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# Stereotactic radiosurgery for multiple brain metastases

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**Abstract.** Whole brain radiation therapy has been the traditional treatment of choice for patients with multiple brain metastases. Although stereotactic radiosurgery is widely accepted for the management of up to 4 brain metastases, its use is still controversial in cases of 5 or more brain metastases. Randomized trials have suggested that stereotactic radiosurgery alone is appropriate in up to 4 metastases without concomitant whole brain radiation. Level 1 evidence also suggests that withholding whole brain radiation may also reduce the impact of radiation on neurocognitive function and also may even offer a survival advantage. A recent analysis of a large multicentre prospective database has suggested that there are no differences in outcomes such as the likelihood of new metastasis or leptomeningeal disease in cases of 2-10 brain metastases, nor in overall survival. Hence in the era of prolonged survival with stage IV cancer, stereotactic radiosurgery is a reasonable alternative to whole brain radiation in order to minimize the impact of treatment upon quality of life without sacrificing overall survival.

## 1. Introduction

The use of stereotactic radiosurgery for the management of brain metastases is a well accepted paradigm, and multiple randomized trials have demonstrated the efficacy of radiosurgery in providing durable tumour control in better than 80% of cases while the risk of severe complications is extremely rare [1-7]. These trials have limited the number of brain metastases to less than 5 lesions, and traditional treatment of more than 4 brain metastases is typically whole brain radiation (WBRT). WBRT has been recommended in such settings because of the perception that when there are more than 4 metastases, it is likely that many more undetected micrometastases lurk in the brain. Another oft quoted assumption is that with multiple brain metastases, even with stereotactic radiation, the amount of radiation necessary to treat multiple lesions in various quadrants of the brain will amount to whole brain radiation anyways. And in particular for linac users, the time to treat multiple isocenters makes it relatively impractical to treat more than 4 lesions.

## 2. Why consider radiosurgery

Should stereotactic radiosurgery be considered for patients with greater than five brain metastases? This is a topic of some controversy and there are a number of arguments both in favor and against the use of radiosurgery for multiple metastases in the brain. High dose single fraction radiation therapy is more likely to provide more durable local control as opposed to conventional fractionated radiation treatment [8-10]. Also, focal radiation treatment is likely to spare a significantly greater amount of normal brain parenchyma which should reduce the toxicity of radiotherapy, even for multiple brain metastases. With



the advent of modern treatment planning and delivery techniques including image guided single isocenter volumetric arc radiation therapy, in which multiple lesions can be accurately treated with a single isocenter, it is significantly less straining on department resources for treating multiple metastases particularly in the setting of linear accelerator based radiosurgery. In addition, there is data that suggests that stereotactic radiosurgery is cost-effective relative to whole brain radiation. Therefore, there are several reasons to consider stereotactic radiosurgery for the management of multiple brain metastases.

### **3. Omitting whole brain radiotherapy**

There are a number of studies that suggest that the omission of WBRT and treatment with only stereotactic radiosurgery maybe an appropriate strategy. For example a small randomized trial from Aoyama et al [7] studied patients with 1 to 4 brain metastasis, each less than 3 cm and then randomized them to receive WBRT plus radiosurgery versus radiosurgery alone. In this trial, WBRT patients received 30 Gy in 10 fractions and radiosurgery, adhering closely to RTOG 90-05 guidelines. Radiation dose was reduced by 30% when combined with WBRT in this small randomized trial. There were no significant differences in median survival with the omission of WBRT. However, there was a significantly higher rate of regional brain recurrence at one year and deterioration in mini mental status exam results in patients who underwent WBRT, although this was not a statistically significant finding. Another small series from the University of Pittsburgh [11] suggest that the total number of metastases is less relevant than the total volume of tumor to be treated. A multivariate analysis demonstrated that the total treatment tumor volume was significant however the number of metastases was not predictive of overall survival. This study was done with patients with four or more intracranial metastases, thus one large volume metastases is more likely to have a worse outcome than multiple small metastases.

Such data suggest that in the setting of multiple metastases, the addition of WBRT does not offer a significant survival benefit. However, it is likely that radiosurgery does improve the probability of local control. A multi-institutional retrospective study of radiosurgery with or without whole brain radiation was published by Sneed et al [12]. In this large series of patients from 10 different institutions there is no significant survival difference with the admission of upfront whole brain radiation and patience to receive radiosurgery. Median survival times were 14 versus 15.2 months for RPA class one patients, and not significantly different. A meta-analysis of 364 patients from three randomized trials comparing radiosurgery versus whole brain radiation found that for younger patients, omitting whole brain radiation may be reasonable. There was a suggestion toward the reduction in the risk of failure after radiosurgery in patients less than 50 years of age and reduced risk of mortality for those treated with radiosurgery alone for those less than age 70 [13].

In terms of complications from whole brain radiation a randomized trial was reported from Chang et al [14] in which patients who were either RPA class one or two, with 1 versus 2 to 3 brain metastases, and also stratified by histology (melanoma renal cell carcinoma versus other) were randomized to either radiosurgery plus whole brain radiation or radiosurgery alone. The whole brain radiation dose was 30 Gy in 12 fractions, and patients were prospectively evaluated for neurocognitive function. It was found in this small study that the additional whole brain radiation to radiosurgery significantly increased the probability of neurocognitive decline (23% versus 49%,  $p = 0.003$ ). Another interesting finding of this study was that there was actually a survival benefit to delaying WBRT ( $p = 0.03$ ). Patients who underwent whole brain radiation plus radiosurgery had twice the decline in Hopkins Verbal Learning Test and memory compared to patients who were treated with radiosurgery alone. Despite the higher rate of distant brain failure when WBRT was omitted, learning and memory outcomes were still superior for patients who did not receive WBRT. These data suggest that a decline in learning and memory is primarily toxicity from radiation rather than due to brain tumor relapse. The authors suggested that initial treatment for 1 to 3 brain metastases should be radiosurgery alone rather than whole brain radiotherapy in addition to radiosurgery.

Yamamoto et al [3] reported on a large multi-center study of 23 gamma knife centers in Japan for patients with 5 to 10 brain metastasis with a KPS of at least 70 and lesions less than 3 cm in size. Mini mental status exam was utilized for neurologic assessment, then these patients were followed on a

regular basis. A total of 1194 patients were treated with radiosurgery alone, with median overall survival of 12 months. A non-inferiority analysis was performed which suggested that although there was a difference when comparing 1 versus more than 1 lesion, when treating 2-4 versus 5-10 lesions, there was no significant difference in overall survival. Similarly, in multivariate analysis, there was a significant difference in overall survival for 1 versus 2 to 10 brain metastases. However, there was no difference in outcomes for 2 to 4 versus 5 to 10 metastasis. The incidence of new lesions with 1 metastasis at initial presentation was found to be 36% at 12 months compared to 54 to 64% for 2 to 4 and 5 to 10 lesions, respectively. At 24 months the likelihood of new metastases in patients who presented with a single metastasis was nearly 50% compared to 65 to 70% for patients with 2 to 4 and 5 to 10 metastases at the time of presentation. There was a significant difference between 1 versus more than 1 but no significant difference between 2 to 4 and 5 to 10 lesions in terms of the likelihood of developing new lesions. Likewise, the risk of leptomeningeal dissemination at 12 months was 7% for patients who presented with a single metastasis versus 8 to 11% if they presented at 2 to 4 or 5 to 10 metastases. And at 24 months, the risk of leptomeningeal disease in a patient who presented with a single lesion was 11% compared to 13% to 21% in patients who had 2 to 4 or 5 to 10 lesions. There was no statistical difference in terms of the likelihood of leptomeningeal disease beyond 1 metastasis. Such data suggest that it may be reasonable to omit whole brain radiation in up to 10 lesions. In terms of mini mental status exam, this study suggests that there was no significant loss of mental status by omitting whole brain radiation despite the presence of up to 10 metastases.

Randomized trials have suggested no overall survival benefit from the addition WBRT radiotherapy. The addition of whole brain radiation to radiosurgery was associated with diminished cognitive functioning and it was also recommended that careful surveillance and judicious use of salvage therapy at the time of brain relapse may be appropriate for patients in order to enjoy a higher quality of life by delaying the initiation of WBRT. Hence, the American Society for Therapeutic Radiation Oncology has suggested that it may be reasonable to omit WBRT upfront for limited brain metastasis [15].

#### **4. Advances in treatment planning and delivery**

Particularly among linear accelerator centers, it has been impractical to offer radiosurgery for multiple isocenters. When each lesion is treated with a unique isocenter, radiosurgery to 10 lesions is essentially 10 different courses of treatment, requiring an individual treatment plan for each lesion and isocenter verification for each lesion at the time of treatment. In this case, 10 lesion treatment is extremely resource intensive for both treatment planning and treatment delivery. With the advent of volumetric arc therapy (VMAT), a single isocenter can be utilized to treat multiple lesions, hence a single course of treatment can effectively treat 10 lesions. Although the treatment planning time may be more than for just a single lesion, automated planning tools may be able to effectively minimize the amount of human input necessary. Since treatment will be with a single isocenter, the entire treatment of 10 lesions will require only one isocenter verification, resulting in a much higher throughput for any given linear accelerator. In essence 10 lesions could be treated in nearly the same time required to treat 1 lesion [16].

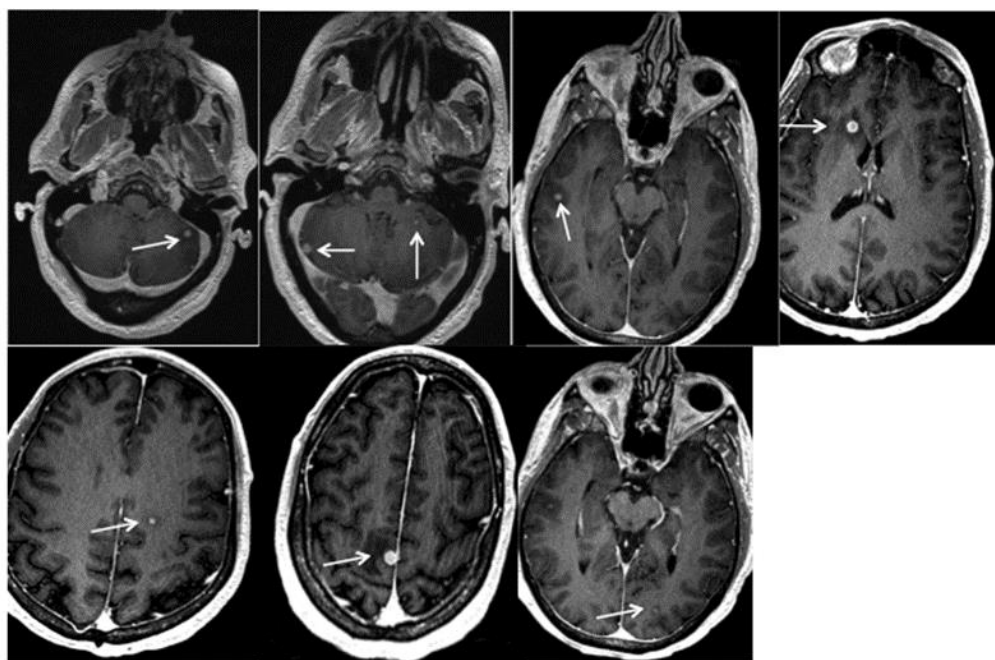
Although there has been evidence to the contrary, recent data from the University of Alabama in Birmingham have suggested that a single isocenter flattening filter free VMAT is equal in dose distributions to gamma knife radiosurgery for multiple lesions in the brain [16]. Single isocenter multi arc flattening filter free VMAT was found to provide equal plans in terms of plan quality and mean brain dose to that generated with Gamma Knife treatment. A randomized controlled trial is being sponsored by the North American Gamma Knife Consortium for patients with five or more brain metastases and with a KPS > 70. These patients will be randomized to WBRT of 30Gy in 10 fractions versus radiosurgery alone (NCT01731704).

An example of the ability to spare normal tissue is presented in this case of a 52-year-old patient with stage four renal cell carcinoma. This patient was asymptomatic with respect to bone and lung metastases that were controlled on systemic treatment. The patient previously had radiosurgery for a lesion in the right temporal lobe and one in the right parietal lobe. Unfortunately, subsequent scans

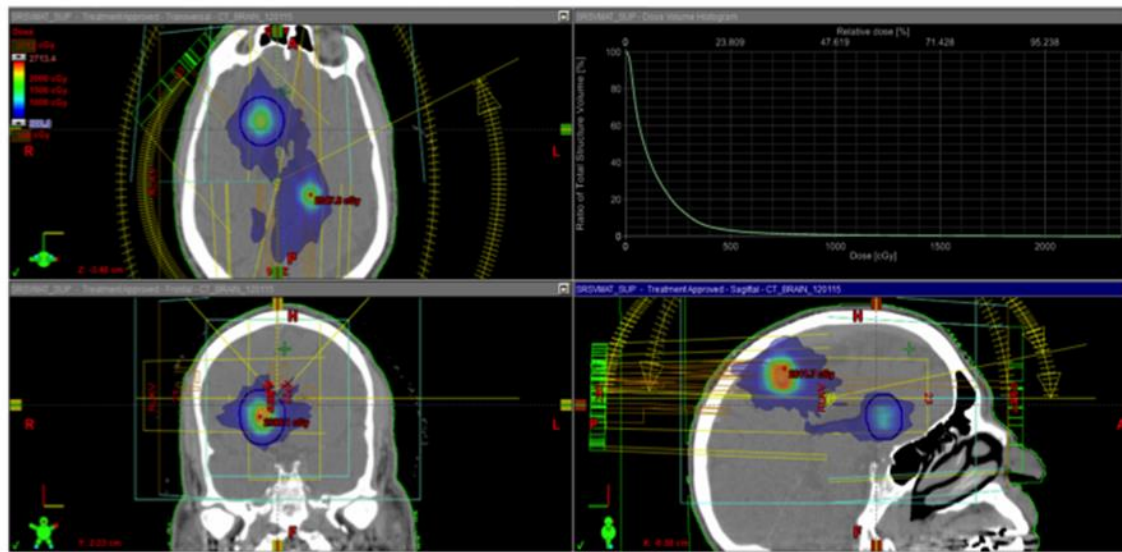
showed multiple new metastases in the right temporal lobe right, medial posterior frontal lobe, right caudate, left frontal centrum ovale, left occipital temporal junction, left cerebellar, right cerebellar, and left brachium pontis areas of the brain (see figure 1). As figure 2 illustrates, despite having multiple brain metastases, when using radiosurgery, a significant proportion of the brain parenchyma receives less than a single fraction of WBRT (3000cGy/10 fractions).

## 5. Summary

There is strong rationale treating patients with multiple metastases with radiosurgery alone and omitting upfront WBRT. There appears to be no detrimental loss of overall survival, and level one evidence suggests that there may be a survival advantage in favour of delaying WBRT. There is a significant benefit in terms of reducing the negative effect of radiation on neurocognition when WBRT is avoided. Although there may be differences in survival when comparing patients who receive radiosurgery for 1 metastasis versus more than 1 metastasis, patients with 2-10 brain metastases will enjoy comparable outcomes in terms of overall survival, as well as the likelihood of developing new brain metastases or leptomeningeal disease. Also with advances in treatment planning and delivery, treating multiple brain metastases has become a practical option to consider. Thus, since there are no significant differences in oncological outcomes when more than one lesion is treated, those who are comfortable in offering radiosurgery for 3 to 4 brain metastases should be equally comfortable in offering radiosurgery for up to 10 brain metastases.



**Figure 1.** A patient with 8 brain metastases demonstrated on axial T1 weighted post gadolinium contrast enhanced T1 weighted MRI imaging.



**Figure 2.** Single isocenter VMAT plan for 8 lesions. The dose color wash is set to 300cGy or greater. Prescription dose was 21 Gy to the 80% isodose line for each lesion.

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