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Stereotactic radiosurgery using the Leksell Gamma Knife Perfexion unit in the management of patients with 10 or more brain metastases

Clinical article

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Object. To better establish the role of stereotactic radiosurgery (SRS) in treating patients with 10 or more intracranial metastases, the authors assessed clinical outcomes and identified prognostic factors associated with survival and tumor control in patients who underwent radiosurgery using the Leksell Gamma Knife Perfexion (LGK PFX) unit.

Methods. The authors retrospectively reviewed data in all patients who had undergone LGK PFX surgery to treat 10 or more brain metastases in a single session at the University of Pittsburgh. Posttreatment imaging studies were used to assess tumor response, and patient records were reviewed for clinical follow-up data. All data were collected by a neurosurgeon who had not participated in patient care.

Results. Sixty-one patients with 10 or more brain metastases underwent SRS for the treatment of 806 tumors (mean 13.2 lesions). Seven patients (11.5%) had no previous therapy. Stereotactic radiosurgery was the sole prior treatment modality in 8 patients (13.1%), 22 (36.1%) underwent whole-brain radiation therapy (WBRT) only, and 16 (26.2%) had prior SRS and WBRT. The total treated tumor volume ranged from 0.14 to 40.21 cm^3, and the median radiation dose to the tumor margin was 16 Gy. The median survival following SRS for 10 or more brain metastases was 4 months, with improved survival in patients with fewer than 14 brain metastases, a nonmelanomatous primary tumor, controlled systemic disease, a better Karnofsky Performance Scale score, and a lower recursive partitioning analysis (RPA) class. Prior cerebral treatment did not influence survival. The median survival for a patient with fewer than 14 brain metastases, a nonmelanomatous primary tumor, and controlled systemic disease was 21.0 months. Sustained local tumor control was achieved in 81% of patients. Prior WBRT predicted the development of new adverse radiation effects.

Conclusions. Stereotactic radiosurgery safely and effectively treats intracranial disease with a high rate of local control in patients with 10 or more brain metastases. In patients with fewer metastases, a nonmelanomatous primary lesion, controlled systemic disease, and a low RPA class, SRS may be most valuable. In selected patients, it can be considered as first-line treatment.
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Key Words • **stereotactic radiosurgery** • **Gamma Knife surgery** • **brain metastasis** • **morbidity**

Cerebral metastases occur in 20%–40% of cancer patients.[23] Each year in the US, metastatic cancer to the brain is diagnosed in more than an estimated 200,000 individuals, with the majority of patients having multiple brain metastases on presentation.[24] The prognosis in these patients is poor: survival data indicate that without treatment of the intracranial disease, median life expectancy is limited,[8,17] although it does increase to 4–6 months on average with the addition of WBRT.[4,9] For decades, the management of brain metastases was predicated on either WBRT or resection of symptomatic, surgically accessible lesions followed by WBRT. In recent years, SRS has emerged as a minimally invasive adjunct or potential alternative to resection plus WBRT for addressing intracerebral metastatic disease. Previous studies, most evaluating patients with 1–4 brain tumors

Abbreviations used in this paper: GKS = Gamma Knife surgery; KPS = Karnofsky Performance Scale; LGK = Leksell Gamma Knife; PFX = Perfexion; RPA = recursive partitioning analysis; RTOG = Radiation Therapy Oncology Group; SRS = stereotactic radiosurgery; WBRT = whole-brain radiation therapy.

each, have indicated that radiosurgery affords excellent local tumor control and prolonged survival in some patients.[1,2,13,18] Management options for patients with 10 or more tumors are controversial and usually associated with futility. The new LGK PFX unit allows efficient treatment of large numbers of tumors in a single outpatient procedure. To better understand the factors that influence patient survival and tumor control, we reviewed our experience with the use of the LGK PFX unit to care for patients with 10 or more brain metastases.

Methods

Data Collection

With approval from the University of Pittsburgh Institutional Review Board, we retrospectively reviewed prospectively collected data on all patients who had undergone SRS with the LGK PFX unit to treat 10 or more brain metastases in a single session at the University of Pittsburgh. Posttreatment imaging studies were used to assess tumor response. Patient records were reviewed for clinical follow-up data. The Social Security Death Index was used to obtain survival data when the information was not available from our records. When no autopsy information was available, the presumed cause of death (neurological vs systemic) was established based on a review of the electronic medical records, as well as the clinical progression of the patient's disease and the imaging findings at the last follow-up appointment. Data were collected by a neurosurgeon who had not participated in patient care.

Statistical Analysis

Statistical analysis was performed using SPSS 17 software (SPSS, Inc.). Kaplan-Meier analyses were performed to assess survival as well as freedom from local and distant failure after undergoing radiosurgery via the LGK PFX unit. Patient censoring occurred at the time of the last clinical follow-up for estimating survival time and at the time of the last radiological assessment for estimating local and distant control. An acceptable Type I error was set a priori at $\alpha = 0.05$ for all statistical tests. When dichotomizing continuous covariates, it is customary to code them based on the mean of the sample—in our case, 13.2. Thus, we a priori split the covariate for statistical analysis at 14 tumors, as this was the next highest integer. Univariate analyses were done using the log-rank test, and stepwise forward conditional multivariate analyses were performed with the Cox proportional hazards model to assess the prognostic value of different variables relative to survival, local tumor control, and distant treatment failure.

Results

Patient Population

Between October 2007 and June 2009, 61 patients underwent SRS using the LGK PFX unit for single-session treatment of 10 or more cerebral metastases. Patients are generally referred to our group for GKS after WBRT has failed or for up-front SRS. These patients are evaluated and undergo SRS if they can tolerate the procedure, if they do not have miliary disease that necessitates WBRT, or if they do not require craniotomy for a large symptomatic tumor. Sometimes during follow-up we identify patients with new metastases following SRS, and we advocate salvage SRS in such cases. The current study population consisted of 27 females (44.3%) and 34 males (55.7%) who varied in age from 34 to 79 years (median 60 years). The mean interval from primary diagnosis to the diagnosis of brain metastases was 49 months (range 0–26.7 years). In 17 patients (27.9%), the metastatic disease was asymptomatic and identified on staging imaging studies. Eight patients (13.1%) presented with seizures, 4 (6.6%) with a tumoral hemorrhage, and 32 (52.5%) with symptoms attributable to focal tumor mass effect.

Previous extracranial disease management involved surgery in 40 patients (65.6%), chemotherapy in 54 patients (88.5%), and local extracranial radiation therapy in 25 patients (41.0%). Previous intracranial therapies included SRS as the sole treatment modality in 8 patients (13.1%), WBRT alone in 22 patients (36.1%), and SRS plus WBRT in 16 patients (26.2%). Craniotomies were performed in 8 patients (13.1%): 3 individuals underwent resection of a single symptomatic, hemorrhagic melanoma metastasis, which had been previously treated with SRS; 2 patients had tumor excisions along with subsequent WBRT; 1 patient underwent removal of a primitive neuroectodermal tumor and then numerous SRS treatments and a course of WBRT; and 2 patients underwent tumor debulking without further therapy. Seven patients (11.5%) received no previous cerebral therapy.

At the time of LGK PFX surgery, 29 patients (47.5%) were asymptomatic, 11 (18.0%) experienced headaches only, 2 (3.3%) had seizures only, 18 (29.5%) presented with focal neurological deficits, and 1 (1.6%) demonstrated only a cognitive disturbance. Cognitive dysfunction was seen in 5 patients (8.2%) at the time of GKS. The median KPS score was 90 (range 50–100). Per evaluation by the referring oncologist, systemic disease status was considered active in 48 individuals (78.7%) and controlled in 13 (21.3%). When stratified according to the RPA classification devised by the RTOG, 8 patients (13.1%) were in Class I, 46 (75.4%) in Class II, and 7 (11.5%) in Class III. Table 1 further summarizes the presentation characteristics of the patient population.

Radiosurgery Procedures

After administering conscious sedation and local anesthesia, a Leksell G frame (Elekta AB) was applied to each patient's head. Magnetic resonance imaging studies of the entire head using 2-mm-thick axial spoiled gradient recalled acquisition in the steady state sequences with double-dose Gd contrast and long-repetition-time sequences were performed. At times, this approach revealed numerous additional metastatic foci that were not visible on the patient's recent diagnostic images from which a referral had been made.

A multidisciplinary team consisting of the attending neurosurgeon, radiation oncologist, and medical physicist designed the dose plans. Using GammaPlan software

TABLE 1: Summary of demographic and clinical data at presentation in 61 patients

Variable	No. (%)
sex	
M	27 (44.3)
F	34 (55.7)
primary histology	
melanoma	19 (31.2)
non–small cell lung cancer	18 (29.5)
breast cancer	15 (24.6)
small cell lung cancer	5 (8.2)
other	4 (6.6)
cerebral presentation prompting radiosurgical intervention	
staging imaging	17 (27.9)
seizure	8 (13.1)
tumoral hemorrhage	4 (6.6)
mass effect	21 (34.4)
headache	11 (18.0)
previous cerebral therapy	
WBRT only	22 (36.1)
SRS only	8 (13.1)
WBRT & SRS	16 (26.2)
craniotomy w/ or w/o WBRT or SRS	8 (13.1)
none	7 (11.5)
extent of systemic disease	
CNS only	3 (4.9)
primary site only	1 (1.6)
primary site & 1 lymph node chain	11 (18.0)
primary site & >1 lymph node chain or visceral metastases	9 (14.8)
disseminated (>2 visceral sites)	37 (60.7)
systemic disease status	
active	48 (78.7)
controlled	13 (22.3)
main neurological symptoms at radiosurgery	
asymptomatic	29 (47.5)
headaches only	11 (18.0)
seizures only	2 (3.3)
focal deficits	18 (29.5)
cognitive deficits	1 (1.6)
KPS score	
90–100	47 (77.0)
≤80	14 (23.0)
RPA class	
I	8 (13.1)
II	46 (75.4)
III	7 (11.5)

(Elekta AB), the team designed a plan that closely conformed to the shape of the tumor. Dosimetry data on each patient were calculated after obtaining averages based on the number of tumors irradiated. The overall mean prescription isodose delivered to the tumor margin varied from 50% to 86% (median 74%). The median radiation dose delivered to the tumor margin was 16 Gy (mean 16.5 Gy, range 12–20 Gy). The exact dose administered was based on tumor size and location and whether the patient had a history of prior brain radiation therapy. The median target volume was 0.37 cm^3 (mean 0.64 cm^3, range 0.01–2.87 cm^3), and the total tumor volume treated varied from 0.14 to 40.21 cm^3 (median 4.86 cm^3, mean 8.05 cm^3). The median volume of tissue receiving 12 Gy was 16.9 cm^3 (mean 20.9 cm^3, range 1.3–112 cm^3). The robotic LGK PFX unit typically allows all tumors to be treated in one run. Should the patient desire a break or require assistance, the radiation session can be paused.

Sixty-three radiosurgical procedures were performed to treat 806 tumors. Two patients underwent staged procedures in which roughly half of the tumors were irradiated in one session, with the remaining lesions addressed in another procedure within 1–2 weeks of the initial session. A mean of 13.2 brain metastases were irradiated per patient (range 10–28 tumors). Six hundred one tumors (74.6%) were located in the cerebral hemispheres, 35 (4.3%) in the deep supratentorial structures (thalamus, basal ganglia, and corpus callosum), 143 (17.7%) in the cerebellum, and 27 (3.3%) in the brainstem.

The first clinical and imaging follow-up assessments were scheduled for 8 weeks posttreatment (earlier if a new symptom developed), and continued evaluation was conducted every 3 months for the 1st year after treatment, with further assessment dictated by each patient's clinical status. The radiological criteria determining the tumor response were based on the Response Evaluation Criteria in Solid Tumors (RECIST): progression was characterized as the sum of the diameters of the lesion increasing by more than 20% as compared with its size at the time of PFX treatment, partial response as more than a 30% reduction in the size of the lesion, complete response as disappearance of the target lesion, and stable disease as a lesion remaining within 70%–120% of its initial size. In addition to the patients with an increased tumor size, those needing additional intervention for a previously irradiated lesion because of worsening symptoms were classified as having progression, even without a change in lesion size.

Patient Survival

At the time of analysis, 50 patients were dead and 11 were alive. The median survival after LGK PFX surgery for 10 or more brain metastases was 4 months (mean 6.6 months, range 0.25–24 months). The median survival was 14 months (mean 19.6 months, range 2–209 months) from diagnosis of the brain metastases and 34 months (mean 68.4 months, range 5–322 months) from initial diagnosis of the primary tumor. Actuarial survival rates were 55.7% at 3 months, 39.3% at 6 months, and 22.4% at 12 months after radiosurgery with the PFX unit (Fig. 1). Twelve patients (24%) died as a result of intracranial disease progression, and 38 (76%) because of systemic disease progression.

Univariate analysis demonstrated that a longer survival time was significantly associated with fewer than 14

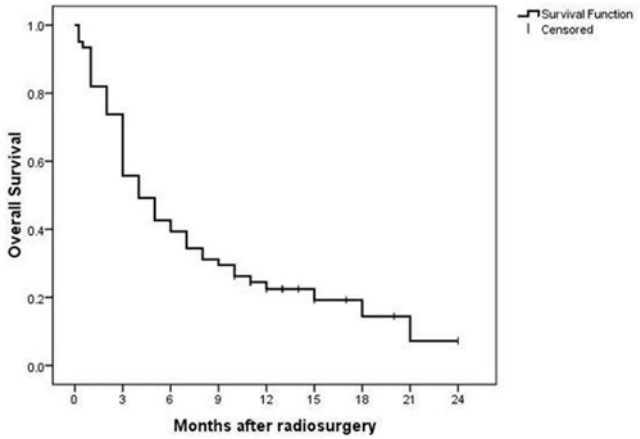

Fig. 1. Kaplan-Meier plot showing overall survival after radiosurgery.

brain metastases (p = 0.02), a nonmelanomatous primary disease diagnosis (p = 0.01), controlled systemic disease (p = 0.008), a KPS score ≥ 90% (p < 0.001), and a lower RPA class (p = 0.001; Table 2). Multivariate analysis confirmed the independent negative prognostic significance of having 14 or more brain metastases (HR 2.51, p = 0.03), melanoma (HR 4.04, p = 0.009), active systemic disease (HR 2.75, p = 0.04), and a higher RPA class (HR 2.65, p = 0.02) on patients' survival. There was no difference in survival among patients treated with LGK PFX as the primary procedure for intracranial disease as compared with patients who underwent LGK PFX as a salvage treatment after failed therapy. Prior WBRT was not a significant predictor of survival.

The median survival after LGK PFX treatment was 3 months in patients with 14 or more brain metastases, as compared with 6 months in those with fewer than 14 tumors (p = 0.02, log-rank test). Actuarial survival rates among those with a higher intracranial disease burden (≥ 14 metastases) was 33.3% at 3 months, 19.0% at 6 months, and 9.5% at 12 months, whereas the rates were 67.5%, 50.0%, and 29.4%, respectively, in patients treated for fewer metastases (Fig. 2). When patients were grouped according to tumor type, the median survival from LGK PFX treatment was 3 months for those with malignant melanoma and 5 months for those with other primary tumors (p = 0.01, log-rank test). Individuals with controlled extracranial disease exhibited a median survival of 18 months after undergoing treatment, in contrast to a 3-month median survival in patients with active disease (p = 0.008, log-rank test). Finally, the median survival in patients with an RPA Class I was 21 months after radiosurgery—a notable disparity over the 4-month median survival for patients with an RPA Class II and the 1-month median survival in patients with an RPA Class III. Actuarial survival rates among key subsets of the study population are displayed in Figs. 2–5.

Among individuals who died because of intracranial disease progression, the only significant prognostic factor associated with the duration of survival was total radiosurgery volume (p = 0.04). The median calculated survival in a patient with fewer than 14 brain metastases,

TABLE 2: Univariate and multivariate analyses of survival after radiosurgery via the LGK PFX unit to treat 10 or more brain metastases

Variable	Univariate p Value	Multivariate p Value	Hazard Ratio (95% CI*)
age	0.32	0.15	
sex	0.65	0.8	
interval from primary diagnosis to brain metastasis diagnosis	0.51	0.82	
presence of ≥14 brain metastases	0.02	0.03	2.51 (1.07–5.87)
melanoma vs other primary tumor type	0.01	0.009	4.04 (1.41–11.57)
prior cerebral treatment (any method)	0.24	0.81	
WBRT as part of prior cerebral treatment	0.67	0.08	
systemic disease status	0.008	0.04	2.75 (1.34–6.88)
extent of systemic disease	0.07	0.7	1.89 (0.94–3.79)
neurological status at time of PFX surgery (asymptomatic vs all others)	0.25	0.65	
neurological deficit at time of PFX surgery	0.75	0.75	
cognitive dysfunction at time of PFX surgery	0.48	0.48	
KPS score	<0.001	0.5	0.3 (0.16–0.58)
higher RPA class	0.001	0.02	2.65 (1.70–6.11)
total radiosurgery vol	0.38	0.59	
radiosurgery vol ≥8 cm^3	0.58	0.58	
presence of deep cerebral metastases	0.06	0.99	
presence of cerebellar metastases	0.31	0.32	
presence of brainstem metastases	0.84	0.45	

* Relative risk.

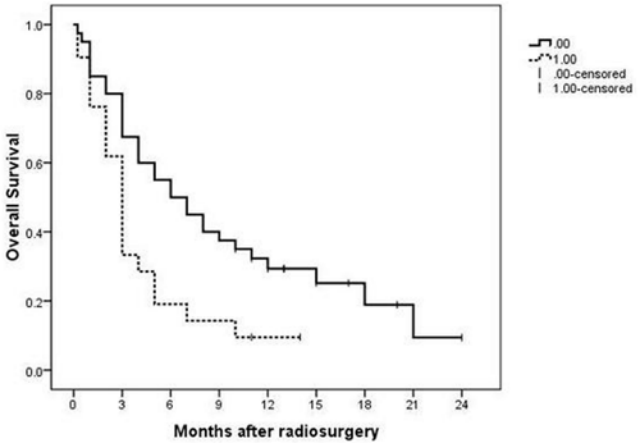

Fig. 2. Kaplan-Meier plot showing overall survival after radiosurgery according to the number of brain metastases. Patients with fewer than 14 brain metastases had significantly longer survivals after radiosurgery (p = 0.03).

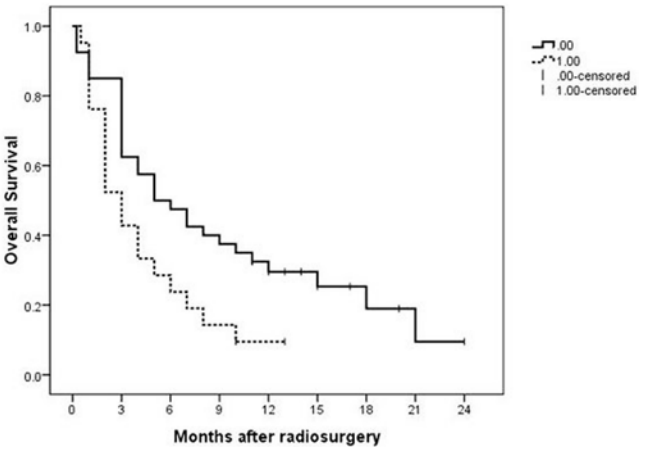

Fig. 3. Kaplan-Meier plot showing overall survival after radiosurgery according to tumor type. Patients with a primary tumor type other than melanoma had significantly longer survival after radiosurgery (p = 0.009).

a nonmelanomatous primary lesion, and controlled systemic disease was 21 months.

Freedom From Local Progression

Follow-up imaging studies were available for 49 individuals (80.3% of the study population) harboring 653 tumors; 12 patients had no imaging follow-up because they died relatively soon (median 1 month) after undergoing LGK PFX surgery. The median imaging follow-up interval was 4 months (mean 5.4 months, range 0.25–17 months). The LGK PFX procedure was successful in achieving local tumor control in 95.1% of the (653) tumors; 40 patients (81.6%) had no further progression of their treated intracranial metastases. The median time to progression of local metastatic disease was 9 months (mean 8 months, range 3–14 months). Among all patients with follow-up imaging, actuarial freedom from local tumor progression was 94.1% at 3 months after LGK PFX surgery, 90.5% at 6 months, and 58.3% at 12 months (Fig. 6). There were no significant predictors of local treatment failure. No differences were seen in the local control rates between patients whose brain metastases were managed with LGK PFX surgery as the primary treatment and those who underwent radiosurgery as a salvage treatment after previous failed therapy. Previous WBRT treatment had no influence on local tumor control following radiosurgery.

Freedom From Distant Progression

New brain metastases were seen in 28 (57%) of the 49 patients on follow-up imaging. Over 80% of the patients with new brain metastases exhibited no symptoms from disease progression; the new brain metastases were detected during the standard radiological follow-up assessment. The median time for patients to present with remote brain metastases after undergoing LGK PFX treatment for 10 or more brain metastases was 3 months (mean 5 months, range 1–14 months). Actuarial freedom from distant treatment failure was 64.6% at 3 months after LGK PFX surgery, 58.5% at 6 months, and 22.4% at 12 months (Fig. 7). Seventy-one percent of the patients with new remote brain disease underwent additional radiosurgery. Multivariate analysis demonstrated the independent prognostic significance of having 14 or more brain metastases (HR 3.14, p = 0.03, log-rank test) and melanoma (HR 4.84, p = 0.019, log-rank test) in distant tumor progression. There were no differences in distant tumor control rates for patients whose brain metastases were managed with LGK PFX surgery as the primary treatment as compared with patients who underwent radiosurgery as a salvage treatment after previous failed therapy. There was no association between distant tumor control and no prior WBRT.

The median freedom from distant progression after LGK PFX treatment was 3 months in patients with 14 or more brain metastases, as compared with 9 months for those with fewer than 14 tumors (p = 0.01, log-rank test). After stratification based on tumor type, the median sur-

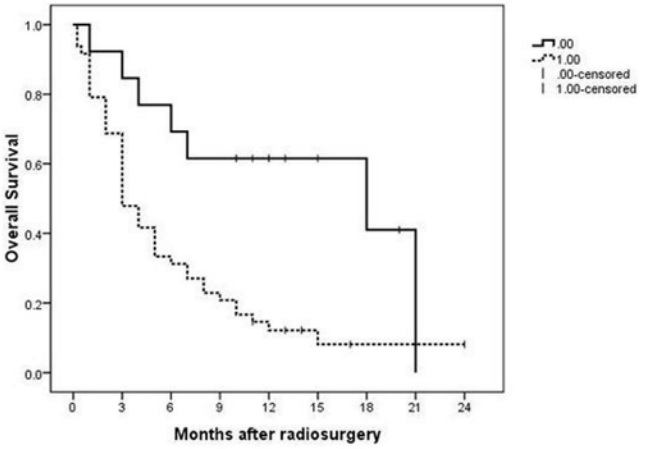

Fig. 4. Kaplan-Meier plot showing overall survival after radiosurgery according to extracranial disease status. Patients with controlled extracranial disease had significantly longer survival after radiosurgery (p = 0.04).

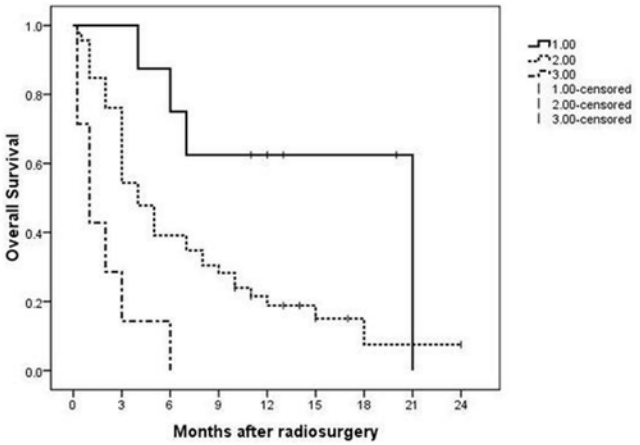

Fig. 5. Kaplan-Meier plot showing overall survival after radiosurgery according to RPA classification. Patients with a lower RPA class had significantly longer survival after radiosurgery (p = 0.02).

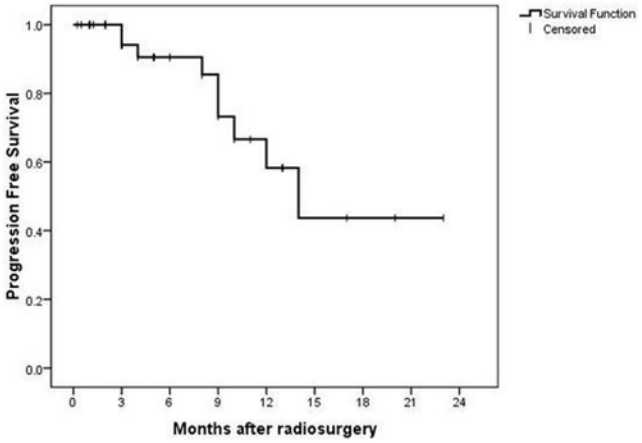

Fig. 6. Kaplan-Meier plot showing freedom from local tumor progression after radiosurgery.

vival from LGK PFX treatment was 3 months for patients with malignant metastatic melanoma; those with other primary lesions had a median survival of 9 months (p = 0.001, log-rank test).

Morbidity and Clinical Outcome

Information regarding clinical status was obtained in all patients. The median clinical follow-up was 4 months after radiosurgery (mean 6.6 months, range 0.25–24 months). Overall, 46 patients (75.4%) had either no change or an improvement in their symptoms after undergoing LGK PFX treatment for 10 or more brain metastases. Of the 32 patients presenting with neurological symptoms, 39% experienced an improvement in symptoms, 27% were stable, and 33% experienced a neurological decline. On subsequent follow-up examinations, 82% remained neurologically stable, with clinical freedom from progression in 91% at 6 months and in 70% at 12 months. Initial clinical response to LGK PFX treatment was a significant predictor of long-term neurological status ($p < 0.001$), as was a presentation KPS score ≥ 90 ($p = 0.002$).

Adverse radiation effects on MR images—seen as changes in long-repetition-time MRI sequences—were noted in 6 patients (10%) at the time of radiosurgery. Imaging evidence of new adverse radiation effects were found during follow-up in 9 patients (18%), only 1 of whom had congruent symptomatology. The total number of metastases, total target volume, volume of brain tissue receiving 12 Gy, and a patient history of some form of cranial radiation treatment did not significantly predict the occurrence of postradiosurgical injury. The only factor that potentially predisposed patients to adverse radiation effects was prior WBRT (p = 0.02, log-rank test). The 1 patient who did experience symptomatic postradiosurgery sequelae presented with 10 metastatic foci in the frontal and temporal lobes as the result of breast cancer. The mean radiation dose that she received to the periphery of her lesions was equivalent to the sample median (16 Gy); she incurred only slightly more than the median 12-Gy tissue volume (21 cm^3 vs the sample median of 16.9 cm^3).

After radiosurgery, 8 patients (13%) acquired a new-onset neurological deficit, a phenomenon that was associated with disease progression in 75% of the patients. The incidence of new neurocognitive dysfunction after LGK PFX surgery was 8% (5 patients); the key predictor of this was a KPS score of 80 or less at the time of treatment (p = 0.05).

Twenty patients (41% of those with imaging follow-up) underwent at least 1 additional radiosurgery procedure for the management of either local disease progression or new brain metastases. Four patients (8%) had WBRT after LGK PFX surgery as a result of the development of new miliary metastatic brain lesions.

Discussion

The efficacy of SRS in patients with an extensive intracranial disease burden (10 or more metastases) has not been fully established. Previous randomized controlled trials on the safety and efficacy of radiosurgery versus other forms of treatment for brain metastases have limited inclusion to patients with solitary or few metastatic foci.[1,2,13] In RTOG 9508, Andrews et al.[1] showed that among patients with good KPS scores, small tumor volumes, and few metastatic foci (1–3 solid tumors), there were significantly improved survival and local control rates for those treated with WBRT plus SRS versus those treated with WBRT alone. In our randomized controlled trial in patients with 2–4 brain metastases that were 2.5 cm or smaller, local disease control was significantly improved with WBRT plus SRS versus SRS alone, and there was a trend toward improved survival in the WBRT plus SRS group.[13] The randomized, controlled multiinstitutional trial by Aoyama et al.[2] compared SRS alone versus WBRT plus SRS. In patients with good KPS scores, small tumor volumes, and 1–4 solid brain metastases, there was no significant difference in median survival between the 2 treatment groups. Within these intent-to-treat analyses, the patients receiving WBRT alone often underwent subsequent radiosurgery. However, the chances for recurrence at a distant site anywhere in the brain was significantly higher in the SRS-alone arm of the trial.

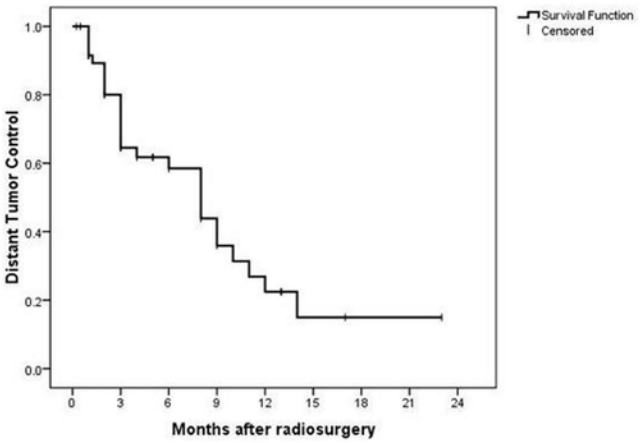

Fig. 7. Kaplan-Meier plot showing freedom from distant brain metastases after radiosurgery.

With close follow-up and salvage SRS, distant recurrence may not have a meaningful impact on outcomes.[14] Taken together, the abundance of evidence confirms the efficacy of SRS for the treatment of select patients with a limited metastatic brain tumor burden.

Whole-brain radiation therapy has been a mainstay of the noninvasive treatment of brain metastases. In contrast to WBRT, SRS typically does not require the use of fractionation schedules (for example, 30 Gy in 10–12 daily fractions). Moreover, WBRT is practically limited to 1 or possibly 2 regimens, whereas SRS can be repeated multiple times.[25] In the current study, including the 2 individuals who underwent staged procedures, all patients received radiation in less than 3 hours and were discharged from the hospital the same day. Intuitively, for patients with limited life expectancies, the shorter the time required to receive and recover from treatment, the better. Moreover, SRS has not been shown to directly lead to a significant decline in learning and memory, as occurs with WBRT.[5] Further, SRS has been shown to have fewer reported side effects, and more patients and their families believe that it is more effective than WBRT.[12] In combination with data demonstrating the safety and efficacy of SRS, concerns over cognitive and quality-of-life difficulties with WBRT have led many investigators to either delay WBRT or exclude it completely from treatment algorithms.

Prior to the current study, there has been a paucity of data on the use of SRS in the treatment of 10 or more brain metastases. Yamamoto et al.[25] calculated the cumulative whole-brain radiation exposure during the treatment of patients with 10 or more radiosurgical targets. The median cumulative whole-brain radiation dose was 4.71 Gy, a dose not above the brain's threshold for necrosis and therefore safe. Serizawa et al.[22] retrospectively compared the efficacy of GKS and WBRT for the treatment of up to 10 brain metastases from non–small cell lung cancer in 96 patients. Sixty-five of these patients (67.7%) had 3 or more brain metastases, and the mean number of lesions treated with SRS, including those treated over the course of the follow-up, was 10.3. The tumor control rate was 94.8% 1 year after therapy. Both the estimated overall survival and estimated intervals free from neurological death were significantly higher in the GKS group (mean survival time 377 days vs 199 days). Univariate analysis revealed that systemic control, treatment method, and pathological composition were prognostic for survival, whereas multivariate analyses confirmed that systemic control and treatment method as well as KPS score were positively prognostic. In a report in which we evaluated radiosurgery for patients with 4 or more metastases, the median overall survival, according to the RTOG RPA classification system, was 18 (Class I), 9 (Class II), and 3 (Class III) months,[3] which proved longer than the historical results for WBRT (7, 4, and 2 months, respectively).[7] Multivariate analysis identified treatment volume, patient age, RPA classification, and tumor margin dose as significant prognostic factors. Treatment volume was the only statistically significant variable associated with local tumor control. Interestingly, the number of metastases was not a significant determinant of either survival or local control.[3] We believe that the cumulative volume of the tumors, and not necessarily their specific number, is probably more important when studying survival. This belief is supported by our present analysis, which demonstrated higher treatment volumes as a negative predictor of survival in patients who died as a result of their intracranial pathology.

In a study of 26 patients with 10 or more brain metastases each, Kim et al.[10] observed an overall median survival of 34 weeks following GKS. Tumor control was 86.9% and 79.5% at 3 and 6 months, respectively, following treatment. On univariate analysis, a synchronous time of discovering brain metastases, a higher KPS score, and controlled primary disease were positive prognostic factors. The use of up-front WBRT, tumor volume, number of metastases, and tumor margin dose had no significant effect on survival. Serizawa et al.[21] reported on GKS in patients with 1–10 brain metastases who had not undergone prophylactic WBRT. Two hundred fifteen of the 778 cases reviewed involved patients harboring 5–10 brain metastases. The mean survival for these patients was 7 months. Significant indicators of a poor prognosis on multivariate analysis included active systemic disease, a KPS score < 70, and male sex.

Our reported survival (4 months median) is somewhat shorter than that cited in the above studies, but we did include patients with higher numbers of tumors and thus increased total tumor volumes. This shorter survival may be attributable to several features of our patient cohort. First, our study contained a high proportion of patients whose primary cancer was melanoma (31.2%), and this cancer is associated with reduced survival given the relatively limited treatment options for extracranial disease. Over 78% of our cohort had active disease at the time of treatment, and in nearly two-thirds of the patients this disease had disseminated to more than 2 visceral sites. Almost one-third of the patients demonstrated focal neurological deficits, and almost one-quarter had a KPS score < 90. Many of these features of our population were borne out in univariate and multivariate analyses, which confirmed that longer survival was associated with controlled systemic disease, nonmelanomatous primary cancer, and a KPS

score ≥ 90. Importantly, the median survival of the patients presented herein is at least in line with the historical results for WBRT (2–7 months),[4,6,11,15,16,19,20,26] especially considering that a substantial proportion of the patients in those cited studies harbored only solitary lesions.[7]

The local tumor control rate of 95.1% and the overall rate of freedom from local tumor progression of 81.2% compare favorably with previously reported results among this patient population.[10] Our actuarial rate of freedom from local progression of 90.5% at 6 months is high but perhaps is attributable to positive prognostic factors such as smaller cumulative tumor volumes and a slightly higher median prescription dose. In addition, individual tumors tended to be smaller in this patient population given that large numbers of larger tumors would have caused a poor neurological condition not suitable for radiosurgery. The overall rate of freedom from progression of 43% and the actuarial rate of freedom from local progression of 64.6% at 3 months, 58.5% at 6 months, and 22.4% at 12 months are lower than those in a previously reported cohort[10] as well as those in the Serizawa et al. study;[21] however, this observation may belie the influence of melanomatous disease and overall number of metastases on distant tumor control, as was demonstrated in our analysis.

In the present study, LGK PFX surgery was well tolerated among patients given that symptomatic adverse radiation effects developed in only 1 patient. While previous cranial radiation—in the form of either WBRT or SRS—did not predict the development of neurocognitive dysfunction after PFX treatment, the recent report by Chang and colleagues[5] does underscore the fact that our sample size may not have been large enough to establish previous radiation therapy as a predictive factor.

Our study has several important limitations. First, as a retrospective series, it is subject to selection bias. It is not unreasonable to suggest that we observed certain outcomes because of the specific makeup of our study population. However, a number of the findings we report have been observed repeatedly: negative prognostic factors of increased tumor volume, melanomatous disease, poor KPS score, lower RPA class, and uncontrolled systemic disease. Moreover, our cohort reflects a patient population that is similar to those documented in large randomized trials comparing WBRT and SRS that have been used by many as the basis for evidence-based clinical practice (Table 3). For example, 77% of our patients had a KPS score of 90–100, a number similar to those reported in RTOG 9508[1] and by Aoyama et al.[2] (approximately 60%). Our RPA class breakdown is similar to that in these 2 studies (RPA Class II of 75% vs 73%[1] and 86%[2]). We did have a larger proportion of patients with active systemic disease, but 24%–40% of such patients were present in the 2 randomized trials cited. Forty-eight percent of our patients possessed asymptomatic brain metastases, right between 37% and 64% for the randomized patients. The heterogeneity of our population (that is, several different tumor histologies, including small cell lung cancer) could have introduced confounding factors that altered our observations; however, this heterogeneity is present in the randomized trials. In the present retrospective study, 94% of the patients had 1 of 4 tumor histologies, which included small cell lung cancer (8%). In the RTOG 9508, 6 major tumor histologies were present, and between 6% and 9% of the patients in the 2 randomized cohorts harbored small cell lung cancer. Although Aoyama et al.[2] did not include patients with small cell lung cancer, patients with 4 major tumor types were included, with some being radiation sensitive (for example, breast) and others radiation resistant (for example, kidney). Thus, although our study is limited in its methodology and requires validation in a prospective randomized fashion, the findings we report are in line with the literature, and the population is consistent with that randomized in our most cited prospective clinical trials.

TABLE 3: Baseline patient characteristics in current study as compared with large randomized clinical trials involving radiosurgery

Baseline Characteristic	% of Cohort		
	Present Study	Andrews et al., 2004	Aoyama et al., 2006
KPS score			
90–100	77	60	59
≤80	23	40	41
RPA class			
I	13	27	14
II	75	73	86
III	12	0	0
systemic disease			
active	78	24	40
stable/controlled	22	76	60
asymptomatic neurological status	48	37	64

Conclusions

Our findings support a role for the use of SRS in treating select patients with extensive intracranial metastatic disease. Gamma Knife surgery, because of its minimal invasiveness and single-fraction approach, may be of particular value in this population given its limited life expectancies.

Disclosure

Drs. Lunsford and Kondziolka are consultants for Elekta AB. Dr. Lunsford holds stock in Elekta AB.

Author contributions to the study and manuscript preparation include the following. Conception and design: Kondziolka, Grandhi, Niranjan, Flickinger, Lunsford. Acquisition of data: Grandhi. Analysis and interpretation of data: Kondziolka, Grandhi, Panczykowski, Monaco, Kano. Drafting the article: Grandhi, Panczykowski, Monaco. 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: Kondziolka. Statistical analysis: Panczykowski, Kano. Administrative/technical/material support: Kano, Niranjan, Flickinger, Lunsford. Study supervision: Grandhi, Lunsford.

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