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Radiological and Hormonal Responses of Functioning Pituitary Adenomas after Gamma Knife Radiosurgery

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In this study, we examined patients with functioning pituitary adenoma that underwent Gamma Knife radiosurgery (GKS). In particular, we assessed the effects of GKS on the growth and endocrinological response of the functioning pituitary adenoma.

Forty-two cases of functioning pituitary adenoma treated with GKS were analyzed. The mean follow-up duration was 42.5 months (range 6 - 98), and the mean tumor volume was 1.4 cm^3 (range 0.1 - 3.8). Multiple isocenters, ranging from 1 to 6 in number (mean 2.7), were used. The tumor margin was covered by an isodose ranging from 50 to 90%. The margin dose was 18 to 40 Gy (mean 28.5) and the maximum dose varied from 35 to 80 Gy (mean 54.1).

Tumor growth was controlled in 96.9% of the cases and tumor shrinkage occurred in 40.6% of the cases. Hormonal response was observed in 35 of the 42 (83.3%) patients after GKS, with a mean duration of 6.8 months. Sixteen of the 42 (38.1%) patients showed hormonal normalization, with a mean duration of 21 months. In our multivariate analysis, high integral dosage (p=0.005) and maximum dosage (p=0.001) correlated significantly with hormonal normalization.

For patients with functioning pituitary adenoma, GKS can be effective in controlling tumor growth and inducing hormonal normalization, especially if patients are reluctant to undergo surgical resection, or are not able to undergo microsurgery under general anesthesia. It appears that early hormonal normalization can be induced by high maximum dosage (at least 50 Gy) and broad coverage of the target volume within the isodose curve, while keeping the maximum dose to the visual pathways below 9 Gy.

Key Words: Gamma knife radiosurgery, functioning pituitary adenoma, tumor growth control, hormonal normalization

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INTRODUCTION

Transsphenoidal or transcranial microsurgery has remained the primary treatment for most patients with pituitary adenoma. Pituitary microadenomas that cause acromegaly, or Cushing's disease, are generally treated by transsphenoidal surgery, with an immediate success rate of 80-90% and low morbidity and mortality rates.[1,2] However, open surgery is less successful when complete resection is not possible in patients with macroadenomas, especially those with suprasellar or parasellar extension.[3,4] In these cases, other treatments are necessary.

Treatment of pituitary adenomas with the Leksell Gamma Knife was developed in the late 1960s.[5] The Gamma Knife was able to irradiate the tumor with great accuracy using a high dose of radiation, while the adjacent nerves received radiation doses generally accepted as safe, reducing the patient's risk of developing complications.

Recently, Gamma Knife radiosurgery (GKS) has gained acceptance as an adjuvant treatment option in combination with microsurgery. Shin, et al.[6] reported that GKS can control tumor growth and induce endocrinological normalization with fewer complications than other procedures. In addition, Izawa, et al.[7] reported that tumor growth was controlled and excessive hormone production significantly reduced in 91% and 80% of the subjects studied, respectively. Optimal results are obtained with a well-defined tumor and precise head fixation during the treatment. Recent advances in neuroradiology have greatly improved the practicability of GKS, while MR imaging has allowed more accurate evaluation of the tumor margin. Therefore, dose planning for GKS has become more precise and safe, reducing the damage to crucial neural structure.

In this study, we studied patients with functioning pituitary adenoma that underwent GKS, and assessed the effect of GKS on the growth and endocrinological response of the functioning pituitary adenoma.

MATERIALS AND METHODS

Patient population

Eighty-five patients with pituitary adenoma were treated with GKS at Yonsei University Hospital Gamma Knife Center between May 1992 and December 2002. Among these, functioning adenoma was diagnosed in 64 patients, and 42 patients, who were followed up for more than 6 months, were observed for this study. Transsphenoidal microsurgery had been performed previously on 13 patients (31.7%); 1 of these patients had undergone two transsphenoidal resections. The ratio of male to female patients was 1 : 2.7. The patients' ages ranged from 18 to 59 years with a mean of 34.7 at the time of the treatment. The mean follow-up duration was 42.5 months (range 6 - 98) at the time of data analysis.

Therapeutic evaluation criteria

The follow-up hormonal parameters were as follows: serum PRL level, GH level, and 24-hour urine-free cortisol level. For PRL and GH-producing tumors, the criteria for hormonal normalization was a serum PRL level below 20 ng/mL and a serum GH level below 5 mIU/L. For adrenocorticotrophic (ACTH)-producing tumors, the criteria for hormonal normalization was a daily urine- free cortisol level below 90 mg. We defined hormonal response as a decline in the measured hormonal level of more than 50% from the pre-GKS hormonal levels. Sellar Dynamic MR images were obtained in 32 cases to evaluate the effect of GKS on tumor growth. When the volume of a tumor decreased by more than 20% on a follow-up MRI, it was defined as shrinkage. When it changed by less than 20%, or increased by more than 20%, it was defined as stasis or enlargement, respectively. Shrinkage and stasis were defined as controlling tumor growth.

Dose planning

Treatment planning was performed with the KULA system until October 1999, and thereafter with the GammaPlan system. The mean tumor volume was 1.4 cm^3 (range 0.1 - 3.8). Multiple isocenters ranging from 1 to 6 in number (mean 2.7) were used. The tumor margin was covered by an isodose ranging from 50 to 90% (mean 53.7). The margin dose was 18 to 40 Gy (mean 28.5) and the maximum dose varied from 35 to 80 Gy (mean 54.1). We made it a rule to keep the maximum dose to the visual pathways below 9 Gy.

Statistical analysis

Cumulative rates for hormonal normalization were calculated using the Kaplan-Meier method. The Cox proportional hazards model was used for performing multivariate analysis. All statistical analyses were performed with commercially available software (SPSS, version 9.0, SPSS Inc., Chicago, IL, USA).

RESULTS

Effect of GKS on tumor growth

Tumor volume was assessed from the follow-up MRIs in 32 cases. Tumor growth was controlled in 96.9% of the cases (prolactinoma, 16/16; acromegaly, 9/9; and Cushing's disease, 6/7). Tumor shrinkage occurred in 40.6% of the cases (prolactinoma, 8/16; acromegaly, 3/9; and Cushing's disease, 2/7). The tumor shrinkage rate was highest in patients with prolactinoma. An example of tumor shrinkage after GKS is shown in Fig. 1.

Effect of GKS on endocrinological response

Forty-two patients received follow-up care. Hormonal response was observed in 35 of the 42 (83.3%) patients after GKS. The mean duration

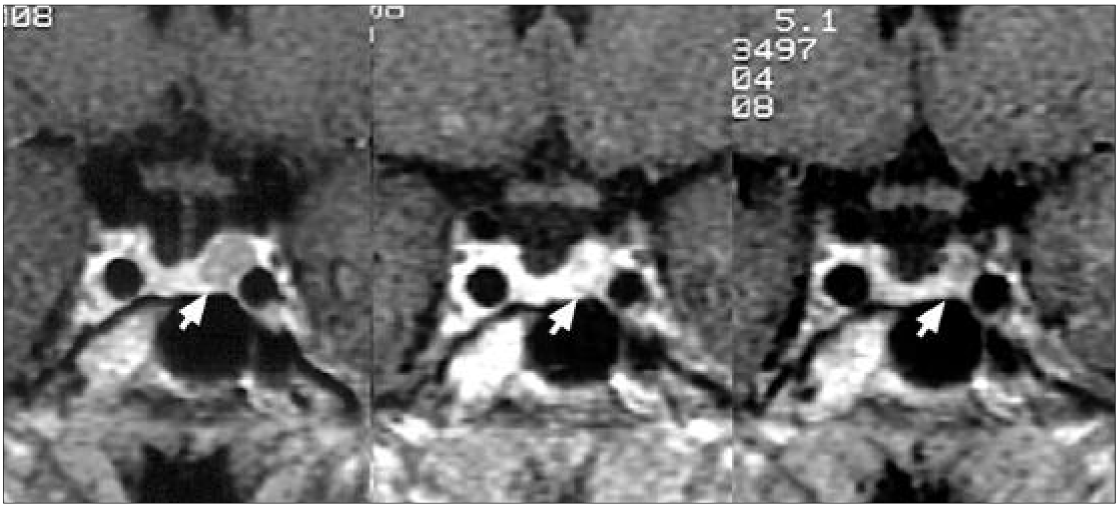

Fig. 1. Sellar dynamic MR images demonstrating the process of pituitary adenoma following Gamma Knife radiosurgery (GKS). Left: Initial MRI showing pituitary adenoma (arrow). Center: MRI obtained 13 months after GKS. Right: MRI obtained 30 months after GKS. Note the marked tumor shrinkage. This patient is a 47-year-old woman who underwent GKS (Maximum dose: 70 Gy, margin: 50%). Her initial PRL level was 337 ng/ml. Hormonal response was observed 3.2 months after GKS. Subsequently, her PRL level dropped to the normal range 42.5 months after GKS.

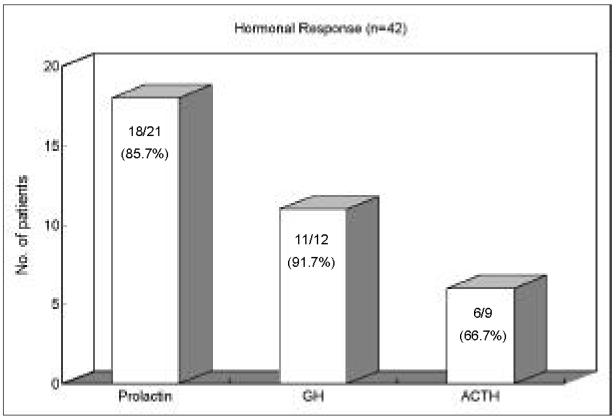

Fig. 2. Graph showing the incidence of postradiosurgical hormonal response (n=42).

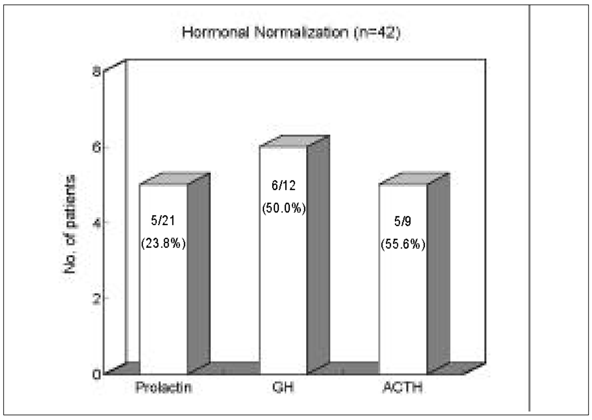

Fig. 3. Graph showing the incidence of postradiosurgical hormonal normalization (n=42). Hormonal normalization was achieved in 16 of the 42 (38.1%) patients.

between GKS and hormonal response was 6.8 months (range 1 week - 25.4 months).

In PRL-secreting adenomas, the serum PRL level normalized in 5 of the 21 (23.8%) patients. Hormonal response was observed in 18 of the 21 (85.7%) patients, as shown in Fig. 2 and 3. In GH-secreting adenomas, hormonal response occurred in 11 of the 12 (91.7%) patients and the serum GH level normalized in 6 of the 12 (50%) patients. In ACTH-secreting adenomas, the serum ACTH level was normalized in 5 of the 9 (55.6%) patients, while hormonal response was observed in 6 of the 9 (66.7%) patients.

Hormonal normalization was observed in 16 of the 42 (38.1%) patients. The mean length of time before hormonal normalization was 21 months (range 2.8 - 59.1 months). One-, 2-, and 3-year cumulative incidence rates were 16.1%, 27.4, and 37.6%, respectively (Fig. 4). The mean age was 34.3 years (range, 18.9 - 62) at the time of the treatment.

Sex, integral dose, hormonal type, number of

Table 1. Analysis of Gamma Knife Radiosurgery Variables for Hormonal Normalization

Variable	Univariate (p-value)	Multivariate (p-value)
Age	0.2124	NS
Sex	0.3103	NS
Hormonal type	0.8230	NS
Integral dose	0.0310	0.005
Number of isocenters	0.7870	NS
Maximum dose	0.0230	0.001
Margin dose	0.1040	NS

NS, not significant.

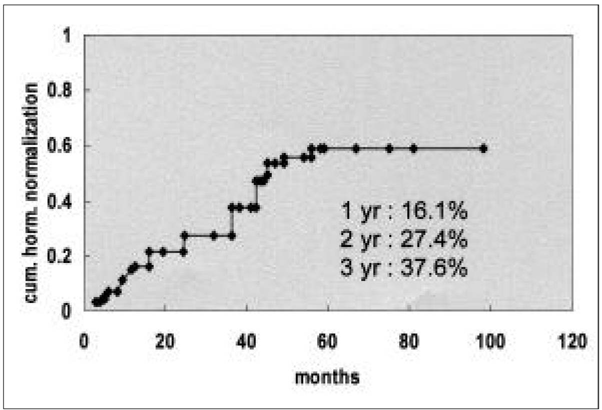

Fig. 4. Actuarial incidence curve for achieving hormonal normalization in our study (16.1% cumulative incidence rates at 1 year, 27.4% at 2 years, and 37.6%, at 3 years, respectively) Multivariate analysis revealed that high integral dose (p=0.005) and maximum dose (p=0.001) were significantly correlated with hormonal normalization.

isocenters, maximum dose, and margin dose were included as variables in a univariate analysis of hormonal normalization. In this multivariate analysis, high integral dosage (p=0.005) and maximum dosage (p=0.001) correlated significantly with hormonal normalization (Table 1).

We did not observe any patients experiencing visual disturbances following GKS, nor did we observe any damage to other cranial nerves. There was no clinical evidence of other adverse radiosurgery-related problems such as cranial neuropathy and hypopituitarism.

DISCUSSION

GKS has been found to be an effective, noninvasive method for treating patients with functioning pituitary adenoma as a complement to microsurgery. Macroadenomas that compress the optic apparatus should be microsurgically removed.[3,4] Particularly in the cavernous sinus, residual tumor, which is not completely resectable due to local invasion, is regarded as a good indication for use of GKS. That is, multiple treatment options are required to achieve a good result in the treatment of functioning pituitary adenoma. At our institute, pituitary adenomas are first microsurgically removed to diminish tumor volume and diagnose tissue. However, GKS may be considered as an alternative treatment to microsurgery if patients are reluctant to undergo surgical resection, or are unable to undergo microsurgery under general anesthesia because of old age or poor medical conditions.

The purpose of GKS, in the case of functioning pituitary adenoma, is to control tumor growth and normalize endocrinological hypersecretion. Conventional radiation therapy had been applied to patients where microsurgery alone was insufficient to control tumor growth and hypersecretion of pituitary hormones.[6,8-11] Several studies have indicated a 80 to 95% tumor control rate and a 40 to 90% hormonal control rate.[9-14] However, the permitted dose was limited to 45-50 Gy with approximately 1.8 Gy given per day. This led to a very slow reduction in the elevated pituitary hormones, and the broad field of radiation caused a high incidence of pituitary insufficiency.[5,10] Furthermore, complications occurred involving damage to the optic pathways, brain necrosis, and even neuropsychological deterioration.[1,7] Visual dysfunction following conventional radiation therapy is reported to vary from 12% to 100%.[14-16]

On the other hand, GKS allows the delivery of radiation to the target with a high degree of precision, while sparing the surrounding normal brain from radiation. In our study (with a mean follow-up of 42 months), tumor growth control and shrinkage was observed in 96.9% and in 40.6% of the cases, respectively.

Several reports have previously been published on GKS for pituitary adenoma. Lunsford and Zierhut reported that the tumor control rate for pituitary adenoma after GKS was between 93% and 94%, and that the tumor shrinkage rate ranged from 46% to 56.7%.[14,17] Our study shows similar results.

In the present study, hormonal response was observed in 35 of the 42 (83.3%) patients following GKS after a mean period of 6.8 months, and the rate of hormonal response appears to be higher in GH-secreting tumors. This finding corresponds with the observations of Witt et al.,[18] who reported that GH-secreting adenoma was the most responsive endocrinopathy following GKS.

According to the literature, the overall rate of hormonal normalization varied from 30.3% to 58%.[6,7] In our study, hormonal normalization was observed in 5 of the 21 patients with PRL-secreting adenomas, 6 of the 12 patients with GH-secreting adenomas, and 5 of the 9 patients with ACTH-secreting adenomas. The overall rate of hormonal normalization in our study was 38.1%. This result is somewhat lower than that reported by Shin, et al.,[6] where hormonal normalization was achieved in 58% of patients with a median follow-up of 3 years. Therefore, it may well be that, after a longer follow-up period, our study would yield improved results.

All variables were included in the multivariate analysis, and the Cox proportional hazards model was used to determine the factors affecting hormonal normalization following GKS. High integral dosage (p=0.005) and maximum dosage (p=0.001) were significantly related to hormonal normalization in the multivariate analysis. An image of functioning pituitary adenomas, usually microadenomas on dynamic MRI, may not be representative of the actual tumor volume. True sensitivity of various techniques in the detection of microadenomas is estimated at about 85-90% for contrast-enhanced MRIs. The actual tumor margin can be obscure on dynamic MRI by the timing of enhancement and susceptibility artifact,[19] so broad coverage of the tumor on imaging for radiosurgery could result in earlier hormonal normalization.

Based on our result, GKS is surely superior to conventional radiation therapy in terms of preventing catastrophic complications. In our study, no patient experienced visual disturbances nor any damage to other cranial nerves following GKS. Complication rates for GKS performed on pituitary adenomas have ranged from 0 to 12.6% in the literature.[18] In our institute, the most important selection criteria for GKS in the case of pituitary adenoma is that, in order to avoid complications, the pituitary tumor is located at least 5 mm away from the optic pathways in sellar dynamic MRI. Great care should be taken during the dose planning stage because it is generally believed that complications are dose dependent. Long-term follow-up after GKS for control of pituitary functions is essential due to the risk of late pituitary insufficiency even when the patient is in remission.

In summary, GKS can be an effective method for controlling tumor growth and inducing hormonal normalization in patients with functioning pituitary adenoma. It appears that early hormonal normalization can be induced by high maximum dosage (at least 50 Gy) and broad coverage of the target volume within the isodose curve, keeping the maximum dose to the visual pathways below 9 Gy.

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