

## Stereotactic radiosurgery for pituitary adenomas: an intermediate review of its safety, efficacy, and role in the neurosurgical treatment armamentarium

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**Object.** Pituitary adenomas are very common neoplasms, constituting between 10 and 20% of all primary brain tumors. Historically, the treatment armamentarium for pituitary adenomas has included medical management, microsurgery, and fractionated radiotherapy. More recently, radiosurgery has emerged as a viable treatment option. The goal of this research was to define more fully the efficacy, safety, and role of radiosurgery in the treatment of pituitary adenomas.

**Methods.** Medical literature databases were searched for articles pertaining to pituitary adenomas and stereotactic radiosurgery. Each study was examined to determine the number of patients, radiosurgical parameters (for example, maximal dose and tumor margin dose), duration of follow-up review, tumor growth control rate, complications, and rate of hormone normalization in the case of functioning adenomas.

A total of 35 peer-reviewed studies involving 1621 patients were examined. Radiosurgery resulted in the control of tumor size in approximately 90% of treated patients. The reported rates of hormone normalization for functioning adenomas varied substantially. This was due in part to widespread differences in endocrinological criteria used for the postradiosurgical assessment. The risks of hypopituitarism, radiation-induced neoplasia, and cerebral vasculopathy associated with radiosurgery appeared lower than those for fractionated radiation therapy. Nevertheless, further observation will be required to understand the true probabilities. The incidence of other serious complications following radiosurgery was quite low.

**Conclusions.** Although microsurgery remains the primary treatment modality in most cases, stereotactic radiosurgery offers both safe and effective treatment for recurrent or residual pituitary adenomas. In rare instances, radiosurgery may be the best initial treatment for patients with pituitary adenomas. Further refinements in the radiosurgical technique will likely lead to improved outcomes.

**KEY WORDS** • stereotactic radiosurgery • gamma knife • pituitary adenoma • Cushing disease • acromegaly • prolactinoma

**P**ITUITARY adenomas are very common lesions, constituting between 10 and 20% of all primary brain tumors.<sup>55,59</sup> Epidemiological studies have demonstrated that nearly 20% of the general population has a pituitary adenoma.<sup>55</sup> Pituitary adenomas are broadly classified into two groups. The first category consists of tumors that secrete excess amounts of normal pituitary hormones and, consequently, present with a variety of clinical syndromes depending on the hormones that are secreted. The most common of these is the prolactinoma, which causes Forbes–Albright syndrome (consisting of amenorrhea–galactorrhea) in women and impotence and infertility in men. Fortunately, prolactinomas can usually be managed medically

with dopamine agonist drugs. The second most common functioning pituitary adenoma is the GH-secreting variant in which acromegaly presents in adults and gigantism appears before closure of the epiphysal plates.<sup>58</sup> Tumors that secrete ACTH produce Cushing disease or, if bilateral adrenalectomies have been performed, Nelson syndrome.<sup>102,103</sup>

The second category of pituitary adenomas is composed of tumors that do not secrete any known biologically active pituitary hormones, and these represent approximately 30% of all pituitary tumors.<sup>76</sup> These so-called nonfunctioning or null-cell pituitary adenomas progressively enlarge in the pituitary fossa and may even extend outside the confines of the sella turcica. These tumors may cause symptoms related to a mass effect, whereby the optic nerves and chiasm are compressed and a bitemporal visual field loss characteristically results. Those patients harboring nonfunctioning adenomas can also have hypopituitarism as a result of compression of the normal functioning pituitary gland.

For both types of pituitary adenomas, a recurrence re-

*Abbreviations used in this paper:* ACTH = adrenocorticotropic hormone; CA = carotid artery; CT = computerized tomography; GH = growth hormone; IGF-I = insulin-like growth factor I; LINAC = linear accelerator; MR = magnetic resonance; UFC = urine free cortisol.

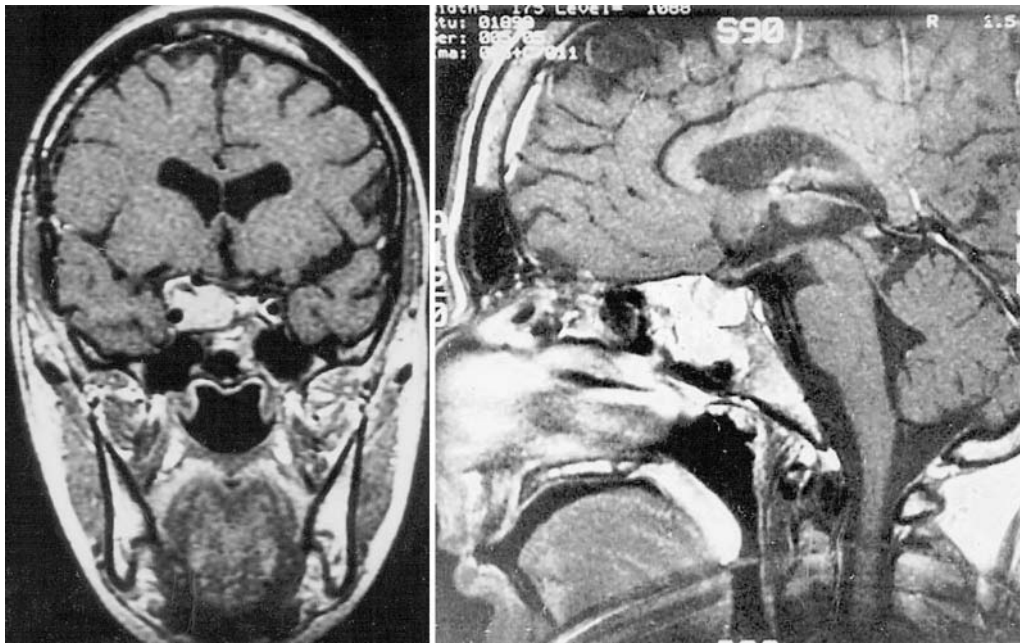


FIG. 1. Preoperative contrast-enhanced coronal (*left*) and sagittal (*right*) T<sub>1</sub>-weighted MR images demonstrating a pituitary adenoma with cavernous sinus invasion on the right side and suprasellar extension.

sulting from tumor invasion into surrounding structures or in complete tumor resection is quite common. Long-term tumor control rates after microsurgery alone vary from 50 to 80%.<sup>10,27,55,59,69</sup> Radiation therapy or radiosurgery can be administered postoperatively as adjuvant therapy to inhibit recurrent growth or later when clinical symptoms or neuroimaging findings indicate a recurrence. These therapies may also be used postoperatively to treat known residual tumor following incomplete resection. The presence of residual tumor is not uncommon in cases of adenomas with either a suprasellar component or cavernous sinus involvement, and the incidence of recurrence has been shown to correlate with dural invasion by a pituitary adenoma (Fig. 1).<sup>73,100</sup>

In 1951 stereotactic radiosurgery was described by Lars Leksell<sup>61</sup> as the “closed skull destruction of an intracranial target using ionizing radiation.” In 1968, Leksell first treated a patient with a pituitary adenoma by using the Gamma Knife. Since that time, stereotactic radiosurgery has been performed in more than 1000 patients to control tumor growth and normalize hormone production from pituitary adenomas. At the same time, great attention and effort in the field of stereotactic radiosurgery have been placed on the preservation of surrounding neuronal, vascular, and hormone-producing structures. The focus of this research is to evaluate the efficacy and define the role of stereotactic radiosurgery for pituitary adenomas.

### Radiosurgical Techniques

Radiosurgery is performed using the Gamma Knife, a LINAC-based system, or proton beams produced by cyclotrons. Gamma knife surgery usually involves multiple isocenters of different beam diameters to achieve a dose plan that conforms to the irregular three-dimensional volumes of most mass lesions (Fig. 2). The total number of isocen-

ters may vary depending on the size, shape, and number of the lesions. The recent version of the Gamma Knife (model C; Elekta Instruments, Atlanta, GA) combines advances in dose planning with robotic engineering and obviates the need to set coordinates manually for each isocenter.<sup>50</sup> In LINAC-based radiosurgery, multiple radiation arcs are used to crossfire photon beams at a target defined in stereotactic space.<sup>28</sup> Most of the presently functioning systems involve nondynamic techniques in which the patient couch is set at an angle and the arc is moved around its radius to deliver radiation that enters the skull through many different points. Numerous techniques have been developed to enhance the conformity of dose planning and delivery when using LINAC-based systems. These include beam shaping and intensity modulation. Newer developments include the introduction of collimator jaws and noncircular and mini- and microleaf collimators. The conformal beam can be delivered using the micromultileaf collimator or conformal blocks.

Proton-beam radiosurgery takes advantage of the intrinsic superior dose distribution of protons, as opposed to photons, because of the Bragg peak at the treatment depth.<sup>67</sup> Unfortunately, the equipment needed for this procedure is only available at a limited number of centers because of financial and logistical constraints.

In preparation for radiosurgery, many centers have recommended a temporary cessation of antisecretory medications during the perioperative time period. In 2000, Landolt, et al.,<sup>51</sup> first reported a significantly lower hormone normalization rate (the rate at which hormone production, secretions, and levels in blood or urine are normalized) in patients with acromegaly who were receiving antisecretory medications at the time of radiosurgery. Since then, the same group as well as others have documented a counterproductive effect of antisecretory medications on the rate of hormone normalization following radiosurgery.<sup>53,92</sup> The

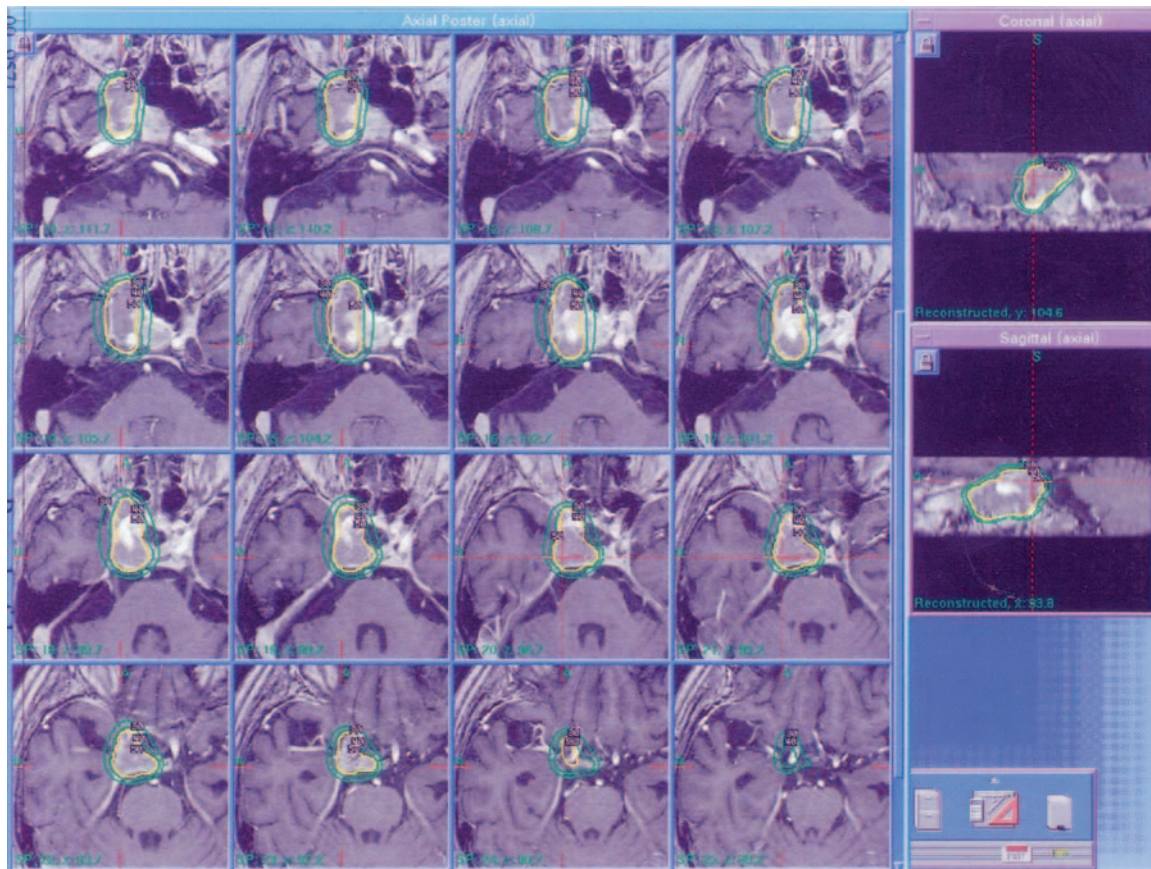


FIG. 2. Gamma knife dose plan used to treat the adenoma featured in Fig. 1. Note the restriction of the treatment isodose to the adenoma and protection of the optic chiasm.

mechanism by which antiseecretory medications lower hormone normalization rates is unknown, but Landolt and colleagues<sup>51,53</sup> have hypothesized that these drugs alter cell cycling and thus potentially decrease tumor-cell radiosensitivity. Moreover, the optimal time period, with respect to stereotactic radiosurgery, to withhold antiseecretory medications is not clear. Landolt and Lomax<sup>53</sup> recommend that dopamine agonists be withheld 2 months prior to radiosurgery. For patients with acromegaly, they recommend altering antiseecretory medication administration as early as 4 months before radiosurgery and completely halting all use of antisecretory medications 2 weeks prior to radiosurgery.<sup>51</sup> Although at many centers clinicians have incorporated such methods into their treatment regimens, the radiosurgical team must weigh the potential risk and benefits of altering antisecretory medication administration. The functional adenoma may be more likely to respond to radiosurgery. In the absence of antisecretory medication control, however, it may also enlarge and thereby place adjacent structures (for example, the optic apparatus) at risk, necessitating a lower prescription dose and making effective treatment more difficult.

The effective delivery of radiation to a target requires clear and accurate imaging of that target. Throughout the past 20 years, significant advances have increased the efficacy and safety of radiosurgical treatment of pituitary lesions. Tumor localization for dose planning is better

achieved using enhanced coronal MR imaging than CT scanning.<sup>49</sup> An MR imaging sequence consisting of contrast-enhanced, thin-slice (for example, 1-mm) volume acquisition is typically used to define the tumor within the sellar region. In patients who have undergone previous surgery, fat-suppression techniques can prove useful for differentiating the tumor from surgical fat grafts. In the pre-MR imaging era, CT scanning was used routinely. Now, however, it is generally reserved for patients who cannot undergo MR imaging (for example, a patient with a pacemaker). For hormonally active lesions, if the tumor is unable to be localized on imaging studies, radiosurgery may still be successful in achieving hormone normalization. In this case, the entire sellar region (including the inferior dura mater) is selected as the radiosurgical target when no definitive tumor can be visualized.<sup>99,103,105</sup>

After frame placement and stereotactic image acquisition, dose planning is performed. Through the strategic selection of isocenters, gamma angle, prescription dose, beam-blocking patterns, and isodose selection, the borders of the tumor can be encompassed and a suitable radiation dose delivered.<sup>25</sup> The radiosurgical team must take into account the radiation falloff characteristics unique to the type of unit that is used. Moreover, if fractionated radiation therapy has previously been administered, the dose and timing of that treatment must be considered when selecting a new dose for radiosurgery.

TABLE 1  
Summary of cases involving radiosurgery in patients with nonfunctioning pituitary adenomas\*

Authors & Year	Radiosurgery Unit	No. of Patients	Mean/Median FU (mos)	Max Dose (Gy)	Tumor Margin Dose (Gy)	Growth Control (%)
Lim, et al., 1998	GK	22	26	48	25	92
Martinez, et al., 1998	GK	14	36	28	16	100
Mitsumori, et al., 1998	LINAC	7	47	19	15	100
Witt, et al., 1998	GK	24	32	38	19	94
Yoon, et al., 1998	LINAC	8	49	21	17	96
Hayashi, et al., 1999	GK	18	16	NR	20	92
Inoue, et al., 1999	GK	18	>24	43	20	94
Mokry, et al., 1999	GK	31	21	28	14	98
Izawa, et al., 2000	GK	23	28	NR	22	94
Shin, et al., 2000	GK	3	19	NR	16	100
Feigl, et al., 2002	GK	61	55	NR	15	94
Sheehan, et al., 2002	GK	42	31	32	16	98
Wowra & Stummer, 2002	GK	30	58	29	16	93
Muramatsu, et al., 2003	LINAC	8	30	26.9	15	100
Petrovich, et al., 2003	GK	56	41	30	15	100
Pollock & Carpenter, 2003	GK	33	43	36	16	97
Losa, et al., 2004	GK	54	41	33	17	96

\* FU = follow up; GK = Gamma Knife; NR = not reported.

**Methods for Review of the Literature**

The PreMedline, Medline, Cochrane, and PubMed databases were searched for articles pertaining to pituitary adenomas and stereotactic radiosurgery. Studies had to be published in peer-reviewed journals to be included in this review. Each study was examined to determine the number of patients, radiosurgical parameters (for example, maximal dose and tumor margin dose), length of follow-up review, tumor growth control rate, complications, and rate of hormone normalization in the case of functioning adenomas. The results of this review are detailed in Tables 1 through 5. A total of 35 published studies involving 1621 patients were reviewed.<sup>3,12,22,29,31,35,37-40,45-47,52,53,59,62,63,70,77,78,80,81,88-93,103,104,106,116-118,120,122</sup>

**Radiosurgical Goals and Expectations Based on the Literature**

For patients with pituitary adenomas, radiosurgery is meant to inactivate the tumor cells, thereby preventing tumor growth and, for functioning adenomas, normalizing hormone overproduction as well as tumor growth. Ideally, these goals are met without damaging the residual normal pituitary gland and surrounding vascular and neuronal structures. Moreover, radiosurgery should be performed in a way to avoid delayed, radiation-associated secondary tumor formation.

*Extent of Pituitary Adenoma Growth Control*

In most series tumor control is defined as either an unchanged or decreased volume on follow-up neuroimaging studies. In nearly all published series, stereotactic radiosurgery afforded excellent control of tumor growth (Table 1 and Fig. 3).<sup>22,35,39,40,63,70,77,78,81,90,91,104,106,116,118,120</sup> In most studies the authors reported a greater than 90% control of tumor size (range 68-100%). A weighted average tumor control rate for all published series detailing such findings and encompassing a total of 1283 patients was 96%. The low-

est value of 68% was reported by Kim, et al.;<sup>46</sup> this number represents the fraction of tumors that had decreased in size. The cessation of tumor growth, not the amount of volume reduction, is still considered successful treatment. Some series have even demonstrated improvement in visual function following radiosurgery on shrinkage of the tumor.<sup>1,11,35,40,65,104,120</sup>

Most pituitary adenomas are slow-growing lesions. As such, it may be misleading to look at series of patients with a relatively short follow-up period. In eight of the published series the mean or median patient follow-up periods were 4 years or longer. In these studies, the tumor control rates varied from 83 to 100%.<sup>22,37,38,47,78,106,118,120</sup>

*Treatment for Cushing Disease*

Cushing disease, perhaps the most famous of pituitary disorders, was described by Harvey Cushing in 1912 as a polyglandular disorder.<sup>64</sup> It was not until 1933 that Cushing first performed neurosurgery to treat a patient with a pituitary adenoma that secreted excess ACTH.<sup>64</sup> Over the years, neurosurgeons and endocrinologists have debated the criteria for defining a cure for Cushing disease. Many favor the use of a 24-hour UFC as the gold standard. Others, however, have argued for the importance of measuring the morning serum cortisol level. Still others measure ACTH or basal serum cortisol and factor these values into the evaluation of endocrinological success or failure in the treatment of Cushing disease. In fact, in a recent consensus statement by leading endocrinologists, there was no widespread agreement regarding the definition of an endocrinological cure, and the remission rates varied according to the criteria used and the time assessed.<sup>2</sup> At most centers an endocrinological remission is defined as a UFC level in the normal range coupled with the resolution of clinical stigmata or a series of normal postoperative serum cortisol levels obtained throughout the day (range 5.4-10.8 µg/dl or 150-300 nmol/L).

Investigators in 22 series have reported the results for 314 patients with Cushing disease treated with radiosurgery (Ta-

TABLE 2  
Summary of cases involving radiosurgery in patients with Cushing disease\*

Authors & Year	Radiosurgery Unit	No. of Patients	Mean/Median FU (mos)	Max Dose (Gy)	Tumor Margin Dose (Gy)	Endocrine Cure Rate (%)	Endocrinological Criteria for Cure	Growth Control (%)
Levy, et al., 1991	proton/He beam	64	NR	150	NR	86	normal basal cortisol & dexamethasone test	NR
Ganz, et al., 1993	GK	4	18	58.25	25	50	a.m. UC <650 nmol/24 hr & p.m. UC <250 nmol/24 hr	100
Lim, et al., 1998	GK	4	26	48	25	25	NR	92
Martinez, et al., 1998	GK	3	36	40	24	100	ACTH <10 µg/L, UFC <650 nmol/24 hr	100
Mitsumori, et al., 1998	LINAC	5	47	19	15	40	NR	100
Morange-Ramos, et al., 1998	GK	6	20	NR	28	67	UFC <90 µg/24 hr, normal ACTH & cortisol	NR
Witt, et al., 1998	GK	25	32	38	19	28	normal 24-hr UFC	94
Yoon, et al., 1998	LINAC	1	49	21	17	NR	NR	96
Hayashi, et al., 1999	GK	10	16	NR	24	10	NR	92
Inoue, et al., 1999	GK	3	>24	43	20	100	NR	94
SH Kim, et al., 1999	GK	8	27	55	29	62	UFC <100 µg/24 hr	68
Laws & Vance, 1999	GK	50	NR	NR	NR	58	normal 24-hr UFC	NR
Mokry, et al., 1999	GK	5	56	35	17	33	NR	98
Izawa, et al., 2000	GK	12	28	NR	22	17	NR	94
Sheehan, Vance, et al., 2000	GK	43	44	47	20	63	normal 24-hr UFC	100
Shin, et al., 2000	GK	7	88	NR	32	50	UFC <90 µg/24 hr	100
Hoybye, et al., 2001	GK	18	204	60-240	NR	83	normal 24-hr UFC	83
Feigl, et al., 2002	GK	4	55	NR	15	NR	NR	84
Kobayashi, et al., 2002	GK	20	64	49	29	35	ACTH <50 pg/ml, cortisol <10 µg/dl	100
Pollock, Nippoldt, et al., 2002	GK	9	42	40	28.5	78	UFC <90 µg/24 hr	100
Choi, et al., 2003	GK	5	42.5	54.1	20	56	UFC <90 µg/24 hr	86
Petrovich, et al., 2003	GK	4	41	30	15	50	normal serum cortisol, ACTH, & 24-hr UFC	NR

\* UC = urine cortisol.

TABLE 3  
Summary of cases involving radiosurgery in patients with acromegaly

Authors & Year	Radiosurgery Unit	No. of Patients	Mean/Median FU (mos)	Max Dose (Gy)	Tumor Margin Dose (Gy)	Tumor Dose (Gy)	Endocrine Cure Rate (%)	Endocrinological Criteria for Cure	Growth Control (%)
Ganz, et al., 1993	GK	4	18	54.25	19.5	19.5	25	GH <5 mIU/L	100
Landolt, et al., 1998	GK	16	NR	50	25	25	81	GH <10 mIU/L & IGF-I <50 mIU/L	NR
Lim, et al., 1998	GK	20	26	48	25	25	38	GH <2 ng/ml	92
Martinez, et al., 1998	GK	7	36	39	25	25	71	normal IGF-I	100
Mitsumori, et al., 1998	LINAC	1	47	19	15	15	0	NR	100
Morange-Ramos, et al., 1998	GK	15	20	NR	28	28	20	GH <5 ng/ml, normal IGF-I	NR
Witt, et al., 1998	GK	20	32	38	19	17	20	normal IGF-I	94
Yoon, et al., 1998	LINAC	2	49	21	17	17	50	GH <5 ng/ml	96
Hayashi, et al., 1999	GK	22	16	NR	24	24	41	NR	92
Inoue, et al., 1999	GK	12	>24	43	20	20	58	NR	94
MS Kim, et al., 1999	GK	2	12	36	22	22	0	GH <5 ng/ml	100
SH Kim, et al., 1999	GK	11	27	55	29	29	46	normal IGF-I for sex & age	68
Laws & Vance, 1999	GK	56	NR	NR	NR	NR	25	GH <7 ng/ml, IGF-I <380 IU/ml	NR
Mokry, et al., 1999	GK	16	46	33	16	16	31	normal IGF-I for age	98
Izawa, et al., 2000	GK	29	28	NR	22	22	41	NR	94
Shin, et al., 2000	GK	6	43	NR	34	34	67	GH <10 mIU/L & IGF-I <450 ng/ml	100
Zhang, et al., 2000	GK	68	34	NR	31	31	96	GH <12 ng/ml	100
Fukuoka, et al., 2001	GK	9	42	41	20	20	50	GH <5 ng/ml & normal IGF-I	100
Ikeda, et al., 2001	GK	17	48	NR	25	25	82	normal IGF-I for age	100
Feigl, et al., 2002	GK	9	55	NR	15	15	NR	NR	94
Pollock, Nippoldt, et al., 2002	GK	26	42	40	20	20	42	GH <2 ng/ml & normal IGF-I for age	100
Attanasio, et al., 2003	GK	30	46	40	20	20	37	GH <2.5 µg/L	100
Choi, et al., 2003	GK	12	42.5	54.1	28.5	28.5	50	GH <5 mIU/L	100
Muramatsu, et al., 2003	LINAC	4	30	24.5	15	15	50	NR	100
Petrovich, et al., 2003	GK	6	41	30	15	15	100	normal IGF-I & GH	NR

ble 2).<sup>12,22,31,35,37,39,40,46,47,59,62,63,70,77,78,80,90,92,103,106,116,120</sup> The mean doses delivered to the tumor margin in these series ranged from 15 to 32 Gy. In nine series the 24-hour urine cortisol collection was part of the criteria used for endocrinological evaluation. Unfortunately, in another eight of these studies the method used to establish endocrinological remission or failure was not reported. In the other series a combination of the aforementioned endocrinological tests was used. Endocrinological remission rates vary from 10 to 100%. In those series with at least 10 patients and a median follow-up period of 2 years, endocrinological remission rates ranged from 17 to 83%. This latter value was reported by Hoybye, et al.,<sup>37</sup> and represents the largest single series of patients with Cushing disease. It is important to note, however, that many of the patients in this series were treated during the pre-CT and MR imaging era of radiosurgery and had to be treated as often as four times before their Cushing disease went into remission.

*Treatment for Acromegaly*

Just as the endocrinological criteria for Cushing disease remain the subject of debate, the criteria for curing acromegaly have also been inconsistent. The most widely accepted guidelines for a remission in acromegaly consist of a GH level less than 1 ng/ml in response to a glucose challenge and a normal serum level of IGF-I when matched for patient age and sex.<sup>33,112</sup>

Twenty-five studies detailed the results of radiosurgical treatment for 420 patients with acromegaly (Table 3).<sup>3,12,22,29,31,35,38-40,45,46,52,59,63,70,77,78,80,81,90,92,106,116,120,122</sup> The mean doses delivered to the tumor margin in these series ranged from 15 to 34 Gy. In seven studies the criteria used to define an endocrinological remission were not reported. In the remaining 18 studies, 12 different criteria were used to define remission. Remission rates following radiosurgery varied from 0 to 100%. In those series with at least 10 patients and a median follow-up period of 2 years, endocrinological remission rates ranged from 20 to 96%. This latter value was reported by Zhang, et al.,<sup>122</sup> and represents the single largest series with 68 patients. Certainly, some of the wide variation in endocrinological remission rates with acromegaly may be attributed to the myriad of criteria used to define a remission. Another confounding variable is the degree to which somatostatin analogs may have been used during the time of radiosurgery and the subsequent endocrinological evaluation in each of the series.

*Treatment for Prolactinomas*

In patients with prolactinomas, the criteria used to define an endocrinological remission are generally more consistent. In most studies a remission is defined as a normal serum prolactin level for the sex of the patient. In 22 radiosurgical studies the results for 393 patients with prolactinomas were reported (Table 4).<sup>12,22,31,35,39,40,45,46,53,59,62,63,70,77,80,81,89,90,92,116,120</sup> The mean radiation dose delivered to the tumor margin varied from 13.3 to 33 Gy. Although in eight of these studies the endocrinological criteria defining a remission were not reported, in the remaining studies relatively similar criteria were used. Remission rates varied from 0 to 84%.

In 11 studies with at least 10 patients and a median or mean follow-up period of 2 years, the range in remission

TABLE 4  
Summary of cases involving radiosurgery in patients with prolactinomas\*

Authors & Year	Radiosurgery Unit	No. of Patients	Mean/Median FU (mos)	Max Dose (Gy)	Tumor Margin Dose (Gy)	Endocrine Cure Rate (%)	Endocrinological Criteria for Cure (PRL level)	Growth Control (%)
Levy, et al., 1991	proton/He beam	20	12	150	NR	60	normal serum PRL	NR
Ganz, et al., 1993	GK	3	18	40	13.3	0	<525 mIU/L for women & <415 mIU/L for men/ postmenopausal women	100
Lim, et al., 1998	GK	19	26	48	25	56	<25 ng/ml	92
Martinez, et al., 1998	GK	5	36	43	33	0	<20 ng/ml	100
Mitsumori, et al., 1998	LINAC	4	47	19	15	0	NR	100
Witt, et al., 1998	GK	12	32	38	19	0	NR	94
Yoon, et al., 1998	LINAC	11	49	21	17	84	<25 ng/ml	96
Hayashi, et al., 1999	GK	13	16	NR	24	15	NR	92
Inoue, et al., 1999	GK	2	>24	43	20	50	NR	94
MS Kim, et al., 1999	GK	20	12	36	22	19	NR	100
SH Kim, et al., 1999	GK	18	27	55	29	17	<20 ng/ml	68
Laws & Vance, 1999	GK	19	NR	NR	NR	7	<20 ng/ml	NR
Mokry, et al., 1999	GK	21	31	30	14	21	<25 ng/ml	98
Moraga-Ramos, et al., 1998	GK	4	20	NR	28	0	<25 ng/ml for women & <20 ng/ml for men	NR
Izawa, et al., 2000	GK	15	28	NR	22	20	NR	94
Landolt, et al., 2000	GK	20	29	50	25	25	<19 ng/ml for women & <16 ng/ml for men	NR
Pan, et al., 2000	GK	128	33	45	32	15	<30 ng/ml	98
Feigl, et al., 2002	GK	18	55	NR	15	NR	NR	94
Pollock, Nippoldt, et al., 2002	GK	7	42	40	20	29	<23 ng/ml	100
Choi, et al., 2003	GK	21	42.5	54.1	28.5	24	<20 ng/ml	86
Muramatsu, et al., 2003	LINAC	1	30	30	15	0	NR	100
Petrovich, et al., 2003	GK	12	41	30	15	83	normal serum PRL	NR

\* PRL = prolactin.

TABLE 5  
*Radiosurgery for patients with Nelson syndrome*

Authors & Year	Radiosurgery Unit	No. of Patients	Mean/Median FU (mos)	Max Dose (Gy)	Tumor Margin Dose (Gy)	Endocrine Cure Rate (%)	Endocrinological Criteria for Cure	Growth Control (%)
Levy, et al., 1991	proton/He beam	17	NR	150	NR	NR	normal ACTH	94
Ganz, et al., 1993	GK	3	18	56.7	NR	0	NR	100
Wolffenbittel, et al., 1998	GK	1	33	40	12	0	NR	100
Laws & Vance, 1999	GK	9	NR	NR	NR	11	NR	NR
Kobayashi, et al., 2002	GK	6	63	49.4	28.7	33	ACTH <50 pg/ml	100
Pollock & Young, 2002	GK	11	37	40	20	36	NR	82

rates following radiosurgery was just as varied. In the largest series conducted by Pan, et al.,<sup>89</sup> a 15% endocrinological remission rate for 128 patients with a median follow-up period of 33 months was reported. Although the remission rates for prolactinomas appear to be less than those for Cushing disease or acromegaly, a substantial number of patients experience a reduction but not complete remission of their hyperprolactinemia following radiosurgery. In a similar fashion to acromegaly, widespread differences in the use of antisecretory dopamine agonists at institutions may confound the efficacy of radiosurgery and the subsequent endocrinological assessment of patients with prolactinomas in these series. In addition, Hoybye, et al.,<sup>37</sup> have demonstrated that radiosurgery may cause an elevation in prolactin levels, possibly through injury or irritation of the infundibulum and impaired transport of dopamine to the anterior pituitary. This elevation can last for several years and may falsely lower the reported remission rates for patients with prolactinomas treated with radiosurgery.

#### *Treatment for Nelson Syndrome*

Compared with nonfunctioning and other functioning pituitary adenomas, much less information is available about the efficacy of stereotactic radiosurgery for the treatment of Nelson syndrome. In patients with ACTH-secreting tumors who have undergone bilateral adrenalectomies, these pituitary adenomas tend to display more aggressive growth rates. As such, endocrinological remission and growth control are critical for Nelson syndrome.

Reports of six studies detailed the results of stereotactic radiosurgery for 47 patients with Nelson syndrome (Table 5).<sup>31,47,59,62,93,117</sup> The mean dose delivered to the tumor margin varied from 12 to 28.7 Gy. Unfortunately, only two reports detailed the endocrinological criteria used to define a remission. Remission rates ranged from 0 to 36%; however, tumor growth control rates were more favorable and varied from 82 to 100%.

#### *Rates of Endocrine Improvement and Late Recurrence*

An ideal treatment would lead to a rapid normalization of endocrinological factors. The rate of hormone improvement and normalization following radiosurgery is difficult to predict. In some series hormone improvement occurred in as little as 3 months after radiosurgery, whereas in others normalization occurred longer than 8 years afterwards.<sup>103,106</sup> Generally, if endocrinological normalization is going to occur after radiosurgery, it usually does so within the first 2 years.<sup>57,59,93,103,122</sup> Several instances of late recurrence of hor-

mone oversecretion have been reported, despite earlier remissions confirmed by symptoms and endocrinologically.<sup>103</sup> As such, long-term neuroimaging and endocrinological follow-up periods are recommended for all patients whose pituitary glands are treated with radiosurgery to detect any possibility of late recurrence and tumor growth.

The effects of treatment volume and dose selection on the rate and extent of hormone normalization remain the subject of debate. Some investigators have found that radiation dose and treatment volume do not affect the rate or extent of hormone normalization.<sup>21,45</sup> Others have found a correlation between hormone normalization and the following: treatment isodose, maximal dose, tumor margin dose, and the absence of hormone-suppressive medications around the time of radiosurgery.<sup>51,53,89,92</sup> There does not appear to be a correlation between the tumor volume response and the endocrinological response following radiosurgery.<sup>22,51,103</sup> Fortunately, because most pituitary adenomas are well within the size of lesion that is suitable for stereotactic radiosurgery, dose-volume considerations are not as much of an issue. The dose is usually limited by the proximity of the adenoma to the optic apparatus, and current shielding techniques can help facilitate the delivery of higher doses. Because the systemic effects of functioning adenomas can be so devastating to patients, it seems intuitive to deliver a reasonably high dose ( $\geq 20$  Gy delivered to the tumor margin) to effectuate hormone normalization and control tumor growth. Nonfunctioning pituitary adenomas appear to require a lower radiosurgery treatment dose than functioning adenomas.<sup>40,41,63,69,88,106</sup> The lowest effective dose for a nonfunctioning tumor is presently not known.

#### *Complications Following Radiosurgery for Pituitary Adenomas*

*Cranial Neuropathies Following Radiosurgery.* In our review of 35 studies involving 1621 patients, there were 16 cases of damage to the optic apparatus. The postradiosurgical visual apparatus deficits ranged from quadrantanopia to complete visual acuity loss. Radiosurgical doses associated with visual field loss varied from 0.7 to 12 Gy. The tolerable level of radiation to the optic apparatus is still a subject of debate. Some advocate that the optic apparatus can tolerate doses as high as 12 to 14.1 Gy.<sup>11,87,109</sup> Others recommend an upper limit of 8 to 10 Gy.<sup>32,111</sup> Small volumes of the optic apparatus exposed to doses of 10 Gy or less may be acceptable in some cases.<sup>60,87</sup> Both the tolerable absolute dose and volume undoubtedly vary from patient to patient. This degree of variability likely depends on the extent of damage

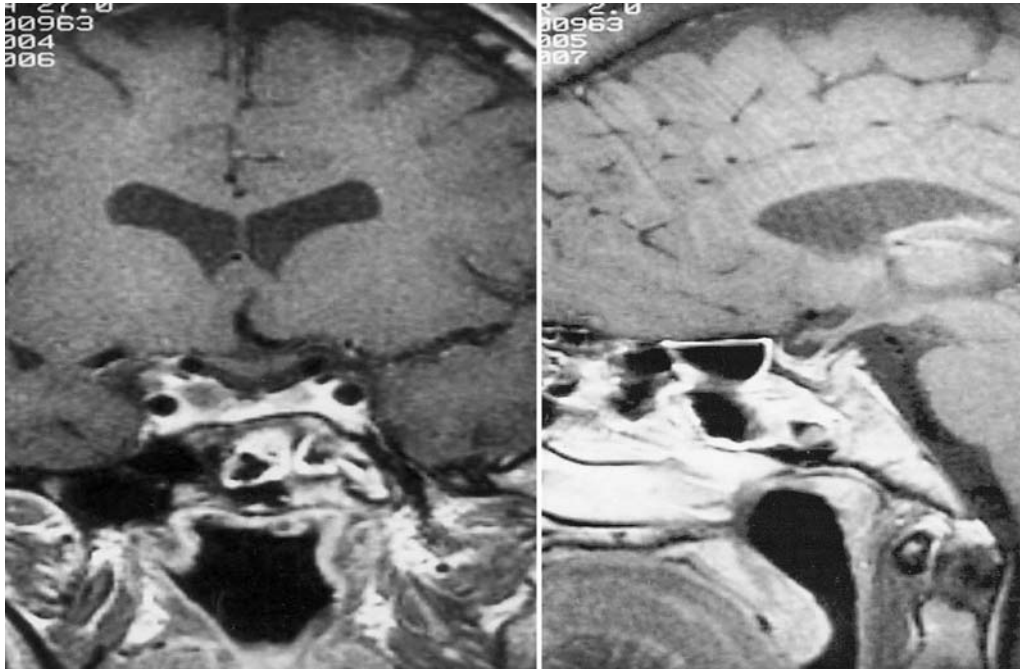


FIG. 3. Postradiosurgical contrast-enhanced coronal (*left*) and sagittal (*right*) T<sub>1</sub>-weighted MR images demonstrating a marked reduction in tumor volume 4 years after gamma knife surgery.

to the optic apparatus by compression due to the pituitary adenoma, ischemic changes, type and timing of previous interventions (for example, fractionated radiation therapy and surgery), patient age, and the presence or absence of other comorbidities (for example, diabetes).<sup>66,98</sup>

The other consideration for limiting damage to the optic apparatus during radiosurgery is the distance between this structure and the residual adenoma. A distance of 5 mm between the adenoma and the optic apparatus is desirable, but as small a distance as 1 to 2 mm may be acceptable; the dose volume of the optic apparatus may be a better way to determine the dose and risk.<sup>11,63,103,116</sup> The tolerable distance is a function of the degree to which a dose plan can be designed to deliver a suitable radiation dose to the adenoma yet spare the optic apparatus. Without achievement of a suitable stereotactic radiosurgery dose plan, an alternative treatment modality (that is, resection, medical management, or fractionated radiation therapy) should be chosen.

Just as visual dysfunction of the optic apparatus has been described following radiosurgery, so too has improvement in visual function. Improvement in visual acuity and in the visual fields has been noted after radiosurgery in some patients with pituitary adenomas and may be a result of tumor shrinkage and optic nerve decompression.<sup>1,11,35,40,82,104,120</sup>

The other cranial nerves in the cavernous sinus appear to be much more resistant to injury from stereotactic radiosurgery. In the 35 studies reviewed, 21 patients experienced new neuropathies in either the oculomotor, trochlear, trigeminal, or abducent nerve, and nearly half of these cranial neuropathies were transient.

*Injury to Adjacent Vascular Structures.* Injury to the cavernous segment of the CA is rare following radiosurgery. A total of four cases have been reported and in only two of these cases did the patients experience symptoms

from CA stenosis.<sup>63,81,92</sup> Pollock and associates<sup>92</sup> have recommended that the prescription dose should be limited to less than 50% of the intracavernous CA vessel diameter. Shin, et al.,<sup>106</sup> recommended restricting the dose to the internal CA to less than 30 Gy.

*Parenchymal Brain Injury.* In the 35 series that we reviewed, 13 cases of parenchymal changes consistent with a radiation effect were noted. These findings were most often associated with the hypothalamic and temporal regions. Clinical manifestations of the parenchymal injury occurred as early as 5 hours and as late as approximately 1 year after radiosurgery. Six of the 13 patients had undergone fractionated radiation therapy prior to radiosurgery.<sup>35,40,62,77,92,93</sup> Clearly, previous radiotherapy represents an added risk factor for the development of necrosis after radiosurgery. Both the timing and total dose of previous radiation should be considered when developing a stereotactic radiosurgery dose plan.

*Hypopituitarism.* The incidence of hypopituitarism after radiosurgery is difficult to determine at present. Reports in the literature for the incidence of postradiosurgery hypopituitarism vary widely. Well-respected groups have reported a low incidence (0–36%) of pituitary dysfunction following radiosurgery.<sup>42,62,91,103,104</sup> A long-term study from the Karolinska Institute with a mean follow-up duration of 17 years, however, indicated a 72% incidence of hypopituitarism.<sup>37</sup> It is important to note that many of the patients in that study were treated with targeting based on antiquated imaging techniques and received doses much higher than those used today. Fiegl, et al.,<sup>22</sup> found that hypopituitarism following radiosurgery correlated with the radiation dose to the pituitary stalk, and Vladyka and associates<sup>113</sup> demonstrated that certain normal adenohypophysis cell types are more susceptible to radiation than others. The difficulty with determin-



ing the exact incidence of radiosurgery-induced hypopituitarism stems in part from the fact that many of the patients have previously undergone resection and some fractionated radiotherapy. In addition, pituitary deficiencies may result in part from aging. Thus, it is likely that hypopituitarism in the postradiosurgical population is multifactorial in cause and related to radiosurgery as well as age-related changes and previous treatments (for example, microsurgery and radiotherapy). The methods of endocrinological follow-up review are inconsistent and unreliable; the indications for obtaining hormone levels and the time at which they were obtained vary widely from study to study. A well-controlled, long-term study focusing on this issue is needed to determine definitively the incidence of radiosurgery-induced hypopituitarism.

*Radiosurgery-Associated Secondary Neoplasms.* The incidence of radiosurgery-induced neoplasms is unknown at present; however, it appears to be quite low and is clearly less than that following fractionated radiation therapy. In the 1621 patients reviewed, there were no reports of radiation-induced neoplasms.

Despite the fact that radiosurgery has been performed in more than 200,000 patients for longer than 30 years, the precise incidence of radiosurgery-induced neoplasms is difficult to estimate because of the delayed fashion in which such lesions may develop and the apparently low rate of occurrence. For a tumor to be considered a result of radiosurgery, the following criteria must be met. 1) The tumor must occur within the previous radiation field. 2) It cannot be present prior to irradiation. 3) Any primary tumor must differ histologically from the induced tumor. 4) There must be no genetic predisposition for the occurrence of a secondary malignancy or tumor progression. 5) A certain latency period is required from treatment to tumor formation (usually 5 years).<sup>9</sup> In a recent review, Ganz<sup>30</sup> noted three reports published in peer-reviewed journals indicating a radiosurgery-induced neoplasm.<sup>34,43,101</sup> In two of these reports a glioblastoma multiforme arose, whereas in the other malignant transformation of a vestibular schwannoma occurred.<sup>34,43,101</sup> Other cases of patients treated with radiosurgery who have later been found to harbor a malignant brain tumor have been reported but they generally do not meet the aforementioned criteria.<sup>17,107,121</sup> Based on the literature, the incidence of stereotactic radiosurgery-induced neoplasms likely ranges between zero to three per 200,000 patients.<sup>30</sup> Certainly, this incidence is quite low, and the potential risk of radiosurgery-associated secondary neoplasia must be weighed against the potential benefits. It is generally believed that the risk will be lower than that seen with fractionated therapy because of the smaller irradiation volumes associated with radiosurgery. Alternative treatments, if available, are not without appreciable risks and sometimes there are no viable options but stereotactic radiosurgery. Although time will reveal the true incidence of complications associated with radiosurgery, the substantial body of information presently available would indicate that its side-effect profile is quite attractive.

For the sake of brevity the University of Virginia Health System, University of Pittsburgh, University of Zurich, and Massachusetts General Hospital stereotactic radiosurgery results for pituitary adenomas have not been specifically detailed in this particular report. Nevertheless, they are consistent with those noted previously and have been detailed

elsewhere.<sup>42,51,53,59,77,103</sup> At each of our institutions, stereotactic radiosurgery plays an important role in the treatment of recurrent or residual pituitary adenomas.

## Discussion

### *Microsurgical Removal of the Pituitary Adenoma*

Microsurgery is the gold standard for treatment of sellar lesions. It offers the advantages of pathological confirmation, immediate decompression of the optic apparatus, and rapid reduction of hormone oversecretion. Transsphenoidal resection is currently the most widely used approach for pituitary adenomas, but the transcranial approach remains a viable alternative for sellar lesions with extensive supra- or parasellar extension. Even in the best of hands, however, microsurgery alone provides long-term tumor control rates of only 50 to 80%.<sup>10,27,54,55,58,69</sup> The rates of endocrinological normalization of functioning adenomas after microsurgery vary as follows: 56 to 91% for patients with Cushing disease,<sup>8,10,27,69,102,110</sup> 42 to 84% for acromegaly,<sup>8,110</sup> 28 to 87% for prolactinomas,<sup>8,79,96,110</sup> and 27 to 70% for Nelson syndrome.<sup>110</sup> Residual or recurrent tumor originating in areas traditionally difficult to resect transsphenoidally, such as suprasellar or cavernous sinus extensions with dural invasion, may proliferate and the symptoms associated with the adenoma may return.<sup>20,39,73,100</sup> Overall recurrence rates following microsurgery vary from 8 to 42% for functioning adenomas.<sup>79,94,110</sup>

Clearly, microsurgical removal of the lesion is not without risks. Complication rates in some of the most experienced hands include 1% mortality, 3.4% major morbidity (for example, visual loss, ophthalmoplegia, and stroke), 4.6% lesser morbidity (for example, sinusitis, diabetes insipidus, and nasal septal perforation), and 3% iatrogenic hypopituitarism.<sup>110</sup> In 1997, a survey of US neurosurgeons who perform transsphenoidal surgery for pituitary tumors revealed the following complication rates: 0.9% mortality, 1.8% risk of a new visual deficit, 3.9% risk of a cerebrospinal fluid leak, and 19.4% risk of postoperative pituitary insufficiency.<sup>14</sup> Moreover, the complication rates are higher and the success rates lower in repeated surgery for recurrent or residual pituitary adenomas.<sup>54,56,58,84,95</sup> Although the risks associated with radiosurgery are not negligible, they are commonly of lesser severity than those associated with surgical resection.

One of the best indications for radiosurgery of secretory or nonsecretory pituitary adenomas is residual or recurrent tumor that is not safely removable when using microsurgical techniques—a lesion located within the cavernous sinus. If it is known before microsurgery that the cavernous sinus is involved and a debulking procedure is considered, then every effort should be made to clear the tumor away from the optic nerves and chiasm prior to radiosurgery. A suprasellar approach should be considered if there is doubt that this can be accomplished through a transsphenoidal approach.

### *Medical Management of Functioning Pituitary Adenomas*

Prolactinomas are the subtype of pituitary adenomas most likely to respond to medical management. Administration of dopamine receptor agonists can result in hormone normalization in 70 to 90% of patients with prolac-

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tinomas.<sup>108,114</sup> Moreover, medical management can result in tumor shrinkage by 80 to 90%.<sup>15,18,23</sup> As such, dopamine receptor agonists can lead to improvement in tumor volume-associated symptomatology (for example, visual field abnormalities, headaches, and so forth) and resolution of symptoms associated with hyperprolactinemia (galactorrhea and amenorrhea). The response time for such agents, however, may vary from days to months and is difficult to predict. In addition, side effects such as nausea, vomiting, and hypotension or the lifelong cost of such drugs may make medical management an unattractive option for some patients. Also, because of the unknown effects of such medications on fetal development, some physicians suggest the cessation of dopamine agonists during attempts to conceive and during pregnancy.<sup>16</sup> Any cessation of medical management may risk tumor expansion and return of prolactin hypersecretion.

In patients with acromegaly, the use of somatostatin analogs (for example, octreotide and lanreotide) and dopamine agonists can result in normalization of GH and IGF-I levels in 55 to 70% of patients.<sup>72,74,75,83</sup> A reduction in tumor size of 20 to 50% can be achieved in 30 to 40% of patients by using somatostatin analogs.<sup>6,26,83</sup> Bromocriptine and cabergoline result in poorer hormone normalization rates of 10 and 34%, respectively.<sup>75</sup> There are some disadvantages to medical management for acromegaly as well. For instance, some of these medications are not available in oral form and must be administered by injection. These medications may cause adverse systemic side effects such as gallstone formation, biliary stasis, and sludging.<sup>44</sup> Also, the medications are often quite costly, particularly when considering the fact that the medication must be continued for the rest of the patient's life.

Medical management of Cushing disease is seldom performed as a first-line treatment. Rather, it is usually provided as a supplementary approach after surgical treatment has failed while other treatment options (for example, radiosurgery, repeated microsurgery, and fractionated radiation therapy) are being considered or initiated. Ketoconazole, an inhibitor of steroid synthesis in the adrenal glands, is the most common medical treatment for Cushing disease; other infrequently administered inhibitors of steroid synthesis are mitotane, metyrapone, and aminoglutethimide. The production of ACTH can be partially inhibited by administration of dopamine agonists,  $\gamma$ -aminobutyric acid agonists, somatostatin analogs, and serotonin antagonists.<sup>85</sup> Finally, in Cushing disease, mifepristone has been used with fairly limited success to block peripheral steroid receptor sites.<sup>5,13</sup>

Radiosurgery is most useful for patients with prolactinomas whose diseases are medically refractory, who cannot tolerate the side-effect profiles, or who are unable to afford the prolonged medical regimen. For patients with Cushing disease, acromegaly, or Nelson syndrome, medical management is used during the latency period between initiation of radiosurgery and delayed endocrinological remission, which typically occurs months afterwards. If possible, medications that directly impact the cellular metabolism of a secretory adenoma (for example, dopamine agonists) should be temporarily suspended around the time of radiosurgery to increase the chances of a successful outcome.

### *Fractionated Radiation Therapy for Pituitary Adenomas*

The use of radiation techniques in the treatment of pitu-

itary lesions has a long history. With the advent of roentgenography in 1896, the sella turcica could be visualized using x-ray films and enlargement of that bony structure was frequently associated with a pathological neuroendocrinological condition. Pituitary tumors were some of the first brain tumors to be treated using conventional radiation therapy. Initial approaches involved the use of horizontally opposed temporal ports and resulted in adverse radiation injury of the CAs, the visual apparatus, and the temporal lobes in many patients.

Current use of multiport radiation therapy has led to refinement of the technique and improvement in outcome. The rate of control of pituitary adenoma growth by using fractionated radiation therapy has varied from 73 to 95%.<sup>4,48,71,119,123</sup> Hormone normalization has been much less successful in functioning adenomas and has varied from 10 to 83%.<sup>4,19,48,123</sup> Conventional fractionated radiation therapy for pituitary tumors still carries a 1 to 3% risk of delayed optic neuropathy and a 50 to 100% rate of long-term pituitary hormone deficiency.<sup>4,123</sup> Conventional radiation must be administered in 20 to 25 fractions and, as such, is less convenient for the patient. More importantly, radiation-induced neoplasms (for example, glioblastoma multiforme or meningioma) develop at a rate of 2.7% by 10 years post-treatment, and the actuarial incidence of a cerebrovascular accident following conventional radiotherapy is 4% at 5 years.<sup>7</sup>

Although the risks of cerebrovascular accidents, optic apparatus injury, radiation-induced neoplasms, and hypopituitarism are not negligible for radiosurgery, based on the current data we suggest that they are less than the risks associated with fractionated radiotherapy. In addition, the radiobiological effect of a single-session large dose of radiation, as with stereotactic radiosurgery, should have a much more substantial impact on aberrant cell behavior than smaller, fractionated doses. Histopathological evaluation of pituitary adenoma specimens following either radiosurgery or fractionated radiation therapy is consistent with the notion of a more potent radiobiological effect of radiosurgery.<sup>86</sup> Radiosurgery also appears to lead to faster normalization of hormone levels than fractionated radiotherapy, further supporting the notion of greater radiobiological potency.<sup>51</sup> The improved radiobiological effects of radiosurgery coupled with the apparently lower risk of complications such as hypopituitarism, visual deterioration, and radiation-induced neoplasms generally make radiosurgery preferable to radiotherapy for the treatment of most pituitary adenomas.

It is noteworthy, however, that under certain circumstances fractionated radiation therapy may be preferable to radiosurgery. When the adenoma is too large to administer an effective radiation dose in a single session without undue risk of complications, fractionated radiotherapy may be more appropriate. Extrapolating from the integrated logistic formula for prediction of complications from radiosurgery, a maximal volume of 23 cm<sup>3</sup> can be treated at a dose of 12 Gy and yield less than a 3% risk.<sup>24</sup> Such a volume, if spherical, would translate to a mean diameter of 35 mm. If the tumor is very close ( $\leq 3$  mm) to the optic apparatus, it may be impossible to achieve an acceptably sharp falloff gradient while using radiosurgery despite the aid of shielding technology. As such, for large-volume sellar lesions or lesions too close to the optic apparatus, conventional fractionated radiation therapy or fractionated stereotactic ra-

diation therapy may be more appropriate treatment choices.<sup>68,76,115</sup>

### Conclusions

Multimodality treatment is often used to manage pituitary adenomas. Therapeutic options include medical management, microsurgery, radiosurgery, and radiotherapy. Except for prolactinomas, microsurgery remains the primary treatment for sellar lesions in surgically fit patients, particularly when the lesion is exerting a mass effect on the optic apparatus or producing hormone overproduction. Nevertheless, 20 to 50% of patients experience recurrence of their adenomas, and adjuvant treatment is recommended for these patients.

Historically, fractionated radiation therapy was used to treat recurrent or residual pituitary adenomas. Nevertheless, fractionated radiation therapy has a prolonged latency for its desired effects (that is, tumor control and hormone normalization) and is associated with a significant risk of undesired effects (that is, radiation-induced tumors, cerebral vasculopathy, necrosis, visual damage, and hypopituitarism). Improvements in the techniques of radiation therapy have led to a decrease in the complication rate associated with fractionated radiotherapy but not an improvement in the long latency for hormone normalization and tumor growth control.

More recently, stereotactic radiosurgery has been demonstrated to be a safe and highly effective treatment for patients with recurrent or residual pituitary adenomas. Radiosurgery affords effective growth control and hormone normalization for patients and has a generally shorter latency period than that of fractionated radiotherapy. This shorter latency period with radiosurgery can typically be managed with hormone-suppressive medications. Furthermore, the complications (for example, radiation-induced neoplasia and cerebral vasculopathy) associated with radiosurgery appear to occur less frequently than those associated with radiotherapy. Radiosurgery may even serve as a primary treatment for those patients deemed unfit for microsurgical tumor removal because they have other comorbidities or demonstrable tumors in a surgically inaccessible location. Radiosurgery can frequently preserve and, at times, even restore neurological and hormone function.

In the future, radiosurgery will likely yield even better results. The introduction of the Gamma Knife Automatic Positioning System, incorporation of new neuroimaging technologies into dose planning, and improvements in the shielding techniques of radiosurgical units will likely result in improved conformity and steeper dose falloff.<sup>36,97</sup> Neurosurgeons and endocrinologists will also need to clarify the optimal timing for cessation of antisecretory medications with regard to the date of radiosurgery. Additional neurological, neuroimaging, and endocrinological follow up of patients must be performed to examine delayed complications or tumor recurrence. Finally, physicians caring for patients with pituitary disorders should establish uniform endocrinological criteria and diagnostic testing for pre- and postradiosurgical evaluations.

### Disclosure

Drs. Lunsford and Kondziolka are consultants for Elekta AB;

however, no funds from any company were used to conduct this research or complete this manuscript.

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Manuscript received April 4, 2004.

Accepted in final form October 25, 2004.

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