Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial

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Summary

Background It is unclear whether the benefit of adding whole-brain radiation therapy (WBRT) to stereotactic radiosurgery (SRS) for the control of brain-tumours outweighs the potential neurocognitive risks. We proposed that the learning and memory functions of patients who undergo SRS plus WBRT are worse than those of patients who undergo SRS alone. We did a randomised controlled trial to test our prediction.

Methods Patients with one to three newly diagnosed brain metastases were randomly assigned using a standard permutated block algorithm with random block sizes to SRS plus WBRT or SRS alone from Jan 2, 2001, to Sept 14, 2007. Patients were stratified by recursive partitioning analysis class, number of brain metastases, and radioresistant histology. The randomisation sequence was masked until assignation, at which point both clinicians and patients were made aware of the treatment allocation. The primary endpoint was neurocognitive function: objectively measured as a significant deterioration (5-point drop compared with baseline) in Hopkins Verbal Learning Test–Revised (HVLT-R) total recall at 4 months. An independent data monitoring committee monitored the trial using Bayesian statistical methods. Analysis was by intention-to-treat. This trial is registered at www.ClinicalTrials.gov, number NCT00548756.

Findings After 58 patients were recruited (n=30 in the SRS alone group, n=28 in the SRS plus WBRT group), the trial was stopped by the data monitoring committee according to early stopping rules on the basis that there was a high probability (96%) that patients randomly assigned to receive SRS plus WBRT were significantly more likely to show a decline in learning and memory function (mean posterior probability of decline 52%) at 4 months than patients assigned to receive SRS alone (mean posterior probability of decline 24%). At 4 months there were four deaths (13%) in the group that received SRS alone, and eight deaths (29%) in the group that received SRS plus WBRT. 73% of patients in the SRS plus WBRT group were free from CNS recurrence at 1 year, compared with 27% of patients who received SRS alone (p=0·0003). In the SRS plus WBRT group, one case of grade 3 toxicity (seizures, motor neuropathy, depressed level of consciousness) was attributed to radiation treatment. In the group that received SRS, one case of grade 3 toxicity (aphasia) was attributed to radiation treatment. Two cases of grade 4 toxicity in the group that received SRS alone were diagnosed as radiation necrosis.

Interpretation Patients treated with SRS plus WBRT were at a greater risk of a significant decline in learning and memory function by 4 months compared with the group that received SRS alone. Initial treatment with a combination of SRS and close clinical monitoring is recommended as the preferred treatment strategy to better preserve learning and memory in patients with newly diagnosed brain metastases.

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Introduction

About 170 000 new brain metastases are diagnosed in the USA each year.[1] For over 50 years, whole brain radiotherapy (WBRT) has served as the standard palliative treatment for brain metastases. More recently, randomised trials have established the added survival benefit of either surgery or stereotactic radiosurgery (SRS) combined with WBRT over WBRT alone for patients with single brain metastases,[2–4] raising questions about the role of WBRT and its possible effect on neurocognitive function.

A strategy to preserve neurocognition in patients with one to three newly diagnosed brain metastases is to use SRS alone with clinical monitoring to defer or completely avoid WBRT.[5] However, SRS plus WBRT is frequently given to maximise disease control, since the omission of WBRT increases the risk of recurrent brain metastases.[6–10] We did a randomised controlled trial to help clarify whether elective WBRT should be given with SRS, or deferred. We proposed that patients treated with SRS plus WBRT would have inferior neurocognitive function based on the Hopkins Verbal Learning Test–Revised (HVLT–R) compared with patients treated with SRS alone.

Methods

Patients

Eligible patients who presented at the Departments of Radiation Oncology, and Neurosurgery, and at the Brain and Spine Center, MD Anderson Cancer Center, Houston,

TX, USA, were recruited to the study. Eligibility requirements were: age 18 years or greater; recursive partitioning analysis (RPA) class one or two (Karnofsky Performance Status [KPS] ≥70); one to three newly diagnosed brain metastases eligible for SRS; brain MRI within 1 month of enrolment; and signed written informed consent. A diagnostic quality single-dose gadolinium contrast-enhanced 1·5 T MRI with acquired axial, coronal, and sagittal views was used for screening potential study participants and assessing entry criteria. Patients were excluded if they had undergone prior brain surgery, SRS, or WBRT; if they were diagnosed with leukaemia, lymphoma, germ-cell tumour, small-cell lung cancer, leptomeningeal disease, or unknown primary tumour; if they were RPA class three (KPS <70); and if they were pregnant. After meeting eligibility criteria, patients were randomly assigned to SRS alone or SRS plus WBRT. Patients were stratified by RPA class (one *vs* two),[11] number of lesions (one or two *vs* three), and radioresistant histology (melanoma or renal cell *vs* other).

Randomisation and masking

From the trial outset, randomisation was done by computer in a 1:1 fashion between group 1 (SRS plus WBRT) and group 2 (SRS alone) using a standard permutated block algorithm in which block sizes were randomly chosen from 2, 4, 6, or 8. The sequence was concealed until interventions were assigned by the Clinical Oncology Research (CORE) database computer. The random group assignment, once made, was revealed to both the study participants and research staff. Study patients were enrolled and informed of their assignment by a research nurse.

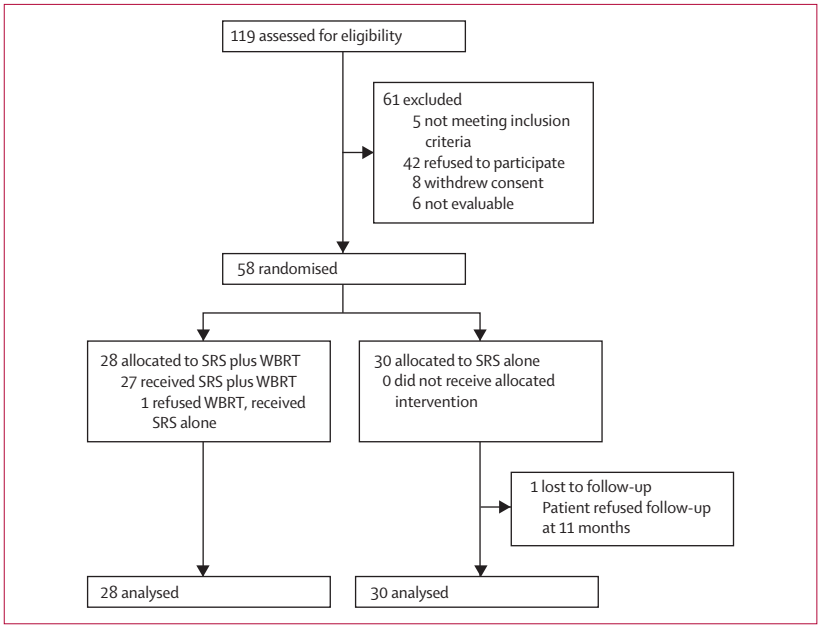

Figure 1: **Trial profile**
SRS=stereotactic radiosurgery. WBRT=whole-brain radiotherapy.

During the study, investigators remained blinded to the trial data except for treatment assignment, which was monitored on an annual basis by the data monitoring committee. The data monitoring committee was chaired by the Chairman of the University of Texas MD Anderson Cancer Center Department of Biostatistics. Additional members included an institutional review board Chair, biostatistics faculty members, clinical faculty members, and a lay person representative from the community.

Procedures

All patients received initial SRS for one to three brain metastases detected with screening brain MRI within 1 month before enrolment. Formal neurocognitive testing and quality of life (QOL) instrument testing with Functional Assessment of Cancer Therapy–Brain (FACT-BR) were scheduled at baseline and each follow-up visit. The battery of neurocognitive tests previously reported and described[5] comprised the HVLT–R (total recall, delayed recall, and delayed recognition), Wechsler Adult Intelligence Scale-III (WAIS-III) digit span and digit symbol, Trail Making Test parts A and B, Multilingual Aphasia Examination Controlled Oral Word Association (COWA), and Lafayette Grooved Pegboard. HVLT–R is widely used as a standardised psychometric instrument with proven sensitivity to the neurotoxic effects of cancer treatment.

The SRS technique used has been previously described.[5,12] The contrast-enhanced metastases were contoured on the stereotactic planning CT images or co-registered MRI, if available. Tumour volumes were obtained from the stereotactic treatment planning computer. Patients assigned to the SRS alone group were monitored according to the study follow-up schedule. Patients assigned to the SRS plus WBRT group received SRS first, followed by WBRT given within 3 weeks. SRS was given before WBRT (as is standard practice at the University of Texas MD Anderson Cancer Center) to ensure that intracranial metastases identified at enrolment could be localised and therefore treated with SRS. (If WBRT was given first, a robust or complete response could preclude subsequent targeting with SRS.) SRS dose was prescribed in general accordance to the Radiation Therapy Oncology Group (RTOG) 90-05 guidelines.[13] WBRT was prescribed to a total dose of 30 Gy given in 12 daily fractions of 2·5 Gy per day. WBRT was delivered from a linear accelerator by using 6 MV photons, opposed lateral technique, and standard whole-brain fields. No systemic agents were used to manage brain metastases in this trial.

Patient follow-up visits comprised a clinic visit with neurological examination, brain MRI, neurocognitive, and QOL assessment. In the first 18 months, patients were scheduled for follow-up visits and testing at 1, 2, 4, 6, 9, 12, 15, and 18 months, and then every 6 months thereafter, following completion of the last radiation treatment. Systemic therapy was given at the discretion of the medical oncologist. Cause of death determinations

were made according to the method described by Patchell and colleagues.[3]

The primary study endpoint was neurocognitive function, as objectively measured by significant deterioration in HVLT-R total recall at 4 months. This change was defined a priori by the Reliable Change Index[14] as a drop of at least 5 points from baseline.[15] Other endpoints include local brain tumour control, distant brain control, and survival. Local brain tumour control of the initial SRS-treated lesions was defined as a complete, partial, or stable response, or less than a 25% increase in diameter on contrast-enhanced MRI follow-up and not requiring resection. Any initial SRS-treated lesions increased by more than 25% in diameter on contrast-enhanced MRI or required resection were considered a local failure. Distant brain control was defined as the absence of any new brain metastasis, distinct from the initial SRS-treated lesion, on follow-up brain MRI.

Statistical analysis

The trial endpoint required 90 patients to be enrolled with about 80% power to detect a 30% difference based on the neurocognitive endpoint of total recall.

Interim monitoring of the trial was done by the data monitoring committee with Bayesian statistical methods.[16] Each patient's total recall score recorded at 4 months was assigned a binary outcome as a success (stable or improved) or failure (declined). A decline in the total recall score of 5 points or greater compared with baseline was considered a failure. A stable or improved score, or a decline of 4 points or less compared with baseline was considered a success. The failure rate for treatment k is designated qk. The failure rates for both treatment groups were modeled as β-distributions with priors of β (1·25, 3·75), assuming a mean of 0·25 for both groups. Early stopping rules specified that during the trial, if the probability of treatment arm k being better (having a lower failure rate) was greater than 0·975, then that group is declared the winner and the trial would be suspended. If, at the maximum enrolment, no treatment group could meet this criterion, then no default final selection would be made.

Patient survival was calculated from the date of protocol registration using the Kaplan–Meier method.[17] Log-rank analysis was used to compare survival between the two groups. Hazards ratios [HR] and associated CI were computed with Cox proportional hazards regression analysis. The Reliable Change Index was used to measure meaningful change between baseline and 4 months for HVLT–R, WAIS-III digit span and digit symbol, Trail Making Test part A and B, COWA, and Lafayette Grooved Pegboard. The Reliable Change Index is derived from the standard error of measurement (SEM) for each test in the battery. The SEM is calculated from the test–retest reliability (r) and the standard deviation of test scores (SD): $SEM=SD\times(1-r)^{0.5}$. The standard error of the difference (SE_{diff}) is then calculated as $SE_{diff}=[2\times(SEM)^2]^{0.5}$. For each test in the neurocognitve battery, the Reliable Change Index value was determined a priori for that particular test to determine whether a change from baseline is clinically meaningful. Analyses were done using Stata 10.0, and were done according to the intention-to-treat principle. This trial is registered at www.ClinicalTrials.gov, number NCT00548756.

	Stereotactic radiosurgery (N=30)	Stereotactic radiosurgery plus whole-brain radiotherapy (N=28)
Median age (years; range)	63 (35–82)	64 (40–78)
Sex		
Male	12 (40)	17 (61)
Female	18 (60)	11 (39)
Ethnic origin		
White	25 (83)	20 (71)
African American	3 (10)	3 (11)
Hispanic	2 (7)	4 (14)
Other	0 (0)	1 (4)
Number of brain metastases		
1	18 (60)	15 (54)
2	7 (23)	8 (28)
3	5 (17)	5 (18)
Recursive partitioning analysis class		
1	7 (23)	3 (11)
2	23 (77)	25 (89)
Graded prognostic assessment[18]		
0–1	3 (10)	3 (10·7)
1·5–2·5	19 (63·3)	19 (67·9)
3	5 (16·7)	5 (17·9)
3·5	3 (10)	1 (3·5)
Primary site		
Breast	4 (13)	4 (14)
Lung	16 (53)	16 (57)
Renal	2 (7)	2 (7)
Melanoma	4 (13)	3 (11)
Other	4 (13)	3 (11)
Liver metastasis		
Yes	2 (7)	5 (18)
No	28 (93)	23 (82)
Bone metastasis		
Yes	9 (30)	9 (32)
No	21 (70)	19 (68)
Lung metastasis		
Yes	13 (43)	12 (43)
No	17 (57)	14 (50)
Unknown	0 (0)	2 (7)
Adrenal metastasis		
Yes	3 (10)	5 (18)
No	27 (90)	23 (82)
Median total intracranial tumour volume (cm^3; range)	1·4 (0·1–20·0; SD 4·6)	2·3 (0·05–27·6; SD 6·3)

Data are n (%) unless otherwise stated.

Table 1: **Patient and treatment characteristics**

	Stereotactic radiosurgery plus whole-brain radiotherapy (N=28)	Stereotactic radiosurgery alone (N=30)
Hopkins Verbal Learning Test–Revised		
Total recall	–1·12 (1·50)	–0·80 (1·53)
Delayed recall	–1·32 (1·74)	–0·73 (1·31)
Delayed recognition	–0·34 (1·37)	–0·30 (1·14)
Trail Making Test		
Part A	–2·15 (3·39)	–1·13 (1·95)
Part B	–2·88 (3·37)	–2·43 (3·98)
Digit span	–0·13 (1·17)	–0·23 (0·97)
Digit symbol	–0·4 (0·97)	–0·1 (1·13)
Multilingual Aphasia Examination Controlled Oral Word-Association test	–0·28 (1·20)	–0·17 (1·25)
Grooved pegboard–dominant	–1·47 (2·36)	–1·30 (3·09)
Grooved pegboard–non-dominant	–1·59 (2·67)	–0·98 (2·06)

All data are mean standardised *Z* score (SD). Data are corrected for age and education where necessary.

Table 2: **Baseline neurocognitive function**

	Stereotactic radiosurgery plus whole-brain radiotherapy (N=11)	Stereotactic radiosurgery alone (N=20)	p (A>B)
Total recall	52%	24%	96%
Delayed recall	22%	6%	86%
Delayed recognition	11%	0%	86%

p (A>B)=Bayesian probability that the proportion with a significant neurocognitive worsening is higher in stereotactic radiosurgery plus whole-brain radiotherapy than stereotactic radiosurgery alone.

Table 3: **Bayesian posterior mean probability of significant neurocognitive decline at 4 months by treatment group, by HopkinsVerbal Learning Test—Revised**

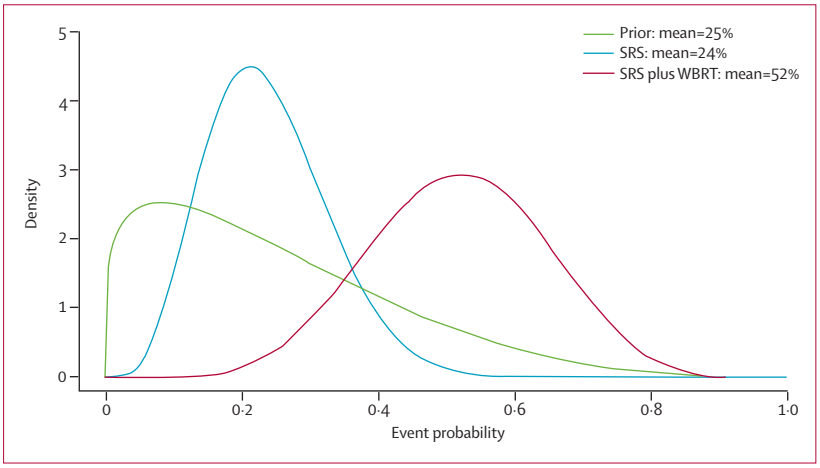

Figure 2: **Prior and posterior distributions of probability of cognitive decline (5 points or greater fall from baseline) assessed by HVLT–R (total recall)**
SRS=stereotactic radiosurgery. WBRT=whole-brain radiotherapy.

See Online for webappendix

Role of the funding source

There was no funding source for this study. ELC, JSW, KRH, PKA, and CAM had full access to the raw data. The corresponding author had full access to all of the data and the final responsibility to submit the manuscript for publication.

Results

58 patients were enrolled and randomly assigned to SRS alone (n=30) or SRS plus WBRT (n=28) from Jan 2, 2001, to Sept 14, 2007 (figure 1) before the trial was halted by the data monitoring committe. The date of last follow-up was Oct 20, 2008. Patient characteristics are presented in table 1. The median follow-up was 9·5 months (range 0·3–66) for the entire study. For the SRS alone group, the median SRS tumour margin dose was 19 Gy (range 15–20). For the SRS plus WBRT group, the median SRS tumour margin dose was 20 Gy (range 15–20). The median prescription target volume ratio (treated volume/target volume) was 1·9 (range 0·8–5·0) and 2·0 (1·4–4·6) for SRS alone and SRS plus WBRT, respectively (p=0·677). The median prescription isodose was 88% (range 81–95) for SRS alone and 87% (range 80–95) for SRS plus WBRT (p=0·103). One patient refused WBRT treatment assignment, resulting in 57 out of 58 (98%) of the enrolled patients completing their assigned treatment. This patient remained in the SRS plus WBRT group and was analysed according to his original assignment. The median time interval between screening MRI and SRS was 10 days (SD 8·4) for SRS plus WBRT, and 11·5 days (SD 11·3) for SRS alone. The standardised neurocognitive test scores obtained at baseline for the two groups is shown in table 2.

The trial was halted by the data monitoring committee according to the early stopping rules on the basis that there was 96% confidence that total recall at 4 months for SRS plus WBRT (seven patients deteriorated of 11 patients assessed; 64%) was inferior to total recall for SRS alone (four patients deteriorated of 20 patients assessed; 20%) based on a mean posterior probability of decline of 52% for the SRS plus WBRT group and 24% for the SRS alone group (table 3; figure 2). The total recall difference persisted at 6 months, with a mean posterior probability of decline of 28% for the SRS plus WBRT group and 8% for the SRS alone group, with 90% confidence. At 4 months, the HVLT–R delayed recall (22% in the SRS plus WBRT group *vs* 6% in the SRS alone group; 86% confidence) and HVLT–R delayed recognition (11% in the SRS plus WBRT group *vs* 0% in the SRS alone group; 86% confidence) tests also indicated that it was highly probable that patients had worse neurocognitive function in the SRS plus WBRT group than the SRS alone group. Bayesian analysis was also used to compare neurocognitive decline between groups in the remaining battery of tests at 4 month from enrolment (webappendix), but because the trial was stopped early, this analysis might have been underpowered for the other neurocognitive function domains that were assessed.

For the FACT–BR, baseline mean was 59·8 for SRS plus WBRT and 64·6 for SRS. The 4-month mean was 58·0 for SRS plus WBRT and 65·6 for SRS alone. The FACT-BR mean difference between the groups at 4 months compared with baseline was 2·8 (95% CI –26 to 21; p=0·76). The wide CI indicates that the results are

inconclusive, and should not be interpreted as indicating no difference between the two groups.

The median survival for all patients in the study was 9·2 months. At the time of analysis, 25 (89%) of 28 patients died in the SRS plus WBRT group, and 20 (67%) of 30 patients died in the SRS alone group. In the SRS plus WBRT group, there were 16 systemic deaths, seven neurological deaths, and two deaths from unknown causes. In the SRS alone group there were ten systemic deaths, eight neurological deaths, and two deaths from unkown causes. In the SRS alone group, which had 30 patients, there were four deaths at the 4-month primary endpoint assessment; there were eight deaths in the SRS plus WBRT group, which had 28 patients, at the same stage. Compared with patients assigned to SRS alone, the HR for death associated with patients assigned to SRS plus WBRT was 2·47 (95% CI 1·34–4·54; p=0·0036). The median and 1-year survival was higher for the SRS alone group than for patients in the SRS plus WBRT group (15·2 *vs* 5·7 months, 63% *vs* 21%; p=0·003; figure 3). The 1-year local tumour control rate was 67% for patients in the SRS group and 100% for patients in the SRS plus WBRT group (p=0·012; figure 4). The 1-year distant brain tumour control rate was 45% for patients in the SRS group and 73% for patients in the SRS plus WBRT group (p=0·02; figure 5). The 1-year freedom from CNS recurrence was 27% (95% CI 14–51) for SRS alone and 73% (46–100) for SRS plus WBRT (p=0·0003). The HR for SRS plus WBRT versus SRS was 2·1 (95% CI 0·8–6·0; p=0·15) for neurological deaths, and 2·4 (1·2–4·8; p=0·013) for systemic deaths. At 4 months, the median KPS was 70 for patients assigned to SRS plus WBRT, and 80 for patients assigned to SRS alone.

Prior to trial enrolment, 21 (75%) patients assigned to the SRS plus WBRT group and 21 (70%) patients assigned to the SRS alone group received systemic therapy. No patient received systemic therapy during protocol radiation therapy, or between initial SRS and WBRT. Systemic therapy was given following completion of SRS plus WBRT in 15 (53%) of 28 patients, and after SRS alone in 20 (66%) of 30 patients (p=0·31). Of those patients who received systemic therapy after SRS alone or SRS plus WBRT, 13 (87%) of 15 of the SRS plus WBRT group, and 18 (90%) of 20 of the SRS alone group started systemic therapy within 4 months of enrolment, before the primary neurocgonitive function endpoint was assessed. The mean difference in the amount of time that elapsed between the date of the SRS procedure and the date of starting systemic therapy for the SRS plus WBRT and SRS alone groups was 38·9 days (95% CI 25·8–51·9). The number of cycles of systemic therapy given to patients after they had completed radiation therapy in the SRS plus WBRT versus the SRS alone group was 5·3 versus 8·6 (mean) and 2 versus 4 (median), respectively. No study patient received systemic agents for the purpose of managing brain metastases.

10 (33%) patients in the SRS alone group underwent 12 salvage craniotomies to resect 12 local brain lesions (all 12 brain lesions had previously been treated with SRS alone, and were therefore considered local failures). At presentation, three patients were asymptomatic, while seven patients had neurological symptoms relieved by surgery. Of the 12 lesions, ten (83%) were carcinomas, while the remaining two (17%) specimens were attributable to necrosis and astrogliosis. Six patients in the SRS alone group underwent eight salvage SRS treatments for distant

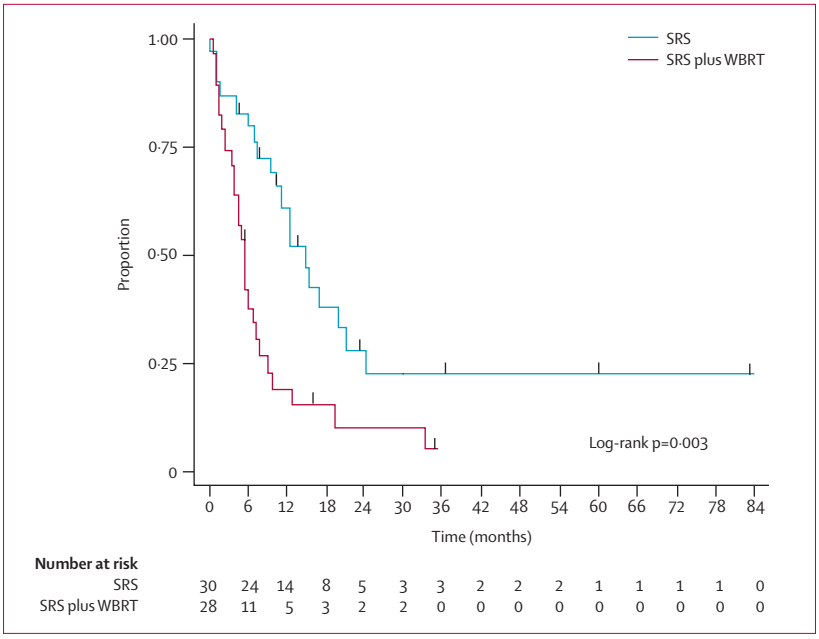

Figure 3: **Actuarial time to death (all causes)**
SRS=stereotactic radiosurgery. WBRT=whole-brain radiotherapy.

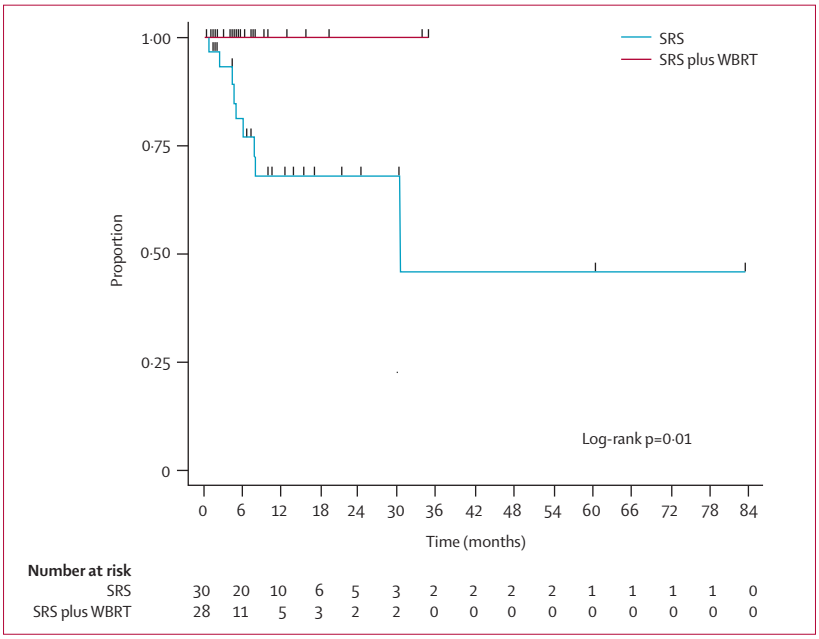

Figure 4: **Actuarial freedom from local tumour progression**
SRS=stereotactic radiosurgery. WBRT=whole-brain radiotherapy.

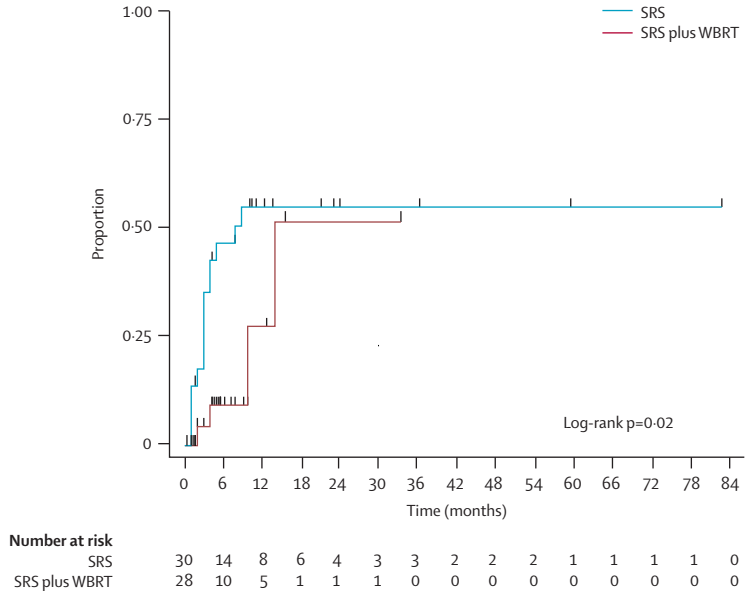

Figure 5: **Cumulative incidence of distant brain tumour recurrence**
SRS=stereotactic radiosurgery. WBRT=whole-brain radiotherapy.

	Stereotactic radiosurgery plus whole-brain radiotherapy (N=28)	Stereotactic radiosurgery alone (N=30)
Salvage stereotactic radiosurgery (n symptomatic/n salvage)	0% (0/2) distant brain progression (8 tumours)	0% (0/6) distant brain progression
Salvage whole-brain radiotherapy (n symptomatic/n salvage)	0% (0/0)	10% (1/10) distant brain progression
Salvage surgery (n symptomatic/ n salvage)	0% (0/0)	70% (7/10) local brain progression (12 tumours)
No salvage treatment (n symptomatic/n recurred)	66% (2/3) distant brain progression (12 tumours)	0% (0/0)

Table 4: **Percentage of patients with intracranial progression who were symptomatic by treatment assignment and type of salvage therapy**

brain lesions. Salvage WBRT was given to 10 (33%) of 30 patients in the SRS alone group. The percentage of symptomatic intracranial progression for each group is given in table 4. The 1-year actuarial freedom from receiving WBRT was 61% in the SRS alone group. The SRS alone group in the current trial used salvage therapies at a rate of 87% (see webappendix for breakdown across groups). Two patients in the SRS plus WBRT group underwent salvage SRS. The first patient underwent three separate sessions of salvage SRS to treat a total of seven distant brain recurrences. The second patient underwent one session of salvage SRS to treat one distant brain recurrence. Both patients were asymptomatic at the time their recurrences were detected by MRI. No SRS plus WBRT patient underwent craniotomy or repeat WBRT.

In the SRS plus WBRT group, one case of grade 3 toxicity (seizures, motor neuropathy, depressed level of consciousness) was attributed to radiation treatment. In the group that received SRS, one case of grade 3 toxicity (aphasia) was attributed to radiation treatment. There were two cases of grade 4 toxicity in the SRS alone group, which manifested as pathologically proven radiation necrosis.

Discussion

Patients randomly assigned to SRS plus WBRT were more likely to show a significant drop in HVLT–R total recall at 4 months than were patients randomly assigned to SRS alone (52% *vs* 24%, respectively), despite the fact that patients in the SRS alone group showed a higher overall brain tumour recurrence than did those patients in the SRS plus WBRT group. This finding persisted at 6-month follow-up.

We proposed that memory would be likely to be affected by radiation therapy, given the adverse effects of radiation on neurogenesis of the hippocampus.[19] Therefore, we designed our primary endpoint to capture changes in memory function. We also proposed that the remaining neurocognitive function domains would be less affected by radiation therapy. In our study, the results of the other neurocognitive function tests mirrored those of the HVLT–R tests, but were not as robust. Patients assigned to SRS plus WBRT showed greater declines in executive function (COWA, Trail Making Test part B) compared with patients in the SRS alone group (webappendix). These findings support the hypothesis that WBRT toxicity has a greater role in causing a decline in verbal learning and memory, and other neurocognitive domains, compared with recurrent brain metastases, which can be discovered early through close surveillance. The effectiveness of close surveillance is supported by the fact that most patients (18 of 21) with distant recurrences were clinically asymptomatic when the recurrences were discovered on follow-up MRI (table 4). It is important to note that prior to radiation treatment, GPA indices and baseline test scores across all neurocognitive domains were well balanced between the SRS plus WBRT and SRS alone groups.

According to a recent review,[6] only two randomised phase 3 trials, the JROSG-99-1[20] and RTOG 95-08,[2] have assessed the adjuvant roles of WBRT and SRS, respectively. However, only JROSG-99-1 has addressed the role of adjuvant WBRT follwing SRS. In JROSG-99-1, 132 patients with one to four brain metastases were randomised to SRS alone or SRS plus WBRT. Both local control and distant brain control improved with adjuvant WBRT, but no significant difference in survival was detected between the two groups (table 5). The cognitive effect of adjuvant WBRT could not be addressed because of a paucity of detailed neurocognitve assessments. To our knowledge, our study represents the first completed randomised controlled trial using formal neurocognitive testing to adequately address the issue of SRS plus WBRT versus SRS alone in the initial management of patients newly diagnosed with one to three brain metastases. Previous studies were limited by either the absence of

neurocognitive testing altogether[21,22] or the use of mini-mental status examination (MMSE),[20,23] which is not sensitive enough to detect more subtle neuropsychological changes. The use and inclusion of neurocognitive endpoints in clinical trials for patients with CNS tumours is increasing, and has been recognised to offer unique information about patient health.[24] The HVLT–R, among other neurocognitive tests, is currently incorporated into a number of RTOG brain tumour and prophylactic radiation therapy trials, as well as trials sponsored by pharmaceutical companies. Neurocognitive test batteries should be used in patients with brain metastases enrolled in clinical trials.[25] In our pilot study using neurocognitive tests on patients with one to three brain metastases treated with SRS alone, it was found that adverse neurocognitive performance correlated with total intracranial tumour volume at baseline.[5] The practical implication of a decline in HVLT–R total recall is an increased need for assistance with the activities of daily living. For example, a patient might need more help managing medications and finances. In patients with brain metastasis, it has also been shown that neurocognitive function and measures of activities of daily living and QOL are correlated. It was found that a decline in neurocognitive function scores from previous visits are predictive of subsequent decline in activities of daily living scores and patient self-reported QOL. Learning and memory function were seen to decline earlier in the course of the disease than other neurocognitive function domains.[26]

The survival (median 15·2 months, 1-year survival 63%) of the SRS alone group in our study is in line with that achieved for RPA class one patients (median 14–15·2 months, 1-year survival 56%) treated in a multi-institutional study of SRS alone versus SRS plus WBRT.[22] A notable difference between the SRS alone group in the JROSG 99-1 trial and the corresponding group in our study is the use of salvage therapies, which were used at almost twice the rate in our study (87%) than in the JROSG 99-1 trial (45%; webappendix). By contrast, the survival in the SRS plus WBRT group in our study was consistent with the SRS plus WBRT group of RTOG 95-08,[2] in which patients with one to three newly diagnosed brain metastases were randomly allocated to either WBRT, or WBRT followed by SRS boost (table 5). One potential explanation for the higher survival associated with patients treated with SRS alone is the local surgical salvage rate of 33% of patients in the SRS alone group with pathologically proven active tumour in most cases. The importance of surgery in the treatment of brain metastases has been reported in previous studies.[3,27–29] Based on a post-hoc analysis of the timing of systemic therapy in our study, patients assigned to the SRS alone group received systemic therapy over 1 month earlier and for a median of two more cycles than patients assigned to SRS plus WBRT. These exploratory findings suggest that more prompt systemic therapy might have contributed to the prolonged survival of patients in the SRS alone group. Another possible explanation for the survival difference is that patients randomly assigned to SRS plus WBRT had a greater systemic disease burden than their counterparts in the SRS alone group at the time of enrolment.

The association between WBRT and an increased risk of systemic deaths has been previously reported in a randomised controlled trial of surgery with or without WBRT.[3] Therefore, despite the benefit of WBRT in reducing the risk of brain-tumour recurrences, there might be systemic deaths related to mechanisms involving CNS injury,[19] a possibility that should be explored in future pre-clinical and clinical studies. Lowered total WBRT doses, and lowered daily fraction sizes below the WBRT regimen of 30 Gy at 2·5 Gy per day should be investigated, since the disease control achieved in the SRS plus WBRT (37·5 Gy) group of RTOG 95-08 and the corresponding group in our study were comparable. For the so-called radioresistant brain metastases from melanoma, renal-cell carcinoma, and sarcoma, it might be even more justified to omit WBRT for one to three brain metastases, as it is thought that WBRT is less effective in this setting.[30]

The major finding of this trial, that memory as assessed by HVLT–R total recall is more likely to be preserved with initial SRS alone than SRS plus WBRT, should be applicable and relevant to other centres using the same entry criteria, given the widespread availability of SRS at many hospitals. However, applicability of the findings is dependent on the willingness of patients and their

	N	Number of lesions	12-month local tumour control	12-month brain tumour recurrence	Median survival (months)
Radiation Therapy Oncology Group 95-08[2] (N=331)					
Whole-brain radiotherapy plus stereotactic radiosurgery	164	1–3	82%	25%	6·5
Whole-brain radiotherapy alone	167	1–3	71%	30%	5·7
Japanese Radiation Oncology Study Group 99-1[22] (N=132)					
Stereotactic radiosurgery plus whole-brain radiotherapy	65	1–4	88·7%	47%	7·5
Stereotactic radiosurgery alone	67	1–4	72·5%	76%	8·0
M D Anderson Cancer Center (N=58)					
Stereotactic radiosurgery plus whole-brain radiotherapy	28	1–3	100%	27%	5·7
Stereotactic radiosurgery alone	30	1–3	67%	73%	15·2

Table 5: **Comparison of randomised trial outcomes**

physicians to adhere to a schedule of close monitoring, having consistent access to high-quality MRI, having access to a neurosurgical team willing and able to perform salvage resections when indicated, and applying strict physics quality-assurance procedures for SRS.

This study provides level 1 evidence to support the use of SRS alone in the initial management of patients newly diagnosed with one to three brain metastases. We recommend that initial SRS alone combined with close clinical monitoring should be the preferred treatment strategy for such patients. Surgical salvage should be used for local failures, and SRS or WBRT for distant failures as indicated. This strategy is consistent with the trend towards personalised medicine and tailoring therapies, rather than applying the "one size fits all" approach of giving WBRT to all patients with brain metastasis.

Contributors

ELC was principal investigator of the study, and wrote the protocol. ELC, JSW, KRH, RBA, JMS, MHM, and CAM contributed to study design. ELC, JSW, KRH, PKA, RBA, AS, and CAM contributed to acquisition of data. ELC, JSW, KRH, PKA, FFL, DGK, RBA, JMS, AS, MHM, and CAM contributed to the analysis and interpretation of the data. The report was written by ELC, with contributions from JSW, KRH, PKA, and CAM. All authors contributed to the critical review and approval of the final manuscript. JSW and CAM did neuropsychological testing. KRH and PKA contributed to statistical analysis. ELC, KRH, and the data monitoring committee participated in study supervision.

Conflicts of interest

The authors declared no conflicts of interest.

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References

1 Posner J. Management of brain metastases. *Revue Neurologique* (Paris) 1992; **148:** 477–87.

2 Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet* 2004; **363:** 1665–72.

3 Patchell R, Tibbs P, Walsh J, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med* 1990; **322:** 494–500.

4 Vecht C, Haaxma-Reiche H, Noordijk E, et al. Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery. *Ann Neurol* 1993; **33:** 583–90.

5 Chang E, Wefel J, Maor M, et al. A pilot study of neurocognitive function in patients with one to three new brain metastases initially treated with stereotactic radiosurgery alone. *Neurosurgery* 2007; **60:** 285–92.

6 Brown P, Asher A, Farice E. Adjuvant whole brain radiotherapy: strong emotions decide but rationale studies are needed. *Int J Radiat Oncol Biol Phys* 2008; **70:** 1305–09.

7 Lo S, Chang E, Suh J. Stereotactic radiosurgery with and without whole-brain radiotherapy for newly diagnosed brain metastases. *Expert Rev Neurotherapuetics* 2005; **5:** 487–95.

8 Patchell R, Regine W, Loeffler J, Sawaya R, Andrews D, Chin L. Radiosurgery plus whole-brain radiation therapy for brain metastases. *JAMA* 2006; **296:** 2089–90.

9 Regine W, Huhn J, Patchell R, et al. Risk of symptomatic brain tumor recurrence and neurologic deficit after radiosurgery alone in patients with newly diagnosed brain metastses: results and implications. *Int J Radiat Oncol Biol Phys* 2002; **52:** 333–38.

10 Regine W, Scott C, Murray K, Curran W. Neurocognitive outcome in brain metastases patients treated with accelerated fractionation *vs* accelerated hyperfractionated radiotherapy: an analysis from Radiation Therapy Oncology Group Study 91–104. *Int J Radiat Oncol Biol Phys* 2001; **51:** 711–17.

11 Gaspar L, Scott C, Rotman M, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys* 1997; **37:** 745–51.

12 Chang EL, Hassenbusch SJ, Shiu A, et al. The role of tumor size in the radiosurgical management of patients with ambiguous brain metastases. *Neurosurgery* 2003; **53:** 272–80.

13 Shaw E, Scott C, Souhami L, et al. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG Protocol 90-05. *Int J Radiat Oncol Biol Phys* 2000; **47:** 291–98.

14 Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *J Consult Clin Psychol* 1991; **59:** 12–19.

15 Brandt R, Schretlen D, Groninger L, Brandt J. Hopkins Verbal Learning Test–Revised: normative data and analyses of inter-form and test-retest reliability. *Clin Neuropsychol* 1998; **12:** 43–55.

16 Thall P, Simon R. Practical Bayesian guidelines for phase IIB clinical trials. *Biometrics* 1994; **50:** 337–49.

17 Kaplan-Meier EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; **53:** 457–81.

18 Sperduto P, Berkey B, Gaspar L, Mehta M, Curran W. A new prognostic index and comparison to three other indices for patients with brain metastases: an analysis of 1960 patients in the RTOG database. *Int J Radiat Oncol Biol Phys* 2008; **70:** 510–12.

19 Monje M, Palmer T. Radiation injury neurogenesis. *Curr Opin Neurol* 2003; **16:** 129–34.

20 Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases. *JAMA* 2006; **295:** 2483–91.

21 Sneed P, Lamborn K, Forstner J, et al. Radiosurgery for brain metastases: is whole brain radiotherapy necessary? *Int J Radiat Oncol Biol Phys* 1999; **43:** 549–58.

22 Sneed PK, Suh JH, Goetsch SJ, et al. A multi-institutional review of radiosurgery alone vs radiosurgery with whole brain radiotherapy as the initial management of brain metastases. *Int J Radiat Oncol Biol Phys* 2002; **53:** 519–26.

23 Aoyama H, Tago M, Katoh N, et al. Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. *Int J Radiat Oncol Biol Phys* 2007; **68:** 1388–95.

24 Meyers C, Brown P. Role and relevance of neurocognitive assessment in clinical trials of patients with CNS tumors. *J Clin Oncol* 2006; **24:** 1305–09.

25 Herman M, Tremont-Lukats I, Meyers C, et al. Neurocognitive and functional assessment of patients with brain metastases. *Am J Clin Oncol* 2003; **26:** 273–79.

26 Li J, Bentzen S, Li J, Reschler M, Mehta M. Relationship between neurocognitive function and quality of life after whole-brain radiotherapy in patients with brain metastasis. *Int J Radiat Oncol Biol Phys* 2008; **71:** 64–70.

27 Bindal A, Bindal R, Hess K, et al. Surgery versus radiosurgery in the treatment of brain metastasis. *J Neurosurg* 1996; **84:** 748–54.

28 Bindal R, Sawaya R, Leavens M, Lee J. Surgical treatment of multiple brain metastases. *J Neurosurg* 1993; **79:** 210–16.

29 Bindal R, Sawaya R, Leavens M, Hess K, Taylor S. Reoperation for recurrent metastatic brain tumors. *J Neurosurg* 1995; **83:** 600–04.

30 Chang E, Selek U, Hassenbusch S, et al. Outcome variation among "radioresistant" brain metastases treated with stereotactic radiosurgery. *Neurosurgery* 2005; **56:** 936–45.