Although pituitary adenomas are histologically benign, the unrelated neurological and physiological consequences can be devastating. Compression of the optic apparatus (nerves, chiasm, tracts) may lead to blindness or loss of peripheral vision. Interference with the function of nerves traversing the cavernous sinus can result in diplopia and/or facial paresthesias. Further expansion of the tumor laterally into the temporal lobes or posteriorly into the hypothalamus can lead to significant cognitive problems. Excessive GH production associated with acromegaly can lead to life-threatening cardiovascular and respiratory conditions, diabetes mellitus, and possibly an increased risk of colon cancer. Prolonged hypersecretion of ACTH in Cushing disease can lead to severe problems with hypertension and osteoporosis. In patients with prolactinomas, galactorrhea and infertility may occur.

Successful management of these tumors can be challenging. Treatment options include microresection, medical therapy, fractionated radiotherapy, and SRS. Stereotactic radiosurgery was defined in 1951 by Lars Leksell as the “closed skull destruction of an intracranial target using ionizing radiation.” Applied to pituitary adenomas, destruction of the target means prevention of the tumor’s growth and normalization of hormone production. Destruction of surrounding neural, endocrine, and vascular structures must not occur. The purpose of this report is to analyze the current status of SRS for pituitary tumors and to examine its utility compared with other treatment modalities.

RADIOSURGICAL TECHNIQUES

Stereotactic radiosurgery is performed using three general types of devices: a cyclotron that generates heavy particles such as protons and helium ions; a linear accelerator that generates x-ray beams; and a GK that generates gamma rays from 201 sources of $^{60}$Co. The majority of studies published in the last 15 years regarding radiosurgery for pituitary adenomas are from centers at which the GK is used. Because the author’s experience is also primarily with the GK, its use in cases of pituitary adenoma radiosurgery will be described in more detail.

Once the decision has been made to treat a patient with SRS, preparation may begin several months prior to the procedure. In 2000, Landolt, et al., first reported a significantly lower incidence of GH and IGF-I normalization in patients with acromegaly in whom antiserotonin medications were administered at the time of radiosurgery. In a separate report on patients with prolactinomas, Landolt and Lomax found that patients not receiving dopamine agonists at the time of radiosurgery have a significantly better chance of experiencing endocrinological cure than those who continue to take these medicines. Since then, others have also documented a negative effect of antiserotonin medications administered at the time of radiosurgery on the reduction of excessive hormone secretion.
less susceptible to radiation. The optimal length of time for these medications to be withheld is not clear. For patients with prolactinomas, Landolt and Lomax recommended that dopamine agonists be withheld for 2 months prior to radiosurgery. For patients with acromegaly receiving the long-acting form of octreotide, the last injection should occur 4 months before the GK. Six weeks later, the medication should be switched to the immediate-release form, which should be maintained until 2 weeks before radiosurgery. In these last 2 weeks before the procedure, no antisecretory medications should be taken. Because the tumor may enlarge once these medications are stopped (Fig. 1), the potential benefits of these medication adjustments must be weighed against the potential risks. A larger tumor may mean a lower prescription dose and a higher risk for surrounding structures.

On the day of the treatment, the stereotactic head frame is applied in the standard fashion. Mild intravenous sedation is administered for adults, and general anesthesia is induced for children. The scalp is prepared with alcohol, and the areas of the pin placements are infiltrated with a long-lasting local anesthetic. It may be helpful to angle the frame parallel to the axis of the optic apparatus. In the author’s experience, this angle approximates a line joining the lateral canthus and the top of the pinna. One purpose of this maneuver is to make identification of the optic nerves, chiasm, and tracts easier by having an MR or CT image that demonstrates the entire optic apparatus in a single slice.

For identification of the tumor, MR imaging is far superior to CT scanning. The latter may be used in cases in which a non–MR imaging–compatible metallic implant exists or if the patient is too large to fit into a closed MR imaging unit (the latter scenario is not unusual in patients with Cushing disease). When MR imaging is used, a post-Gd thin-slice (1-mm) volume-acquisition sequence is recommended. Depending on the patient’s history of treatment and findings on preradiosurgery images, acquisition of precontrast studies or use of fat-suppression techniques may help in identification of the tumor. If there is significant flow artifact across the sella from the CAs, the phase/frequency-encoding direction can be flipped so that this artifact extends in an anteroposterior direction and does not obscure the sella.

One relatively common problem in patients with Cushing disease is the inability to detect the tumor on the imaging study, which may occur if the tumor is extremely small or because neoplastic cells invaded the dura or have diffusely infiltrated the gland. As long as pre-GKS tests strongly suggest that the tumor does reside in the sella, radiosurgery may still be successfully performed. Semple, et al., and Shimon, et al., have reported successful outcomes in microsurgical series when the tumor cannot be identified on a preoperative MR images. Inferior petrosal sinus sampling can successfully predict lateralization of the tumor 81% of the time. Without the aid of direct visualization and histological analysis at the time of surgery, however, the predictive value of inferior petrosal sinus sampling may not be accurate enough to allow the radiosurgeon to target just one half of the gland. It is probably more reasonable to select the entire sella as the radiosurgical target in cases in which the tumor cannot be visualized to minimize chances of failure to normalize excessive hormone production.

After stereotactic images have been acquired and transferred into a computer workstation, multiple isocenter dose planning is performed to enclose the borders of the tumor within the prescription isodose line. The 50% isodose is the most common prescription isodose line in GKS series because this line is where the slope of the radiation falloff is the steepest. Beam blocking plug patterns are often used to distort the peripheral isodose curves away from the optic apparatus because of the radiosensitivity of this structure (Fig. 2). The need to use plug patterns can be reduced by adjusting the gamma angle so that the anteroposterior axis of the peripheral isodose curves is parallel to the optic apparatus in the sagittal plane. If the frame is placed parallel to the course of the optic apparatus, then a gamma angle of 90° may be used. This maneuver takes advantage of the extremely steep falloff of radiation dorsal to the isocenter. Selection of the prescription dose is based partially on the integrated logistic formula as well as specific strategies for protecting the optic apparatus, controlling tumor growth, and establishing and maintaining normal endocrinological function.

**EXPECTATIONS IN RADIOSURGERY**

There are two therapeutic goals when performing SRS for pituitary tumors. One goal is the arrest of tumor growth and the prevention of future problems from mass...
Review of SRS for pituitary adenomas

lesion-induced effect. The second is normalization of excessive hormone production. The results obtained in 29 series published within the last 5 years will be discussed in terms of these goals. The reports contain information on 1255 patients. Their data are presented in Tables 1 through 5 for endocrine-inactive adenomas, GH-secreting adenomas, prolactin-secreting adenomas, Cushing disease, and Nelson syndrome, respectively.

Growth Control

One common interseries feature for almost all types of tumor is the excellent growth control rate (92–100%). The one exception is the series of patients with Nelson syndrome reported by Pollock and Young, in which tumor growth occurred in two of 11 patients. The ACTH-producing tumors in patients who have undergone adrenalectomy, however, tend to be more biologically aggressive neoplasms. Because most pituitary adenomas are slow-growing benign tumors, some skepticism concerning the value of short-term follow-up studies is warranted, although the follow-up duration in seven of these 29 studies includes periods longer than 8 years, and in one study by Hoybye et al. the mean follow-up period was 17 years (range 12–22 years). In this latter study, three patients needed surgery for persistent endocrinopathy; no patient has required surgery or irradiation because of uncontrolled tumor growth. Therefore, the present data on growth control for pituitary tumors augments the ever-expanding literature on radiosurgery for growth control of other benign tumors.

Another growth control concept that can be extrapolated from Tables 1 through 5 is that radiosurgeons tend to use a lower margin dose for an endocrine-inactive tumor than for a secretory adenoma. This point becomes more obvious after examining the data from series that only include patients with endocrine-inactive tumors. In the other series, many authors reported one mean or median margin dose for the entire group of tumors, endocrine-active and -inactive lesions alike. The fact that their lower margin and maximum doses have been sufficient for achieving growth control is not surprising, because these doses have been reported to control other benign tumors. One unanswered question, however, is whether a higher dose is helpful in normalizing excessive hormone production. This issue will be subsequently addressed.

Acromegaly in Radiosurgery

A significant problem with the interpretation of the results of radiosurgically treated secretory adenomas is the lack of consistency in reporting “normal” results. This problem is most apparent in the series of patients with GH-producing tumors (Table 2). Endocrine cure rates vary from 0 to 96% with improvement shown in an additional 0 to 67% of patients. Out of the 20 series reported, however, six groups did not cite their criteria for a cure. Of the 14 other studies, there are 11 different criteria used to define cure. Endocrinologists have developed a consensus for what they consider a cure: GH less than 1 ng/ml in response to a glucose challenge and normal serum IGFI-I matched for age and sex. Of these two parameters, the IGFI-I level is probably more significant. A random GH level is not considered reliable for assessment of cure. There have been reports of persistent and progressive acromegaly in patients with normal GH levels but elevated IGFI-I levels. As long as these levels remain elevated, the acromegaly-related morbidity also remains elevated. If one examines the series in Table 2 in which the authors followed criteria closest to the endocrinologists’ consensus, a fairly wide variation in results persists (20–82%). One possible explanation for these variations may be differences in the number of patients in each series receiving somatostatin analogs at the time of radiosurgery, because these medications appear to affect the impact of radiation on hormone secretion.

Prolactinoma in Radiosurgery

The endocrine cure rates for prolactinomas after radiosurgery are less than 30% in 13 of the 16 studies listed in Table 3. In a substantial number of patients (range 29–100%) significant reductions in PRL levels did occur. Fortunately, variations in the definition of a normal PRL level are not as extreme as those in the assessment of GH function. The upper limits of normal values only vary between 15 and 29 ng/ml (Table 3). Analysis of the results of prolactinoma-related results, however, may be significantly confounded by variations in the number of patients receiving antisecretory dopamine agonists at the time of radiosurgery. Additionally, because patients with non-PRL-secreting adenomas may experience a slight hyperprolactinemia after radiosurgery secondary to mild radia-
tion-induced stalk effect, it may be that persistent post-radiosurgery elevation of PRL in a patient with a prolactinoma is due to a similar stalk effect and not hypersecretion by residual tumor.

**Cushing Disease**

Endocrinologists continue to debate the criteria that should be used to define the endocrine cure of a patient with Cushing disease. Most authors prefer to use the level of UFC in a 24-hour urine collection to measure response to treatment because, unlike serum ACTH and serum cortisol levels, it is not susceptible to hourly physiological fluctuations. Nevertheless, Newell-Price recently argued that the 9 a.m. serum cortisol level should be the standard by which to define cure. Of the 18 studies listed in Table 4, eight groups did not report their criteria for establishing cure. Although some of the differences in the reported criteria from the other centers are subtle, there remain seven different definitions of cure among the 10 reporting investigators. With this in mind, rates of endocrine cure vary from 10 to 100%. Two of the centers reporting 100% success rates only treated three patients in each of their studies, and the 83% success rate reported by Hoybye, et al., was achieved by treating patients up to four times in the pre–CT/MR imaging era. If these three series are not considered, the best result is the 78% cure rate obtained by Pollock, et al.

**Nelson Syndrome**

The limited data on SRS for ACTH-producing tumors in patients who have undergone bilateral adrenalectomy are presented in Table 5. Based on this information, it appears that radiosurgery can be used successfully to control this tumor type. Perhaps because of its potential to be relatively biologically aggressive, however, growth control rates and endocrine cure rates may be lower than for other pituitary adenomas.

**Rate of Endocrine Response**

The speed at which a treatment causes normalization of hormone production is important. In the series examined in this paper, a decrease in hormone hypersecretion could be seen as early as 3 months after radiosurgery; on the other hand, normalization could take up to 8 years. If normalization is going to occur, it frequently does so within the first 2 years. Some investigators have found that the latency interval between radiosurgery and endocrine normalization is not dependent on margin dose. In addition, Kim, et al., found that dose and treatment volume do not affect the extent of hormonal response. These same investigators demonstrated that maximum dose and the volume of tumor within the prescription isodose have a significant influence on the latency interval to normalization. They recommended a maximum dose of at least 55 Gy for secretory adenomas. Other investigators have observed a correlation between dose and hormonal response. Pollock, et al., found that in multivariate analysis the only factors influencing extent of hormonal response were the absence of hormone-suppressive therapy at the time of radiosurgery and a maximum dose greater than 40 Gy. In fact, none of the patients in this series experienced an endocrine cure if receiving antisecretory medications at the time of radiosurgery. Pan, et al., also found a positive correlation between dose and hormonal response and have recommended a margin dose of greater than 30 Gy for secretory adenomas. Even though a high margin or maximum dose may not be conclusively proven to reduce excessive hormone production, because the results of radiosurgery for normalizing hormone production are less than excellent, it seems reasonable to continue to administer high doses for secretory tumors until a more effective strategy becomes apparent.

**Cranial Neuropathy**

In the 1255 patients evaluated in the studies reviewed in this paper, there were 11 cases (0.9%) of new optic neuropathy; one of these deficits was transient. The severity of these deficits varied from homonymous quadrantanopsia to nonspecifically decreased visual
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Acuity to blindness. The estimated doses at which these deficits occurred varied from 0.7 to 12 Gy to the optic apparatus. Interestingly, one case of blindness was reported by Pollock, et al.,72 to have occurred at an estimated dose of 8 to 10 Gy, whereas four other patients in the same series remained asymptomatic despite treatment with greater than 12 Gy to the optic apparatus. Other investigators have subjected the optic apparatus to doses as high as 14.1 and 12 Gy without evidence of optic neuropathy.3,70 Most investigators have chosen an upper limit of 8 to 12 Gy as an acceptably safe radiation dose for the optic nerve. The more conservative upper limit of 8 Gy is based on data reported by investigators from the University of Pittsburgh and the Joint Center for Radiation Therapy in Boston.50 From both a clinical and a theoretical radiobiological standpoint, authors of more recent reports have suggested that a small volume of the optic apparatus may be exposed to doses as high as 10 Gy without a significantly increased risk of optic neuropathy.47,70 Both the absolute dose and the volume of exposed tissue appear to be important in the probability of new visual deficits due to radiosurgery.

An important criterion for deciding whether a tumor is a candidate for SRS is its proximity to the optic apparatus. A clearance of at least 23.96 to 553.82 mm is desired. The candidate for SRS is its proximity to the optic apparatus. radiosurgery. An important criterion for deciding whether a tumor is a candidate for SRS is its proximity to the optic apparatus. A clearance of at least 23.96 to 553.82 mm is desired. The absolute distance between these structures is not the limiting factor by itself. This distance defines how steeply the radiation gradient must be constructed so that a tolerable dose is delivered to the optic apparatus and an effective dose is still delivered to the tumor. If an acceptable gradient cannot be constructed, then alternative treatments should be performed.

As reported in series in which meningiomas were treated radiosurgically, the nerves of the cavernous sinus (oculomotor, trochlear, abducent, trigeminal) appear to be quite tolerant of high single-session radiation doses.8 In the 29 series reviewed in this paper, there were 13 new deficits in 10 patients involving the third, fourth, or sixth cranial nerves.3,57,66,70,73,85,96,102 Seven of these deficits in five patients were transient; thus, the permanent complication rate was 0.4% (five of 1255) patients regarding these nerves. New trigeminal neuropathy was reported in only (0.2%) two patients.96

Although radiosurgery is not usually performed with the expectation of improving neurological function, post-radiosurgery improvement in cranial nerve function including vision has been reported in a small number of patients.53,25,31,83,100

Vascular Injury

There has been one case of infarction due to ICA occlusion after radiosurgery for a pituitary adenoma. Lim, et al.,72 reported on a 35-year-old man who underwent SRS with a maximum dose of 40 Gy to a residual pituitary adenoma that encased both CAs. The dose to the right ICA was estimated to be less than 20 Gy. Four years after GKS radiosurgery, he developed left hemiparesis and a small right internal capsule lacunar infarct was found. Imaging studies at that time also revealed that the tumor had significantly decreased in size. Doppler ultrasonography revealed total right ICA occlusion. The patient had no other known vascular risk factors. Pollock, et al.,72 reported two cases of asymptomatic ICA stenosis and recommended that the prescription dose coverage of the ICA

### TABLE 2

**Effects of SRS on endocrinopathy and tumor volume in patients with acromegaly**

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Device</th>
<th>No. of Patients</th>
<th>Follow Up (mos)*</th>
<th>Margin Dose (Gy)*</th>
<th>Max Dose (Gy)*</th>
<th>Endocrine Cure (%)†</th>
<th>Criteria for Cure</th>
<th>Endocrine Improvement (%)‡</th>
<th>Growth Controls (%)§</th>
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</tr>
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<td>normal IGF-I</td>
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<td>NR</td>
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<td>GK</td>
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<td>NR</td>
<td>NR</td>
<td>100</td>
</tr>
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<td>GK</td>
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<td>28</td>
<td>20</td>
<td>normal IGF-I</td>
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<td>92</td>
</tr>
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<td>LINAC</td>
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<td>49</td>
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<td>96</td>
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<td>GK</td>
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<td>16</td>
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<td>&gt;24</td>
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<td>normal IGF-I</td>
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<td>94</td>
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<td>41</td>
<td>normal IGF-I</td>
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<td>normal IGF-I</td>
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<td>normal IGF-I</td>
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<td>NR</td>
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<td>NR</td>
<td>NR</td>
<td>94</td>
</tr>
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<td>42</td>
<td>40</td>
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<td>42</td>
<td>normal age-adjusted IGF-I</td>
<td>19</td>
<td>100</td>
</tr>
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</table>

* Expressed as either mean or median.
† Normal values off medication.
‡ Either normal values on medication or improved values, still not normal.
§ Absence of growth.
** Expressed as percentage of tumors that decreased in size.

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should be limited to less than 50% of the vessel diameter. Shin, et al., 85 recommended keeping the ICA dose to less than 30 Gy.

Brain Injury

In the 1255 patients reviewed in these 29 series, there were 10 cases (0.8%) of irritation or radiation necrosis of the surrounding brain tissue. In two of these cases, the hypothalamus was affected. Kalapurakal, et al., 33 reported a patient suffering acute hyperthermia (105°) 5 hours after radiosurgery for a pituitary adenoma. The hypothalamus was estimated to have received 16 Gy in this CT scan–based plan. Within 20 hours, the patient’s temperature normalized and no other explanation for the elevated temperature could be found. Witt, et al., 96 reported a patient in whom the hypothalamus enhanced 11 months after CT scan–based radiosurgery for a pituitary tumor that had been surgically treated and subjected to fractionated radiotherapy as well. Five months after the onset of this enhancement, the patient suffered a seizure and died. The remaining eight patients suffered temporal lobe injury following radiosurgery for pituitary adenomas. Four of these eight patients had also undergone prior fractionated radiotherapy. Two of the eight patients developed seizure disorders, and one patient required a temporal lobectomy for radiation necrosis. A relatively lower dose should be considered in patients who have previously undergone fractionated radiotherapy.

Pituitary Insufficiency

There is wide variation in the reported incidence of hypopituitarism following radiosurgery for pituitary adenomas. Some groups reported no patients requiring new hormone replacement. Others reported a relatively low incidence (1.5–29%) of some degree of anterior pituitary insufficiency. The authors of studies dedicated to the examination of this question11 or with a very long (mean 17 years) follow-up period have revealed a moderately high (49 and 72%, respectively) degree of hypopituitarism. It should be noted that the long-term report from the Karolinska Institute, in which the incidence of hypopituitarism was 72%, included patients treated without CT or MR imaging–based plans, with doses up to 240 Gy. Feigl, et al., 11 found that the only factor positively associated with the eventual development of hypopituitarism was the radiation dose to the pituitary stalk. Factors not significant included sex, age, integral dose to tumor, preradiosurgery endocrine status, target volume, dose to hypothalamus, normal pituitary gland, or median eminence. The authors suggested that the higher incidence of hypopituitarism may have been due to the longer follow-up period, more detailed testing, relatively large tumor volume, and the fact that all 92 patients had undergone prior microsurgery. Pollock, et al., 14 suggested a correlation between prescription treatment volume and the risk of anterior pituitary insufficiency.

Secondary Neoplasms

There were no reports of new intracranial neoplasms in the 1255 patients reviewed in this paper. Of approximately 200,000 patients who have undergone GKS worldwide, there are eight patients who have been treated with stereotatic GKS and in whom a malignant brain tumor has later been diagnosed. The possibility of a link

### Table 3

**Effects of SRS on endocrinopathy and tumor volume in patients with prolactinomas**

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Device</th>
<th>No. of Patients</th>
<th>Follow Up (mos)*</th>
<th>Margin Dose (Gy)*</th>
<th>Max Dose (Gy)*</th>
<th>Endocrine Cure†</th>
<th>Criteria for Cure (PRL level)</th>
<th>Endocrine Improvement (%)§</th>
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<td>NR</td>
<td>69</td>
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<td>GK</td>
<td>18</td>
<td>27</td>
<td>29</td>
<td>55</td>
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<td>&lt;20 ng/ml</td>
<td>67</td>
<td>68†</td>
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<td>GK</td>
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<td>NR</td>
<td>7</td>
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<td>GK</td>
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<td>31</td>
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<td>Izawa, et al., 2000</td>
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<td>20</td>
<td>NR</td>
<td>53</td>
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<tr>
<td>Landolt, et al., 2000</td>
<td>GK</td>
<td>20</td>
<td>29</td>
<td>25</td>
<td>50</td>
<td>25</td>
<td>&lt;19 ng/ml (F); &lt;16 ng/ml (M)**</td>
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<td>NR</td>
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<td>Pollock, et al., 2002</td>
<td>GK</td>
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<td>29</td>
<td>&lt;23 ng/ml</td>
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* Expressed as either mean or median.
† Normal values off medication.
‡ Either normal values on medication or improved values still not normal.
§ Absence of growth.
** Different values for females (F) and males (M).
†† Expressed as percentage of tumors that decreased in size.
between radiosurgery and the malignant tumor is stronger in some cases, weaker in others, and conclusively proven in none.

ALTERNATIVE TREATMENT OPTIONS

Stereotactic Radiosurgery at Indiana University

At the author’s institution, 22 patients have undergone stereotactic GKS for pituitary adenomas since September 1997: three patients with endocrine-inactive tumors; two with prolactinomas; eight with Cushing disease; two with Nelson syndrome; six with GH-secreting tumors; and one with a mixed GH–PRL secreting tumor. Age at the time of radiosurgery ranged from 17 to 86 years (median 49 years). Eleven men and 11 women were treated. Nineteen patients (86%) had undergone at least one resection prior to radiosurgery. Five patients had undergone two resections and two had received fractionated radiotherapy before GKS. The three patients with secretory adenomas who did not undergo resection were very poor medical candidates for general anesthesia and/or had tumor involvement of the cavernous sinus.

In all patients, multiple isocenter dose planning was conducted to enclose the borders of the tumor within the 50% isodose curve. The three endocrine-inactive tumors were treated with margin doses of 13, 16, and 20 Gy, respectively. The 19 secretory adenomas were treated with 16 to 28–Gy margin doses (median 24 Gy). Dose plans were constructed to attempt to keep the dose to the optic apparatus less than 8 Gy; in two patients a small volume of optic tissue received 9 Gy.

Six of the patients in our series were treated within 6 months of submission of this paper and will not be included in follow-up analysis. The follow-up interval in the other 16 patients varied from 6 to 48 months (median 24 months). No MR imaging evidence of tumor growth has been demonstrated. Five tumors (31%) have decreased in size. No patient has developed a new neurological deficit. One patient with an ACTH-producing tumor in the cavernous sinus experienced marked improvement in third and sixth cranial nerve palsies as well as post-GKS shrinkage of the tumor.

Of the four patients with GH-secreting tumors, normalization of the IGF-I level has occurred in only one patient. This patient harbors a mixed GH-PRL–producing tumor and was receiving bromocriptine at the time of radiosurgery. His IGF-I level was 409 ng/ml before radiosurgery and was 76 ng/ml 36 months after the procedure. He continues to receive bromocriptine (at a lower dose [2.5 mg/day]), and his PRL level is normal. In the other three patients, the IGF-I level remains unchanged at 31 months, 78% of the pretreatment level at 12 months, and 66% of the pretreatment level at 6 months. None of these patients was taking a somatostatin analog at the time of radiosurgery.

TABLE 4

Effects of SRS on endocrinopathy and tumor volume in patients with Cushing disease

<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>Device</th>
<th>No. of Patients</th>
<th>Follow Up (mos)*</th>
<th>Margin Dose (Gy)*</th>
<th>Max Dose (Gy)*</th>
<th>Endocrine Cure (%)‡</th>
<th>Criteria for Cure</th>
<th>Endocrine Improvement (%) §</th>
<th>Growth Control (%) ¶</th>
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<tr>
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<td>GK</td>
<td>3</td>
<td>36</td>
<td>24</td>
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<td>100</td>
<td>ACTH &lt;10 µg/L; UFC &lt;650 nmol/24 hr</td>
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<td>100</td>
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<td>Lim, et al., 1998</td>
<td>GK</td>
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<td>48</td>
<td>25</td>
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<td>92</td>
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<tr>
<td>Mitsumori, et al., 1998</td>
<td>LINAC</td>
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<td>47</td>
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<td>19</td>
<td>40</td>
<td>NR</td>
<td>100</td>
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<td>28</td>
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<td>67</td>
<td>UFC &lt;90 µg/24 hr; normal ACTH; normal cortisol</td>
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<td>32</td>
<td>19</td>
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<td>normal 24 hr UFC</td>
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<td>&gt;24</td>
<td>20</td>
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<td>62</td>
<td>UFC &lt;100 µg/24 hr; normal 24 hr UFC</td>
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<td>58</td>
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<td>GK</td>
<td>43</td>
<td>44</td>
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<td>normal 24 hr UFC</td>
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<td>83**</td>
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<tr>
<td>Hoybye, et al., 2001</td>
<td>GK</td>
<td>18</td>
<td>204</td>
<td>NR</td>
<td>60–240</td>
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<td>GK</td>
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<td>55</td>
<td>15</td>
<td>NR#</td>
<td>NR</td>
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<td>20</td>
<td>64</td>
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<td>49</td>
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<td>ACTH &lt;50 pg/ml; cortisol &lt;10 µg/dl</td>
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<td>Pollock, et al., 2002</td>
<td>GK</td>
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<td>42</td>
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<td>40</td>
<td>78</td>
<td>UFC &lt;90 µg/24 hr</td>
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<td>100</td>
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</tbody>
</table>

* Expressed as either mean or median.
† Normal values off medication.
‡ Either normal values on medication or improved values, still not normal.
§ Absence of growth.
** Expressed as percentage of patients who did not need further surgery.
†† Expressed as percentage of tumors that decreased in size.

* Expressed as either mean or median.
† Normal values off medication.
‡ Either normal values on medication or improved values, still not normal.
§ Absence of growth.
** Expressed as percentage of patients who did not need further surgery.
†† Expressed as percentage of tumors that decreased in size.
A more encouraging endocrine response has been demonstrated in the two patients with prolactinomas. Neither was receiving dopamine agonists at the time of radiosurgery. In one patient the PRL level dropped by 80% within the first 6 months after treatment and is normal, off medication, at 48 months. The second patient was placed back on cabergoline after radiosurgery. Twelve months after her procedure, her PRL level on medication is 36% of the pretreatment on medication level.

Both patients with Nelson syndrome had a significant decrease in ACTH level as well as a significant decrease in tumor volume after radiosurgery, the ACTH decreased by 90% at 34 months in one patient and by 68% at 25 months in the other. The level, however, has not normalized in either case.

Only one of our eight patients with Cushing disease has had a radiographically identifiable tumor. In this patient an 84% reduction in ACTH level was demonstrated at 35 months but remission has not occurred. Our strategy for treating patients in whom a discrete tumor cannot be identified has changed over the years. At first, we used information derived from examination of the patient’s prior transsphenoidal resection specimen as well as postoperative inferior petrosal sinus sampling to select one half of the pituitary gland as the target. We then confirmed our prescription isodose to this half of the sella, from the level of the pituitary stalk to the medial margin of the ICA as the lateral margin. We have treated three patients in this fashion. In two patients the 24-hour UFC values were normal at 10 and 24 months, respectively; in the third patient severe clinical signs of Cushing disease exist, and the patient requires ketoconazole. Despite the somewhat promising results in two of these patients, we now select the entire gland for the radiosurgical target in patients without a radiographically visible tumor. The morbidity attendant on failing to treat tumor cells in the other half of the gland seems greater than that associated with of treating the entire gland. The two patients in whom we have targeted the entire gland have experienced only modest improvement in urinary free cortisol and ACTH levels at 13 months.

Additional treatment options for patients with pituitary adenomas include microresection, medical therapy, and fractionated irradiation. These treatments are not necessarily exclusive of each other or SRS. For some patients with particularly challenging tumors, a combination of two or more modalities may be required. As with radiosurgery, each treatment method has advantages and limitations. These benefits and risks will be placed in perspective relative to those associated with radiosurgery.

**Microsurgery of the Lesion**

If a patient is neurologically compromised as a result of pituitary adenoma–induced mass effect, microresection is usually the procedure of choice. Microsurgery also allows for the most rapid reduction in excessive hormone levels. Endocrine remission may be achieved in 56 to 91% of patients with Cushing disease,45,58,64 28 to 72% of those with acromegaly,29,45 and 24 to 87% of patients with prolactinomas.55,56,69 Long-term tumor control rates for patients with endocrine-inactive tumors vary from 50 to 90%.83 Remission and control rates are significantly lower for patients with invasive extrasellar tumors. Current complication rates in the most experienced hands are less than 0.5% mortality, 1.5% major morbidity, and less than 3% iatrogenic hypopituitarism.85 A survey in 1997 of neurosurgeons in the US, however, showed that transsphenoidal surgery for pituitary tumors is associated with a 3.9% risk of CSF leak, a 1.8% risk of new visual deficit, a 19.4% risk of pituitary insufficiency, and a 0.9% risk of death.4 In cases in which surgery for residual or recurrent tumors is performed after prior therapy, significantly lower success rates and significantly higher complication rates have been reported.44

**Medical Therapy**

Administration of dopamine agonists such as bromocriptine, cabergoline, quinagolide, metergoline, and lisuride inhibits PRL production, causes individual cell volume to decrease, and subsequently induces tumor shrinkage. Normalization of PRL levels resulting from dopaminergic therapy has been reported to be as high as 70 to 100%. The tumor mass decreases by 80 to 90%. The time course of these responses, however, can vary from days to months, and the degree of reduction is variable and unpredictable as well. Side effects may limit the length of time that a patient is able to tolerate a certain medication dose. These side effects include nausea, vomiting, dizziness, postural hypotension, headaches, and behavioral disturbances. Another drawback of dopaminergic therapy is that it is a lifelong treatment regimen; if drug therapy is stopped, tumor expansion and PRL hypersecretion will resume.59

Patients with acromegaly can undergo medical management involving somatostatin analogs such as octreotide as

**TABLE 5**

*Effects of SRS on endocrinopathy and tumor volume in patients with Nelson syndrome*

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Device</th>
<th>No. of Patients</th>
<th>Follow Up (mos)*</th>
<th>Margin Dose (Gy)*</th>
<th>Max Dose (Gy)*</th>
<th>Endocrine Cure (%)†</th>
<th>Criteria for Cure</th>
<th>Endocrine Improvement (%)‡</th>
<th>Growth Control (%)§</th>
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<td>NR</td>
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<td>Pollock, et al., 2002</td>
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<td>20</td>
<td>40</td>
<td>36</td>
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<td>54</td>
<td>82</td>
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</tbody>
</table>

* Expressed as either mean or median.
† Normal values off medication.
‡ Either normal values on medication or improved values still not normal.
§ Absence of growth.
Review of SRS for pituitary adenomas

well as the aforementioned dopamine agonists. Somatostatin analogs normalize GH and IGF-I levels in 50 to 79% of treated patients. These medications also cause a modest (30–50%) reduction in tumor volume in 40 to 73% of patients. Some endocrinologists advocate somatostatin analog therapy as the second-line treatment after microsurgery and the first-line therapy if the patient is not a good candidate for surgery. Dopamine agonists will help lower GH levels in only approximately 10% of patients. There are some significant disadvantages of long-term somatostatin analog therapy for patients with acromegaly. The drug may take several months to have an impact on GH levels and tumor volume. Gastrointestinal side effects are common. The drug must be administered by injection; this has become less of a limitation, however, because of the development of long-acting forms that can be administered once every 4 weeks. Normalization of GH and IGF-I levels and reduction of tumor volume do not always occur concomitantly. In one study by Bevan, et al., only 29% of patients achieved all three parameters of normal GH, normal IGF-I, and a greater than 30% reduction in tumor volume. The drug is very expensive, and if it is to be used as the sole treatment modality, it needs to be continued for the rest of the patient’s life.

Cushing disease is less commonly treated medically than acromegaly or hyperprolactinemia. The most common drug used in Cushing disease is ketoconazole, an antifungal drug that inhibits steroid biosynthesis in the adrenal gland. Other less frequently used inhibitors of steroid synthesis at the adrenal level include aminoglutethimide, metyrapone, and mitotane. The peripheral receptor sites for glucocorticoid drugs can be blocked by mifepristone. The production of ACTH can be inhibited by serotonin antagonists (cyproheptadine), dopamine agonists (bromocriptine), GABA agonist (depakote), and somatostatin analogs such as octreotide.

Fractionated Radiotherapy

Fractionated radiotherapy has been used for decades to treat patients with unresectable pituitary adenomas. Rates of tumor growth control vary from 76 to 97%. Fractionated radiotherapy has been less successful (30–83%) in reducing hypersecretion of hormones by tumors. Complications related to fractionated irradiation include a relatively high rate (12–100%) of hypopituitarism and a low but still significant risk (1–3%) of optic neuropathy and induction of a secondary tumor (2.7% actuarial incidence at 15 years). Fractionated irradiation also contributes to the development of cognitive function in patients who have already undergone surgery for pituitary tumors.

Although the risks of hypopituitarism, brain radionecrosis, and radiation-induced neoplasia may not be non-existent with radiosurgery, they risks to be significantly higher in patients in whom have radiotherapy for pituitary adenomas. Radiobiologically, the doses currently delivered in single-session radiosurgery are equivalent to those that would be too toxic to be given by multiple-fraction radiotherapy. Therefore, radiosurgery would be expected to have a greater impact on hormone production than radiotherapy. Comparison of results of hormone normalization in radiosurgery series to radiotherapy series is made difficult by the inconsistent standards of normal values used by different investigators. In series in which the data are examined by the same authors, radiosurgery appears to lead to hormone level normalization significantly faster than radiotherapy. The use of stereotactic methods in the delivery of fractionated irradiation may be expected to decrease some of the complications of conventional fractionated radiotherapy because less normal tissue is irradiated, but the radiobiological effect on the target tumor should not be any different than the effects of conventional radiotherapy. The results of fractionated stereotactic radiotherapy are currently too limited in numbers of patients and follow-up duration to allow adequate comparison to radiosurgery or conventional radiotherapy series.

There are some situations in which fractionated radiotherapy may be preferable to radiosurgery. One involves a tumor volume that is so large that an effective radiation dose cannot be safely delivered in a single session. The minimally effective dose to control a benign tumor has not been established, but doses as low as 12 Gy have been administered to achieve successfully long-term growth control in vestibular schwannomas. Extrapolating from the integrated logistical formula, the maximum volume that can be treated at this dose with a less than 3% risk of complications is approximately 23 cm³. A spherical structure of this volume would have a mean diameter of 35 mm. Fractionated radiotherapy may also be preferable to radiosurgery if the tumor is too close to the optic apparatus to achieve an acceptable falloff gradient with single-session irradiation.

CONCLUSIONS

Stereotactic radiosurgery can be a relatively safe, effective procedure for patients with pituitary adenomas. There are certainly cases in which radiosurgery is not the most appropriate treatment. In a patient harboring a relatively small, medically refractory tumor in a surgically inaccessible location, however, radiosurgery may provide the best opportunity for long-term preservation of neurological function and for the restoration as well as preservation of normal endocrine function.

There are several challenging issues that stereotactic neurosurgeons and radiation oncologists should address to improve the outcomes of patients undergoing pituitary adenoma radiosurgery. The optimal timing of administration of antiserotonergic medications with respect to the date of radiosurgery needs to be clarified. Attempts should be made to identify other factors that can improve the response of secretory adenomas to radiosurgery. The optimal target in a patient with an “invisible” tumor needs to be determined. The function of the normal pituitary gland following radiosurgery for a pituitary adenoma should be studied more thoroughly. Along with physicians in other specialties who care for these patients, a consistent definition of endocrine cure needs to be established and followed to determine the optimal treatment for individual patients.
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Address reprint requests to: Thomas C. Witt, M.D., Indiana University Medical Center, 535 Barnhill Drive RT 447, Indianapolis, Indiana 46202. email: tcwitt@iupui.edu.