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Gamma Knife Radiosurgery for Central Neurocytomas

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Abstract

The long-term outcome of gamma knife radiosurgery (GKS) for central neurocytomas remains unclear. In the present study, we retrospectively reviewed the medical records of 7 patients with 8 central neurocytomas who underwent GKS between March 1997 and April 2007. They were 3 men and 4 women age ranging 9 to 53 years old (mean 32.5 years old). The tumor volume at the time of GKS was 0.34–6.10 cm^3 (mean 3.86 cm^3). All patients had undergone 1 to 3 incomplete surgical resections (mean 1.75) before GKS, the surgical specimen being evaluated histologically and immunohistochemically. The follow-up period after GKS was 15 to 136 months (mean 63.6 months). The tumors were treated with a marginal dose of 12–18 Gy (mean 13.9 Gy). Only one of the seven patients died of tumor recurrence and intracranial hemorrhage 40 months after GKS. The other tumors remained progression-free. The control rate of the tumor growth was 7/8. Although histological malignant transformation is rare, the postoperative course of this tumor is not always good, showing tumor progression, intracranial hemorrhage, or craniospinal dissemination. Therefore, we recommend GKS for residual or recurrent tumors especially at early detection before tumor progression.

Key words: central neurocytoma, radiosurgery, gamma knife, recurrence, malignancy

Introduction

Central neurocytoma is a rare type of neuronal tumor with benign histology and biological behavior, which accounts for approximately 0.1% of all the primary central nervous system (CNS) tumors.[2,3,5–14,16,19,31,32,36] They are usually located in the lateral ventricles with or without extension to the third ventricles in young adults.[2,3,8,10,19]

Standard initial treatment for central neurocytomas is a total resection whenever possible.[1,2,8,16,17,19,27] Histological and immunohistochemical examinations are necessary to establish the diagnosis differentially from oligodendroglioma or ependymoma.[3,8,9,13,15,19,22,29] The prognosis is usually favorable after gross total resection. However, malignant transformation is known to occur in a few cases, resulting in tumor progression, intracerebral hemorrhage, or craniospinal dissemination.[3,7,11,24,30,34] Malignant transformation is associated with atypical neurocytoma after total or incomplete resection followed by conventional radiotherapy, which can be differentiated from malignant neuronal tumors, such as cerebral neuroblastoma or primitive neuroectodermal tumor.[9,15,20,29] Local recurrence is not rare after incomplete surgical resection, leading to tumor progression, intracerebral hemorrhage, or craniospinal dissemination, with or without any indication of malignant change.[3,4,6,7,11,12,14,15,17,21,24,27,29,30,32]

Central neurocytoma tends to be radiosensitive, so postoperative conventional radiotherapy and radiosurgery have been used to treat residual tumors after incomplete surgical resection or recurrence.[15,20,23–26,31,32,34] Gamma knife radiosurgery (GKS) is effective against postoperative residual tumors or local recurrences of central neurocytomas.[1–3,6,9,13,14,25,27,28,35,37] However, central neurocytoma is rare and often resected completely, with conservative treatment for the relatively small residual or recurrent tumors. Therefore, radiosurgery is indicated for very few tumors, so many of these studies have involved small patient and tumor populations, which are not adequate for definitive conclusions, and the long-term efficacy remains unclear.

The present study retrospectively investigated the results of GKS in patients with central neurocytomas to assess the efficacy for tumor growth control and clarify the clinical indications for GKS in these tumors.

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Materials and Methods

Seven patients, three men and four women aged from 9 to 53 years (mean 32.5 years), with eight central neurocytomas were treated by GKS at Yokohama Rosai Hospital between March 1997 and April 2007. All patients had undergone 1 to 3 total or subtotal surgical resections (mean 1.75) before GKS, and all tumors were identified histologically and were immunohistochemically positive for synaptophysin. No patient had received conventional radiotherapy or chemotherapy after the surgical procedures. Seven tumors were located in the lateral ventricle, one of which extended into the third ventricle, and one tumor was confined to the third ventricle. The tumor volume at the time of GKS ranged from 0.34 to 6.10 cm^3 (mean 3.86 cm^3). GKS was performed for residual tumor after subtotal surgical resection in 7 patients with 7 tumors, and recurrent tumor in one patient. The period from surgical resection to radiosurgical procedure ranged from 1 to 51 months (mean 18.4 months).

Stereotactic GKS was performed with the Leksell gamma unit (model B; Elekta Instrument AB, Stockholm, Sweden) and Gamma Plan software (Elekta Instrument AB) based on magnetic resonance (MR) imaging. The marginal dose was 12–18 Gy (mean 13.9 Gy) (Table 1) with the 50–75% isodose line (mean 55.6%), and the maximum dose was 16–34.1 Gy (mean 25.8 Gy). All patients underwent periodic clinical and radiological follow-up MR imaging at 6-month intervals after the radiosurgical procedure.

Clinical and radiographic examinations were obtained from the patients and their referring physicians. The retrospective analysis evaluated the changes in tumor size measured on axial and coronal MR images by the same investigator (S.M.) in conformity to RECIST (Response Evaluation Criteria In Solid Tumors).[33] The effect of GKS was classified using the following categories: complete remission, complete disappearance; partial remission, decrease in tumor size of more than 25% but not disappearance; no change, no obvious change in tumor size; and progression, increase in tumor size of more than 25%. Complete remission, partial remission, and no change were considered to indicate tumor growth control.

Table 1 Marginal dose and number of tumors

Number of tumors	Dose delivered to the tumor margin (Gy)						
	12	13	14	15	16	17	18
Controlled	2	1	2	0	1	0	1
Uncontrolled	1	0	0	0	0	0	0

Tumors were treated with a marginal dose of 12–18 Gy (mean 13.9 Gy), using a marginal dose of more than 13 Gy to obtain good tumor growth control.

Results

MR imaging showed complete remission in 1 tumor, partial remission in 4 tumors, no change in 2 tumors, and progression in 1 tumor (Table 1). Therefore, the tumor growth control rate was 7/8. One patient died of neurological damage induced by tumor progression with intracranial hemorrhage at 40 months after GKS. The follow-up period ranged from 15 to 136 months (mean 63.6 months). No radiation-induced peripheral edema or radiation necrosis was found in our patients during the follow-up period.

Illustrative Case 1, controlled tumor: A 32-year-old man initially presented with facial dysesthesia. MR imaging showed a slightly enhanced mass in the left

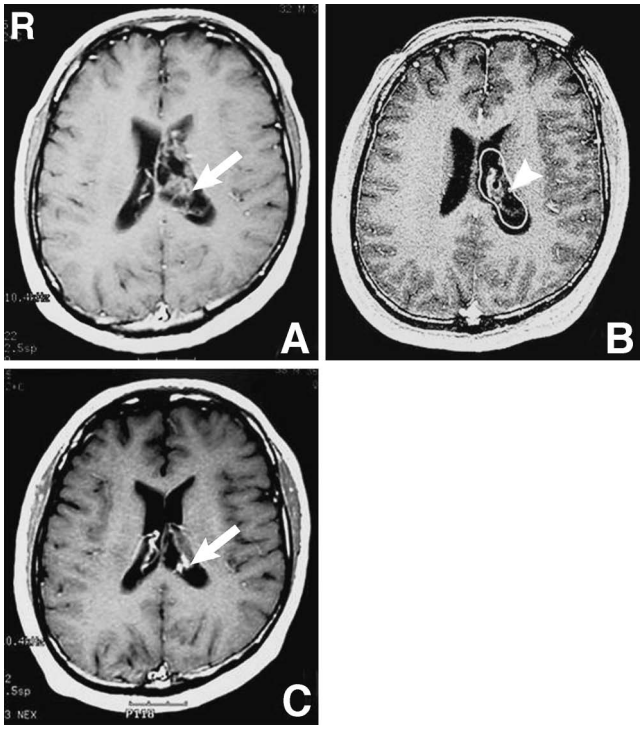

Fig. 1 Case 1. Axial T_1-weighted magnetic resonance images with gadolinium enhancement, (A) on admission revealing a slightly enhanced mass in the left lateral ventricle without hydrocephalus (*arrow*), (B) after incomplete surgical excision showing the radiosurgical plan for the residual tumor (*arrowhead*), and (C) 49 months after gamma knife radiosurgery showing shrinkage of the residual tumor (*arrow*).

lateral ventricle without hydrocephalus (Fig. 1A). Subtotal surgical excision was performed through the anterior transcallosal approach. Histological and immunohistochemical findings indicated typical neurocytoma. Three months after craniotomy, he underwent GKS for the residual tumor with a peripheral dose of 14 Gy to the 55% isodose line (Fig. 1B). He tolerated the procedure well without neurological deficit. Follow-up MR imaging demonstrated the residual tumor had shrunk and no radiation-induced morbidity had occurred by 49 months after the radiosurgical procedure (Fig. 1C). He has remained well without neurological deficit and continues to undergo periodic follow-up MR imaging.

Illustrative Case 2, controlled and uncontrolled tumors: A 41-year-old woman underwent initial total surgical resection of a left lateral ventricle tumor associated with hydrocephalus in another institution in February 1989. Histological and immunohistochemical examinations identified typical neurocytoma with benign characteristics. Follow-up MR imaging revealed tumor recurrence, so linear accelerator radiosurgery with a peripheral dose of 25 Gy was performed in April 1997. However, 22 months after radiosurgery the tumor enlarged, so surgical resection was performed and pathological diagnosis was radiation necrosis without tumor cell. At a later time, MR imaging indicated a newly developed tumor outside of irradiated area, so the tumor was removed incompletely in November 1998. Histopathological analysis was similar to initial surgical specimen (Fig. 2A). She was then referred to us for GKS to treat the residual tumor in April 1999. The peripheral dose was 12 Gy to the 50% isodose line. Follow-up MR imaging 11 months after GKS showed complete regression of the residual tumor. However, MR imaging 25 months after radiosurgical procedure indicated tumor recurrence in several regions remote from the irradiated area in the left lateral ventricle, mainly in the inferior horn. Therefore, GKS was repeated with a peripheral dose of 12 Gy to the 75% isodose line in October 2001 (Fig. 3A). Although MR imaging demonstrated significant reduction in tumor volume 6 months after radiosurgical procedure (Fig. 3B), MR imaging after 19 months suggested gradual increase in tumor volume (Fig. 3C). Therefore, the tumor was subtotally resected through a third craniotomy in June 2003. Histological examination indicated malignant transformation with many mitotic figures and vascular proliferation (Fig. 2B), and higher MIB–1 labeling index than that of the primary tumor. The residual

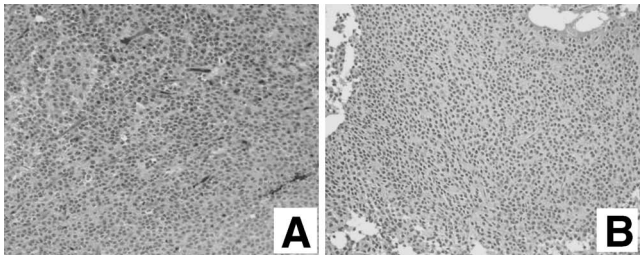

Fig. 2 Case 2. Photomicrographs of the surgical specimen demonstrating (A) sheets of small and round cells with central regular nucleus and perinuclear halos in the background suggesting typical neurocytoma, and (B) malignant transformation with enlarged and pleomorphic cells, mitotic figures, and vascular proliferation. Hematoxylin and eosin stain, original magnification ×100.

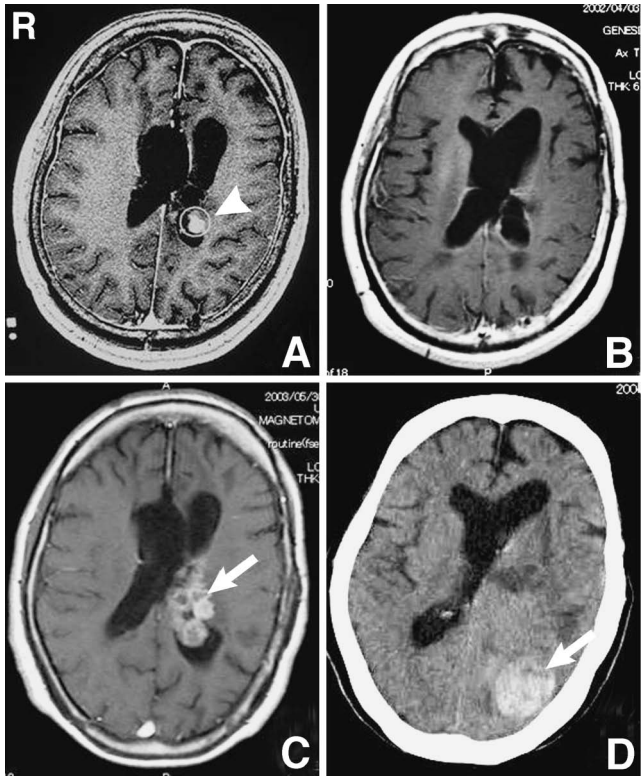

Fig. 3 Case 2. (A) Axial T_1-weighted magnetic resonance (MR) image with gadolinium enhancement at second gamma knife radiosurgery (GKS) demonstrating the 75% isodose curve surrounding the margin of the recurrent tumor in the left lateral ventricle, mainly in the inferior horn (*arrowhead*). (B) Follow-up MR image showing significant reduction in the tumor volume 6 months after second GKS. (C) Repeat MR image at 19 months after second GKS suggesting increased tumor volume (*arrow*) which was treated subtotally by third craniotomy. (D) Computed tomography scan 17 months after third craniotomy showing rapid progression of the residual tumor and intracerebral hemorrhage in the left occipital lobe (*arrow*).

tumor remained stable for some time, but computed tomography 17 months after the third craniotomy showed tumor progression and intracerebral hemorrhage in the left occipital lobe (Fig. 3D). She died in February 2005, 16 years after the first craniotomy.

Discussion

Recent studies of central neurocytomas treated with radiosurgery since 1997 have demonstrated good response and tumor growth control (Table 2).[1–3,6,9,13–15,18,22,23,25,27,28,35,37] Radiosurgery is generally indicated for patients with residual tumors after incomplete resection or tumor recurrence after early detection, so tumor volumes were relatively small in many cases. Central neurocytomas tend to have high radiosensitivity because of their high vascularity.[8,13,15] Therefore, a relatively low dose of not more than 20 Gy delivered to the tumor margin tends to obtain good tumor growth control and reduces the risk of radiation injury. The present study found that the relatively low marginal dose of 13 to 18 Gy could suppress local recurrence (Table 1).

Central neurocytomas usually arise from the neuronal cells of the septum pellucidum, fornix, or subependymal plate of the lateral or third ventricle, so these tumors are surrounded by cerebrospinal fluid and occur as a small tumor attached to normal structures.[7,8,10,16,26,27,31] Therefore, radiosurgery has a lower risk of radiation injury than conventional radiotherapy because of the small target volume, relatively low marginal dose for tumor growth control, and steep fall-off into the peripheral normal tissue. The present series included no complication caused by radiation-induced peripheral edema or radiation necrosis, and previous studies identified only one case of side effects (Table 2). Conventional radiotherapy and radiosurgery tended to be significantly effective for suppression of residual or recurrent tumor progression, but showed no significant effects for local tumor growth control and survival.[20,27] Therefore, we recommend GKS for residual central neurocytomas after subtotal resection or early detection of tumor recurrence with relatively small volume, which will reduce the long-term risk of radiation injury to the surrounding normal brain tissue compared with conventional radiotherapy. We recommend that conventional radiotherapy should be reserved for cases of craniospinal dissemination, especially in young patients.

Central neurocytomas are generally described as benign, but relatively high local recurrence rates of 21–33% have been reported for CNS primary benign tumors over long follow-up periods, even after complete resection or radiotherapy after incomplete resection.[3,5,19] Only Case 2 in our series remained uncontrolled after GKS due to tumor progression with recurrence during the long-term follow up after initial craniotomy. The tumor had recurred repeatedly after remaining in remission despite several surgical resections. GKS-induced tumor volume reduction and almost complete disappearance were

Table 2 Reported cases of central neurocytoma treated by radiosurgery

Author (Year)	Number of patients	Number of tumors	Method of SRS	Mean marginal dose (Gy)	Mean tumor volume (cm^3)	Number of tumors progressing after SRS	Number of patients with radiation injury	Mean follow-up period (mos)
Schild et al. (1997)[28]	1	1	GKS	15	ND	0	0	ND
Kim et al. (1997)[18]	1	1	ND	ND	ND	0	0	ND
Maruyama et al. (1999)[23]	1	1	LINAC	24	ND	0	0	6
Anderson et al. (2001)[1]	4	4	GKS	17	7.0	0	0	16.5
Bertalanffy et al. (2001)[2]	3	3	GKS	12.8	3.9	0	0	32
Cobery et al. (2001)[6]	4	4	GKS	10.5	14.8	0	0	44
Pollock and Stafford (2001)[25]	1	1	GKS	18	2.7	0	0	34
Tyler-Kabara et al. (2001)[35]	4	4	GKS	16.3	3.4	0	0	45.8
Hara et al. (2003)[9]	1	1	GKS	20	5.7	0	0	12
Javedan et al. (2003)[13]	1	1	GKS	18	ND	0	0	25
Kim et al. (2003)[15]	1	1	LINAC	17.5	ND	0	0	17.5
Martin et al. (2003)[22]	4	4	LINAC	17.6	3.2	0	1 (edema)	33
Bertalanffy et al. (2005)[3]	3	3	GKS	9.6–16	ND	0	0	127
Rades and Schild (2006)[27]	21 (15/6)	21 (15/6)	GKS/LINAC	15	ND	1	0	42
Yen et al. (2007)[37]	7	9	GKS	16	6.0	0	0	60
Kim et al. (2007)[14]	13	13	GKS	15	10.7	2	0	61
Present study	7	8	GKS	13.9	3.9	1	0	63.6

GKS: gamma knife radiosurgery, LINAC: linear accelerator, ND: not described, SRS: stereotactic radiosurgery.

achieved twice, for the residual and recurrent tumor after surgical procedures. However, the tumor recurred again in a neighboring region to the primary tumor several years later. Ultimately she died of the effects of tumor progression with intracranial hemorrhage after several surgical and radiosurgical procedures. Similar cases of change in the biological behavior of the tumor from benign to malignant variants with aggressive growth have been reported.[4,6,14,15,17,21,27,29,32,36] Therefore, central neurocytomas may not always remain benign in the long term.

Central neurocytoma tends to show local recurrence leading to clinical malignant sequelae such as tumor progression, intracranial hemorrhage, or craniospinal dissemination, although histological examination often indicates benign origin and rarely shows malignant transformation. Therefore, we recommend GKS for small residual or recurrent tumors rather than conservative follow up, using a marginal dose of more than 13 Gy to obtain good tumor growth control. Patients with central neurocytomas treated by GKS should be followed up for a long period, and repeat GKS should be considered for tumor growth control after early detection of recurrent tumor. An intergroup study is needed to assess the efficacy of GKS for central neurocytomas to provide statistical analysis of a large number of patients and long-term follow up.

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Commentary

Matsunaga et al. reported a case series of seven patients with eight central neurocytomas managed with adjuvant gamma knife radiosurgery (GKS). Tumor control was achieved in seven of eight tumors without radiation-related complications. Interestingly, authors showed a unique experience that the response to GKS was different with malignant transformation in a patient. The total resection of tumor is curative, but is not always feasible because of hypervascularity, deep location and surrounding critical structures. The radiosurgery is an attractive adjuvant treatment modality for central neurocytoma. Firstly, the results of conventional radiotherapy revealed radiosensitive characteristics and long-term tumor control. Secondly, there were several structural advantages for radiosurgery. The tumor is located in the ventricle and only a small portion of tumor is attached to the normal parenchyma. The cerebrospinal fluid (CSF) between tumor and surrounding structures makes it possible to reduce radiation to normal parenchyma. In addition, the tumor is round in shape and the margin is easily demarcated from the surrounding tissue on imaging studies. Based on these features, GKS for central neurocytoma showed satisfactory results in local tumor control, survival, and treatment-associated complications. Typical radiological findings such as intraventricular location, multiple intratumoral cysts and calcification allow the presumptive diagnosis and the trial of GKS as a primary treatment without histopathologic evidence. The planning of radiosurgery is the most important factor for successful results. In some cases, it is not easy to delineate the whole tumor margin because the signal intensity of tumor on magnetic resonance (MR) imaging is similar to that of CSF or normal white matter. There-

fore, regular long-term follow-up MR imaging should be mandatory to validate the procedure. This manuscript pointed out the role of GKS as an important adjuvant treatment and is a valuable contribution to the management of central neurocytoma.

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Matsunaga and colleagues report a series of seven cases of intracranial central neurocytomas treated by multimodality management which included one or more surgical procedures and one or more gamma knife radiosurgical procedures in follow up. All patients had histological confirmation of the diagnosis prior to radiosurgery. One patient died of tumor progression and delayed intracranial bleeding. Most patients with central neurocytomas require multimodality management, and early radiosurgery is important. Because of their histological properties and anatomic location arising from the septum pellucidum or in the region of the fornix and lateral ventricle, histological diagnosis is critical to separate this tumor out from those tumors that can mimic their initial imaging presentation. Such tumors include subependymoma, ependymoma, and oligodendroglial tumors.

This paper also reports the potential of neurocytomas to undergo malignant progression after both surgery and radiosurgery. Such anaplastic tumors behave aggressively and have high recurrence rates, either locally or in distant regions within the brain or in the cerebrospinal fluid pathways. The radiosurgical dose that is necessary to control such tumors is not currently well defined. Doses of 12 Gy at the edge of the imaging-defined tumor volume correspond to a minimal tumor dose of fractionated radiation therapy of approximately 48 Gy, although during radiosurgery most of the tumor gets a much higher radiobiological dose. This is most likely one tumor where dose reduction may increase the chance of delayed tumor progression and ultimate failure. We have found that dose reduction in hemangiopericytoma is also associated with higher recurrence rates. The critical structure is often the fornix in the midline, and the overall radiation tolerance of this structure is not clear. It is certainly a white matter pathway, tended by oligodendroglia which represent the most radiation-sensitive cells. It is likely that the overall dose and volume of radiation to the fornix may be the most important dose-limiting factor. Forniceal injury could be associated with a significant amnestic syndrome. In our experience, central neurocytomas often ''melt away'' after radiosurgery. They are, in fact, the most likely tumor to have significant regression of all the glial/neuronal tumors. Long-term follow up is critical for such patients, and the need for re-operation may present itself over time. The goal of multimodality treatment (initial aggressive resection followed by radiosurgery) is to provide the longest opportunity for symptom-free recurrence while at the same time minimizing the risk of early deficits associated with aggressive resection, especially if the tumor is invasive in the fornix. We have found that stereotactic endoscopic resection using an Endoport system is a valuable way to initially resect the tumor in one or more operations.[1] Early radiosurgery is important, as delayed regrowth is expected in subtotally resected tumors, and the risks of treatment are much less when the tumor volume is smaller.

The authors' case of malignant progression after radiosurgery (or was it the surgery itself that led to this malignant degeneration?) is of concern. We believe that such rare tumors can be best evaluated using multicenter consortia. It is for this reason that, 2 years ago, we formed the North American Gamma Knife Consortium to evaluate outcomes of radiosurgery in rare tumors as well as to develop prospective clinical trials using common technology. Hopefully, the outcomes after central neurocytoma radiosurgery may be a topic in the future.

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