The Impact of Stereotactic or Whole Brain Radiotherapy on Neurocognitive Functioning in Adult Patients with Brain Metastases: A Systematic Review and Meta-Analysis

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\textbf{Keywords}
Brain metastases · Cognition · Neurocognitive functioning · Stereotactic radiosurgery · Whole-brain radiotherapy

\textbf{Abstract}

\textbf{Background & Objectives:} Radiotherapy is standard treatment for patients with brain metastases (BMs), although it may lead to radiation-induced cognitive impairment. This review explores the impact of whole-brain radiotherapy (WBRT) or stereotactic radiosurgery (SRS) on cognition.

\textbf{Methods:} The PRISMA guidelines were used to identify articles on PubMed and EmBase reporting on objective assessment of cognition before, and at least once after radiotherapy, in adult patients with nonresected BMs.

\textbf{Results:} Of the 867 records screened, twenty articles (14 unique studies) were included. WBRT lead to decline in cognitive performance, which stabilized or returned to baseline in patients with survival of at least 9–15 months. For SRS, a decline in cognitive performance was sometimes observed shortly after treatment, but the majority of patients returned to or remained at baseline until a year after treatment.

\textbf{Conclusions:} These findings suggest that after WBRT, patients can experience deterioration over a longer period of time. The cognitive side effects of SRS are transient. Therefore, this review advises to choose SRS as this will result in lowest risks for cognitive adverse side effects, irrespective of predicted survival. In an already cognitively vulnerable patient population with limited survival, this information can be used in communicating risks and aid in making educated decisions.

\textbf{Introduction}

Local and systemic treatment for extracranial cancers is improving, leading to longer life expectancy. New challenges arise due to increased survival rates including the development of brain metastases (BMs). BMs occur in at least 10% of patients diagnosed with cancer and this incidence continues to rise [1, 2]. BMs are difficult to treat systemically because chemotherapeutic agents barely pass the blood-brain barrier. The median overall survival, despite systemic and focal treatment, is limited spanning months to several years, depending on factors such as lesion number, Karnofsky performance status, and the primary cancer as reflected in GPA calculators [3, 4]. Treatment (shared) decisions in this vulnerable patient population are tailored toward gaining the best disease control while maintaining adequate quality of life (QoL) during the remaining life span.
Treatment for BMs consists of different (palliative) options, including surgery, chemotherapy, immunotherapy, and radiotherapy [5]. One of the concerns with radiotherapy treatment is how to achieve the optimal balance between maximizing antitumor effects and minimizing possible adverse side effects. The 2 prominent strategies for radiotherapy in BMs are whole-brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS). WBRT is typically advised for patients with more than 3 BMs since treatment covers all brain tissue and has the advantage of sterilizing not-yet visible BMs [6, 7]. The main disadvantage is that WBRT can lead to radiation-induced tissue damage across the entire brain. SRS has mainly been applied in selected patients with 1 to 3 BMs and a favorable prognosis [8]. During SRS, high precision localized irradiation is delivered to the BMs in a single fraction to maximize local tumor control and minimize the dose to the surrounding, healthy brain tissue. Patients with BMs compose a vulnerable patient group since a high percentage of patients already experience cognitive impairment before starting radiotherapy as a direct result of BMs but also due to previous cancer treatments [9–11]. Deteriorated cognitive functions have been related to impaired financial, work, and social activities, which are all important in maintaining good QoL and autonomy [12, 13]. Although the literature on the cognitive changes after radiotherapy has been reviewed both for WBRT and SRS separately [14, 15], to date no publication exists comparing WBRT with SRS in relation to the cognitive outcome after treatment. Since SRS is increasingly being favored over WBRT in current practice [16], we performed a systematic review on changes in cognitive functioning provoked by either WBRT or SRS in adult patients with nonresected BMs to gain insight on whether current evidence regarding cognitive side effects substantiates contemporary shifts in treatment preference.

Table 1. Criteria for assessing the quality of the data of the articles for the review, including reasons for assessing these criteria

| Criteria | Reason |
|----------|--------|
| 1. Inclusion of >20 patients at baseline | (Avoid type II errors for baseline data) |
| 2. ≥50% of patients available for first follow-up measurements | (Avoid type II errors for follow-up data) |
| 3. Neurocognitive performance scores corrected to norms for age, sex, and education when appropriate | (Bias by demographical variables) |
| 4. Definition of change in cognitive performance was provided | (Bias by definition of change) |
| 5. Cognitive performance at follow-up time points were adjusted for baseline performance | (Bias by differences in baseline performance) |
| 6. Use of parallel versions of neuropsychological tests for retesting procedures was stated in the article | (Bias by learning effects due to repeated administration) |
| 7. Diversity of neurocognitive assessment, assessed by fulfilling (1/2 point each): a. ≥3 different neuropsychological tests used AND b. ≥3 cognitive constructs assessed with test battery | (Quality of cognitive testing procedures) |

Methods

Search Strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used in conducting and reporting this systematic review [17]. We reviewed all published articles on the neurocognitive effects of WBRT or SRS in adult patients with BMs from 1 January 1950 until 4 January 2021. The search strategy combined terms for BMs, radiotherapy, and cognition and was developed for PubMed and adapted for Embase. The complete search strings can be found in online suppl. material 1; for all online suppl. material, see www.karger.com/doi/10.1159/000518848. Additionally, reference lists were manually screened for potentially relevant studies. Articles were screened by 2 researchers (E.E.G. and S.H.J.N.) and disagreement was resolved through consensus meetings. The screening of the studies was facilitated by Covidence systematic review software (Veritas Health Innovation, Melbourne, VIC, Australia). Reasons for exclusion were documented for each article.

Eligibility

The search was confined to articles in English and Dutch. Studies were selected in which objective neurocognitive assessment was performed at baseline (defined as any time point between presentation of the BMs and start of radiotherapy) and at least once after radiotherapy in adult patients with BMs. Only objective cognitive measurements were included since self-reports may be biased due to impairments caused by the BMs and (previous) cancer treatments [18]. Moreover, subjective cognitive complaints do not represent underlying cognitive deficits per se and may be more indicative of psychological distress than actual cognitive impairment [19, 20]. Studies solely utilizing short neurocognitive-screening tools, such as the Mini-Mental Status Examination, were excluded since these tests lack the sensitivity to detect subtle changes in cognitive functioning expected to be present after radiotherapy [21–23]. Furthermore, all articles including patients with resected BMs were excluded since co-acting cortical tissue damage adjacent to the resection site can influence cognitive performance. Studies investigating the influence of treatments concurrent to radiotherapy (e.g., memantine) that did not report on a radiotherapy-only control group were also excluded. Case reports, reviews, commentaries, editorials, and protocols were excluded. If multiple articles reported on the same dataset, the results were combined and reviewed as one cohort.
Data Extraction and Analysis

The follow-up time points were converted to units of “months after radiotherapy.” To aid comparability across studies and following the classification used in previous studies, time points were clustered: short-term follow-up 1–4 months after radiotherapy, midterm follow-up 5–8 months after radiotherapy, and long-term follow-up 9–15 months after radiotherapy. Baseline measurements always refer to the assessment before start of radiotherapy treatment. Additionally, neuropsychological tests were attributed to cognitive constructs in a data-driven classification, based on the subdivision as reported in the majority of the included studies (online suppl. material 2). Data were collected from text, tables, and figures from the articles and then tabulated. Missing data points were excluded from analyses and changes in sample size due to attrition were considered. For meta-analysis of the incidence of cognitive decline compared to baseline performance, we used the inverse variance method in a DerSimonian-Laird random effects model. For individual studies Clopper-Pearson confidence intervals were calculated. Heterogeneity between studies was assessed using Cochran’s Q test and the I² statistic. Statistical analyses were performed with R 3.5.1 open-source software with the “meta” package (http://www.R-project.org).

Data Quality

A critical appraisal of the included studies was performed to assess data quality as reported in the articles, for which a checklist consisting of 7 criteria were constructed (shown in Table 1). One point was awarded if the criterion was met and zero points if not or if it was unclear based on the available information. A maximum score of 7 points could be obtained. A score between 5 and 7 indicates good to high quality, 3 and 4 medium quality, and scores below 2 indicate low quality.

Results

Study Inclusion

The initial search yielded 867 unique articles. After applying the in- and exclusion criteria, 20 articles reporting on 14 original datasets were included in this review (shown in Fig. 1). The majority of these studies were rated as good to high quality (shown in Table 2). The one study rated as low quality was excluded from further analysis [24]. Study and baseline patient characteristics and the main conclusions of the selected articles are shown in Tables 3 and 4, respectively. Patient numbers varied considerably across studies with a median sample size of 81 (range: 20–208) and 35 (range: 7–111) at baseline for the WBRT and SRS studies, respectively. In total, 751 WBRT patients were included and 300 SRS patients. Since data on the incidence of cognitive decline were absent in some articles, the meta-analysis could only be performed for those studies that reported on these data.

Baseline Cognitive Performance

Data on baseline cognitive performance before WBRT were solely explicitly reported for the Mehta et al. [18] study (N = 208). The other included studies reported relative scores to an unreported baseline. Before starting WBRT, 91% of the patients displayed cognitive impairment (Z-score ≤1.5) on ≥1 neuropsychological test and 42% on ≥4 neuropsychological tests. Fine motor coordination was impaired in 63–65%, learning and memory (L&M) in 21–60%, executive function (EF) in 44%, and verbal fluency in 33%. Lower baseline cognitive perfor-
Fig. 1. PRISMA flow chart illustrating the systematic process conducted to identify the articles included in this review. 14 original datasets*. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
| RT type | Authors | Study type | Radiation schedule | N   | Sex (M:F) | Median age in years (range or patients, N) | KPS (patients, N) | Number of BMs (patients, N) | Median total volume of BMs in cm³ | Median overall survival in months | Primary tumor location (patients, N) |
|---------|---------|------------|-------------------|-----|-----------|-------------------------------------------|------------------|-----------------------------|----------------------------------|----------------------------------|-----------------------------------|
| WBRT   | Mehta et al. [7, 18, 38, 74] | Phase III RCT | WBRT 30 Gy/10 fr | 208 | 90:118   | 58 (N.A.)                               | 70 (43) | 1 (41)                        | N.A.                             | 4.9                             | Lung (128) Breast (42) Other (38) |
|        | Gondi et al. [26] | Phase II trial | HA-WBRT 30 Gy/10 fr | 100 | N.A.     | 61 (28–83)                               | 70 (19) | N.A.                          | 6.7                             | 6.8                             | Lung (56) Breast (15) Other (29) |
|        | Saito et al. [28] | Prospective trial | WBRT 30 Gy/10 fr | 18  | 21:13    | 65.5 (39–86)                             | ≤70 (22) | N.A.                          | N.A.                             | N.A.                            | Lung (20) Breast (7) Other (7)   |
|        | Deng et al. [35] | Retrospective trial | WBRT 30 Gy/10 fr | 16  | 64:2    | ≤60 (38)       | ≥80 (71) | N.A.                          | 7.3                             | Lung (109)                        |
|        | Cheng et al. [34] | Prospective trial | WBRT 40 Gy/20 fr | 81  | 48:33    | <65 (39)       | ≥80 (81) | N.A.                          | <3 (54)                          | ≥3 (23)                          | Lung (49) Other (32)               |
|        | Zhan et al. [39] | RCT | WBRT 30 Gy/15 fr | 117 | 68:49    | ≤60 (51)       | ≥70 (85) | N.A.                          | ≥2 (94)                          | ≥2 (23)                          | N.A.                              |
|        | Zhu et al. [40] | Retrospective trial | WBRT 40 Gy/20 fr | 33  | 18:15    | ≤61 (14)       | >61 (19) | N.A.                          | ≥4 (33)                          | N.A.                            | Lung (33)                          |
|        | Westover et al. [41] | Phase II trial | HA-WBRT + SIB 20 Gy/10 fr + 40 Gy/10 fr | 49  | 24:25    | 60 (54–65)      | ≥70 (49) | 1–3 (19) | 4–6 (20) | 7–8 (10) | 0.8 | 9.0 | Lung (39) Breast (5) Other (5) |
|        | Onodera et al. [25] | Nonrandomized pilot study | WBRT 35 Gy/14 fr | 20  | 11:9    | 62.6 (N.A.)    | 70 (1) | 3 (6)                          | N.A.                            | 6.7                             | Lung (17) Breast (1) Other (2)   |
|        | Onodera et al. [25] | Nonrandomized pilot study | SRS 25 Gy/1 fr or 28–35 Gy/4 fr | 7   | 2:5     | 56.3 (N.A.)    | 70 (1) | 1 (7) | 2.8 | N.A. |

**Table 3.** Study characteristics and baseline patient characteristics categorized by type of radiotherapy
| RT type | Authors | Study type | Radiation schedule | N | Sex (M:F) | Median age in years (range or patients, N) | KPS (patients, N) | Number of BMs (patients, N) | Median total volume of BMs in cm³ | Median overall survival in months | Primary tumor location (patients, N) |
|---------|---------|------------|-------------------|---|-----------|---------------------------------------------|------------------|----------------------------|----------------------------------|-----------------------------------|----------------------------------|
| SRS     | Chang et al. [29] | Prospective pilot study | SRS median 20 Gy (14–21 Gy) | 15 | 5:10 | 64.9 (31.5–77) | 70 (1) | 80 (2) | 90 (8) | 100 (4) | 1 (11) | 2–3 (4) | 1.8 | 7.2 | Lung (8) | Renal (3) | Melanoma (4) |
|         | Chang et al. [31] | RCT | SRS median 19 Gy (15–20 Gy) | 30 | 12:18 | 63 (35–82) | ≥80 (30) | 1 (18) | 2–3 (12) | 1.4 | 15.2 | Lung (16) | Breast (4) | Renal (2) | Melanoma (4) | Other (4) |
|         | Brown et al. [32] | RCT | SRS median 20 Gy (14–21 Gy) | 111 | 54:57 | <60 (53) ≥60 (58) | N.A. | 1 (55) | 2 (39) | 3 (17) | N.A. | 10.4 | Lung (80) | Breast (11) | Melanoma (3) | Other (17) |
|         | Habets et al. [30, 43] | Prospective trial | SRS median 19 Gy (15–20 Gy) | 97 | 46:51 | 63 (33–82) | 60–80 (62) | 1 (43) | 2 (31) | 3 (18) | 4 (5) | 7.8 | 7.7 | Lung (48) | Breast (8) | Melanoma (9) | Other (32) |
|         | Minniti et al. [42] | Prospective trial | SRS 22 Gy (<2 cm lesion) 16–18 Gy (≥2 cm lesion) | 40 | 23:17 | 57 (37–74) | ≥60 (40) | 10–14 (32) | 15–21 (8) | 4.7 | 14.1 | Lung (17) | Breast (7) | Melanoma (10) | Kidney (8) |

BM(s), brain metastases; Fr, fractions; Gy, RT dose in Gray; HA-WBRT, hippocampal avoidance whole-brain radiotherapy; KPS, Karnofsky performance status; N.A., not available; RCT, randomized controlled trial; RT, radiotherapy; SIB, simultaneous integrated boost; SRS, stereotactic radiosurgery; WBRT, whole-brain radiotherapy; N.A., not available.
Table 4. Main message of the studies categorized by type of radiotherapy

| RT type | Authors | Patients, N | Time points NCF assessed in months after RT | Definition of cognitive change | Main message |
|---------|---------|-------------|---------------------------------------------|---------------------------------|--------------|
| WBRT    | Mehta et al. [7, 18, 38, 74] | 208 | T0 T1 T2 T3 T4 T5 T6 T9 T12 T15 T18 | ≤2 SD change in average Z-score | T3: Most patients deteriorate on fine motor coordination and least patients on verbal fluency  
T4: Significant deterioration compared to T0 on L&M and verbal fluency  
T5: Significant improvement compared to T0 on verbal fluency, fine motor coordination, and information processing speed |
|         | Gondi et al. [26] | 109 | T0 T2 T4 T6 | RCI | T2: 7–18% mean decline from T0 in L&M performance  
T4: In a subset of 33 patients with T0 MRI, the change in L&M performance was correlated with BMs volume (immediate and delayed recall), age (immediate recall), and volume of white matter injuries pre-treatment (recognition)  
T6: Certain aspects of L&M declined (delayed recall), while others remained stable (immediate recall and recognition). The mean relative decline from T0 to T6 was 0–3% |
|         | Saito et al. [28] | 34 | T0 T4 T8 | RCI | T4: L&M deteriorated significantly compared to T0 in those who only completed T0 and T4 assessments. In total, 27–33% of the patients had deteriorated  
T8: On an average, stable cognitive performance was observed on L&M in subgroup completing assessments at all 3 time points. Of this subgroup, 11–26% had deteriorated L&M performance compared to baseline |
| WBRT    | Deng et al. [35] | 81 | T0 T1 | N.A. | T1: Significantly decreased performance compared to T0 on global cognitive performance, attention, verbal fluency, and event-based prospective memory. Stable performance on time-based prospective memory |
|         | Cheng et al. [34] | 117 | T0 T1 T2 T3 T4 T5 T6 | RCI | T3: 19% of the patients deteriorated on L&M performance  
T6: 35% of the patients deteriorated on L&M performance |
|         | Zhan et al. [39] | 33 | T0 T3 T6 T9 | RCI | T3: Deteriorated cognitive performance was found on L&M, EF, and verbal fluency in 19%, 29%, and 28% of the patients, respectively  
T6: Deteriorated cognitive performance was found on L&M, EF, and verbal fluency in 48%, 48%, and 50% of the patients, respectively  
T9: Deteriorated cognitive performance was found on L&M, EF, and verbal fluency in 50%, 58%, and 57% of the patients, respectively |
|         | Zhu et al. [40] | 47 | T0 T3 T6 T9 T12 | ≤1 SD decline from the mean | T3: Compared to T0, L&M performance declined in 17% of the patients on delayed recall with a mean decline of 11%. No significant changes were found on the other cognitive tasks, but there were large variations  
T6: Mean L&M performance (delayed recall) recovered to pre-treatment values |
Table 4 (continued)

| RT type | Authors | Patients, N | Time points NCF assessed in months after RT | Definition of cognitive change | Main message |
|---------|---------|-------------|---------------------------------------------|-----------------------------|--------------|
| WBRT    | Westover et al. [41] | 20 | T0 | N.A. | T4: Patients receiving WBRT deteriorated significantly compared to T0 on L&M (delayed recall). Additional analysis showed only patients with a brain edema volume ≥16.8 cc. Decreased on L&M (delayed recall) and EF T8: Patients receiving WBRT deteriorated significantly compared to T0 and T4 on L&M (immediate recall) Improvements in immediate and delayed recall at T8 compared to T4 were only observed in patients with a <4.0 cc total volume of BM at T0 T12: In the subgroup of patients followed for at least 12 months, L&M (delayed recognition) had significantly declined compared to T0 at both T4 and T12. This subgroup also had significantly declined EF at T4 compared to T0, with a similar trend at T12. Additionally, L&M (immediate recall) had returned to baseline values at T12 after a significant improvement at T8 No changes in verbal fluency, information processing speed, or on cognitive screening measure at any time point |
|         | Onodera et al. [25] | 17 | T4 | N.A. | |
|         | 14 | T8 | |
|         | 9  | T12 | |
| SRS     | Chang et al. [31] | 111 | T0 | ±1 SD | T4: Most cognitive decline on tests for L&M (20% of the patients on total recall). The mean posterior probability of decline was 24% for total recall, 6% for delayed recall end 0% for delayed recognition. Analysis were also performed for other cognitive tests but might have been underpowered since the trial was stopped prematurely due to significant larger probability of decline on L&M (total recall) after 4 months in the SRS + WBRT versus the SRS alone group T6: The mean posterior probability of decline on total recall was 8% |
|         | 63 | T1.5 | |
|         | 10–12* | T3 | |
|         | 12–14* | T6 | |
|         | 9–10* | T9 | |
|         | 11 | T12 | |
|         | 21 | T12 | |
| SRS     | Chang et al. [29] | 30 | T0 | RCI | T4: Most cognitive decline on tests for L&M (20% of the patients on total recall). |
|         | 20 | T1 | |
|         |     | T2 | |
|         |     | T4 | |
|         |     | T6 | |
|         |     | T12 | |
|         |     | T15 | |
|         |     | T18 | |
| SRS     | Brown et al. [32] | 97 | T0 | ≤1.5 SD mean of healthy controls | T6: The majority of the patients maintained their pre-treatment levels of cognitive performance over the entire study period. Only verbal fluency performance showed trend towards improvement |
|         | 39 | T3 | |
|         | 29 | T6 | |
| SRS     | Habets et al. [30, 43] | 38 | T0 | RCI | T3: Compared to T0, L&M performance declined in 13%, 16%, and 19% of the patients on immediate recall, recognition, and delayed recall. The mean decline varied between 10 and 14% T6: Compared to T0, L&M performance declined in 12%, 15% and 15% of the patients on immediate recall, recognition and delayed recall The mean decline varied between 5 and 9% T12: Compared to T0 L&M performance declined in 5%, 10% and 14% of the patients on immediate recall, recognition and delayed recall. The mean decline varied between 2 and 5% |
|         | 32 | T3 | |
|         | 26 | T6 | |
|         | 21 | T12 | |

T: time point in months after radiotherapy; N.A., not available; NCF, neurocognitive functioning; RCI, reliable change index; RT, radiotherapy; SD, standard deviations; SRS, stereotactic radiosurgery; WBRT, whole-brain radiotherapy; L&M, learning and memory; EF, executive function. * Ranges in patient numbers are caused by different numbers of patients completing the different cognitive tests during the study-procedures.
mance correlated with higher total BMs volume at baseline but not with number of BMs [18, 25]. On the contrary, in another study, neither the volume of BMs nor volume of white matter injury correlated with L&M performance before radiotherapy in a subset of patients [26, 27]. Patients with a KPS of ≥80 and patients ≤65 years performed better at baseline on subtests of L&M [28].

Data on the incidence of baseline cognitive impairment before SRS were explicitly reported for the pilot study by Chang et al. [29, 31] (N = 15) and by Habets et al. [30, 43] (N = 77) [29, 30]. Pre-radiotherapy, 53–67% of patients had cognitive impairment (Z-score ≤ 1.5 SD) on ≥1 neuropsychological test. At baseline, EF was impaired in 47% of the patients, fine motor coordination in 40%, L&M in 31%, visual memory and visuoconstruction in 22%, information processing speed in 10%, and verbal fluency in 7%. Before SRS, the mean Z-scores of both the Chang et al. [29, 31] (N = 30) and the Brown et al. [32] cohort (N = 111) were impaired [31, 32]. The worst group performance was observed on tests for EF and information processing speed. Patients with a baseline BMs volume of >3 cm³ performed worse on attention than those with smaller lesion volumes [29]. Similarly, Onodera et al. [25] reported higher total lesion volume but not the number of BMs at baseline corresponded with worse cognitive performance, while Habets et al. [30, 43] reported no significant association with BMs volume [25, 30].

**Post-Radiotherapy Cognitive Performance**

At short-term follow-up (1–4 months), the majority of the WBRT studies (N = 455 patients) found consistent declines in cognitive performance on most cognitive constructs [18, 25, 26, 28, 33–40]. Overall, between 19 and 37% of the patients deteriorated regarding L&M performance. Gondi et al. [26] found that patients treated with hippocampal avoidance WBRT (HA-WBRT) had significantly less mean relative decline in L&M performance compared to the patients of Mehta et al. [7, 18] who received conventional WBRT (7% vs. 30%, respectively) [18, 26]. The change in L&M performance was correlated to pre-treatment BMs volume, age, and the volume of white matter injuries [27]. Other impaired cognitive constructs in the WBRT studies were EF (29–38%), fine motor coordination (31%), information processing speed (28%), and verbal fluency (7–32%). Even though Westover et al. [41] observed a decline in 17% of their patients (N = 18) regarding L&M performance, on the group level, no significant changes from baseline were found for the other cognitive constructs [41]. Nevertheless, large variations in mean relative change were found for all cognitive constructs (L&M, information processing speed, EF, and verbal fluency).

At midterm follow-up (5–8 months), the results were more variable. The 29 patients who received HA-WBRT had a mere relative decline of 0–3% on multiple tests for L&M at midterm follow-up compared to baseline [26, 33]. Similarly, patients who survived more than 6 months after HA-WBRT with simultaneous integrated boost recovered to baseline scores regarding L&M performance [41]. On the contrary, performance on most cognitive tasks declined in at least 114 patients who received conventional WBRT [35, 39, 40]. L&M performance was most often affected, with 53% of the patients showing decline [35]. Moreover, the percentage of patients with declined performance increased from 19% at short-term to 35% at midterm follow-up [39]. Although group performance declined compared to both baseline and short-term follow-up when considering all 17 patients in the Onodera et al. [25] cohort, improvements were observed in a subgroup of patients with a baseline BMs volume of <4.0 cm³ and in BMs patients surviving at least 12 months [25]. A similar trend was reported by Saito et al. [28] where the subgroup surviving at least 8 months (N = 19) had stable L&M performance over time [28]. Thus, most patients further decreased in cognitive performance at midterm follow-up, but in a subgroup of patients, stable or improved cognitive performance was observed over time.

At long-term follow-up (9–15 months), performance on most cognitive constructs either returned to baseline values or remained stable compared to midterm follow-up. Mehta et al. [7, 18] found slight improvements or stable functioning (N = 9) regarding verbal fluency, information processing speed, and fine motor coordination compared to baseline [18]. In the Zhu et al. [40] cohort (N = 22), 48% of the patients had deteriorated on L&M performance, which is comparable to the 50% at midterm follow-up, suggesting most patients had stable cognitive performance from mid- to long-term follow-up [40]. Similarly, for the 9 patients in the Onodera et al. [25] study, performance on tests for verbal fluency and information processing speed remained stable over the entire study. L&M performance (delayed recognition) significantly declined compared to both baseline and midterm follow-up, and a similar trend was seen for EF. Forest plots of the incidence of patients with cognitive decline for each construct at each time point are presented in online suppl. material 3. The analyses indicated significant heterogeneity between studies for L&M at midterm follow-up. The meta-analysis suggests an increase in the amount of patients with cognitive decline over time until midterm follow-up, with a (relatively) stable or even lower incidence was found at long-term (shown in Fig. 2a).

In accordance with the results described above, Gondi et al. [26] reported a trend toward deteriorated performance on L&M tasks 1 month after WBRT, which stabilized and reverted back to baseline values after that time point. In the Mehta et al. [7, 18] study, cohort time to neurocognitive deterioration was on average shortest for...
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fine motor coordination, L&M, and EF [18]. Additionally, they found that time to neurocognitive deterioration significantly differed between patients showing a volume reduction below or above 45% after 2 months, with patients with more volume reduction (classified as good responders) having a longer time to deterioration on fine motor coordination.

At short-term follow-up (1–4 months) after SRS, the majority of studies reported a decline in cognitive performance when compared to baseline. Overall, declined performance was most common regarding L&M (23–54%) and fine motor coordination (35–46%) [29, 31, 32]. Similarly, between 13 and 19% of the patients in the Minniti et al. [42] cohort (N = 32) showed a mean decline of 10–14% from baseline. For the other assessed cognitive constructs (verbal fluency, attention, information processing speed and EF) the amount of patients in the Chang et al. [29, 31] study that had deteriorated were balanced out by those that had improved [29]. Contrarily, 18% showed a decline in EF in the other study by Chang et al. [29, 31] (N = 20) and 17% on information processing speed in the study by Brown et al. [32] (N = 60) [31, 32]. Both studies found least deterioration on tasks for attention (6%) and verbal fluency (2%). The 2 other studies assessing short-term cognitive performance found no change in cognition compared to baseline [25, 30]. For example, it was reported that 78–100% of the patients (N = 19) had stable performance regarding the different cognitive constructs, where the small percentage of patients that showed declined cognitive performance on the different tests (3–8%) was balanced by those that improved (3–17%) [30]. At both midterm (5–8 months) and long-term follow-up (9–12 months), all studies reported either stable or slightly improved cognitive performance compared to baseline performance [25, 29–32, 42, 43]. To illustrate, the percentage of patients with declined performance on L&M decreased at both mid- and long-term follow-up compared to short-term [42]. Additionally, the mean decline reduced to 2–5% at long-term follow-up compared to 10–14% at short-term, suggesting that both the number of patients as well as the severity of the cognitive decline decreased.
Forest plots of the incidence of patients with cognitive decline for each construct at each time point are presented in online suppl. material 3. There was no significant heterogeneity between studies for any cognitive construct at any time point for the SRS studies. The meta-analysis suggests a relatively constant amount of patients experiencing cognitive decline over time after SRS, albeit with large confidence intervals (shown in Fig. 2b).

Discussion

The aim of this study was to systematically assess the current evidence on the cognitive changes across different cognitive constructs after either WBRT or SRS in adult patients with nonresected BMs with objective neurocognitive assessments performed at baseline and after treatment. Our meta-analysis indicates that after WBRT, the majority of patients show a decline in cognitive performance until midterm follow-up (5–8 months), whereas a subset of patients with relatively good outcome showed stable cognitive performance in the long-term (9–15 months). For SRS, an initial dip (1–4 months) in cognitive performance in patients was observed by half of the studies, whereas at mid- and long-term follow-up, all studies reported that the majority of the patients performed at pre-treatment levels. Since cognitive decline was assessed relative to baseline performance, differences in cognitive performance prior to radiotherapy were accounted for and thus cannot explain the differences between WBRT and SRS. This suggests that while the cognitive side effects of SRS are transient, after WBRT patients can experience deterioration over a longer period of time. This especially holds for those patients with shorter survival. Thereby, this review points toward SRS resulting in lowest risks for cognitive adverse side effects in this already cognitively vulnerable patient population with limited survival. Since cognitive decline was assessed relative to baseline performance, differences in cognitive performance prior to radiotherapy were accounted for and thus cannot explain the differences between WBRT and SRS. This suggests that while the cognitive side effects of SRS are transient, after WBRT patients can experience deterioration over a longer period of time. 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This especially holds for those patients with shorter survival. Therefore, better discernment of short and midterm follow-up an increase in the incidence of WBRT patients with cognitive impairment was found, while a (relatively) stable or even lower incidence was found in the long-term. This suggests that while some patients show a decline in cognitive performance up until midterm follow-up after WBRT, a (relatively) good outcome is often accompanied by stable cognitive performance over time. To illustrate, stronger reduction in tumor volume 4 months after WBRT was related to better preservation of cognitive performance over time [18, 36–38]. It is unclear whether the observed decline in cognitive performance is characteristic of the worse responders (i.e., patients with less tumor shrinkage) or that the good responders survive long enough to recover from this dip in performance. Nonetheless, the data suggest that for patients with a longer survival (at least 9–15 months), the benefits of WBRT radiotherapy outweigh the costs in the long-term. Currently, the majority of patients do not (yet) survive long-term, despite improvements in life expectancy with the introduction of immunotherapies and targeted therapies [45–47]. While early delayed effects (1–4 months after WBRT) are generally considered to be transient, the cognitive decline traditionally characterized as a late delayed effect (5–9 months after WBRT) is thought to be progressive and irreversible [48]. Therefore, the cognitive decline found at short- and midterm should not be discounted against the possible stable long-term cognitive performance in those with a good survival and should be discussed with BMs patients during shared decision-making. However, better discernment of short and long survival should be included in evaluating this.
Results regarding cognitive performance after SRS at short-term follow-up (1–4 months) were variable; approximately half of the included studies observed cognitive deterioration, most frequently for verbal L&M, fine motor coordination, and EF [29, 31, 32, 42]. The other studies found no changes in cognition compared to baseline [25, 30, 43]. At both midterm (5–8 months) and long-term follow-up (9–12 months), all studies reported either stable or (slightly) improved cognitive performance compared to baseline [25, 29–32, 42, 43]. The meta-analysis largely confirms these results; a relatively stable incidence of patients with cognitive decline from baseline was observed up until long-term follow-up, albeit with large confidence intervals. The initial dip in cognitive performance in some of the patients could be attributed to an increase in peri-lesional edema which is sometimes observed shortly after SRS but is often resolved 6 months later [49]. Moreover, adjuvant systemic treatment will often be (re-)initialized shortly after SRS. The short-term side effects of systemic treatments could therefore be the cause of this initial dip, rather than the radiotherapy treatment. Conclusively, after SRS an initial, transient dip in cognitive performance can occur, but at mid- and long-term, the majority of patients will have returned to or remained at pre-radiotherapy cognitive levels.

Looking in more detail at the affected cognitive constructs, not one is specifically affected by WBRT or SRS. Rather, change in cognitive performance was observed across several cognitive constructs, including, but not limited to verbal L&M, EF, information processing speed, and fine motor coordination, which have been linked to damage to white matter fibers has been shown to be directly associated with cognitive deterioration in cancer patients [62].

Strengths and Limitations
Cognitive functioning after cranial radiotherapy has been gaining research interest as reflected by the included studies (published between 2003 and 2020), with most studies (9/14) published over the last 5 years. Nonetheless, studying cognitive changes after radiotherapy in patients with BMs remains challenging for multiple reasons. First, different factors could influence cognitive functioning over the follow-up period, including tumor progression, adjuvant systemic treatment, or changes in mood. Additionally, a substantial number of patients drop out during the study period, most often due to high disease burden. Especially in the long-term, results are therefore based on the small numbers of patients that are fit enough to stay compliant. Unfortunately, this is inevitable in this vulnerable patient population with limited overall survival.

Additionally, numerous challenges hinder in-depth comparison across studies, including differences in patient characteristics (e.g., age), disease characteristics (e.g., primary tumor type), and treatment characteristics (radiotherapy schedule) of the study populations. For example, 2 studies investigated HA-WBRT (N = 149), while all others investigated conventional WBRT. We chose not to exclude these since during HA-WBRT, less brain tissue is irradiated and including this in the review would lead to an underrepresentation rather than an overrepresentation of the cognitive damage to be expected after WBRT compared to SRS. Also, there was much heterogeneity across studies regarding both the methodology (e.g., definition for cognitive impairment and decline and timing of cognitive testing) and reported data (e.g., baseline cognitive data). To illustrate, most studies did not control for practice effects due to repeated testing over time and only 5 out of fourteen studies reported using parallel test for the repeated neuropsychological testing, even though cognitive assessment was repeated up to 9 times within a 1-year period in some studies. These methodological shortcomings could have led to an underestimation of the cognitive changes after radiotherapy as cognitive problems might be masked by repeated testing effects. In order to aid comparability across studies, we chose to cluster the follow-up time points according to classifications used in previous studies. However, the subtle dynamics of cognitive change may not be ideally assessed by this classification. To illustrate, a difference in cognitive deterioration-free survival of merely 0.7 months was found in favor of patients with resected BMs who received SRS (3.7 months) compared to WBRT (3 months) [63]. Thus, the time point clustering used in this study could have masked slight differences that are present between the SRS and WBRT patient groups.

The heterogeneity between studies was also reflected by our meta-analysis on the incidence of cognitive decline over time; the meta-analysis indicated significant heterogeneity between studies regarding the reported incidence of cognitive decline for L&M at midterm for the WBRT studies. This could be explained by the fact that the definition used to assess cognitive change varied greatly between studies and, moreover, was not always reported. Additionally, the meta-analysis shows relatively broad confidence intervals due to the low number of patients for whom the data were available. Nonetheless, even with a small number of studies reporting the incidence of patients with cognitive decline, the meta-analysis indicated significant heterogeneity only for one type of radiotherapy, at one time point, and for one cognitive construct.
In this review, 20 articles reporting on 14 original datasets were included. We chose to include all 20 articles since they answered different questions regarding cognitive functioning, thus did not present overlap. Results were summarized together per dataset to avoid overrepresentation of the same patients in this review. Strict inclusion criteria were used to minimize the potential confounding effects on cognitive performance (e.g., no resected BMs were included). Additionally, a critical appraisal was performed to ensure the quality of the data as reported in the article, which indicated that the majority of the included studies (75%) was of good to high quality. Therefore, we believe our conclusions are warranted.

**Future Directions**

Currently, multiple single center trials are collecting and analyzing prospective data that will hopefully further improve our understanding of cognitive impairment after brain irradiation (e.g., [64–67]). Ideally, all future studies should at minimum use the neuropsychological tests recommended by the International Cancer and Cognition Task Force since these tests have been proven to be sensitive to the neurotoxic effects of cancer treatment [68]. A valuable line of research is to explore possible additional therapeutic strategies that could reduce treatment toxicity. As the mechanisms leading to radiation-induced cognitive impairment are multifactorial, several strategies, each addressing different mechanisms, have been proposed to potentially reduce the neurocognitive toxicity of radiation [69, 70]. For example, avoiding high-dose radiation on hippocampi and adding synthetic metallotaxaphyrin motexafin gadolinium or memantine to WBRT have shown encouraging but mixed results [50, 51, 71–76]. These strategies provide promising prospects for the future, but do require further research.

**Conclusion**

This review indicates that after treatment with WBRT, most patients show declined cognitive performance until at least 8 months after treatment, after which those with a longer overall survival show stable cognitive performance. A proportion of SRS-treated patients first show a decline in cognitive performance, but the majority of the patients return to pre-treatment levels already 5 months after SRS and continue to display stable cognitive performance up until 1 year after SRS. It remains challenging to disentangle the effects of radiotherapy on cognitive functioning from the possible deleterious effects of systemic treatments, the effects of BMs themselves and patient’s psychological state. Nonetheless, this current review indicates that while the cognitive side effects of SRS are transient, after WBRT patients can experience deterioration over a longer period of time. Thus, SRS will result in lowest risks for cognitive adverse side effects in this already (cognitively) vulnerable patient population with limited survival. This information can be used in communicating risks to patients and aid in making educated (shared) treatment decisions toward maintaining optimal QoL.

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**Statement of Ethics**

An ethics statement is not applicable because this study is based exclusively on published literature.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

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**Author Contributions**

All authors contributed to the study design. E.E.G. and S.H.J.N. collected all data by screening of the manuscripts and extracting the relevant information. E.E.G. performed qualitative data analysis and S.H.J.N. performed statistical analyses. E.E.G. prepared the first draft of this manuscript. S.H.J.N., J.J.C.V., and M.E.J.Z. contributed and commented on the draft. All authors read and approved the final manuscript.

**Data Availability Statement**

Data from the published literature were used exclusively in this study. All the literature is referenced in the manuscript.

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