Long-term results of gamma knife surgery for craniopharyngioma

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Object. One hundred seven cases of craniopharyngiomas were treated using gamma knife surgery (GKS) at Komaki City Hospital during the past 12 years. The authors report the long-term results obtained in 100 patients who were followed for 6 to 148 months (mean 65.5 months).

Methods. All patients underwent GKS. The mean tumor diameter and volume were 18.8 mm and 5.8 ml, respectively; lesions were treated with a maximum dose of 21.8 Gy and marginal dose of 11.5 Gy (mean isocenters 4.5). Overall tumor responses were complete in 19, partial in 44, no change in 14, and disease progression in 23, yielding a complete response rate of 19%, overall response rate of 63%, control rate of 77%, and progression rate of 23%. Considering factors such as patient age, nature of the tumor (solid, mixed, cystic), frequency of previous treatments, and tumor size, the age and nature of the tumor were significant prognostic factors.

Changes in neurological and pituitary–hypothalamic symptoms after GKS were evaluated in 91 patients. Overall improvement was demonstrated in 17 (18.7%), no change in 59 (64.8%), and deterioration in 15 (16.5%). Outcome was documented in 93 cases: excellent in 42, good in 23, fair in seven, poor in three, and dead in 18 patients.

Conclusions. Stereotactic GKS is a safe and effective treatment as an adjuvant or boost therapy for postresection residual and/or recurrent craniopharyngiomas; the effects are durable and side effects acceptable.

KEY WORDS • craniopharyngioma • stereotaxy • gamma knife surgery • long-term outcome

A craniopharyngioma is a benign tumor thought to be derived from a residual cell nest of stomodeum. Treatment, however, has been controversial. Although total microsurgical removal is ideal, it has been difficult to obtain a complete resection without jeopardizing neurological function because of the lesion's proximity to the hypothalamus, pituitary gland, and optic pathway. It has been also reported that the recurrence rate is not low even after "total" excision. Another strategy has been combined treatment in which partial removal of the tumor is followed by fractionated focal irradiation; it has been difficult to cure or control the tumor completely, however, and the late-onset radiation-induced injury of surrounding organs cannot be overlooked as a side effect. Recently stereotactic radiosurgery has been shown to be an effective and safe treatment for craniopharyngioma. The purpose of this study was to evaluate the long-term results and outcome achieved in 100 patients treated at Komaki City Hospital since 1991.

CLINICAL MATERIAL AND METHODS

Patient Population

One hundred seven patients with craniopharyngioma

Abbreviations used in this paper: CR = complete response; GKS = gamma knife surgery; MR = magnetic resonance; NC = no change; PR = partial response; VP = ventriculoperitoneal.

were treated using GKS at Komaki City Hospital during the past 12 years; this figure represents 3.4% of all brain tumors and 7.1% of benign tumors. Of these, 100 patients were followed for more than 6 months after treatment. The characteristics of these cases are listed in Table 1. There were 40 children (age at diagnosis < 15 years) and 60 adults. The male/female ratio was 55:45. The nature of the tumor was classified as solid in 43, cystic in 25, and mixed in 32 cases.

Previous Treatments

Surgical treatments prior to GKS included subtotal removal in 24, partial removal in 107, biopsy sampling in 10, placement of an Ommaya reservoir in 26, and insertion of a VP shunt in five cases. Fractionated focal irradiation and bleomycin-based chemotherapy were combined with surgical treatments in 13 and three patients, respectively.

Dose Planning and GKS

The dose planning for GKS was determined using T₁-weighted contrast-enhanced three-dimensional MR imaging performed using the GammaPlan. An accurate dose plan was attempted using small multiple isocenters in cases in which the tumor was located close to the optic pathways. The mean diameter and volume of the tumors were 18.8 mm and 5.8 ml, respectively. The mean maximum dose to the tumor was 21.8 Gy, and the mean mar-

TABLE 1

*Summary of tumor response classifications and associated factors in 100 cases**

Factors	CR	PR	NC	PG	Total
no. of cases	19	44	14	23	100
age					
child	4	16	7	13	40
adult	15	28	7	10	60
nature of lesion					
solid	12	23	3	5	43
cyst	6	4	6	9	25
mixed	1	17	5	9	32
prior therapy	25	66	26	57	174
op					
subtotal	7	5	4	8	24
partial	13	45	15	34	107
biopsy	2	5	1	2	10
omaya	0	10	6	10	26
shunt	1	1	0	3	5
chemotherapy	0	3	0	0	3
radiotherapy	0	6	2	5	13
size (cm)					
I: <1 cm	4	6	2	0	12
II: 1–2 cm	12	21	7	10	50
III: 2–3 cm	2	12	3	9	26
IV: >3 cm	1	5	2	4	12

* PG = progression of tumor.

ginal dose was 11.5 Gy (mean numbers of isocenter 4.5 [Table 2]).

The mean dose to optic nerve was less than 10.7 Gy in the most recent 31 cases, whereas it was 12.7 Gy in the first 30 cases. The treated tumor volume was smaller in the most recently treated cases (Table 3). The mean tumor diameter was less than 20 mm in 62 and greater than 20 mm in 38 cases.

Posttreatment Course

After treatment, the patients underwent follow-up evaluation every 3 to 6 months. We evaluated repeated MR images, changes in neuroendocrinological status, and side effects. Imaging findings were classified into four groups: CR (entirely disappeared), PR (> 25% decrease), NC (no decrease or < 25% decrease), and progression (increase in tumor size). Univariate statistical analyses (chi-square test) were performed to determine factors related to the effects of GKS.

RESULTS

The mean follow-up period in 100 patients was 65.5 months (range 6–148 months) and the median period was 63 months. The overall tumor response was CR in 19 (19%), PR in 44 (44%), NC in 14 (14%), and progression in 23 cases (23%). Thus a CR rate of 19%, overall response rate of 63%, tumor control rate of 77%, and progression rate of 23% were obtained. Characteristics determined in the CR group included the following: a child/adult ratio of 4:15; mean age of 37.6 years; solid-type tumor in 12 and cyst–mixed type tumor in seven cases; and tumor size less than 2 cm in 16 and greater than 2 cm in three cases. In the CR group patients had undergone a

TABLE 2

Dose planning for 107 craniopharyngiomas

Criteria	Value
mean diameter (mm)	18.8
mean volume (ml)	5.8
maximum dose (Gy)	21.8
marginal dose (Gy)	11.5
no. of isocenters	4.54

mean of 1.31 surgical treatments per individual and no radiotherapy sessions before GKS. In this group, the CR was maintained for a mean duration of 75.1 months. There was one accidental death due to head injury 9 years after treatment. Of the 44 patients in the PR group, 33 lesions responded partially after treatment during a mean follow-up period of 59.5 months. In seven cases progression was indicated by the presence of new lesions at a mean time of 48.4 months; these patients underwent resection or repeated GKS, and their status was considered PR for a mean duration of 80.1 months. Final outcome was not obtained in four patients. There were seven deaths in this group during a mean follow-up interval of 38.7 months. The cause of death was hypothalamic–pituitary dysfunction in two, stroke in two, infirmity in two, and coronary arrest in one patient. In the NC group of 14 cases, no alteration in tumor size was observed in seven after a mean period of 62.4 months after GKS. In the remaining seven, temporary progression was demonstrated at mean time of 39.9 months; in these patients surgery or repeated GKS was performed, and NC status was thereafter observed for a mean follow up of 58.1 months. There was one posttreatment death due to septicemia at 40 months. There were 23 cases in the progression group; the mean age was 25.8, and the child/adult ratio was 13:10. The tumor was solid in five and cyst–mixed type lesion in 18. These patients had undergone a mean of 2.47 surgeries per person and radiotherapy had been conducted in five patients. The diameter of the tumor was greater than 2 cm in 13 patients. There were two types of response in this group: 1) initial PR in six patients for mean of 39.5 months, which was followed by slow progression of the tumor for a mean period of 72 months; 2) progression throughout the postoperative course in which the mean time to detection of progression was 19.2 months and the mean follow up interval was 37.8 months. In 12 (66.7%) of the 18 patients with mixed-type cysts, cyst enlargement was shown, and disease progression led to death in six of these patients.

TABLE 3

Changes in dose planning stratified by year of treatment

Years	No. of Lesions	Diameter (mm)	Vol (ml)	No. of Isocenters	Dose (Gy)	
					Max	Marginal
1991–1995	30	19.1	5.1	4.5	24.7	12.7
1995–1997	31	21.4	10.1	5.6	22.8	11.4
1997–1999	31	18.6	5	4.2	20.6	11.1
2000–2002	31	16.3	3.1	3.8	19.2	10.7
total/mean	123	18.8	5.8	4.54	21.8	11.5

Gamma knife surgery for craniopharyngioma

There were nine deaths in this group at a mean time of 43.2 months. The cause of death was progression of tumor in six patients and infection, hydrocephalus, and thrombocytopenia in one case each (Table 1).

Changes in neurological and endocrinological symptoms were examined by assessing clinical records or questionnaires obtained in 91 cases. Overall results were improved in 17 (18.7%), no change in 59 (64.8%) and deterioration in 15 patients (16.5%). Improved symptoms were frequently found in the CR group (36.8%), and deterioration was often demonstrated in the progression group (39.1%). Among the 17 cases of improvement, 10 were visual and seven were hypothalamic-pituitary functions. Of 15 patients in whom symptoms deteriorated, two cases of visual and one case of endocrinological deterioration were found to be side effects of GKS in the PR and NC group. Other new neurological symptoms occurred in three cases: stroke and spinal metastasis. Another nine cases of deterioration were found in progression group, and all died of tumor progression (Table 4).

Outcome in 93 patients was determined directly or by questionnaire. Outcome was classified into five groups: excellent (doing well at work or attending school independently, without severe neurological deficits); good (unable to go to work but working at home independently, with minor neurological or endocrinological deficits); fair (at home and dependent all the time); poor (bedridden or requires assistance); and death (of tumor progression or other causes). Overall outcome was excellent in 42, good in 23, fair in seven, poor in three, and death in 18 patients. Excellent results were frequently demonstrated in CR cases (68.4%) but infrequently in progression cases (8.6%). Death was the most common in progression cases (39.1%) (Table 5).

ILLUSTRATIVE CASES

Case 1

This 9-year-old boy with short stature suffered deterioration of visual acuity in his left eye (1.0, 0.2) and bitemporal hemianopsia in October 1991. A suprasellar tumor was subtotally removed via a right frontotemporal approach. Although visual symptoms normalized, a small residual tumor was found at retrochiasmatic portion and in

TABLE 4
Changes in neurological and/or endocrinological symptoms in 91 cases after GKS

Response Group	Symptotic Result (%)			Total
	Improved*	Unchanged	Deteriorated†	
CR	7 (36.8)	12 (63.2)	0 (0)	19
PR	7 (19.4)	24 (66.6)	5 (13.9)	36
NC	2 (15.3)	10 (76.9)	1 (7.7)	13
PG	1 (4.3)	13 (56.5)	9 (39.1)	23
total	17 (18.7)	59 (64.8)	15 (16.5)	91

* Ten of 17 had improved visual function and seven had improved endocrinological function.

† Two visual and one case of endocrinological deterioration of six in the PR and NC groups; three others exhibited new symptoms. In nine patients in the progression group both visual and endocrinological deterioration occurred.

TABLE 5
Outcome in 93 patients after GKS

Response Group	Overall Outcome (%)					Total
	Excellent	Good	Fair	Poor	Dead*	
CR	13 (68.4)	3 (15.8)	2 (10.5)		1 (5.3)	19
PR	22 (50)	11 (25)			7 (15.9)	40
NC	5 (35)	4 (28.6)	2 (14.3)	1 (7.1)	1 (7.1)	13
PG	2 (8.6)	5 (21.7)	3 (13)	2 (8.6)	9 (39.1)	21
total	42 (45.2)	23 (24.7)	7 (7.5)	3 (3.2)	18 (19.4)	93

* Death due to tumor progression in eight and unrelated causes in 10 cases.

contact with the pituitary stalk 3 months postoperatively. The mean diameter of the GKS-treated tumor was 13.6 mm and was treated with a marginal dose of 15 Gy (five isocenters). The tumor decreased size by 12 months and disappeared (CR) by 15 months after GKS; this status has been maintained for 116 months (Fig. 1). His mental and physical development have returned to normal, and he successfully graduated from university.

Case 2

In November 1994 MR imaging demonstrated a suprasellar mixed tumor in this 47-year-old man. The patient had diabetes insipidus and loss of visual acuity (0.2, 0.1) at admission. The solid tumor was partially removed and the cyst was evacuated via an lamina terminalis approach. The diabetes insipidus and visual acuity improved (1.2, 1.2). The residual solid tumor in the third ventricle was treated with GKS in March 1995. The mean diameter of the tumor was 18.2 mm, which received a maximum dose of 21.8 Gy and a marginal dose of 12 Gy (seven isocenters). The tumor showed a marked response (near CR) at 6 months after the treatment and has been stable for 38 months (Fig. 2). The patient is doing well at his job and enjoying life without any neurological deficits.

Case 3

This 40-year-old man had been treated for craniopharyngioma at age 18 years. During a 20-year interval, resection followed by focal radiotherapy had been performed on three occasions. The patient suffered severe visual loss (0, 0.01), diabetes insipidus, and hypopituitarism. Magnetic resonance imaging revealed a recurrent large mixed tumor in the suprasellar region and third ventricle. The fourth surgery was refused. The tumor diameter and volume were 28.7 mm and 12.4 ml, respectively. We performed GKS with a maximum dose of 25 Gy and a marginal dose of 11.25 Gy (eight isocenters) in March 1995. The tumor response was marked, and his symptoms have been stable for 7 years (Fig. 3).

Case 4

This 18-year-old woman experienced severe headache, nausea, and vomiting in July 1999. An MR imaging study revealed a very large cyst in the right frontal lobe and contiguous suprasellar solid mass. In August 1999 a diagnostic biopsy specimen was obtained and the cyst was drained through an Ommaya system after the patient underwent a craniotomy. The collapsed cyst wall and solid

Fig. 1. Case 1. Pretreatment and posttreatment MR images. A suprasellar solid mass compressing the optic nerve was subtotally removed, and a residual small tumor (13.6 mm) at retrochiasmatic region was treated using GKS (marginal dose 15 Gy, five isocenters). The tumor showed a decrease in size at 12 months (*upper and lower images, second from right*). CR was obtained at 15 months and remained stable for more than 116 months (*upper and lower right*).

tumor were treated using GKS (maximum dose 16 Gy, marginal dose 10.4 Gy, six isocenters) in September 1999. The tumor showed marked response (PR) at 30 months, and the patient suffered no neurological or endocrinological deficits (Fig. 4). She recently married and conceived a child.

Case 5

This 17-year-old man presented with the initial symptoms of headache, nausea, and vomiting in March 1988. Computerized tomography scanning revealed suprasellar tumor and hydrocephalus. Subtotal resection of the tumor was achieved and a VP shunt was placed. Tumor recurrence was later found, and an Ommaya reservoir was placed to manage the cystic mass in August 1992. The recurrent tumor was again totally removed in March 1993, and the diabetes insipidus became permanent. The recurrent tumor was mixed type, with a mean diameter of 26.2 mm, and was treated using GKS (maximum dose 24 Gy, marginal dose 12 Gy). Although the solid portion of the tumor was markedly reduced, the two cysts were enlarged

and produced intracranial hypertension at 6 months after treatment (Fig. 5).

DISCUSSION

As a treatment strategy for craniopharyngioma, total microsurgical removal is ideal, although it has often been difficult to achieve complete excision without jeopardizing neuroendocrinological function. Authors have noted that its rate of recurrence is not low, even after total removal.^{7,19} Another modality has been combined treatment in which partial removal is followed by fractionated radiotherapy for residual or recurrent tumors. It has also been difficult to cure or control the tumor, however, and the late-onset radiation-induced injury cannot be overlooked as a side effect.^{3,5,17} Fischer, et al.,⁴ and Hetelekidis, et al.,⁶ have reported that the survival rate of 10 years was excellent but that neuroendocrinological deficits were significant side effects. New modalities involving radiotherapy for central nervous system lesions has been developed. Radioisotope-based intracavitary irradiation^{1,8} and recent-

Fig. 2. Case 2. Pre- and posttreatment MR images. *Left*: A large mixed suprasellar and third ventricular mass was demonstrated. *Center*: The residual suprasellar solid tumor (18.2 mm) was treated with GKS (marginal dose 12 Gy, seven isocenters). *Right*: The tumor showed marked response (near CR) at 6 months and has been stable for 38 months.

Fig. 3. Case 3. Pretreatment and posttreatment MR images. *Left:* A large recurrent mixed-type tumor (28.7 mm) in the suprasellar region and third ventricle was demonstrated after three procedures involving partial removal and radiotherapy during the past 20 years. The tumor was treated using GKS radiosurgery (maximum dose 25 Gy, marginal dose 11.25 Gy). *Right:* The tumor showed marked response (PR) and has been stable for more than 7 years without symptomatic changes.

ly stereotactic radiosurgery^{1,10} have been used as an interstitial irradiation.

Gamma knife surgery is defined as the delivery of high-dose radiation to a relatively small intracranial volume in a single session without causing significant damage to the surrounding brain.¹³ The first GKS-based experience involving craniopharyngioma was reported by Leksell, et al.,¹³ and Backlund, et al.¹ These authors documented good results in some cases. The minute evaluation of the tumors or the treatment effects, however, were difficult to determine at that time. Since MR imaging became available for dose planning and follow-up study, many studies have been conducted.^{2,9,10,18} Kobayashi, et al.,¹⁰ reported that the higher response rate including the disappearance of the tumor (CR) was obtained using GKS in solid-type tumors with relatively low marginal doses. In a previous study we described results obtained in 33 cases in which the mean follow-up period was 42.1 months. The high response (81.8%) and control rates (84.8%) were obtained with large numbers of CR (30%). The rate of progression was also as high as 15.1%, which was due to enlargement of the cysts after treatment.⁹ Chung, et al.,² reported similar results in the treatment of 31 patients followed for 36

months. More recent results, however, which demonstrate a lower response rate and higher progression rate after radiosurgery, are probably due to longer follow-up time and delivery of a smaller marginal dose. The factors related to better responses (CR and PR) after radiosurgery were older age, solid tumor, fewer previous treatments, and smaller-sized tumor. Of these factors age was only significant as a favorable prognostic factor ($p = 0.046$).

Factors indicative of disease progression after radiosurgery, however, were younger age, a cystic or mixed-type tumor, a high number of previous treatments, and greater tumor size. Of these factors, the nature of the tumor (cyst) was the only significant variable suggestive of disease progression ($p = 0.035$). In other words, responses in cystic tumors were not as good as those in solid tumors. Because 56.5% of all cystic tumors showed progression due to cyst enlargement, other non-GKS strategies are necessary to control cysts. In 1972, Backlund, et al.,¹ introduced a new strategy for treating the solid part of lesions by radiosurgery and the cystic portion by internal irradiation; this strategy was well confirmed by our group in 1981.⁸ Another modality is the placement of an Ommaya reservoir system to manage the cystic part¹⁵ and the provision of radiosurgery after the collapse of the cyst, as was shown in Case 4.

We conducted an analysis of data obtained in cases in which disease progression occurred. Two groups can be identified within the progression group; in six cases a PR had been shown for a mean period of 39.5 months but progression finally occurred at the time of the survey. In the other 17 cases progression was demonstrated at a mean time of 19.2 months without decrease in size. The former cases could be considered to reflect a PR if the follow-up period were less than 3 years. Death frequently occurred in this group (nine [39.1%] of 23 patients) but its causes varied among groups. In eight deaths occurring in patients from the CR and PR groups, tumor progression was the cause in only two, and stroke (two cases), infirmity (two cases), head injury (one case), and cardiac arrest (one case). Of 10 deaths occurring in the progression and NC groups, six were due to tumor progression, two to infection, and one each to thrombocytopenia and acute brain injury. Overall the cause of death was due to tumor pro-

Fig. 4. Case 4. Pretreatment and posttreatment MR images. *Left:* A huge cyst was demonstrated in the right frontal lobe and a suprasellar solid tumor was found. A diagnostic biopsy sample was obtained and the cyst was drained using an Ommaya reservoir system after craniotomy. *Center:* The collapsed cyst wall and residual solid tumor were treated using GKS (marginal dose 10.4 Gy, six isocenters). *Right:* The tumor showed marked response (PR) at 30 months.

Fig. 5. Case 5. Pretreatment and posttreatment MR images. A recurrent, mixed tumor (26.2 mm) was found in the suprasellar region after three procedures entailing excision and VP shunt placement. The tumor was treated by GKS (marginal dose of 12 Gy). Although the solid part of the tumor disappeared, two cysts enlarged, producing intracranial hypertension 6 months after the treatment.

gression in eight patients (44.4%) and to unrelated causes in 10 patients (55.6%). We found also that the mean time from GKS to death was 44.8 months.

Regarding the lesions' radiosensitivity, our findings may suggest that craniopharyngioma has potentially greater radiosensitivity not only when fractionated therapy is undertaken^{4,6} but also with radiosurgery.^{1,2,9,10} Additionally it has been emphasized that craniopharyngioma is effectively treated with a low marginal dose of approximately 10 Gy, which is thought to be same as the tolerable dose to the optic nerve.¹² In the previous study¹⁰ the marginal dose was 12.8 Gy but this was decreased to 11.5 Gy in this series, which may suggest that the optimal dose to this tumor is between 11 and 12 Gy.

With attention to radiobiology, Larson, et al.,¹¹ reported that the tolerance of the surrounding normal brain is higher when treated using multiple small isocenters than with a single large isocenter. Marks and Spencer¹⁴ also stated that a tolerable dose to the normal brain is related to the volume delivered to the nearby tumor. The results were excellent in our patient in Case 1, in whom the small 1.3-ml cystic tumor attached to the optic nerve was treated with a marginal dose of 15 Gy in five isocenters. Another approach to saving optic function would be stereotactic radiotherapy for craniopharyngioma to reduce the side effects in the surrounding brain and to enhance the tumoricidal effects.¹⁶ The long-term results in a significant number of cases, however, have been lacking.

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