

Gamma Knife Surgery in Pituitary Microadenomas

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The application of transsphenoidal microsurgery in the management of pituitary microadenoma, long regarded as effective surgical treatment, has had a relatively low mortality and morbidity rate. However early failure and late recurrence has been reported in no small numbers. It has been proposed that stereotactic radiosurgery is an alternative treatment modality. Recent advances in neuroimaging permits precise targeting in radiosurgery of microadenomas. Additionally, a prompt hormonal reduction after the treatment is important for the patients with hormonally active microadenomas. The authors performed Gamma Knife radiosurgery in 27 patients with pituitary adenomas and observed the hormonal changes after radiosurgery in 19 patients with functioning microadenomas (5 with Cushing's disease, 7 with acromegaly, and 7 with prolactinoma). The maximum dose administered ranged from 25 to 75 Gy. The margin of the tumor was encompassed within the 50 to 90% isodose volume. The endocrinological status was assessed pre- and post-operatively. We measured the serum growth hormone and prolactin level, as well as the 24-hour urinary free-cortisol level. Normalization of the hormonal level was achieved in 6 cases, the majority of them within 10 months. The other 6 cases showed marked reduction of hormonal levels (less than 50% of preoperative levels) with a strong possibility of hormonal remission at further follow-up. The remaining 6 were failures. The cure for one case is still pending. It took approximately 1~3 months after the radiosurgery before the reduction of hormonal secretion began to show up with some improvement of symptoms. When the GKS was successful, hormonal secretion seemed to return to normal within 10 months. Although further follow-up is necessary to evaluate the long-term tumor control rate and hormonal effect, these initial results indicate a potential therapeutic role of radiosurgery in controlling hormone hypersecretion in pituitary microadenomas. Gamma knife radiosurgery is very promising in managing pituitary microadenoma with complementary of the transsphenoidal surgery.

Key Words: Pituitary adenoma, Gamma Knife radiosurgery, prolactinoma, acromegaly, Cushing's disease

In 1954, using a heavy-charged-particle proton beam, Lawrence *et al.* performed a destructive surgery of pituitary glands in pa-

tients with breast cancer (Lawrence, 1957; Lawrence *et al.* 1962). This method was then applied in the treatment of pituitary adenoma (Levy *et al.* 1991). Also, Gamma Knife surgery (GKS) was introduced for treatment of pituitary tumors by the surgeons in the Karolinska Hospital (Degerblad *et al.* 1986; Thoren *et al.* 1991), Sweden. However, the evolving technology of the CT scan was still at an early stage. Therefore, radiosurgery could not selec-

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tively target the tumor, and it was difficult to irradiate the tumors exclusively without inflicting damage to the optic nerves and/or without producing other side effects. Radiosurgery advanced rapidly in the late 1980s after the high resolution MRI became available. In using MRI, the location of the optic nerve can be visualized and the microadenoma can be differentiated from the normal pituitary tissues when used with the contrast enhancing medium gadolinium (Newton *et al.* 1989; Maroldo *et al.* 1992). The accuracy of radiosurgery has improved dramatically ever since and the use of radiosurgery in the treatment of pituitary tumors has attracted new interest. Radiosurgery can be used either as a primary therapeutic modality for microadenoma or as an adjunctive modality after microsurgery to eliminate residual tumor cells. To control the pituitary tumor more effectively, microsurgery and radiosurgery can be used together, complementing each other. The important question which should be raised here is which one of these treatment tools should be applied first for patients, especially those with the microadenoma. To decide the efficacy of radiosurgery in the treatment of pituitary adenoma, we monitored the changes of pituitary hormonal levels and evaluated the clinical symptoms and signs of the patients who received the GKS using high resolution MRI at Yonsei medical center.

MATERIALS AND METHODS

We performed 28 GKSs in 27 patients with pituitary adenomas from May 1992 to September 1995. The procedure of the Gamma-Knife surgery was the same as that described elsewhere in detail (Degerblad *et al.* 1986; Thoren *et al.* 1991; Stephanian *et al.* 1992). In these patients, we monitored pituitary hormonal levels, clinical symptoms and signs, and MR imagings to assess the results of the radiosurgery. In patients with acromegaly and prolactinoma, growth hormone (GH) and prolactin levels of serum were monitored to determine if the treatment was successful or not. In the pa-

tients with Cushing's disease, changes of 24-hour urinary free-cortisol(UFC) level was used to assess the effectiveness of the treatment. The mean follow-up duration was 15.4 ± 10.02 months and in some cases the follow-up was insufficient to define the results of the treatment. The results were classified into five categories. ① Group 1, clinical remission with normalization of hormonal levels; the hormone returned to normal levels(GH <5 ng/mL, prolactin <20 ng/mL, UFC <100 mg/day). ② Group 2, clinical improvement with marked decline in hormonal levels; the clinical symptoms and signs improved and hormonal level dropped significantly (more than 50% of preradiosurgical levels) but failed to return to normal levels, with a strong possibility of the remission on further follow-up. ③ Group 3, continued decline in hormonal levels at the latest follow-up; the clinical symptoms and signs undetermined and hormonal level dropped to less than 50% of preradiosurgical levels and failed to return to normal values, further follow-up is required with some possibility of the remission. ④ Group 4, minor or no effect from the radiosurgery; the hormonal level was not reduced to less than 50% of preoperative levels 1 year after GKS. And ⑤ no follow-up or lost to follow up.

RESULTS

The clinical characteristics of the 27 cases are summarized in Table 1. In one patient with Cushing's disease, the GKS was performed twice since the first surgery failed to reduce the hormonal level. Three cases of acromegaly, TSH secreting adenoma and inactive adenoma were treated for the residual tumors following TSA. The 2 cases with normal hormonal levels before radiosurgery were excluded from the analysis of postoperative hormonal follow-up. Also, 5 cases with prolactinoma and 1 case with Cushing's disease had no follow-up. Nineteen cases with hormonally active microadenoma were included in this study.

The results of radiation dosimetry planning

are presented in Table 2. The tumors were treated using single or multiple irradiation isocenters. All tumors were enclosed within a 50% or greater isodose shell. The average maximal central dose of irradiation was 50.2 Gy (range, 16-75 Gy). The average marginal dose delivered to the tumor was 27.1 Gy (range, 8-37.5). The isodose conformation and the margin dose were adjusted so that the visual pathways always received less than 8 Gy.

In all 7 patients with acromegaly, plasma

Table 1. Clinical characteristics of 28 pituitary adenomas in 27 patients

Hormone type	No of Cases ^a
ACTH	7/6(1 repeat GKS)
GH	7(1 after TSA)
Prolactin	12
TSH	1 ^b (after TSA)
Inactive	1 (after TSA)

Male:Female=7:20

Age:14.1-63.2 year old (mean 35.7 + 12.7)

a:GKS: Gamma Knife surgery, TSA: transsphenoidal surgery

B: Macroadenoma in 1 case

GH basal levels could be assayed postoperatively (Table 3, Fig. 1). In 3 of 7 patients, the hormonal levels returned to normal 2.8, 4.1, and 5.9 months after the GKS respectively. In one patient, the hormonal level was reduced progressively almost to normal range until 9.5 months after GKS but elevated again and fi-

Table 2. Gemma Knife radiosurgical dosimetry of 29 lesions

67 isocenters/28tumors		
Colimators used	No.	
4 mm	20	
8 mm	38	
14 mm	9	
Marginal treatment isodose(%)		
50%	22	
70%	5	
90%	1	
	Mean±S.D.	(Range)
No. of isocenter	2.34±1.47	(1-7)
Maximum dose	50.2±13.3	(25-75)Gy
Margin dose	27.1±6.9	(12.5-37.5)Gy

Table 3. Result of Gamma Knife radiosurgery in 25 patients with hormonally active microadenoma

	Acromegaly	Cushing's disease	Prolactinoma	Total (n)
Clinical remission with normalization of hormonal levels	4	2		6
Clinical improvement with marked decline in hormonal levels	1		5	6
Continued decline in hormonal levels at the latest follow-up		1		1
Minor or no effect from the radiosurgery	2	2	2	6
No follow-up or lost to follow-up		1	5	6
Total	7	6	12	25

Kruskal-Wallis 1 Way ANOVA: Not significant

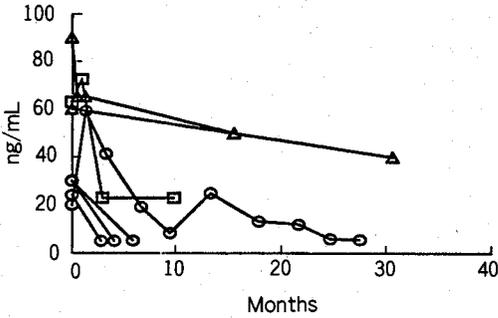


Fig. 1. Change of serum GH basal levels in 7 cases with acromegaly before and after GKS. Circles, rectangles, and triangles indicate the serial changes of hormonal levels of each case after GKS.

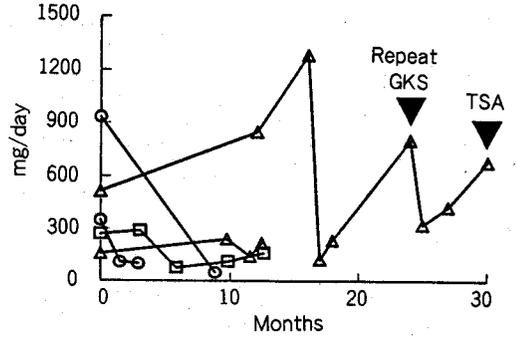


Fig. 2. Change of 24-hour urine-free cortisol levels in 5 cases with Cushing's disease before and after GKS. Arrow heads indicate second GKS and subsequent TSA in a case who failed to respond to first GKS.

nally normalized 27.5 months after GKS. One patient showed a marked reduction of the hormonal level from 62.9 ng/mL of the preoperative level to 22.9 ng/mL 3 months after GKS and remained the same until 9.9 months after GKS. In the remaining 2 cases, the hormonal levels were reduced by less than 50% of the preoperative levels 1 year after the GKS.

In 5 of 6 patients with Cushing's disease, postoperative UFC levels were measured (Table 3, Fig. 2). In 2 of these 5 cases, the UFC returned to normal and clinical symptoms were improved after 1.5 months in one patient and 8.8 months in another following the GKS. In one patient, the 5.8 months postoperative UFC level was reduced to 76.3 mg/day but elevated again thereafter, and did not return to normal until 12.6 months after the GKS. In another patient, the marked reduction of the UFC level was detected at 17 months follow-up but was elevated again. This patient therefore received second GKS 2 years after the first GKS. However, the UFC level was not reduced and TSA was performed. In one other case, the UFC level was not reduced until 12.4 months after GKS.

In 8 of 12 patients with prolactinoma, serum prolactin levels were assayed postoperatively

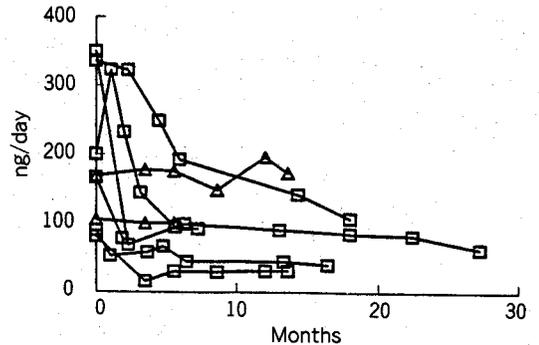


Fig. 3. Change of serum prolactin levels in 7 cases with prolactinoma before and after GKS.

(Table 3, Fig. 3). One case receiving bromocriptine was excluded. In 5 of the 7 cases followed, the hormonal levels were reduced to less than 50% of the preoperative level but not to normal levels. However, menstruation returned in all of them, and one female became pregnant. In 2 other patients, the hormonal level was not reduced until 5.2 and 12.6 months after the GKS respectively.

In all 19 patients discussed above, 6 patients were hormonally cured and another 6 had a strong possibility of hormonal remission at

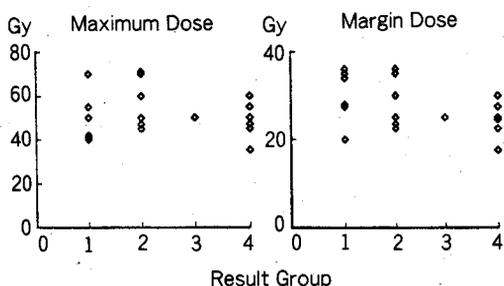


Fig. 4. Maximum and marginal dose according to result groups.

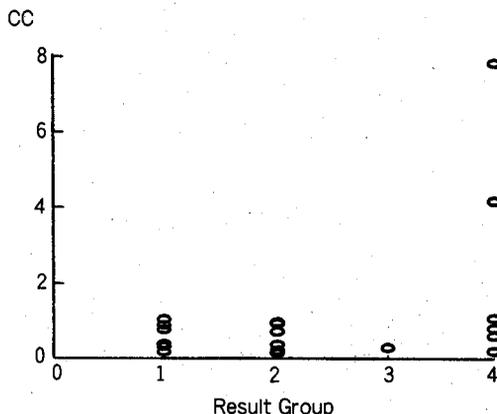


Fig. 5. Tumor volume in each group.

Table 4. The result of Cox proportional hazard regression analysis of hormonal reduction (less than 50% of preoperative levels) after GKS based on 19 patients with microadenoma

	p
Volume	0.18
Risk probability*	0.67
No. of isocenter	1.00
Minimum dose	0.34
Maximum dose	0.48
Marginal isodose(%)	0.74

*: Risk prediction calculated from exponential integrated logistic formula

further follow-up. The remaining 6 were failures. The cure for one case is still pending.

In our cases, hormonal levels could not be measured frequently after they were discharged from the hospital. Although our patients were scheduled to have their first check-up at three months after the GKS, several patients delayed longer than six months after surgery. For this reason, it was hard to exactly point out the length of time needed for reduction of the hormonal level. However, in all 12 cases, in which the patients' hormonal levels definitely responded to GKS, the reduction became apparent within 3~10 months.

We conducted a statistical analysis of 19 patients with microadenoma. The cases of group 1 and 2 were regarded as hormonally

responsive to GKS. The results of univariate Cox proportional hazard analysis are shown in Table 4. We calculated the risk probabilities for each patient and used these results to predict hormonal response after GKS with the exponential version of the integrated logistic formula (Flickinger *et al.* 1992). The tumor volume, risk probability, number of isocenters, maximum dose, minimum dose (Fig. 4), and treatment isodose were all not statistically correlated with decline of hormonal levels. However, the two cases with tumor volume more than 4cc failed to respond at all.

Twenty-one of these patients had MRI taken between 2.8 and 33.2 months after GKS. In 15 of the 21 patients, the size of tumors were not reduced. In the rest of the 6 patients, the size was reduced between 2.8 and 15.8 months after GKS (Table 5). Among the 6 cases, only 2 cases showed marked decline of hormonal levels (group 2), and the remaining 4 cases were in group 4. No case was in group 1. Therefore, it seems that the size reduction of tumors after GKS has no correlation with the functional recovery following the radiosurgery. None of our 19 patients showed any complication such as disturbance of vision, cranial nerve deficits or hypopituitarism during short period of follow-up after GKS.

Table 5. Results of pituitary microadenectomy reported in the literature(2, 15-18, 23).

Author(year)	No. of cases	Early failure rate(%)	Late recurrence
Burch W(1983, a survey)		5~50%	
Rauhut <i>et al.</i> (1988)	26	4(26%)	
Parl <i>et al.</i> (1986)	13(PRL ^a)		4(30.8%)
Webster <i>et al.</i> (1992)-(PRL)			
Tumor size <5 mm	19	7(37%)	3(15.8%)
5~9 mm	26	1(4%)	3(6%)
10~19 mm	30	6(20%)	2(6.7%)
> 19 mm	7	4(43%)	
Scamoni <i>et al.</i> (1991)	43(PRL)	13(31.3%)	0(0%)
Post <i>et al.</i> (1990)			
Prolactinoma	100	12(12%)	15(17%)
Cushing's disease	37	8(22%)	1(2.5%)

a:PRL=Prolactinoma

DISCUSSION

To treat the patients with pituitary adenoma, many factors should be considered and the best approach should be selected after all the possible treatment modalities are compared in their merits and disadvantages (Andrews, 1994). There are some advantages in surgical treatment of adenomas. For examples, tumors can be taken out quickly and the abnormal hypersecretion of hormones returns to normal level immediately following the surgery. On the other hand, the disadvantage of the surgery is that it is sometimes difficult to remove tumors completely due to the limited operative field. Burch found a low rate of success (55%) of TSA surgery in his patients with ACTH secreting adenomas which were mostly microadenomas. Subsequently, Burch surveyed the rate of success from 30 major hospitals (Burch, 1983). His survey revealed that the success rates greatly varied from hospital to hospital and overall results were poorer than he had expected. Since Burch's study was done more than 10 years ago, we reviewed the cases of pituitary micro-

adenomas treated with TSA from the literature between 1986 and 1992 (Table 5) (Burch, 1983; Parl *et al.* 1986; Rauhut *et al.* 1988; Post and Habas, 1990; Scamoni *et al.* 1991; Webster *et al.* 1992). According to these data, the rate of complete cure without recurrence has been approximately 50-90%, with great variation, depending on the surgeons who were performing the operation.

Although pituitary tumors can sometimes invade into the dura matter, they are basically benign tumors and tumors usually have a well-defined anatomical boundary (Marks, 1993). Therefore, these tumors can be good candidates for radiosurgical treatment. The radiosurgical treatment, however, has some drawbacks. The effects of treatment tend to show up slowly and the long term effects are not yet fully understood. Also, there can be negative effects. Cranial nerves in the cavernous sinus and pituitary stalk are known to be less susceptible to radiation (De Salles *et al.* 1993). However, optic pathways are most vulnerable to radiation damage and pose the main obstacle in radiosurgery of pituitary adenomas. Especially, radiation damage to the optic chiasm can cause the complete loss of bilateral vision. Dosage of irradiation in radiosurgery is

adjusted so that it does not produce injury to the optic chiasm. Subsequently, the dosage of irradiation to the tumor is reduced, resulting in a possibility of incomplete sterilization of the tumor cells. Usually, the pituitary tumors located at least 5 mm away from the optic nerves are considered to be the good candidates for radiosurgery. Most microadenomas fall into this category but the macroadenomas are difficult to treat with radiosurgery. Moreover, the patients with pituitary tumors who exhibit pressure symptoms, apoplexy, or cystic lesion should be primarily treated with TSA. The hormonally inactive adenomas can not be detected until they sufficiently grow to produce visual symptoms. For these reasons, when the GKS is applied as a primary treatment tool of pituitary tumors, the prime candidate is mostly the hormonally active microadenoma.

There are two primary goals in the management of the hormonally active adenomas. First, the hormonal secretion should be lowered to normal values as soon as possible in order to restore normal physiological function. Second, tumor cells should be completely eradicated to prevent regrowth of tumors. Among microadenomas, aggressive and assertive strategies are required for the management of Cushing's disease since its symptoms are the most serious compared to other adenomas. This tumor also weakens the immune system and general physical condition of the patient. And also, the patient with Cushing's disease has a very high risk of developing complications after surgery. Considering these facts, radiosurgery may be considered as a good treatment method for the patient with Cushing's disease. Similarly, all things aforementioned are to be considered in the management of other types of hormonally active microadenomas. Judging from our clinical experience, it took approximately 1~3 months after the GKS before the reduction of hormonal secretion began to show up. And when the GKS was successful, hormonal secretion seemed to return to normal within 10 months. Since we reached this tentative conclusion in a small number of patients in a relatively short follow-up duration, we plan to

continue this study to enriching our understanding of this treatment.

It has been generally agreed to use radiosurgery for the patients with Cushing's disease and acromegaly since their clinical symptoms are most serious and there is a limited choice of treatment at the present time. On the other hand, for the treatment of patients with prolactinoma, radiosurgery is still controversial as a primary treatment tool because clinical symptoms are comparatively mild. Bromocriptine can be used as an adjuvant treatment modality to TSA, but it does not cure the patient completely. Considering the fact that the major drawback of TSA is a possible regrowth of the tumor after surgery, radiosurgery may be necessary as an primary or adjunctive treatment to increase the chances of long term and total cure.

In the management of the residual or regrowing tumors following TSA, several methods have been employed such as chemotherapy, radiation therapy, and repeated surgery. For complete removal of these residual tumors, a second surgery might be most idealistic. But in reality, it is not easy because of the high risk of complications and a possibility of a repeated failure of the complete resection. The residual tumor within sellar is sometimes very difficult to localize on MRI due to poor identification from surgical reaction, packing materials, and scar tissue. Moreover, it is the same in surgical field. Radiation therapy has been frequently used in the treatment of remnant or recurring tumor. However, it often fails to control the tumor growth in addition to the side effects such as radiation necrosis or hypopituitarism. Most of the pituitary adenomas are basically benign tumors and usually have a well-defined anatomical boundary. For this reason, radiosurgical treatment using focal irradiation is a better choice for treating these patients than radiation therapy in a large area of the brain (Valentino, 1991; Marks, 1993). Therefore, radiosurgery is a useful tool to be employed for eradication of the regrowing tumors if they are located at least 5 mm away from the optic nerves and are localized within the sellar turcica. On the other hand if the regrowing

tumor is located close to the optic nerves, a second TSA surgery or craniotomy should be considered first. Radiosurgery can also be considered if the patients are not to be subjected to a second surgery for various reasons, considering that the optic pathways should not be exposed to radiation more than 8-10 Gy. However, we do not have enough experience and data to draw a positive conclusion on this issue until further studies are undertaken.

We believe that both TSA surgery and radiosurgery are good methods for the management of pituitary adenomas. However it is sometimes possible that either method can fail to eradicate the tumor completely. If one of these treatments fail, a second chance is difficult to take. Even though these two methods must often be used to complement each other, it is necessary to determine which method should be tried first. In patients who have to receive radiosurgery after the TSA surgery, it is difficult for the surgeons to differentiate tumors from the surrounding tissues on the MRI. We encountered these difficulties three to twelve months after TSA due to surgical reaction. Subsequently, it is hard to expect a successful outcome of the treatment and one must take into account that there is a high possibility of complications such as hypopituitarism. On the other hand, if radiosurgery is used as a primary treatment method and fails to eradicate the tumor, TSA can be performed as usual. We believe that, in order to increase the overall chance of successful treatment, GKS is a better choice as a primary treatment modality of selected cases with hormonally active microadenomas.

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