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Gamma Knife surgery for the treatment of 5 to 15 metastases to the brain

Clinical article

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Object. It has been generally accepted that Gamma Knife surgery (GKS) is an effective primary or adjunct treatment for patients with 1–4 metastases to the brain. The number of studies detailing the use of GKS for 5 or more brain metastases, however, remains minimal. The aim of the current retrospective study was to elucidate the utility of GKS in patients with 5–15 brain metastases.

Methods. Patients were chosen for GKS based on prior MRI of these metastatic lesions and a known primary cancer diagnosis. Magnetic resonance imaging was used post-GKS to assess tumor control; patients were also followed up clinically. Overall survival (OS) from the date of GKS was used as the primary end point. Statistical analysis was performed to identify prognostic factors related to OS.

Results. Between 2003 and 2012, 96 patients were treated for a total of 704 metastatic brain lesions. The histology of these lesions varied among non–small cell lung cancer (NSCLC), breast cancer, melanoma, renal cancer, and other more rare carcinomas. At the initial treatment, 18 of the patients (18.8%) were categorized in Recursive Partitioning Analysis (RPA) Class 1 and 77 (80.2%) in RPA Class 2; none were in RPA Class 3. The median number of treated lesions was 7 (mean 7.13), and the median planned treatment volume was 6.12 cm^3 (range 0.42–57.83 cm^3) per patient. The median clinical follow-up was 4.1 months (range 0.1–40.70 months). Actuarial tumor control was calculated to be 92.4% at 6 months, 84.8% at 12 months, and 74.9% at 24 months post-GKS. The median OS was found to be 4.73 months (range 0.4–41.8 months). Multivariate analysis demonstrated that RPA class was a significant predictor of death (HR = 2.263, p = 0.038). Number of lesions, tumor histology, Graded Prognostic Assessment score, prior whole-brain radiation therapy, prior resection, prior chemotherapy, patient age, patient sex, controlled primary tumor, extracranial metastases, and planned treatment volume were not significant predictors of OS.

Conclusions. In patients with 5–15 brain metastases at presentation, the number of lesions did not predict survival after GKS; however, the RPA class was predictive of OS in this group of patients. Gamma Knife surgery for such patients offers an excellent rate of local tumor control.
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Key Words • **Gamma Knife surgery** • **stereotactic radiosurgery** • **multiple metastases** • **brain metastasis**

Of the approximately 1.6 million patients in whom cancer will be diagnosed in 2012, it is estimated that metastases to the brain will develop in up to 40%.[13] Of these patients, approximately 50% will present with multiple metastases.[13] The presence of intracranial metastases portends an extremely poor prognosis with a median OS estimated to be as short as 1 month for patients with untreated symptomatic lesions.[31] Treatment of multiple brain metastases often includes a combination of WBRT, chemotherapy, resection, and stereotactic radiosurgery, depending on a multitude of clinical factors and patient preference. Stereotactic radiosurgery for patients with 1–4 metastatic lesions is well proven as an adjunctive treatment to WBRT and has been associated with improved local tumor control, OS, and quality of

Abbreviations used in this paper: GKS = Gamma Knife surgery; GPA = Graded Prognostic Assessment; JLGK = Japan Leksell Gamma Knife; KPS = Karnofsky Performance Status; NSCLC = non–small cell lung cancer; OS = overall survival; PTV = planned treatment volume; RECIST = Response Evaluation Criteria in Solid Tumors; RPA = Recursive Partitioning Analysis; RTOG = Radiation Therapy Oncology Group; UVA = University of Virginia; WBRT = whole-brain radiation therapy.

life.[1,12,15,21–23] In addition, radiosurgery as a primary treatment for 1–4 metastases has frequently shown comparable outcomes to WBRT alone with the benefit of a more favorable neurological and neurocognitive side effect profile.[5,10,12,14,17,19,20,27,33] However, evidence is limited for the application of GKS in patients with 5 or more lesions. Expert opinion is divided, with slightly more than half of a surveyed group of neurosurgeons stating that treatment with GKS in patients with more than 5 metastases is appropriate.[9] Numerous studies have found no differences in OS based on the number of metastases;[3,24,25] therefore, authors of recent studies have begun to examine the efficacy of GKS in treating more than 5 metastases with positive results.[2,6–8,11,18,24,25,30]

The purpose of this article was to present an additional single-institution retrospective analysis of the effectiveness of GKS in patients with 5–15 metastatic brain lesions of mixed histology and to examine prognostic factors related to OS.

Methods

Study Design and Patient Selection

This is a retrospective analysis of a prospectively maintained, institutional review board–approved database. For the period from January 2003 to March 2012, we identified patients with 5–15 lesions on initial presentation who met the study criteria. These patients had been treated in a single session of GKS for brain metastases demonstrable on MRI. Inclusion criteria consisted of initial presentation with between 5 and 15 lesions identified on MRI and a known, histologically proven, primary cancer diagnosis. If the patient initially presented with brain metastases, staging and primary source diagnosis were undertaken in collaboration with a neurooncologist. Imaging characteristics of all lesions had to be consistent with a diagnosis of brain metastases. Excluded from our analysis were patients with small cell lung cancer, those with fewer than 5 or more than 15 metastatic lesions, those with unknown primary cancer, and those with contraindications to MRI. Patients were also excluded if they had previously undergone GKS for fewer than 5 lesions or for a boost to a tumor resection bed.

Radiosurgical Technique

Stereotactic surgery was performed in the usual, previously described fashion at UVA.[26] To briefly summarize, in the operating room with the patient under monitored anesthesia, a stereotactic Leksell G frame is placed. Patients are then transported from the operating room to neuroradiology where stereotactic MRI is performed. Imaging is performed as thin-slice (1 mm) axial and coronal T1-weighted pre- and postcontrast MR sequences. In this series, there were no patients with a contraindication for MRI. Thus, all stereotactic imaging was performed using MRI as opposed to stereotactic CT. A neurosurgeon, medical physicist, and radiation oncologist then formulate treatment plans in collaboration. The Leksell C model (Elekta Instruments, Inc.) was used until 2008 when the Leksell Perfexion unit replaced it. The date of GKS was defined as the date of initial treatment in these patients. Treatment planning was performed with Elekta's Gamma Plan software. In general, dose selection was based on RTOG 95-08 guidelines. However, additional parameters, such as total number of metastases, tumor volume, and prior or planned WBRT, were also factored into the dose selection process.

Data Collection and Follow-Up

Patient charts were reviewed for pertinent data including demographic information, KPS score, tumor histology, dates and doses of previous WBRT, prior resection, prior chemotherapy, status of primary tumor, and presence or absence of extracranial tumors. Radiosurgical parameters, such as number of lesions, number of isocenters, PTVs, tumor dimensions, and radiation dosages were also collected. Whole-brain radiation therapy was defined as "prior" if it was completed more than 1 month before the date of GKS and "concurrent" if completed within 1 month before or after GKS. Several parameters were then calculated. Age at GKS was defined from the date of birth to the date of GKS. Tumor burden was assessed using PTV, defined as the sum of all individual tumor prescribed isodose treatment volumes. Overall survival, where applicable, was determined using the date of death from the social security death index. Overall survival was defined from the date of GKS to the date of death.

Both clinical and radiological follow-up data were obtained when available, including subsequent treatments, tumor control, and number of new metastatic lesions. Clinical follow-up was performed by the treating neurosurgeon at UVA. Typically, follow-up clinical evaluation and MRI of the brain occurred at 3-month intervals from the time of initial GKS. In cases in which practical limitations prohibited the patient's return to UVA, information was gathered from the local collaborating physicians. Radiographic follow-up studies were also performed at UVA or by the referring physician. Follow-up T1-weighted MR images were obtained with 1-mm axial slices pre- and postcontrast. A neuroradiologist as well as the treating neurosurgeon at UVA reviewed the follow-up MR images. The applied tumor response criteria were based on the revised RECIST guidelines published in 2009 and have been used in other GKS studies.[4,6] These guidelines state that a tumor increase is defined as a change of more than 20% in the sum of the sagittal, axial, and coronal maximum dimensions. A partial response is defined as a decrease of 30% in the sum of the 3 axes dimensions as compared with baseline. Complete response is defined as disappearance of the lesion. Stable disease qualifies for neither partial response nor absence of progression. For this analysis, tumor control was defined as complete response, partial response, or stable disease.

From the data collected, individual RPA classes were assigned. Additionally, patients were assigned a GPA score. This scoring system is an alternative to RPA classification and has been shown to be equally prognostic, less subjective, and more quantitative.[28,29,34]

Statistical Analysis

Statistical analyses were performed using the statistical software SPSS 20 (IBM SPSS, Inc.) and Microsoft Excel (Microsoft, Inc.). Cox regression analysis was used for both univariate and multivariate analyses to identify factors related to OS. Factors were included in the multivariate analysis if their univariate p value was < 0.1. All statistical studies were 2-tailed. A p value < 0.05 was considered significant. Actuarial tumor control was determined using the Kaplan-Meier method.

Results

Patient Demographics and Treatment Characteristics

Of the 96 patients eligible for inclusion in the study, 42 (43.8%) were male, and 54 (56.2%) were female. The median age at the date of GKS was 57 years. The median (mean) number of treated lesions was 7 (7.13). At the time of radiosurgery, 18 patients (18.8%) were categorized in RPA Class 1, 77 (80.2%) in RPA Class 2, and none in RPA Class 3. When grading by the GPA score, 24 patients (25%) scored 0–1, 64 (67%) 1.5–2.5, 7 (7.3%) 3, and 0 (0%) 3.5–4. Sixty-five patients (67.7%) received prior chemotherapy for their primary disease. Thirty-three patients (34.4%) and 12 patients (12.5%) received prior and concurrent WBRT, respectively. Prior to GKS, only 11 patients (11.4%) underwent resection. A majority of patients (54 [56.2%]) had an uncontrolled primary tumor, and a majority (59 [61.4%]) also presented with extracranial metastases. Tumor histology was mixed, with the biggest proportion having NSCLC (36 [37.5%]), followed by 31 (32.3%) with melanoma, 24 (25.0%) with breast cancer, 2 (2.1%) with colorectal carcinoma, and 1 (1.0%) each with renal cell carcinoma, transitional cell carcinoma of the bladder, and esophageal adenocarcinoma.

Radiosurgical parameters included a median number of isocenters of 15 per patient and a range of 5–42. A total of 704 lesions were treated. The median maximum dimension for each lesion was 0.6 cm with a range of 0.1–7.4 cm. The median maximum radiation dose to each tumor was 27.5 Gy (range 18.4–57.1 Gy) with a median peripheral dose of 20 Gy (14–36.4 Gy). The median isodose line was 75% (30%–98%). The median PTV was 0.26 cm^3 (0.007–46.54 cm^3) per tumor and 6.12 cm^3 (0.42–57.83 cm^3) per patient.

Table 1 summarizes demographic and prognostic information, whereas Table 2 summarizes radiosurgical parameters.

Clinical and Radiographic Follow-Up

Clinical follow-up was performed for 84 patients (88.0%). The median duration of clinical follow-up was 4.1 months (range 0.1–40.7 months). Of these 84 patients, 59 (70.2%) had a clinical follow-up greater than 2 months. At the last clinical follow-up, 48 patients (57.1%) had undergone at least one form of additional treatment. Of those 48 patients, 8 (16.7%) were treated with additional GKS, 15 (31.2%) with WBRT, 24 (50%) with chemotherapy, and only 1 (2.1%) with resection. The median time to the first additional treatment was 1.6 months (range 0.13–18.9

TABLE 1: Summary of demographics, prognostic scores, and previous treatments at the time of GKS in 96 patients*

Factor	No.
no. of patients (%)	96
male	42 (43.8)
female	54 (56.2)
no. of treated lesions	
median	7
range	5–15
age at GKS in yrs	
median	57
range	27–85
histology (%)	
NSCLC	36 (37.5)
melanoma	31 (32.3)
breast cancer	24 (25.0)
RCC	1 (1.0)
other	4 (4.2)
KPS score (%)	
100	26 (27.4)
90	37 (38.9)
80	24 (25.3)
70	8 (8.4)
<70	0 (0)
unknown	1
RPA class (%)	
1	18 (18.8)
2	77 (80.2)
3	0 (0)
GPA score (%)	
0–1	24 (25)
1.5–2.5	64 (67)
3	7 (7.3)
3.5–4	0 (0)
prior treatment (%)	
no WBRT	51 (53.1)
WBRT	33 (34.4)
concurrent WBRT	12 (12.5)
chemotherapy	65 (67.7)
resection	11 (11.4)
disease status (%)	
uncontrolled primary	54 (56.2)
extracranial metastasis	59 (61.4)
lesion location (%)	
supratentorial	28 (29.2)
infratentorial	2 (2.1)
combination	65 (67.7)

* RCC = renal cell carcinoma.

TABLE 2: Summary of median radiosurgical parameters

Factor	No. (range)
total no. lesions treated	704
no. isocenters	15 (5–42)
max lesion dimension in cm	0.6 (0.1–7.4)
max radiation dose in Gy	27.5 (18.4–57.1)
peripheral dose in Gy	20 (14–36.4)
isodose line in %	75 (30–98)
PTV per tumor in cm^3	0.26 (0.007–46.54)
PTV per patient in cm^3	6.12 (0.42–57.83)

months). Of the patients who underwent a single additional treatment, 22 (45.8%) underwent further treatment with additional GKS, chemotherapy, or WBRT. At the last follow-up, 15 (15.6%) patients were alive. Seventy patients (72.9%) were known to be deceased with a median OS of 4.73 months (range 0.4–41.8 months). Of the deceased patients, 13 (18.6%) survived longer than 12 months, and 7 (10%) survived longer than 24 months.

Radiographic follow-up was obtained in 61 patients (64%). The median duration of radiographic follow-up was similar to that for clinical follow-up at 3.73 months (range 0.1–39.9 months). Of these 61 patients, 45 (73.8%) had a follow-up longer than 2 months. Follow-up was obtained on 448 (63.6%) of the 704 lesions treated. At the last follow-up, 25 patients (41.0%) were found to have additional lesions. Tumor control of the metastases treated with initial GKS was 88.7% at the date of the last radiological follow-up. On follow-up MRI, no evidence of radiation-induced necrosis was seen despite the use of radiosurgery and, at times, concurrent WBRT to treat multiple intracranial metastases.

Table 3 summarizes the clinical and radiological follow-up.

Statistical Analysis of OS and Tumor Control

Table 4 summarizes results of univariate and multivariate analyses. The only statistically significant predictor of OS on univariate analysis was RPA class (HR = 2.378, p = 0.009). Patient sex, age, KPS score, GPA score, controlled primary tumor, extracranial metastases, prior WBRT, concurrent WBRT, prior chemotherapy, prior resection, histology, salvage chemotherapy, and salvage WBRT were all nonsignificant in predicting OS. The number of lesions was analyzed both as a continuous variable and divided into 5–9 versus > 9 lesions. As a continuous variable, the number of lesions was not a significant predictor of OS (p = 0.257). When split into subgroups, the median survival for those with 5–9 brain metastases (86 patients) was 4.77 months, and for those with 10–15 brain metastases (10 patients) 3.42 months. There was no difference in OS between these 2 groups (p = 0.801). On multivariate analysis, RPA class remained significant (HR = 2.263, p = 0.038), with GPA score, melanomatous histology, and patient sex remaining statistically nonsignificant. Actuarial tumor control was also calculated as 92.4% at 6 months, 84.8% at 12 months, and 74.9% at 24 months post-GKS. Figure 1 displays a Kaplan-Meier curve of OS by RPA class and by tumor control.

TABLE 3: Summary of clinical and radiological follow-up data in 84 patients with multiple metastases*

Factor	No.
clinical	
no. patients w/ clinical FU (%)	84 (88.0)
median duration of FU in mos (range)	4.1 (0.1–40.7)
no. patients w/ FU >2 mos (%)	59 (70.2)
no. patients treated post-GKS (%)	48 (57.1)
median time to 1st additional treatment in mos (range)	1.6 (0.13–18.9)
first additional treatment (%)	
GKS	8 (16.7)
WBRT	15 (31.2)
chemotherapy	24 (50)
resection	1 (2.1)
no. patients retreated w/ same or different modality	22 (45.8)
outcome (%)	
alive	15.6
lost to FU	11.4
deceased	72.9
median OS in mos (range)	4.73 (0.4–41.8)
radiological	
no. patients w/ radiological FU (%)	61 (64)
median duration of FU in mos (range)	3.73 (0.1–39.9)
no. patients w/ FU >2 mos (%)	45 (73.8)
no. lesions followed up (%)	448 (63.6)
no. patients w/ new lesions at last FU	25 (41.0)
tumor control (%)	
at last FU	88.7
actuarial 6 mos	92.4
actuarial 12 mos	84.8
actuarial 24 mos	74.9

* FU = follow-up.

Discussion

Stereotactic radiosurgery for brain metastasis is generally used when there are 1–4 lesions or in patients with new brain metastasis after prior WBRT. The upfront use of radiosurgery along with concurrent WBRT or in lieu of WBRT in patients with 5–15 brain metastases remains controversial.[6] The results of the prospective trial underway in Japan by the JLGK will undoubtedly be analyzed by numerous groups to this end. Until those results are available, however, the foundation of evidence for the treatment of patients with 5 or more metastatic lesions is based on retrospective studies.

Similar to previous studies in patients with smaller numbers of brain metastases treated with radiosurgery, our analysis indicates that RPA class predicts OS in pa-

TABLE 4: Results of Cox regression analysis

Covariate	p Value	HR	95% CI
univariate analysis			
patient age	0.662	1.13	0.66–1.92
patient sex	0.084	0.64	0.38–1.06
KPS score <80	0.34	0.99	0.96–1.01
RPA Class 1 vs 2	0.009	2.38	1.24–4.55
controlled primary tumor	0.124	0.67	0.40–1.12
extracranial metastases	0.122	1.52	0.89–2.57
prior chemotherapy	0.501	0.83	0.49–1.42
prior resection	0.338	0.66	0.28–1.55
no WBRT vs prior or concurrent WBRT	0.81	0.94	0.57–1.54
GPA score	0.09	0.68	0.44–1.06
no. of lesions	0.257	0.94	0.85–1.04
5–9 vs >9 lesions	0.801	0.90	0.41–2.01
total PTV/patient	0.504	1.01	0.99–1.03
NSCLC	0.191	1.40	0.85–2.33
melanoma	0.095	1.58	0.92–2.68
breast cancer	0.6	0.85	0.47–1.55
RCC + other	0.47	1.41	0.56–3.54
chemotherapy after GKS	0.162	0.65	0.36–1.19
WBRT after GKS	0.561	1.23	0.62–2.45
multivariate analysis			
patient sex	0.198	0.66	0.34–1.25
RPA class	0.038	2.26	1.05–4.89
GPA score	0.954	0.99	0.62–1.56
melanoma histology	0.82	1.08	0.56–2.10

tients with 5–15 brain metastases treated with GKS. In the present study, the majority of patients fell into RPA Class 2, but there was a wide range of outcomes within this group. To better predict survival in RPA Class 2 patients, there have been numerous attempts to create new indices, such as the GPA, or to modify the existing RPA system.[28,29,34,35] For instance, Yamamoto et al.[35] have recently proposed subdividing RPA Class 2 into 3 subgroups based on tumor number, primary tumor status, KPS score, and evidence of metastases outside the brain. Although these systems have shown promise in various analyses, they are less widely used in day to day clinical practice than the original RPA classification.[28,29,34,35]

Table 5 compares results of the current study with those of previously published studies with a similar design and patients with more than 5 metastases. These studies' results reveal the difficulty in identifying significant predictors of outcome, as not every study shows the same predictors to be significant. Three of the 6 studies, including our own, demonstrated that RPA class is a significant predictor of survival. Furthermore, 3 of the 6 show KPS to be a significant predictor, but the cutoff for the KPS score is inconsistent among the studies. Grandhi et al.[6] found a KPS score ≥ 90 to be a positive predictor, whereas Hunter et al.[7] and Kim et al.[8] found a KPS score ≥ 80 to be predictive. Only 2 of the 6 studies revealed controlled primary disease as a positive predictor, and only one showed extracranial disease as significant. One consistency among these studies is perhaps more pertinent than the statistically significant predictors of outcome. The statistical nonsignificance of tumor number is consistent across 5 of the 6 studies. The Grandhi et al.[6] analysis is the only one to demonstrate that the presence of more than 14 lesions is negatively associated with OS. In our analysis, we found no association between the number of lesions and OS when we treated the number as both a continuous and a dichotomous variable (5–9 lesions vs > 9 lesions).

Although not directly comparable, 2 other recent publications that also demonstrate a lack of correlation between OS and tumor number should be highlighted. Chang et al.[3] analyzed the outcomes of 323 patients based on the number of metastatic lesions treated with GKS. They grouped patients into 4 categories by lesion number: 1–5, 6–10, 11–15, and > 15. They found no differences in median survival or tumor control among these groups (p = 0.554 and p = 0.989, respectively). They did find a tendency for the development of new lesions in patients with > 15 lesions (p = 0.014). Another analysis by Serizawa et al.[24,25] attempted to foreshadow the results of the currently underway JLGK0901 prospective trial (UMIN

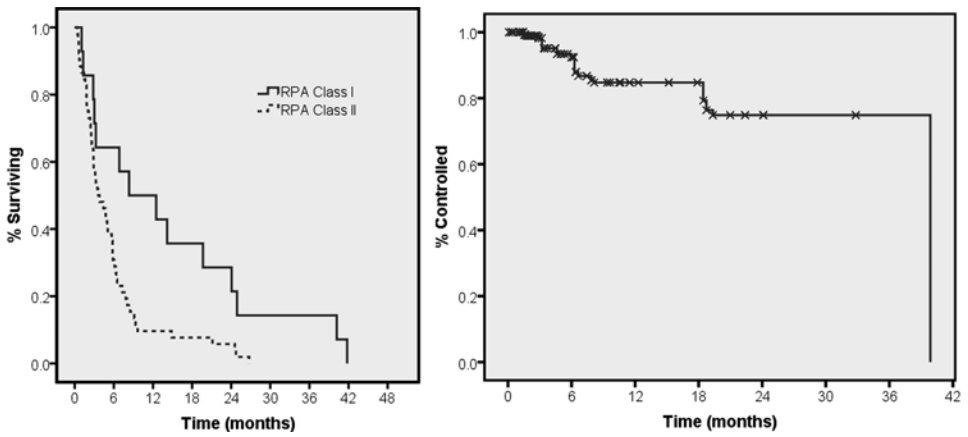

Fig. 1. **Left:** Kaplan-Meier curve showing cumulative survival rate stratified by RPA class. **Right:** Kaplan-Meier curve of local tumor control.

TABLE 5: Comparison of published literature*

Authors & Year	No. of Patients	Median No. of Lesions (range)	Median OS (mos)	Median PTV (cm^3)	RPA Class	Statistically Significant Prognostic Indicators of Positive Outcome
current study	96	7 (5–15)	4.7	6.12	1, 18.8%; 2, 80.2%; 3, 0%	RPA class
Grandhi et al., 2012	61	13.2†	4	4.86	1, 13.1%; 2, 75.4%; 3, 11.5%	KPS ≥90, RPA class, nonmelanomatous lesion, extracranial disease, <14 lesions
Hunter et al., 2012	64	6 (5–10)	7.5	4.908	1, 27%; 2, 63%; 3, 11%	KPS ≤70 vs KPS ≥80, prior vs concurrent WBRT
Bhatnagar et al., 2006	205	5 (4–18)	8	6.8	1, 10%; 2, 75%; 3, 15%	planned treatment vol, patient age, RPA class, tumor margin dose
Lee et al., 2011	36	7† (4–10)	9.1	1.2	1, 8.3%; 2, 88.9%; 3, 2.8%	uncontrolled primary tumor
Kim et al., 2008	26	16.6† (10–37)	34‡	10.9	1, 11.5%; 2, 88.5%; 3, 0%	uncontrolled primary tumor, KPS ≥80, short duration from diagnosis to metastases, >2 cycles chemotherapy post-GKS

* Lesions of mixed histology in all studies.
† Mean value.
‡ Expressed in weeks.

ID 0000001812, http://www.umin.ac.jp/) by performing a preliminary analysis of patients meeting that trial's eligibility criteria. They analyzed 1508 patients divided into 3 groups: 1 lesion, 2–4 lesions, ≥ 5 lesions. While they did note a statistically significant difference in OS among the 3 groups, after multivariate analysis, this difference fell away and was attributed to the significant prognosticators of patient sex, RPA class, and tumor histology. They noted improved survival with a solitary lesion, but no significant difference between patients with 2–4 lesions and those with ≥ 5 lesions.

While guidelines, meta-analyses, and consensus statements support the use of radiosurgery in patients with 1 to as many as 4 brain metastases, such work usually lags behind the clinical practice at leading centers and may not always reflect expert opinion.[9,13,16,19,32] There is continued evidence that the number of lesions is not the sole or, for some patients, even a major predictor of outcome after stereotactic radiosurgery.[25] If the trend toward lesion number being a nonsignificant prognosticator continues to hold true through the results of the JLGK trial, it could change the treatment paradigm in patients with multiple metastases. Rather than exposing patients to the significant side-effect profile of WBRT from the outset, this procedure could be reserved for salvage therapy. The practicality of treating patients with 5 or more lesions has also been greatly enhanced by the current Gamma Knife Perfexion system along with other radiosurgical devices that have increased efficiency for treating multiple lesions in a single session.

Given that most patients treated with radiosurgery will succumb to systemic disease prior to intracranial dysfunction, the goal in treating intracranial metastases should be to prevent symptom progression and maintain functional status. This is accomplished through adequate tumor control. The actuarial local tumor control rates demonstrated herein are excellent at 92.4% at 6 months, 84.8% at 12 months, and 74.9% at 24 months. These rates are similar to those published by other authors. Grandhi et al.[6] showed 3-, 6-, and 12-month control rates of 94.1%, 90.5%, and 58.3%, respectively. Bhatnagar et al.[2] demonstrated a 12-month control rate of 71%. These control rates support GKS as a viable option for the primary treatment of patients with ≥ 5 metastases. Nevertheless, distant brain metastases may form over time, but they can be treated with salvage therapies (for example, additional radiosurgery, WBRT, or resection) when clinically indicated.

While the challenge of identifying and creating a unified system to predict outcome in patients with brain metastases continues to elude the field, the results of this analysis support the push for expanding radiosurgical indications to include patients with more than 4 brain metastasis. However, there are limitations to our study. First, this is a retrospective analysis, and therefore it is subject to the limitations inherent to this study design. Additionally, it is a single-institution study and therefore reflects the patient selection and practice bias of our institution, location, and practitioners. For instance, there was a selection bias in this approach, which limited its application to patients in RPA Class 1 and 2. The study specifically does not address the use of radiosurgery for multiple metastases in patients in RPA Class 3. Although 96 patients is a large sample for this type of analysis, it still represents a limited number of patients and therefore limited statistical power in determining small differences in outcome. For instance, subgroup analysis of the individual histologies comprising the "other" category was not possible due to limited sample sizes. In addition, given the broad referral area for our center and the nature of Stage 4 metastatic disease, complete follow-up data were not available for all patients. Further study in a prospective fashion is underway at Japanese centers, and another such study is under consideration by the North American Gamma Knife consortium.

Conclusions

In patients with 5–15 brain metastases at presentation, the number of lesions did not predict survival after

GKS. However, RPA class was predictive of OS in this group, and GKS for such patients offers an excellent rate of local tumor control for those with ≥ 5 brain metastases.

Disclosure

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

Author contributions to the study and manuscript preparation include the following. Conception and design: all authors. Acquisition of data: Salvetti, Nagaraja, McNeill, Xu. Analysis and interpretation of data: Salvetti, Nagaraja, Xu. Drafting the article: Salvetti, Nagaraja. 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: Sheehan. Statistical analysis: Salvetti, Nagaraja, Xu. Study supervision: Sheehan.

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