



Evaluation of Dose-Staged Gamma Knife Radiosurgical Treatment Method for High-Risk Brain Metastases

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■ **OBJECTIVES:** The study aim was to evaluate the utility of 2-fraction, dose-staged Gamma Knife radiosurgery (GKRS) in patients with large, high-risk brain metastases (BMs).

■ **METHODS:** A total of 63 large BMs in eloquent areas in 61 patients were treated with GKRS in 2 reduced doses. Treatment planning was conducted on the 50% isodose line and included the whole tumor volume as seen on T1 contrast-enhanced and T2-weighted magnetic resonance imaging sections. The median margin and central dose were 12 Gy and 24 Gy, respectively, for both fractions. Patients were assessed using the Graded Prognostic Assessment, Recursive Partitioning Analysis, and Score Index for Radiosurgery.

■ **RESULTS:** Thirty-two patients (53%) had been diagnosed with multiple BMs, and extracranial metastases were present in a majority of patients before GKRS treatment. Significant decreases in tumor volume were observed between the first and second treatment stages. At 3-month follow-up, a majority of patients presented with stable or decreased lesion volumes. The remaining patients showed intralesional hemorrhaging or increasing edema that was managed conservatively. Three patients were diagnosed with tumor progression at the last follow-up and received microsurgical treatment. The median time to radiologic progression was 7 months. The median survival time after initial BM diagnosis was 6 months. Survival times were

significantly longer than 3 of 4 calculated prognostic survival estimates.

■ **CONCLUSION:** The new 2-fraction, dose-staged GKRS concept seems to be a well-tolerated and effective treatment option for large BMs. This method may be indicated in elderly patients or patients with surgical contraindications with large or high-risk brain metastases.

INTRODUCTION

Brain metastases (BMs) occur in 20%–40% of cancer patients, are being diagnosed with rising frequency, and are a significant cause of morbidity and mortality.¹⁻⁴ The current treatment options for BMs include surgical resection, radiotherapy, radiosurgery, and combinations thereof.^{2,4} Molecular systemic therapies may be beneficial in specific patient subgroups, but there are limited data documenting drugs that can penetrate the blood-brain barrier and be used as primary treatments for noninvasive BM treatment in the future.⁵⁻⁸ Radiosurgery has emerged as an alternative to surgical resection, especially in patients with solitary BMs with eloquent or deep-seated localization.^{9,10} Considering the minimal invasiveness of radiosurgical procedures and a low rate of adverse effects relative to whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS) has more recently been described as a suitable alternative even for patients with up to 10 brain metastases.¹¹ Prescription doses in

Key words

- Brain metastases
- Dose-staged Gamma Knife radiosurgery
- Radionecrosis

Abbreviations and Acronyms

- BMs:** Brain metastases
- CI:** Confidence interval
- EBRT:** External beam radiation therapy
- GI:** Gastrointestinal
- GKRS:** Gamma Knife radiosurgery
- GPA:** Graded Prognostic Assessment
- GU:** Genitourinary cancer
- KPS:** Karnofsky Performance status
- MRI:** Magnetic resonance imaging
- PET:** Positron-emission tomography

RPA: Recursive Partitioning Analysis

SIR: Score Index for Radiosurgery

WBRT: Whole brain radiation therapy

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Citation: *World Neurosurg.* (2016) 94:352-359.
<http://dx.doi.org/10.1016/j.wneu.2016.07.038>

Journal homepage: www.WORLDNEUROSURGERY.org

Available online: www.sciencedirect.com

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Table 1. Sample Characterization at Time of First Dose-Staged Gamma Knife Radiosurgery (GKRS)*

| | Time of First Dose-Staged GKRS |
|---------------------------------------|--------------------------------|
| Age in years, median (range) | 72 (37–93) |
| Female-to-male ratio | 31:30 |
| KPS in %, median (range) | 80 (20–90) |
| Main neurology | |
| Hemiparesis | 6 (10%) |
| Sensory disturbances | 0 (0%) |
| Headache | 7 (11%) |
| Vertigo | 9 (15%) |
| Aphasia | 3 (5%) |
| Seizures | 4 (7%) |
| Visual disturbances | 7 (11%) |
| Ataxia/gait disturbance | 8 (13%) |
| Other | 6 (10%) |
| None | 11 (18%) |
| Primary tumor | |
| Lung cancer | 25 (41%) |
| Breast cancer | 9 (15%) |
| Melanoma | 8 (13%) |
| GI cancer | 11 (18%) |
| GU cancer | 6 (10%) |
| Other | 2 (3%) |
| Treatment of primary tumor | |
| None | 11 (18%) |
| Chemotherapy alone | 9 (15%) |
| Radiotherapy alone | 1 (2%) |
| Surgical resection alone | 6 (10%) |
| Chemotherapy + radiotherapy | 4 (6%) |
| Surgery + chemotherapy + radiotherapy | 14 (23%) |
| Surgery + chemotherapy | 14 (23%) |
| Surgery + radiotherapy | 2 (3%) |
| Prior CNS treatment | |
| None | 52 (86%) |
| Surgical resection alone | 3 (5%) |
| Continues | |

radiosurgery are determined according to tumor volume, the histology of the primary tumor, and prior treatment. In particular, tumor volume is a critical and outcome-influencing factor in radiosurgical treatment since the irradiation of larger tumor volumes has been associated with side effects due to

Table 1. Continued

| | Time of First Dose-Staged GKRS |
|---|--------------------------------|
| Surgical resection and EBRT | 2 (3%) |
| WBRT | 2 (3%) |
| GKRS | 2 (3%) |
| KPS, Karnofsky Performance Status Scale; GI, gastrointestinal; GU, genitourinary; CNS, central nervous system; EBRT, external beam radiation therapy; WBRT, whole brain radiation therapy. | |
| *Prior CNS treatment was mainly performed for distant brain metastases (BMs). Thus BMs treated with 2-fraction, dose-staged GKRS had not undergone prior treatment with the exception of BMs in 3 patients who had been treated with WBRT and 1 patient where a new progression was located in the previously irradiated resection cavity. The time between WBRT and first staged GKRS was 8 months in those 3 cases. | |

toxicity. Reducing the prescription dose required per tumor volume has been associated with significantly poorer tumor control.^{4,9,12-14} As a solution, hypofractionated stereotactic radiotherapy has been described for the treatment of larger BMs.¹² Hardly any data have been published on the fractionated, dose-staged Gamma Knife radiosurgery treatment method.¹⁵ Therefore the aim of the present study was to evaluate the utility of 2-fraction dose-staged Gamma Knife radiosurgery (GKRS) for the treatment of large, high-risk brain metastases.

PATIENTS AND METHODS

Patient Sample and Data Evaluation

A total of 63 BMs in 61 patients were treated with GKRS treatment. All data in this study were evaluated retrospectively. Patient characteristics are summarized in **Table 1**, and the localizations of treated BMs are shown in **Table 2**. BMs qualified as high risk and eligible for 2-staged radiosurgery if the tumor volume was $>5 \text{ cm}^3$ or the tumor was localized in eloquent brain regions such as the basal ganglia and brainstem, central region, insular region, or posterior fossa.

Table 2. Lesion Localization of 63 Brain Metastases Irradiated According to Dose-Staged GKRS Treatment Concept

| Localization | Number | % |
|-------------------------|--------|----|
| Frontal | 6 | 9 |
| Parietal | 5 | 8 |
| Cerebellar | 12 | 19 |
| Temporal | 5 | 8 |
| Insular | 5 | 8 |
| Central | 17 | 27 |
| Occipital | 7 | 11 |
| Brainstem/basal ganglia | 5 | 8 |
| Cingulate gyrus | 1 | 2 |

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