Gamma Knife surgery for Cushing’s disease

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Object. In this study the authors address the efficacy and safety of Gamma Knife surgery (GKS) in patients with adrenocorticotrophic hormone–secreting pituitary adenomas.

Methods. A review of data collected from a prospective GKS database between January 1990 and March 2005 was performed in patients with Cushing’s disease. All but one patient underwent resection for a pituitary tumor, without achieving remission. Successful endocrine outcome after GKS was defined as a normal 24-hour urinary free cortisol (UFC) concentration posttreatment after a minimum of 1 year of follow up. Patient records were also evaluated for changes in tumor volume, development of new hormone deficiencies, visual acuity, cranial nerve neuropathies, and radiation-induced imaging changes. Ninety evaluable patients had undergone GKS, with a mean endocrine follow-up duration of 45 months (range 12–132 months). The mean dose to the tumor margin was 23 Gy (median 25 Gy).

Normal 24-hour UFC levels were achieved in 49 patients (54%), with an average time of 13 months after treatment (range 2–67 months). In the 49 patients in whom a tumor was visible on the planning magnetic resonance (MR) image, a decrease in tumor size occurred in 39 (80%), in seven patients there was no change in size, and tumor growth occurred in three patients. Ten patients (20%) experienced a relapse of Cushing’s disease after initial remission; the mean time to recurrence was 27 months (range 6–60 months). Seven of these patients underwent repeated GKS, with three patients achieving a second remission. New hormone deficiencies developed in 20 patients (22%), with hypothyroidism being the most common endocrinopathy after GKS. Five patients experienced new visual deficits or third, fourth, or sixth cranial nerve deficits; two of these patients had undergone prior conventional fractionated radiation therapy, and four of them had received previous GKS. Radiation-induced changes were observed on MR images in three patients; one had symptoms attributable to these changes.

Conclusions. Gamma Knife surgery is an effective treatment for persistent Cushing’s disease. Adenomas with cavernous sinus invasion that are not amenable to resection are treatable with the Gamma Knife. A second GKS treatment appears to increase the risk of cranial nerve damage. These results demonstrate the value of combining two neurosurgical treatment modalities—microsurgical resection and GKS—in the management of pituitary adenomas.

KEY WORDS • pituitary adenoma • cranial nerve deficit • recurrent disease • endocrine remission • Gamma Knife surgery

CUSHING’s disease is an endocrine disorder with many potentially devastating neurological and systemic sequelae. Resection of the pituitary adenoma remains the mainstay of treatment in Cushing’s disease, with remission rates ranging from 50 to 90%, 1,5,22,31,34 Nevertheless, tumors associated with Cushing’s disease, particularly macroadenomas with suprasellar or cavernous sinus extension, are very difficult to cure surgically. Resection can be associated with complications, including damage to the optic pathways, carotid artery injury, damage to other cranial nerves (that is, the third, fourth, and sixth cranial nerves), cerebrospinal fluid leakage, and the development of permanent diabetes insipidus and hypopituitarism.

The success of stereotactic radiosurgery in treating a number of sellar and parasellar lesions1,8 has led to investigation of the efficacy of both the Gamma Knife and linear accelerator–based radiosurgery as adjuvant treatments for Cushing’s disease.20,41 The Gamma Knife is well suited for treating Cushing’s disease, because these pituitary tumors tend to be small, facilitating the delivery of highly focused radiation to the lesion or the remaining pituitary gland while sparing surrounding structures.20,40 We report our experience with the safety, efficacy, and complications of GKS in patients with ACTH-secreting pituitary adenomas.
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Clinical Material and Methods

Records of patients treated with GKS for Cushing’s disease between January 1990 and March 2005 were reviewed. Detailed records of endocrine studies were evaluated for normalization of 24-hour UFC levels after treatment, development of new hormone deficiencies, and complications. Patients with more than 12 months of follow up or remission in less than 12 months post-GKS were included in the study. Patients with Nelson’s syndrome were excluded.

Laboratory information, including endocrine studies obtained at our institution and laboratory data from other medical centers, was analyzed. Remission was defined as a normal 24-hour UFC level obtained while the patient was not receiving a cortisol-lowering medication. All patients underwent an endocrine evaluation prior to radiosurgery; routinely, this included a 24-hour UFC, ACTH, serum cortisol, prolactin, free T4, luteinizing hormone, follicle-stimulating hormone, gonadotropin-releasing hormone, testosterone, and insulin-like growth factor–I. In addition to studies of the cortisol axis, posttreatment tests were obtained in response to clinical signs or symptoms noted during follow up.

Patient Population

One hundred seven patients with elevated 24-hour UFC levels underwent Gamma Knife treatment at our institution between January 1990 and March 2005 (Fig. 1). Patients were included in the analysis if they had completed more than 12 months of follow up, or if they had achieved a remission in less than 12 months after GKS. Seventeen patients had less than 12 months or no follow up, and were therefore excluded from the study, leaving 90 patients as evaluable. Age at presentation ranged from 12 to 68 years (mean 39 years). Sixty-five patients were female and 25 were male.

Postradiosurgical follow-up imaging consisted of MR imaging studies, which were performed at 6 and 12 months posttreatment and annually thereafter. The tumor volume after radiosurgery was compared with the value obtained during the pretreatment study. These values were measured using software developed to calculate the tumor volume based on MR imaging studies performed without the stereotactic frame. The program uses polygonal estimation methods to evaluate an area of interest drawn by a neuroradiologist on each slice. The area in each slice is then multiplied by the slice thickness and integrated over the relevant sections. On evaluation, the margin of error for this method is approximately ±10% for lesions smaller than 1 cm³ and ±8% for volumes larger than 1 cm³.

Gamma Knife Technique

The Gamma Knife, which consists of 201 independent cobalt-60 radiation sources, delivers highly focused ionizing beams to an intracranial target in a single session. All patients underwent stereotactic frame placement in the operating room after induction of monitored anesthesia. This method ensures sterile conditions during the frame placement and minimizes patient discomfort.

After frame placement, stereotactic neuroimaging was performed. If not contraindicated, MR imaging was used. Nonenhanced and contrast-enhanced T₁-weighted spin

![Gamma Knife: Cushing's Disease](chart)

Fig. 1. Flowchart summarizing the patients treated in this series. Ad = adrenalectomy; F/U = follow up; GK = Gamma Knife; Med = medication; mo = months; Rx = prescribed; TSS = transphenoidal surgery.

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echo axial images and coronal TR-weighted images with slice separation of 1.5 mm were obtained. If an MR imaging study was contraindicated, thin axial sliced (1.5 mm) stereotactic CT scans were performed with and without contrast material. In all cases, preoperative neuroimaging studies and the intraoperative findings at the time of microsurgery were weighted at the time of dose planning by the treating neurosurgeons (L.S. and J.P.S.).

From 1989 until the middle of 2001, a model U Gamma Knife unit was used for radiosurgery, and since the middle of 2001 the model C (both models manufactured by Elekta AB) has been used. The dose rate varied from 3.66 Gy/minute in 1989 to 1.59 Gy/minute in October 1995, when the source was reloaded; and the dose rate was 3.56 Gy/minute from 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 2.29 Gy/minute in March 2005. Treatment planning between 1989 and 1993 was performed using the KULA system, and after 1993 Gamma Plan (Elekta AB) software was used. Shielding of eloquent structures was performed as necessary. Radiosurgical planning was performed in a way that respected the principle of limiting the therapeutic dose entirely within the lesion and to ensure as steep a dose gradient as possible. As a rule, multiple isocenters were used. Dose selection was made on the basis of tumor volume, location, previous fractionated radiation therapy, and the prescription isodose. All GKS procedures were performed by Dr. Steiner or Dr. Sheehan. Much of the follow-up endocrine assessment and evaluation of recurrent disease was performed by Dr. Vance.

Statistical Analysis

Statistical analysis was performed using GAUSS version 5.0 (Aptech Systems, Inc.) and SAS version 9.1 (SAS Institute, Inc.) software. The level used to determine statistical significance was a probability value less than 0.05. Statistical analysis was performed by Dr. Mark Conaway, Division of Epidemiology, University of Virginia Health System.

Results

All but one patient had undergone previous transsphenoidal operations (mean 1.4 procedures), and three patients had undergone a prior craniotomy. Three patients also had received prior conventional fractionated radiation therapy. Additionally, two patients had been treated previously with radiosurgery (one with a linear accelerator and one with a Gamma Knife at another institution). One patient who had a cavernous sinus tumor underwent GKS as a primary treatment, without resection.

Endocrine follow-up duration ranged from 12 to 132 months (mean 41.3 months, median 45 months). The duration of neuroimaging follow-up review ranged from 4 to 75 months (mean 36 months, median 31 months). Sixty-three patients (70%) had an endocrine or imaging follow-up duration of greater than 24 months, and 30 patients (33%) had a follow-up duration of greater than 48 months. During the follow-up period patients continued to undergo yearly imaging, and we performed endocrine studies every 6 months, with the end point recorded as the most recent MR imaging study and 24-hour UFC level. Either no change or shrinkage of the adenoma was defined as tumor control. Endocrine remission was defined as a normal 24-hour UFC level without cortisol-lowering medication.

Treatment parameters and dose selection varied depending on the patient’s clinical history, findings on neurological and ophthalmological examinations, and tumor location. Factors considered in dose selection included the dose and timing of any previous radiation therapy, adenoma size, distance between the adenoma and the optic apparatus, and the extent of preoperative visual deficits. Maximal doses ranged from 18 to 60 Gy (mean 49 Gy), and margin doses ranged from 8 to 30 Gy (mean 23 Gy). Treatment isodose (the ratio of the dose to the tumor margin in relation to the total dose) varied from 30 to 70%. It is well known that cavernous sinus invasion by functioning adenomas is a common cause of failed microsurgery.\(^9,10\) For this reason, in 23 cases in which no tumor was identified on planning neuroimaging studies despite endocrine evidence of persistent Cushing’s disease, the entire sellar contents of the adjacent cavernous sinuses were targeted. Fourteen of these 23 patients had undergone a total hypophysectomy (by E.R.L.).

Tumor Volume

Gamma Knife planning and posttreatment MR images were used to compare tumor volumes in the 67 patients in whom there was visible tumor. A decrease in tumor size was seen in 62 patients (92%); two patients (3%) had no change in tumor size and three (4.8%) experienced tumor enlargement. In 29 patients, the decrease in tumor size was associated with normalization of 24-hour UFC levels. Thirty-three patients, however, did not achieve a normal 24-hour UFC level, despite a decrease in tumor volume.

Endocrine Remission

Normalization of 24-hour UFC levels was achieved in 49 patients (54%), with a mean time to remission of 13 months (median 16, range 2–67 months) (Table 1). Of the 41 patients who remained in remission, four achieved endocrine remission within 3 months of treatment, 11 within the first 6 months and 26 within the 1st year after GKS (Fig. 2 upper). Ten patients (20%) who achieved remission after GKS suffered a recurrence of Cushing’s disease (Table 2). The mean time to initial normalization of 24-hour UFC levels in these patients was 8.9 months, and the mean time to recurrence was 27 months after radiosurgery (Fig. 2 lower). The mean maximal tumor dose in these patients was 51 Gy, and the mean margin dose was 22 Gy. There was no significant difference in total or peripheral dose or

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Endocrine outcomes in 90 patients who underwent GKS for a pituitary adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal 24-Hr UFC</td>
<td>No. of Patients (%)</td>
</tr>
<tr>
<td>yes</td>
<td>49 (54)</td>
</tr>
<tr>
<td>no</td>
<td>41 (46)</td>
</tr>
<tr>
<td>total</td>
<td>90 (100)</td>
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</tbody>
</table>
time to remission between these 10 patients and the 39 who did not suffer a recurrence.

Seven patients underwent repeated GKS after recurrence. Three of these patients (43%) achieved remission after a second Gamma Knife treatment, with a mean time of 8 months to second remission. The median dose to the tumor margin in these patients at the time of the second Gamma Knife treatment was 22.5 Gy. Of the patients who achieved a second remission, none had a second recurrence at the most recent follow-up evaluation.

**Active Disease**

Forty-one patients did not achieve remission of Cushing’s disease. Six of them died, either because of sequelae of their disease or because of other medical problems. Sixteen patients in this study ultimately underwent a bilateral adrenalectomy (two after repeated GKS).

**Type and Rate of Complications**

An open-ended follow-up period is required to determine the true rate of complications. The most serious complication of GKS was the development of cranial nerve palsies. In five patients in our series ophthalmoplegia developed after Gamma Knife treatment; four of these patients also experienced a new decrease in visual acuity. Four of the patients with ophthalmoplegia had previously undergone Gamma Knife procedures, with a mean dose to the tumor margin of 24 Gy at the time of the first GKS (range 20–27 Gy), and a mean time course of 20 months between Gamma Knife procedures (range 8–42 months).

The most commonly affected cranial nerves were the third (three patients) and sixth (two patients). The mean dose to the tumor margin in these patients was 26 Gy, and the mean time course to identification of the deficit was 6 months postradiosurgery (range 2–15 months). Two patients had received prior fractionated radiation therapy (doses of 17 and 50 Gy, administered 31 and 36 months prior to GKS, respectively). The dose to the optic apparatus in the patients in whom ophthalmological symptoms developed varied from 2 to 7 Gy (mean 3.2 Gy).

In one patient who received both repeated GKS and fractionated radiosurgery, a change in visual fields developed; this was manifested by progression to blindness in both eyes more than 12 months after radiosurgery. This patient had received 50 Gy of fractionated radiation therapy 36 months before his first Gamma Knife procedure and had experienced a bitemporal hemianopia prior to GKS. The patient did not achieve a remission of his Cushing’s disease following the initial Gamma Knife treatment and elected to undergo a second radiosurgical procedure, which was performed 12 months later. He subsequently achieved an endocrine remission 7 months after his second Gamma Knife treatment. Magnetic resonance imaging performed 1 year after the second Gamma Knife procedure revealed enhancement in the parasellar area consistent with radiation-induced changes.

Two other instances of radiation-induced changes were noted on MR images, although clinical symptoms did not develop in these patients. In the one symptomatic and the two asymptomatic patients, imaging changes were seen in the cavernous sinus and around the optic apparatus.

Endocrine deficiency was present in 37 patients (41%) prior to the initial procedure. Hormone deficiencies after GKS occurred in 20 patients (22%). The most common new endocrinopathy was hypothyroidism (nine patients) followed by growth hormone deficiency (seven patients). In three (15%) of the 20 patients in whom new hormone deficiencies developed, the entire sella was targeted. New hormone deficits were diagnosed at a mean of 16 months posttreatment (range 4–36 months). No instances of new diabetes insipidus occurred after GKS. No instances of carotid artery stenosis, stroke, or radiation-induced neoplasms were diagnosed in any of the 90 patients.
Although fractionated radiation therapy has historically been the treatment of choice for controlling tumor growth and reducing hormone hypersecretion,1 it can be associated with damage to surrounding sellar and parasellar structures, and, on occasion, the development of new tumors.5 Although fractionated radiation therapy can result in remission for 56 to 83% of patients with Cushing’s disease,1,11 it can be associated with complications such as hypopituitarism, radiation necrosis, damage to surrounding sellar and parasellar structures, and, on occasion, the development of new tumors.5,9,10,32,33 The incidence of loss of pituitary function after fractionated radiation therapy varies between 50 and 100%.3,41

The concept of stereotactic radiosurgery was developed by Lars Leksell.33 Many researchers have suggested that this modality is a preferred treatment for selected recurrent or residual pituitary adenomas.16,33 To date, there have been more than 20 published studies in which the effectiveness of the Gamma Knife for patients with Cushing’s disease has been detailed. These studies, however, have been limited by the small number of patients, short follow-up periods, and incomplete ophthalmological and endocrine follow up (Table 4). Moreover, many of the studies were performed before the MR imaging era, limiting the assessment of tumor size.

As detailed in a study by Dickerman and Oldfield,9 Rahn and colleagues16 reported on 77 patients, 59 of whom were followed for 2 to 15 years after undergoing GKS for Cushing’s disease. The cases were divided into two groups, the first a series of 51 patients in whom stereotactic localization of the tumor was performed using pneumoencephalography/CT scanning, and the second a series of eight patients in whom stereotactic MR imaging and CT scanning were used. In the first group, 42 patients (82%) were “cured” and another eight (16%) had improvement in their disease. In other studies endocrine “cure” rates of between 17 and 83% have been reported after GKS.9,13–33 The wide range of “cure” rates is probably a result of differences in the criteria for “cure” and the duration of follow up.

The rate of hormone normalization after radiosurgery for Cushing’s disease appears difficult to predict. In some series endocrine remission within 3 months of radiosurgery has been reported, and in others normalization occurring more than 8 years after treatment has been detailed.16,17 Our results confirm the conclusions in the majority of published studies, which indicate that if endocrine normalization is going to occur after radiosurgery, it typically occurs within the first 2 years, especially in patients with microadenomas.18,19,29,42

**TABLE 3**

Univariate results for time to remission, tumor volume, and time to recurrence*

<table>
<thead>
<tr>
<th>Factor</th>
<th>24-Hr UFC (49 patients)</th>
<th>Tumor Control (67 patients)</th>
<th>Time to Recurrence (49 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>p Value</td>
</tr>
<tr>
<td>craniotomies</td>
<td>NA</td>
<td>NA</td>
<td>0.03</td>
</tr>
<tr>
<td>preop tumor vol</td>
<td>0.86</td>
<td>0.67–1.10</td>
<td>0.23</td>
</tr>
<tr>
<td>isocenters</td>
<td>0.94</td>
<td>0.83–1.07</td>
<td>0.83</td>
</tr>
<tr>
<td>tumor extension</td>
<td>0.95</td>
<td>0.48–1.88</td>
<td>0.89</td>
</tr>
<tr>
<td>cavernous</td>
<td>1.23</td>
<td>0.62–2.45</td>
<td>0.55</td>
</tr>
<tr>
<td>suprasellar radiation dose max</td>
<td>1.02</td>
<td>0.98–1.05</td>
<td>0.36</td>
</tr>
<tr>
<td>suprasellar radiation dose marginal</td>
<td>0.97</td>
<td>0.94–1.01</td>
<td>0.19</td>
</tr>
<tr>
<td>suprasellar radiation isodose</td>
<td>0.98</td>
<td>0.96–1.01</td>
<td>0.23</td>
</tr>
</tbody>
</table>

* Normalization of 24-hour UFC was classified as remission, and volume was measured among those with discernible tumor. Abbreviations: CI = confidence interval; HR = hazard ratio; NA = not applicable; OR = odds ratio.
† None of the patients who underwent craniotomy achieved a normal 24-hour UFC level, leading to an infinite estimate of the hazard ratio. The probability value was computed using the Fisher exact test.
‡ All of the patients who underwent craniotomy achieved control of tumor size, leading to an infinite estimate of the odds ratio. The probability value was computed using the Fisher exact test.
§ None of the 48 patients who initially achieved a normal 24-hour UFC level had undergone a craniotomy.

**Statistical Analysis**

Univariate analysis was performed to identify factors related to endocrine remission, effect on tumor volume control, and recurrence; the results are summarized in Table 3. There was no significant relationship between remission and tumor extension into the cavernous sinus, suprasellar extension, maximum or margin dose, or treatment isodose.

Preoperative tumor volume was related to achievement of an endocrine remission (p = 0.05), but absence of tumor growth was not related to preoperative treatment factors, including tumor volume, suprasellar tumor extension, previous transsphenoidal surgery, the treatment isodose, or the dose to the tumor margin. Patients in whom a craniotomy had been performed previously were more likely to experience control of tumor volume but less likely to obtain an endocrine remission. Recurrence of Cushing’s disease was not related to the treatment dose (maximal or peripheral), the preoperative tumor volume, or suprasellar/cavernous sinus extension.

**Discussion**

Microsurgical resection of a pituitary adenoma is the initial treatment for patients with Cushing’s disease. For patients with persistent disease after attempted tumor extirpation, fractionated radiation therapy has historically been the treatment of choice for controlling tumor growth and reducing hormone hypersecretion. Although fractionated radiation therapy can result in remission for 56 to 83% of patients with Cushing’s disease,6,11 it can be associated with complications such as hypopituitarism, radiation necrosis, damage to surrounding sellar and parasellar structures, and, on occasion, the development of new tumors.5,19,10,32,33 The incidence of loss of pituitary function after fractionated radiation therapy varies between 50 and 100%.3,41

The concept of stereotactic radiosurgery was developed by Lars Leksell.33 Many researchers have suggested that
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as others have found a correlation between remission and the treatment isodose, maximal dose, and margin dose.\(^{21,29}\)

We observed no such relationship between remission and either the dose or the tumor volume.

There was no correlation between change in tumor volume and the endocrine response after radiosurgery.\(^{16,23,28}\)

Most ACTH-secreting tumors are less than 1 cm in maximum dimension, and, provided that there is sufficient distance between the adenoma and the optic apparatus, they are well suited for radiosurgery.\(^{36,37}\)

Given that the systemic effects of Cushing’s disease can be so devastating, it seems intuitive to deliver a reasonably high dose (≥ 20 Gy) to the margin, to optimize the probability of endocrine remission and control of tumor growth. Blocking patterns can often be devised to deliver an adequate dose to the tumor while sparing the optic apparatus.\(^{36,38}\)

Relapse of Cushing’s disease has been reported after GKS, despite symptomatic and initial remission.\(^{21}\)

In our series, 20% of our patients had a relapse after one Gamma Knife treatment. In the group that experienced recurrence, the initial time to remission was not significantly different from that of the patients whose disease remains in remission. The occurrence of relapses underscores the importance of long-term endocrine and radiological follow-up evaluation for all patients with pituitary lesions treated with radiosurgery.

Our data also confirm previous reports that retreatment of recurrent pituitary adenomas can be successful, although with a higher rate of complications, as occurred in this series. There was a 43% success rate in achieving normal 24-hour UFC levels after a second Gamma Knife procedure.\(^{16,23,28}\)

Investigators at the Karolinska Institute reported that four (36%) of 11 patients achieved normal UFC levels after repeated radiosurgery.\(^{9}\)

In our series, the risk of delayed hypopituitarism in the group that underwent retreatment does not appear to be significantly higher than after the first treatment, although the actual risk associated with retreatment will only be ascertained after longer follow up in this subgroup.

The reported incidence of hypopituitarism after radiosurgery varies widely. Some investigators have reported a low incidence (0–36%) of pituitary dysfunction after radiosurgery.\(^{16,23,28}\)

Others have reported an eventual 72% incidence of hypopituitarism over the course of 18 years.\(^{17}\)

Although Feigl and colleagues\(^ {13}\) postulated that hypopituitarism after radiosurgery correlated with the radiation dose to the pituitary stalk, we observed no difference in the delivered dose in patients who experienced hormone deficiencies and those who did not.

The risk of damage to suprasellar and parasellar structures in our series was 5%. The tolerable level of radiation to the optic apparatus and parasellar structures remains the subject of investigation. Some investigators suggest that the optic apparatus can tolerate doses as high as 12 to 14.1 Gy.\(^ {6,25,30}\)

Whereas others recommend an upper limit of 8 Gy.\(^ {15,38}\)

The presence of postradiosurgical visual decline and opthalmoparesis in our series, despite relatively low doses of radiation to the optic chiasm and tumor margin, underscores the degree of variability in the optic apparatus and in cranial nerve sensitivity. Even without overt visual deficits, patients with pituitary adenomas may not have entirely normal optic pathways.\(^ {24}\)

The underlying abnormalities in the visual pathways may arise as a result of pituitary adenoma compression, ischemic changes, and the type and timing of previous interventions (for example, fractionated radiation therapy and resection). The acceptable dose to the cavernous sinus is also largely unknown. In our series some patients were able to tolerate doses as high as 30 Gy to the parasellar structures without opthalmoparesis, whereas in others evidence of damage developed with doses as low as 18 Gy. As expected, it appears that patients who have undergone previous radiation treatments are at higher risk for cranial nerve damage.\(^ {38}\)

In summary, our study is notable for two new observations. First, the 20% rate of relapse of Cushing’s disease after an initial remission is unexpected and emphasizes the need for long-term follow-up evaluation in these patients after GKS. No difference in the total or margin radiation dose or the size of the treatment field was observed between the patients in whom relapse occurred and those who remained in remission. It is likely that the patients who experienced relapse had infiltrative disease that was not visible on the imaging studies. Second, the incidence of cranial nerve dysfunction after GKS has not been reported previously; this occurred in four (57%) of seven patients who received a second course of GKS. Most studies emphasize the amount of radiation exposure and tolerance of the optic nerves and chiasm. There has been a presumption that structures in the cavernous sinus, such as the cavernous carotid artery and cranial nerves, are less susceptible to

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**TABLE 4**

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Patients</th>
<th>Mean or Median FU (mos)</th>
<th>Margin Dose (Gy)</th>
<th>Endocrine Cure Rate (%)</th>
<th>Endocrinological Criteria for Cure</th>
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</thead>
<tbody>
<tr>
<td>Levy et al., 1991</td>
<td>64</td>
<td>NR</td>
<td>NR</td>
<td>86</td>
<td>normal basal cortisol &amp; dexamethasone test results</td>
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<tr>
<td>Witt et al., 1996</td>
<td>25</td>
<td>32</td>
<td>19</td>
<td>28</td>
<td>normal 24-hr UFC</td>
</tr>
<tr>
<td>Hayashi et al., 1999</td>
<td>10</td>
<td>16</td>
<td>24</td>
<td>10</td>
<td>NR</td>
</tr>
<tr>
<td>Izawa et al., 2000</td>
<td>12</td>
<td>28</td>
<td>22</td>
<td>17</td>
<td>NR</td>
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<tr>
<td>Laws et al., 2000</td>
<td>50</td>
<td>&gt;12</td>
<td>NR</td>
<td>58</td>
<td>normal 24-hr UFC</td>
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<td>Sheehan et al., 2000</td>
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<td>44</td>
<td>20</td>
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<td>normal 24-hr UFC</td>
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<td>Hoybye et al., 2001</td>
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<td>NR</td>
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<td>Feigl et al., 2002</td>
<td>4</td>
<td>55</td>
<td>15</td>
<td>NR</td>
<td>NR</td>
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<td>Kobayashi et al., 2002</td>
<td>20</td>
<td>64</td>
<td>29</td>
<td>35</td>
<td>ACTH &lt;50 pg/ml; cortisol &lt;10 μg/dl</td>
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<td>Pollock et al., 2002</td>
<td>9</td>
<td>42</td>
<td>20</td>
<td>78</td>
<td>UFC &lt;90 μg/24 hrs</td>
</tr>
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</table>

* FU = follow up; NR = not reported.
radiation damage. The precise radiation tolerance of the cranial nerves is not known and has been estimated to be between 7 and 17 Gy on initial treatment. The incidence of cranial nerve palsy in our study raises questions regarding the accuracy of previous estimates of a “safe” radiation dose to the cranial nerves, which leads us to favor bilateral adrenalectomy over repeated GKS after failed treatment.

Conclusions

Gamma Knife surgery is a safe and effective treatment for patients with ACTH-secreting pituitary adenomas. We observed endocrine remission in 54% and control of tumor growth in 96% of patients with Cushing’s disease. Ongoing surveillance for tumor growth, disease recurrence, the development of new hormone deficiencies, and damage to the optic pathways and brain remains necessary.

References

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