Radiosurgery in the management of brain metastasis: a retrospective single-center study comparing Gamma Knife and LINAC treatment

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OBJECTIVE The authors present a retrospective analysis of a single-center experience with treatment of brain metastases using Gamma Knife (GK) and linear accelerator (LINAC)-based radiosurgery and compare the results.

METHODS From July 2010 to July 2012, 63 patients with brain metastases were treated with radiosurgery. Among them, 28 (with 83 lesions) were treated with a GK unit and 35 (with 47 lesions) with a LINAC. The primary outcome was local progression-free survival (LPFS), evaluated on a per-lesion basis. The secondary outcome was overall survival (OS), evaluated per patient. Statistical analysis included standard tests and Cox regression with shared-frailty models to account for the within-patient correlation.

RESULTS The mean follow-up period was 11.7 months (median 7.9 months, range 1.7–32 months) for GK and 18.1 months (median 17 months, range 7.5–28.7 months) for LINAC. The median number of lesions per patient was 2.5 (range 1–9) in the GK group and 1 (range 1–3) in the LINAC group ($p < 0.01$, 2-sample t-test). There were more radio-resistant lesions (e.g., melanoma) and more lesions located in functional areas in the GK group. Additional technical reasons for choosing GK instead of LINAC were limitations of LINAC movements, especially if lesions were located in the lower posterior fossa or multiple lesions were close to highly functional areas (e.g., the brainstem), precluding optimal dosimetry with LINAC. The median marginal dose was 24 Gy with GK and 20 Gy with LINAC ($p < 0.01$, 2-sample t-test). For GK, the actuarial LPFS rate at 3, 6, 9, 12, and 17 months was 96.96%, 96.96%, 96.96%, 88.1%, and 81.5%, remaining stable until 32 months. For LINAC the rate at 3, 6, 12, 17, 24, and 33 months was 91.5%, 91.5%, 91.5%, 79.9%, 55.5%, and 17.1% (log-rank $p = 0.03$). In the Cox regression with shared-frailty model, the risk of local progression in the LINAC group was almost twice that of the GK group (HR 1.92, $p > 0.05$). The mean OS was 16.0 months (95% CI 11.2–20.9 months) in the GK group, compared with 20.9 months (95% CI 16.4–25.3 months) in the LINAC group. Univariate and multivariate analysis showed that a lower graded prognostic assessment (GPA) score, noncontrolled systemic status at last radiological assessment, and older age were associated with lower OS; after adjustment of these covariables by Cox regression, the OS was similar in the 2 groups.

CONCLUSIONS In this retrospective study comparing GK and LINAC-based radiosurgery for brain metastases, patients with more severe disease were treated by GK, including those harboring lesions of greater number, of radioresistant type, or in highly functional areas. The risk of local progression for the LINAC group was almost twice that in the GK group, although the difference was not statistically significant. Importantly, the OS rates were similar for the 2 groups, although GK was used in patients with more complex brain metastatic disease and with no other therapeutic alternative.

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KEY WORDS Gamma Knife surgery; brain metastases; linear accelerator; oncology; stereotactic radiosurgery

ABBREVIATIONS GK = Gamma Knife; GPA = graded prognostic assessment; GTV = gross tumor volume; HR = hazard ratio; IQR = interquartile range; KPS = Karnofsky Performance Status; LINAC = linear accelerator; LPFS = local progression-free survival; OS = overall survival; PTV = planning target volume; RPA = recursive partitioning analysis; SIR = score index for radiosurgery; WBRT = whole-brain radiotherapy.

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RADIOSURGERY was invented by the Swedish neurosurgeon Lars Leksell at the beginning of the 1950s¹⁹ and defined as the “delivery of a single, high dose of ionizing radiation to a small and critically located intracranial volume through the intact skull.”¹⁹ The main principle is that the radiation dose is concentrated within the target (conformity) while minimizing the irradiating of the surrounding healthy tissue, due to a very steep gradient (selectivity). Originally, Leksell conceived radiosurgery as a primary tool for functional disorders.^{18,19} In the 1960s, he created the Gamma Knife (GK), a tool for radiosurgery using multiple focusing cobalt-60 sources.¹⁸ Later on, other devices for performing radiosurgery appeared, including gantry-based (e.g., Novalis TX, Brainlab) and robotic (e.g., CyberKnife, Accuray) linear accelerator (LINAC) systems.²⁰ Until recently, the use of radiosurgery has remained an unusual treatment for brain metastases, depending on the medical center and treated pathology. For example, in the US, only 6.1% of 7684 patients treated with radiation therapy within 2 months after the diagnosis of brain metastases from non-small cell lung cancer between 2000 and 2007 were treated with stereotactic radiosurgery.⁹

Brain metastases cause significant morbidity and mortality for patients with cancer and appear in 10%–40% of all cancer patients, after dissemination via the vascular or lymphatic system. There are currently 4 grading systems, allowing estimation of survival for patients with brain metastases: recursive partitioning analysis (RPA),³³ the score index for radiosurgery (SIR),⁴³ the basic score for brain metastases (BSBM),²¹ and the graded prognostic assessment (GPA).^{37,38} In general, they all show that the more advanced the disease is, the worse the prognosis, raising the question of the categories of patients that should benefit the most from radiosurgery for brain metastases.

The increased use of radiosurgery for single and multiple brain metastases raises new technical challenges for optimal treatment delivery and dosimetry (Fig. 1). The current study is a retrospective analysis of a single-center experience in the treatment of brain metastases with either GK or LINAC during a specific time period—the first 2 years after the installation of Leksell Gamma Knife Perfexion (Elekta Instruments AB). The current literature on radiosurgery for brain metastases is sparse and lacking this type of comparative approach. Thus, our study proposes a novel methodology, involving patients treated with more than one method of radiosurgery in the same institution, while comparing long-term results of radiosurgery for brain metastases after treatment with GK, LINAC, or both.

Methods

This study was a single-institution retrospective cohort study. All patients were examined prior to treatment, and an MRI study was performed to confirm the diagnosis of brain metastasis. Follow-up details, both clinical and radiological, were collected during the regular follow-up visits or from the medical records (from the same hospital where the radiosurgical treatment was performed or the related zonal establishments).

This study focuses only on the patients who were treated with GK or LINAC-based radiosurgery either separately or in combination (including GK after LINAC, e.g., in recurrent cases, these being rather exceptional situations) at the Lausanne University Hospital, between July 2010 and July 2012.

Participants

The inclusion criteria were as follows: diagnosis of at least 1 brain metastasis; age of at least 18 years at the time of treatment; radiographic evidence on pretreatment MRI or CT (if MRI was contraindicated) of at least 1 brain metastasis; treatment with either GK or LINAC radiosurgery; a Karnofsky Performance Status (KPS) score $\geq 70\%$ (i.e., able to care for themselves); any primary tumor; radiosurgical treatment date between June 2010 and July 2012; and type of treatment, LINAC or GK or both, clearly noted. Previous surgery or whole-brain radiotherapy (WBRT) was not grounds for exclusion.

The exclusion criteria were tumors measuring more than 3 cm (in largest diameter) and/or having symptomatic mass effect (referred to surgery), a KPS score $< 70\%$, or refusal of therapy.

Recruitment

All patients had been initially evaluated by an oncologist (radiation oncologist and/or medical oncologist). Based on several parameters, such as age, primary tumor, systemic disease status, number of brain metastases and their size, and prognostic scores, they were referred for surgery, WBRT, and/or radiosurgery (either GK or LINAC). Currently, the Swiss Federal Health Care system routinely covers the costs of radiosurgery for brain metastases with LINAC only. Thus, at the time of the study, the use of LINAC-based radiosurgery was considered first, in most cases. Patients were considered and/or referred for GK (usually by the physicists) only in specific situations.

Pretreatment Evaluation

For GK patients, the preoperative assessment included brain MRI and CT with a stereotactic frame, acquired during day of treatment after frame application. Because of the artifacts and distortion issues induced by the frame, MRI was acquired on a Siemens 1.5-T MR scanner. For LINAC patients, brain MRI was performed on the day(s) before the treatment, on a 3-T MRI unit. CT scans were always performed either during the treatment day for patients undergoing GKS, or a few days before treatment for patients undergoing LINAC-based radiosurgery. Additionally, the extent of the disease was evaluated, either by thoracoabdominal CT scan or by PET-CT detailed imaging.

GK Technique

After application of a Leksell Model G stereotactic frame (Elekta Instruments AB) under local anesthesia, all patients underwent stereotactic MRI and CT, for target definition. The MRI sequences used to identify the brain metastases were adapted to the primary tumor and were T2-weighted (axial, 0.5-mm thickness) without contrast, T2* (mainly for melanoma as primary tumor), and T1-

FIG. 1. Illustrative examples of cases treated with GK radiosurgery for brain metastases, including eloquent area location, such as brainstem (**A** and **B**), or motor cortex (**C**), low position in the posterior fossa (**D**), proximity to the optic pathways (**E**), and very close anatomical location (**F**, with additional consistent volumes). Figure is available in color online only.

weighted with and without contrast enhancement (1-mm thickness; 5- to 10-minute pause after injection of gadolinium¹⁷). Bone CT routinely supplemented the neuroimaging investigation to correct for any distortion errors that might be encountered on the MR images.^{32,41} Dosimetry planning was performed using Leksell Gamma Plan (version 10.0, Elekta Instruments AB). The GK radiosurgery treatment was completed using a Leksell Gamma Knife Perfexion system (Elekta Instruments, AB) in all cases. For GK the planning target volume (PTV) was equal to gross tumor volume (GTV).

LINAC Technique

Before LINAC radiosurgery treatment, patients underwent high-resolution MRI with 1-mm-thick contrast-enhanced imaging. Patients were immobilized with a custom-fit Brainlab bivalve-style thermoplastic mask incorporating a bite bar. A high-resolution CT scan was then performed for fiducialization.

Imaging data were transferred and fused via a local area network to a planning workstation running BrainScan software (version 5, Brainlab). These data included anatomical structures at risk, although not targeted, such as the brainstem, optic apparatus, cochlea, and/or others depending on the region to be treated.

Treatment plans were created using forward-planning methods incorporating either dynamic multileaf collimated non-coplanar arcs or circular collimated non-coplanar arcs. A single isocenter per lesion was used for all treatments. For each lesion, the optical tracking system was used for initial patient positioning. Stereoscopic x-ray imaging was then performed, and the results were fused with digitally reconstructed radiographs based on CT imaging via the ExacTrac system (Brainlab). A positioning offset was then calculated. Patient positioning corrections were made for each of 6 degrees of freedom using a robotically actuated couch in concert with the real-time optical tracking system. Treatment was initiated when linear offsets

were no more than 0.5 mm and angular offsets were 1° or less. Treatment time was typically under 20 minutes per lesion. For LINAC, the PTV was equal to the GTV plus 1 mm.

Following completion of dose delivery, patients were released from the mask and discharged home with anti-convulsant and corticosteroid medications where appropriate.

Follow-Up Monitoring

After the treatment of brain metastases, patients were evaluated every 3 months, by the means of neurological examination and 3-T MRI and assessment of systemic disease by the means of total body scan. A radiation or clinical oncologist evaluated the patient and wrote a summary of the follow-up findings; he or she decided about recommendations for additional systemic or local treatment options, if needed.

Definitions of Outcome Measures

The primary outcome measure was local progression-free survival (LPFS, patient alive, no local recurrence on postoperative follow-up MRI); progression was considered treatment failure.

The secondary outcome measure was overall survival (survival until death from any cause).

Covariables included age, sex, primary tumor type, neurological signs and symptoms at the time of diagnosis, treatment method, number of months of follow-up, length of time between the diagnosis of the primary tumor and brain metastasis, prior oncological treatments and/or surgery, previous or previewed WBRT, target volume (individual and global—by addition—in multiple brain metastases), maximum and marginal (at the specific isodose) doses for radiosurgery, the use of radiosurgery as a boost/ or not, and the number, histology, and location of brain metastases (Table 1).

Additionally, the cause of death was determined for all

TABLE 1. Basic demographic data

Characteristic	GK	LINAC	p Value
No. of patients	28	35	
Sex (M:F)	16:12	17:18	>0.05
Mean age in yrs	63	63	>0.05
Follow-up in mos			
Mean	11.7	18.1	
Median	7.9	17	
Range	3–32	7.5–28.7	
Overall survival in mos			
Median	9.7	23.6	>0.05
Range	2–34	1–34	
Single lesion	9	24	
Multiple lesions	19	11	
Total no. of lesions	83	47	
No. of lesions at follow-up	81	36	
No. of lesions/patient			
Median	2.5	1	<0.01
Range	1–9	1–3	
No. of previous ops	10	14	
Same lesion, 1 op	7	12	
Other lesion, 1 op	1	1	
Same lesion, 2 ops	2	1	
No. of ops after RS	5	6	
WBRT before RS	4	3	
GKS after SRS	11	9	
Same lesion	0	3	
Other lesion	7	5	
Same lesion, 2 SRS*	4	1	
Location			
Convexity	50 (60.2%)	39 (83%)	<0.05
Frontal	17	21	
Parietal	8	8	
Temporal	14	3	
Occipital	11	7	
Cerebellum	15 (18.3%)	8 (17%)	
Motor cortex	6 (7%)	0 (0%)	
Basal ganglia	3 (3.6%)	0 (0%)	
Brainstem	1 (1.2%)	0 (0%)	
Skull base	7 (8.4%)	0 (0%)	
Ventricle	1 (1.2%)	0 (0%)	
Histology of primary tumor			
Melanoma	12 (48.8%)	2 (5.7%)	<0.05
Lung	11 (39.3%)	22 (62.9%)	
Renal	2 (7.1%)	1 (2.8%)	
GI tract	2 (7.1%)	2 (5.7%)	
Breast	1 (3.6%)	7 (20%)	
Ovarian	0 (0%)	1 (2.8%)	

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TABLE 1. Basic demographic data

Characteristic	GK	LINAC	p Value
Dosimetry			
Median marginal dose in Gy	24	20	<0.05
Marginal dose range, Gy	12–24	14–24	
Marginal dose distribution			
24 Gy	43 (51.8%)	3 (6.4%)	
22 Gy	7 (8.4%)	0 (0%)	
20 Gy	21 (25.3%)	32 (68.1%)	
18 Gy	8 (9.6%)	10 (21.3%)	
16 Gy	2 (2.4%)	1 (2.1%)	
14 Gy	1 (1.2%)	1 (2.1%)	
12 Gy	1 (1.2%)	0 (0%)	
Isodose (%)			
Median	50	80	
Range	50–80	80–90	
Lesions w/ hemorrhage	8†	1	<0.05

GI = gastrointestinal; GKS = GK surgery; RS = radiosurgery; SRS = stereotactic RS.

* Same lesion previously treated twice by means of SRS.

† Melanoma.

Data Collection

Patients underwent a complete evaluation every 3 months until their death. The multidisciplinary team included general medical doctors in charge of patient care, oncologists (both medical and radiation oncologists), neurosurgeons, and other specialists (depending on the site of primary tumor etc.). All details of follow-up were gathered by M.L. and C.T. for the neurosurgery team, with the help of the radiation oncologists (primarily L.N.) and physicists (for LINAC-treated patients) involved in the patients' care.

Statistical Analyses

All statistical analyses were conducted using STATA version 11 (STATA Corp.) and GraphPad Prism software 5.02 (GraphPad Software Inc.). The primary outcome was LPFS, which was evaluated on a per-lesion basis. As lesions were not independent within the same patient, a Cox regression with shared-frailty model was used to take into account the within-patient correlation.^{12,22,30} For the j th lesion in the i th patient, the hazard is $h_{ij}(t) = h_0(t) \alpha_i \exp(x_{ij}\beta)$, where α_i is the patient-level frailty. The frailties are unobservable positive quantities and are assumed to have mean value of 1 and variance of θ . They are estimated from the data. The estimate of θ is used to measure the degree of within-patient correlation, and the shared-frailty model reduces to a standard Cox model when $\theta = 0$. Results from univariate analyses (Table 2) and likelihood-ratio tests of $H_0: \theta = 0$ showed a significant frailty effect, meaning that the correlation of lesions in the same patient cannot be ignored.

The secondary outcome was the overall survival (OS), evaluated per patient. Data were first described for patients alive or deceased at the time of last follow-up separately. The median and the interquartile range (IQR) and/or full range were reported for continuous variables and

patients. Patients were considered to have died of neurological causes if they had stable systemic disease and progressive neurological dysfunction. The systemic cancer was considered the only cause of death if patients with neurological improvement or stabilization had fatal infections, hemorrhages, or failure of vital organ systems other than the brain.

TABLE 2. Variables with potential influence on local progression-free survival

Variable	HR	p Value	θ	p Value*
Device: LINAC	1.92	0.45	3.2	0.001
Sex: M	1.13	0.88	3.6	<0.001
Age	1.01	0.73	3.99	<0.0001
Marginal dose: ≥ 20 Gy	1.89	0.50	3.7	<0.0001
Max dose: ≥ 20 Gy	0.23	0.34	3.5	<0.0001
Primary tumor: radioresistant (melanoma, esophagus, renal)	2.64	0.29	3.3	<0.0001
GPA index	1.03	0.93	<0.0001	0.5
GPA, n (%)			<0.0001	0.5
2.5–3	0.59	0.41		
3.5–4	1.08	0.91		

* LR test of $\theta = 0$.

the frequencies and percentages for categorical variables. Survival over time was examined using Kaplan-Meier estimates, and differences between groups were tested using the log-rank survival functions test. To identify which factors were associated with survival, a univariable Cox regression analysis was performed. The strength of association was assessed using hazard ratios (HRs) and associated p values. Due to insufficient sample size, no multivariable analysis was performed.

Results

Basic Demographic Data and Follow-Up

From July 2010 to July 2012, 28 patients underwent GK radiosurgery for the treatment of brain metastases (9 patients with single brain metastases and 19 with multiple brain metastases), and 35 underwent LINAC-based radiosurgery (24 patients with single brain metastases and 11 with multiple brain metastases). The mean age was 63 years for both groups. The mean duration of follow-up was 11.7 months for the GK group and 18.1 months for the LINAC group. (For details, please see Table 1.)

Primary Tumor and Number of Lesions

The most common primary tumor types were melanoma (48.4% in the GK group, 2.8% in the LINAC group) and lung cancer (35.5% in the GK group, 62.9% in LINAC group). For other tumor types, see Table 1. The total number of treated lesions was 83 (81 at last follow-up) for the GK group and 47 (36 at last follow-up) for the LINAC group. The median number of lesions per patient was 2.5 (range 1–9) for the GK group and 1 (range 1–3) for the LINAC group ($p < 0.01$, 2-sample t-test).

Anatomical Location

No motor cortex, brainstem, or skull base brain metastases were treated with LINAC. The anatomical locations of treated metastases were as follows, for GK and LINAC treatment, respectively: convexity, 50 (60.2%) versus 39 (83%); cerebellum, 15 (28.3%) versus 8 (17%); motor cortex, 6 (7%) versus 0 (0%); basal ganglia, 3 (3.5%) versus

0 (0%); brainstem, 1 (1.2%) versus 0 (0%); skull base, 7 (8.4%) versus 0 (0%); and ventricle, 1 (1.2%) versus 0 (0%).

Other Treatments

Seven patients had WBRT before radiosurgery (4 in the GK group and 3 in the LINAC group); 13 patients had WBRT after radiosurgery (8 in the GK group and 5 in the LINAC group). With respect to repeat radiosurgery, analyzed on a per-lesion basis, 11 of the lesions in the GK group were in patients who had previously undergone GK treatment; in 4 instances, the current treatment was delivered to the lesion that had been previously treated (same lesion) and in 7 instances the previous treatment had been delivered to a different lesion. In the LINAC group, 9 lesions had been previously treated with radiosurgery. In 1 instance the lesion had been treated twice previously. In the other 8 instances, the patients had previously received radiosurgical treatment for a different lesion (5 lesions) or were undergoing LINAC-based radiosurgery for a lesion that had been previously treated with radiosurgery only once (3 lesions).

Target Volume and Dose and Isodose Prescriptions

The mean radiosurgical GTV was 2.65 cm³ in the GK group compared with 3.33 cm³ in the LINAC group. The median marginal dose prescription was 24 Gy in GK (range 12–24 Gy at the median 50% isodose line [range 50%–80%]) compared with 20 Gy in LINAC (range 14–24 at the median 80% isodose line [range 80%–90%]) ($p < 0.01$, 2-sample t-test). The mean marginal dose was 24 Gy in the GK group and 20 Gy in the LINAC group. Details of the marginal dose distribution are provided in Table 1.

Local Progression-Free Survival

At last follow-up, local progression (treatment failure) was observed in a total of 25 of 130 lesions, 18 in the LINAC group and 7 in the GK group. For GK, the actuarial LPFS rates were as follows: at 3, 6, 9, 12, 15, 18, 21, 24, 30, and 33 months, respectively, the rates were 96.9%, 96.9%, 96.9%, 88.1%, and 81.4%, remaining stable until 33 months. For LINAC, the rates at 3, 6, 9, 12, 15, 18, 21, 24, 30, and 33 months were 91.5%, 91.5%, 91.5%, 91.5%, 84%, 79%, 70.6%, 70%, 40%, and 17.1%, respectively (Fig. 2).

The risk of local progression for the LINAC group was almost twice that of the GK group (HR 1.92, $p > 0.05$). None of the other factors tested were significantly associated with LPFS, including the GTV ($p > 0.05$). Please see Table 2 for details.

Overall Survival

The median OS was 9.7 months (range 2–34 months) for the GK group and 23.6 months (range 1–34 months) for the LINAC group (Fig. 3). The mean survival time was 16.0 months (95% CI 11.2–20.9) in the GK group compared with 20.9 months (95% CI 16.4–25.3) in the LINAC group. In univariate Cox proportional hazard regression analysis (Table 3), the type of radiosurgery was not significantly associated with OS (HR 0.59, $p = 0.10$). The risk of death increased significantly with patient age (HR 1.06, $p = 0.002$), with the tumors' total volume (HR 1.07, $p =$

FIG. 2. Actuarial LPFS rates as estimated by the Kaplan-Meier method. The number at risk for GK and LINAC, respectively, was 53 and 29 at 6 months; 34 and 27 at 12 months; 26 and 19 at 18 months; 15 and 14 at 24 months; and 1 and 6 at 32 months; log-rank test, $p = 0.03$.

FIG. 3. Actuarial OS rates as estimated by the Kaplan-Meier method. The number at risk for GK and LINAC, respectively, was 19 and 28 at 6 months; 13 and 23 at 12 months; 9 and 16 at 18 months; 4 and 9 at 24 months; and 2 and 4 at 30 months; log-rank test, no adjustment, $p = 0.09$.

0.05), with RPA score (HR 3.7, $p = 0.01$), and with systemic progression on last radiological assessment (HR 2.57, $p = 0.02$). GPA score was significantly associated with OS. An increase of GPA score by 1 unit decreased risk of death by 58% (HR 0.42, $p < 0.0001$). Furthermore, the SIR (HR = 0.85, $p = 0.007$) and no need for additional GK treatment (HR 0.31, $p = 0.03$) were positively associated with survival. We further calculated a corrected hazard ratio (HR 0.72, $p = 0.51$) for the respective device by adjusting to the GPA score (Fig. 4), systemic progression on last radiological assessment (Fig. 5), and age (Fig. 6, with adjustment on the GPA score and systemic status at last follow-up).

GK in Lieu of LINAC Due to Technical Limitations

Some technical and dosimetry limitations have made LINAC radiosurgery difficult at our center in particular patients (Fig. 7), who we felt would benefit from GK radiosurgery. In patients with single brain metastases, in our experience, the reason for choosing GK was tumor location close to, or in highly functional areas, especially since most of these tumors were intended to be treated with high-dose radiosurgery (24 Gy at the margin) because of their histology (3 melanomas and 1 renal cell tumor). In patients with multiple brain metastases, in our experience, the reason for choosing GK was related to the anatomical location of the lesions and was either technical (limitation of LINAC movements, especially for treatment of tumors in lower posterior fossa locations) or the presence of multiple lesions close to highly functional areas (typically, multiple posterior fossa brain metastases close to the brainstem) would have hindered optimal dosimetry with LINAC. Again, this was made more critical in patients with multiple metastases needing high-dose radiosurgery (6 patients with melanoma and 2 with hypernephroma).

Discussion

To the best of our knowledge, this is the first comparative study of the treatment of brain metastases with 2 different types of radiosurgery systems. The importance of

our work is multiple. First, it provides an overview of the characteristics of patients treated with GK or LINAC at our institution, analyzing several covariables including primary tumor, number of lesions per patients, anatomical location of tumors, and absolute prescribed doses. Second, it provides data on LPFS rates achieved with these 2 different radiosurgery techniques. Although the risk of local progression in the LINAC group was almost twice that of the GK group, the difference was not statistically significant. None of the other factors tested were significantly associated with LPFS. Additionally, uni- and multivariate analysis showed that a lower GPA score, noncontrolled systemic disease status at last radiological assessment, and older age were associated with lower OS; after adjustment of these covariables by Cox regression, the OS was similar between groups. The observed difference in mean survival time between the 2 groups is difficult to interpret, as patients were not assigned randomly to GK or LINAC treatment. A better comparison of the survival times between the GK and LINAC groups would be made by adjusting a multivariable model, in which we force the device variable. However, because of the insufficient number of patients who were alive at the last follow-up time point (25 alive, 38 dead), it is not possible to perform a true multivariate analysis. Our analysis does, however, provide support for our observation that the OS of patients treated with GK radiosurgery, whose cases are typically more complicated at our institution, will be similar to that of patients treated with LINAC radiosurgery. Thus, GK treatment allows these patients to benefit from radiosurgery, which would have been difficult with LINAC. Our results regarding both LPFS and OS are comparable to published data.^{1-4,6-8,10,11,13,14,23-27,31,35,39,40}

The main limitation of our study is its retrospective nature and related biases, in particular patient and treatment selection bias. While useful for investigations of new technologies (such as GK and LINAC), retrospective studies tend to raise ethical concerns, because they do not require active participation and consent. Some particular issues

TABLE 3. Variables with potential influence on overall survival

Variables	Alive (n = 25, 39.7%)	Died (n = 38, 60.3%)	HR	p Value
Device: LINAC	17 (68)	18 (47.4)	0.59	0.10
Sex: M	12 (48)	21 (55.3)	1.09	0.77
Age in yrs, mean (SD)	56.6 (11.9)	66.4 (8.8)	1.06	0.002
Primary tumor: radioresistant*	5 (20)	14 (36.8)	1.39	0.32
Single or multiple: single	14 (56)	20 (52.6)	0.83	0.58
Total tumor vol, median [IQR]	2.1 (4.8)	3.6 (9.7)	1.07	0.05
Marginal dose, mean, median [IQR]	20 (0.0)	20 (3.7)	1.04	0.57
Prescription isodose, median [IQR]	80 (30)	61.6 (30)	0.98	0.12
Max dose, mean, median [IQR]	25.3 (12)	36 (15.1)	1.03	0.09
Anatomical location, n (%): motor cortex, basal ganglia, brainstem	1 (4)	4 (10.5)	1.29	0.64
GPA, median [IQR]	2.5 (1.5)	2 (1)	0.42	<0.0001
GPA, n (%)				
2.5–3	11 (44)	11 (18.9)	0.32	0.003
3.5–4	7 (28)	2 (5.3)	0.17	0.01
RPA, n (%), Classes 2 & 3	15 (60)	34 (89.5)	3.7	0.01
SIR, median [IQR]	7 (2)	6 (6)	0.85	0.007
BSBM, median [IQR]	3 (1)	2.5 (2)	0.97	0.75
Resection before RS	7 (28)	11 (29.7)	0.98	0.96
WBRT before RS	2 (8)	5 (13.2)	1.76	0.24
Radiological edema: not present	22 (88)	31 (81.6)	0.51	0.11
No GKS after initial RS	8 (32)	4 (10.5)	0.31	0.03
Systemic control assessment: progressive	11 (45.8)	21 (72.4)	2.57	0.02
Local control on last MRI: progressive	9 (36)	6 (20.1)	0.49	0.12
No hemorrhage on last MRI	2 (8.3)	3 (10.3)	1.36	0.62

BSBM = basic score for brain metastases.

Values represent number of patients (%) unless otherwise indicated.

* As in Table 2.

warrant further explanation. First, especially for the LINAC cases, we depended on the availability and accuracy of the patients' medical records. These records were usually not designed for the study itself but for medical follow-up

issues; accordingly, the available data might have been, in some cases, of poor quality, or might have not reflected sufficient attention to some important aspects. Additionally, for the missing data we needed to rely on information

FIG. 4. Actuarial OS rates as estimated by the Cox proportional hazards regression with regard to GPA score. The number at risk for GK and LINAC, respectively, was 19 and 28 at 6 months; 13 and 23 at 12 months; 9 and 16 at 18 months; 4 and 9 at 24 months; and 2 and 4 at 30 months; $p = 0.02$.

FIG. 5. Actuarial OS rates as estimated by the Cox proportional hazards regression with regard to systemic status. The number at risk for GK and LINAC, respectively, was 19 and 28 at 6 months; 13 and 23 at 12 months; 9 and 16 at 18 months; 4 and 9 at 24 months; and 2 and 4 at 30 months; $p = 0.04$.

FIG. 6. Actuarial OS rates as estimated by the Cox proportional hazards regression after adjustment for the systemic status and the GPA score. The number at risk for GK and LINAC, respectively, was 19 and 28 at 6 months; 13 and 23 at 12 months; 9 and 16 at 18 months; 4 and 9 at 24 months; and 2 and 4 at 30 months; $p = 0.4$.

recorded by doctors from other units (both from our hospital and other university and/or peripheral ones), general practitioners, or even physicians in private practice. The information bias thus consisted of differences in the quality and extent of information. Differential losses to follow-up in the 2 populations might also have biased the study. Second, there was selection and sampling bias. While most of the cases were discussed during an appropriate multidisciplinary meeting, some patients were directly referred for GK treatment by the physicists due to technical limitations of LINAC or were even referred specifically for GK or LINAC treatment based on some “a priori” data from the current literature; in rare cases, we ourselves (one or more of the authors) determined which treatment a patient would receive. Third, this case series was uncontrolled. It is difficult, in situations like this, to identify an appropriate exposed cohort and an appropriate comparison group, as we tried to do. Due to the previously mentioned issues, it is very challenging to make accurate comparisons between the GK and LINAC groups. Additional issues could include the following: some other risk factors might have been present and were not measured; systemic treatments might have been different in the 2 groups even for the same

primary cancer, influencing OS and further leading to a misclassification bias, while misclassifying mainly systemic disease status; and the temporal relationship was probably difficult to assess in some instances. Moreover, the small sample size limits the statistical power of our study, and as noted above, there was no randomization, which means that imbalances in patients’ characteristics might have occurred. Compared with a comparable prospective cohort study that might have been done (though difficult to organize in the frame of our institution), our retrospective study provides an inferior level of evidence.

The recent American Society for Radiation Oncology evidence-based guidelines actually reflect a change in paradigm in the treatment of brain metastases, as follows:⁴⁰ the addition of WBRT after surgical excision does not improve OS or duration of functional independence but does improve local control of the treated brain metastases and overall brain control;^{15,28} in patients with a good prognosis and a single brain metastasis (< 3 cm), either surgery or radiosurgery may be considered;⁴⁰ selected patients with brain metastases may be treated with radiosurgery alone;⁴⁰ and radiosurgery as a boost added to WBRT in patients with multiple brain metastases and good prognosis improves control over treated brain metastases as compared with WBRT alone.^{4,16} Two randomized trials showed that the omission of WBRT after radiosurgery is associated with better neurocognitive outcomes^{5,36} and with better health-related quality of life;³⁶ the randomized trial RTOG 9508,³ of the Radiation Therapy Oncology Group, found an improvement in KPS score and decreased steroid use at 6 months with the use of a radiosurgery boost added to WBRT, but WBRT alone may be considered, as there is no survival advantage with radiosurgery added to WBRT in patients with multiple brain metastases.⁴⁰ Previous studies have also reported the role of the target volumes and the radiosurgical delivered dose, with their respective impact on LPFS. The RTOG Protocol 90-05 dose-escalation study³⁴ established that the size of the lesion directly influences the risk of side effects due to increased vasogenic edema and radionecrosis. The study demonstrated that patients with tumors with a diameter between 21 and 40 mm were significantly more likely to develop serious neurotoxicity than those with tumors with a diameter less than 20 mm. Therefore, generally only metastases with a tumor

FIG. 7. Examples of technical limitations precluding optimal dosimetry with LINAC: closeness of multiple lesions to highly functional areas (typically, multiple posterior fossa brain metastases close to the brainstem) (A); low posterior fossa location (B); highly functional area (C). Figure is available in color online only.

diameter less than 30 mm were accepted for radiosurgery. In our series, the mean tumor diameters for both device groups were less than 20 mm. Surgery is still recommended for larger brain metastases ($> 8\text{--}10\text{ cm}^3$) with a significant mass effect, as 2 prospective randomized controlled trials found significantly improved survival and improved functionally independent survival after resection in comparison with fractionated radiotherapy alone.^{29,42}

In our retrospective analysis, we observed a higher treatment difficulty and complexity of the lesions in patients treated by GK (mainly radioresistant tumors, recurrences after LINAC, median number of lesions/patient, etc.). Furthermore, some technical difficulties would have made LINAC treatment difficult in some patients who we thought would benefit from GK radiosurgery. Specifically, for patients with single brain metastases, the reason for choosing GK was an anatomical location close to or in highly functional areas or the histology (radioresistant); for patients with multiple brain metastases, the reason for choosing GK was related to the anatomical location of the lesions, and it involved either technical concerns (limitations of LINAC movements, especially lower posterior fossa locations) or anatomical concerns such as closeness of multiple lesions to highly functional areas, precluding optimal dosimetry with LINAC.

Conclusions

In our center, we have used GK for the initial treatment of brain metastases in particularly complex and difficult cases. In addition GK has provided a valuable alternative in cases in which technical difficulties preclude an optimal radiosurgery treatment with LINAC. In both situations we believed that other options were less attractive, and GK proved a valuable tool. GK radiosurgery offered fair LPFS actuarial rates, despite the previously enunciated issues, and an OS rate similar to the rates we achieved with LINAC, generally for more challenging cases.

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References

1. Akyurek S, Chang EL, Mahajan A, Hassenbusch SJ, Allen PK, Mathews LA, et al: Stereotactic radiosurgical treatment of cerebral metastases arising from breast cancer. *Am J Clin Oncol* **30**:310–314, 2007
2. Amendola BE, Wolf AL, Coy SR, Amendola M, Bloch L: Gamma knife radiosurgery in the treatment of patients with single and multiple brain metastases from carcinoma of the breast. *Cancer J* **6**:88–92, 2000
3. Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, et al: Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomized trial. *Lancet* **363**:1665–1672, 2004
4. Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, et al: Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA* **295**:2483–2491, 2006
5. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, et al: Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol* **10**:1037–1044, 2009
6. Chidel MA, Suh JH, Barnett GH: Brain metastases: presentation, evaluation, and management. *Cleve Clin J Med* **67**:120–127, 2000
7. Firlik KS, Kondziolka D, Flickinger JC, Lunsford LD: Stereotactic radiosurgery for brain metastases from breast cancer. *Ann Surg Oncol* **7**:333–338, 2000
8. Flickinger JC, Kondziolka D, Lunsford LD, Coffey RJ, Goodman ML, Shaw EG, et al: A multi-institutional experience with stereotactic radiosurgery for solitary brain metastasis. *Int J Radiat Oncol Biol Phys* **28**:797–802, 1994
9. Halasz LM, Weeks JC, Neville BA, Taback N, Punglia RS: Use of stereotactic radiosurgery for brain metastases from non-small cell lung cancer in the United States. *Int J Radiat Oncol Biol Phys* **85**:e109–e116, 2013
10. Hasegawa T, Kondziolka D, Flickinger JC, Germanwala A, Lunsford LD: Brain metastases treated with radiosurgery alone: an alternative to whole brain radiotherapy? *Neurosurgery* **52**:1318–1326, 2003
11. Hoffman R, Sneed PK, McDermott MW, Chang S, Lamborn KR, Park E, et al: Radiosurgery for brain metastases from primary lung carcinoma. *Cancer J* **7**:121–131, 2001
12. Hougaard P: Frailty models for survival data. *Lifetime Data Anal* **1**:255–273, 1995
13. Iwai Y, Yamanaka K, Yasui T: Boost radiosurgery for treatment of brain metastases after surgical resections. *Surg Neurol* **69**:181–186, 2008
14. Jawahar A, Matthew RE, Minagar A, Shukla D, Zhang JH, Willis BK, et al: Gamma knife surgery in the management of brain metastases from lung carcinoma: a retrospective analysis of survival, local tumor control, and freedom from new brain metastasis. *J Neurosurg* **100**:842–847, 2004
15. Kocher M, Soffietti R, Abacioglu U, Villà S, Fauchon F, Baumert BG, et al: Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. *J Clin Oncol* **29**:134–141, 2011
16. Kondziolka D, Patel A, Lunsford LD, Kassam A, Flickinger JC: Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases. *Int J Radiat Oncol Biol Phys* **45**:427–434, 1999
17. Kushnirsky M, Nguyen V, Katz JS, Steinklein J, Rosen L, Warshall C, et al: Time-delayed contrast-enhanced MRI improves detection of brain metastases and apparent treatment volumes. *J Neurosurg* **124**:489–495, 2016
18. Leksell L: Cerebral radiosurgery. I. Gammathalanotomy in two cases of intractable pain. *Acta Chir Scand* **134**:585–595, 1968
19. Leksell L: The stereotaxic method and radiosurgery of the brain. *Acta Chir Scand* **102**:316–319, 1951
20. Levivier M, Gevaert T, Negretti L: Gamma Knife, CyberKnife, TomoTherapy: gadgets or useful tools? *Curr Opin Neurol* **24**:616–625, 2011
21. Lorenzoni J, Devriendt D, Massager N, David P, Ruiz S, Vanderlinden B, et al: Radiosurgery for treatment of brain metastases: estimation of patient eligibility using three stratification systems. *Int J Radiat Oncol Biol Phys* **60**:218–224, 2004
22. McGilchrist CA, Aisbett CW: Regression with frailty in survival analysis. *Biometrics* **47**:461–466, 1991
23. Mori Y, Kondziolka D, Flickinger JC, Kirkwood JM, Agarwala S, Lunsford LD: Stereotactic radiosurgery for cerebral metastatic melanoma: factors affecting local disease control and survival. *Int J Radiat Oncol Biol Phys* **42**:581–589, 1998

24. Muacevic A, Kreth FW, Horstmann GA, Schmid-Elsaesser R, Wowra B, Steiger HJ, et al: Surgery and radiotherapy compared with Gamma Knife radiosurgery in the treatment of solitary cerebral metastases of small diameter. **J Neurosurg** **91**:35–43, 1999
25. Muacevic A, Kreth FW, Mack A, Tonn JC, Wowra B: Stereotactic radiosurgery without radiation therapy providing high local tumor control of multiple brain metastases from renal cell carcinoma. **Minim Invasive Neurosurg** **47**:203–208, 2004
26. Muacevic A, Kreth FW, Tonn JC, Wowra B: Stereotactic radiosurgery for multiple brain metastases from breast carcinoma. **Cancer** **100**:1705–1711, 2004
27. Muacevic A, Wowra B, Siefert A, Tonn JC, Steiger HJ, Kreth FW: Microsurgery plus whole brain irradiation versus Gamma Knife surgery alone for treatment of single metastases to the brain: a randomized controlled multicentre phase III trial. **J Neurooncol** **87**:299–307, 2008
28. Patchell RA, Tibbs PA, Regine WF, Dempsey RJ, Mohiuddin M, Kryscio RJ, et al: Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. **JAMA** **280**:1485–1489, 1998
29. Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, et al: A randomized trial of surgery in the treatment of single metastases to the brain. **N Engl J Med** **322**:494–500, 1990
30. Pickles A, Crouchley R: Generalizations and applications of frailty models for survival and event data. **Stat Methods Med Res** **3**:263–278, 1994
31. Pirzkall A, Debus J, Lohr F, Fuss M, Rhein B, Engenhart-Cabillic R, et al: Radiosurgery alone or in combination with whole-brain radiotherapy for brain metastases. **J Clin Oncol** **16**:3563–3569, 1998
32. Régis J, Metellus P, Hayashi M, Roussel P, Donnet A, Bille-Turc F: Prospective controlled trial of gamma knife surgery for essential trigeminal neuralgia. **J Neurosurg** **104**:913–924, 2006
33. Sanghavi SN, Miranpuri SS, Chappell R, Buatti JM, Sneed PK, Suh JH, et al: Radiosurgery for patients with brain metastases: a multi-institutional analysis, stratified by the RTOG recursive partitioning analysis method. **Int J Radiat Oncol Biol Phys** **51**:426–434, 2001
34. Shaw E, Scott C, Souhami L, Dinapoli R, Kline R, Loeffler J, et al: Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90-05. **Int J Radiat Oncol Biol Phys** **47**:291–298, 2000
35. Sheehan JP, Sun MH, Kondziolka D, Flickinger J, Lunsford LD: Radiosurgery in patients with renal cell carcinoma metastasis to the brain: long-term outcomes and prognostic factors influencing survival and local tumor control. **J Neurosurg** **98**:342–349, 2003
36. Soffietti R, Kocher M, Abacioglu UM, Villa S, Fauchon F, Baumert BG, et al: A European Organisation for Research and Treatment of Cancer phase III trial of adjuvant whole-brain radiotherapy versus observation in patients with one to three brain metastases from solid tumors after surgical resection or radiosurgery: quality-of-life results. **J Clin Oncol** **31**:65–72, 2013
37. Sperduto PW: What is your patient's GPA and why does it matter? Managing brain metastases and the cost of hope. **Int J Radiat Oncol Biol Phys** **77**:643–644, 2010
38. Sperduto PW, Berkey B, Gaspar LE, Mehta M, Curran W: A new prognostic index and comparison to three other indices for patients with brain metastases: an analysis of 1,960 patients in the RTOG database. **Int J Radiat Oncol Biol Phys** **70**:510–514, 2008
39. Tsao MN, Khuntia D, Mehta MP: Brain metastases: what's new with an old problem? **Curr Opin Support Palliat Care** **6**:85–90, 2012
40. Tsao MN, Rades D, Wirth A, Lo SS, Danielson BL, Vichare A, et al: International practice survey on the management of brain metastases: Third International Consensus Workshop on Palliative Radiotherapy and Symptom Control. **Clin Oncol (R Coll Radiol)** **24**:e81–e92, 2012
41. Tuleasca C, Carron R, Resseguier N, Donnet A, Roussel P, Gaudart J, et al: Patterns of pain-free response in 497 cases of classic trigeminal neuralgia treated with Gamma Knife surgery and followed up for least 1 year. **J Neurosurg** **117** Suppl:181–188, 2012
42. Vecht CJ, Haaxma-Reiche H, Noordijk EM, Padberg GW, Voormolen JH, Hoekstra FH, et al: Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery? **Ann Neurol** **33**:583–590, 1993
43. Weltman E, Salvajoli JV, Brandt RA, de Morais Hanriot R, Prisco FE, Cruz JC, et al: Radiosurgery for brain metastases: a score index for predicting prognosis. **Int J Radiat Oncol Biol Phys** **46**:1155–1161, 2000

Disclosures

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

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Conception and design: Tuleasca, Gevaert, Levivier. Acquisition of data: Tuleasca, Negretti, Magaddino, Levivier. Analysis and interpretation of data: all authors. Drafting the article: Tuleasca, Levivier. Critically revising the article: Tuleasca, Negretti, Magaddino, Gevaert, von Elm, Levivier. Reviewed submitted version of manuscript: Tuleasca, Negretti, Magaddino, Gevaert, von Elm, Levivier. Approved the final version of the manuscript on behalf of all authors: Tuleasca. Statistical analysis: Tuleasca, Faouzi, von Elm. Administrative/technical/material support: Tuleasca, Negretti, Faouzi, Magaddino, von Elm, Levivier. Study supervision: Negretti, von Elm, Levivier.

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