Predictors of Survival, Neurologic Death, Local Failure, and Distant Failure After Gamma Knife Radiosurgery for Melanoma Brain Metastases

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Key words
- Brain metastasis
- Gamma knife
- Hemorrhage
- Melanoma
- Neurologic death
- Stereotactic radiosurgery

Abbreviations and Acronyms
DBF: Distant brain failure
GK: Gamma Knife radiosurgery
LBF: Local brain failure
OS: Overall survival
RPA: Recursive partitioning analysis
WBRT: Whole-brain radiotherapy

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Citation: World Neurosurg. (2014).
http://dx.doi.org/10.1016/j.wneu.2013.02.025

Journal homepage: www.WORLDNEUROSURGERY.org

Available online: www.sciencedirect.com

OBJECTIVE: **This study sought to assess clinical outcomes in patients receiving gamma knife radiosurgery (GK) for treatment of brain metastases from melanoma and evaluate for potential predictive factors.**

METHODS: **We reviewed 188 GK procedures in 129 consecutive patients that were treated for brain metastases from melanoma. The population consisted of 84 males and 45 females with a median age of 57 years. Fifty-five patients (43%) had a single metastasis. Seventy-one patients (55%) received chemotherapy, 58 patients (45%) received biologic agents, and 36 patients (28%) received prior whole brain radiation therapy (WBRT). The median marginal dose was 18.8 Gy (range 12 to 24 Gy).**

RESULTS: **Actuarial survival was 52%, 26%, and 13% at 6, 12, and 24 months, respectively. The median survival time was 6.7 months. Local tumor control was 95%, 81% 53% at 6, 12, and 24 months, respectively. The median time to LBF was 25.2 months. Freedom from distant brain failure was 40%, 29%, and 10% at 6, 12, and 24 months, and the median time to DBF was 4.6 months. At the time of data analysis, 108 patients (84%) had died. Fifty-eight patients (52%) died from neurologic death. The median time to neurologic death from GK treatment was 7.9 months. Multivariate analysis revealed that hemorrhage of metastases prior to GK ($P = .02$) and LBF ($P = .03$) were the dominant predictors of neurologic death.**

CONCLUSIONS: **GK achieves excellent local control and may improve outcomes as a component of a multidisciplinary treatment strategy. Distant brain failure and neurologic demise remain problematic and prospective trials are necessary.**

INTRODUCTION

Melanoma is the third most common cancer to metastasize to the brain (12, 22) and brain metastases from melanoma contribute significantly to death and reduction in quality of life in this patient population (3, 25). Current treatment options are insufficient; the median survival with treatment is typically less than 1 year after the development of brain metastases, and patients commonly die of brain metastases.

Controversy has arisen regarding the optimal management of patients with brain metastases from melanoma. Although local control rates are high for melanoma brain metastases treated with radiosurgery (9), melanoma histology has been identified as one of the major risk factors for distant brain failure (DBF) after primary radiosurgical management of brain metastases (26). However, whole-brain radiotherapy (WBRT) yields suboptimal results, in part secondary to subsets of radioresistant phenotypes (2, 4). Further adding to the clinical dilemma is the fact that several classes of novel treatment strategies have evolved over time, including immunotherapy (11, 13), BRAF inhibitor therapy (19), and cytotoxic chemotherapy that penetrates the blood-brain barrier (8, 19). It is unclear what effect these agents have had on the natural history of melanoma brain metastases, although recent literature suggests that systemic agents may alter the natural history of disease of brain metastases (8, 18).

The purpose of this study is to review our series of patients with melanoma brain metastases treated with gamma knife radiosurgery (GK) to assess survival data, local brain failure (LBF), and DBF. We have focused on prognostic factors for dying of neurologic death because this end point provides a measure of the efficacy of central nervous system–directed therapies.

METHODS

Data Acquisition

This study was approved by the Wake Forest University Institutional Review Board. The Wake Forest University Medical Center Department of Radiation

Oncology Gamma Knife Tumor Registry was searched for all patients who underwent GK and had a diagnosis of melanoma. One hundred twenty-nine patients with melanoma were identified who were treated with GK between April 2000 and July 2009 at Wake Forest University Baptist Medical Center in Winston-Salem, North Carolina. Patient outcomes were determined using the patients' electronic medical records.

Patient characteristics are summarized in Table 1. Patient factors such as age, recursive partitioning analysis (RPA) class, status of extracranial metastatic disease, and previous systemic therapeutic regimens were determined from patients' electronic medical records. The RPA class was defined per the Radiation Therapy Oncology Group analysis reported by Gaspar et al. (20). The status of extracranial metastatic disease was reported as none, oligometastatic, or widespread. Oligometastatic disease was defined as 5 or fewer nonbrain metastases.

Table 1. Patient Characteristics

Total patients	129
Male/female ratio	84:45
Median age (years)	57.0
Median interval from primary to brain metastasis (months)	28.6
Brain metastases at presentation (number, %)	
1 lesion	55 (43)
2–4 lesions	53 (41)
>4 lesions	14 (16)
Location of metastases (number, %)	
Supratentorial	123 (95)
Infratentorial	39 (30)
Brainstem	12 (9)
Disease status at first gamma knife radiosurgery (number, %)	
None	15 (12)
Oligometastatic	45 (35)
Widespread	69 (53)
Karnofsky Performance Status class (number, %)	
60	7 (5)
70	17 (13)
80	85 (66)
90	16 (12)
100	4 (3)
Recursive partitioning analysis class (number, %)	
I	10 (8)
II	111 (87)
III	7 (5)

Gamma Knife Procedures

Radiosurgery was performed on the Leksell Gamma Knife model, B, C, or Perfexion (Elekta AB, Stockholm, Sweden). A total of 188 GK procedures were performed to treat a total of 550 brain metastases. The median number of tumors treated during the first GK session was 2. Eighty-five patients (66%) had only 1 gamma knife session, whereas 44 patients (34%) had multiple procedures.

The decision to treat melanoma brain metastases was made by a multidisciplinary team consisting of medical oncologists, radiation oncologists, and neurosurgeons. An individualized therapeutic plan was formulated based on a patient's degree of symptoms, extent of brain metastases, and systemic disease status. Melanoma patients with minimally symptomatic oligometastatic central nervous system disease generally received GK initially. When melanoma lesions were resected initially, GK treatment to the resection cavity routinely followed. GK was used as a salvage therapy for DBF after initial surgical resection, GK, or WBRT. GK was also offered in select cases as a boost after WBRT.

The Gamma Plan treatment planning system (Elekta AB, Stockholm, Sweden) was used to develop a conformal treatment plan with a median marginal dose of 18.8 Gy (range 12 to 24 Gy). The dose selected was based on the lesion size and volume as previously described by Shaw et al. (27). Table 2 summarizes GK treatment data.

Patient Follow-Up

Follow-up assessments were typically conducted at 4 to 6 weeks after GK treatment, and subsequently every 3 months for the first year. In cases with intracranial progression of disease after GK treatment, additional GK treatment was often offered if patients had previously received WBRT or if patients without previous WBRT did not experience early or numerous (>4) DBF.

Time intervals that were recorded include time to local failure, distant failure, and death. Neurologic death was defined as previously described by Patchell et al. in patients who had stable systemic disease and progressive neurologic dysfunction or if they had both advancing systemic and neurologic function simultaneously (23).

Local failure was defined as either a pathologically proven recurrence of melanoma within the GK treatment field or a combination of imaging and clinical characteristics of local treatment failure. Patients with suspected treatment failure were generally followed up with serial imaging and treated conservatively with either steroid therapy or a combination of vitamin E and pentoxifylline before determination of a treatment failure. Imaging characteristics of treatment failure included serial increases in size of enhancement and/or increased perfusion on perfusion-weighted imaging. Hemorrhage was detected using signal patterns on T2- and T1-weighted MRI sequences, and on