen, zoals immunotherapie (hierbij wordt het immuunsysteem van de patiënt gebruikt om de kankercellen aan te vallen) en doelgerichte therapie (behandeling met medicijnen die de groei en deling van kankercellen blokkeren), kunnen nu naast bestralingstherapie worden gebruikt. Dit biedt meer mogelijkheden voor een behandeling op maat. Hierbij is het belangrijk om een evenwicht te vinden tussen tumorcontrole enerzijds en de toxiciteit die gepaard gaat met de behandeling anderzijds (ofwel een behandeling die de tumorgroei effectief aanpakt met minimale nadelige effecten voor de patiënt).

Hersenmetastasen kunnen normale functies van de hersenen verstoren. Klachten kunnen variëren afhankelijk van het aantal, de locatie en grootte van de hersenmetastasen. Veel voorkomende klachten zijn hoofdpijn, evenwichtsstoornissen en epileptische aanvallen. Daarnaast ervaren veel mensen met hersenmetastasen cognitieve klachten zoals problemen met het geheugen of de aandacht. Dit kan veroorzaakt worden door de metastasen, door epilepsie of het gebruik van medicatie (bijvoorbeeld anti-epileptica of chemotherapie).

Ook radiotherapie kan cognitieve klachten of bijwerkingen veroorzaken. Deze cognitieve klachten kunnen aanzienlijke impact hebben op het dagelijks leven

van patiënten en hun naasten, en uiteindelijk de algehele kwaliteit van leven verminderen. Er zijn twee soorten radiotherapie voor de behandeling van hersenmetastasen: een volledige hersenbestraling of een heel gerichte bestraling (stereotactische radiochirurgie). Bij een volledige hersenbestraling worden de gehele hersenen bestraald, meestal in vijf sessies verspreid over verschillende dagen. Stereotactische radiochirurgie daarentegen is een eenmalige behandeling waarbij enkel de hersenmetastasen heel precies worden bestraald en het omliggende gezonde hersenweefsel nauwelijks of geen straling ontvangt. Beide vormen van radiotherapie hebben bewezen een effectieve behandeling te zijn voor (meerdere) hersenmetastasen met vergelijkbare algehele overleving. De stralingsbelasting voor het normale/gezonde hersenweefsel is lager bij stereotactische radiochirurgie in vergelijking met een volledige hersenbestraling. Daarom worden minder cognitieve klachten verwacht na stereotactische radiochirurgie.

Het is belangrijk om te onderzoeken welke behandeling de minste cognitieve stoornissen veroorzaakt, zeker nu steeds meer patiënten langer leven door meer en betere systemische behandelopties. Tenslotte zijn cognitieve vaardigheden van essentieel belang voor het dagelijks leven. Tot op heden zijn er echter geen gepubliceerde studies die het effect op het cognitief functioneren van stereotactische radiochirurgie en gehele hersenbestraling direct met elkaar vergelijken. Het gaat dan om objectief neuropsychologisch onderzoek bij patiënten met meerdere hersenmetastasen. Dit vormde de aanleiding om deze wetenschappelijke onderzoeken te doen.

Cognition and Radiation (CAR) Studies A en B

In dit proefschrift onderzochten we het effect van een volledige hersenbestraling en van Gamma Knife radiochirurgie, een vorm van stereotactische radiochirurgie waarbij de bestralingsdosis wordt toegediend met het Gamma Knife. Gemeten werd het effect op de cognitieve vaardigheden over een langere periode bij patiënten met maximaal 10 (**CAR-Study A**), of 11 tot 20 hersenmetastasen (**CAR-Study B**). De studies werden door ZonMw gesubsidieerd en worden uitgevoerd binnen het Gamma Knife Centrum in Tilburg, Elisabeth-TweeSteden ziekenhuis, in samenwerking met Tilburg University.

CAR-Study A is een prospectief longitudinaal onderzoek. De cognitieve vaardigheden van 92 patiënten met 1-10 hersenmetastasen werden beoordeeld voorafgaand aan Gamma Knife radiochirurgie en elke drie maanden daarna, tot 21 maanden na de behandeling. Voor dit proefschrift werden de gegevens gebruikt tot en met het meetmoment negen maanden na de behandeling.

CAR-Study B is een prospectief gerandomiseerd (multicenter) onderzoek dat cognitieve effecten vergelijkt tot 15 maanden na Gamma Knife radiochirurgie of een volledige hersenbestraling. De resultaten van een tussentijdse analyse die werd uitgevoerd nadat de eerste 41 patiënten waren geïncludeerd (allen bij het Gamma Knife Centrum in Tilburg) worden in dit proefschrift beschreven.

Neuropsychologisch onderzoek

Het cognitief functioneren van patiënten is gemeten met behulp van een gevalideerde testbatterij bestaande uit zes neuropsychologische testen. Om de belasting van dit onderzoek voor patiënten zo laag mogelijk te houden is gekozen voor een kort neuropsychologisch onderzoek, niet langer dan 90 minuten per keer. Specifieke cognitieve domeinen waaronder verbale leerprestaties en geheugen, aandacht, cognitieve flexibiliteit, woordvloeiendheid, werkgeheugen, verwerkingssnelheid (de snelheid waarmee iemand in staat is om, in dit geval, visuele informatie te ontvangen, begrijpen, verwerken en hierop te reageren) en fijne motoriek (van de dominante en niet-dominante hand) zijn onderzocht. In totaal werden met de testbatterij 11 verschillende testvariabelen gemeten. Daarnaast hebben we drie vragenlijsten afgenomen om vermoeidheid, gezondheidsgerelateerde kwaliteit van leven en symptomen van angst en depressie te meten. We hebben dezelfde testen en vragenlijsten ook afgenomen bij een controlegroep van 104 volwassenen zonder een (eerdere) vorm van kanker. Dit deden we om referentiewaarden vast te stellen en zo de ernst van eventuele cognitieve stoornissen bij patiënten te kunnen beoordelen. Deze controlegroep is 3 en 6 maanden na de eerste beoordeling opnieuw getest. Hiermee konden we rekening houden met zogeheten oefen/leereffecten.

Beknopte samenvatting van de belangrijkste onderzoeksbevindingen

Stereotactische radiochirurgie wordt steeds vaker toegepast bij patiënten met hersenmetastasen en wordt verondersteld minder schadelijke effecten op cognitieve functies te hebben dan een volledige hersenbestraling. Niettemin zijn er relatief weinig studies verricht naar de cognitieve bijwerkingen van stereotactische radiochirurgie. **Hoofdstuk 2** presenteert een systematische review van bestaande prospectieve studies over de effecten van stereotactische radiochirurgie op cognitieve functies bij patiënten met hersenmetastasen. Deze studies werden gevonden door systematisch te zoeken in medische databases met geschikte zoektermen. Slechts acht studies voldeden aan de selectiecriteria. Over het algemeen tonen de resultaten dat patiënten met hersenmetastasen kort na stereotactische radiochirurgie weinig tot geen objectieve cognitieve achteruitgang vertonen, gevolgd door een trend naar verbetering of stabilisatie tot 12 maanden na de behandeling. Er waren echter ernstige methodologische beperkingen in de meeste studies, zoals

bijvoorbeeld het ontbreken van correctie voor leereffecten in de testprestaties. Dit kan de resultaten hebben beïnvloed. Bovendien gebruikten slechts enkele studies objectieve neuropsychologische tests om cognitieve vaardigheden na stereotactische radiochirurgie te beoordelen.

In **Hoofdstuk 3** onderzochten we het cognitief functioneren van 92 patiënten met 1 tot 10 hersenmetastasen (CAR-Study A) voorafgaand aan de behandeling met het Gamma Knife. Deze baselinemeting of nulmeting is belangrijk omdat het dient als referentiepunt waartegen latere veranderingen in testprestaties kunnen worden geëvalueerd. Een grondige baselinemeting is dus een voorwaarde voor het evalueren van verandering in cognitieve functies na behandeling. Daarnaast hebben we onderzocht of er factoren waren die de testprestaties vóór behandeling konden voorspellen. Deze factoren kunnen mogelijk ook een rol spelen bij het voorspellen van cognitieve uitkomsten na radiochirurgie. Uit de resultaten bleek dat respectievelijk 62% en 46% van de patiënten reeds stoornissen had in ten minste twee of drie verschillende cognitieve functies (testvariabelen), wat aangeeft dat patiënten al (ernstige) cognitieve problemen hadden vóór de behandeling met radiochirurgie. Het percentage stoornissen was het hoogst voor verwerkingssnelheid (55,3%), fijne motoriek (43,2%) en cognitieve flexibiliteit (28,7%). Deze cognitieve beperkingen kunnen dagelijkse activiteiten belemmeren en het vermogen van patiënten om (gezamenlijke) behandelingsbeslissingen te nemen, beïnvloeden. Dit benadrukt het belang van een (standaard) cognitieve screening, nog vóór behandeling van de hersenmetastasen. Zowel klinische (kenmerken van de hersenmetastasen) als psychologische (mentale vermoeidheid) factoren beïnvloedden de cognitieve prestaties. Noch het aantal, noch het volume van de hersenmetastasen voorspelde de testprestaties van patiënten.

In **Hoofdstuk 4** onderzochten we vóór en negen maanden na Gamma Knife radiochirurgie de veranderingen in cognitieve testprestaties bij 41 patiënten met 1 tot 10 hersenmetastasen (CAR-Study A). Hierbij hebben we gecorrigeerd voor de mogelijke leereffecten die konden ontstaan door de herhaalde afname van cognitieve tests. Daarnaast is onderzocht of er factoren waren die de cognitieve testprestaties van patiënten over tijd (voorafgaand aan de behandeling tot negen maanden erna) konden voorspellen. Negen maanden na Gamma Knife radiochirurgie verbeterden het onmiddellijk geheugen, het werkgeheugen en de verwerkingssnelheid van patiënten als groep. Andere prestaties bleven stabiel; er was geen cognitieve achteruitgang op groepsniveau. Zowel het aantal als het volume van de hersenmetastasen waren niet voorspellend voor veranderingen in testprestaties over tijd na Gamma Knife radiochirurgie. Er werden daarnaast geen structurele voorspellers voor veranderingen

in het cognitief functioneren gevonden. Evaluatie van individuele cognitieve veranderingen (per individuele patiënt en per individuele test, met correctie voor leereffecten) toonde ook stabiele of verbeterde cognitieve prestaties bij de meeste patiënten (73%) tot negen maanden na radiochirurgie, behalve voor prestaties op fijne motoriek van de niet-dominante hand. Voor deze meting was er significant meer verbetering (27%) evenals achteruitgang (24%) bij patiënten vergeleken met onze controlegroep. De resultaten op groepsniveau weerspiegelden deze individuele variaties in handmotoriek niet. Dit benadrukt dat analyses op individueel niveau naast groepsanalyses van groot belang zijn, omdat groepsanalyses mogelijk individuele cognitieve veranderingen kunnen maskeren. Negen maanden na de behandeling presteerden patiënten nog steeds slechter op de meeste tests in vergelijking met controles, hetgeen de blijvende aard van de cognitieve beperkingen illustreert.

Hoofdstuk 5 omvat het studieprotocol van CAR-Study B. In CAR-Study B werden volwassen patiënten met 11 tot en met 20 hersenmetastasen gerandomiseerd naar Gamma Knife radiochirurgie of naar een gehele hersenbestraling. Vóór de behandeling (en vóór de randomisatie) werd het cognitief functioneren gemeten met behulp van de eerder beschreven neuropsychologische testbatterij. Na de behandeling kwamen patiënten elke drie maanden terug voor een controle MRI-scan en de tests, beide tot 15 maanden na de behandeling. Omdat cognitieve vaardigheden cruciaal zijn voor het dagelijkse functioneren en de kwaliteit van leven, was het van belang om te onderzoeken welke van de twee behandelingen gepaard ging met de minste achteruitgang in cognitieve functies. Bij de randomisatie (een soort gewogen loting) is rekening gehouden met een aantal (stratificatie)factoren zoals het totale volume van de hersenmetastasen, de histologie van de primaire tumor, de leeftijd en fysieke conditie van de patiënt en de testprestaties op de geheugentaak voorafgaand aan de behandeling. Dit hebben we gedaan om de twee groepen (volledige hersenbestraling versus stereotactische radiochirurgie) zoveel mogelijk vergelijkbaar te maken. De belangrijkste (primaire) uitkomstmaat van CAR-Study B is het verschil tussen de groepen in het percentage patiënten met significante geheugenachteruitgang na 3 maanden. Secundaire uitkomstmaten zijn algehele overleving, lokale tumorcontrole, ontwikkeling van nieuwe hersenmetastasen, cognitieve functies in de loop van de tijd, kwaliteit van leven, depressie, angst en vermoeidheid. Kennis die met dit onderzoek wordt verkregen, kan worden gebruikt om individuele patiënten met hersenmetastasen nauwkeuriger te informeren over de te verwachten cognitieve effecten van de behandeling, en om zowel artsen als patiënten te ondersteunen bij het maken van gezamenlijke behandelbeslissingen. In het studieprotocol van CAR-Study B zijn zogenaamde stopregels opgenomen die gebaseerd zijn op een eerdere studie van Chang en collega's (Chang et al., 2009, The Lancet). Als met 97.5% zekerheid

geconcludeerd kan worden dat de kans op een cognitieve achteruitgang op 3 of 6 maanden na de behandeling significant groter is na de ene behandeling in vergelijking met de andere behandeling, zal de inclusie worden stopgezet en de studie vroegtijdig worden beëindigd.

Hoofdstuk 6 bespreekt de resultaten van de eerste tussentijdse analyse die werd uitgevoerd in januari 2020 nadat 41 geschikte patiënten waren geïncludeerd en gerandomiseerd naar Gamma Knife radiochirurgie (20 patiënten) of een gehele hersenbestraling (21 patiënten). Het belangrijkste doel van deze tussentijdse analyse was om te controleren of de grens van de (Bayesiaanse) stopregels voor cognitieve achteruitgang na 3 en 6 maanden werden overschreden. Een ander doel was om cognitieve veranderingen na de behandeling tussen de groepen te vergelijken. De tussentijdse resultaten toonden dat de grens van de stopregels niet werd overschreden. Daarom werd er op dat moment doorgegaan met het includeren van patiënten in de studie.

De voorlopige bevindingen laten zien dat de cognitieve testprestaties van patiënten na Gamma Knife radiochirurgie in de loop van de tijd minder achteruit gingen in vergelijking met patiënten die behandeld werden met een gehele hersenbestraling. Dit zagen we zowel op groeps- als op individueel niveau en na correctie voor leereffecten. Op groepsniveau verschilden veranderingen in cognitieve prestaties significant tussen de groepen gedurende een periode van zes maanden (9 patiënten in beide groepen). Er waren statistisch significante afnames in onmiddellijk en vertraagd verbaal geheugen en informatieverwerkingssnelheid na een gehele hersenbestraling, maar er waren geen significante veranderingen na Gamma Knife radiochirurgie. De vijf langetermijnoverlevenden (patiënten die het neuropsychologisch onderzoek na 15 maanden voltooiden) in de Gamma Knife radiochirurgie-groep vertoonden stabiele of verbeterde prestaties op deze metingen, terwijl we een achteruitgang in prestaties op deze metingen observeerden bij twee van de vier langetermijnoverlevenden in de andere groep (gehele hersenbestraling). Op individueel niveau zagen we meer patiënten met verslechterde prestaties na een gehele hersenbestraling in de periode van zes maanden na de behandeling in vergelijking met de patiënten die met Gamma Knife radiochirurgie behandeld werden. Een tweede tussentijdse analyse werd uitgevoerd in april 2022 nadat 81 patiënten waren geïncludeerd. Deze keer toonden de gegevens voldoende ondersteuning om vroegtijdige beëindiging van het onderzoek te rechtvaardigen omdat de vooraf gespecificeerde stopregel van kracht werd: de kans op achteruitgang van het verbale geheugen na zes maanden was groter na een gehele hersenbestraling dan na Gamma Knife radiochirurgie. Als gevolg daarvan werd de inclusie stopgezet. Dit lijkt onze eerdere voorlopige conclusies te bevestigen. Resultaten van de tweede tussentijdse analyse zijn niet besproken in dit proefschrift

omdat de beschikbare gegevens momenteel worden verwerkt en geanalyseerd. Belangrijk is nogmaals te benadrukken dat de bevindingen van CAR-Study B in dit proefschrift voorlopig zijn. Aanvullende analyses en onderzoek zijn noodzakelijk om een meer definitieve uitspraak te kunnen doen over de effecten van stereotactische radiochirurgie versus volledige hersenbestraling op cognitieve functies bij patiënten met 11 tot 20 hersenmetastasen. Alle (langere termijn) metingen zijn afgerond in januari 2023 en momenteel worden (storende) factoren onderzocht die mogelijk (ook) invloed hebben gehad op de cognitieve veranderingen over tijd na behandeling met volledige hersenbestraling of stereotactische radiochirurgie. Hierbij zijn onder andere de intracraniële tumorcontrole (veranderingen in volume van de metastasen over tijd), de status van de extracraniële ziekte (ziekte buiten het hoofd), systemische therapieën, peritumoraal oedeem (zwelling van weefsel rondom een tumor) en de locatie van de hersenmetastasen van belang.

De uitdagingen van CAR-Study B

De uitvoering van CAR-Study B bleek een uitdaging, ondanks de uitgebreide ervaring met de logistieke planning van grote longitudinale onderzoeken binnen ons samenwerkende onderzoeksteam van het Elisabeth TweeSteden Ziekenhuis en Tilburg University. Bij de start van CAR-Study B verliep de werving en inclusie van deelnemers langzamer dan verwacht. Dit werd deels veroorzaakt door vertraging bij de ethische goedkeuring. De medisch-ethische commissie had aanvankelijk aarzelingen over het toepassen van Gamma Knife radiochirurgie bij patiënten met meer dan 10 hersenmetastasen. Ons onderzoeksteam moest aanvullend wetenschappelijk bewijs en een goed onderbouwde rationale aanleveren om de haalbaarheid en effectiviteit van Gamma Knife radiochirurgie voor deze patiënten te benadrukken. Daarnaast was er aanvankelijke terughoudendheid bij artsen om patiënten met meerdere hersenmetastasen door te verwijzen voor behandeling met Gamma Knife radiochirurgie. Echter, na verloop van ongeveer twee jaar ontstond er een verschuiving in deze houding. Deze verandering kwam voort uit de voorkeur van patiënten en hun artsen voor behandeling met Gamma Knife radiochirurgie, waarbij ze nu juist terughoudend waren om willekeurig te worden ingedeeld en mogelijk behandeld te worden met een gehele hersenbestraling. Zoals inherent aan deze patiëntenpopulatie, kampte ook CAR-Study B met een relatief hoog uitvalpercentage. Dit kwam ofwel doordat patiënten overleden voor de eerste vervolgafspraak, of omdat de afspraak werd geannuleerd wegens de verslechterde gezondheidstoestand van de patiënt. Ten slotte nam het verzamelen van de neuropsychologische gegevens veel tijd in beslag vanwege de langetermijnopvolging van 15 maanden.

Nederlandse richtlijn hersenmetastasen

De CAR-Studies zijn in 2015 gestart. Volgens de toen geldende Nederlandse richtlijn hersenmetastasen (2011) werden patiënten met meer dan 3 of 4 hersenmetastasen nog standaard doorverwezen voor een gehele hersenbestraling. De introductie van stereotactische radiochirurgie als behandeling bij patiënten met maximaal 20 hersenmetastasen betekende voor Nederland dan ook een fundamentele verandering, een paradigma shift, in het behandelmanagement van deze patiënten. De nu geldende herziene Nederlandse richtlijn (2020) weerspiegelt deze verandering en raadt aan om stereotactische radiochirurgie te overwegen als behandeloptie voor patiënten met een goede gezondheid en tot 10 hersenmetastasen, en zelfs voor geselecteerde patiënten met meer dan 10 hersenuitzaaiingen, zolang het totale volume van de metastasen niet te groot is. De behandeling van deze patiënten is complex en om een optimaal individueel behandelplan op te stellen is multidisciplinair overleg van groot belang.

Dagelijkse uitdagingen en behandelingsbeslissingen

Mensen met hersenmetastasen ervaren in hun dagelijks leven vaak verschillende symptomen en cognitieve problemen zoals geheugen- of concentratieproblemen of vertraagde informatieverwerking, samen met emotionele en fysieke klachten zoals angst, depressie, stemmingswisselingen, (hoofd)pijn, slaapproblemen en vermoeidheid. Dit alles kan het uitvoeren van dagelijkse taken aanzienlijk belemmeren, waardoor zelfs eenvoudige handelingen zoals een gesprek voeren of het schakelen tussen taken moeilijk kunnen worden. Sociale interacties kunnen hierdoor als minder plezierig of lastig worden ervaren. Cognitieve stoornissen, zoals moeilijkheden bij het verwerken en onthouden van (nieuwe) informatie, kunnen ook van invloed zijn op het nemen van (gezamenlijke) beslissingen over medische behandelingen. Patiënten met cognitieve stoornissen hebben hierbij mogelijk extra begeleiding nodig. Bijvoorbeeld door de informatieoverdracht te vertragen en herhaling toe te passen, door ook informatie schriftelijk te verstrekken die duidelijk en begrijpelijk is voor alle patiënten (ongeacht hun opleidingsniveau), door gebruik te maken van beslissingshulpmiddelen, familie en verzorgers te betrekken, en actief te proberen de doelen van patiënten in het leven en op het gebied van gezondheid te beluisteren en te begrijpen. Dit zorgt ervoor dat patiënten, ondanks eventuele cognitieve stoornissen, actief kunnen meebeslissen over hun zorg.

Conclusies

In dit proefschrift is ons onderzoek naar de effecten van behandeling op het cognitief functioneren van patiënten met hersenmetastasen beschreven. We gebruikten een internationaal aanbevolen neuropsychologische testbatterij om cognitieve testprestaties vóór en (langere tijd) na stereotactische radiochirurgie of een gehele hersenbestraling te evalueren. Hierbij corrigeerden we voor eventuele leereffecten als gevolg van herhaald testen.

Onze bevindingen toonden aan dat de meeste patiënten reeds vóór behandeling cognitieve stoornissen hadden. Bij de groep patiënten met 1 tot 10 hersenmetastasen (CAR-Study A), veroorzaakte Gamma Knife radiochirurgie geen extra achteruitgang; cognitieve functies bleven stabiel of verbeterden gedurende negen maanden na behandeling. Slechts een minderheid van de patiënten vertoonde individuele cognitieve veranderingen. Noch het aantal noch het cumulatieve volume van de hersenmetastasen beïnvloedde het beloop van de cognitieve testprestaties na behandeling. Met betrekking tot het behoud van cognitieve functies, is Gamma Knife radiochirurgie een geschikte behandelingsoptie bij patiënten met 1 tot 10 hersenmetastasen.

CAR-Study B is een van de eerste gerandomiseerde onderzoeken die cognitieve testprestaties vergelijkt na een gehele hersenbestraling of stereotactische radiochirurgie bij patiënten met 11 tot 20 hersenmetastasen. Patiënten werden neuropsychologisch getest voor, en tot maximaal 15 maanden na de behandeling. Het doel van CAR-Study B is te onderzoeken welke behandeling, Gamma Knife radiochirurgie of een gehele hersenbestraling, de minste cognitieve stoornissen veroorzaakt. De voorlopige bevindingen van de eerste tussentijdse analyse suggereren meer cognitieve achteruitgang na een gehele hersenbestraling. Na een tweede tussenanalyse werd CAR-Study B stopgezet omdat de vooraf opgestelde stopregel van kracht werd: De kans op verbale geheugenvermindering na zes maanden was groter na een gehele hersenbestraling dan na Gamma Knife radiochirurgie. Dit bevestigt onze voorlopige conclusie. Alvorens de definitieve studieresultaten gepresenteerd kunnen worden, worden momenteel mogelijke storende variabelen onderzocht. Dit zijn factoren zoals intracraniële tumorcontrole, die ook van invloed kunnen zijn geweest op de veranderingen in het cognitief functioneren over tijd. CAR-Study B heeft de bewustwording onder verwijzers vergroot over de verschuiving in de behandeling van hersenmetastasen, waarbij stereotactische radiochirurgie ook kan worden overwogen als een behandelingsoptie voor geselecteerde patiënten met meer dan 10 hersenmetastasen. Uiteindelijk heeft CAR-Study B het potentieel om de standaardzorg voor patiënten met meerdere hersenmetastasen te verbeteren door de impact op cognitieve vaardigheden te minimaliseren en zo de levenskwaliteit van patiënten te

verhogen. De opkomst van nieuwe, gerichte en immunologische therapieën zal de toekomstige rol van radiotherapie in de behandeling van hersenmetastasen verder doen evolueren. Behoud van cognitieve functies en kwaliteit van leven blijven belangrijke behandeluitkomsten in toekomstige onderzoeken.

List of publications

Schimmel WCM, Verhaak E, Hanssens PEJ, Gehring K, Sitskoorn MM. A randomised trial to compare cognitive outcome after gamma knife radiosurgery versus whole brain radiation therapy in patients with multiple brain metastases: Research protocol CAR-study B. *BMC Cancer* 2018; 18: 218.

Schimmel WCM, Gehring K, Eekers DBP, Hanssens PEJ, Sitskoorn MM. Cognitive effects of stereotactic radiosurgery in adult patients with brain metastases: A systematic review. *Advances in Radiation Oncology* 2018; 3: 568–81.

Schimmel WCM, Gehring K, Hanssens PEJ, Sitskoorn MM. Cognitive functioning and predictors thereof in patients with 1-10 brain metastases selected for stereotactic radiosurgery. *Journal of Neuro-Oncology* 2019; 22: 1–12.

Verhaak E, **Schimmel WCM**, Sitskoorn MM, Bakker M, Hanssens PEJ, Gehring K. Multidimensional assessment of fatigue in patients with brain metastases before and after Gamma Knife radiosurgery. *Journal of Neuro-Oncology* 2019; 144: 377–84.

Schimmel WCM*, Verhaak E*, Bakker M, Hanssens PEJ, Sitskoorn MM, Gehring K. Group and Individual Change in Cognitive Functioning in Patients With 1 to 10 Brain Metastases Following Gamma Knife Radiosurgery. *Clinical Oncology* 2021; 33: 314–21.

Verhaak E*, **Schimmel WCM***, Gehring K, Emons WHM, Hanssens PEJ, Sitskoorn MM. Health-related quality of life after Gamma Knife radiosurgery in patients with 1–10 brain metastases. *Journal of Cancer Research and Clinical Oncology* 2021; 147: 1157–67.

Verhaak E, **Schimmel WCM**, Gehring K, Hanssens PEJ, Sitskoorn MM. Cognitive Functioning and Health-Related Quality of Life of Long-Term Survivors With Brain Metastases Up to 21 Months After Gamma Knife Radiosurgery. *Neurosurgery* 2021; 88: E396–405.

Schimmel WCM, Verhaak E, Hanssens PEJ, Kavelaars XM, Mulder J, Kaptein MC, Sitskoorn MM, Gehring K. P01.06.B Interim results from CAR-Study B: An ongoing randomized trial on the effect of SRS or WBRT on cognitive performance in patients with 11-20 brain metastases. *Neuro-Oncology* 2022; 24: ii24.

Verhaak E, **Schimmel WCM**, Sitskoorn MM, Hanssens PEJ, Butterbrod E, Gehring K. The long-term course and relationship with survival of multidimensional fatigue in patients with brain metastases after Gamma Knife radiosurgery. *J of Cancer Research and Clinical Oncology* 2023; 149: 9891–901.

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Para ser grande, sê inteiro: nada

To be great, be complete:
don't exaggerate or exclude anything.
Be each thing. Put yourself
in the littlest thing you do.
So, in each lake the full moon shines
because it rises so high.

Fernando Pessoa from *Pessoa in Lisboa*, translation Sharon Dolin

Para ser grande, sê inteiro: nada

Wees, om groot te zijn, geheel: maak niets wat jouw is
Groter of tot niets.
Wees al in alles. Leg zoveel je bent
In 't minste dat je doet.
Zo blinkt de maan in ieder meer geheel
Wijl zij verheven leeft.

Fernando Pessoa in *Gedichten*, vertaling August Willemsen
(Amsterdam Uitgeverij De Arbeiderspers, 1978)