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ORIGINAL ARTICLE

Is two-staged gamma knife surgery a reasonable management option for very large cerebellar metastases? A case series of three patients

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Abstract

Objective Two-staged gamma knife surgery (GKS) is a method that may extend the upper tumor volume limit for using GKS in the management of brain metastases. However, the safety of treating very large posterior fossa lesions with this technique has not been well demonstrated. Therefore, we analyzed our experience in treating cerebellar metastases larger than 12 cm^3 with two-staged GKS.

Methods Four consecutive patients harboring 12 to 30 cm^3 cerebellar metastases scheduled two-staged GKS were included in the study, and all but one patient completed the treatment. The treatment doses were 10–13 Gy. All patients were followed with regular MR imaging and clinical assessments, and the tumor volumes were measured on all treatment and follow-up images.

Results Tumor progression was not demonstrated in any of the patients. Tumor volumes decreased by, on average, more than half between the two stages. The median survival was 22 months, and no patient died due to intracranial tumor progression. Peritumoral edema at the first GKS resolved in all patients, replaced by asymptomatic mild T2 changes in two of them not requiring any treatment. No radiation-induced complication has developed thus far.

Conclusion Staged GKS seems to be a feasible management option for very large cerebellar metastases.

Keywords Staged GKS · Gamma knife radiosurgery · Brain metastases · Stereotactic radiosurgery · SRS

Abbreviations

GKS	Gamma knife radiosurgery
LINAC	Linear accelerator
MRI	Magnetic resonance imaging
WBRT	Whole brain radiotherapy

Introduction

Surgical resection is the treatment of choice for very large cerebellar metastases. However, for patients unable to undergo surgery and in whom systemic treatment does not control the intracerebral disease, radiation treatment is an option. The conventional radiation treatment for these patients has been whole brain radiation therapy (WBRT), which typically takes place over 2 weeks. The reported results are, however, suboptimal. A 0% complete response rate and a 47% partial response rate were reported following WBRT for tumors larger than 10 cm^3 [12]. Hypofractionated radiotherapy in three to five sessions is a relatively new treatment option for large brain metastases. The literature has so far been sparse, but the results are promising [2, 3, 5, 11]. We were unable to find any literature supporting the use of hypofractionation for very large cerebellar metastases.

Single-session radiosurgery for very large cerebellar metastases is not appealing due to the risk for severe complications. Sturm et al. reported a case of acute

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radiation-induced edema following radiosurgery for a cerebellar lesion, which exacerbated the pre-existing edema. As a consequence, herniation developed, and the patient died 15 h after the treatment [15]. Acute hydrocephalus developed during the treatment in another patient [16]. The patient would have succumbed should a ventricular drain not been acutely inserted. Instead, the patient recovered completely. These two cases serve as a warning for treating very large cerebellar metastases with radiosurgery.

Another concept that allows safe treatment of large metastases is staged GKS. The treatment is divided into two or three sessions, using around 12 Gy per session with around a month interval between the sessions [1, 4, 17]. There are two conceptual benefits with this treatment option, as compared to hypofractionation. One is that the tumor volume is likely to decrease after the first treatment, thus decreasing the radiation burden to the surrounding brain tissue at the second treatment. The second benefit is that the treatments are frame-based, eliminating the uncertainties caused by image co-registration and potential movements during the treatment, thus obviating the need to add a margin to the tumor volume when deciding the target volume [6]. The feasibility for this treatment option for very large cerebellar lesion, with the exception of a case report [9], is not yet reported. A small number of patients with very large cerebellar metastases have been treated in our center using two-staged GKS, and we are now reporting our experience and outcome.

Materials and methods

The study was approved by the National University Hospital Domain-Specific Regulatory Board (DSRB 2022/00177). All patients harboring very large cerebellar metastases (defined as a tumor volume of > 12 cm^3) and scheduled for two-staged GKS between January 2021 to December 2022 were prospectively included in the study. Informed consent was obtained. Patients who declined open surgery were given the options of staged GKS or radiotherapy. All who opted for staged GKS were included in the study. All patients were treated as inpatients, allowing close monitoring post-treatment and timely preparation for surgical interventions if needed. Treatment was scheduled as a two-staged GKS with a 1-month interval between the sessions. Steroids were given to all patients prior to the treatments. Additional metastases, if any, were treated with standard GKS. Adjuvant WBRT was omitted. The treatment dose was defined as the dose covering 95% of the tumor volume. The conformity factor was defined as the volume within the treatment dose divided by 95% of the tumor volume. For example, a conformity factor of 1.1 means that 90% of the volume within the target dose is tumor and 10% non-tumor. The patient and treatment statistics are presented in Table 1.

All patients were followed up with magnetic resonance imaging (MRI) and clinical visits every 3 months or when clinically indicated, and for as long as it was deemed clinically meaningful. None of the patients were lost to follow-up, and the latest information was collected on the date of manuscript submission. The treatments were completed in all but one patient, in whom the extracranial disease progressed so rapidly that further treatment of the cerebellar metastasis was deemed meaningless. However, a MR scan 3 weeks before the patient succumbed showed that the cerebellar lesion was stable in size as compared to at the time of the first GKS (GKS1).

The primary outcome was the change in tumor volume following GKS1, as measured on contrast-enhanced MR images acquired at the time of GKS1 and GKS2, as well as on the follow-up images. Secondary outcome was survival time following GKS1. The cause of death (extracranial or intracranial) was also documented. The tumor volumes were calculated in the Leksell GammaPlan software for the treatments, and in the open-source software 3D Slicer for the follow-up images [7].

Results

Survival time

One patient died 2 months and another 22 months after GKS1 (= median survival time), while the other two are alive 21 and 31 months following GKS1. Both patients that died did so due to their extracranial disease. Specifically, P4 deteriorated prior to the second stage of GKS due to severe pneumonia with significant functional decline, and subsequently decided that he did not want to continue further treatment and opted for best supportive care.

Tumor volume dynamics

The tumor volume responses following two-staged GKS are illustrated in Fig. 1. The tumor volume decreased significantly between GKS1 and GKS2 in 3 patients, and remained stable in the fourth. The reduction in tumor volume was, on average, 57% between the stages. There was no correlation between the tumor volume at GKS1 and relative volume decrease. Figure 2 shows representative MR images at the two GKS sessions and on the latest follow-up for all patients.

The tumor volume decrease was not continuous in 2 patients. In one (P1), the tumor reduced from 21 to 1 cm^3, after which it increased to 2 cm^3, which then remained stable for the last 7 months. In the other (P3), it reduced from

Table 1 Patient demographics

Patient	Age, years	Sex	Primary tumor	First session (GKS1)				Days between GKS	Second session (GKS2)					Chemotherapy post GKS	Follow-up time, months	Survival status
				Tumor volume, cm^3	Treatment dose, Gy	Conformity	Edema		Tumor volume, cm^3	Treatment dose, Gy	Conformity	Edema	Size reduction			
P1	51	M	NSCLC	20.8	12	1.07	Significant	29	7.5	12	1.04	Moderate	−64%	Carboplatin, pemetrexed, pembrolizumab	31	Alive
P2	69	F	Ovarian	12.2	13	1.14	Moderate	30	5.6	13	1.09	Moderate	−54%	Carboplatin, gemcitabine	22	Dead
P3	52	M	NSCLC	31.7	10	1.05	Significant	32	15.8	10	1.11	Significant	−50%	Lorlatinib	21	Alive
P4*	67	M	Colon	30.4	13	1.10	Significant	NA	NA	NA	NA	NA	NA	NA	2	Dead

*This patient did not go on to receive his second GKS dose due to systemic disease progression unrelated to the brain metastasis

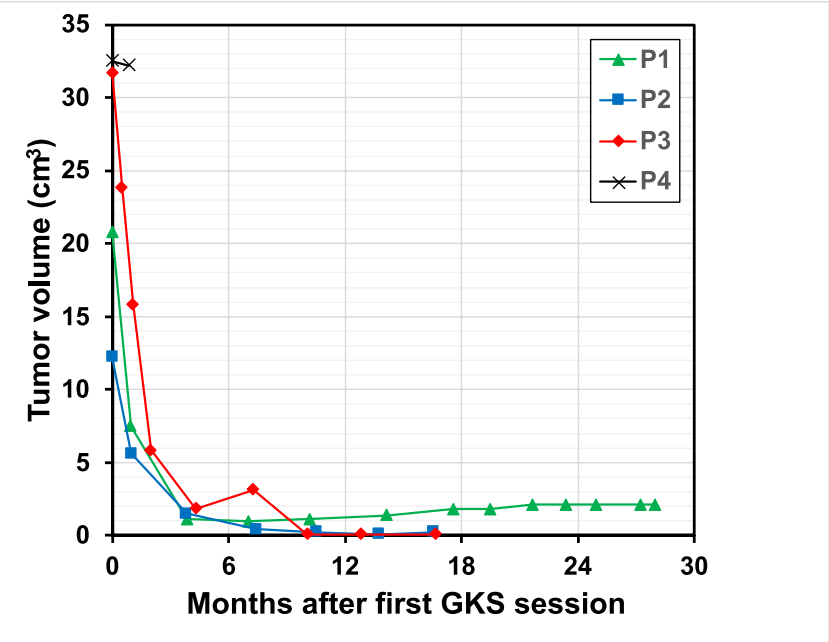

Fig. 1 The changes in the treated tumor volume over time. Three of the 4 patients had a significant reduction in volume that reached the plateau at 3 months. P4 passed away early due to systemic progression, prior to GKS2

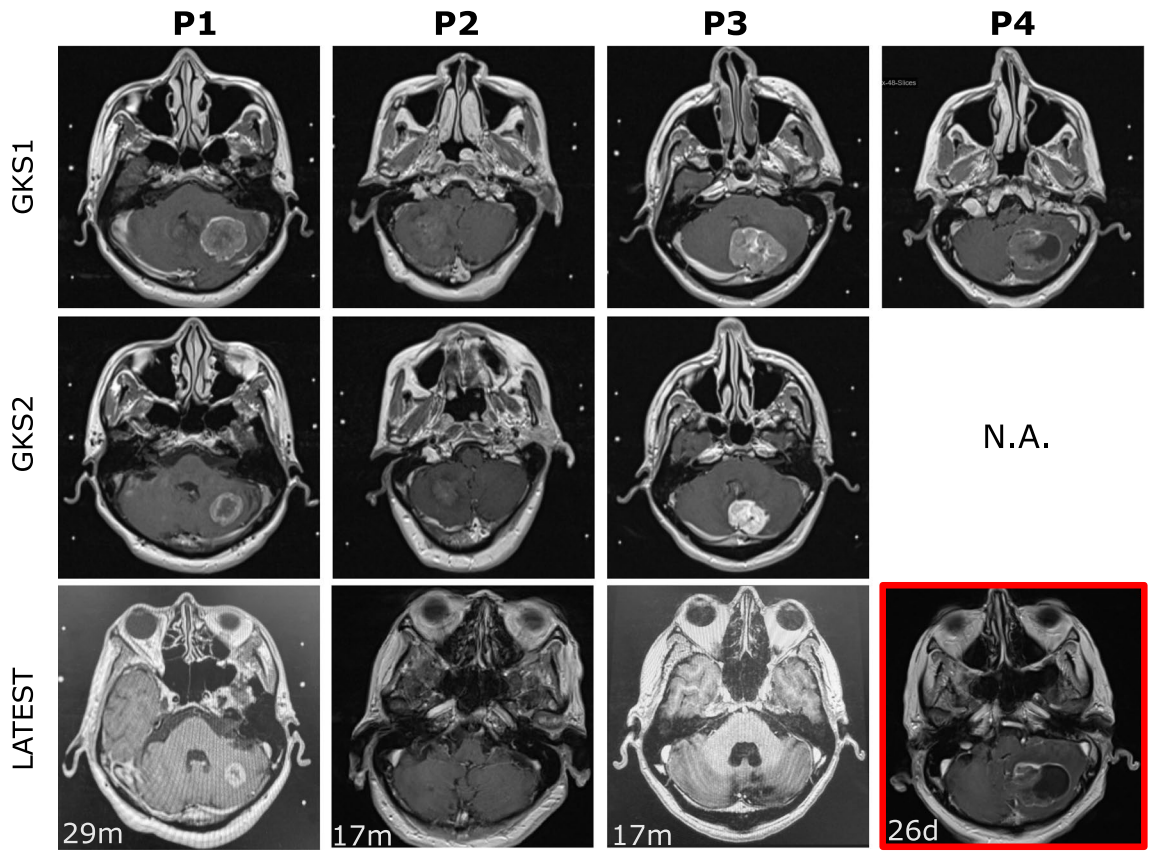

Fig. 2 Stereotactic MRI, T1w contrast-enhanced sequence, demonstrating the reduction in lesion size during the first and second gamma knife surgery session (GKS1 and GKS2, respectively), as well as on the latest follow-up images (at 29 months, 17 months, and 17 months respectively post-GKS1). For P4, only one treatment of the two intended doses was given prior to systemic progression and eventual death

32 to 1.8 cm^3, and thereafter increased to 3.1 cm^3. Three months later, the tumor was barely visible, and it has been stable since.

T2 changes

Three of the lesions were associated with significant edema before GKS1, while the edema was moderate in the fourth. The edema resolved in all 3 patients who completed both treatments. However, asymptomatic T2 changes developed at 7 and 14 months following GKS1, respectively, in 2 of the patients. The intensity of the T2 changes varied with time, suggestive of radiation-induced changes rather than that caused by tumor activity, and the patients remained entirely asymptomatic. The T2 changes had so far been managed conservatively.

Impact of systemic treatment for tumor control

One of the two survivors (P3) received lorlatinib, which is known to penetrate the blood–brain barrier well and thus might also have contributed to intracranial tumor control [14]. P1 was treated with carboplatin, pemetrexed, and pembrolizumab, which were unlikely to contribute to cerebellar tumor control [10]. The patient (P2), who passed away after 22 months, received carboplatin and gemcitabine, with poor central nervous system penetration. Patient P4, in whom the cerebellar lesion was treated in only one session, did not receive any chemotherapy.

Discussion

Surgical resection is, in our opinion, the preferred treatment option for large cerebellar metastases. However, staged GKS with close monitoring can be a feasible option when surgery is contraindicated or when the patient is asymptomatic. We have demonstrated that the tumor volumes decreased significantly in our case series. None of the patients in our small series developed any complications, nor did they need any surgical intervention, or any additional radiation treatment. Still, the risk that post-GKS surgery will be needed needs to be taken into consideration when informing the patients of the risks with staged GKS.

Local tumor control rate

Although the literature is sparse, the local tumor control rate following two-staged GKS for large tumors larger than 10 cm^3 seems inferior, but still satisfactory, to that of single-session GKS for smaller tumors. The reported local tumor recurrence rates were 12% [4], 14% [9], 25% [13], and 39% [17]. The treatment of cerebellar metastases larger than 10 cm^3 has not been reported specifically, with the exception of one case report that reported stable tumor volume 8 months following radiosurgery [9]. Our series is likewise too small to allow any conclusion about tumor control rate to be made, but it appears to be compatible with those reported above.

Acute hydrocephalus

As mentioned earlier, acute obstructive hydrocephalus following radiosurgery for large cerebellar metastases can be lethal [15], but also reversible if promptly addressed with cerebrospinal fluid (CSF) diversion [8, 16]. It is possible that two-staged GKS using 10–13 Gy per session decreases the risk for acute hydrocephalus, but it is unlikely to eliminate it. Thus, our recommendation is that patients should be hospitalized and closely monitored following staged GKS for very large cerebellar metastases, so that the potential development of acute hydrocephalus can be properly identified and treated.

Other radiation treatment options

The patients in this series were treated with frame-based two-staged GKS. Based on experience published by Serizawa et al., there does not seem to be any clear advantage of three-staged over two-staged GKS [13], and, as a third stage would have incurred additional costs and inconvenience, we opted for two-staged GKS. Other management options would have been three-staged mask- or frame-based GKS, hypofractionated mask-based GKS or linear accelerator (LINAC) treatments, or radiotherapy with more than five fractions. The intention of reporting our small series is not to claim superiority of two-staged frame-based GKS over these alternatives, but to indicate that this technique seems to be a feasible treatment option for very large cerebellar metastases.

Limitations of this study

A major limitation is that the potential impact of central nervous system penetrating drugs on intracranial tumor control is not taken into account. Furthermore, the small number of patients in this series does not permit us to draw any definite conclusions about the resulting risk–benefit relation following the treatment. However, it serves as an argument to initiate randomized multi-center prospective trials to conclude, which, if any, of the alternative radiation treatments is non-inferior to conventional surgical resection of large cerebellar metastases.

Conclusion

Two-staged GKS appears to be a reasonable management alternative for large cerebellar metastases for patients in whom surgical removal is unappealing.

Author contribution Yu Tung Lo: formal analysis; visualization; writing — original draft. Bengt Karlsson: conceptualization; data curation; investigation; methodology; supervision. Andrea Wong, Balamurugan A. Vellayappan, Tseng Tsai Yeo, Vincent Diong Weng Nga: writing — review and editing.

Data availability Not applicable.

Code availability Not applicable.

Declarations

Ethics approval This study has been approved by the Institutional Regulatory Board (DSRB 2022/00177).

Consent to participate Informed consent was obtained from all patients.

Consent for publication The patients have consented to the submission of clinical data for publication.

Conflict of interest The authors declare no competing interests.

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