A CROMEGALY is associated with reduced life expectancy and increased rates of death caused by cardiovascular, cerebrovascular, and respiratory diseases. Patients with acromegaly have excessive GH secretion, which is almost always caused by a GH-secreting pituitary adenoma. The diagnosis of acromegaly is generally established approximately 10 years after the development of the GH-secreting adenoma. The widespread use of high-resolution MR imaging has led to increased detection of GH-secreting adenoma without acromegalic features. Early treatment of GH-secreting pituitary adenoma is desirable to prevent the adverse metabolic effects caused by long-standing elevated GH levels.

Transsphenoidal surgery for removal of a GH-secreting pituitary adenoma is the first choice for treatment; however, invasion by the GH-secreting pituitary adenoma frequently leads to a relatively high failure rate, because the initial surgical treatment is directed at the pituitary gland. Conventional pituitary radiation therapy has been important in the treatment of acromegaly, but in reevaluations in which modern cure criteria are used it has been found that less than 20% of patients have attained a cure 10 years after radiation treatment. Recently, GKS has gained acceptance as an adjuvant treatment in combination with surgery, because GH-secreting adenomas are affected more rapidly and more efficiently, and there are minimal adverse effects compared with conventional radiotherapy.

In this study we describe the results of long-term follow up in patients with GH-secreting pituitary adenoma treated with combined transsphenoidal surgery and GKS by using the recently accepted biochemical cure criteria and biological cure (normalization of IGF-I) criteria.

**Clinical Material and Methods**

**Patient Population**

Ninety patients (42 male and 48 female patients) whose ages ranged from 11 to 75 years (mean age 47 years) underwent transsphenoidal surgery for GH-secreting pituitary adenoma between January 1989 and March 2000. The criteria for a diagnosis of GH-secreting adenoma were defined as a GH level of greater than 3 ng/ml and an elevated IGF-I level, with evidence on MR imaging of a sellar mass. Histological confirmation of GH production was obtained using immunohistochemical studies in all cases. The mean preoperative GH levels ranged from 3.1 ng/ml.
to 456 ng/ml (mean 51.2 ng/ml). Preoperatively, 25 patients had received medical therapy prescribed by a physician; and 14 had evidence of impaired anterior pituitary function based on measurement of their morning cortisol level, thyroid functions, and luteinizing hormone and follicle-stimulating hormone levels. Three patients had panhypopituitarism, five had hypogonadism only, three had both hypogonadism and hypothyroidism, and two had hypothyroidism only (Table 1).

Tumor size was determined using preoperative MR images. A microadenoma was defined as a tumor measuring 10 mm or less and a macroadenoma as a tumor measuring more than 10 mm. There were seven microadenomas and 83 macroadenomas. The maximum diameter of the adenomas ranged from 5 to 58 mm (mean 23 mm).

**Definition of Biochemical Remission**

As shown in Fig. 1, a biochemical cure for GH-secreting adenomas was defined as normalization of the IGF-I level 6 months after the operation or a fall in serum GH to below 1 ng/ml following oral administration of 75 g of glucose (the OGTT). Biological remission for GH-secreting adenomas was defined as the normalization of the age-adjusted IGF-I level. Recurrence was defined as an increase in the IGF-I level or failure of the GH level to fall to less than 1 ng/ml after an OGTT was administered following postoperative biochemical remission. The biochemical remission criteria were used to evaluate the total surgical extirpation of adenoma cells, whereas the biological remission criteria were used to evaluate the effect of adjuvant therapy such as radiotherapy and medical treatment.

**Treatment Protocol**

All patients underwent transsphenoidal microsurgical adenomectomy performed via the sublabial approach by the senior author (H.I.). The extent of tumor invasion and the extent of resection were ascertained by the surgeon. Gamma knife surgery, which became available in 1991 in our department, was administered for persistent biochemical evidence of GH hypersecretion in 16 patients and for clear regrowth of the residual tumor in the CS in two patients (Table 2). Three patients were considered unsuitable for GKS, either because of multiple residual tumors on MR imaging or because the residual tumor was too close to the optic pathway for safe dose planning, so in their cases conventional radiation therapy was performed instead.

**Table 1**

*Preoperative and postoperative endocrinological status in 37 patients with GH-secreting adenomas*

<table>
<thead>
<tr>
<th>Disease</th>
<th>No. W/ Disease</th>
<th>Preop</th>
<th>Postop</th>
<th>Improvement (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>panhypopituitarism</td>
<td>3</td>
<td>3</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>hypogonadism</td>
<td>5</td>
<td>1</td>
<td>4 of 5 (80)</td>
<td></td>
</tr>
<tr>
<td>hypothyroidism</td>
<td>2</td>
<td>1</td>
<td>1 of 2 (50)</td>
<td></td>
</tr>
<tr>
<td>hypothyroidism &amp; hypogonadism</td>
<td>3</td>
<td>2</td>
<td>1 of 3 (33)</td>
<td></td>
</tr>
<tr>
<td>hyperprolactinemia</td>
<td>24</td>
<td>0</td>
<td>24 of 24 (100)</td>
<td></td>
</tr>
</tbody>
</table>

**Gamma Knife Surgery**

The decision to institute gamma knife treatment was made more than 6 months after the operation, when both the location and shape of the residual tumor had stabilized and normal pituitary tissue and residual tumor were easy to discriminate. The target tissue and the normal tissue were exposed to different doses of radiation (Fig. 2). The radiation treatment plan was designed to limit exposure of the optic apparatus to less than 10 Gy (Table 2). The tumor volume was included within the 50% or greater isodose curve. The standard dose to the tumor margin was 25 Gy, but the doses were modified according to the tumor volume and shape. Inside the target periphery the radiation dose to the pituitary adenoma increases within a few millimeters from 20 to 40 Gy, depending on normalization, whereas outside the target periphery the dose to the normal pituitary tissue decreases within a few millimeters to 5 to 10 Gy and beyond that to probably insignificant levels (Fig. 2). During dose planning, radiation levels were adapted to the irregular shape of the residual adenoma and the dose to the optic pathway was reduced by distributing several shots (1–11, mean 4.4) with small collimator sizes (4, 8, 14, and 18 mm) throughout the target volume (Table 2). If necessary, adjustment of the gamma angle and the source blocking technique were used to change the shape of isodose curves to minimize the exposure of normal pituitary tissue (Fig. 2).

**Determination of Residual Tumor Volume**

The effect of GKS on the residual tumor volume was...
Combined surgical and gamma knife treatment for pituitary adenoma

evaluated by comparing the tumor volume measured on MR imaging before the treatment (> 6 months postoperatively); at 6, 12, 18, and 24 months after GKS; and then at yearly intervals afterward. The size of the residual tumor was measured using a reliable empirical formula for volume estimation published by Petersen, et al.30

Endocrinological Follow-Up Protocol

The basal levels of the pituitary hormones were measured twice: at 3 weeks and at 6 months after the operation. Endocrinological remission was evaluated based on the data obtained 6 months postoperatively. If the basal level of any pituitary hormone was abnormal 6 months after the operation, the mixture loading test was performed (thyroid-stimulating hormone + luteinizing hormone-releasing hormone + corticotropin-releasing hormone + GH-releasing hormone). Patients treated with GKS underwent endocrinological examination just before their treatment; at 6, 12, 18, and 24 months after GKS; and then every year thereafter.

Results

Biochemical Remission After Transsphenoidal Surgery

According to the biochemical criteria of GH less than 2 ng/ml after the OGTT and/or IGF-I normalization, 60 patients (67%) were cured after surgery (Fig. 1). The cure rate was 54 (65%) of 83 macroadenomas and six (86%) of seven microadenomas. The surgical cure rate was all (100%) of 48 noninvasive adenomas, but only 12 (28%) of 42 invasive adenomas. Among the patients in whom normalization of IGF-I was found, 35 (83%) of 42 patients fulfilled the cure criteria of nadir GH less than 1 ng/ml after the OGTT (Fig. 1). An age-adjusted IGF-I level was used for three patients (an 11-year-old girl, a 16-year-old man, and a 19-year-old woman).

Biological Remission After Adjuvant GKS

Fourteen (82%) of 17 patients, who were followed up after adjuvant GKS was administered for residual tumor invading the CS, fulfilled the biological cure criteria. The IGF-I value became normal 2 years after gamma knife treatment (Fig. 3 left), and it became stable 4 years after GKS. The plasma GH value also became stable 4 years after GKS (Fig. 3 right). One patient did not show remission during a follow-up interval of more than 5 years, probably due to multiple residual tumors, because the irradiated portion had shrunk and the appearance of the area on MR imaging had changed to hypointense on T1-weighted and hyperintense on T2-weighted imaging, which indicated a full effect of the GKS in the targeted area.16 Gamma knife surgery had resulted in more than a 50% tumor volume reduction 4 years after the treatments in all patients (Fig. 4). Thus, all patients exhibited an effective response consisting of volume reduction based on neuroimaging. There was no significant relationship between the tumor margin dose and the time to remission (Fig. 5).

Postoperative Complications

No perioperative mortality occurred in this series. One patient required reoperation for correction of cerebrospi-
cause more strict biochemical cure criteria have been accepted recently, the cure rate can be expected to fall. In our series, 83% of patients who fulfilled the criteria of a nadir GH level less than 2 ng/ml after the OGTT also fulfilled the recently accepted cure criteria. Thus, the overall surgical cure rate in our series was assumed to be 57% based on the biological cure criteria. The results also vary with the experience of the surgeon. In our series, all operations were performed by the same surgeon and strict biochemical criteria were adopted to give an overall cure rate of 57%.

The recently accepted biochemical cure criteria are very useful in judging the remission of acromegaly, but whether these strict criteria are also applicable to the patients after adjuvant treatment remains unclear. Gamma knife surgery does not eradicate the tumor but rather shrinks the tumorous mass and renders it harmless. Therefore, the endocrinological stimulation test will be meaningless, and in fact we encountered a strange endocrinological condition, that is, dissociation of plasma adrenocorticotropic hormone and cortisol levels, after gamma knife treatment of Cushing adenoma. In two of six patients, normalization of cortisol levels and clinical remission of Cushing syndrome were found, although their plasma levels of adrenocorticotropic hormone remained high. For these reasons, we used the biological cure criteria to assess the results of GKS for GH-producing adenoma.

Magnetic resonance imaging allows more accurate de-
tection of tumor invasion into surrounding tissue than computerized tomography, as well as evaluation of the margin of the residual tumor. Therefore, dose planning for GKS has become more precise and safe, reducing the damage to surrounding normal tissue. In two of the patients who had nadir GH levels of 1.1 ng/ml and 1.3 ng/ml after the OGTT, residual tumor invading the CS was demonstrated on MR imaging. Three years after surgery, one patient showed a high value of GH after the OGTT, although there was no remarkable change in the size of the residual tumor. Although the strict biochemical criteria may provide better prognostic information,6 we must follow up diligently for patients with clear evidence of residual tumor.

Conventional radiotherapy can be effective for control of pituitary adenoma but is never curative.11,19,32 The end effect may only be reached after 4 to 15 years, and in a rather high number of cases postradiation pituitary insufficiency is seen.8,10,15 The side effects may also be considerable. Therefore, radiation should be reserved for cases of acromegaly refractory to surgery and medication.

Surgical results greatly depend on the presence of CS invasion; the most difficult portion of the tumor to remove is that invading the CS. Thus, the ideal adjuvant therapy would effectively control the tumor invading the CS.

The GH and IGF-I levels show large decreases after GKS, and the plateau value is lower than that after conventional radiation.4 Thus, GKS provided an adequate effect within 2 years, which continued after 4 years, and the effect was permanent as far as we know. The volume reduction of the residual tumor occurs earlier than the normalization of IGF-I after GKS. Volume reduction was achieved in all patients treated with GKS (Fig. 4). The efficacy of GKS for achieving the biochemical criteria for cure was high; 14 (82%) of 17 patients were cured in our series. Because Fig. 3 left demonstrates that the IGF-I value became normal 2 years after GKS, and there were three patients with less than 2 years of follow up, the cure rate may be expected to rise above 82%. One patient did not have remission even after 5 years of follow up after adjuvant GKS, probably because of incomplete removal of the tumor rather than failure of GKS. The results of our series are superior to previous reports in which computerized tomography scanning was used,22 presumably because of the introduction of MR imaging. The latter modality offers accurate positional information and thus enables better dose planning for the residual tumor. Three patients who received doses of 25 Gy or less to the tumor margin showed no remission during approximately 1.5 years of follow up.22 This is probably because the follow-up period in that study was not long enough to detect remission; in our two cases of active GH-producing adenoma, the patients, who received radiation doses of less than 25 Gy to the tumor margin, had experienced remission of their disease 2 years later. There were no major side effects in our series.

The biologically effective dose formula14 indicates that pituitary adenoma receives the radiobiological effect of 100 to 200 Gy or more by fractionated radiotherapy, whereas the normal tissue within a narrow rim a few millimeters from the target receives only 10 to 25 Gy. Fractionated doses of 10 to 25 Gy will not induce hypopituitarism after 10 or more years.23 In our series, no patient had hypopituitarism after GKS during the follow-up period (mean 4.9 years). Therefore, our follow-up period is long enough to reveal any adverse effect of radiosurgery on normal pituitary tissue.

In this context, the most important factor in achieving the adjuvant effect of the gamma knife treatment is to remove the tumor completely, except for the part invading the CS, by transsphenoidal surgery. Prior transsphenoidal surgery is important to maximize the effectiveness of GKS and to minimize adverse effects. Transsphenoidal microsurgical extirpation of the tumor can separate the optic pathway and the tumor and demarcate the normal pituitary tissue (Fig. 2), allowing subsequent delivery of the optimal radiation dose to the tumor while sparing the optic pathway and normal pituitary tissue. In this study we found that GKS is superior to other options for adjuvant therapy, such as conventional radiation therapy and medical treatment in which bromocriptine or octreotide are used.

Conclusions

The outcome in patients with GH-secreting adenoma should be assessed either by biochemical cure criteria after surgery or biological cure criteria after adjuvant therapy, and normal pituitary gland function and absence of permanent surgical complications should be considered.
Among the adjuvant therapies for GH-producing adenoma, our study revealed that the effectiveness of GKS is superior to other options. Thus, the optimal treatment for GH-producing adenoma is surgery performed by an experienced practitioner, with adjuvant GKS if necessary for residual tumor.

Acknowledgment
We thank Dr. Akira Shimazu, Division of Internal Medicine, Kyoto National Hospital, for helpful discussion.

References
Combined surgical and gamma knife treatment for pituitary adenoma


Manuscript received February 9, 2000.
Accepted in final form April 25, 2001.
Address reprint requests to: Hidetoshi Ikeda, M.D., Department of Neurosurgery, Tohoku University School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai, Japan. email: ikeda@nsg.med.tohoku.ac.jp.