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


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.

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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 investigators4,6 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.6 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

<table>
<thead>
<tr>
<th>Recursive partitioning analysis classes for brain metastases&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Class 1</th>
<th>Class 2</th>
<th>Class 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPS</td>
<td>≥70</td>
<td>≥70</td>
<td>&lt;70</td>
</tr>
<tr>
<td>Primary status</td>
<td>Controlled</td>
<td>Uncontrolled</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>&lt;65</td>
<td>≥65</td>
<td></td>
</tr>
<tr>
<td>Extracranial disease status</td>
<td>Brain only</td>
<td>Brain plus other</td>
<td>sites</td>
</tr>
</tbody>
</table>

Table 1: RPA class definitions
Figure 1: Trial profile

Table 2: RTOG CNS toxicity criteria

<table>
<thead>
<tr>
<th>Largest metastasis</th>
<th>WBRT+stereotactic surgery (n=164)</th>
<th>WBRT alone (n=167)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 cm</td>
<td>83 (50-59)</td>
<td>98 (59%)</td>
</tr>
<tr>
<td>&gt;2 cm to &lt;3 cm</td>
<td>57 (27%)</td>
<td>45 (27%)</td>
</tr>
<tr>
<td>&gt;3 cm to &lt;4 cm</td>
<td>24 (14-5%)</td>
<td>24 (14%)</td>
</tr>
</tbody>
</table>

Table 3: Patients’ baseline characteristics

- **Age**: Mean (range) (years)
  - <65 58 (19-82) 109 (66%)
  - ≥65 55 (34%) 66 (40%)
- **Largest metastasis**
  - <2 cm 83 (50-59)
  - >2 cm to <3 cm 57 (27%)
  - >3 cm to <4 cm 24 (14-5%)
- **Men**: 86 (52%)
- **Histological status**: Squamous 19 (12%)
  - Adenocarcinoma 84 (51%)
  - Large cell 27 (16%)
  - Small cell 14 (9%) 10 (6%)
  - Melanoma 7 (4%)
- **Renal**: 5 (3%) 5 (3%)
- **Other**: 5 (8%) 11 (7%)
- **Information missing**: 0
- **Primary tumour site**: Breast 15 (9%)
  - Lung 105 (64%)
  - Skin/melanoma 7 (4%)
  - Other 23 (14%)
  - Kidney 2 (1%)
  - Bladder 0
  - Colon 4 (2%)
  - Ovarian 1 (1%)
  - Unknown primary 7 (4%)
- **Neurological function**: No symptoms 54 (33%)
  - Minor symptoms 81 (50%)
  - Moderate symptoms 37 (22%)
  - Information missing 2 (1%)
- **RPA class**: 1 46 (28%)
  - 2 118 (72%)
- **KPS**: 90-100 93 (57%)
  - 70-80 71 (43%)
- **Primary site**: Controlled/absent 126 (77%)
  - Unknown control 38 (23%)
- **Metastases**: Brain alone 52 (32%)
  - Brain and one other extracranial site 61 (37%)
  - Brain and two others extracranial sites 35 (21%)
  - Brain and >2 additional sites 16 (10%)
- **Number of brain metastases**: 1 92 (56%)
  - 2 39 (24%)
  - 3 13 (8%)
  - 4 10 (6%)
- **MMSE**: 15–24 16 (10%)
  - 25–30 138 (84%)
  - Information missing 10 (6%)

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

References:
1. 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.
2. 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.

We assigned radiosurgery doses in accordance with prescriptions from an earlier dose-escalation RTOG radiosurgery trial (90–05). 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...
### Table 4: Reasons for not receiving stereotactic radiosurgery

<table>
<thead>
<tr>
<th>Reason</th>
<th>Single metastasis (n=14)</th>
<th>Multiple metastases (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician refusal</td>
<td>1 (7%)</td>
<td>2 (12%)</td>
</tr>
<tr>
<td>Patient refusal</td>
<td>5 (36%)</td>
<td>4 (24%)</td>
</tr>
<tr>
<td>No tumour</td>
<td>1 (7%)</td>
<td>4 (24%)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>4 (29%)</td>
<td>5 (29%)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (7%)</td>
<td>2 (12%)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (14%)</td>
<td>0</td>
</tr>
</tbody>
</table>

### Table 5: Treatment-related toxicities

#### Acute toxicities

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>WBRT+stereotactic surgery (n=160)</th>
<th>WBRT alone (n=166)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WORST REPORTED TOXICITY GRD</td>
<td>69 (43%) 28 (18%) 3 (2%) 1 (1%)</td>
<td>59 (36%) 43 (26%) 0 0</td>
</tr>
</tbody>
</table>

#### Late toxicities

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>WBRT+stereotactic surgery (n=113)</th>
<th>WBRT alone (n=112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WORST REPORTED TOXICITY GRD</td>
<td>16 (14%) 7 (6%) 3 (3%) 3 (3%)</td>
<td>16 (14%) 8 (7%) 2 (2%) 1 (1%)</td>
</tr>
</tbody>
</table>

### Post-treatment surveillance

We did clinical evaluations and MRI scans at 3 month intervals up to 1 year. 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). 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 glucocorticoids 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 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 permuted 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 colleagues, to ensure intergroup homogeneity and also to assess outcomes according to RPA class (table 1).
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. 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).

**Statistical analyses**

Analysis was by intention to treat. We treated all outcomes as independent hypotheses, and we did not adjust for multiple comparisons. 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 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.

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**Table 6: Causes of death**

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

SRS=stereotactic surgery.
univariate analysis

Performance measurements at 6 months

Table 8: *p=0.0331. †Most patients were not taking steroids by 3 months. ‡p=0.0158.

Table 9: Radiographic responses at 3 months’ follow-up

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

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).
noted between groups when assessing dose delivered more than 2 cm in diameter. No survival advantage was provided to patients with either single metastases, RPA class 1, or whose largest metastasis was between groups (figure 2). Likewise, we did not note a survival benefit to patients with either single metastases, RPA class 1, or whose largest metastasis was not allocated boost treatment. 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 statistically 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.
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 isodose 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, but no survival benefit.21

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

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Data type</th>
<th>Metastases</th>
<th>Comparison</th>
<th>Mean survival time (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patchell, 1990</td>
<td>48</td>
<td>Level I, Single institution</td>
<td>Single</td>
<td>Surgery/WBRT vs WBRT alone</td>
<td>10, 3-75</td>
</tr>
<tr>
<td>Noordijk, 1994</td>
<td>63</td>
<td>Level I, Multiple institutions</td>
<td>Single</td>
<td>Surgery/WBRT vs WBRT alone</td>
<td>10, 6</td>
</tr>
<tr>
<td>Mintz, 1996</td>
<td>84</td>
<td>Level I, Multiple institutions</td>
<td>Single</td>
<td>Surgery/WBRT vs WBRT alone</td>
<td>5-6, 6-3</td>
</tr>
<tr>
<td>Bindal, 1996</td>
<td>93</td>
<td>Level IV, Single institution</td>
<td>Single and multiple</td>
<td>Surgery/WBRT vs SRS/WBRT</td>
<td>16-4, 7-5</td>
</tr>
<tr>
<td>Kondziolka, 1995</td>
<td>27</td>
<td>Level I, Single institution</td>
<td>Multiple</td>
<td>SRS/WBRT vs WBRT</td>
<td>11, 7-5</td>
</tr>
<tr>
<td>Sanghavi, 2001</td>
<td>502</td>
<td>Level IV, Multiple institutions</td>
<td>Not specified</td>
<td>SRS/WBRT</td>
<td>8-6, 8-2</td>
</tr>
<tr>
<td>Sneed, 2002</td>
<td>559</td>
<td>Level IV, Multiple institutions</td>
<td>Single and multiple</td>
<td>SRS/WBRT vs SRS alone</td>
<td>8-6, 8-2</td>
</tr>
</tbody>
</table>

**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 radioreistant 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 Planders 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 Jr 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.

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References
3 Weissman DE. Glucocorticoid treatment for brain metastases and 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.

ARTICLES
