Fractionated Gamma Knife Radiosurgery Combined with Ommaya Reservoir Implantation for Large Cystic Brain Metastases.

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Abstract

Introduction: Large cystic brain metastases are relatively rare and are not good candidates for stereotactic radiosurgery. Stereotactic aspiration followed by Gamma Knife radiosurgery (GKRS) is a reasonable and effective management strategy. However, even with aspiration, the target lesion tends to exceed the dimensions of an ideal target for stereotactic radiosurgery. This study aimed to investigate the effectiveness of frameless fractionated GKRS (f-GKRS) for large cystic brain metastases with cyst aspiration using Ommaya reservoir implantation.

Methods: Between May 2018 and April 2021, eight consecutive patients with nine lesions were treated with f-GKRS in five or ten sessions after cyst aspiration. The aspiration was repeated as needed throughout the treatment course to maintain the cyst size and shape. The patient characteristics, radiologic tumor response, and clinical course were reviewed using medical records. The mean follow-up duration was 10.2 months (2–28 months).

Results: The mean pre-GKRS volume and maximum diameter were 16.7 mL (5–55.8 mL) and 39.0 mm (31–79 mm), respectively, and the mean tumor volume reduction achieved by aspiration was 55.4%. The tumor volume decreased for all lesions, and symptoms were alleviated in all patients. The median overall survival was 10.0 months, and the estimated one-year survival rate was 41.7% (95% CI: 10.9–70.8%). The local tumor control rate was 100%. No irradiation-related adverse events were observed.

Conclusions: Ommaya reservoir implantation and aspiration followed by frameless f-GKRS is a less invasive, effective, and safe method, and should be considered as a management option for large cystic brain metastases.

Introduction

A large cystic component in metastatic brain tumors is relatively rare, and no standard therapy has been established for these lesions. Gamma Knife radiosurgery (GKRS) has become a crucial treatment strategy for brain metastases; however, it is traditionally perceived to have a poor effect on cystic tumors [1]. In particular, cysts > 3 cm [2, 3] in diameter or 10 mL [4] in volume are more likely to be associated with radiation necrosis and other critical adverse events after this treatment.

Since large cysts often cause neurological symptoms due to their mass effect, the primary purpose of treatment is to relieve the patient from the symptoms. Traditionally, tumor resection has been performed to treat large cystic lesions, though with a potential risk of tumor cell dissemination. Stereotactic tumor aspiration is another well-established and less invasive treatment, effective in alleviating neurological symptoms immediately without scattering the capsuled fluid. Tumor resection by craniotomy is assumed to be associated with a higher risk of tumor spillage [5] although the risk of surgery-related dissemination is reduced for cyst aspiration. Aspiration is not a radical treatment for metastatic tumors, and it may be used as an adjunct to GKRS. Reducing the tumor volume by aspirating the encapsulated fluid facilitates GKRS. The combination of stereotactic tumor aspiration and GKRS has been reported to be effective for large cystic metastases [6–14]; however, even after aspiration, the tumor may remain larger than the size of a suitable candidate for GKRS. The irregular shape of the shrunken cyst is also challenging to treat. The results of the tumor control rate tend to be insufficient in previous reports.

With technological advances in Gamma Knife, ICON™ has provided the option to perform safely fractionated frameless treatments for larger lesions. With this case series, we introduced two adjunctive procedures, fractionated GKRS (f-GKRS) and cyst aspiration by Ommaya reservoir implantation, as treatment strategies for large cystic metastatic tumors.

Methods

Three hundred thirty-seven patients underwent GKRS for metastatic brain tumors in our center between May 2018 and April 2021. Among these, eight patients (2.4%) with nine large cystic tumors were treated with Ommaya reservoir implantation and aspiration followed by frameless f-GKRS using Gamma Knife ICON™ (Elekta Instrument AB, Stockholm, Sweden). Pre- and post-aspiration tumor volumes were measured using the Leksell Gamma Plan (Elekta Instrument AB) on magnetic resonance imaging (MRI) scans. The follow-up MRIs were scheduled every month for the first three months after treatment, and the subsequent follow-up intervals were set to a maximum of three months if the treated lesions were stabilized. Additional procedures during outpatient visits, including CT scans and Ommaya reservoir punctures, were scheduled if required. The patient characteristics, tumor radiologic response, and clinical course were retrospectively reviewed using the medical records. Local tumor control was defined as a decrease in size or stabilization.

A simple fluid recollection was not regarded as tumor progression. The study protocol was approved by the institutional ethics review committee, and the requirement for informed consent was waived due to the retrospective nature of the study.

The data that support the findings of this study are available from the corresponding author, Ryuichi Noda, upon reasonable request.

Operative procedure

The Ommaya reservoir was implanted under general anesthesia, and a side-inlet-type reservoir was used for all patients. The Ommaya reservoir catheter was placed using the StealthStation™ Surgical Navigation System (Medtronic Co., Ltd, Minneapolis, MN, USA) or ultrasound guidance with a burr-hole type probe. Catheter insertion was performed using a single cranial burr hole with a small skin incision. The tip of the catheter was placed at the center of the cyst. The Ommaya reservoir was fixed at the subgaleal layer. The skin incision was closed layer by layer using 4-0 nylon sutures. After the reservoir placement, the cyst was aspirated via valve puncture.

Radiosurgical technique

The f-GKRS was performed using thermoplastic masks (frameless) for fixation, fractionated on either five or ten consecutive business days. The target volume was defined by MRI T1-weighted images with gadolinium enhancement, performed one business day before the first GKRS fraction. The tumor cyst was aspirated through the Ommaya reservoir immediately before this MRI to reduce the target volume maximally. The treatment was planned using the Leksell Gamma Plan Treatment Planning System (Elekta Instrument). In the treatment plan, the marginal dose was set with an additional margin of 1-2 mm from the contrast-enhanced area. The Ommaya reservoir punctures were performed regularly during the treatment period, before each fraction. Additional MRI for interim appraisal was performed on the fifth day for ten-fractionated patients, and the treatment plan was modified if necessary.

Statistical analysis

The means were calculated for the parameters of interest. Local tumor control and overall survival (OS) were analyzed using Kaplan–Meier curves. All statistical analyses were performed using R statistical software (R version 4.1.0; The R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

This study included six men and two women aged 64–82 years (median, 69 years). Five cystic tumors were located in the frontal lobes, two in the parietal lobes, one in the cerebellum, and one in the temporal lobe. The mean and median tumor volume was 48.2 mL, 27.3mL (13.0–145.6 mL). One patient underwent two procedures at the temporal and frontal lobes. The primary tumor was non-small-cell lung cancer in six patients (adenocarcinoma, four patients; squamous cell carcinoma, two patients), pancreatic cancer in one, and ureteral cancer in the other patient. The baseline patient demographics and clinical characteristics are presented in Table 1.

Surgical results

The mean volume of aspirated fluid was 37.3 mL (6–120 mL). The median interval between the Ommaya reservoir placement and f-GKRS was six days (2–7 days). GKRS was fractionated in five sessions for six lesions and ten sessions for the remaining three. The mean and median pre-GKRS volume (also defined as post-aspiration), were 16.7 mL and 10.1mL (5.0–55.8 mL) respectively. The mean maximum diameter was 39.0 mm (31.0–79.0 mm). The mean tumor reduction after the aspiration was 55.4% (13.2–90.9%; Fig. 1). The symptoms were alleviated for all patients after the operation. The prescription dose was 30–40 Gy, with a maximum dose of 42.9–54.1 Gy. During each treatment session, 1-13 lesions (the cysts and other general metastases) were treated. Only one patient had more than 30 lesions, and seven of these (possibly causing neurological symptoms) were selected and included in the treatment. All patients were followed up for at least two months afterward. The mean MRI follow-up duration was 9.2 (2–28) months, and the mean clinical follow-up duration was 10.2 (2–28) months. One patient had an Ommaya reservoir infection eight months after the surgery; a removal procedure was performed followed by six weeks of antibiotic treatment. Another patient had a tube obstruction one month after the surgery. This patient had the tube substituted with another because intermittent cyst aspiration via the Ommaya reservoir was still required. No adverse events related to irradiation were observed. The tumor volume was controlled for all nine lesions. The median OS was 10.0 months, and the estimated one-year survival rate was 41.7% (95% CI: 10.9-70.8%; Fig. 2). The tumor control rate was 100%.

Illustrative cases

Case 2

A 70-year-old male with right lung cancer (adenocarcinoma) was referred to our hospital to treat brain metastasis. MRI revealed multiple metastases, including a large cystic lesion in the right frontal lobe (Fig. 3a). Ommaya reservoir implantation was performed, and the tumor was reduced by 54.6%. Two days after surgery, GKRS was performed in five fractions (12.0 mL, 30 Gy/5 fractions, maximum dose 42.9 Gy), and its coverage included other small lesions (0.6 mL, 30 Gy/5 fractions, maximum dose 41.9 Gy; 0.3 mL, 30 Gy/5 fractions, maximum dose 42.9 Gy) (Fig. 3b). Aspiration from the Ommaya reservoir was performed only once (1 mL) during the GKRS; it was not performed after treatment. The treated lesions showed complete regression after two months and were maintained under control for 28 months after GKRS (Fig. 3c).

Case 3

A 65-year-old male with right lung cancer (adenocarcinoma) presented to the hospital with complaints of lethargy and deterioration of consciousness, lasting for a few weeks. MRI revealed multiple metastases, including a large cystic lesion in the left frontal lobe (Fig. 3d). Ommaya reservoir implantation was performed, and the tumor fluid was completely evacuated; the tumor volume was reduced by 90.9%. The neurological symptoms showed rapid improvement afterwards. Five days after surgery, GKRS was administered in ten fractions (10.1 mL, 35 Gy/10 fractions, maximum dose 48.6 Gy) to the shrunk cystic lesion (Fig. 3e) and other small lesions simultaneously (0.1 mL, 35 Gy/10 fractions, maximum dose 44.9 Gy; 0.1 mL, 35 Gy/10 fractions, maximum dose 46.1 Gy; 5.3 mL, 35 Gy/10 fractions, maximum dose 50.0 Gy). Aspiration from the Ommaya reservoir was performed twice (1 mL each) during the GKRS and only once in two months after treatment (10 mL). The treated lesions showed complete regression within six months and were under control for 25 months after GKRS (Fig. 3f).

Case 5

A 64-year-old male with left lung cancer (squamous cell carcinoma) presented to the hospital complaining of headaches. Physical examination revealed slight deterioration of consciousness and weakness in the left extremities. MRI revealed two cystic lesions in the right temporal lobe (Figure 3g) and right frontal lobe. Ommaya reservoir implantation was performed for the relatively large cystic tumor in the temporal lobe. After tumor fluid evacuation, reducing the tumor volume by 79.5%, the neurological symptoms rapidly improved. GKRS was started six days after the surgery and administered in ten fractions to the shrunk cystic lesion (8.1 mL, 35 Gy/10 fractions, maximum dose 47.3 Gy, Fig. 3h) and the other lesion (6.0 mL, 35 Gy/10 fractions, maximum dose 47.3 Gy). Aspiration from the Ommaya reservoir was performed before each GKRS fraction (1-13 mL) and every 1–2 weeks for the following two months (1.5–12 mL). The treated lesions showed complete regression within four months; the patient underwent another cyst aspiration and f-GKRS to the right frontal lesion four months later (Case 6). However, he died of lung cancer aggravation ten months after the first treatment. The treated lesion was controlled on the MRI performed right before his decease (Fig. 3i).

Discussion

In our report, the incidence of large cystic tumors treated with cyst aspiration and GKRS was 2.7%, consistent with previous reports [12–14]. The mean volume of the cystic tumors previously reported was 20.3–35.3 mL [6–10, 12–14]; in our series, it was 48.2 mL due to two massive cysts (145 and 110 mL). All of our cases had cystic lesions larger than 10 mL in volume and 3 cm in diameter; therefore, they were resistant to radiation therapy and had a high risk of radiation necrosis [2–4].

The cyst must be aspirated before GKRS to reduce the volume of the targeted lesion. This treatment method has been previously reported (Table 2) as a possible treatment strategy. The aspirated cyst fluid may also be used as a diagnostic specimen to exclude the possibility of brain abscess, which has a radiological appearance similar to cystic brain metastases. However, this method has some disadvantages. First, the high risk of recurrence even after the cyst fluid is successfully aspirated. In fact, the treatment effect of GKRS appears after a few months; fluid recollection in the cyst may occur after treatment, requiring another aspiration. Second, the tumor remains relatively large in volume and often has an irregular shape; therefore, it is an unfavorable candidate for stereotactic radiosurgery. This behavior may be the reason why local tumor control was not satisfactory in most of the previous reports.

Life expectancy has increased due to the rapid development of chemotherapy in recent years. Accordingly, the local tumor control rate of brain metastases should also be improving, and f-GKRS may be used for these conditions. The Gamma Knife ICON™ allows

fractionated frameless treatments for larger lesions. In a previous report, fractionated treatments were associated with a high tumor control rate and low morbidity [15]. On the other hand, the main drawback of fractionation is cyst re-expansion during GKRS sessions; consequently, the target may change shape or volume due to fluid collection during the treatment period. In this case, another aspiration is necessary, and GKRS must be re-scheduled.

The Ommaya reservoir may solve this problem by allowing repeated cyst aspiration. This device was designed as continuous ventricular access to the intrathecal space for cerebrospinal fluid sampling and chemotherapeutic delivery to the central nervous system. This reservoir eliminates the need for repeated lumbar punctures to obtain specimens or administer medication [16]. The procedure is straightforward and minimally invasive. The use of this device for cystic tumors has already been reported in previous articles and has been practiced in actual clinical settings. The tumor reduction rate is reported to be 52.6–77.9% of the volume [6, 7, 9, 14], consistent with our case series. Oshima et al. reported that successful catheter placement contributes to effective tumor reduction; the catheter tip should be placed in the cyst center to achieve maximum reduction of the cystic tumor [9]. We adopted this method for our cases by using an intraoperative navigation system. The Ommaya reservoir may prevent fluid recollection and maintain the target volume and shape by performing intermittent fluid aspiration during the f-GKRS treatment session. Repeated Ommaya reservoir punctures were required during and after GKRS sessions in our cases. There have been no reports of Ommaya reservoir implantation followed by f-GKRS in the past (Table 2).

Our treatment results are sufficiently favorable than those in previous articles reporting the combination of stereotactic cystic tumor aspiration and conventional GKRS. Compared with other reports, the tumor control rate improved with our approach. Therefore, f-GKRS combined with Ommaya reservoir implantation is a reasonable and effective method to treat large cystic brain metastases safely. It decreases the risk of radiation necrosis by fractionating the radiation dose and decreasing the cyst volume by Ommaya reservoir aspiration, which also prevents recollection of the intra-cystic fluid during and after the treatment, if necessary.

This treatment strategy has some limitations. One of the few disadvantages is the possible surgical site infection of the Ommaya reservoir, reported for 5.5–8% of patients in the literature [17–20]. We encountered one case of Ommaya reservoir infection during the chronic phase of the condition. Several punctures to the reservoir may be associated with the risk of infection-related complications. Moreover, our management strategy is high-maintenance and time-consuming. Intermittent aspiration from the reservoir before every fraction, or every few fractions, is required to maintain the cyst in its shrunken state (volume and shape similar to the initial treatment plan). In addition, the patient requires hospitalization for at least two weeks to undergo both the operative and radiosurgical treatments. Thus, the indication has to be considered in patients who are expected to have a relatively favorable prognosis. Considering all these factors, we believe that a favorable outcome still exceeds the negative aspects of this management. Our study is limited in number, and further data should be collected to expand the sample size.

This report is the first to demonstrate the effectiveness of Ommaya reservoir implantation and aspiration, followed by frameless f-GKRS. The significance of this report is that we have applied fractionation to the conventional treatment management of cystic brain metastases, by modifying simple cyst aspiration to intermittent Ommaya reservoir aspiration during and after treatment.

Conclusions

Ommaya reservoir implantation and aspiration followed by frameless f-GKRS is effective and safe. It should be considered as a management option for large cystic brain metastases to overcome the limitations of other modalities and improve patient outcomes.

Declarations

Funding: None declared.

Competing interests: None declared.

Author contributions: None declared.

Data availability statement: The data that support the findings of this study are available from the corresponding author, Ryuichi Noda, upon reasonable request.

Ethics approval: The study protocol was approved by the institutional ethics review committee.

Informed consent: The requirement for informed consent was waived due to the retrospective nature of the study.

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Tables

Table 1. Clinical characteristics of the 10 treated lesions.

Case	Age	Sex	Primary Cancer	Location	KPS	Pre-Asp (ml)	Post-Asp (ml)	Volume reduction rate (%)	No of Mets	Fractions	Margin dose(Gy)	Max dose (Gy)
1	68	Female	NSCLC (Adeno)	CER	60	27.3	23.7	13.2	3	10	40.0	54.1
2	70	Male	NSCLC (Adeno)	F	90	26.4	12.0	54.6	3	5	30.0	42.9
3	65	Male	NSCLC (Adeno)	F	60	110.8	10.1	90.9	4	10	35.0	48.6
4	65	Male	Pancreas	P	60	42.3	19.7	53.4	2	5	30.0	42.9
5	64	Male	NSCLC (Squamous)	T	70	39.4	8.1	79.5	2	10	35.0	47.3
6				F	70	13.0	9.1	29.7	1	5	32.5	44.5
7	70	Male	Ureter	P	70	145.6	55.8	61.7	2	5	30.0	50.1
8	73	Male	NSCLC (Squamous)	F	60	14.5	7.1	51.1	13	5	32.5	43.9
9	82	Female	NSCLC (Adeno)	F	60	14.1	5.0	64.6	>30*	5	32.5	45.2

*7 lesions were selected for treatment

NSCLC; Non-small cell lung cancer, Adeno; Adenocarcinoma, Squamous; Squamous cell carcinoma, CER; Cerebellum, F; Frontal lobe, P; Parietal lobe, T; Temporal lobe,

KPS; Karnofsky Performance Scale, Pre-Asp; Pre aspiration volume, Post-Asp; Post aspiration volume, No of Mets; Number of metastasis

Table 2. Previously published studies of Gamma knife radiosurgery combined with stereotactic aspiration.

Author	No of Pt	No of Mets	Aspiration method	Pre-Asp (ml)	Post-Asp (ml)	Reduction rate (%)	PD (Gy)	FU (month)	LTC (%)	OS (month)
Yamanaka Y et al., 2006 ¹⁴	22	28	Ommaya	33.8 (10.3-102.1)*	13.4 (3.6-48.2)	60.4	13.5 (8.0-20.0)	11.5 (4.0-36.0)	67.9	7.0
Franzin A et al., 2008 ¹²	30	33	Stereotactic	21.8 (3.8-68.0)	10.1 (1.2-32.0)	50.8	19.5 (12.0-25.0)	11.3 (1.0-36.0)	91.3	15.0
Park WH et al., 2009 ⁶	24	25	Ommaya 12 cases	23.2 (7.9-100.9)	4.3 (0.2-19.0)	77.9	20.2 (13.0-25.0)	13.1 (1.0-39.0)	54.2	17.8
Higuchi F et al., 2012 ¹³	25	25	Stereotactic	20.3 (8.0-64.2)	10.3 (3.0-36.2)	49.3	>20.0	11.0 (1.0-27.0)	76.2	NA
Jung TY et al., 2014 ⁷	24	NA	Ommaya	32.7 (12.1-103.3)	12.4 (3.7-38.1)	62.1	16.0 (14.0-20.0)	NA	58.6	6.8
Wang H et al., 2016 ⁸	48	NA	Stereotactic	26.8 (19.0-75.7)	5.4 (1.0-16.0)	79.9	18.0 (14.0-20.0)	36.2 (24.0-72.0)	91.7	19.5
Oshima A et al., 2017 ⁹	38	40	Ommaya	28.8 (4.4-94.0)	13.7 (1.0-66.3)	52.6	NA	NA	NA	NA
Sadik ZHA et al., 2021 ¹⁰	52	57	Stereotactic	35.3 (10.0-111.5)	14.2 (4.2-47.0)	56.4	20.0 (20.0-25.0)	NA	60.9	12.0
Current study	8	9	Ommaya	48.2 (13.0-145.6)	16.7 (5.0-55.8)	55.4	32.5	10.2 (2.0-28.0)	100.0	10.0

*The tumor volume was calculated by the diameter provided in the report.

No of Pt; Number of patients, No of Mets; Number of metastases, Pre-Asp; Mean pre-aspiration volume, Post-Asp; Mean post-aspiration volume,

PD; Prescription dose, FU; Follow-up, LTC; Local tumor controle, OS; Overall survival

Figures

Figure 1

The tumor reduction rate

Figure 2

Kaplan-Meier curve for overall survival

Figure 3

(a) Axial contrast-enhanced T1-weighted magnetic resonance image (CE-MRI) showing a large cystic metastasis located in the right frontal lobe ($41 \times 36 \times 37$ mm, 26.4 mL)

(b) GKRS dose-planning images of the shrunk cystic lesion after Ommaya reservoir aspiration. The yellow line indicates the 30-Gy margin, and the blue line shows the 20-Gy margin. The max dose is 42.9 Gy

(c) 28 months after GKRS, the tumor is kept control

(d) Axial CE-MRI reveals a large cystic brain metastasis in the left frontal lobe ($79 \times 48 \times 67$ mm, 110.8 mL)

(e) GKRS dose-planning images of the shrunk cystic lesion after Ommaya reservoir aspiration. The yellow line and the blue line indicate the 35-Gy margin and the 20-Gy margin, respectively. The max dose is 48.6 Gy

(f) 25 months after GKRS, the tumor is kept control

(g) Axial CE-MRI shows a large cystic brain metastasis in the right temporal lobe ($28 \times 31 \times 29$ mm, 39.4 mL)

(h) GKRS dose-planning images of the shrunk cystic lesion after Ommaya reservoir aspiration. The yellow line and blue line indicate the 35-Gy margin and 20-Gy margin, respectively. The max dose is 47.3Gy

(i) Ten months after GKRS, the tumor is controlled