Gamma surgery in the treatment of nonsecretory pituitary macroadenoma

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**Object.** The authors report on a retrospective analysis of the imaging and clinical outcomes following gamma surgery in 100 patients with nonsecretory pituitary macroadenoma.

**Methods.** Between June 1989 and March 2004, 100 consecutive patients with nonsecretory pituitary macroadenoma were treated at the Lars Leksell Center for Gamma Surgery, University of Virginia Health System (Charlottesville, VA). Ninety-two patients had residual or recurrent macroadenoma following one or more surgical procedures. In eight patients, gamma surgery was the primary treatment. Ten patients received conventional fractionated radiotherapy before the gamma surgery. Sixty-nine patients required hormone replacement therapy for one or more deficits before gamma knife treatment. Peripheral doses between 5 and 25 Gy (mean 18.5 Gy) were administered.

Imaging and endocrinological follow-up evaluations were performed in 90 patients; these studies ranged from 6 to 142 months (mean 44.9 months) and 6 to 127 months (mean 47.9 months), respectively. Tumor volume decreased in 59 patients (65.6%), remained unchanged in 24 (26.7%), and increased in seven (7.8%). The minimal effective peripheral dose was 12 Gy; peripheral doses greater than 20 Gy did not seem to provide additional benefit. Of 61 patients with a partially or fully functioning pituitary gland and follow-up data, 12 (19.7%) suffered new hormone deficits following gamma surgery. In patients with endocrinological follow-up data that had been collected over more than 2 years, the rate of new deficits was 25%. No neurological morbidity or death was related to treatment.

**Conclusions.** Current experience suggests that gamma surgery is an appropriate means of managing recurrent or residual nonsecretory pituitary macroadenoma following microsurgery and a primary treatment in selected patients. To evaluate definite rates of recurrence and new endocrine deficiencies, long-term follow-up studies are needed.

**KEY WORDS** • nonsecretory pituitary macroadenoma • hypopituitarism • Gamma Knife • gamma surgery • transphenoidal surgery

**Nonsecretory** pituitary adenomas are defined as tumors without endocrine hypersecretion, but they may have immunoreactivity for one or more adenohypophysial hormones and specific ultrastructural differentiation.\(^2\) They account for 18 to 31% of all surgically treated pituitary adenomas.\(^9,22\) The lesion’s size at diagnosis, proximity to optic pathways, tendency to invade the parasellar space (cavernous sinus) or infiltrate osseous structures, and lack of hormone hypersecretion determine the goals and strategies of treatment.

Before the advent of radiosurgery, the mainstay in nonsecretory pituitary adenoma management was surgery with or without conventional fractionated radiotherapy. Transsphenoidal surgery is the most widely used surgical procedure, yielding satisfactory results and a reasonably low complication rate. When invasive tumors involve the parasellar space, radical removal is difficult to achieve and residual tumor frequently remains, as revealed on follow-up imaging studies. First and second recurrence risk rates vary between 6 and 21%, and 46%, respectively.\(^9,9,25,26,31\) Laws, et al.,\(^24\) stated that repeated microsurgery for recurrent pituitary adenomas is especially difficult, and the risks associated with repeated transsphenoidal surgery are significantly greater than those for the initial operation. In 2005 Benveniste and colleagues\(^3\) contended that refinements in the transsphenoidal surgery technique had made repeated transsphenoidal surgery with a low complication rate feasible and that immediate relief of clinical symptoms due to mass effect could be achieved in 94% of patients. Note, however, that 15% of the patients in that study still experienced tumor recurrence after a mean follow-up period of 32 months.

Postoperative fractionated radiotherapy reduced the recurrence rates to between 5 and 9% in pituitary adenomas with or without the involvement of the para- and suprasellar spaces.\(^4,11,15,34\) Gittoes and associates\(^35\) compared two groups of patients that had been treated using surgery alone or in combination with radiotherapy and found that the progression-free survival rate was 93% both 10 and 15 years after treatment in the former group and 47 and 33%, respectively, in the latter. In a long-term study by Breen, et al.,\(^7\) in which 120 patients were treated using radiotherapy, the recurrence rate was 12.5% at 10 years after treatment, 22.4% at 20 years, and 35.3% at 30 years. Damage to the visual path-
Gamma surgery for nonsecretory pituitary adenoma

ways following radiotherapy, presumably due to vasa nervorum injury, has been quoted as 1 to 2%, with a latency between 2 months and 4 years after the administration of radiation,4,7,12,35,44,55 and seems to be related to both total and single-fraction doses.14,16 Radiation-induced hypopituitarism due to direct damage to the pituitary gland, the pituitary infundibulum, and/or hypothalamus occurs frequently.4,42 Brada, et al.,4 reported occurrences of secondary hypopituitarism requiring hormone replacement in 30% of patients 10 years after conventional radiotherapy and in 50% at 19 years thereafter. Thyroid-stimulating hormone seems to be particularly sensitive to radiation.52 The occurrences of a second tumor such as a glioma, meningioma, or parasellar fibrosarcoma have also been reported; however, it is difficult to assess their real incidence because such cases have usually been published sporadically.1,7,12,52 It is assumed that the cumulative risk of tumor induction following radiotherapy is 1.3% at 10 years and 1.9% at 20 years, 10 times higher than that in the normal population.6

Gamma surgery has been used in the management of pituitary adenomas as an initial treatment or as a complement to surgery. Its purpose is tumor shrinkage or the prevention of further growth.18,20,28,32,40,42,49 In the present study, we present the imaging and clinical outcomes in 100 patients with nonsecretory pituitary macroadenoma treated using the Gamma Knife either primarily or following surgery.

Clinical Material and Methods

Patient Characteristics

Between June 1989 and March 2004, of 434 patients with pituitary adenoma treated at the Lars Leksell Center for Gamma Surgery, Department of Neurological Surgery, University of Virginia Health System, 100 had a nonsecretory adenoma (Table 1). The mean age in the 60 men and 40 women was 51.1 years (range 21–82 years). In eight patients, gamma surgery was applied as the initial treatment. Ninety-two patients underwent transcranial or transsphenoidal operations before the gamma knife procedure. Forty-five patients had undergone one prior resection; and 47, more than one prior resection (two resections in 37 patients, three resections in nine patients, and four resections in one patient). In 10 patients, the resection was followed by conventional radiotherapy before the gamma surgery was undertaken. At the time of gamma treatment, 37 patients had decreased visual acuity and/or a visual field defect, six had diabetes insipidus, and 69 had anterior pituitary hormone deficiencies, including 31 with partial and 38 with complete pituitary insufficiency.

Tumor Parameters

All tumors were macroadenomas—either initial or residual following previous microsurgery. The mean tumor volume was 4.8 cm³ (range 0.6–27 cm³) at the time of gamma treatment. In 68 patients, the tumors involved one or both parasellar spaces. Immunohistochemical analysis was performed on 64 surgical specimens. Thirty-three of these were positive for hormone immunoreactivity: 21 stained for a gonadotrophic hormone (luteinizing hormone, follicular stimulating hormone, and alpha subunit), 11 for adrenocorticotropic hormone, and one for growth hormone. The remainder were categorized as null cell adenomas.

TABLE 1

Summary of patient characteristics and treatment parameters in 100 patients with nonsecretory pituitary macroadenoma treated using gamma surgery.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>male/female ratio</td>
<td>60:40</td>
</tr>
<tr>
<td>mean age in years (range)</td>
<td>51.1 (21–82)</td>
</tr>
<tr>
<td>no. of ops before GS</td>
<td>92</td>
</tr>
<tr>
<td>single</td>
<td>45</td>
</tr>
<tr>
<td>multiple (2–4)</td>
<td>47</td>
</tr>
<tr>
<td>no. of radiotherapy procedures before GS</td>
<td>10</td>
</tr>
<tr>
<td>no. of immunoreactivity results</td>
<td></td>
</tr>
<tr>
<td>null cell</td>
<td>31</td>
</tr>
<tr>
<td>gonadotroph</td>
<td>21</td>
</tr>
<tr>
<td>ACTH</td>
<td>11</td>
</tr>
<tr>
<td>GH</td>
<td>1</td>
</tr>
<tr>
<td>no. of tumors w/ parasellar space involvement</td>
<td>68</td>
</tr>
<tr>
<td>mean tumor vol in cm³ (range)</td>
<td>4.8 (0.6–27)</td>
</tr>
<tr>
<td>mean peripheral dose in Gy (range)</td>
<td>18.5 (5–25)</td>
</tr>
<tr>
<td>mean maximal dose in Gy (range)</td>
<td>41.5 (10–70)</td>
</tr>
<tr>
<td>mean isodose configuration in % (range)</td>
<td>44.5 (30–53)</td>
</tr>
</tbody>
</table>

* ACTH = adrenocorticotropic hormone; GH = growth hormone; GS = gamma surgery.

Treatment Variables

Gamma surgery was performed using the Leksell Gamma Unit, model U until July 2001, and model C (both Elekta Instruments, Inc., Norcross, GA) thereafter. The dose rate varied: from 3.66 Gy/minute in 1989 to 1.59 Gy/minute in October 1995 when the cobalt sources were reloaded, and from 3.56 Gy/minute in November 1995 to 2.31 Gy/minute in July 2001 when the model C unit was installed. The dose rate of the model C unit ranged from 3.67 Gy/minute in July 2001 to 2.58 Gy/minute in March 2004. The treatment planning was performed by a neurosurgeon. The planning software programs were approved by the US Food and Drug Administration and are proprietary to Elekta Instruments, Inc. The KULA software was used from 1989 to June 1994; and the Gamma Plan software (versions 1.045.12), from June 1994 to the present.

Computed tomography was the only imaging modality available for treatment planning until 1990. Afterward, MR imaging was used unless it was contraindicated, in which case CT was performed. Thin-slice (1.5 mm) axial CT scanning was performed to visualize both soft tissue and osseous structures. For MR imaging, axial contrast-enhanced T₁-weighted spin echo and coronal T₂-weighted sequences were obtained with a slice separation of 1.4 mm.

Tumor volume, distance to the optic pathways, and history of previous radiotherapy influenced gamma surgery dose selection. The mean peripheral dose was 18.5 Gy (range 5–25 Gy) to the 30 to 53% isodose configuration. The mean maximal dose was 41.5 Gy (range 10–70 Gy). The mean number of isocenters used per patient was 6.6 (range 1–24 isocenters). The dose to the visual pathways was typically limited to 1 to 4 Gy (mean 2.5 Gy). In a few cases in which the tumors were close to the optic pathway, only a small amount of nerve (< 2%) received doses greater than 8 Gy. Whenever necessary, shielding was utilized to limit the radiation dose to the optic apparatus.

Follow-Up Evaluation

Clinical follow-up data were obtained by examination of
the patient or by written or verbal communication with both the patient and the referring physician. For the purposes of this study, relevant additional information was collected using a questionnaire, and assessments were performed by the referring endocrinologists. Follow-up MR imaging (or CT scanning if MR imaging was contraindicated) was performed at 4- to 12-month intervals. Special software allowing the estimation of tumor volume based on MR images or CT scans without a stereotactic frame was developed. It evaluates the area of interest on each slice as drawn by the observer by using polygonal estimation techniques. The area on each slice is multiplied by the slice thickness and integrated over the relevant slices. The tumor volume was evaluated, and reviewed by both neurosurgeons and neuroradiologists. Changes in volume were approximated to the nearest 10th of 1 percent. A tumor was considered to have changed significantly if the volume change exceeded 15%.

Four patients underwent repeated gamma surgery because of adenoma growth or new lesion occurrence, and another four underwent transsphenoidal resection of the tumor after gamma surgery had been unsuccessful. The date of repeated treatment was designated as the end point of the follow-up evaluation in these eight patients.

Statistical Analysis

The imaging and endocrinological outcomes were analyzed using a one-way analysis of variance, the independent t-test for univariate analysis of continuous variables (age, tumor volume, peripheral dose, isodose configuration, and duration of imaging and endocrinological follow up), and the chi-square test for dichotomous variables (gender, previous radiotherapy, single or multiple surgeries, and parasellar space involvement). Logistic regression was used for multivariate analysis. The development of new pituitary dysfunction was analyzed using the Kaplan–Meier method. All statistical analyses in this study were performed using a commercially available statistical software (version 10.1; SPSS, Inc., Chicago, IL). Statistical significance was set at a probability value less than 0.05.

Results

Imaging Outcome

Imaging studies were available in all but 10 patients who had undergone less than 6 months of follow up. The mean follow-up evaluation in 90 patients was 44.9 months (range 6–142 months). The tumor decreased in size in 59 patients (65.6%), remained unchanged in 24 (26.7%), and increased in seven (7.8%). The cumulative outcome is shown in Fig. 1. Of the eight patients who had undergone gamma surgery as the primary therapy, shrinkage in tumor volume occurred in three and there was no change in five after a mean follow-up period of 34 months. In the group of 82 patients who had been treated after one or more resections, a reduction in tumor volume occurred in 56, no change was detected in 19, and an increase occurred in seven. The median time to onset of tumor shrinkage was 9 months (range 6–48 months) after treatment. An example of a tumor volume reduction is illustrated in Fig. 2.

Among 61 tumors involving the parasellar space and with imaging follow-up data, 39 shrank, 17 remained unchanged, and five increased in size. Of 29 tumors confined to the sellar space, 20 shrank, seven remained unchanged, and two increased in size. Statistically, the imaging outcome did not differ between these two types of tumors. Five patients harbored tumors in proximity to the optic pathways; shielding these pathways led to the delivery of lower radiation doses to adjacent parts of the tumors. Despite this strategy, less than 10% of the tumor volume received suboptimal doses with appropriate use of shielding methods. Of these tumors, one increased in size, two remained unchanged, and two decreased in size.

Among the nine parameters analyzed statistically, peripheral dose and duration of follow up were significantly related to imaging outcome according to a univariate analysis. A higher peripheral dose was associated with better results. In the subgroup in which the tumors had remained unchanged, the duration of the follow-up evaluation was significantly shorter than that in the groups in which the tumor had increased or decreased in size. The other factors were not statistically significant (Table 2). Based on multivariate analysis, only the peripheral dose correlated with imaging outcome. Peripheral doses between 12 and 20 Gy, compared with doses greater than 20 Gy, resulted in no significant difference in the imaging outcome, whereas a dose less than 12 Gy was associated with a poorer result (Table 3). No radiation-induced adverse effects were observed on the follow-up MR images.

Four patients underwent repeated gamma surgery 35, 37, 61, and 108 months after the first treatment: two for regrowth of the tumor and two for new lesions involving the contralateral parasellar space. Two new lesions and one tumor regrowth decreased in size after the second gamma surgery. The imaging follow-up data were not available in the fourth patient. Additionally, four patients required repeated transsphenoidal resection 16, 50, 51, and 93 months after gamma surgery: three due to tumor enlargement and one with unchanged tumor size but persistent headache.

Clinical Outcome

Clinical information was available in all 100 patients. No adverse effects due to the gamma surgery were observed. No patient with normal visual function experienced a visual deficit following treatment. In one patient, a preexisting visual deficit worsened and was related to tumor growth into the optic canal. Eight deaths unrelated to the tumor or gamma surgery occurred at least 1 year after treatment. Among these patients, tumor progression occurred in two, shrinkage in two, and no change in four.
Endocrinological Findings

In 69 patients with residual pituitary function at the time of gamma surgery, endocrinological follow-up data were available in 61 (range 6–127 months, mean 47.9 months). Basal serum levels of cortisol, free thyroxine, and prolactin were evaluated in all 61 patients. Gonadal function was assessed in men clinically and by measuring serum testosterone. The loss of menses in premenopausal women indicated gonadotropin failure. Testing for growth hormone changes was not performed in all patients. Pituitary insufficiency was defined as a condition requiring hormone replacement.

Among patients with normal or partially preserved pituitary function, 12 (19.7%) suffered new hormone deficits 8 to 107 months (mean 26 months) after treatment. Nine patients (14.8%) required thyroid hormone replacement from 8 to 107 months (mean 27.7 months) after gamma surgery. Four patients (6.6%) required a glucocorticoid replacement 11 to 25 months (mean 16.5 months) after gamma surgery. A new onset growth hormone deficit was diagnosed in two patients and required hormone replacement 13 and 39 months after gamma surgery. A summary of characteristics in the 12 patients with new hormone deficits is provided in Table 4, and a Kaplan–Meier curve is shown in Fig. 3. None of the nine clinical and treatment variables we analyzed was significantly related to endocrinological outcome.

Discussion

Some authors of previous publications have reported on gamma knife treatment of pituitary adenomas without describing the separate outcomes for secretory or nonsecretory tumors, indicating tumor control rates from 92 to 100% and shrinkage rates from 30 to 83%. Recent analyses focused on nonsecretory pituitary tumors revealed tumor control rates of 93 to 100%, whereas only a few studies involved the quantitative assessment of tumor size, indicating shrinkage rates between 22 and 43%. In the present study we address the outcome only in nonsecretory macroadenomas, most of which involved the parasellar space and/or infiltrated osseous structures. All except eight patients underwent one or more resections; 10 had also received radiotherapy. The gamma surgery performed in some cases might be defined as salvage treatment. Following this treatment, significant tumor shrinkage occurred in 66% of patients at a median time of 9 months. No evi-

**Table 2**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Increased</th>
<th>Unchanged</th>
<th>Decreased</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>7</td>
<td>24</td>
<td>59</td>
</tr>
<tr>
<td>male/female ratio</td>
<td>4:3</td>
<td>15:9</td>
<td>36:23</td>
</tr>
<tr>
<td>mean patient age in yrs</td>
<td>44.4 ± 6.3</td>
<td>56.8 ± 16.4</td>
<td>49.8 ± 15.0</td>
</tr>
<tr>
<td>patients w/ previous radiotherapy procedures</td>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>patients w/ multiple ops</td>
<td>5</td>
<td>10</td>
<td>26</td>
</tr>
<tr>
<td>patients w/ parasellar space involvement</td>
<td>5</td>
<td>17</td>
<td>39</td>
</tr>
<tr>
<td>tumor vol (cm³)</td>
<td>5.5 ± 2.8</td>
<td>4.7 ± 4.1</td>
<td>4.6 ± 4.7</td>
</tr>
<tr>
<td>peripheral dose (Gy)</td>
<td>13.0 ± 7.5†</td>
<td>18.2 ± 6.9</td>
<td>19.2 ± 5.2</td>
</tr>
<tr>
<td>isodose configuration (%)</td>
<td>38.6 ± 9.0</td>
<td>46.4 ± 7.8</td>
<td>43.5 ± 8.3</td>
</tr>
<tr>
<td>duration of imaging FU (mos)</td>
<td>57.6 ± 34.2</td>
<td>26.7 ± 25.3‡</td>
<td>50.8 ± 30.9</td>
</tr>
</tbody>
</table>

* Values are presented as the means ± standard errors of the mean. Abbreviation: FU = follow up.
† p < 0.05, compared with unchanged and decreased groups.
‡ p < 0.05, compared with increased and decreased groups.
Even lower doses may shrink or arrest tumor growth, the risk of damage to the optic pathways may be less than that in patients with a secretory pituitary adenoma. This argument was borne out by the fact that the longer the tumors were followed up, the more likely they would show an increase or a decrease in size.

**Tumor Volumetry**

In computing volume, the area of the tumor was defined on MR imaging or CT slices and approximated via an interpolation formula using the slice separation. Slice thickness and separation, segmentation of the region of interest, and image quality (pixel, size, and noise) may determine the magnitude of the marginal error. Detailing the imaging protocol, Tables 5 and 6 list the average relative volumetric error percentage and the standard deviation compared with slice separation, as well as the number of slices on which the tumor was visualized. According to these findings, one should visualize the tumor in as many slices as possible. In other words, the slice thickness should be as small as possible, and the reduction or enlargement in volume should be considered significant only if it exceeds the marginal error by approximately 15%. Hence, in this series, a change in tumor size was validated when the magnitude of the change was at least 15%.

**Dose Selection**

In hormonally active pituitary tumors, peripheral doses as high as 25 to 35 Gy may be required to reduce endocrine hypersecretion. Even lower doses may shrink or arrest tumor growth in both hormonally active and nonsecretory tumors. In the present series of nonsecretory tumors, a peripheral dose of 12 Gy often induced tumor shrinkage. Doses greater than 20 Gy did not improve the success rate. Given that relatively low doses are required to inhibit tumor growth, the risk of damage to the optic pathways may be less than that in patients with a secretory pituitary adenoma.

**Tumors Involving the Parasellar Space**

One of the most common causes of incomplete removal of pituitary macroadenomas is the extension of the tumor into the parasellar space. The rate of failure with either transsphenoidal or transcranial approaches is not consequential. Surgery, even by an experienced pituitary neurosurgeon, still carries the risk of new cranial nerve damage or vascular injury. Sixty-eight patients in the present series were treated for tumors involving the parasellar space; no restriction of the dose was considered necessary in these patients. The results were comparable with those in the patients whose tumor had no parasellar space involvement. New cranial neuropathy or carotid artery injury did not occur following gamma surgery.

**Tumor Involving the Optic Pathways**

Failure to dissect the tumor away from the optic path-

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**TABLE 3**

Summary of characteristics and outcomes in patients in three groups based on different peripheral doses

<table>
<thead>
<tr>
<th>Variable</th>
<th>Peripheral Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 12 Gy</td>
</tr>
<tr>
<td>no. of patients</td>
<td>16</td>
</tr>
<tr>
<td>peripheral dose (Gy)</td>
<td>9.3 ± 1.8</td>
</tr>
<tr>
<td>age (yrs)</td>
<td>58.1 ± 17.3</td>
</tr>
<tr>
<td>tumor vol (cm³)</td>
<td>5.8 ± 2.6</td>
</tr>
<tr>
<td>imaging FU (mos)</td>
<td>51.9 ± 34.7</td>
</tr>
<tr>
<td>hormone FU (mos)</td>
<td>63.5 ± 27.3*</td>
</tr>
<tr>
<td>no. of tumors (%)</td>
<td>7 (44)*</td>
</tr>
<tr>
<td>size increased</td>
<td>4 (25)*</td>
</tr>
<tr>
<td>new endocrine deficiency (%)</td>
<td>3/8 (37.5)†</td>
</tr>
</tbody>
</table>

* p < 0.05, compared with 12 to 20-Gy and > 20-Gy groups.
† The denominator represents the number of patients at risk for developing a new endocrine deficiency.

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**TABLE 4**

Summary of characteristics in patients in whom new hormone deficits developed following gamma surgery

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Tumor Vol (cm³)</th>
<th>Peripheral Dose (Gy)</th>
<th>Hormone Deficiencies</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44, M</td>
<td>3.0</td>
<td>25.0</td>
<td>gonadotroph, cortisol</td>
</tr>
<tr>
<td>2</td>
<td>48, F</td>
<td>1.2</td>
<td>25.0</td>
<td>none, gonadotroph, cortisol</td>
</tr>
<tr>
<td>3</td>
<td>59, M</td>
<td>2.8</td>
<td>24.0</td>
<td>gonadotroph, cortisol</td>
</tr>
<tr>
<td>4</td>
<td>77, M</td>
<td>2.8</td>
<td>11.5</td>
<td>gonadotroph, cortisol</td>
</tr>
<tr>
<td>5</td>
<td>35, F</td>
<td>3.1</td>
<td>15.0</td>
<td>none, gonadotroph, cortisol</td>
</tr>
<tr>
<td>6</td>
<td>46, M</td>
<td>8.9</td>
<td>9.0</td>
<td>none, gonadotroph, cortisol</td>
</tr>
<tr>
<td>7</td>
<td>63, M</td>
<td>1.5</td>
<td>20.0</td>
<td>TH (107)</td>
</tr>
<tr>
<td>8</td>
<td>27, F</td>
<td>3.7</td>
<td>25.0</td>
<td>cortisol (11)</td>
</tr>
<tr>
<td>9</td>
<td>55, F</td>
<td>9.4</td>
<td>12.0</td>
<td>cortisol (18)</td>
</tr>
<tr>
<td>10</td>
<td>44, M</td>
<td>2.3</td>
<td>9.0</td>
<td>cortisol (39)</td>
</tr>
<tr>
<td>11</td>
<td>27, F</td>
<td>1.5</td>
<td>24.0</td>
<td>TH (17)</td>
</tr>
<tr>
<td>12</td>
<td>62, M</td>
<td>2.4</td>
<td>23.0</td>
<td>TH (33)</td>
</tr>
</tbody>
</table>

* TH = thyroid hormone.

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**Fig. 3.** Graph showing the time from gamma surgery to the development of new pituitary deficits requiring hormone replacement.
Gamma surgery for nonsecretory pituitary adenoma

### TABLE 5
Volumetric error compared with number of intercepting slices for compact lesions*

<table>
<thead>
<tr>
<th>Lesion Volume (cm³)</th>
<th>7 Slices</th>
<th>6 Slices</th>
<th>5 Slices</th>
<th>4 Slices</th>
<th>3 Slices</th>
<th>2 Slices</th>
<th>1 Slice</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;0.1 &amp; &lt;1.0</td>
<td>3.5 (1.3)</td>
<td>5.1 (1.5)</td>
<td>6.4 (1.8)</td>
<td>11.4 (2.4)</td>
<td>21.2 (3.6)</td>
<td>43.1 (4.9)</td>
<td>93.1 (0.7)</td>
</tr>
<tr>
<td>&gt;1.0 &amp; &lt;5</td>
<td>1.8 (0.8)</td>
<td>3.6 (0.5)</td>
<td>4.3 (0.6)</td>
<td>9.6 (2.2)</td>
<td>19.0 (2.6)</td>
<td>40.9 (6.4)</td>
<td>86.7 (1.6)</td>
</tr>
<tr>
<td>&gt;5 &amp; &lt;10</td>
<td>3.5 (1.2)</td>
<td>4.1 (1.2)</td>
<td>7.2 (2.5)</td>
<td>13.1 (3.2)</td>
<td>22.9 (2.4)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>&gt;10</td>
<td>4.4 (1.6)</td>
<td>5.1 (1.6)</td>
<td>8.1 (2.0)</td>
<td>13.5 (2.2)</td>
<td>25.4 (1.0)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

* If there are at least four visible lesion slices, then the volumetric error would generally be less than 15%. Using this criterion, the estimation of the expected error is independent of tumor size. Abbreviation: NA = not applicable.

### TABLE 6
Volumetric error compared with slice thickness for compact lesions*

<table>
<thead>
<tr>
<th>Lesion Volume (cm³)</th>
<th>1-mm Slice</th>
<th>2-mm Slice</th>
<th>3-mm Slice</th>
<th>4-mm Slice</th>
<th>5-mm Slice</th>
<th>6-mm Slice</th>
<th>7-mm Slice</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;0.1 &amp; &lt;1.0</td>
<td>1.4 (0.8)</td>
<td>13.0 (6.6)</td>
<td>30.5 (9.6)</td>
<td>75.6 (19)</td>
<td>78.4 (17.2)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>&gt;1.0 &amp; &lt;5</td>
<td>0.4 (0.3)</td>
<td>2.8 (1.5)</td>
<td>6.5 (2.8)</td>
<td>16.4 (8.2)</td>
<td>18.5 (5.9)</td>
<td>35.3 (10.9)</td>
<td>39.2 (6.0)</td>
</tr>
<tr>
<td>&gt;5 &amp; &lt;10</td>
<td>0.3 (0.5)</td>
<td>1.0 (0.7)</td>
<td>2.3 (1.4)</td>
<td>4.3 (2.0)</td>
<td>10.8 (5.5)</td>
<td>10.7 (4.5)</td>
<td>19.7 (5.1)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>0.2 (0.4)</td>
<td>0.6 (0.4)</td>
<td>1.7 (1.0)</td>
<td>3.5 (1.9)</td>
<td>5.1 (2.2)</td>
<td>7.6 (3.2)</td>
<td>11.6 (4.4)</td>
</tr>
</tbody>
</table>

* As tumor volume decreases, slice thickness must also decrease to maintain the volumetric error at suitably low levels. A fixed follow-up imaging protocol will eventually lose the power to discriminate significant volume changes of a continuously shrinking lesion.

ways and to create an appropriate distance between the residual adenoma and optic apparatus makes it difficult or sometimes impossible to perform radiosurgery effectively. The proximity of the tumor to the optic apparatus increases the risk of damage to the optic pathways. Shielding the optic pathways will also shield the adjacent tumor portion, thereby limiting the chance for a favorable outcome. A similar problem is encountered when a large part of the normal pituitary gland is included in the radiation field. To avoid this situation, a space between the tumor and the respective radiation-sensitive structures should be created. The use of fat or muscle grafts often fails to maintain the necessary distance because tissue grafts usually move from the place of insertion or shrink after placement. More innovative solutions remain to be investigated.

**Gamma Surgery as an Initial Treatment**

In the present series, gamma surgery was generally used as complementary treatment for residual or recurrent tumors following microsurgery, except in eight patients with an advanced age (six patients, 76–82 years old) and/or unstable medical conditions that precluded resection (two patients). We believe that whenever a surgeon is confident that he can remove the tumor without damaging a patient’s quality of life, he should do so. Such a philosophy generally restricts the primary use of GKS. Furthermore, some have recently proposed performing immunohistochemical staining of nonsecretory tumors given that asymptomatic corticotrophic adenomas may behave more aggressively and require vigilant follow-up monitoring and potent treatment.

In contrast, with small noninvasive pituitary tumors, whether secretory or nonsecretory, the results of gamma surgery have been satisfactory. Clinical remission in patients who have undergone gamma surgery as the primary therapy for secretory adenomas has been reported to be comparable with that following microsurgery.

### Adverse Effects

Optic neuropathy has been sporadically reported in gamma knife studies, and the risk is dose dependent. The software Gamma Plan, which permits shielding of these structures by selective beam blocking, reduces the radiation dose to the visual pathways. The distance between the tumor and the optic pathways was at least 3 to 5 mm in most of the patients in this study, and only small volumes of the optic nerves and chiasm received doses higher than 8 Gy. Nonetheless, if the distance between tumor and optic pathways was less than 3 mm, part of the tumor was also shielded, thus reducing the effectiveness of treatment. Recently, the dose threshold for the development of radiation-induced optic neuropathy has been questioned. Stafford, et al., reported a low incidence rate even if the optic apparatus received a dose of up to 12 Gy.

Reported anecdotal complications of gamma surgery in para- or suprasellar regions include occlusion of the internal carotid artery in the parasellar space, temporal lobe epilepsy caused by radiation necrosis, and malignant hyperthermia.
mia likely as a result of hypothalamic damage.\textsuperscript{21} These complications were not observed in our patients. We also did not observe nerve damage in the parsellar space despite the fact that occasionally some nerves received up to 30 Gy.

Radiation-induced secondary tumors following radiotherapy in the sellar region have been documented.\textsuperscript{1,4,6,7} Although rare instances of radiosurgery-induced neoplasia have been reported,\textsuperscript{22} the long latency for tumor induction and the fact that no single series of pituitary tumors treated with radiosurgery has involved a long enough follow-up evaluation prevent an accurate estimation of the true occurrence of this complication.

Hypopituitarism is a relatively frequent complication after radiation is applied to the sellar region. The steep dose gradient provided by gamma surgery potentially spares residual normal pituitary gland, infundibulum, or hypothalamus and thus theoretically reduces the risk of this adverse effect. Landolt, et al.,\textsuperscript{23} in comparing two groups of acromegalic patients treated with radiotherapy and gamma surgery, reported a higher incidence of hypopituitarism in the group treated with fractionated radiotherapy. In the present series, new hormone deficits developed in 19.7\% of the patients 8 to 107 months after treatment. If we consider only those cases with an endocrinological follow-up period longer than 2 years, however, the rate of new deficits approaches 25\% (Fig. 3). In the literature, the incidence of new hormone deficits following GKS is between 0 and 19.2\%,\textsuperscript{21,28,30}.\textsuperscript{32,37,40,42,51} The difference in the reported incidence of new pituitary insufficiency may be explained in part by disparity in the ambition to detect it.

**Linear Accelerator Radiosurgery and Stereotactic Fractionated Radiotherapy**

In studies of pituitary adenomas treated using LINAC-based radiosurgery, tumor control was achieved satisfactorily, although the incidence of complications has been relatively high.\textsuperscript{33,41} In 36 patients followed up for a mean period of 21 months, Rocher, et al.,\textsuperscript{40} reported 100\% tumor control, 33\% new optic neuropathy, and 43\% new hormone deficits. Mitsumori, et al.,\textsuperscript{36} reported 100\% tumor control, but the incidence of complications (including headache, visual field defect, and radiation necrosis) in their study was 28\%. Plowman and Dougherty,\textsuperscript{41} in comparing the dosimetry of GKS and LINAC-based radiosurgery, found that the dose gradient at the level of the optic chiasm was more favorable with gamma surgery. A higher incidence of adverse effects has prompted many centers using LINAC-based radiosurgery to deliver fractionated doses (fractionated stereotactic radiotherapy). The limited track record of this method does not permit evaluation of its efficacy.

**Conclusions**

The application of gamma surgery in the management of pituitary macroadenomas following resection or, in selected cases, as the primary treatment is relatively safe. The combined use of a transsphenoidal approach and gamma surgery is beneficial in many of these difficult cases. In some patients, however, optimal control of tumor growth is not achieved. Innovative improvements in techniques are required to avoid pituitary insufficiency and to reduce the number of cases in which gamma surgery is not feasible because of tumor proximity to optic pathways.

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Gamma surgery for nonsecretory pituitary adenoma

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