The effect of Gamma Knife radiosurgery on large posterior fossa metastases and the associated mass effect from peritumoral edema

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OBJECTIVE Gamma Knife radiosurgery (GKRS) as monotherapy is an option for the treatment of large (≥ 2 cm) posterior fossa brain metastases (LPFMs). However, there is concern regarding possible posttreatment increase in peritumoral edema (PTE) and associated compression of the fourth ventricle. This study evaluated the effects and safety of GKRS on tumor and PTE control in LPFM.

METHODS The authors performed a single-center retrospective review of 49 patients with 51 LPFMs treated with GKRS. Patients with at least 1 clinical and radiological follow-up visit were included. Tumor, PTE, and fourth ventricle volumetric measurements were used to assess efficacy and safety. Overall survival was a secondary outcome.

RESULTS Fifty-one lesions in 49 consecutive patients were identified; 57.1% of patients were male. At the time of GKRS, the median age was 61.5 years, and the median Karnofsky Performance Status score was 90. The median number of LPFMs and overall brain metastases were 1 and 2, respectively. The median overall tumor, PTE, and fourth ventricle volumes at diagnosis were 4.96 cm³ (range 1.4–21.1 cm³), 14.98 cm³ (range 0.6–71.8 cm³), and 1.23 cm³ (range 0.3–3.2 cm³), respectively, and the median lesion diameter was 2.6 cm (range 2.0–5.07 cm). The median follow-up time was 7.3 months (range 1.6–57.2 months). At the first follow-up, 2 months posttreatment, the median tumor volume decreased by 58.66% (range –96.95% to +48.69%, $p < 0.001$), median PTE decreased by 78.10% (range –99.92% to +198.35%, $p < 0.001$), and the fourth ventricle increased by 24.97% (range –37.96% to +545.6%, $p < 0.001$). The local control rate at first follow-up was 98.1%. The median OS was 8.36 months. No patient required surgical intervention, external ventricular drainage, or shunting between treatment and first follow-up. However, 1 patient required a ventriculo-peritoneal shunt at 23 months from treatment. Posttreatment, 65.30% received our general steroid taper, 6.12% received no steroids, and 28.58% required prolonged steroid treatment.

CONCLUSIONS In this retrospective analysis, patients with LPFMs treated with GKRS had a statistically significant posttreatment reduction in tumor size and PTE and marked opening of the fourth ventricle (all $p < 0.001$). This study demonstrates that GKRS is well tolerated and can be considered in the management of select cases of LPFMs, especially in patients who are poor surgical candidates.

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KEYWORDS peritumoral edema; large posterior fossa metastases; Gamma Knife radiosurgery; brain metastasis; whole-brain radiotherapy; oncology; stereotactic radiosurgery

ABBREVIATIONS GKRS = Gamma Knife radiosurgery; KPS = Karnofsky Performance Status; LPFM = large posterior fossa brain metastasis; OS = overall survival; PTE = peritumoral edema; RCC = renal cell carcinoma; SRS = stereotactic radiosurgery; STM = supratentorial metastasis; WBRT = whole-brain radiotherapy.

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BRAIN metastases are the most common cause of intracranial neoplasms and typically arise from the lung, breast, and skin.⁴² They occur in approximately 20%–40% of all patients with cancer and are associated with higher patient mortality and morbidity due to the extensive local and systemic therapy required. Various treatment options and modalities must be evaluated and carefully chosen in order to optimize the management of the intracranial disease and the patient's quality of life.^{9,14} Stereotactic radiosurgery (SRS), such as Gamma Knife radiosurgery (GKRS), is an effective treatment modality for brain metastases and has been reported to demonstrate efficacy in previous trials either as monotherapy or in conjunction with whole-brain radiotherapy (WBRT).^{2,3,20,33,41,43} Monotherapy with GKRS has recently gained favor as it is associated with fewer toxicities and neurocognitive side effects in comparison with WBRT alone, or combined GKRS therapy with WBRT.^{8,11,22,28,39}

The effect of radiosurgery on control of peritumoral edema (PTE), however, is not well understood.^{25,37,38} It is known that PTE around brain metastases can lead to various neurological sequelae depending on the location and the severity of the edema.^{33,37} One significant concern is that large metastases located in the posterior fossa when associated with significant PTE have the potential to compress the brainstem and obliterate the CSF pathways, with resultant rapid neurological deterioration and a high risk of mortality. High-dose steroids can initially be used to prevent acute neurological deterioration secondary to the mass effect induced by significant PTE.^{7,32,37} However, there is a paucity of literature on the effect of GKRS on PTE, and neurosurgeons are inclined to favor resection of large (≥ 2 cm) posterior fossa brain metastases (LPFMs) with PTE to prevent devastating neurological sequelae secondary to the worsening of PTE and the associated mass effect.^{1,7,16,17}

A limited number of studies in the literature have addressed the effect of GKRS on PTE around cerebral metastases.^{18,23,27,37,38} The lesions evaluated in these previous studies were heterogeneous with respect to the size, location, presence of tumor-associated hemorrhage, and treatment received (WBRT with or without surgery). None of these studies additionally analyzed the effect of GKRS on PTE around LPFMs. The aim of our study was to objectively evaluate the effect of GKRS on LPFMs and associated PTE as well as the associated mass effect on the adjacent fourth ventricle, thereby improving our understanding of the treatment outcomes of GKRS in this group of patients and enhancing our decision-making process in the management of large tumors in this challenging location.

Methods

This was an IRB-approved retrospective chart review evaluating patients with LPFMs (defined as ≥ 2 cm in the largest diameter, based on previously published series⁴) who underwent GKRS in a single fraction at our institution. We identified 51 lesions in 49 patients treated from January 1, 2009, to December 31, 2017. Patients were included in the study if they were 18 years or older, had at least 1 LPFM, and had at least 1 clinical and radiological follow-up after GKRS. Those who underwent surgi-

cal excision of these lesions and those with evidence of intratumoral hemorrhage either at the time of diagnosis or at first follow-up were excluded from the study, as the hemorrhage could potentially alter the total volume of the tumor and PTE, and moreover it could change the MRI signal intensity around the lesions. Prior WBRT (20 patients, 40.8%) was not an exclusion criterion. The presence or absence of PTE was neither an inclusion nor exclusion criterion. None of the patients received subsequent or staged GKRS to the lesion. Also, patients were excluded if they had any clinical or radiological evidence of leptomeningeal disease. The detailed inclusion and exclusion criteria for our study are summarized in Supplementary Table 1.

The following data were obtained from medical records: patient demographics, clinical presentation, Karnofsky Performance Status (KPS) score, lesion diameter (in cm) and volume (in cm³), number of metastases in the posterior fossa, details of WBRT, GKRS prescribed dose, and duration of posttreatment follow-up. GKRS was performed using the Leksell Gamma Knife Perfexion (during the initial study period; Elekta AB) and the Icon (post-March 2017). Pre-GKRS and post-GKRS volumetric measurements of the tumor and fourth ventricle were performed using gadolinium-enhanced T1-weighted MRI sequences, and PTE volume was measured on T2-weighted FLAIR sequences using Brainlab software (iPlan Net 3.6.0) (Fig. 1). When contouring the fourth ventricle on iPlan, the superior extent of the fourth ventricle was defined as the inferior-most border of the sylvian aqueduct, and the inferior extent of the fourth ventricle was the foramen of Magendie. On either side, the foramen of Luschka was considered as the lateral extent of the fourth ventricle.²⁴ In each patient, the presence of any hydrocephalus was assessed by calculating the ratio of the maximal dimensions of the frontal horn to the distance between the inner diameters of the skull at this level on axial MRI ($< 40\%$ is considered normal, 40% – 50% is considered borderline, and $> 50\%$ is hydrocephalus).^{26,45} These clinical and radiological parameters were collected at the time of diagnosis and subsequent follow-up (median number of follow-ups 2, range 1–4). Response to treatment was evaluated using criteria similar to those used in the RECIST (Response Evaluation Criteria in Solid Tumors) guidelines for solid tumors (version 1.1);¹⁵ response was defined as a decrease in tumor volume $\geq 30\%$, progression if tumor volume increased by $\geq 20\%$, and stable otherwise. As is the convention in brain radiosurgery studies, local control is traditionally reported as metastases that are stable or smaller after GKRS.

The GKRS technique at our center has been previously described.⁴ In brief, all patients had a preliminary preprocedural evaluation by a neurosurgeon and radiation oncologist to determine appropriateness for GKRS. On the day of treatment, volumetric MRI of the head was performed, followed by stereotactic CT scanning (Leksell Frame G). Target delineation was planned on the GammaPlan planning system (Elekta). Typically, the prescribed doses depended on the maximal dimension of the lesion according to standard practice at our institution and were consistent with the RTOG (Radiation Therapy Oncology Group) 90-

TABLE 1. Baseline patient demographics, disease characteristics, and radiosurgical parameters used in the treatment of LPFM

	Value
Age, yrs	
Median	61.5
Range	29–94
Sex, n (%)	
Female	21 (42.9)
Male	28 (57.1)
KPS score	
Median	90
Range	60–90
Follow-up period, mos	
Median	7.3
Range	1.6–57.2
Cerebellar metastases, n	
Median	1
Range	1–4
Overall no. of brain metastases	
Median	2
Range	1–17
Lesion diameter, cm	
Median	2.6
Range	2–5.07
Primary tumor, n (%)	
Lung	22 (44.9)
Breast	13 (26.5)
Colon	5 (10.2)
RCC	4 (8.2)
Melanoma	2 (4.1)
Other	3 (6.1)
LPFM location, n (%)	
Rt cerebellar hemisphere	22 (43.1)
Lt cerebellar hemisphere	21 (41.2)
Vermis	8 (15.7)
Prescription dose to LPFM, Gy	
Median	18
Range	12–24
Conformality index for LPFM	
Median	1.497
Range	1.115–2.495
Isodose line for LPFM, %	
Median	53
Range	53–73

05 dosing schedule and guidelines.^{34,35} Of note, 1 lesion that measured 5.07 cm in diameter was treated with 12 Gy. In our series the median isodose line used was 53% (range 50%–64%), and the median conformality index was 1.497 (range 1.115–2.495). All lesions were treated with a single fraction. Prior to treatment, all plans were reviewed and

FIG. 1. Contours demonstrating volumes of tumor (red), PTE (yellow), and fourth ventricle (green) on MR images obtained pre-GKRS (A) and post-GKRS (B; at the first follow-up). Blue arrows point to the tumor location.

approved by a neurosurgeon, radiation oncologist, and medical physicist. Most patients had follow-up scans in the 6- to 12-week window, and the adverse radiation effects were graded using CTCAE (Common Terminology Criteria for Adverse Events) v5.0 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

Statistical analysis was performed using the Wilcoxon signed-rank test and t-test. Overall survival (OS) was analyzed using the Kaplan-Meier method. All statistical analyses were performed using R version 3.5.0. Statistical significance was set at $p < 0.05$.

Results

Complete patient demographics, disease characteristics, and treatment details were obtained from 49 patients

TABLE 2. Clinical presentation of patients at the time of GKRS treatment

	No. of Patients (%)
Asymptomatic	18 (37)
Nonspecific symptoms	19 (39)
Symptomatic	12 (24)
Gait imbalance	8 (67)
Headache	6 (50)
Nausea/vomiting	2 (17)
Dysarthria	1 (8)
Dysmetria	6 (50)
Dysdiadochokinesia	6 (50)

who had 51 lesions and met the inclusion and exclusion criteria, which are summarized in Table 1. The median age was 61.5 years (range 29–94 years). Twenty-eight patients (57.1%) were male. The median KPS score at the time of GKRS was 90 (range 60–90), the median number of cerebellar metastases was 1 (range 1–4), and the median number of total brain metastases for each patient was 2 (range 1–17). The median prescription dose to the lesion was 18 Gy, and the median lesion diameter was 2.6 cm (range 2.0–5.07 cm). The most common primary source was the lung in 22 patients (44.9%). Breast carcinoma was the second most common pathology treated, with 13 patients (26.5%); 5 patients (10.2%) had colon cancer, 4 patients (8.2%) had renal cell carcinoma (RCC), 2 patients (4.1%) had melanoma, and 1 patient each (2%) had a neuroendocrine tumor, esophageal cancer, and laryngeal cancer. Twenty patients (40.8%) had a history of prior WBRT, including 5 patients (10.2%) with small cell lung carcinoma.

The location of LPFMs was the right cerebellar hemisphere in 22 cases, left cerebellar hemisphere in 21 cases, and vermis in 8 cases. Seventeen lesions (33.3%) were single LPFMs, and 32 lesions (62.7%) were LPFMs with other posterior fossa or supratentorial metastases (STMs). All non-LPFMs and STMs were treated with GKRS according to the RTOG 90-05 dosing schedule,³⁵ which is standard at our institution. Two patients had 2 LPFMs: one had 2 LPFMs in the left cerebellar hemisphere and the other had bilateral LPFMs. In addition to cerebellar disease, 31 patients (63.3%) had STMs, of whom 10 (32.3%) had a single STM, 11 patients (35.5%) had 2 STMs, 5 patients (16.1%) had 3 STMs, 2 patients (12.9%) had 4 STMs, and 1 patient (3.2%) had 14 STMs. Eighteen patients (36.73%) were asymptomatic at the time of GKRS, 19 patients (38.77%) had nonspecific signs or symptoms, and 12 patients (24.48%) had signs and symptoms of cerebellar disease (24.5%). The clinical presentation of these patients is summarized in Table 2.

As this initially was a novel approach at our institution, we were more cautious and as a standard practice we admitted patients for 48 hours to monitor signs and symptoms of hydrocephalus. None of the patients required any temporary or permanent surgical intervention or CSF diversion procedure during that observation period. The

median tumor, PTE, and fourth ventricle volumes at diagnosis were 4.96 cm³ (range 1.4–21.1 cm³), 14.98 cm³ (range 0.6–71.8 cm³), and 1.23 cm³ (range 0.3–3.2 cm³), respectively. For statistical analysis, in patients with multiple LPFMs, the total tumor burden and PTE burden were calculated by combining the posterior fossa tumors and their accompanying PTE for each patient. The median volume of tumor plus PTE at diagnosis was 19.61 cm³ (range 2.88–91.28 cm³).

At the first follow-up (median 8.1 weeks, range 6–12 weeks), combined tumor and PTE volumes decreased in 47 lesions (92.15%) and increased in 4 (7.84%). The median tumor volume was 2.05 cm³ (range 0.20–15.79 cm³), the median PTE was 3.27 cm³ (range 0.01–46.34 cm³), and the median fourth ventricle volume was 1.77 cm³ (range 0.49–4.09 cm³). The median tumor volume decreased by 58.66% (range –96.95% to +48.69%, $p < 0.001$), median PTE decreased by 78.10% (range –99.92% to +198.35%, $p < 0.001$), and the fourth ventricle increased by 24.97% (range –37.96% to +545.6%, $p < 0.001$) (Fig. 2). The median follow-up duration was 7.3 months (range 1.6–57.2 months). The local control rate at first follow-up was 98.1% (76.5% decreased, 21.6% remained stable, and 1.9% progressed). None of the patients in our series developed radiological evidence of leptomeningeal disease in the follow-up period. The median KPS score at diagnosis of the study population was 90 (range 60–90). A KPS score of 90 was seen in 27 (55.1%) of 49 patients; 12 (24.49%), 9 (18.37%), and 1 (2.04%) patients had KPS scores of 80, 70, and 60, respectively. At the first follow-up, the overall KPS score improved in 6 patients (12.24%), was unchanged in 36 (73.46%), and decreased in 7 (14.28%). Among the 6 patients with improvement in KPS scores, the scores in 5 had increased by 10 points and in 1 patient by 20 points. Among the 7 patients with a decrease in KPS score, 6 patients' KPS scores decreased by 10 and in the other patient by 40 (which was due to progression of systemic disease). Overall, there was no statistically significant change in KPS score ($p = 0.80$) at follow-up. The median OS was 8.36 months, which was plotted on a Kaplan-Meier curve (Fig. 3). At the final follow-up (median 7.3 months), we observed a significant decrease in the median tumor (71.33%, range –99.66% to +128.38%) and PTE (79.96%, range –99.97% to +199.04%) volumes and an increase in the fourth ventricle volume (38.20%, range –41.14% to +655.08%) (Fig. 4).

Clinical symptoms were noted in detail before and after GKRS and at every subsequent follow-up. Patients were grouped into those with cerebellar symptoms, those who were asymptomatic, and those with nonspecific neurological symptoms such as generalized weakness, occasional headaches, and treatment-related neuropathy. At the first follow-up (6–12 weeks), clinical improvement was seen in 6 of the 12 patients who presented with cerebellar symptoms, 5 patients remained unchanged, and 1 patient worsened (developed new-onset nonspecific symptoms thought to be secondary to progression of their systemic disease). One of the 19 patients in the nonspecific-symptoms group developed new-onset cerebellar symptoms at the first follow-up. Overall, 3 (6%) of 49 patients had worsening of their neurological symptoms at first follow-up. None of the

FIG. 2. Waterfall plots demonstrating the change in tumor, PTE, and fourth ventricle volumes at the first follow-up. The median tumor volume decreased by 58.66% (range -96.95% to +48.69%, $p < 0.001$), median PTE decreased by 78.10% (range -99.92% to +198.35%, $p < 0.001$), and fourth ventricle increased by 24.97% (range -37.96% to +545.6%, $p < 0.001$). *Radioresistant tumors: triple-negative breast cancer, RCC, melanoma, and colon cancer. There was no statistically significant difference in the response rates of radioresistant tumors versus radiosensitive tumors at the first follow-up ($p = 0.058$) or last follow-up ($p = 0.11$).

patients in our series had evidence of hydrocephalus based on clinical and radiological evaluation (as evidenced by the normal frontal horn to internal diameter ratio [frontal horn/inner diameter ratio]), at the time of diagnosis and at first follow-up ($p = 0.11$) (Fig. 5). After GKRS, a tapering dose of steroids was given to 47 patients, of whom 14 (29.79%) required steroids beyond our typical steroid taper regimen (tapered over a maximum period of 4 weeks). There was no statistically significant correlation between change in tumor and PTE volume at diagnosis and at the first follow-up with more prolonged use of steroids versus a routine taper dose of steroids ($p = 0.40$). Steroid-related complications were seen in 5 patients; 3 of them had worsening of preexisting type II diabetes mellitus and 2 developed steroid myopathy and cushingoid features with weight gain and facial puffiness. None of the patients required bevacizumab (anti-vascular endothelial growth

FIG. 3. Kaplan-Meier curve for overall survival in patients with LPFMs undergoing GKRS.

factor) in the post-GKRS period for treatment of tumor-related edema; however, 1 patient required bevacizumab as an adjuvant in the treatment of his primary tumor.

In the event of increasing lesion size at first follow-up after GKRS, radiological and/or pathological information was used to discriminate progression and radiation necrosis. Specifically, stabilization or shrinkage of a previously enlarging lesion and/or decreased cerebral blood volume on perfusion MRI was considered related to radiation necrosis, whereas continuous increase in mass and/or increased cerebral blood volume was considered progression. Three patients (6.1%) developed symptomatic radiation necrosis. One of these 3 patients underwent laser interstitial thermal therapy 14 months post-GKRS, the second patient was treated with bevacizumab and required a ventriculoperitoneal shunt 23 months after GKRS, and the third patient had symptomatic radiation necrosis 15 months after GKRS and was treated with steroids alone. Two other patients had asymptomatic radiation necrosis and required no treatment for it. Two patients developed new cerebellar metastasis during the follow-up period and were treated with GKRS.

Discussion

Brain metastases are considered an advanced stage of systemic malignancy, and the treatment of large brain metastases remains challenging due to many potential complications, especially if the lesions are located in the posterior fossa.^{1,6,7,12} There are many treatment options available today for posterior fossa metastases, including surgery, WBRT, and GKRS, either alone or in combination.^{2,3,6,8,16} However, an appropriate treatment option for a patient with brain metastasis should be decided after considering various factors, such as the underlying primary pathology, the location of the lesion, the size of the lesion, the clinical status of the patient, and the burden of the systemic disease.

In patients with brain metastases, the major advantage of GKRS over surgery is that it is less invasive and not associated with significant recovery time so that systemic therapy can be administered sooner than would be oth-

FIG. 4. Box plots demonstrating the change in tumor (A), PTE (B), and fourth ventricle (C) volumes at the first (median 8.1 weeks) and final (median 7.3 months) follow-up.

erwise possible following open surgical intervention. In a retrospective case series of 92 patients with posterior fossa metastases managed surgically, patients with posterior fossa metastatic lesions had a poor prognosis with a median OS of 6 months, and surgical management was not found to be a significant prognostic factor.⁴⁴ In addition, GKRS has the potential to treat multiple lesions in the same session and to treat deep-seated brain lesions.^{7,8,20,28,33} Furthermore, GKRS was also found to be associated with a lower incidence of leptomeningeal disease when compared with surgery, whereby GKRS obviated the potentially serious complications associated with surgery and resulted in an equivalent OS rate and improved initial performance status.⁴⁰

WBRT is another modality used to treat patients with brain metastases, especially those with multiple lesions and those who are poor surgical candidates. Currently,

in many centers, radiosurgery has overtaken WBRT as a preferred modality to treat metastatic lesions, due to concerns for increased cognitive toxicity in patients undergoing WBRT and better tumor control rates with SRS.^{5,8,10,13,36,46} In a randomized clinical trial investigating the effect of SRS alone in comparison to SRS with WBRT on cognitive function in patients with brain metastases, the use of SRS alone resulted in less cognitive deterioration without a significant difference in OS rate.⁸ Such findings suggest that SRS alone can be a preferred therapeutic option for patients with brain metastases amenable to radiosurgery. Moreover, in contrast to SRS, WBRT was positively correlated with worsened PTE at follow-up, and hence these patients required a prolonged duration of steroid therapy.^{18,27} These studies also demonstrated that, in contrast to WBRT, SRS was efficacious in controlling PTE.^{18,27}

In comparison to other treatment modalities such as resection, SRS demonstrates an equivalent local tumor control in most patients and a decreased need for the interruption of chemotherapy for the systemic disease control.^{5,8,29,37} Tumor control is an important outcome measure in patients with brain metastases; however, control of the associated mass effect is important for treatment safety and improves the neurological deficits secondary to the tumor and associated PTE, and hence is important for improving the patient's quality of life.^{27,37,38} With the paucity of available literature on the effect of SRS on PTE around LPFMs, our aim was to study the impact of this in patients treated at our institution. In areas in which the tumors were not restricted to the posterior fossa, improvement in neurological function has been observed to be associated with a reduction in PTE after GKRS.^{27,37,38} In the series by Mori et al., improvement in motor weakness was seen in 5 of 20 patients after SRS.²³ Of the 5 patients in their series who improved, 3 of them had improvement in PTE on MRI at the first follow-up.²³ Moreover, longer survival has also been observed in patients who had better control of PTE at follow-up.^{18,27,37,38} Therefore, effective management of PTE is correlated with improved overall patient outcomes following GKRS or SRS therapy.

The management of PTE may play an important role in preventing surgical intervention to address compression of the fourth ventricle leading to hydrocephalus.³⁰ Suboccipital craniectomy with dural opening for decompression

FIG. 5. Changes in the pre- and post-GKRS ratio of the largest width of the frontal horn (FH) to the internal diameter (ID) from inner table to inner table at this level, showing that there was no statistically significant ($p = 0.11$) increase in the size of the lateral horns at the first follow-up.

followed by shunting for CSF diversion is associated with significant risks of shunt infections and/or malfunctions requiring revisions and leads to a prolonged recovery period wherein chemotherapy must be delayed or deferred.^{30,31} In addition, rare complications, such as extracranial, peritoneal seeding of tumor cells through ventriculoperitoneal shunts leading to the formation of malignant CSF ascites, and intratumoral hemorrhage immediately following a shunt procedure, have been reported.^{19,21} Such potential complications can significantly exacerbate patient morbidity, performance status, and overall clinical outcomes and are avoided by effective PTE control and management of fourth ventricle compression in GKRS.

Another factor that influences the efficacy and safety of GKRS seen in previous studies is histology of the primary tumor.^{37,38} Shuto et al. studied the effect of GKRS on control of cerebral metastases and the PTE around them in 280 patients with various-sized metastases and primary pathologies that were located in both the supratentorial and infratentorial compartments.³⁷ Their study demonstrated that PTE associated with metastases from primary lung and breast malignancies (non-RCC) was less frequently found at initial diagnosis and was better controlled after GKRS on follow-up MRI than PTE associated with RCC metastases.³⁷ In a subsequent study, the effect of resection alone was compared with GKRS in patients with large RCC metastases that measured > 2 cm in maximal diameter and were associated with extensive PTE.³⁸ The PTE improved in all of their patients who underwent resection, whereas only 63.8% of patients who underwent GKRS had control of PTE.³⁸ Based on these observations, it was concluded that RCC as the primary histology is a poor prognostic factor for PTE control.^{37,38} Given that there were only 4 patients with RCC metastases in our series, and 1 of them had worsening of PTE and the other 3 had reduction of PTE at the first follow-up after GKRS, we cannot draw definitive conclusions regarding the efficacy and safety of GKRS in RCC metastatic patients in terms of local tumor control and PTE management; this will require further larger series.

High-dose steroids are widely utilized after GKRS as a medical therapy to control PTE in metastatic lesions. In the available literature, conflicting results are found with respect to the use of steroids in the control of PTE. Pan et al. observed control of PTE in patients who received steroids after GKRS, whereas Shuto et al. demonstrated that steroid administration was not correlated with PTE control on follow-up MRI.^{27,37,38} Similarly, in our study, we did not find a significant correlation between the use of steroids after GKRS and control of PTE. Previous studies have shown that significant preexisting edema did not influence the tumor response or clinical outcome, and resolution of edema was related to better quality of life but not to longer survival.²⁷ In our series of LPFMs with preexisting surrounding PTE, it was found that the size of the lesion does not always correlate directly with the severity of clinical symptoms; hence, a relatively conservative approach, like GKRS, performed under close observation could be justified.

While the results of this study are encouraging, our analysis was limited by the retrospective study design,

small sample size, and various tumor pathologies, including a variety of relatively radiosensitive and radioresistant tumors. Also, we did not test for differences between the patients who did not meet the inclusion criteria and those who were not included due to the absence of repeat MRI and/or follow-up, potentially introducing a selection bias. We recognize that while the clinically meaningful data were delineated and reviewed, long-term potential differences in clinical outcomes were not reviewed, given the variability of the long-term follow-up in this cohort. Additional prospective studies with a larger sample size investigating the correlation with clinical outcome changes are warranted to further analyze the role of GKRS in the management of large posterior fossa metastases and the associated edema. Finally, we cannot emphasize enough that this is a highly selected group of patients; strict criteria were maintained during case selection and these cases were performed in a setting with vast experience in GKRS. The majority of patients in this group were only minimally symptomatic and patients with symptomatic hydrocephalus, hemorrhage, and presence of symptoms related to brainstem compression were promptly excluded. Moreover, until larger prospective studies substantiate the safety and efficacy of GKRS in LPFM, caution and judicious patient selection should be exercised in selecting this approach.

Conclusions

In this retrospective analysis of patients with LPFMs, GKRS resulted in a statistically significant reduction in PTE and tumor size as well as the desired increase in the size of the fourth ventricle (all $p < 0.001$) at both the first posttreatment follow-up and final follow-up without significant treatment-related toxicity. Hence, GKRS monotherapy can be considered a potential treatment option for patients with LPFMs, including those lesions that are associated with marked PTE and compression/distortion of the fourth ventricle.

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Disclosures

Dr. Mohammadi: consultant for Monteris Medical. Dr. Suh: consultant for Chrysalis Biotherapeutics.

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Conception and design: Angelov, Muhsen, Joshi. Acquisition of data: Muhsen, Joshi, Lee, Thapa, Borghei-Razavi. Analysis

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Supplemental Information

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