Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial

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Summary

Background After brain metastasis resection, whole brain radiotherapy decreases local recurrence, but might cause cognitive decline. We did this study to determine if stereotactic radiosurgery (SRS) to the surgical cavity improved time to local recurrence compared with that for surgical resection alone.

Methods In this randomised, controlled, phase 3 trial, we recruited patients at a single tertiary cancer centre in the USA. Eligible patients were older than 3 years, had a Karnofsky Performance Score of 70 or higher, were able to have an MRI scan, and had a complete resection of one to three brain metastases (with a maximum diameter of the resection cavity ≤4 cm). Patients were randomly assigned (1:1) with a block size of four to either SRS of the resection cavity (within 30 days of surgery) or observation. Patients were stratified by histology of the primary tumour, metastatic tumour size, and number of metastases. The primary endpoint was time to local recurrence in the resection cavity, assessed by blinded central review of brain MRI scans by the study neuroradiologist in the modified intention-to-treat population that analysed patients by randomised allocation but excluded patients found ineligible after randomisation. Participants and other members of the treatment team (excluding the neuroradiologist) were not masked to treatment allocation. The trial is registered with ClinicalTrials.gov, number NCT00950001, and is closed to new participants.

Findings Between Aug 13, 2009, and Feb 16, 2016, 132 patients were randomly assigned to the observation group (n=68) or SRS group (n=64), with 128 patients available for analysis; four patients were ineligible (three from the SRS group and one from the observation group). Median follow-up was 11·1 months (IQR 4·8–20·4). 12-month freedom from local recurrence was 43% (95% CI 31–59) in the observation group and 72% (60–87) in the SRS group (hazard ratio 0·46 [95% CI 0·24–0·88]; p=0·015). There were no adverse events or treatment-related deaths in either group.

Interpretation SRS of the surgical cavity in patients who have had complete resection of one, two, or three brain metastases significantly lowers local recurrence compared with that noted for observation alone. Thus, the use of SRS after brain metastasis resection could be an alternative to whole-brain radiotherapy.

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Introduction

Brain metastases are a tremendous health-care burden.[1] Surgical resection is a mainstay of treatment for single metastases and has been shown to improve survival compared with that for whole brain radiotherapy (WBRT) alone.[2] Surgical resection alone is thought to be insufficient to provide durable local control, and the addition of postoperative WBRT decreases the likelihood of recurrence within the resection cavity (local recurrence).[3] Although WBRT is often considered the standard of care after surgical resection of brain metastases to improve time to local recurrence, results from studies have shown an association with cognitive decline.[4–6] Consequently, its routine use has been questioned, and WBRT is now frequently withheld after resection, especially for patients with a low number of brain metastases.[7,8] As an alternative to WBRT, stereotactic radiosurgery (SRS) can be used post-operatively to deliver a high dose of targeted radiation, in one session, to the margins of the resection cavity to minimise local recurrence. Therefore, SRS should decrease local recurrence without the adverse effects of WBRT; however, only retrospective studies have been published that show the feasibility of administering post-operative SRS to the resection cavity, and its efficacy remains unknown.[9,10]

Surgical techniques and adjuncts have improved substantially since the original studies of management of brain metastases by Patchell and colleagues,[2,3] with recent studies indicating that local control could be improved through more modern surgical techniques, particularly for smaller tumours.[11] Our primary aim was to determine whether administering postoperative SRS to the resection cavity improved time to local recurrence compared with that for surgical resection alone.

Research in context

Evidence before this study

To our knowledge, there have been no completed randomised, controlled trials to assess the efficacy of stereotactic radiosurgery (SRS) to improve local control after surgical resection of brain metastases. Whole brain radiotherapy (WBRT) after surgical resection has been the standard of care but it is associated with cognitive deficits. Many clinicians have advocated the use of SRS after surgical resection to improve local control and avoid the cognitive side-effects of WBRT.

We searched PubMed for articles published in English between Jan 1, 1980, and Dec 31, 2016, which reported the use of radiation to improve local tumour control after surgical resection of brain metastases. Search terms included "brain", "local control", "metastasis", "neoplasm", "radiation", "surgery", and "survival". Numerous retrospective studies have been reported, but these are subject to various limitations. We filtered for randomised, controlled trials and identified 49 articles. We then limited the search results to studies that specifically addressed the use of radiation to increase local tumour control after surgical resection of brain metastases, which yielded three studies. All three studies evaluated the utility of WBRT in the context of surgical resection of brain metastases. No study evaluated the use of SRS after surgical resection. Therefore, level 1 evidence supporting the use of SRS to improve local control after surgical resection of brain metastases is absent. Moreover, the most recent study evaluating the use of radiation after surgical resection (using WBRT) was in 1998. Since that time, surgical techniques have evolved substantially and no recent studies have evaluated local control after surgical resection alone.

Added value of this study

The results of this trial add to the existing evidence for the management of brain metastases by showing a significant improvement in local control when SRS is used after resection of one to three brain metastases compared with that for resection alone. The results also reinforce that surgical resection alone is insufficient to provide durable local control.

Implications of all the available evidence

Our results suggest that SRS might be an alternative to WBRT for patients after surgical resection of one to three brain metastases. Future trials should explore increased radiation doses to improve local control and report outcomes with respect to quality of life.

Methods

Study design and participants

In this randomised, controlled, phase 3 trial, done in a single tertiary cancer institution in the USA, we enrolled patients older than 3 years with a Karnofsky Performance Score of 70 or higher who were able to have an MRI scan and who had between one and three resected brain metastases. Complete resection was verified by the study neuroradiologist. The exclusion criteria were age younger than 3 years; previous radiotherapy administered to the brain; previous resection of any brain metastasis done before the study; evidence of leptomeningeal disease, small-cell lung cancer or haematological malignancies; pregnancy; and a postoperative cavity of more than 4 cm (at the time of SRS), as determined by the study neuroradiologist (SAh). Systemic disease was assessed at baseline using RECIST (version 1.1) criteria,[12] primarily by CT scans. Patients were permitted to have active extracranial disease and could be treated with systemic agents while on the study. Patients gave written informed consent for inclusion in the study (if younger than 18 years, consent was given by the parent or guardian). The study was approved by The University of Texas MD Anderson Cancer Center Clinical Research Committee and Institutional Review Board and was monitored by the institutional Data and Safety Monitoring Board. The full protocol is supplied in the appendix (pp 1–13).

Randomisation and masking

Patients were enrolled by the study nurse and randomly assigned (1:1) with an institutional, computerised patient registration system to receive either SRS or observation. A block randomisation schedule with a block size of four was used to generate the random allocation sequence. To conceal the sequence, records were pre-allocated to each stratum. Patients were stratified by histological type (melanoma *vs* non-melanoma), preoperative size of brain metastases (<3 cm *vs* ≥3 cm, based on the largest cross-sectional diameter on contrast-enhanced T1-weighted MRI results), and number of brain metastases (one *vs* two or three). The treatment team (excluding the neuroradiologist) and patients were informed of the group allocations after randomisation. The neuroradiologist was masked with respect to the study group after patient enrolment.

Procedures

All patients in the SRS group were treated within 30 days of surgery and underwent a single session of treatment. The SRS target volume was defined as the surgical cavity on the volumetric MRI scan, with a 1 mm circumferential margin added. Prescription doses and SRS target volumes were 16 Gy (for ≤10 cc), 14 Gy (for 10·1–15 cc), and 12 Gy (for >15 cc). Treatment with SRS was done using the Elekta Perfexion Gamma Knife unit (Elekta, Stockholm, Sweden). Patients undergoing SRS had a Leksell (Elekta) stereotactic headframe applied on the day of the procedure. A volumetric MRI was done on the morning of the procedure after headframe placement. The volumetric MRI comprised an axial-T1-weighted 3D-fast spoiled gradient echo sequence done at 1 mm slice thickness with a gap of 0 mm, after the administration of meglumine gadobenate (MultiHance, Bracco, Milan, Italy). We routinely obtained sagittal and coronal reconstructed images for interpretation in all

See Online for appendix

three planes. All studies were done on 1.5 or 3.0 Tesla scanners (General Electric, Boston, MA, USA; Siemens, Berlin, Germany). All radiation plans were reviewed by the treating radiation oncologist, neurosurgeon, and medical physicist to verify protocol-specific volume delineation and radiation dosimetry. If the lesion was close to the dura, a meningeal margin was included. The surgical tract (particularly for deep-seated tumours) was not included in the planning. Dose constraints were less than 12 Gy for brainstem and less than 9 Gy for the optic nerve and tract. Patients in both groups had surveillance brain MRI and clinical assessment (including an evaluation for adverse events) within 5–8 weeks after the craniotomy, and then every 6–9 weeks for the first year, then brain MRI every 9–12 weeks. Unscheduled follow-ups were also recorded to assess adverse events. Adverse events related to SRS were recorded at each clinical visit. They included complications related to stereotactic frame placement and radiation treatment. All MRI scans were reviewed centrally by the study neuroradiologist. Local recurrences (in either group) were treated at the discretion of the physician and treatments could include surgery if appropriate, or SRS if the patient was in the observation group. New distant brain metastases distinct from the treated site(s) that did not require WBRT were noted and treated at the physician's discretion. Patients with new distant brain metastases remained in the study. Unresected lesions, if present, were treated with SRS as clinically indicated.

Outcomes

Time to local recurrence was the primary endpoint (defined as the time from randomisation). Local recurrences were defined as radiographic evidence of a new contrast-enhancing lesion (specifically, any new, progressive, enhancing nodularity), contiguous with or within the resection cavity, as confirmed by the study neuroradiologist. For any patient who had more than one lesion resected, local recurrence in any surgical cavity was considered a local recurrence. Equivocal areas of enhancement that were ultimately found to represent local recurrences were retroactively censored on the date of the first ambiguous MRI scan.

Secondary endpoints were time to distant brain recurrence (defined as time from randomisation to the development of a new brain lesion separate from the surgical site) and overall survival (defined as the time from randomisation to death). The type of death was categorised as neurological if metastatic brain disease was the proximate cause of death, or systemic if the patient died from extracranial disease.

Statistical analysis

On the basis of the available literature, local recurrence after surgical resection only was expected to occur in 50% of patients within 6 months, whereas local recurrence after treatment of the resection cavity with SRS was expected to occur in 25% of patients within 6 months.[3] On the basis of the exponential distribution, these values suggest a median time to local recurrence of 6 months in the observation group and 14·5 months in the SRS group (hazard ratio [HR] 0·415). Under the alternative hypothesis for a log-rank test, a two-sided type I error of 0·05, and two interim futility looks, a total of 132 patients (61 in each group) would have 99·6% power to detect differences based on an HR of 0·415, and approximately 80% power to detect differences based on an HR of 0·596. Estimates of freedom from local recurrence at 6 months were 55% (95% CI 43–70) for the observation group and 82% (73–94) for the SRS group. Thus, the maximum sample size to be accrued was 132 patients. Estimating an accrual rate of two to three patients per month, the projected time to complete the study was 44–66 months. The University of Texas MD Anderson Cancer Center Data Safety Monitoring Board monitored the study annually. Differences in time to local recurrence were to be evaluated after a total of 39 events occurred, after 77 events occurred, and after at least 115 events occurred. We used a test statistic based on a stratified log-rank test. The interim stopping rule consisted of a group sequential test based on a gamma family type I error spending function. The stopping boundaries for the interim analysis were based on the stratified log-rank test with p values of 0·9866 (for first look) and 0·4692 (for second look). On March 22, 2016, the protocol was amended (after accrual had completed but before data were analysed) to clarify analysis plans (appendix pp 12–13).

The primary and secondary analyses were done on a modified intention-to-treat basis that excluded ineligible patients from the analysis, preserved the original treatment assignment, and was based on the stratified log-rank test. For all time-to-event endpoints, a univariate test comparing treatment groups was conducted using a log-rank test along with Kaplan-Meier estimates. For the primary and secondary endpoints, patients dying without evidence of CNS recurrence were censored, and patients remaining event free at the end of follow-up were censored. The HR comparing SRS with observation was computed for each endpoint with and without adjustment for other covariates (treatment [SRS *vs* observation], site of primary cancer, systemic disease status, graded prognostic assessment score, number of brain metastases, and tumour size). For the primary endpoint, we calculated the stratified adjusted p value. For the secondary endpoints we calculated the unadjusted p value, and also the adjusted p values. Multivariable analysis of time to local recurrence, time to distant brain recurrence, and overall survival was done with the Cox proportional hazards model. A prespecified analysis of freedom from WBRT in each group (defined as time from randomisation to WBRT) was done; patients who did not receive WBRT were censored. A prespecified analysis of freedom from leptomeningeal

disease in each group (defined as time from randomisation to leptomeningeal disease) was also done and patients who did not develop leptomeningeal disease were censored. Analyses for freedom from WBRT and leptomeningeal disease were done using Kaplan-Meier estimates and univariate Cox proportional hazards regression to estimate the hazard ratio, confidence intervals, and p value. Finally, we did analyses of time to local recurrence irrespective of treatment group according to the three stratification factors (histological type [melanoma *vs* non-melanoma], size of metastases [<3 cm *vs* ≥3 cm], and number of metastases [one *vs* two or three]) and the prespecified variables of systemic disease status (no evidence of disease or partial response *vs* progressive disease *vs* stable disease) and the graded prognostic assessment score (2·5–3·0 *vs* 1·0–2·0 and 3·5–4·0 *vs* 1·0–2·0). An analysis according to common histologies (breast, lung, and other) and tumour size (≤2·5 cm, 2·5–3·5 cm, and >3·5 cm) was done post hoc. We assessed the significance of the stratification subset differences by fitting Cox proportional hazards regression models with treatment–covariate interaction terms. A post-hoc analysis of tumour size by treatment–covariate interaction terms was also done. A prespecified analysis of time to local recurrence using competing risk proportional hazards regression analysis (Fine and Gray model) was done to verify the results of the primary analysis. The competing risks were local CNS recurrence, distant CNS recurrence requiring WBRT, other CNS recurrence, and death without CNS recurrence.

No analysis of complications was done because there were none.

The statistical analysis was done using TIBCO Spotfire S+. This study is registered with ClinicalTrials.gov, number NCT00950001.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Aug 13, 2009, and Feb 16, 2016, we enrolled 132 patients who had undergone resection of at least one brain metastasis between Oct 6, 2009, and Sept 1, 2015. Four patients were declared ineligible after randomisation and were excluded from the analysis: one patient had prior head and neck radiation extending into the brain; one patient's MRI result on the day of SRS revealed a residual tumour, indicating incomplete resection; one patient withdrew from the study; and one patient was randomised to the observation group more than 30 days after surgery because of treatment for a pulmonary embolism. The final analysis included

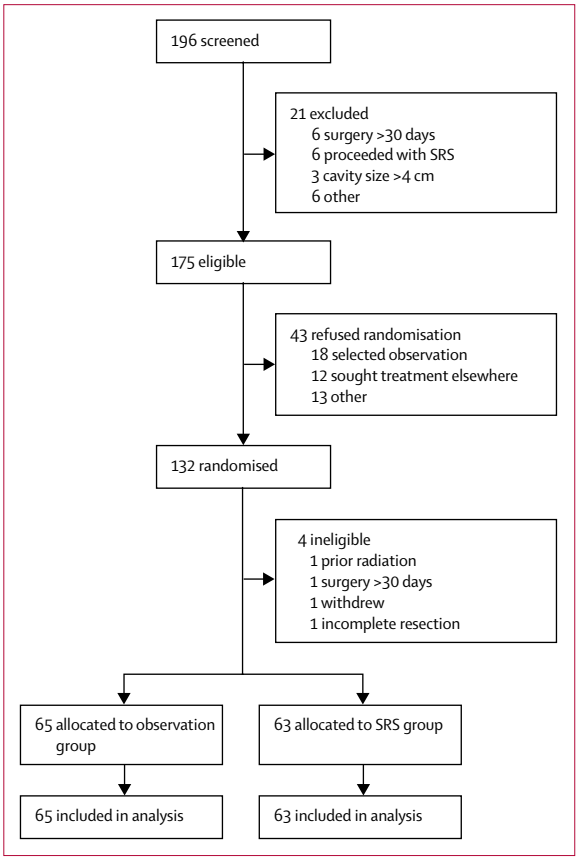


Figure 1: **Trial profile**
SRS=stereotactic radiosurgery. Of the four ineligible patients, three were in the SRS group and one was in the observation group.

128 patients (65 in the observation group and 63 in the SRS group; figure 1). Median follow-up was 11·1 months (IQR 4·8–20·4). By the conclusion of the study, 85 patients had died (39 in the observation group and 46 in the SRS group).

Table 1 shows the demographic and baseline characteristics of all eligible randomly assigned patients. The median age of the whole cohort was 59 years (IQR 20–80). The median dose of postoperative radiation was 16 Gy (range 12–18) to the 50% isodose line. The median preoperative tumour maximal diameter was 3·0 cm (range 0·6–5·3) in the SRS group and 3·0 cm (0·7–5·7) in the observation group. The median SRS-treated cavity volume was 8·9 cc (range 0·9–28·6). In the SRS group, 66 lesions were treated (in 63 patients). Five dosing deviations from the protocol occurred: three patients received 18 Gy to the 50% isodose line because of physician preference, and two received 14 Gy to the 50% isodose line because of lesion proximity to the motor cortex.

In the observation group, 31 (48%) of 65 patients developed local recurrence of their treated lesion. Of these patients, 13 subsequently had SRS alone, nine had WBRT

	Observation group (n=65)	Stereotactic radiosurgery group (n=63)
Sex		
Female	34 (52%)	26 (41%)
Male	31 (48%)	37 (59%)
Race		
White	49 (75%)	45 (71%)
Other	16 (25%)	18 (29%)
Age (years)		
Median (range)	57 (29–79)	58 (20–80)
<50	11 (17%)	18 (29%)
51–65	36 (55%)	27 (43%)
>65	18 (28%)	18 (29%)
Primary cancer		
Melanoma	13 (20%)	14 (22%)
Lung	13 (20%)	13 (21%)
Breast	14 (22%)	9 (14%)
Other	25 (38%)	27 (43%)
Systemic disease status		
No evidence of disease or partial response to systemic therapy	21 (32%)	21 (33%)
Progressive disease	28 (43%)	26 (41%)
Stable disease	16 (25%)	16 (25%)
Graded prognostic assessment score		
1·0–2·0	29 (45%)	25 (40%)
>2·0–3·0	23 (35%)	29 (46%)
>3·0–4·0	13 (20%)	9 (14%)
Number of metastases		
1	41 (63%)	38 (60%)
2	14 (22%)	18 (29%)
3	10 (15%)	7 (11%)
Tumour size		
0·5–2·5 cm	19 (29%)	21 (33%)
>2·5–3·5 cm	19 (29%)	21 (33%)
>3·5 cm	17 (26%)	16 (25%)

Data are n (%) or median (range).

Table 1: **Baseline characteristics**

alone, three had surgery followed by WBRT, two had WBRT and SRS, one had surgery followed by SRS, one had surgery followed by fractionated external beam radiation, one had surgery alone, and one opted for non-treatment. In the SRS group, 15 (24%) of 63 patients developed local recurrence of their treated lesion. Of these patients, seven subsequently had WBRT, three had additional SRS, three had surgery (the pathological specimen confirmed metastatic cancer in all three cases), one had laser interstitial thermal therapy, and one opted for non-treatment.

The 12-month freedom from local recurrence was 43% (95% CI 31–59) in the observation group and 72% (60–87) in the SRS group (HR 0·46 [95% CI 0·24–0·88]; stratified log-rank p=0·015; figure 2A). The median time to local recurrence was 7·6 months (95% CI 5·3 months to not reached [NR]) in the observation group and was not reached (15·6 months to NR) in the SRS group. The results from a competing risk analysis were similar (HR 0·41 [95% CI 0·21–0·80]; p-value from Fine–Gray regression=0·0097). 6-month cumulative incidence of local recurrence was 34% (95% CI 23–46) for the observation group and 15% (6–23) for the SRS group.

The median overall survival was 18 months (95% CI 13 months to NR) in the observation group (39 deaths) and 17 months (13–22) in the SRS group (46 deaths; HR 1·29 [95% CI 0·84–1·98]; p-value from Cox regression=0·24; figure 2B). The cause of death was neurological in 25 (64%) of 39 patients in the observation group and 22 (48%) of 46 patients in the SRS group (with a difference in proportions of 16% [95% CI –5 to 37; p=0·13]). For the 38 patients who died of systemic disease progression (14 in the observation group and 24 in the SRS group), the main system involved at the time of death was lung (2 in the observation group and 8 in the SRS group), liver (2 in the observation group and 2 in the SRS group), skeletal (2 in the observation group and 2 in the SRS group), lymphatic involvement (1 in the observation group and 1 in the SRS group), multiple organ systems (2 in the observation group and 3 in the SRS group), and other (5 in the observation group and 8 in the SRS group). 12-month freedom from distant brain recurrence was 33% (95% CI 22–49) in the observation group (43 events) and 42% (30–58) in the SRS group (35 events; HR 0·81 [95% CI 0·51–1·27]; p=0·35; figure 2C). Distant brain metastasis management is shown in the appendix (p 15).

30 (46%) of 65 patients in the observation group subsequently had WBRT, and 24 (38%) of 63 patients in the SRS group subsequently had WBRT. The median WBRT-free survival in all eligible patients (n=128) was 15 months (95% CI 8·6–42·5) in the observation group and 16 months (10·1 to NR) in the SRS group (HR 0·8 [95% CI 0·47–1·37]; p-value from Cox regression=0·42; appendix p 14). Median overall survival in the 54 patients who had subsequent WBRT was 6·0 months (95% CI 5·1–9·2). Median overall survival was 5·4 months (4·2–10·6) in the observation group and 7·5 months (3·1–12·0) in the SRS group. 20 patients developed leptomeningeal disease (8 in the observation group and 12 in the SRS group). At 12 months, the incidence of leptomeningeal disease was 16% (95% CI 4–26) in the observation group and 28% (12–40) in the SRS group (HR 1·4 [95% CI 0·6–3·4]; p=0·46). 19 of the 20 patients with leptomeningeal disease subsequently had WBRT (8 in the observation group and 11 in the SRS group).

12-month freedom from local recurrence was 60% (95% CI 46–79) in patients with graded prognostic assessment scores of 1·0–2·0 (n=54), 58% (48–76) in those with scores greater than 2·0–3·0 (n=52), and 44% (25–75) in those with scores greater than 3·0 to 4·0 (n=22; >2·0–3·0 *vs* 1·0–2·0, HR 1·2 [95% CI 0·6–2·3];

>3·0–4·0 *vs* 1·0–2·0, HR 1·6 [0·7–3·4]; log-rank p=0·53; appendix p 16). In a post-hoc analysis, 12-month freedom from local recurrence was 91% (95% CI 81–100) for patients with tumours with a maximum diameter of up to 2·5 cm (n=40), 40% (27–60) for patients with tumours greater than 2·5–3·5 cm in diameter (n=55), and 46% (31–68) for patients with tumours greater than 3·5 cm in diameter (n=33; figure 3A). 12-month local recurrence was 74% (95% CI 61–88) for tumours smaller than 3 cm in diameter and 44% (32–60) for tumours of 3 cm in diameter or more (HR 2·3, 95% CI 1·2–4·4; p=0·0078).

In view of the significant correlation between small tumours and longer time to local recurrence, we did a post-hoc analysis to determine if there was an association between treatment and lesion size (appendix p 19).

12-month freedom from local recurrence was 54% (95% CI 44–67) in 101 patients with non-melanoma primary tumours and 66% (46–94) in 27 patients with melanoma primary tumours (HR 0·7, 95% CI 0·3–1·6; p=0·31; figure 3B). Post-hoc analysis of local recurrence-free survival by any histology is shown in the appendix (p 17).

12-month freedom from local recurrence was 53% (95% CI 42–67) for patients with one resected brain metastasis (n=79), and 62% (47–81) for patients with two or three resected brain metastases (n=49; figure 3C). A comparison of one versus two versus three brain metastases is shown in the appendix (p 18).

12-month freedom from local recurrence was 51% (95% CI 38–70) for patients with no evidence of disease at the time of SRS (n=42), 65% (50–84) for patients with progressive disease at the time of SRS (progressive disease *vs* no evidence of disease, HR 0·6 [95% CI 0·3–1·1]; n=54), and 48% (30–76) for patients with stable disease at the time of SRS (stable disease *vs* no evidence of disease, HR 0·9 [95% CI 0·4–1·7]; n=32; log rank p=0·26).

In the multivariable analysis for time to local recurrence, the significant predictors of local recurrence were SRS and metastasis size; primary cancer histological type, systemic disease status, graded prognostic assessment score, and number of brain metastases were not associated with time to local recurrence (table 2). The only significant predictor of overall survival was stable disease compared with progressive disease (HR 3·6 [95% CI 2·0–6·6]; p<0·0001; appendix p 21). The only significant predictor of distant brain recurrence was the presence at presentation of one brain metastasis compared with three brain metastases (HR 3·1 [95% CI 1·5–6·4]; p=0·0016).

In treatment–covariate interaction tests, there was no significant difference in time to local recurrence between groups on the basis of histological subtype, number of brain metastases, or size of brain metastases (appendix p 20).

No patients had adverse events related to placement of a stereotactic frame or treatment with SRS. One patient in the observation group had a pulmonary embolism after the initial surgery. The treatment for this embolism resulted in subsequent SRS being given outside of the

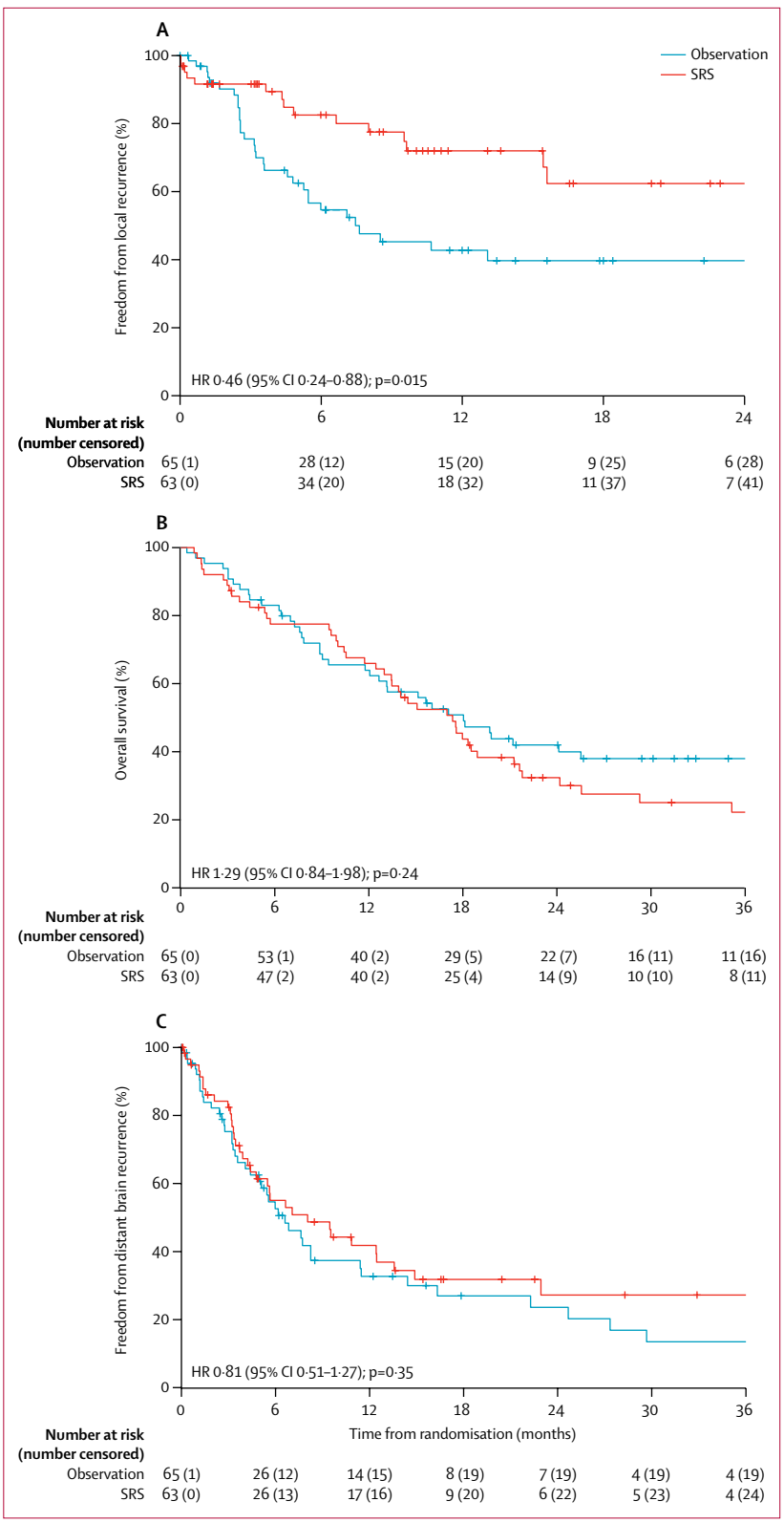
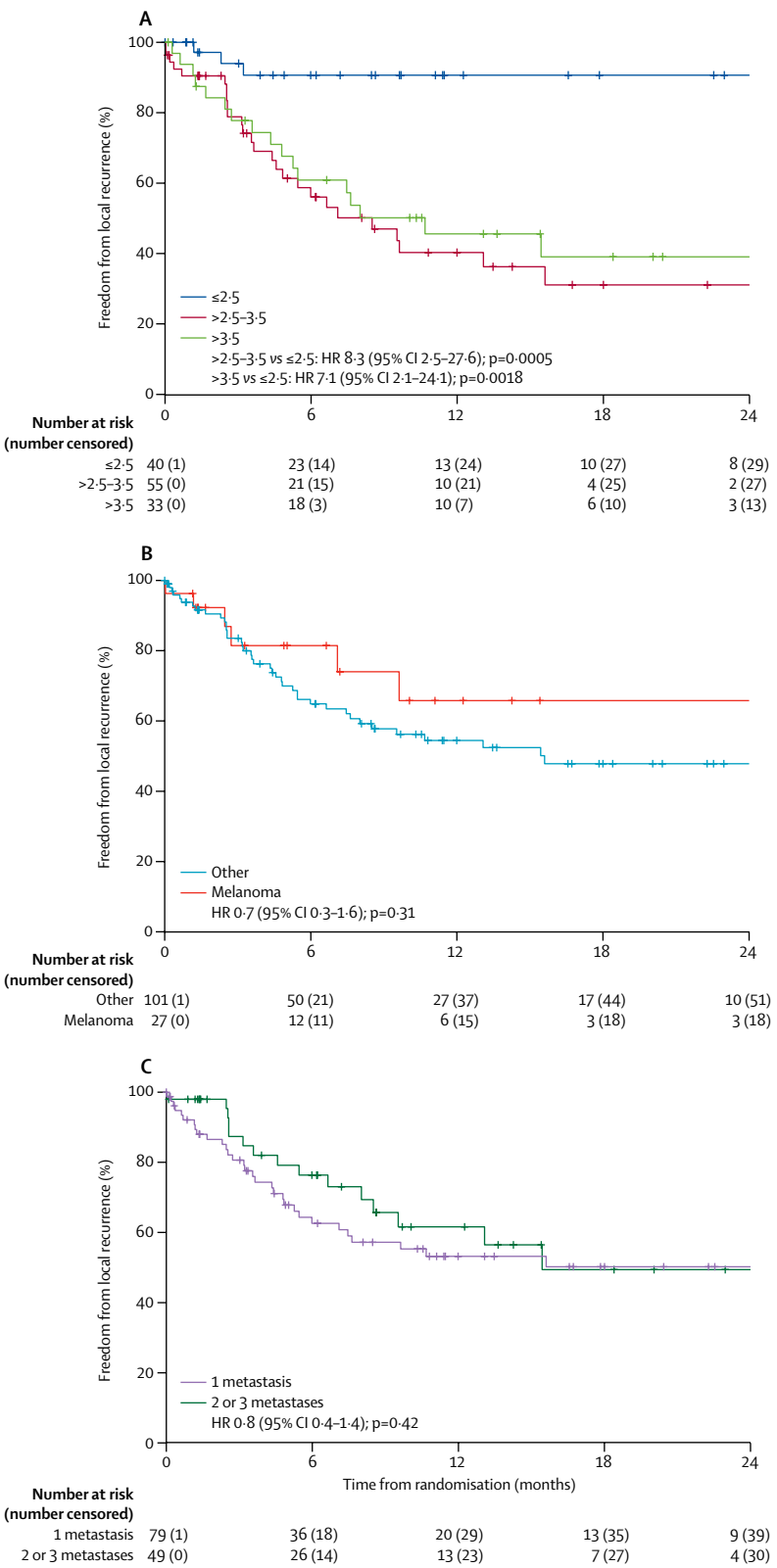


Figure 2: **Kaplan-Meier estimates of freedom from local recurrence (A), overall survival (B), and freedom from distant brain recurrence (C)**
HR=hazard ratio. SRS=stereotactic radiosurgery.



30-day treatment window, which made the patient ineligible for analysis. There were no treatment-related deaths in either group. There was no radiographic evidence of necrosis in the SRS group.

Discussion

In this randomised trial of patients undergoing surgical resection for one, two, or three brain metastases, time to local recurrence was significantly higher after post-operative SRS in the resection cavity than with observation. We also confirmed that surgical resection of brain metastases is insufficient to provide durable local control. In previous studies, the benefit of surgical resection followed by WBRT has been well described, both for improved survival and increased local tumour control.[2,3] However, WBRT is associated with negative side-effects.[4–6] Treating the surgical cavity postoperatively with SRS is an appealing strategy to limit the neurocognitive insult while improving local tumour control. Indeed, several retrospective studies have reported that SRS can increase time to local recurrence;[1,9] however, the efficacy of postoperative SRS has not yet been validated with level I evidence. Our results support administering SRS to the resection cavity after resection for one to three brain metastases.

In the entire cohort, metastasis size was inversely associated with better local control. Notably, patients with tumours up to 2·5 cm in maximal diameter had greater than 90% freedom from local recurrence. This suggests that small tumours that have been resected could instead be put under surveillance without additional treatment after resection; however, in the post-hoc analysis, SRS to lesions less than 2·5 cm showed a higher freedom from local recurrence than did observation, suggesting that even these smaller tumours might benefit from SRS after resection. Conversely, larger tumours had worse time to local recurrence than smaller tumours. Given the absence of toxicity in the SRS cohort, increasing the prescribed radiation dose for larger tumours is reasonable and could lead to improved local control for these tumours. There might be an opportunity to improve local control by escalating dose by at least 2 Gy per size category. An alternative to single-fraction SRS, as described in this study, might be hypofractionated stereotactic radiotherapy (HSRT).[13,14] In retrospective series, HSRT has been shown to have favourable local control and can provide higher cumulative radiation doses (eg, 30 Gy in five fractions) to the resection cavity than single-fraction SRS.[13,14] This strategy might provide a higher freedom from local recurrence by delivering a higher dose of radiation, provided there is an acceptable toxicity profile.

Figure 3: **Kaplan-Meier estimates of freedom from local recurrence in stratification factor groups, irrespective of treatment group.**
(A) Freedom from local recurrence by tumour size. (B) Freedom from local recurrence by primary tumour histology. (C) Freedom from local recurrence by number of metastases. HR=hazard ratio.

No difference was identified in the development of parenchymal distant brain metastases between the two study groups, which is not surprising given the local nature of the initial treatment. Nor did we find a difference in the incidence of leptomeningeal disease between the study groups, although this study was underpowered to determine the effect of post-surgical SRS on development of leptomeningeal disease. In a recent study, leptomeningeal disease adjacent to the surgical cavity after radiosurgical treatment was reported to be as high as 16·9%, suggesting that this is a potential risk of local radiation that should be evaluated in future studies.[15] A predictor of freedom from distant brain metastases was an initial presentation with only one brain metastasis, suggesting that patients with multiple metastases on presentation were at higher risk for distant brain metastases. WBRT and SRS were used independently or in combination to treat distant brain metastases: SRS for a limited number of additional metastases or WBRT for numerous metastases or leptomeningeal disease. The median time to WBRT administration was 16 months in the observation group and 15 months in the SRS group. More than half of the entire cohort was able to avoid WBRT altogether.

Despite our finding that local control is improved after SRS compared with observation, overall survival was similar for both groups. Notably, our finding of a median overall survival of more than 17 months for both cohorts shows higher survival relative to other reports.[4,6] These studies compared SRS treatment alone with WBRT in patients with up to three brain metastases, and the results showed significant cognitive decline and worse overall survival in the WBRT cohort. The higher survival could be because our study was done at a tertiary cancer centre and could also reflect improvements in systemic treatments. The ability to deliver timely systemic treatments that prolong a patient's life can be facilitated by local adjuvant treatments (ie, SRS) instead of WBRT. Although neurocognitive outcomes were not specifically addressed in our study, it can be speculated that delaying WBRT until absolutely necessary might help patients maintain a higher quality of life and receive effective multidisciplinary care. Future studies evaluating local treatments such as SRS should include outcomes such as quality of life. A recently completed phase 3 study (NCT00377156)[16] addresses the value of WBRT compared with SRS in a surgical resection cavity. Although the study included incompletely resected metastases and resection cavities without an upper size limit, the results of this study show that there is no survival benefit for WBRT compared with SRS after resection of one to three metastases, similar to the results of our study. Further, the phase 3 study showed a poorer cognitive outcome associated with WBRT compared with SRS. Their conclusion is that SRS after surgical resection is superior to WBRT, primarily because it is less toxic.

	Hazard ratio (95% CI)	p value
Treatment		
SRS *vs* observation	0·5 (0·3–1·0)	0·041
Primary cancer histological type		
Lung *vs* breast	0·9 (0·3–2·6)	0·82
Melanoma *vs* breast	0·7 (0·3–2·1)	0·56
Other *vs* breast	1·2 (0·5–2·6)	0·73
Systemic disease status		
Progressing *vs* NED/PR	0·6 (0·3–1·2)	0·15
Stable *vs* NED/PR	0·8 (0·4–1·6)	0·45
Graded prognostic assessment score		
2·5–3·0 *vs* 1·0–2·0	1·3 (0·6–2·5)	0·52
3·5–4·0 *vs* 1·0–2·0	1·1 (0·5–2·6)	0·82
Number of brain metastases		
2 *vs* 1	0·8 (0·4–1·8)	0·59
3 *vs* 1	0·9 (0·3–2·6)	0·90
Size of brain metastases		
>2·5–3·5 cm *vs* 0–2·5 cm	6·7 (2·0–23)	0·0021
>3·5 cm *vs* 0–2·5 cm	6·6 (1·9–23)	0·0032

SRS=stereotactic radiosurgery. NED=no evidence of disease. PR=partial response.

Table 2: **Multivariable analysis for freedom from local recurrence**

Our study is subject to the biases of a single-institution study. As a tertiary cancer centre, the patient population might be eligible for specialised care and clinical trials that are not widely available. Moreover, these patients might have the resources to undergo increased clinical surveillance and imaging examinations. We note that our overall survival was several months longer than the survival reported in the phase 3 study comparing WBRT with SRS (approximately 17 months *vs* approximately 11·5 months). Although our study was done at a single, high-volume institution, it took more than 6 years to complete. During that time, systemic treatments have evolved and could influence survival and possibly local control. We also used the same SRS unit for the entire study. The treating physicians (except the study neuroradiologist) were aware of which treatment group each patient was in, potentially introducing some element of bias. Conversely, more than 15 different neurosurgeons and nine different radiation oncologists treated the patients, perhaps making the study more generalisable.

Surgical techniques have evolved since the original studies that showed the utility of surgical resection in managing metastatic brain disease.[2,17] Stereotactic navigation and cortical mapping are used ubiquitously in surgically managing brain metastases. In this study, we evaluated whether modern surgery, without SRS, was sufficient to provide satisfactory local tumour control. The 12-month freedom from local recurrence was only 45% for the surgery-alone group, which is lower than the 54% for surgery alone described by Patchell and

colleagues in 1998.[3] Despite improvements in surgical techniques and adjuncts, our results show that surgery alone is insufficient to provide durable local control. Our shorter time to local recurrence compared with that described by Patchell and colleagues,[3] could be due to our more frequent surveillance, which was every 2 months post-surgery, versus every 3 months in their study. Ultimately, we suspect, as Patchell and colleagues did, that after a gross total resection, residual microscopic tumours can locally recur. Unlike other excisional procedures, which can be extended to include negative tumour margins, the continued resection of surrounding normal brain parenchyma to achieve negative tumour margins is generally not feasible. Thus, additional methods are necessary to address microscopic tumour cells at the edge of the resection cavity. We intend to report the patterns of local failure, which should further clarify the dosing and margins to be used for postoperative SRS to maximise local control.

Contributors

AM, MFM, JL, PDB, SS, SM, ES, AG, JSW, SSP, FFL, NL, IEM, SAz, DC, CT, ABH, SF, FD, SR, RS, and GR did the data collection. AM, SAh, KRH, JY, and GR did the data analysis. AM, SAh, MFM, PDB, SM, FFL, DC, NG-T, RS, and GR did the data interpretation. AM, KRH, and GR wrote the report.

Declaration of interests

We declare no competing interests.

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