Articles

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

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Background Brain metastases occur in up to 40% of all patients with systemic cancer. We aimed to assess whether stereotactic radiosurgery provided any therapeutic benefit in a randomised multi-institutional trial directed by the Radiation Therapy Oncology Group (RTOG).

Methods Patients with one to three newly diagnosed brain metastases were randomly allocated either whole brain radiation therapy (WBRT) or WBRT followed by stereotactic radiosurgery boost. Patients were stratified by number of metastases and status of extracranial disease. Primary outcome was survival; secondary outcomes were tumour response and local rates, overall intracranial recurrence rates, cause of death, and performance measurements.

Findings From January, 1996, to June, 2001, we enrolled 333 patients from 55 participating RTOG institutions—167 were assigned WBRT and stereotactic radiosurgery and 164 were allocated WBRT alone. Univariate analysis showed that there was a survival advantage in the WBRT and stereotactic radiosurgery group for patients with a single brain metastasis (median survival time 6·5 *vs* 4·9 months, p=0·0393). Patients in the stereotactic surgery group were more likely to have a stable or improved Karnofsky Performance Status (KPS) score at 6 months' follow-up than were patients allocated WBRT alone (43% *vs* 27%, respectively; p=0·03). By multivariate analysis, survival improved in patients with an RPA class 1 (p<0·0001) or a favourable histological status (p=0·0121).

Interpretation WBRT and stereotactic boost treatment improved functional autonomy (KPS) for all patients and survival for patients with a single unresectable brain metastasis. WBRT and stereotactic radiosurgery should, therefore, be standard treatment for patients with a single unresectable brain metastasis and considered for patients with two or three brain metastases.

Lancet 2004; **363:** 1665–72

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Introduction

Brain metastases occur in 20–40% of patients with systemic cancer;[1] 30–40% present with a single metastasis.[2] Outlook for patients is poor with a median survival time of 1–2 months with corticosteroids,[3] which can be extended to 6 months with whole brain radiation therapy (WBRT),[4,5] and some investigators[6,7] report that survival can be further lengthened when WBRT is preceded by surgical resection. Originally developed by the Swedish neurosurgeon Lars Leksell,[8] radiosurgery is a technique that involves single treatment radiation precisely focused at intracranial targets. Radiosurgery is frequently used to treat brain metastases, sometimes preferred to surgery as a less invasive alternative. We report results of the first multi-institutional prospective randomised comparison of WBRT with or without stereotactic radiosurgery for patients with one to three brain metastases.

Methods

Participants

The study population included patients with confirmed systemic malignant disease. All patients were aged 18 years or older with no previous cranial radiation. Entry criteria included a contrast-enhanced MRI scan showing one to three brain metastases with a maximum diameter of 4 cm for the largest lesion and additional lesions not exceeding 3 cm in diameter.[9] Metastases were deemed unresectable if they were located in deep grey matter or in eloquent cortex. Postoperative patients with either residual or distal brain metastases were eligible if the total number of metastases remained three or fewer. We excluded patients who had Karnofsky Performance Status (KPS) score of less than 70, haemoglobin concentration less than 80 g/L, absolute neutrophil count of less than

	Recursive partitioning analysis classes for brain metastases[11]		
	Class 1	Class 2	Class 3
KPS	⩾70	⩾70	<70
Primary status	Controlled	Uncontrolled	
Age (years)	<65	⩾65	
Extracranial disease status	Brain only	Brain plus other sites	

Table 1: **RPA class definitions**

	Grade 1	Grade 2	Grade 3	Grade 4
Motor	None or no change	Subjective weakness/ no objective findings	Mild objective weakness without significant impairment of function	Objective weakness with impairment of function
Sensory	None or no change	Mild paraesthesias/ loss of deep tendon reflexes	Mild or moderate objective sensory loss/ paraesthesias	Severe objective sensory loss or paraesthesias that interfere with function

For other neurological signs and symptoms, see http://www.rtog.org/members/toxicity/tox.html.

Table 2: **RTOG CNS toxicity criteria**

1000 cells/μL, or platelet count less than 50 000 cells per μL. Patients with metastases in the brain stem, or within 1 cm of the optic apparatus were excluded since no safety data for these sites were available from the antecedent phase I study, RTOG 9005.[10] Patients who had received treatment for systemic cancer within 1 month of enrolment were judged to have active disease and were excluded. Patients with newly diagnosed cancer presenting with brain metastases or patients with unknown primaries were both considered to have unknown disease control and were included in the study.

The Cancer Therapy Evaluation Program (CTEP) at the National Cancer Institute and the ethics review boards at each RTOG participating institution reviewed and approved the trial protocol. Patients gave written informed consent.

Interventions

Patients were randomly allocated either WBRT alone or WBRT with stereotactic radiosurgery boost. All patients received WBRT in daily 2·5 Gy fractions to a total of 37·5 Gy over 3 weeks.

Patients allocated stereotactic radiosurgery boost received this treatment within 1 week of completing WBRT. We chose this schedule in anticipation of tumour shrinkage that would minimise radiosurgery treatment volume. If patients were registered at RTOG centres not performing radiosurgery, this also streamlined referrals during WBRT to RTOG institutions with established radiosurgery programmes including both Gamma Knife and LINAC-based systems.[10]

We assigned radiosurgery doses in accordance with prescriptions from an earlier dose-escalation RTOG radiosurgery trial (90–05).[10] We treated metastases up to 2·0 cm in broadest diameter with a surface isodose prescription of 24·0 Gy; metastases larger than 2 cm but equal to or smaller than 3 cm with 18·0 Gy; and metastases larger than 3 cm and less than or equal to 4 cm

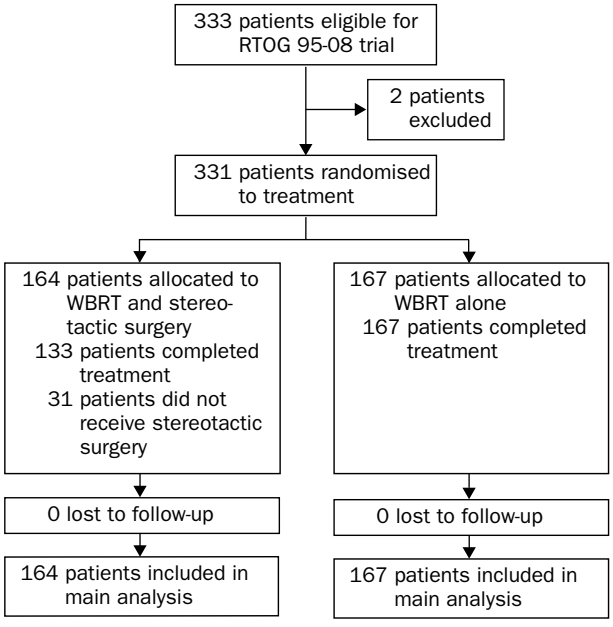


Figure 1: **Trial profile**

	WBRT+stereotactic surgery (n=164)	WBRT alone (n=167)
Age (mean [range]) (years)	58·8 (19–82)	59·9 (24–90)
<65	109 (66%)	101 (60%)
⩾65	55 (34%)	66 (40%)
Largest metastasis		
<2 cm	83 (50·5%)	98 (59%)
>2 cm to ⩽3 cm	57 (35%)	45 (27%)
>3 cm to ⩽4 cm	24 (14·5%)	24 (14%)
Men	86 (52%)	89 (53%)
Histological status		
Squamous	19 (12%)	19 (11%)
Adenocarcinoma	84 (51%)	78 (47%)
Large cell	27 (16%)	25 (15%)
Small cell	14 (9%)	10 (6%)
Melanoma	7 (4%)	7 (4%)
Renal	5 (3%)	5 (3%)
Other	5 (8%)	11 (7%)
Information missing	0	1 (<1)
Primary tumour site		
Breast	15 (9%)	19 (11%)
Lung	105 (64%)	106 (63%)
Skin/melanoma	7 (4%)	9 (5%)
Other	23 (14%)	17 (10%)
Kidney	2 (1%)	2 (1%)
Bladder	0	3 (2%)
Colon	4 (2%)	2 (1%)
Ovarian	1 (1%)	2 (1%)
Unknown primary	7 (4%)	0
Neurological function		
No symptoms	54 (33%)	67 (40%)
Minor symptoms	81 (50%)	72 (43%)
Moderate symptoms	27 (17%)	28 (17%)
Information missing	2 (1%)	0
RPA class		
1	46 (28%)	45 (27%)
2	118 (72%)	122 (73%)
KPS		
90–100	93 (57%)	105 (63%)
70–80	71 (43%)	62 (37%)
Primary site		
Controlled/absent	126 (77%)	125 (75%)
Unknown control	38 (23%)	42 (25%)
Metastases		
Brain alone	52 (32%)	52 (31%)
Brain and one other extracranial site	61 (37%)	59 (35%)
Brain and two others extracranial sites	35 (21%)	35 (21%)
Brain and >2 additional sites	16 (10%)	21 (13%)
Number of brain metastases		
1	92 (56%)	94 (56%)
2	39 (24%)	46 (28%)
3	33 (20%)	27 (16%)
MMSE		
15–24	16 (10%)	10 (6%)
25–30	138 (84%)	142 (85%)
Information missing	10 (6%)	15 (9%)

MMSE=mini-mental state examination. Data are n (%) unless otherwise stated.

Table 3: **Patients' baseline characteristics**

	Single metastasis (n=14)	Multiple metastases (n=17)
Physician refusal	1 (7%)	2 (12%)
Patient refusal	5 (36%)	4 (24%)
No tumour	1 (7%)	4 (24%)
Disease progression	4 (29%)	5 (29%)
Death	1 (7%)	2 (12%)
Other	2 (14%)	0

Table 4: **Reasons for not receiving stereotactic radiosurgery**

with 15·0 Gy. The protocol stipulated isodose prescriptions within ratios of prescription isodose/tumor volume (PITV) and maximum dose/prescribed dose (MDPD) previously set by the RTOG.[10] Treatment plans could use either MRI or CT imaging sets.

Primary outcome was overall survival in patients with solitary or multiple brain metastases. Secondary outcomes were tumour response and local control rates, overall intracranial recurrence rates, cause of death, and performance measurements.

Sample size

The study was designed to detect a 50% improvement in median survival time for all patients receiving stereotactic radiosurgery boost from 7·1 months to 10·6 months after treatment with 80% statistical power. Based on this assumption, we estimated that a sample size of 124 patients per group would be needed. We assumed that 5% of patients would be ineligible or unassessable, and thus calculated that we should have a total sample size of 262 patients. Additionally, the study included a predefined hypothesis in the single brain metastasis patients with 80% statistical power to detect a 75% improvement in median survival time. On the assumption that 50% of patients had a single brain metastasis, the original projection of 62 patients was modified after two interim analyses by the RTOG Data Monitoring Committee. Because 15% of people allocated to stereotactic radiosurgery did not receive this treatment, the number of patients with a single metastasis was increased to 94 patients per group for a final adjusted target sample size of 326 patients.

Randomisation

Patients were stratified by number of brain metastases (single *vs* 2–3) and extent of extracranial disease (none *vs* present). Randomisation within strata by permutated blocks was done by use of computerised techniques at RTOG headquarters when member institutions telephoned to enrol eligible patients. We compared pretreatment characteristics between treatment groups using the Wilcoxon rank-sum test or Fisher's exact test to assess balance. Our analysis included assignments of patients to RTOG recursive partitioning analysis (RPA) classes for brain metastases in accordance with methods described by Gaspar and colleages,[11] to ensure intergroup homogeneity and also to assess outcomes according to RPA class (table 1).

Post-treatment surveillance

We did clinical evaluations and MRI scans at 3 month intervals up to 1 year.[12] Acute toxicities were identified as events that arose within 90 days of the start of radiotherapy and late toxicities as events that occurred thereafter according to RTOG CNS toxicity criteria (table 2).[10] Treatment responses and local control rates were reported by institution over the course of the study. Local control was defined as unchanged or improved serial post-treatment MRI scans judged initially as either a complete response, partial response, or stable disease. Complete response was defined as total radiographic disappearance of all lesions with stabilisation of the neurological examination after glucocoriticoids had been stopped. Partial response was defined as greater than a 50% decrease in size of all lesions with improvement or stabilisation of the neurological examination with stable glucocorticoid dose. Stable disease was defined as a 0–50% decrease in size of all lesions with improving or stable neurological examination. Progressive disease was

	WBRT+stereotactic surgery (n=160)				WBRT alone (n=166)			
	Grade 1	2	3	4	Grade 1	2	3	4
Acute toxicities*								
Nausea/vomiting	20	7	1	0	16	9	0	0
Hearing loss	1	1	0	0	2	1	0	0
Skin (acute)	64	9	0	0	56	20	0	0
Skin (subacute)	9	3	0	0	7	1	0	0
Neurological (central)	12	10	2	1	9	11	0	0
Neurological (peripheral)	5	2	1	0	3	2	0	0
Other	16	7	0	0	10	10	0	0
Worst reported toxicity grade per patient	69 (43%)	28 (18%)	3 (2%)	1 (1%)	59 (36%)	43 (26%)	0	0
	WBRT+stereotactic surgery (n=113)				**WBRT alone (n=112)**			
Late toxicities†								
Nausea/vomiting	4	0	1	0	2	0	1	0
Hearing loss	2	1	1	0	2	2	1	0
Skin (chronic)	5	0	0	0	11	4	0	0
Neurological (central)	11	3	2	0	4	1	1	1
Neurological (peripheral)	3	1	0	0	0	0	0	0
Other	1	3	0	2	0	2	0	0
Worst reported toxicity grade per patient	16 (14%)	7 (6%)	3 (3%)	3 (3%)	16 (14%)	8 (7%)	2 (2%)	1 (1%)
Age ⩽70 years	(n=128)				(n=129)			
Worst reported acute toxicity grade per patient	56 (44%)	24 (19%)	0	1 (1%)	47 (36%)	32 (25%)	0	0
Age >70 years	(n=32)				(n=37)			
Worst reported acute toxicity grade per patient	13 (41%)	4 (13%)	3 (9%)	0	12 (32%)	11 (30%)	0	0
Worst reported acute toxicity grade by stereotactic surgery dose in patients with single metastasis								
15 Gy (n=20)	4 (20%)	4 (20%)	..	..				
18 Gy (n=29)	11 (38%)	7 (24%)	..	1 (3%)				
24 Gy (n=33)	17 (52%)	1 (3%)	1 (3%)	..				

*Events occurring within 90 days of radiation treatment. †Events occurring at or beyond 90 days.

Table 5: **Treatment-related toxicities**

	Single brain metastasis		⩾2 brain metastases		Total	
	WBRT and SRS (n=73)	WBRT alone (n=82)	WBRT and SRS (n=64)	WBRT alone (n=67)	WBRT and SRS (n=137)	WBRT alone (n=149)
Brain metastases	19 (26%)	22 (27%)	20 (31%)	24 (36%)	39 (28%)	46 (31%)
Cancer at other Site	38 (52%)	44 (54%)	31 (48%)	36 (54%)	69 (50%)	80 (54%)
Complications of radiotherapy	0	0	1 (2%)	0	1 (1%)	0
Pneumonia	3 (4%)	2 (2%)	1 (2%)	0	4 (3%)	2 (1%)
Pulmonary embolism	0	3 (4%)	0	1 (1%)	0	4 (3%)
Myocardial infarction	0	1 (1%)	1 (2%)	0	1 (1%)	1 (1%)
Other	5 (7%)	6 (7%)	6 (9%)	2 (3%)	11 (8%)	8 (5%)
Unknown	8 (11%)	4 (5%)	4 (6%)	4 (6%)	12 (9%)	8 (5%)

SRS=stereotactic surgery.

Table 6: **Causes of death**

defined as an increase in the size of any lesion, the development of new intracranial lesions or stable disease with deterioration of the neurological examination. The reappearance of tumour in the brain MRI scan constituted recurrent disease. If a patient developed a recurrence or one or more new brain metastases, further treatment was allowed as clinically indicated. Cause of death was judged as either systemic or neurological failure by the reporting institution. Patients were ascribed a neurological death if they had stable systemic disease but succumbed to intracranial disease progression associated with progressive neurological dysfunction.

Post-treatment MRI scans were also sent to RTOG headquarters for central review by a neuroradiologist (AEF). At central review, treatment responses were assessed at 3 months and local control rates at 1 year.[13] Variations in slice thickness, field strength, or imaging planes were accepted.

We excluded patients for any of five reasons: mixing modalities (eg, MRI and CT); same modalities but missing a key pulse sequence (eg, a T2/FLAIR or post contrast T1); missing films of a sequence that reportedly was done; no follow-up study of any kind; or uninterpretable copies.

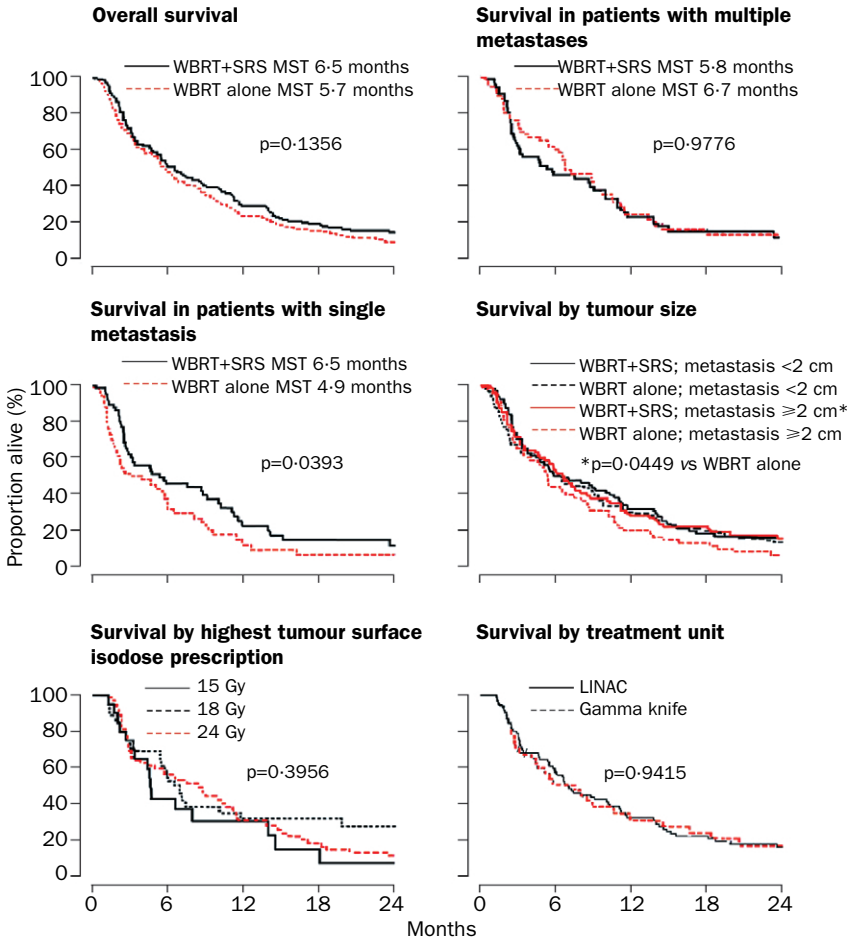
This protocol did not stipulate steroid management, but steroid dose prescriptions were recorded at each visit. Dosimetry, radiosurgery isosurface prescriptions, dose conformality and homogeneity calculations were all centrally reviewed by two physicians (DWA and PWS) and a medical physicist (MS).[10]

Statistical analyses

Analysis was by intention to treat. We treated all outcomes as independent hypotheses, and we did not adjust for multiple comparisons.[14] Subsequent exploratory subsets within these hypotheses were subject to inflation of the type I error. There were nine subsequent subsets of survival for an adjusted significance level of 0·0056. This significance level was applied when assessing the p for survival subsets other than single metastasis patients. Survival was measured from the date of randomisation until death or last follow-up. Survival was estimated with the Kaplan-Meier method and groups were compared via the log-rank statistic. To assess the effect of prognostic variables, we did univariate and multivariate Cox proportional hazards analyses[15] for variables including age, KPS, known extracranial metastases (yes *vs* no), and RPA class. Univariate tests were not adjusted for multiple comparisons. Multivariate analyses were done to estimate the effect of treatment group on outcome, adjusting for RPA class.

Role of the funding source

The sponsor had no role in study design, data collection, data analysis, data interpretation, or the writing of the report.



MST=mean survival time.

Figure 2: **Intention-to-treat outcomes by tumour size, extent of intracranial disease, radiation dose, and treatment technique**

	Number	Mean survival time	p	Better prognosis association
Univariate analysis				
Overall				
WBRT alone	167	6·5		
WBRT plus SRS	164	5·7	0·1356	Not significant
Single metastasis				
WBRT alone	94	4·9	0·0390	Boost SRS, single
WBRT plus SRS	92	6·5		metastasis
Other subgroups				
Largest tumour >2 cm				
WBRT alone	69	5·3	0·0449	Not significant at
WBRT plus SRS	81	6·5		0·0056 level
RPA class 1				
WBRT alone	45	9·6	0·0453	Not significant at
WBRT plus SRS	45	11·6		0·0056 level
Squamous/non-small cell lung carcinoma				
WBRT alone	29	3·9	0·0508	Not significant
WBRT plus SRS	27	5·9		
Karnofsky 90—100				
WBRT alone	105	7·4	0·0714	Not significant
WBRT plus SRS	92	10·2		
Brain alone				
WBRT alone	52	8·6	0·5207	Not significant
WBRT plus SRS	50	10·2		
Brain plus one extracranial site				
WBRT alone	59	6·7	0·1686	Not significant
WBRT plus SRS	61	8·0		
Brain plus two extracranial sites				
WBRT alone	35	5·0	0·8245	Not significant
WBRT plus SRS	34	3·3		
Multivariate analysis				
Overall*	327			
RPA class 1 *vs* class 2		2·254	<0·0001	Class 1
Histology		1·348	0·0121	Lung primary
WBRT *vs* WBRT+SRS		NC	0·1249	Not significant
Single metastasis†	184			
RPA class 1 *vs* class 2		2·897	<0·0001	Class 1
WBRT *vs* WBRT+SRS		NC	0·0533	Not significant

SRS=Stereotactic surgery. NC=not calculated; *Data not complete in four patients; †Data not complete in two patients.

Table 7: **Univariate and multivariate survival analyses**

Results

Between January 31, 1996, and June 15, 2001, 333 patients were recruited to the study. Follow-up data were reported to January, 2002. Patients were from 55 RTOG member institutions, with 20 institutions enrolling one or two patients. We excluded two patients (in one case, no confirmation of eligibilty was provided; in the other, the patient had too many metastases), leaving 331 patients in the final analysis—167 randomly allocated WBRT and 164 randomly allocated WBRT and stereotactic radiosurgery (figure 1). Patients characteristics are summarised in table 3. 31 (19%) patients assigned to the stereotactic radiosurgery group did not receive the additional treatment (table 4). Of these, 8 (26%) were RPA class 1 and 23 (74%) were RPA class 2. Early and late toxicities did not differ greatly between treatment groups, even after controlling for age (table 5). Within the stereotactic radiosurgery group, we analysed the single metastasis subgroup to assess dose-related toxicity. Higher radiosurgery dose prescriptions were not associated with a greater incidence of toxicity. Causes of death showed that the rate of neurological deaths did not differ between groups (table 6).

	WBRT+stereotactic surgery	WBRT alone
KPS	(n=79)	(n=75)
Improved	10*	3
Worsened	43	50
Unchanged	23	16
Data missing	3	6
Steroids†	(n=76)	(n=75)
Increased	7	6
Decreased	41‡	25
Unchanged	15	24
Data missing	13	20
Mental status	(n=79)	(n=75)
Improved	20	24
Worsened	21	24
Unchanged	9	12
Data missing	29	15

*p=0·0331. †Most patients were not taking steroids by 3 months. ‡p<0·0158.

Table 8: **Performance measurements at 6 months' follow-up**

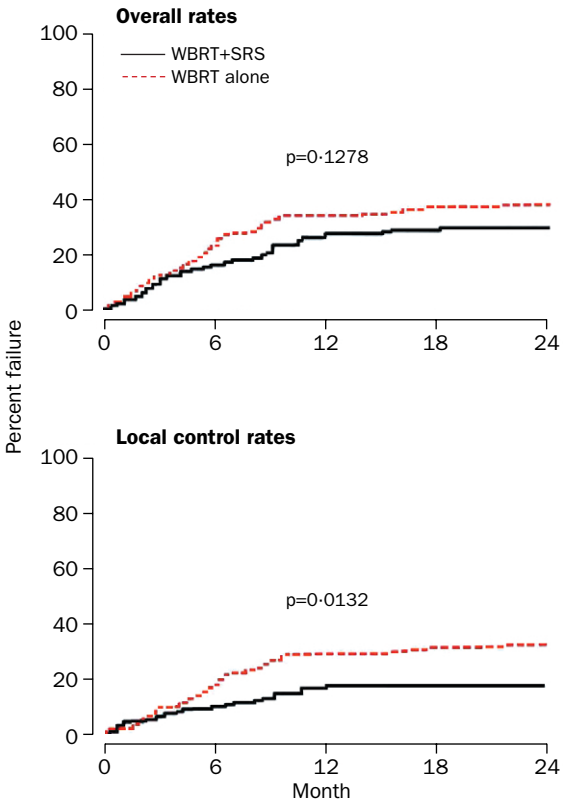


Figure 3: **Intention-to-treat intracranial disease control rates**
SRS=stereotactic surgery.

	WBRT+stereotactic surgery (n=135)	WBRT alone (n=135)
Lesions*		
Not reviewed	60 (44%)	57 (42%)
Not applicable	1 (0.7%)	0
Complete response	12 (9%)	6 (5%)
Partial response	43 (32%)	42 (31%)
Stable	11 (8%)	17 (13%)
Progression	8 (6%)	13 (10%)
Oedema†		
Not reviewed	60 (44%)	57 (42%)
Not applicable	5 (4%)	6 (5%)
Complete response	14 (10%)	5 (4%)
Partial response	38 (28%)	32 (24%)
Stable	11 (8%)	21 (16%)
Progression	7 (5%)	14 (10%)

Based on MRI scans assessed at central review. p values represent distribution across all categories. *p=0·0438. †p=0·0017.

Table 9: **Radiographic responses at 3 months' follow up**

	Overall results		
	Lesion A	Lesion B	Lesion C
Tumour size			
Mean (range) (mm^3)	207·0 (0·08–3400)	1204·1 (0·05–27 000)	163·9 (0·06–3300)
Median diameter (cm)	3·3	1·4	1·3
Isosurface prescription			
>90%	76 (81%)	29 (83%)	9 (90%)
⩾80% <90%	16 (17%)	5 (14%)	1 (10%)
<80%	2 (2%)	1 (3%)	0
MDPD			
Per protocol	87 (95%)	30 (97%)	12 (92%)
Minor acceptable deviation	3 (3%)	1 (3%)	1 (8%)
Major acceptable deviation	2 (2%)	0	0
PITV			
Per protocol	53 (67%)*	15 (58%)†	4 (44%)‡
Minor acceptable deviation	22 (28%)	6 (23%)	3 (33%)
Major acceptable deviation	4 (5%)	5 (19%)	2 (22%)
Results by treatment unit			
Isosurface prescription (median)			
Linac (N)	85 (73)	85 (28)	80 (12)
Gamma knife (N)	50 (31)	50 (7)	[51·5] (2)
Not designated (N)	78·5 (6)	[81] (1)	NA
MDPD (median)			
Linac (N)	1·2 (58)	1·2 (24)	1·3 (10)
Gamma knife (N)	2·0 (29)	1·8 (6)	[2·1] (1)
Not designated (N)	1·2 (5)	[1·3] (1)	NA
PITV (median)			
Linac (N)	1·9 (55)	1·7 (20)	2·1 (10)
Gamma knife (N)	1·4 (27)	1·5 (6)	[2·0] (1)
Not designated (N)	1·2 (6)	[0·7] (2)	NA

MDPD=maximum dose prescribed dose. PITV=prescribed isodose tumour volume. RTOG radiosurgery quality assurance criteria are available at http://www.rtog.org/members/protocols/95-08/95-08.pdf, Section 6.4. If the MDPD ratio was <2, the case was scored as per protocol; if the ratio was >2 but <2.5, the case was scored as a minor acceptable deviation; if the ratio was >2.5, the case was scored as a major acceptable deviation. The same intervals applied for PITV ratios. In this case, per protocol was complete coverage of the tumour volume, a minor acceptable deviation represented marginal coverage of the tumour volume, and a major acceptable deviation was a partial miss of the tumour volume—in all cases at the isodose prescription line. *Nine cases had PITV values that did not fall within the protocol specified ranges for the categories; range 0·07–0·80; †2 cases had PITV values that did not fall within protocol specified ranges for categories; both were 0·7; ‡2 cases had PITV values that did not fall within the protocol specified ranges for the categories; values were 0·55 and 0·6.

Table 10: **Summary of radiosurgery treatment variables**

Survival and performance measurements

Figure 2 shows intention-to-treat outcomes by maximum tumour size, number of brain metastases, and treatment technique. Mean survival time did not differ much between groups (figure 2 and table 7). Likewise, we did not note a survival benefit between groups in patients with multiple metastases (figure 2). Patients with single metastasis in the stereotactic radiosurgery group, however, had significantly better survival than did those who were not allocated boost treatment.

These findings were supported by univariate analysis that indicate that WBRT plus stereotactic radiosurgery provided survival benefit to patients with either single metastases, RPA class 1, or whose largest metastasis was more than 2 cm in diameter. No survival advantage was noted between groups when assessing dose delivered (figure 2), or machine used (Gamma Knife *vs* Linac, figure 2). On multivariate analysis, only RPA class and type of tumour (squamous or non-small cell) still had a statistical significant effect on survival (table 7).

Performance measurements that included assessments of KPS, steroid use, and mental status assessment are shown in table 8. We noted a statistically significant improvement in KPS and decreased steroid use at 6 months in the stereotactic radiosurgery boost treatment group, but no difference in mental status was noted between groups.

Rates of response and local control

Based on institutional reporting, we did not note significant differences between treatment groups with respect to overall time to intracranial tumour progression (figure 3, p=0·1278) or neurological death rates. At 3 month central film review, 153 MRI sets were assessed while 117 MRI sets were deficient. In the WBRT only group, 32 patients died and 57 cases were not assessed, leaving 78 MRI sets for analysis. In the WBRT plus stereotactic radiosurgery arm, 29 patients died and 60 cases were not assessed, leaving 75 MRI sets for analysis. Central review showed higher response rates at 3 months (table 9) and better control of the treated lesions at 1 year in the WBRT plus radiosurgery group (41 (82%) *vs* 37 (71%); p=0·01). This finding was supported by better local control rates reported by institution in the radiosurgery arm (figure 3, p=0·0132). With use of Cox's model, we assessed prognostic factors for local control. Only treatment was significant, and the risk of developing

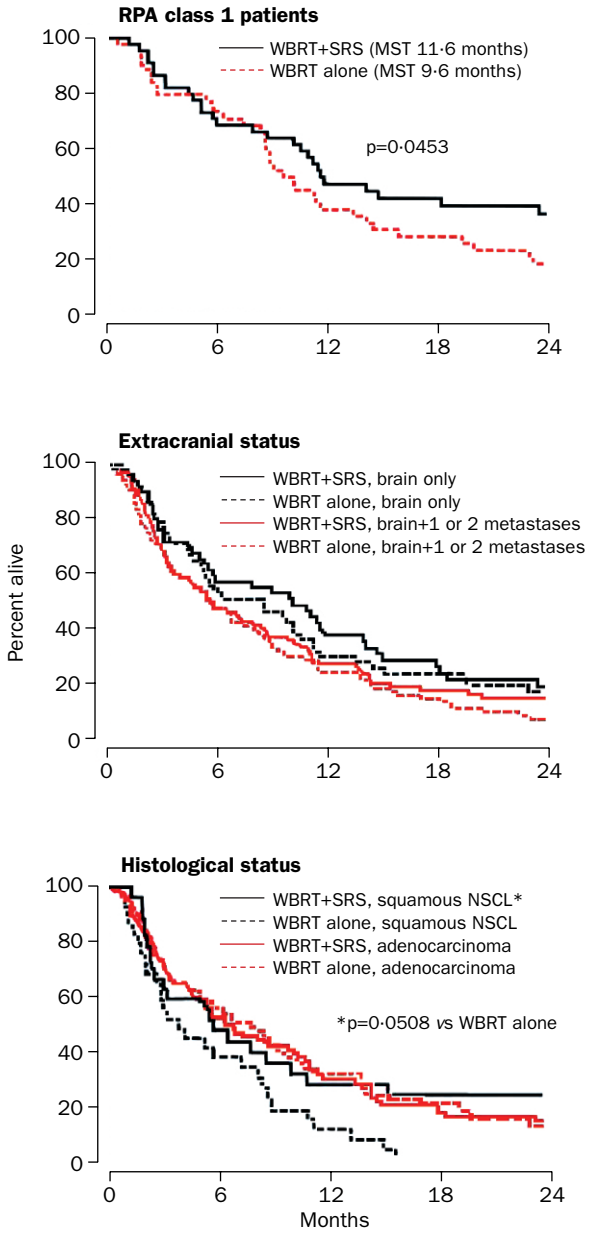


Figure 4: **Intention-to-treat outcomes by prognostic variable**
SRS=stereotactic surgery. NSCL=non-small-cell lung cancer.

	n	Data type	Metastases	Comparison	Mean survival time (months)
Patchell, 1990[7]	48	Level I, Single institution	Single	Surgery/WBRT *vs* WBRT alone	10, 3·75
Noordjik, 1994[6]	63	Level I, Multiple institutions	Single	Surgery/WBRT *vs* WBRT alone	10, 6
Mintz, 1996[16]	84	Level I, Multiple institutions	Single	Surgery/WBRT *vs* WBRT alone	5·6, 6·3
Bindal, 1996[23]	93	Level IV, Single institution	Single and multiple	Surgery/WBRT *vs* SRS/WBRT	16·4, 7·5
Kondziolka, 1999[21]	27	Level I, Single institution	Multiple	SRS/WBRT *vs* WBRT	11, 7·5
Sanghavi, 2001[17]	502	Level IV, Multiple institutions	Not specified	SRS/WBRT	
				RPA Class 1	16·1
				RPA Class 2	10·3
				RPA Class 3	8·7
Sneed, 2002[24]	559	Level IV, Multiple insititutions	Single and multiple	SRS/WBRT *vs* SRS alone	8·6, 8·2

Table 11: **Literature review of adjuvant treatments with or without WBRT for brain metastases**

a local recurrence was 43% greater with WBRT alone (p=0·0021). Higher isodose prescriptions did not affect local control rates in the radiosurgery boost arm.

Summary of radiosurgery treatment data

164 patients were assigned to boost therapy and data pertaining to radiosurgery techniques are summarised in table 10. Most dose prescriptions conformed to RTOG guidelines when either PITV or MDPD ratios were assessed. Major deviations were included for study to assess any higher incidence of local recurrences or toxicities, but none was noted. PITV ratios and isosurface prescriptions were higher on the Linac units when compared to the Gamma Knife units, the result of use of larger collimators.

RPA class and histology

When assessing individual RPA criteria (table 1), all patients were assigned to either RPA class 1 or 2 (we excluded RPA class 3 patients). No differences were noted between groups with respect to age or extent of extracranial disease (figure 4; brain only: p=0·5207; brain and one or two sites: p=0·8245). Histological subtypes of either squamous cell or non-small-cell tumours, usually seen in patients with lung cancer had longer survival in the radiosurgery arm compared with the control group (figure 4, mean survival time 5·9 months *vs* 3·9 months). These histological subtypes reached significance in multivariate analysis (table 7, p=0·0121).

Multivariate analysis

We did a Cox regression analysis to assess the prognostic importance of treatment, RPA class, and histological status, in a comparison of all patients with patients with single brain metastasis (table 7). RPA class 1 remained the most significant prognostic factor independent of number of metastases, reflected in death rates that were about 2 to 3-fold greater for RPA class 2 patients. Histological status was a significant prognostic factor for all patients except those with a single metastasis. Treatment was not a significant variable.

Discussion

Reports of WBRT with adjuvant treatments are featured in table 11. Recent published data from two small randomised trials support surgical intervention before WBRT as a means of improving prognosis in patients with single brain metastases;[6,7] however, other investigators noted no benefit.[16] The advent of stereotactic radiosurgery has held the promise of a less invasive means of achieving an outcome similar to surgery.[17–20] Only one small study done in a single institution has provided data from a randomised trial that showed comparable local control rate but no survival benefit.[21]

The current study represents the first completed multicentre trial to assess whether radiosurgery boost after WBRT improves survival in patients with newly detected brain metastases. Our most important finding was of a significant survival benefit in patients with a single unresectable brain metastasis allocated to the stereotactic surgery group—despite a 19% failure to receive the treatment, predominantly in RPA class 2 patients. These data also support the use of stereotactic surgery boost after WBRT to improve performance in patients with up to three brain metastases, in agreement with other reported series.[18,22]

When we assessed subgroups, RPA class 1 assignment and histological status were the only significant variables in a multivariate analysis.

We noted significantly greater complete response and local control rates in the stereotactic boost group. Despite this finding, the neurological death rate did not differ between the two groups. Since attributing a cause of death involves subjective judgments, the absence of a difference in neurological death rates between groups might be the result of variations generated by institutional reporting. The rate of neurological deaths in the radiosurgical boost group was within a range of 25–50% reported in other surgery and radiosurgery series.[22,23]

We did not note any survival advantage associated with stereotactic boost treatment in patients with multiple brain metastases, an observation that accords with all radiosurgery series except one.[21] We did note, however, a much better KPS and less steroid use in patients who had boost treatment compared with those who did not. These observations were supported by more complete responses and a better local control rate.

We did not note any survival advantage based on the type of radiosurgery unit used,[17] which is in contrast with results from the previous RTOG trial 9005.[10] We also failed to note a survival advantage in the WBRT plus stereotactic boost treatment group for patients with unfavourable prognostic factors.[18,24]

Tumours in eloquent cortex or deep-seated tumours are usually thought to be unresectable. For these cases, radiosurgery has served as a compelling alternative to surgery, conferring survival and quality-of-life benefits as well as potential cost savings.[25,26] For resectable metastases, whether radiosurgery or surgery provides better survival benefit remains unclear, even for patients with single brain metastases.[27] To date, attempts to do randomised trials that compare surgery and radiosurgery have not accrued patients because of the stark difference between treatments and the strong biases held by not only treating physicians but also informed patients.[28] These treatment options, therefore, will remain clinical judgments. Whether WBRT is needed with stereotactic boost for patients with radioresistant tumours remains an open question. The Eastern Cooperative Oncology Group (ECOG) and the American College of Surgical Oncology Group (ACOSOG) are both doing trials to compare stereotactic surgery alone with stereotactic treatment and WBRT for patients with one to three brain metastases.

In conclusion, our data suggest that radiosurgery boost after WBRT is better than WBRT alone for surgically unresectable single brain metastasis. The radiosurgery boost, which is not associated with any other toxicity, should, therefore, be standard treatment after WBRT for patients with a single metastasis. Because of improved performance in all patients who had radiosurgery boost, with or without previous craniotomy and within reasonable size constraints, WBRT and stereotactic radiosurgery should also be considered for patients with two or three brain metastases.

Contributors

D W Andrews was study chair, and he had the idea for, designed, and wrote the protocol in collaboration with colleagues from various clinical subspecialties (C Scott for statistics, P W Sperduto for radiation oncology, M Schell for medical physics, and A E Flanders for neuroradiology). M P Mehta was chair of the RTOG Brain Tumor Section and he reviewed initial drafts of the manuscript and suggested changes. W J Curran Jnr was chair of RTOG and he oversaw the approval of the protocol at National Cancer Institute; M Werner-Wasik contributed patients to the trial; L E Gaspar, W Demas, J Ryu, J-P Bahary, L Souhami, and M Rotman were principal investigators at their institutions and contributed patients to the trial.

Conflict of interest statement

None declared.

Acknowledgments

We thank RTOG dosimetrist Bernadine Dunning for her diligent efforts, and Raymond Sawaya for his helpful comments. This publication was supported by grant number (RTOG U10 CA21661, CCOP U10CA37422, Stat U10 CA32115) from the National Cancer Institute. Contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

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