Interim report of the JROSG99-1 multi-institutional randomized trial, comparing radiosurgery alone vs. radiosurgery plus whole brain irradiation for 1-4 brain metastases.

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Background

- Whole brain irradiation has long been the standard of care for the treatment of multiple brain metastases. Stereotactic radiosurgery is often combined with whole brain treatment in an effort to increase local control. However, radiosurgery alone is frequently used to treat patients with up to 4 brain metastases despite the lack of phase III data to support this.
- This study was undertaken to compare stereotactic radiosurgery surgery alone versus radiosurgery combined with up-front whole brain therapy in patients with 1-4 brain metastases.

Materials and Methods

- Multi-institutional two arm randomized prospective phase III trial enrolling 132 patients (67 SRS alone and 65 combined group) out of 160 eligible candidates between 10/99 and 12/03.
- Patients were randomized to stereotactic radiosurgery alone versus radiosurgery preceded by whole brain irradiation with stratification according to primary tumor site (lung versus other), primary tumor status (active versus inactive), and number of brain metastases (1 versus 2-4).
- Eligibility characteristics included pathologically confirmed systemic disease, 1-4 brain metastases on enhanced MRI imaging, age greater than 18 years, and no history of prior brain radiation or brain surgery. In addition, the histologies of small cell carcinoma, lymphoma, germinoma, myeloma, and skin cancer other than melanoma were excluded.
- Primary endpoint was overall survival, and secondary endpoints were local control, cause of death (by Patchell's definition), freedom from new brain metastases rate, KPS score preservation (at least 70), neurological function preservation rate, local control, and late radiation morbidity (by RTOG scale).
- Whole brain radiation treatment was 30 Gy delivered over 10 fractions of 300 cGy each.
- Results were analyzed on an intention-to-treat basis.

Results

- The median follow-up at the time of interim analysis was 7 months (range: 1-46).
The median marginal radiosurgery dose was 21.9 Gy in the radiosurgery group and 16.5 Gy in the combined group as part of a planned 30-40% reduction in radiosurgery dose delivered after whole brain treatment.

There was no significant difference in overall survival (7.9 mos. SRS alone versus 7.6 mos. combined therapy, p=0.64), KPS preservation rate at one year (27% SRS alone versus 32% combined therapy, p=0.72), neurological preservation rate at one year (71% SRS alone versus 70% combined therapy, p=0.34), or causes of death from neurologic etiology (9 pts. SRS alone versus 6 pts. combined therapy, p=0.48).

There was a significant difference favoring the combined group with respect to freedom from new brain metastases rate at 6 months (48% SRS alone versus 82% combined therapy, p=0.0001) and local control at one year (70% SRS alone versus 86% combined therapy, p=0.001).

There was no significant difference in acute adverse effects (8 pts. in SRS alone versus 3 pts. in combined group, p=0.12) or late adverse effects (2 pts. in SRS alone versus 6 pts. in combined group, p=0.13).

**Author’s Conclusions**

- There is a significant benefit to whole brain radiation treatment followed by stereotactic radiosurgery in patients with up to four metastases with respect to local control and freedom from new brain metastases.
- There was no benefit with combined therapy as applied to overall survival, functional status preservation, neurological preservation, or prevention of death due to neurological etiology.
- Stereotactic radiosurgery alone should be delivered only when close follow-up is available due to the high frequency of brain relapse.

**Clinical/Scientific Implications**

The authors of this study favor radiosurgery combined with up-front whole brain radiation over stereotactic radiosurgery alone in patients with up to 4 brain metastases. Indeed, despite no increase in survival, the regimen appears superior with respect to local control of existing metastases and development of new metastases while possessing a similar side effect profile. However, the study is limited by the absence of quality of life data, as Karnofsky performance and neurological preservation should not be extrapolated to infer quality of life. In addition, there is some concern that the patients in the combined group might have been significantly underdosed via radiosurgery, potentially affecting survival, functional, and morbidity outcomes. Ultimately, this is an early analysis of maturing data, and more definitive conclusions may be drawn after longer follow-up.