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Critical Review

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

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Abstract

Purpose: Stereotactic radiation surgery (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 and highly relevant treatment goal. This review systematically and specifically evaluates the current literature on the cognitive effects of SRS in patients with BM.

Methods and materials: 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 methodologic 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 to 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

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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 BMs 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 assessments of cognitive functioning in patients with BM.[6–10]

Concern about potential late, progressive, and persistent adverse effects of whole brain radiation therapy (WBRT) on cognitive function has substantially changed the management of BM.[1,11,12] 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 the 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 assessments of cognitive functioning, were reviewed. We use the term "SRS" to refer to radiation therapy that is delivered via stereotactic guidance with approximately a 1-mm targeting accuracy in 1 to 5 fractions using a linear accelerator, a Gamma Knife, or a particle beam accelerator.[19] Additionally, we 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 and highly relevant treatment goal.

Methods and materials

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 (ie, 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) and similar search terms.

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× 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 solely on the Mini-Mental State Examination (MMSE; 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.,[21] 15 patients with newly diagnosed BM (1-3; ≤4 cm) were treated with SRS only (14-21 Gy).[15] 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 a decline on ≥2 tests. This was most common for the

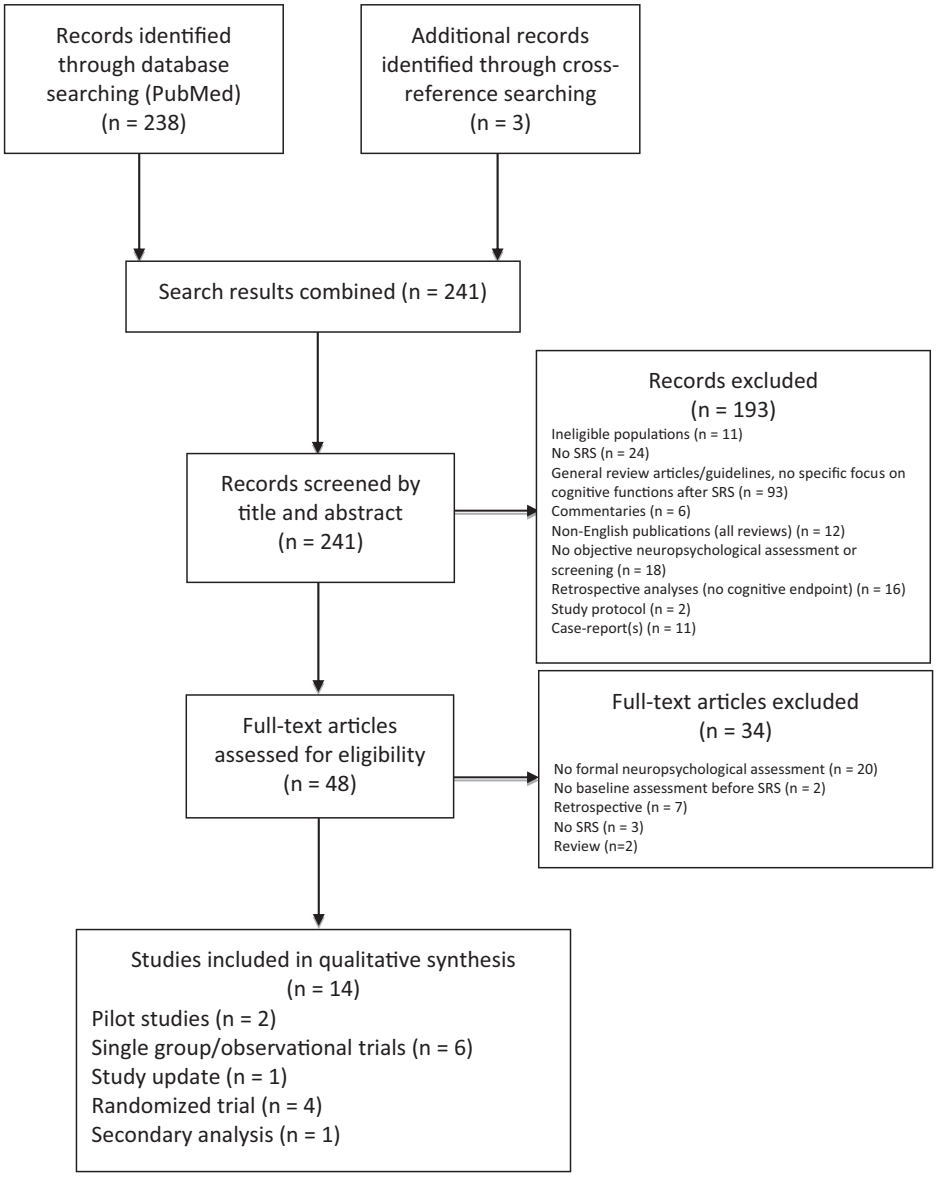

Figure 1 A PRISMA flow diagram illustrating the flow of information through the different phases of the systematic review.

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 of 5 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 3 weeks; n = 28) and group 2 (received SRS alone; n = 30). The primary endpoint was a significant decline (5-point drop compared with baseline) in Hopkins Verbal Learning Test–Revised total recall at 4 months. A reliable change index was used to determine meaningful change.

The trial was halted prematurely because the 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 with patients treated with SRS only. At 4 months, 7 of 11 patients (64%) in the SRS+WBRT group versus 4 of 20 patients (20%) in the SRS group had a decline in memory (total recall). This significant difference persisted until 6 months.

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 months, 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
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)

(*continued on next page*)

Table 1 (*continued*)

Study	Population (n)	Modality (n)	LC (1-yr)/ Median OS Neurological death rate (%)	NP tests	Cognitive outcome
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 y 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 steroid medications 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 y (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 Radiation Therapy Oncology Group 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: 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 × 2.5 Gy).

‡ PTV was defined as GTV + 2 mm margin. The PTV received, depending on the volume and location, a single fraction of 18-21 Gy or 24 Gy in 3 fractions.

§ SRS+WBRT arm: WBRT 3 weeks after SRS. WBRT: 30 Gy (12 × 2.5 Gy).

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 × 2.5 Gy, 2 weeks after SRS).

Table 2 Studies that evaluated cognitive effects of SRS with the MMSE*

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 y (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%
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 y); 68% (2 y); 92% (3 y) of surviving patients Decline at 4 mo: 6% (n = 662); 1 y: 9% (n = 366); 2 y: 6% (n = 128); 3 y: 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 y); 57% (2 y); 50% (3 y); 49% (4 y) of surviving patients Decline at 4 mo: 6% (42 of 662); 1 y: 9% (32/366); 2 y: 8% (15/185); 3 y: 6% (6/100); 4 y: 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.

Dose and fractionation:

* 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.

† 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 × 2.5 Gy).

‡ Based on RTOG protocol 90-05 (Shaw et al., 2000): 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 × 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 assigned to SRS+WBRT also demonstrated a 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 patients in the SRS+WBRT group than those in the SRS-alone group 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 with patients 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 nonrandomized 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 at 4, 8, and 12 months after treatment. No analyses to compare between-group differences of outcomes were performed because the groups were not balanced for number of BM or baseline test performance (ie, 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 a significant decline in list recognition at 4 and 12 months and in 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 nonrandomized (and imbalanced) study must be interpreted cautiously because the number of participants was very low.

Patients (n = 49) with 1 to 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 the 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 cm^3) versus medium (4.8-12.6 cm^3) or small (<4.8cm^3) total tumor volume, and (3) patients with active versus stable systemic disease status.

Baseline scores were available for 77 patients. At the 6-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 speeds 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 patients (52%) at follow-up and was attributed solely to DR in 27 patients. Total tumor volume after SRT decreased ≥50% in 25 of 90 patients (28%). 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

Table 3 Studies in progress evaluating cognitive effects of SRS in patients with BM (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 $\leq$30 cm^3	SRS (n = 100) GK	March 2019 *Active, not recruiting* Target accrual reached	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 $\leq$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 $\leq$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
J. Debus NCT03303365 Germany	Randomized (SPACE vs. conventional sequence) New occurrence or progression of >10 BM (12 mo)	1-10 BM (pMRI)	SRS SPACE (n = 100) SRS CyberKnife (n = 100)	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.

patients with 1 to 3 BM (<3 cm).[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 ($\geq$1 SD from baseline on $\geq$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 declining scores (1 SD on at least 1 test) at each subsequent assessment compared with 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 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.

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 the 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).

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 (ie, 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 of ≥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 a 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 (aged >70 years) with 1 to 4 BM after SRS (16-20 Gy; n = 102; median age: 77 years).[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 with baseline. In 9 patients, intracranial progression presumably caused the decline in MMSE scores; in 2 patients, the decline was attributed to RN. Severe neurologic 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, and 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 = 1194).[34] Patients were split into groups based on 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 patients) 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] with an extended follow-up period of 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 because patients 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 of these 12 patients, MMSE data were available and showed deterioration ≥3 MMSE points in 2 patients.

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 the cognitive effects of SRS in patients with BM 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 suffer from ≥1 (methodologic) 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 (eg, anti-epileptic drugs and dexamethasone). Other (more psychological) factors may also affect cognitive performance (ie, 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 (ie, 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 neuropsychologic 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 and inaccurate measure for cognitive change after radiation therapy,[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 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 (ie, 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 (eg, 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 the cognition 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]

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 Immediate recall Delayed recall Recognition	Verbal learning and memory	Benedict, R. H. B., Schretlen, D., Groninger, L., & Brandt, J. (1998). Hopkins verbal learning test - Revised: Normative data and analysis of inter-form and test-retest reliability. Clinical Neuropsychologist, 12(1), 43-55. Benedict et al., Clinical Neuropsychologist, 1998.
Controlled Oral Word Association Test	Verbal fluency (aspect of executive functioning)	Benton AL. Neuropsychological assessment. Annu Rev Psychol. 1994;45:1–23.
Wechsler Adult Intelligence Scale Digit Span Digit Symbol-Coding	Working memory/attention Information processing speed	Wechsler, San Antonio, 2008 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 Clin Neuropsychol. 1994;9:427–36. Sherer et al., Arch Clin Neuropsycol, 1994
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 Clin Neuropsychol. Oxford University Press; 2004;19:203–14. Lezak, Oxford University Press, 2004 Tombaugh, Arch Clin Neuropsychol, 2004
Lafayette Grooved Pegboard	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 Cogn. 2005;58:258–68. Bryden & Roy, Brain and Cognition, 2005

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 6-8 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) BM, 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.

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Supplementary data

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