Stereotactic radiosurgery for hypersecreting pituitary tumors: part of a multimodality approach

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Object. Surgical and medical therapies successfully achieve biochemical remission in the majority of patients with secretory pituitary adenomas. Nevertheless, continued hypersecretion after first-line therapy occurs and requires adjunctive therapy to prevent morbidity and premature mortality. For patients in whom medical and surgical therapy have failed, gamma knife surgery (GKS) is performed with the goal of controlling tumor growth and excess growth hormone (GH) production. The authors report their experience with GKS in patients in whom surgical and medical therapies failed.

Methods. The neuroendocrine service at the University of Virginia has treated 220 patients with secretory adenomas. The authors evaluated the biochemical results in patients with acromegaly followed for greater than 18 months (64 patients) as well as those with Cushing disease (45 patients), Nelson syndrome (14 patients with adequate follow up [27 overall]), and prolactinomas (19 patients) followed for at least 12 months posttreatment. Biochemical remission occurred in 36% of patients with GH-secreting adenomas, 73% of those with Cushing disease, 14% of those with Nelson syndrome, and 11% of those harboring prolactinomas. Recurrence after biochemical remission was documented in four patients with Cushing disease. New hormonal deficits have occurred in 28% of patients with acromegaly, 31% with Cushing disease, 36% with Nelson syndrome, and 21% with prolactinomas. Minor visual deterioration developed in one patient with Cushing disease.

Conclusions. Gamma knife surgery offers an important treatment modality in patients with secretory adenomas refractory to surgical and medical interventions.

Key Words • pituitary adenoma • stereotactic radiosurgery

The current treatment paradigms for functioning pituitary adenomas require a multidisciplinary approach. Surgeons, endocrinologists, radiation therapists and radiosurgeons each have an ongoing role in the individualized management of these often-complex tumors. Each therapeutic modality has a complementary role in the comprehensive treatment of patients with pituitary adenomas.

In the overwhelming majority of patients, surgical or medical therapy is the most appropriate first-line treatment. Whereas transsphenoidal surgery remains the first-line therapy for acromegaly and Cushing disease, the vast majority of prolactinomas are best treated initially with medical therapies. Patients with acromegaly and Cushing disease in whom hypersecretion persists postoperatively undergo medical therapy. If this fails, radiotherapy is an alternative. In addition, although pharmacotherapy can control excessive hormone levels in patients with acromegaly and Cushing disease, it does not currently effect a “cure.” Radiotherapy may offer this cure.

Patients with prolactinomas in whom there is no response to dopamine agonist therapy often require a combination of surgery and radiotherapy. Surgery may offer cure in patients with small noninvasive prolactinomas; however, those who harbor large tumors or tumors invading the cavernous sinus will require radiotherapy. Transsphenoidal surgery is often performed prior to radiotherapy to reduce tumor burden and to provide a safe margin between the tumor and the optic chiasm.

In this article we examine our experience with adjunctive GKS after unsuccessful surgical and medical interventions.

CLINICAL MATERIAL AND METHODS

Pretreatment Management

Patients undergo a full assessment of baseline pituitary function prior to GKS. Because there are data to suggest that the efficacy of radiotherapy is diminished in patients with acromegaly wjp are receiving somatostatin analogs at the time of radiation therapy, we now delay medical treatment until at least 6 weeks after radiosurgery.25 Similar data regarding responsiveness to radiosurgery in patients with prolactinomas have led us also to delay dopa-
mine agonist therapy for 6 weeks. Medical therapy is not withheld prior to radiosurgery in patients with Cushing disease because of the significant deleterious effects of excessive adrenal cortisol production and because medical therapy (ketoconazole) has no direct effect on the pituitary gland.

**Endocrinological Follow-Up Examination**

Because radiotherapy is known to produce new endocrinological deficits, patients are evaluated every 6 months after GKS for the development of secondary hypothyroidism, hypogonadism, adrenal insufficiency, and GH deficiency. By obtaining a complete clinical history we screen for these hormonal deficiencies. Clinically, hypothyroidism is characterized by diminished physical and mental function. Symptomatically, fatigue, weight gain, constipation, cold intolerance, decreased alertness, headache, and depression may be evident. Male hypogonadism manifests with diminished libido or erectile dysfunction. In women, amenorrhea, diminished libido, and hot flashes may occur. Patients with adrenal insufficiency often report weakness, fatigue, anorexia or weight loss, gastrointestinal symptoms, myalgia, arthralgia, and postural dizziness. Growth hormone deficiency manifests with diminished tolerance to exercise, increased central adiposity, a diminished mood or sense of well-being, and increased anxiety.

Guided by the clinical history, hormonal studies should be performed. These studies should include evaluation of serum thyroxine, testosterone, estradiol, and morning cortisol levels. Growth hormone deficiency may be screened using IGF-I levels, but a stimulation test, such as insulin-induced hypoglycemia, is necessary to document the need for GH replacement therapy.

The biochemical efficacy of radiosurgery is also evaluated at these 6-month intervals. Medical therapy is discontinued 4 to 6 weeks prior to evaluation. In cases of acromegaly a normal age- and sex-adjusted IGF-I level defines remission. Patients with Cushing disease are evaluated using the 24-hour UFC determination. Patient with Nelson syndrome are assessed with a serum ACTH level. Remission in patients with prolactinomas is determined by simply using a single random serum PRL measurement. Neuroimaging evaluation is performed annually by using magnetic resonance imaging.

**Patient Population**

Under the guidance and direction of Ladislau Steiner, our multidisciplinary neuroendocrine service at the University of Virginia performed GKS in 354 patients with pituitary disorders between June 1989 and May 2002. The typical GKS marginal dose was 15 Gy. Of the 354 patients, 220 harbored secretory adenomas, including 91 patients with acromegaly, 73 with Cushing disease, 27 with Nelson syndrome, and 29 with prolactinomas. Only those patients with GH-secreting tumors followed for more than 18 months were included. A follow-up period of greater than 12 months was considered adequate for patients with Cushing disease, Nelson syndrome, and prolactinomas. Thus, the population included 64 patients with acromegaly, 45 with Cushing disease, 14 with Nelson syndrome, and 19 with prolactinomas.

### RESULTS

#### Patients With Acromegaly

Of the 64 patients with adequate follow up, age- and sex-adjusted IGF-I levels normalized in 36% (23 patients) (Table 1). The mean time to normalization was 28 months (range 5–98 months). One patient, in whom disease remission did not occur, underwent a repeated GKS. There have been no recurrences in this population after biochemical remission. New hormonal deficiencies were noted in 28% (18 patients). One patient in the group died of uncertain causes during the follow-up period.

#### Cushing Disease and Nelson Syndrome

Of the 45 patients with Cushing disease, a normalized 24-hour UFC was achieved in 73% (33 patients). The mean time to remission was 16 months (range 2–62 months). Recurrent disease occurred in two patients who underwent repeated GKS. New hormonal deficits were noted in 31% (14 patients). One patient experienced minor visual deterioration (partial quadrantanopsia). Three patients died during the follow-up period, one of progressive Cushing disease, one of myocardial infarction, and one of sepsis.

In two of the 14 patients with Nelson syndrome a normalized ACTH level was documented. New hormonal deficits developed in 36% (five patients). Three patients died, two of progressive disease and one of unknown causes.

#### Patients With Prolactinoma

Of the 19 patients with prolactinomas, normalization of serum PRL levels was documented in 11% (two patients). The mean time to remission was 20.5 months (range 18–23 months). No disease recurrence developed after remission. New hormonal deficiency was noted in 21% (four patients). Three patients died during the follow-up period, two of disease progression and one of myocardial infarction.

#### DISCUSSION

**Role of GKS in Multimodal Therapy**

The efficacy of GKS for secretory pituitary adenomas must be understood in the context of an overall multimodal treatment plan. Patients selected for GKS are those in whom first- and second-line therapies have failed and who remain at significant risk for morbidity and premature mortality associated with hormonal hypersecretion. It

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Remission (%)</th>
<th>Mean No. Mos. to Remission (Range)</th>
<th>New Hormonal Deficits (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>acromegaly</td>
<td>23 (36) of 64</td>
<td>28 (5–98)</td>
<td>18 (28) of 64</td>
</tr>
<tr>
<td>Cushing disease</td>
<td>33 (73) of 45</td>
<td>16 (2–62)</td>
<td>14 (31) of 45</td>
</tr>
<tr>
<td>nelson syndrome</td>
<td>2 (14) of 14</td>
<td>11.5 (3–20)</td>
<td>5 (36) of 14</td>
</tr>
<tr>
<td>prolactinoma</td>
<td>2 (11) of 19</td>
<td>20.5 (18–23)</td>
<td>4 (21) of 19</td>
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is within the context of these difficult circumstances that the role of GKS should be appreciated.

**Acromegaly.** Transsphenoidal surgery, when performed as primary therapy, can achieve biochemical remission in 87% of patients with microadenomas and 50% of those with macroadenomas. In patients in whom surgery achieves biochemical remission, recurrence at 10 years is nearly 10%. Reoperation is often a viable option, and in our experience, 48% of patients with acromegaly achieved remission after repeated operation. Nevertheless, the likely need for adjuvant medical therapy or radiotherapy is recognized for cases involving large tumors and tumors with cavernous sinus invasion.

Although dopamine agonists provide symptomatic relief in the majority of patients, they are relatively ineffective in normalizing GH or IGF-I levels. Its effectiveness in normalizing GH or IGF-I levels is demonstrated in fewer than half of the patients. Somatostatin analogs provide a more effective treatment option and can normalize IGF-I levels in 50 to 60% of patients. The more recently introduced GH receptor antagonists appear to have encouraging prospects. In series of patients with disease refractory to surgery and maximum conventional medical therapy, some investigators have shown that up to 100% of patients experience hormonal normalization and a halt in tumor growth after treatment with GH receptor antagonists. Despite these encouraging results, the likelihood is that a certain percentage of patients with otherwise refractory GH-secreting adenomas will continue to need the radiosurgical option. That an additional 36% of patients may experience hormonal normalization makes GKS a viable option.

**Cushing Disease and Nelson Syndrome.** In our experience, transsphenoidal adenomectomy achieves biochemical remission in 90% of patients with microadenomas and 46 to 60% of patients harboring macroadenomas. Of the patients experiencing biochemical remission, recurrence is demonstrated in approximately 12%. Pharmacotherapy involving adrenolytic therapy (ketoconazole, mitotane) can significantly reduce UFC levels but normalization is demonstrated in fewer than half of the patients. Patients with refractory Cushing disease appear to benefit significantly from GKS. In our series, biochemical remission occurred in nearly 75% of patients and did so in a mean of 16 months.

**Prolactinomas.** Medical therapy remains the first-line treatment of PRL-secreting adenomas. The dopamine agonists (bromocriptine, pergolide, cabergoline) normalize prolactin levels in 67 to 89% of patients. Tumors recede by at least 50% in nearly two thirds of patients, and visual field deficits improve in 90%. Tumor reduction occurs within 6 weeks in the majority of patients. Patients in whom pharmacotherapy fails may be categorized into two groups: those who are intolerant of and those who are resistant to medical therapy. A small percentage of patients are unable to tolerate the mostly gastrointestinal side effects of the dopamine agonists. Resistance is characterized by either failure of prolactin levels to normalize or failure of the tumor to decrease in size. In these circumstances, surgery is indicated.

Depending on the preoperative PRL level, surgery can normalize this function in 50 to 88% of patients harboring microadenomas. In patients with microprolactinomas, the lesion recurs in 17 to 50%. In patients with macroadenomas surgical remission is less successful, occurring in 28 to 53% of patients. The recurrence rate is also greater (as high as 80%). Based on this series, it is our finding that in difficult cases GKS can induce a remission in an additional 11% of patients off medication.

**Comparison of GKS and Conventional Radiotherapy.**

An exact comparison of radiosurgery and conventional radiotherapy is not possible in this study. Attempts to compare our results with those published in past conventional radiotherapy–based studies are difficult because the latter did not use modern definitions of remission. In addition, follow-up data have been collected over a longer period for conventional radiotherapy, allowing a more accurate determination of its related long-term efficacy and complications. Nevertheless, an attempt will be made to draw certain reasonable comparisons.

**Acromegaly.** Conventional fractionated radiotherapy has been shown to normalize IGF-I levels in 16 to 60% of patients after 10 years. Remission increases with time after radiotherapy; whereas normalized IGF-I levels occurred in 27% cases before 6 years, Powell and colleagues reported that remission increased to 69.2% after an interval of greater than 6 years. Similarly Barrande, et al. reported that IGF-I levels were normalized in 25% of the patients by 5 years and 60% by 10 years. Biernas and colleagues reported better results noting that normalized IGF-I levels occurred in 18 (60%) of 30 patients at 5 years, 23 (74%) of 31 at 10 years, and 16 (84%) of 19 at 15 years. Comparing these results with our series is, of course, imperfect. In the 36% of our patients in whom biochemical remission was achieved, however, remission occurred in a mean of 28 months. It does appear that the effect of GKS manifests earlier than conventional fractionated radiotherapy. The results of other studies seem to support this conclusion. Landolt and colleagues reported that IGF-I and GH levels normalized with a mean of 1.4 years after stereotactic radiosurgery compared with a mean of 7.1 years after conventional fractionated radiotherapy.

**Cushing Disease.** We found that in patients treated with GKS a biochemical remission rate of 73% was documented in 16 months. Other authors have also reported this rapid remission. Conventional fractionated radiotherapy also appears effective after failed transsphenoidal surgery. Savage and colleagues reported biochemical remission in 82% after a median period of 8 years. Conventional radiotherapy is also reported to induce remission (normal UFC and suppression after high-dose dexamethasone) in 83% of patients in a mean follow-up period of 42 months. Eighty-eight percent of these remissions were reported to have occurred during the first 2 years after treatment. Others, however, have reported a lower remission rate as well as a significant incidence of recurrence after normalization in patients treated with conventional radiotherapy.

**Prolactinomas.** Conventional fractionated radiotherapy has been reported to achieve normalized PRL levels in 50% of patients at a mean of 8.5 years. Although the remission rate was lower in our present series (11%), this normalization occurred at a mean of 20.5 months following radiosurgery.
Late Endocrinopathy. Both GKS and conventional radiotherapy are associated with long-term injury to the normal pituitary gland. In our series, new endocrine deficits were evident in 21 to 36% of patients. The literature pertaining to conventional radiotherapy indicates that at 10 years conventional irradiation induces thyroid dysfunction in 35 to 78%, glucocorticoid deficiency in 22 to 82%, and gonadal dysfunction in 22 to 80% of patients. At least partial hypopituitarism was reported in 50% at 10 years and 75% at 15 years. More extended follow-up intervals in the radiosurgical population is certainly necessary because endocrinopathies should increase with time. The higher-dose radiation provided by the gamma knife, which appears to provide more rapid biochemical remission, may also cause a higher incidence of endocrinopathy.

CONCLUSIONS

Gamma knife radiosurgery has a significant role in the multimodal treatment of secretory pituitary adenomas. The gamma knife is most effective in the setting of unsuccessful transsphenoidal surgery for Cushing disease. Nevertheless, it does provide a biochemical remission in patients without medication in nearly 30% of the cases involving with acromegaly and 11% involving prolactinomas. Gamma knife radiosurgery appears to effect remission more rapidly than conventional radiotherapy. A longer follow-up period is necessary, however, to determine whether the remissions are durable.

References


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