

Gamma Knife Radiosurgery for Cancer Metastasized to the Ocular Choroid

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Objective : Choroidal metastases (CMs) are the most common intraocular tumor. Management is mainly radiation therapy with goals of pain control and visual improvement. However, many radiation-related complications are reported. Since gamma knife radiosurgery (GKS) for CM was first reported in 1995, few cases have been reported. We report 7 cases of CMs treated with GKS.

Methods : From April 2011 to November 2014, 7 patients with CM underwent GKS. Their median age at treatment was 64 years (range, 51–71 years). Four males and three females were treated. Lung cancer was the most common primary pathology, followed by renal cell carcinoma and stomach cancer. Four patients had multiple cerebral lesions and were treated simultaneously for choroidal lesions. The median marginal dose of 20 Gy (range, 15–25 Gy) was administered at the 50% isodose line.

Results : Median follow-up period after GKS was 8 months (range, 2–38.3 months). Four patients expired due to underlying malignancy progression. Except for two patients who were not followed with magnetic resonance image after GKS, all patients showed size reduction in the treated lesions, but a new choroidal lesion appeared in one patient and one recurred. Six of seven patients reported subjectively improved visual symptoms. Visual acuity improved in 2 patients, and 2 were stable upon objective examination. One patient showed no improvement in visual acuity, but ocular pain was relieved; another patient showed improved vision and tumor remission, but visual deterioration recurred.

Conclusion : GKS was shown to be safe and effective and should be considered for CM treatment.

Key Words : Gamma knife radiosurgery · Choroid · Metastasis · Orbit.

INTRODUCTION

Choroidal metastases (CMs) are the most common intraocular tumor⁸⁾. The differential diagnosis includes primary choroidal melanomas, benign lesions such as hemangiomas, and inflammatory granulomas. Generally, CMs occur later than metastases to other organs¹⁰⁾. The frequency in autopsy studies varies from 0.5% to 10%²⁾. However, as patients are living lon-

ger with metastatic cancer, choroidal metastases may become more common⁵⁾. Management of CMs was treated by globe enucleation until the 1980s, but radiotherapy has become popular with goals of pain control, visual improvement, and eyeball preservation¹¹⁾. The most commonly used radiation therapies are external beam radiotherapy (EBRT) and plaque brachytherapy. Local tumor control is acceptable in both methods, although 85–93% regression is seen in patients

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treated with EBRT and 94% regression in patients treated with plaque brachytherapy⁴). Treatment-related complications were reported in 12–17% of EBRT patients and 8% of brachytherapy patients^{4,15,17}. Patients who live longer have a higher probability of developing side effects, and as new modalities of treatment prolong life expectancy, the number of ocular complications from radiotherapy is also expected to rise¹⁵. Gamma knife radiosurgery (GKS) is frequently used to treat intracranial metastatic lesions, but few cases have been reported for treating tumors metastasized to the choroid^{9,12}. We report 7 CM patients who were treated with GKS to alleviate their ocular symptoms. The purpose of this study was to evaluate the safety and effectiveness of GKS over conventional treatment methods as a treatment for CMs.

MATERIALS AND METHODS

Patient demography

Between April 2011 and November 2014, 12 patients underwent GKS for choroidal tumors. Five patients were diagnosed as having primary choroidal melanoma using imaging studies such as magnetic resonance imaging (MRI), ultrasonography, and funduscopy exams. Seven patients who had a choroidal tumor with metastatic features on image findings were diagnosed with CM, and tumor origin was estimated from pathology of the underlying malignancy. Median choroidal metastasis patient age was 64 years (range, 51–71 years), and four were male. Underlying patient malignancy pathologies were lung cancer in 5 (4 adeno-carcinoma and 1 small cell carcinoma), 1 advanced gastric cancer, and 1 renal cell carcinoma.

Ophthalmologic exam

Visual acuity (VA) was assessed before and after GKS using the modified Snellen chart. Change in VA was reviewed retrospectively from electric medical records. VA was followed after GKS and was measured at the first visit in the outpatient office and at every visit afterward (median, 8; range, 2–39.8 months). Ocular ultrasonography A and B-scans were performed in 4 patients for differential diagnosis of metastasis pathologies. MRI of the orbit or brain was performed every other 3 months before other treatments needed for progressive disease. Five patients were followed with MRI, but two pa-

tients who presented with rapidly worsened systemic disease did not receive MRIs after GKS. Choroid examination with funduscopy was performed in every patient before GKS, and 4 were followed for an average of 7.2 months (range, 0.4–18.9 months).

Radiosurgery technique

Every patient was treated with the Leksell Gamma Knife model Perfexion (Elekta AB, Stockholm, Sweden). Retrobulbar block and bridle suture were performed by an ophthalmologist before treatment. Then, the Leksell stereotactic frame was fixed on the patient's head, and the suture was tied to the frame. Critical structures such as optic nerve, macula, and lens were mapped to avoid radiation if possible. The median dose delivered to the tumor was 20 Gy (range, 15–25 Gy) at the 50% isodose line. Four patients (57.1%) had multiple brain metastases that were treated simultaneously with different doses depending on tumor size and volume.

Patient demographics, results of radiologic and ophthalmologic exams, and their follow-up exams were reviewed and approved by the Institutional Review Board of Samsung Medical Center, Seoul, Korea (IRB No. SMC 2016-04-063).

RESULTS

Worsening of VA was the most common complaint at choroidal metastasis diagnosis, reported in 6 of 7 patients (85.7%). Visual field defects, ocular pain, and headache were seen in 2 patients (28.6%). Median follow-up period from diagnosis was 26.8 months (range, 0.4–53.2 months). Median follow-up period after GKS was 8 months (range, 2–38.3 months). Four patients expired due to progression of underlying malignancy.

Radiologic outcomes

Five patients who were followed with MRI showed complete ocular tumor remission. One (14.3%) developed new choroidal metastasis, and another (14.3%) showed tumor recurrence in the anteromedial aspect of the original lesion. Findings seen on MRI pre- and post-GKS are displayed in Fig. 1. Two patients (28.6%) showed reduction of choroidal and cerebral tumors after initial treatment but developed new metastatic intracranial lesions and received repeated GKS for those lesions.

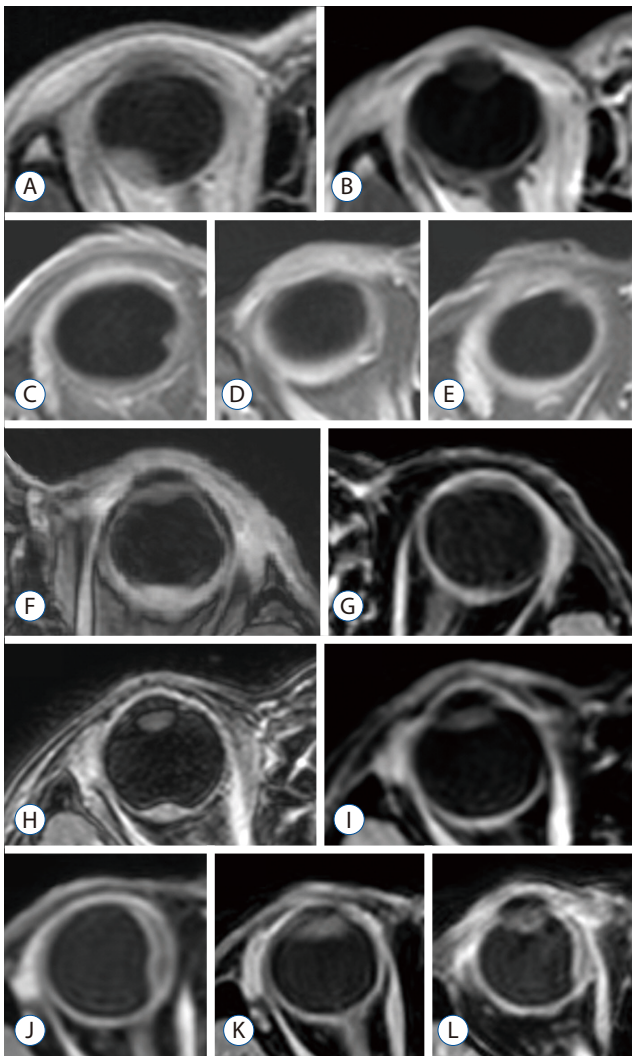


Fig. 1. Magnetic resonance image findings before (A, C, F, H, J) and after gamma knife radiosurgery (B, D, G, I, K). Complete tumor remission was seen in cases 1, 3 and 4 (B, G, I). In case 2, complete remission was noted with a new choroidal metastasis (D and E). A recurrent tumor was found in case 7 (L).

Four patients presented with multiple cerebral metastases. Among them, 2 had more than 10 metastases that were locally controlled but were aggravated by newly developed lesions at other sites in the brain. Two other patients had only one cerebral lesion and one choroidal lesion, which were both successfully diminished after GKS.

Ophthalmologic outcomes

Six of seven (85.7%) patients showed subjective symptom improvement after GKS. Improvements in VA were confirmed by objective examination in 2 patients (28.6%), while 2

(28.6%) showed subjective improvement but unchanged objective values. One (14.3%) patient who complained of severe ocular pain and could not perceive light in the eye on the same side as the tumor reported improvements in pain but not VA. One (14.3%) patient's VA was not improved after treatment though his treated lesion disappeared after 2 months. A new lesion developed supero-anteriorly in this patient, and he complained of eyeball pain. One other patient's (14.3%) symptoms were stable, with near complete tumor remission seen on MRI at the 4 month follow-up. However, her vision began to decline, and a tumor recurred in the choroid and also at multiple brain sites 9 months after GKS. In this patient, fundusoscopic findings after GKS showed disappearance of the tumor with retinal degeneration and flattening of subretinal detachments due to fluid collection.

Complications

One patient (14.3%) presented with cataract, which were aggravated and needed surgery after GKS. He had bilateral thin epiretinal membranes (ERM) and also showed bilateral positive cortical opacity before GKS. He underwent an operation on the contralateral eye just 5 months after GKS and the ipsilateral eye at 19 months after GKS. Another patient complained of eyeball pain after GKS and experienced increased eye pressure up to 26 mmHg. His MRI showed disappearance of the initial treated lesion but appearance of a new lesion. There were no complications directly related to treatment. Patient outcomes and complications after GKS are described in Table 1.

Case illustrations

Case 4

A 67-year-old male with lung adenocarcinoma had hyperemia and reported slight pain in his left eye. A brain MRI conducted to evaluate metastatic lesions showed tumors on the posterior wall of the left eyeball and parietal lobe (Fig. 1H). Fundusoscopic exam showed an inferior choroidal mass with exudative retinal detachment (Fig. 2A). Visual acuity was 0.08 before treatment, and the superior field was dark. The patient had ERM and bilateral dimmed lens opacity before GKS. For treatment, 20 Gy at the 50% isodose line was applied to both choroidal and cerebral lesions. Follow-up MRI showed decreased tumor size in both lesions, which was sustained for 27

Table 1. Demographics and outcomes of patients

	Sex	Age	Primary cancer	Initial Sx	BCVA pre	BCVA post	Tumor change	Subjective outcome	Complications
Case 1	F	51	NSCLC	Decreased VA	0.15	0.15	CR	Widened vision, distinguish colors	-
Case 2	M	64	RCC	Ocular pain	lp-	lp-	CR/new lesion	Pain relief	-
Case 3	M	67	AGC	Foreign sense with dimness	hm+	hm+	CR	Worse vision	Eyeball pain*
Case 4	M	71	NSCLC	Visual field defect	0.08	0.8	CR	Improved upper visual field improved vision after cataract OP	Cataract†
Case 5	F	54	NSCLC	Difficulty focusing	1.0	1.0	CR	Improved vision	-
Case 6	M	70	SCLC	Blurred vision	0.2	0.8	N/A	Improved vision	-
Case 7	F	60	NSCLC	Ocular pain and decreased VA	0.9	0.2	Recurrence	Vision initially improved but then worsened	-

All NSCLC were adenocarcinoma subtype. *Elevated eye pressure with newly developed metastases. †Cataract may have been aggravated by radiation but already existed before treatment. Sx : symptom, BCVA : best corrected visual acuity, F : female, NSCLC : non-small cell lung cancer, CR : complete remission, M : male, RCC : renal cell carcinoma, lp- : cannot detect light, hm+ : able to detect hand motion, AGC : advanced gastric cancer, SCLC : small cell lung cancer, N/A : not available

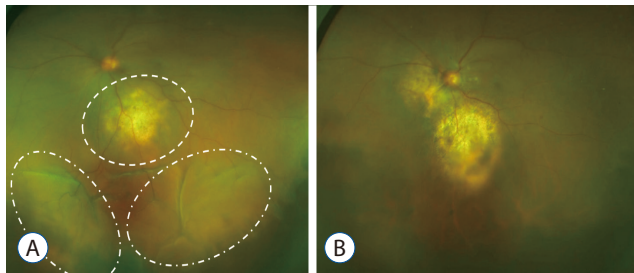


Fig. 2. Funduscopy exam of case 4. A : Choroidal mass with exudative retinal detachment is seen on the inferior side of the macula. B : Mass disappearance and fluid collection with retinal flattening are shown. Elevated retina due to tumor is marked with a short dashed line, and fluid collection is marked with a dot and dash line.

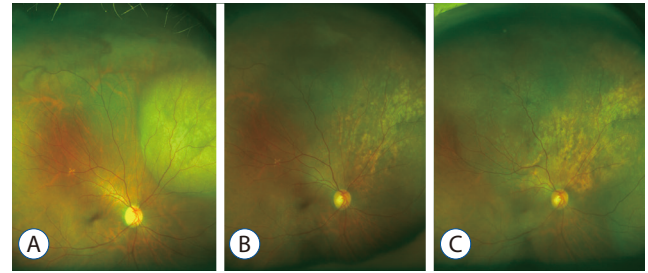


Fig. 3. Funduscopy exam of case 7. A : Mass with subretinal fluid collection is found on the superolateral side of the macula. B : Flattening of retinal detachment and decrease in mass size are seen after 5 months. C : After 9 months, increasing size of metastases with subretinal fluid collection was noted.

months (Fig. 1I). However, multiple intracerebral lesions developed and were treated with repeated GKS. His VA improved to 0.6 after GKS and to 0.8 after cataract surgery 19 months after GKS. His funduscopy exam showed disappearance of the mass and fluid accumulation with retinal flattening (Fig. 2B).

Case 7

A 60-year-old female with lung adenocarcinoma reported intermittent flashing in her right eye and mild supraorbital tenderness. She had metastases on her choroid and cerebellum on MRI, and funduscopy exam showed a mass with subreti-

nal fluid collection (Fig. 3A). Her VA was 0.9 and showed no field defects. She was treated with 15 Gy to the choroid and 24 Gy to the cerebellar lesion at the 50% isodose line. Her tumor almost disappeared and was stable for 5 months. Funduscopy exam also showed flattening of the retinal detachment and a decrease in mass size (Fig. 3B), but VA gradually worsened, and MRI after 9 months showed a recurrent tumor on the choroid and multiple newly developed intracranial lesions. Additionally, her funduscopy exam also showed increasing metastases sizes with subretinal fluid collection (Fig. 3C). Her VA dropped to 0.2, and her systemic cerebral lesions were

again treated with GKS.

DISCUSSION

The goal of therapy for choroidal metastasis is to preserve VA and to reduce pain. To these ends, a variety of radiation treatment methods have been used^{3,7}. EBRT and brachytherapy are used with acceptable tumor reduction rates^{4,17}. However, the relatively high doses of radiation in EBRT could affect radiosensitive intraocular structures near treated lesions and the contralateral orbit. In addition, the long treatment periods, 3 to 5 weeks, needed for fractionation can be another disadvantage of conventional EBRT^{15,21}. Brachytherapy can be used to treat either primary diagnoses or tumors that were not controlled with EBRT and results in good outcomes¹⁷. However, the technique requires general anesthesia and invasive surgery for insertion and removal of the plaque under the sclera. There are also complications related to this radiation treatment including maculopathy, retinopathy, and optic neuropathy. All of these complications affect overall VA, and 26–62% of treated eyes experience a loss of 2 or more Snellen lines²⁰.

GKS delivers a single dose of ionizing radiation to a well-defined volume that has steep dose gradients outside the target, thus minimizing radiation complications. GKS has been widely used for treatment of intracerebral lesions especially in cases of multiple brain metastases. GKS has also been performed in intraocular lesions, especially in primary choroidal melanoma^{6,13}. The local control rate of choroidal melanoma with GKS was 94.4% with an 81.6% eye preservation rate¹⁹. Odell¹⁴ showed that radiation sparing in GKS was excellent compared to brachytherapy. However, only 2 cases of choroidal metastasis treated with GKS have been reported^{9,12}.

In this study, we treated 7 choroidal tumors metastasized from other primary organs with GKS. Most patients showed improvement in subjective symptoms, and radiological improvement was noted in every case. Though the median follow-up period was not long enough to evaluate radiation-related complications (39.5 weeks), 2 patients who were followed more than one year showed no complications related to GKS. A limitation of this study is that patients with systemic cancer seldom survive long term. However, emerging therapeutic agents such as biomarker-targeted agents are extending cancer patients' lives. Once radiation treatment is applied, side effects

follow. As a patient lives longer, complications from radiation treatment will increase¹⁵. GKS may target lesions more precisely with good lesion control rates and good visual sparing with fewer complications.

In our small series of 7 cases, 4 showed multiple cerebral lesions accompanied by choroidal lesions. Though there are no direct correlations between incidence of brain metastases and choroidal metastases, choroidal metastases are known to occur at late stages of cancer, and the average interval is 3 to 6 years from diagnosis¹⁸. The interval between initial cancer diagnosis and cerebral metastases varies depending on original pathology, but the average is 2 months to 3.6 years¹⁶. Comparing the time course of brain and choroidal metastases, there is greater chance of choroidal metastases combined with brain metastases. Though GKS has already been shown to achieve excellent local control of intracranial lesions, it is especially recommended when choroidal metastases occur in combination with cerebral metastases.

Systemic chemotherapy, immunotherapy, or hormone therapy is also known to affect CMs^{1,18}. One limitation of this study is that those who were being treated with systemic chemotherapy changed their regimen when CM progression was found. Thus, the effects of systemic chemotherapy on CM could not be excluded. However, 3 patients who were not receiving systemic treatment also showed CM regression. Further study comparing systemic treatments should be conducted.

CONCLUSION

GKS for treatment of choroidal metastasis is not widely used. However, as GKS overcomes the limitations of EBRT widely used to treat intracranial lesions, choroidal lesions can also be treated safely and effectively with GKS. Patients harboring choroidal metastases and other multiple cerebral metastases could also be treated with GKS. Furthermore, GKS might play a major role or even be substituted for conventional radiotherapies.

PATIENT CONSENT

The patient provided written informed consent for the publication and the use of their images.

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