Long-term results of gamma knife surgery for growth hormone–producing pituitary adenoma: is the disease difficult to cure?

TATSUYA KOBAYASHI, M.D., PH.D., YOSHIMASA MORI, M.D., PH.D., YUKIO UCHIYAMA, M.P., M.SC., YOSHIHISA KIDA, M.D., PH.D., AND SHIGERU FUJITANI, M.D.

Radiotherapy Center, Nagoya Kyoritsu Hospital and Gamma Knife Center, Komaki City Hospital, Nagoya, Japan

Object. The authors conducted a study to determine the long-term results of gamma knife surgery for residual or recurrent growth hormone (GH)–producing pituitary adenomas and to compare the results with those after treatment of other pituitary adenomas.

Methods. The series consisted of 67 patients. The mean tumor diameter was 19.2 mm and volume was 5.4 cm³. The mean maximum dose was 35.3 Gy and the mean margin dose was 18.9 Gy. The mean follow-up duration was 63.3 months (range 13–142 months).

The tumor resolution rate was 2%, the response rate 68.3%, and the control rate 100%. Growth hormone normalization (GH < 1.0 ng/ml) was found in 4.8%, nearly normal (< 2.0 ng/ml) in 11.9%, significantly decreased (< 5.0 ng/ml) in 28.5%, decreased in 21.4%, unchanged in 21.4%, and increased in 16.7%. Serum insulin-like growth factor (IGF)–1 was significantly decreased (IGF-1 < 400 ng/ml) in 40.7%, decreased in 29.6%, unchanged in 18.5%, and increased in 11.1%, which was almost parallel to the GH changes.

Conclusions. Gamma knife surgery was effective and safe for the control of tumors; however, normalization of GH and IGF-1 secretion was difficult to achieve in cases with large tumors and low-dose radiation. Gamma knife radiosurgery is thus indicated for small tumors after surgery or medication therapy when a relatively high-dose radiation is required.

KEY WORDS • gamma knife surgery • growth hormone–producing pituitary adenoma • insulin-like growth factor

STANDARDIZED treatments for pituitary adenomas have long relied on a combination of resection, pharmacotherapy, and radiation therapy. This strategy has also been applied to GH–producing adenomas. Fractionated radiation therapy has been used to control tumor growth and GH production. Significant control has been achieved with these treatments; however, realization of the desired effects takes a long time to achieve and the side effects of radiation therapy are potentially serious. Hypothalamic–pituitary hypofunction is the most common adverse effect, and this is followed by deterioration of visual function and mental (especially memory) disturbances. The mortality rate observed in acromegalic patients with uncontrolled hormone secretion is also high.

Stereotactic radiosurgery has also been undertaken in the treatment of pituitary adenomas. Gamma knife surgery based on high-resolution MR imaging has made selective irradiation of pituitary adenomas possible without significant side effects. The purpose of this study was to determine the effectiveness of GKS for GH–producing adenomas in patients with relatively long-term follow up (mean follow-up period > 5 years). The results are compared with those results of GKS for other types of pituitary adenoma.

Clinical Material and Methods

Of 267 GKS-treated pituitary adenoma cases since 1991, 136 were functioning adenomas. Of these cases, 71 were acromegaly, 33 were prolactinomas, and 32 had Cushing disease. In this study, 67 of 71 acromegaly cases underwent follow-up examinations for more than 1 year. The mean age was 47 years (range 19–83 years) and the male/female ratio was 23:44. Treatments prior to GKS consisted of resection in 49 cases, medication therapy in 42, and conventional radiation therapy in two. In nine cases GKS was the initial treatment. The mean tumor diameter was 19.2 mm (range 7.3–32.9 mm). The mean volume was 5.4 cm³. Residual or recurrent tumors were treated with GKS in which the mean maximum dose was 35.3 Gy and the mean margin dose was 18.9 Gy (Table 1).
Results

The mean follow-up period was 63.3 months (range 13–142 months) and changes in tumor size were evaluated by MR imaging every 3 to 6 months in 49 cases. The tumor showed complete remission in one case, partial remission in 31, and no change in 17. None showed progression of tumor as outlined in Table 2. The serum GH level was tested pre- and posttreatment in 42 cases. The level dropped below 1 ng/ml (normal) in two cases (4.8%), below 2 ng/ml in five (11.9%), below 5 ng/ml in 10 (23.8%), decreased but still exceeded 50% of the preoperative level in nine (21.4%), was unchanged in nine (21.4%), and increased in seven (16.7%). These changes are specified in Table 3. Serum IGF-1 levels were determined in 27 cases. Serum IGF-1 dropped below 400 ng/ml in 11 cases (40.7%), and the changes essentially ran in parallel with those in GH levels as shown in Table 4.

The clinical outcome and side effects were determined by assessing clinical records and/or by questionnaire. Vision was improved or unchanged in 26.6%, deteriorated in 11.1%, and showed no deficit in 62.3%. Hypopituitarism was improved or unchanged in 39.0%, deteriorated in 14.6%, and showed no deficit in 46.3% as shown in Table 5. Three patients died, and only in one death was due to a pituitary cause, namely hypopituitarism. According to questionnaire results, 24 (66.7%) were satisfied with radiosurgery, 10 (27.8%) were dissatisfied, and two (5.5%) did not respond. Dissatisfaction was generally attributed to persistently pathological GH level or to a lack of change in symptoms or to MR imaging findings.

Case Illustrations

Case 1

This 26-year-old woman had a residual microadenoma (10.8 mm in diameter and 0.66 cm³ in volume) with increased GH and IGF-1 levels (1.66 and 590 ng/ml, respectively) after undergoing transsphenoidal surgery. The tumor was treated with a margin dose of 25 Gy. The tumor shrunk and serum hormone levels had normalized (GH 0.8; IGF-1 312 ng/ml) 7 years after treatment as illustrated in Fig. 1.

Case 2

This 46-year-old woman had an intrasellar macroadenoma with a mean diameter of 23.1 mm. The lesion was treated with a margin dose of 25 Gy. The tumor shrunk and serum hormone levels had normalized (GH 0.8; IGF-1 312 ng/ml) 7 years after treatment as illustrated in Fig. 1.
Gamma knife surgery for GH-producing pituitary adenoma

ed with a margin dose of 16 Gy because medical treatment had been ineffective. The tumor gradually decreased in size and had disappeared at 97 months. The GH and IGF-1 levels also significantly decreased (7.76 and 290 ng/ml, respectively) as illustrated in Fig. 2.

Case 3

This 57-year-old woman had a very large adenoma, with suprasellar extension, which was initially treated by intracranial surgery for debulking of the tumor mass and optic nerve decompression. The 32.9-mm-diameter and 18.7-cm³ tumor was treated with a margin dose of 12 Gy. The tumor showed a partial remission at 36 months after treatment. A second GKS was administered with the goal of reducing tumor size (now 27 mm in diameter and 10.3 cm³ in volume). A margin dose of 14 Gy was used. The tumor showed a further size reduction, and hormone levels decreased at 8 years after the initial treatment as shown in Fig. 3.

Discussion

Selective tumor irradiation became possible in the early 1990 when MR imaging was introduced into dose planning. In 1991, Thoren, et al.,17 reported results after using 40- to 70-Gy GKS in 21 cases and found that two had been cured and that improvement of symptoms and a significant decreased GH levels were obtained in eight. Ganz, et al.,4 reported four cases treated with a mean marginal dose of 19.9 Gy. Hormone levels decreased in all four but only one case was considered cured. Witt, et al.,18 reported 29 cases treated with a mean marginal dose of 19.2 Gy. Normalization of GH was obtained in 72% but IGF-1 normalized in only 27%. Landolt, et al.,11 treated 16 cases of refractory acromegaly with a mean marginal dose of 25 Gy and compared the results with those obtained in 50 patients who underwent fractionated radiotherapy. Gamma knife surgery resulted in normalization of both GH and IGF-1 levels within a mean period of 1.4 years in 50% of cases, whereas normalization was not seen until 7.1 years after fractionated radiotherapy. Normalization was not achieved in three cases in which doses lower than 25 Gy were used. There was no correlation between tumor volume reduction and hormone level normalization. The major side effect of conventional radiotherapy was hypopituitarism, which developed in eight
cases (16%), in five of which hormone replacement was required. In one case with a progressive 19-month history of hypothalamic disturbance the patient ultimately became blind. There were no side effects in the GKS-treated group. The authors later pointed out the possibility that drugs such as octreotide might reduce the efficacy of radiation therapy.\textsuperscript{10}

Zhang, et al.,\textsuperscript{19} reported the results of initial GKS treatment for 68 acromegaly cases. The tumors, with a mean diameter of 13 mm, were treated with a mean marginal dose of 31.3 Gy. The GH levels normalized in 96\% and the tumor volume reduced in 92\%, during a mean follow-up period of 34 months, although the criteria for normalization were not presented. Niranjan, et al.,\textsuperscript{13} recently reported the results of 26 cases in which the mean tumor diameter was 14.6 mm; in all 26 the mean marginal dose was 21 Gy. The tumor disappeared in six, reduced in 12, and was unchanged in five cases after 4 years. The GH hormone levels were below 1 ng/ml in eight (36.4\%) and below 5 ng/ml in 14 (63.6\%) cases 57 months after treatment. Ikeda, et al.,\textsuperscript{7} reported the results of 17 cases in which transsphenoidal surgery was followed by GKS. The IGF-1 level had normalized in 14 cases (82.3\%) 2 years after the treatments. The authors also mentioned that pituitary function deteriorated less than after fractionated radiotherapy. Pollock, et al.,\textsuperscript{14} reported the results of treating hormone-producing adenomas in 14 cases. Hormone secretion was normal in 47\% at 36 months, and the 4-year actuarial cure rate was 61\%. These results are difficult to compare with each other and no simple conclusion emerges because of the variety of treatment conditions, different criteria for normalization of hormone levels, biases. Analysis of the present results, however, reveals that the goal of controlling of GH secretion has been difficult to achieve, probably due to the tumors being large and the marginal doses being smaller than in previous studies. Thus, smaller tumors treated with a higher margin dose are more likely to be cured and we recommend that tumors be less than 15 mm in diameter,\textsuperscript{13} and that the margin dose be greater than 25 Gy.\textsuperscript{11}

The definition of normal GH levels for acromegaly has been evolving over the years.\textsuperscript{5,6} Proposed criteria including a GH level below 1 ng/ml,\textsuperscript{13} normal IGF-1 value according
Gamma knife surgery for GH-producing pituitary adenoma

to patient age and sex,2,3,5 or both normal GH and IGF-1,5 although parallel hormone responses are not always seen.2,5 Growth hormone–producing adenomas have long been considered among the more difficult tumors to cure2,6 even with the combination of microsurgery and stereotactic radiosurgery.2,3,5 This has been attributed to the fact that they are already too large at the time of diagnosis for high-dose radiotherapy. In addition, medications administered to control GH secretion may confer resistance to radiation effects.10 Complications such as visceromegaly, hypertension, and diabetes mellitus often reduce quality of life3,12 and can become life threatening.1 Furthermore, it has been suggested by some that GH adenomas may be less radiosensitive than other pituitary adenomas.16,17

Conclusion
Gamma knife surgery was effective and safe for the control of GH-producing pituitary adenomas. Selective high-dose irradiation of residual and recurrent adenomas could be administered without significant side effects. Small or microadenomas can be cured with GKS alone. Normalization of GH and IGF-1 secretion was difficult to achieve in cases in which larger tumors received low doses of radiation. Gamma knife surgery is indicated for small residual or recurrent tumors.

References