

Survival among patients with 10 or more brain metastases treated with stereotactic radiosurgery

Clinical article

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Object. The goal of this study was to evaluate outcomes in patients with ≥ 10 CNS metastases treated with Gamma Knife stereotactic radiosurgery (GK-SRS).

Methods. Patients with ≥ 10 brain metastases treated using GK-SRS during the period between 2004 and 2010 were identified. Overall survival and local and regional control as well as necrosis rates were determined. The influence of age, sex, histological type, extracranial metastases, whole-brain radiation therapy, and number of brain metastases was analyzed using the Kaplan-Meier method. Univariate (log-rank) analyses were performed, with a p value of < 0.05 considered significant.

Results. Fifty-three patients with ≥ 10 brain metastases were treated between 2004 and 2010. All had a Karnofsky Performance Status score of ≥ 70 . Seventy-two percent had either non-small cell lung cancer (38%) or breast cancer (34%); melanoma, small cell lung cancer, renal cell carcinoma, and testicular, colon, and ovarian cancer contributed the remaining 28%. On average, 10.9 lesions were treated in a single session. Sixty-four percent of patients received prior whole-brain radiation therapy. The median survival was 6.5 months. One-year overall survival was 42% versus 14% when comparing breast cancer and other histological types, respectively ($p = 0.074$). Age, extracranial metastases, number of brain metastases, and previous CNS radiation therapy were not significant prognostic factors. Although the median time to local failure was not reached, the median time to regional failure was 3 months. Female sex was associated with longer time to regional failure ($p = 0.004$), as was breast cancer histological type ($p = 0.089$). No patient experienced symptomatic necrosis.

Conclusions. Patients with ≥ 10 brain metastases who received prior CNS radiation can safely undergo repeat treatment with GK-SRS. With median survival exceeding 6 months, aggressive local treatment remains an option; however, rapid CNS failure is to be expected. Although numbers are limited, patients with breast cancer represent one group of individuals who would benefit most, with prolonged survival and extended time to CNS recurrence. (<http://thejns.org/doi/abs/10.3171/2013.4.JNS121751>)

KEY WORDS • Gamma Knife • stereotactic radiosurgery • brain metastases • breast cancer • oncology

MORE than 1.5 million estimated new cases of cancer will be diagnosed in 2012, and 30%–40% of patients are expected to develop brain metastases during the course of their disease. These numbers probably underestimate the current impact of metastatic CNS disease. First, the availability and utilization of MRI provides for a sensitive, noninvasive study to detect small lesions. In addition, improved and novel systemic treatments continue to extend survival among patients with metastatic disease. In patients with single or symptomatic brain metastases, definitive local treatment is associated with an overall survival advantage.^{2,15} Treatment options for 2–4 brain metas-

tases include single-modality SRS with or without WBRT. For these patients a median survival of 6–10 months can be expected.^{2,3,11} Stereotactic radiosurgery alone is a well-established, noninvasive treatment performed using definitive doses of highly conformal radiation that has superior local control (between 70% and 90%) and spares normal tissue compared with WBRT. Furthermore, SRS carries a lower risk of long-term neurocognitive toxicity.⁴ Whereas the median survival among patients with 1–4 brain metastases ranges between 6 and 10 months as noted in multiple large randomized trials, retrospective studies show equivocal outcomes for patients with > 4 and < 10 metastases, with survival rates between 7 and 10 months following ag-

Abbreviations used in this paper: GK-SRS = Gamma Knife stereotactic radiosurgery; KPS = Karnofsky Performance Status; WBRT = whole-brain radiation therapy.

This article contains some figures that are displayed in color online but in black-and-white in the print edition.

gressive local treatment.^{5,16,19} However, for patients with ≥ 10 CNS metastases, the role of SRS alone, if any, remains unclear. We report our experience with GK-SRS for patients with ≥ 10 CNS metastatic lesions.

Methods

Inclusion Criteria and GK-SRS Treatment

In compliance with institutional review board approval, we retrospectively reviewed the records of 490 individuals treated with GK-SRS for brain metastases between 2004 and 2010. Fifty-three patients with ≥ 10 brain metastases were identified. All had a KPS score of ≥ 70 . The histological type of the primary lesion, extent of extracranial metastatic disease, previous CNS radiation therapy, and the number of brain metastases were verified by reviewing medical records and imaging (MRI, CT, or PET-CT). All patients underwent a diagnostic MRI to identify the initial burden of CNS disease. On the day of GK-SRS treatment a stereotactic MRI study was performed, including a high-resolution T1-weighted sequence (that is, a 3D magnetization-prepared rapid acquisition gradient echo sequence) with 2-mm slice thickness that was used for target localization and delineation and for treatment planning. Intravenous “double-contrast” (0.1 mmol/kg) gadolinium was administered. Imaging was reviewed by the treating neurosurgeon, neuroradiologist, and radiation oncologist and then compared with prior imaging to identify all new or progressive lesions. GK-SRS was performed using a Leksell Gamma Knife Model C (Elekta, Inc.). Dose was prescribed based on tumor size according to the recommendations from the Radiation Therapy Oncology Group 90–05.¹⁷ The target included the tumor with a 1- to 2-mm margin expansion. Lower doses were used in cases in which tumors were near the brainstem or other sensitive structures.

Study End Points

Overall survival, time to local and regional brain recurrence, and rate of necrosis were determined. Overall survival was defined from the time of GK-SRS treatment until the time of death, or at censoring (last documented visit in the medical record). A regional recurrence was documented when a new enhancing lesion that was not present at the time of the GK-SRS planning MRI scan was noted on follow-up imaging. Although increasing edema on the T2-weighted and FLAIR sequences or increased contrast enhancement was considered suspicious for local recurrence, MR spectroscopy and MR perfusion analysis consistent with local recurrence or a biopsy with viable tumor cells was required before assigning this end point. Imaging studies that were suggestive of necrosis, MR spectroscopy, and MR perfusion analysis were followed; however, pathological confirmation of necrotic tissue was required for diagnosis. Suspicious but indeterminate lesions were followed with serial imaging until local failure or necrosis could be established. Only lesions that were treated with GK-SRS were included for analysis of local and regional control.

Statistical Analyses

Statistical analyses were performed with IBM SPSS Statistics version 19. Survival, local control, and regional control curves were generated using the Kaplan-Meier method. On univariate analysis, the influence of age, sex, histological type, extracranial metastatic disease, previous CNS radiation, and number of brain metastases was evaluated using the log-rank test. A p value of < 0.05 was necessary to be considered a significant difference.

Results

Patient Characteristics

The average age for the 53 patients was 57.8 years (Table 1). Females and males constituted 75% and 25%, respectively, of the group. Non–small cell lung cancer (38%) and breast cancer (34%) represented the most common histological types. Sixty-four percent of patients had received prior WBRT and 66% had uncontrolled systemic metastatic disease. The average number of brain metastases on the diagnostic MRI was 5.7, whereas 14.5 were then identified on the GK-SRS planning MRI. The average interval between the diagnostic MRI and stereotactic MRI was 4.7 weeks. For GK-SRS treatment, 10.9 lesions were treated per patient, with a mean dose of 16.6 Gy (range 12–22 Gy) prescribed between the 40% and 70% isodose lines. Reasons for not administering treatment to all lesions included inaccessible location (1 patient), unacceptable treatment duration (1 patient), and treatment to large symptomatic lesions only (6 patients).

Survival Rates

The median survival was 6.5 months (Fig. 1). The 6-month, 1-year, and 2-year survival rates were 51%, 22%, and 12%, respectively. On univariate analysis, age, extracranial metastatic disease, number of brain metastases (10–15, 16–20, or > 20), and previous CNS radiation treatment were not significant prognostic factors (Table 2). Patients with breast cancer had a median survival of 7.4 months compared with 5.8 months for those with other primary sites of disease ($p = 0.074$). The 1-year survival for women with metastatic breast cancer, at 42%, was markedly greater than the 14% 1-year survival appreciated for patients with brain metastases from a different site (Fig. 2).

Local Failure, Regional Failure, and Toxicity

Seven patients (13.2%) had a documented local failure and the median time to local recurrence was not reached (Fig. 3). This is in contrast to regional failure in 27 patients (50.9%). The median time to regional failure was 3 months, and the 1-year actuarial regional failure rate was 90%. On univariate analysis, time to regional failure occurred earlier for males compared with females (4.5 months for females vs 1.6 months for males, $p = 0.004$) (Table 3). The association between breast cancer histological type and the time to regional failure did not reach statistical significance (4.7 months for breast vs 3 months for nonbreast cancer histological type [$p = 0.089$]) (Table 3 and Fig. 2). At the time of regional failure, the average number of new lesions

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TABLE 1: Summary of characteristics in 53 patients with brain metastases at the time of GK-SRS

Characteristic	Value
age	57.8 yrs (range 35–86 yrs)
sex	
M	25%
F	75%
histological type	
non–small cell lung cancer	20 (38%)
breast	18 (34%)
melanoma	7 (13%)
small cell lung cancer	3 (6%)
renal cell carcinoma	2 (4%)
colon	1 (2%)
testicular	1 (2%)
ovarian	1 (2%)
metastatic disease	
controlled	34%
uncontrolled	66%
interval btwn diagnostic & planning MRI	4.7 wks
no. of metastases per patient	
diagnostic MRI	5.7 (range 1–17)
GK-SRS planning MRI	14.5 (range 10–41)
GK-SRS treatment	10.9 (range 10–34)
initial CNS treatment	
WBRT	64%
GK-SRS	42%
GK-SRS treatment	
dose	16.6 Gy (range 12–22 Gy)
prescription isodose	40%–70%

identified was 4.2 (range 1–15). Age, previous WBRT, extracranial metastatic disease, and number of brain metastases were not predictive of regional CNS control. No patient developed symptomatic necrosis; however, in 7 patients (13%) imaging changes on MR spectroscopy or MR perfusion analysis that are characteristic of necrosis were noted. No treatment-related deaths were identified.

Discussion

The impact of CNS metastases on patient quality of life will undoubtedly increase as survival is extended using novel, more aggressive, and targeted systemic treatments. Thus, to improve patient care in the setting of metastatic dissemination, control of disease in sanctuary sites will be critical. Central nervous system progression through systemic treatments can result in debilitating neurological symptoms and premature CNS-related morbidity and death. In addition to CNS disease control, attention should also be directed toward reducing treatment-related toxicity in individuals who might survive long enough to experience these unwanted and potentially debilitating effects.

As a local therapy, SRS is effective for control of limited CNS metastases. The median survival generally

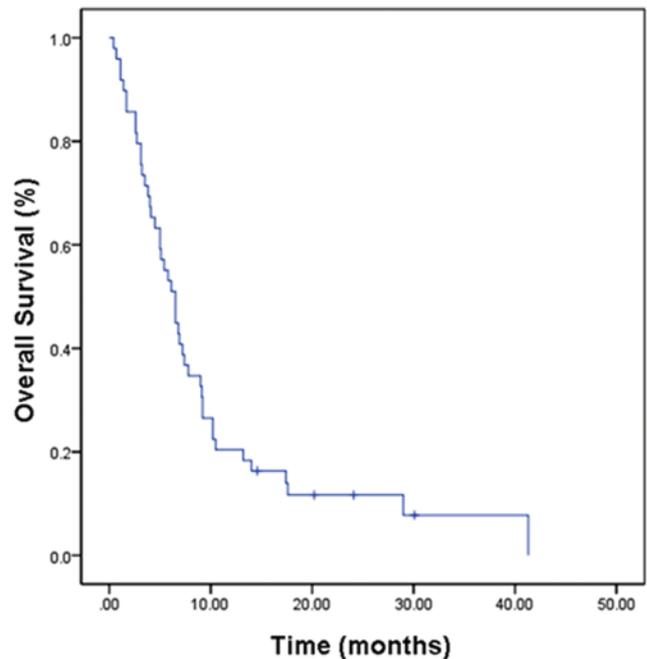


Fig. 1. Graph showing overall survival in 53 patients with ≥ 10 metastases.

ranges from 5 to 11 months.^{2,3,11,14,15} Neurological symptoms and duration of steroid use are reduced. Additionally, a survival advantage exists for treating single metastases with SRS; however, this has not been reproduced for patients with 2–4 brain metastases.^{2,14} We demonstrate excellent local control with SRS in patients with ≥ 10 brain metastases. The median time to local failure was not reached, and 1-year local control was $> 70\%$. Considering the burden of CNS disease and the history of previous treatment in this population, this outcome is encouraging. Others have demonstrated excellent local control rates (79%–94%) following SRS in patients with multiple brain metastases as well.^{18,23} Serizawa et al.¹⁸ reviewed patients with 1–10 lesions and showed a 1-year local control rate of 94%. Similarly, Vesagas et al.²³ treated 136 brain lesions in 24 patients and reported 85% local control, a 10.5-month mean time to local control failure, and a median survival > 8 months. With a mean follow-up period of 7.5 months, they also showed that KPS scores remained stable following aggressive local treatment with GK-SRS. In addition, the data presented by Serizawa et al.¹⁸ suggest that both neurological survival and qualitative survival were extended in patients treated with SRS compared with WBRT. Thus, local control of brain metastases can improve quality of life. It is also well established that SRS has better local control compared with WBRT alone.¹² Controversy remains regarding whether local control of multiple CNS metastases impacts overall survival since many patients will die of progressive systemic disease. However, it must also be considered that an intracranial cause of death has been reported in 20%–40% of patients with brain metastases.¹⁵

For patients who have recurrence after prior WBRT with multiple CNS metastases (≥ 10 lesions), treatment options are unfortunately limited. These include best

TABLE 2: Influence of factors on overall survival determined using a univariate log-rank risk analysis

Characteristic	Median Overall Survival (mos)	p Value
sex		
M	4.5	0.432
F	6.5	
histological type		
breast	7.4	0.074
other	5.8	
age in yrs		
≤65	6.5	0.226
>65	6.1	
initial WBRT		
yes	6.5	0.405
no	6.1	
metastatic disease		
controlled	6.5	0.729
uncontrolled	6.1	
no. of lesions on diagnostic MRI		
<10	6.5	0.892
≥10	5.8	
no. of lesions on GK-SRS planning MRI		
10–15	6.5	0.951
16–20	6.5	
>20	3.6	

supportive care, repeat WBRT, and salvage SRS. Best supportive care results in only 1- to 2-month survival.⁸ Although some studies have reported on the feasibility of repeat WBRT, it is often avoided for fear of cognitive effects and radiation necrosis.⁴ Three series that include 210 patients show a 30%–70% improvement in neurological function and a median survival of 4–5 months following repeat WBRT at doses ranging from 20 to 25 Gy.¹ However, only 2 of the 3 series reported long-term toxicity, and although acceptably low, further experience

is warranted before recommending this approach to patients predicted to have extended survival. In our cohort, salvage SRS was well tolerated, with an acceptably low rate of imaging changes (13%), none of which was symptomatic or required medical or surgical intervention.

We show a median survival of 6.5 months, which is encouraging for this difficult-to-treat population and is superior to that in patients treated with best supportive care alone.¹³ Our experience compares favorably with others' accounts of SRS for recurrent CNS disease.^{5,9,10,22} In 2000, Suzuki et al. reported a median survival of 2.5 months in 24 patients with ≥ 10 metastatic brain lesions, whereas more recently Kim et al. reviewed their experience of 26 patients with a mean of 16.6 brain metastases and showed a median survival of 7.8 months following SRS. Median survival times of 13 months and 8 months for patients with 11–15 (n = 17) and > 15 (n = 33) brain metastases, respectively, were observed by Chang et al.⁵ Interestingly, no disparity between patients with ≤ 10 lesions compared with > 10 lesions was reported. In a 30-year overview of GK-SRS for brain metastases involving 1921 patients, survival was comparable for patients with 2, 3–4, 5–8, or > 8 brain metastases after correcting for systemic disease status.⁹ Thus, patients who present with extensive CNS disease can have survival comparable to that of patients who are considered to be at lower risk; however, systemic disease status should be considered because this is a well-recognized prognostic factor for both survival and brain recurrence.⁶ Although cure is not feasible, effective local control and prolonged time to neurological progression and prevention of an early intracranial cause of death are realistic end points.

Unfortunately, many patients will experience recurrence within the CNS prior to death. We show a 3-month median time to regional CNS recurrence compared with a median survival of 6.5 months. Salvage options for these patients need to be considered on an individual basis. Repeat treatment with SRS is a reasonable approach. However, we restrict this approach to patients who maintain good KPS status and have controlled extracranial metastatic disease, have previously received WBRT, and whose expected survival is > 6 months. For patients who

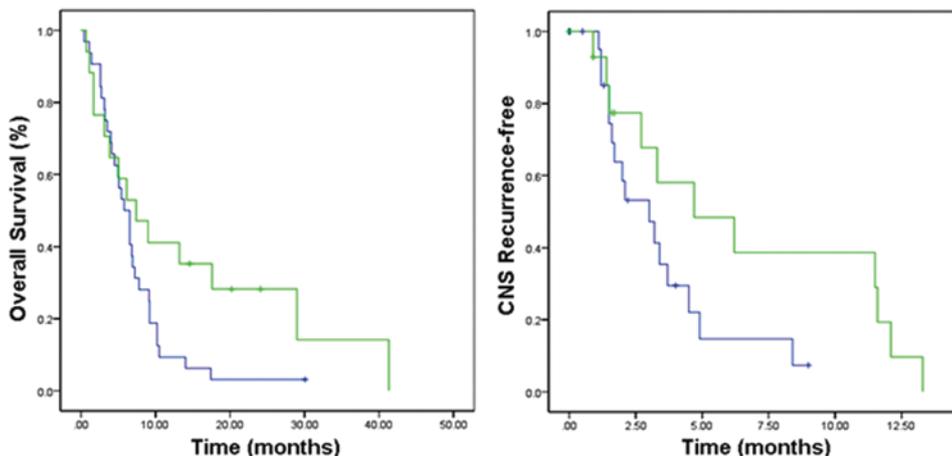


Fig. 2. Graphs showing overall survival (left) and time to CNS recurrence (right) for breast cancer (green line) and other histological types (blue line).

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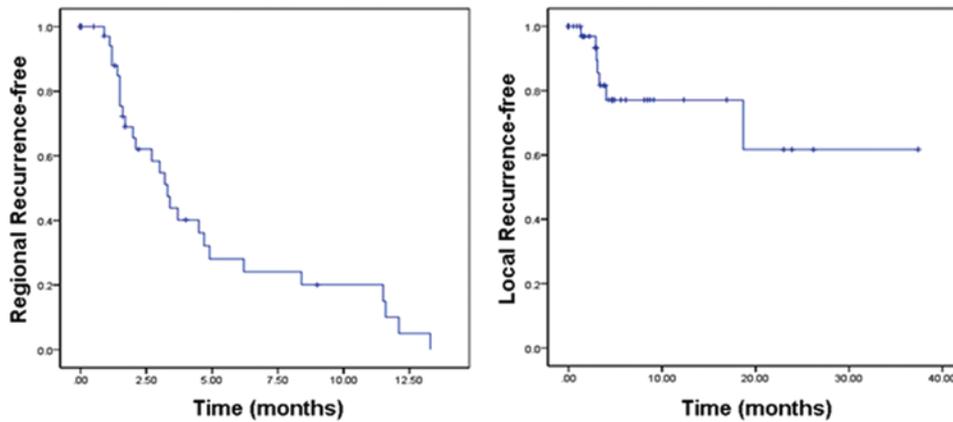


Fig. 3. Graphs showing CNS control as the time to regional failure (left) and local failure (right).

do not meet these criteria, options such as supportive care and repeat WBRT may be more appropriate.

Treatment with GK-SRS should not be standard for all patients with multiple, recurrent CNS metastases, but should be reserved for those with an expected prolonged survival in whom control of CNS disease is expected to have an impact on outcomes. Prognostic factors such as age, KPS status, primary site, histological type, extent of systemic disease, extent of CNS disease, and other factors can assist in defining suitable candidates. A “Graded Prognostic Assessment” that is diagnosis spe-

cific has been described and independently verified for newly diagnosed brain metastases.^{20,24} In this model, primary disease significantly influences outcome. Survival is greater for patients with breast cancer compared with other primary sites (11.9 vs 6.7 months median survival), and importantly, the number of brain metastases does not predict survival as noted for other histological types. In our analysis, the only variable that approached significance was breast cancer histological type, and although only 14% of all other patients survived longer than 1 year, > 40% of patients with metastatic breast cancer survived more than 1 year. Sperduto et al.²¹ reported on risk grouping among women with breast cancer and brain metastases that was based on hormone receptor status as well as Her2-neu and predicted median survival between 9.1 and 26.8 months. Our cohort is too small for such an analysis, however, and although these criteria were developed for patients with newly diagnosed brain metastases, they may be helpful for predicting survival in patients with multiple recurrent brain metastases as well.

This study has all the limitations previously described for small, nonrandomized retrospective reports. In addition, most of the patients included had low-volume disease, with the majority of lesions only identified on high-resolution, double-contrast MRI sequences. Thus, the results presented here may not be extrapolated to patients with high-volume disease. Distant CNS failure is the main limitation to this approach, yet recent data suggest that stereotactic MRI improves detection of subclinical disease and might reduce the development of regional failure.⁷ Last, patients with metastatic disease are a diverse group and the outcomes of aggressive local treatment undoubtedly vary as a result of multiple confounding factors specific to the individual. Each case therefore requires careful consideration of patient characteristics to develop an appropriate care plan.

Conclusions

We show that patients with extensive CNS metastatic disease (≥ 10 lesions) can be safely treated with SRS and achieve long-term local control. Regional recurrence occurs within months, limiting this approach for de novo treatment where WBRT may be appropriate. However, in

TABLE 3: Influence of factors on time to CNS recurrence determined using a univariate log-rank risk analysis

Characteristic	Median Time to CNS Recurrence (mos)	p Value
sex		
M	1.6	0.004
F	4.5	
histological type		
breast	4.7	0.089
other	3.0	
age in yrs		
≤ 65	3.3	0.220
> 65	2.7	
initial WBRT		
yes	4.9	0.511
no	3.2	
metastatic disease		
controlled	3.3	0.477
uncontrolled	3.4	
no. of lesions on diagnostic MRI		
< 10	3.3	0.995
≥ 10	3.2	
no. of lesions on GK-SRS planning MRI		
10–15	3.2	0.320
16–20	3.3	
> 20	8.4	

patients with recurrence after prior WBRT, salvage SRS for ≥ 10 CNS metastases should be considered in well-selected patients because modest survival can be achieved. In particular, a subset of patients with a primary breast lesion can experience prolonged survival beyond 1 year, making them more likely to benefit from SRS from the perspective of improved local control and reduced likelihood of developing late radiation effects associated with repeat WBRT.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in the paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Rava, Hepel. Acquisition of data: Rava, Leonard, Sioshansi. Analysis and interpretation of data: Rava, Leonard, Sioshansi, Norén, Hepel. Drafting the article: Rava, Leonard, Sioshansi, Wazer, Cosgrove, Norén, Hepel. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Rava. Statistical analysis: Rava, Leonard. Administrative/technical/material support: Curran, Wazer, Norén, Hepel. Study supervision: Hepel.

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