

Current Concepts in Stereotactic Radiosurgery for Pituitary Adenomas

Jason P. Sheehan, MD, PhD, Brian Williams, MD and Edward R. Laws, MD

University of Virginia, Charlottesville, Virginia (JPS, BW)
Harvard University, Boston, Massachusetts (ERL)

Address Correspondence to:

Jason Sheehan

Box 800-212

Department of Neurological Surgery

Health Sciences Center

Charlottesville, VA 22908 USA

jps2f@virginia.edu

Voice: (434) 924-8129

FAX: (434) 243-6726

I. Introduction

Pituitary adenomas represent a fairly common intracranial pathology.[1, 2] Epidemiological studies have demonstrated that nearly 20% of the general population harbor a pituitary adenoma.[1] Pituitary adenomas are broadly classified into two groups: functioning (endocrinologically-active) and nonfunctioning tumors. The first category of tumor is those that secrete excess amounts of normal pituitary hormones and, consequently, present with a variety of clinical syndromes depending upon hormones secreted. Such functioning adenomas include those with Cushing's disease, acromegaly, prolactinomas, and Nelson's syndrome; rarely, a functioning adenoma can overproduce more than one hormone.[3-5]

The second class of pituitary adenomas is comprised of tumors that do not secrete any known biologically active pituitary hormones, and these represent approximately 30% of pituitary adenomas.[6] These nonfunctioning or null cell pituitary adenomas progressively enlarge in the pituitary fossa. They can extend beyond the confines of the sella turcica into the cavernous sinus, suprasellar region, infrasellar region, and even invade the clivus.

These tumors can cause symptoms related to mass effect whereby the optic nerves and chiasm are compressed. Less commonly, cavernous sinus neural and vascular structures can be compressed. Patients with nonfunctioning adenomas can develop hypopituitarism as a result of direct compression of the normal functioning pituitary gland.

For those with pituitary adenomas, recurrence as a result of tumor invasion into surrounding structures (e.g. dural or cavernous sinus invasion) or incomplete tumor resection is a common occurrence.[7, 8] Long-term tumor remission rates after resection alone vary from 50% to 90%.[1, 2, 9-11]

In 1951, stereotactic radiosurgery was first described by Leksell as the "closed skull destruction of an intracranial target using ionizing radiation." [12] In 1968,

Leksell treated the first pituitary adenoma patient with the Gamma knife. Since that time, stereotactic radiosurgery has become an important tool in the neurosurgical treatment of patients with pituitary adenomas.

II. Radiosurgical Techniques

Radiosurgery is delivered via a multidisciplinary approach. At a minimum, the treatment team is comprised of a neurosurgeon, radiation oncologist, and medical physicists. For pituitary adenoma, patients, other members of the team may include an endocrinologist and an ophthalmologist.

Radiosurgery can be delivered using a variety of devices. Such devices include the Gamma Knife, modified linear accelerators (e.g. Cyberknife, Novalis, Trilogy, Synergy, etc), or cyclotrons producing charged particles such as protons. All of these devices have specific advantages and limitations inherent to their design and the type of energy utilized. However, the devices share a common goal of using target immobilization, image guidance, focal delivery of radiation to the target, and a steep fall off of radiation to the surrounding tissues.

In preparation for radiosurgery, many centers now institute a temporary cessation of antiseptory medications in the perioperative time period. In 2000, Landolt et al. first reported a significantly lower hormone normalization rate in acromegalic patients who were receiving antiseptory medications at the time of radiosurgery.[13] Since then, others have documented a counterproductive effect of antiseptory medications on the rate of hormonal normalization following radiosurgery.[14, 15] Depending upon the antiseptory agent's pharmacokinetics, 2 to 4 months cessation of the drug prior to radiosurgery seems prudent for most cases of functioning adenomas.[13, 14, 16]

The effective delivery of radiation to a target requires clear and accurate imaging of that target. Over 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 with enhanced coronal MR than with CT imaging.[17] An MRI sequence consisting of post-contrast, thin-slice (e.g. 1 to 1.5 mm) volume acquisition is typically utilized to define the tumor within the sellar region.

In patients with previous surgery, fat suppression techniques can prove useful for differentiating tumor from surgical fat grafts. CT is generally reserved for patients who cannot undergo an MRI (e.g. a patient with a pacemaker). PET imaging may also be used to define the location of a functioning adenoma for radiosurgical targeting.[18]

Through the strategic selection of beam entry, prescription dose, blocking patterns, and isodose selection, the borders of the adenoma can be encompassed and a suitable radiation dose delivered (Figure 1). The radiosurgical team should take into account the radiation fall off characteristics unique to the type of unit utilized. Also, prior treatment history such as surgery, radiation therapy, etc. should be factored into the timing, technique, and dose planning for each pituitary adenoma patient.



Figure 1 A Gamma Knife radiosurgery dose plan illustrating treatment of a pituitary adenoma (yellow) and the contouring of the lens and optic apparatus (blue).

III. Radiosurgical Goals and Results

Unlike most intracranial tumors, growth control alone is not the sole objective. Adenoma growth control following radiosurgery is important. However, for those with functioning adenomas, timely normalization of the overproduced hormone is of paramount importance. These goals can often be achieved.

Nevertheless, one does not want to have the cure be worse than the disease. Radiosurgery should be performed in a way so as to minimize the risks of neurovascular injury (e.g. to the optic apparatus, cavernous sinus structures) and to the normal functioning pituitary gland. Radiosurgical results for pituitary adenoma patients treated at the University of Virginia are summarized in Table 1.

Summary of the University of Virginia's Radiosurgical Results for Pituitary

Adenoma Patients

A. Pituitary Adenoma Growth Control

Control of adenoma growth is one goal for radiosurgery in patients with pituitary adenomas. Tumor control is defined as either an unchanged or decreased volume on follow-up radiological imaging studies. In major published series, stereotactic

radiosurgery afforded excellent control pituitary adenomas.[19-34] The majority of studies reported achievement of greater than 90% tumor control. Some series have even demonstrated improvement in visual function following radiosurgery related to shrinkage of the tumor.[20, 22, 30, 34-37] However, most pituitary adenomas are slow growing tumors. As such, it is important to perform long-term neuro-imaging follow-up of radiosurgical patients. Our experience has been that the longer the follow-up the more likely a patient's pituitary adenoma falls into one of two categories—tumor enlargement or tumor reduction. Tumor stability may simply be a result of limited follow-up after radiosurgery.

B. Radiosurgery for Cushing's Disease

Cushing's disease, perhaps the most famous of pituitary disorders, was described by Harvey Cushing in 1912 as a polyglandular disorder.[38] It was not until 1933 that Cushing first performed neurosurgery to treat a patient with a basophilic pituitary adenoma presumed to be secreting excess ACTH.[38] Over the years, neurosurgeons and endocrinologists have debated the criteria for defining "cure" for Cushing's disease.[39] Currently, most centers define an endocrinological remission as a 24-hour UFC in the normal range coupled with the resolution of clinical stigmata, or a series of normal post-operative serum cortisol levels obtained throughout the day (range 5.4-10.8 micrograms/dl or 150-300 nmol/liter).[40]

Fifteen series utilized the urine cortisol collection as part of the criteria for endocrinological evaluation [2, 5, 15, 19-26, 28, 31, 34, 41-47]. In those series with at least ten patients and a median follow-up of 2 years, endocrinological remission rates range from 17% to 83%. The wide range of endocrinological remission rates are likely a result of the testing utilized and the practice of some centers to perform testing while patients remain on steroid synthesis inhibiting agents (e.g. ketoconazole). Some cases of delayed recurrence following initial radiosurgical remission have been observed at the University of Virginia. Delayed recurrence underscores the need for long-term periodic endocrinologic testing.

C. Radiosurgery for Acromegaly

The most widely accepted guidelines for remission in acromegaly consist of a GH level less than 1 ng/ml in response to a glucose challenge and a normal serum IGF-1 when matched for age and gender.[48-51]

Remission rates following radiosurgery for acromegaly vary from 0% to 100% [2, 15, 19-28, 31, 32, 34, 41, 46, 52-59]. In those series with at least ten patients and a median follow-up of 2 years, endocrinological remission rates still vary with a wide range (4.8% to 96%). Certainly, some of the variation in endocrinological remission rates with acromegaly may be attributed to the inconsistent criteria defining remission. Another confounding variable is the degree to which somatostatin analogs may have been utilized during the time of radiosurgery and subsequent endocrinological evaluation in each of the series.

D. Radiosurgery for Prolactinoma

Most prolactinomas are treated effectively through medical management. For those patients who are refractory to or unable to tolerate dopamine agonist

medications, radiosurgery represents an alternative. Most endocrinologists define remission as a patient who has a normal serum prolactin level for gender. Reported radiosurgical remission rates for prolactinoma patients vary from 0% to 84% [2, 3, 14, 15, 19-25, 27, 28, 32, 34, 41, 42, 45, 46, 56, 57, 59, 60]. In our series of patients,[16] we observed a significant improvement in prolactinoma remission in patients who were not receiving antisecretory medications at the time of their radiosurgery. At most centers including our own, the endocrinological remission rate for prolactinoma patients appears lower than that for Cushing's disease or acromegaly patients.

IV. Complications following Radiosurgery for a Pituitary Adenoma

Much has been written about the complications that can occur following radiosurgery for a pituitary adenoma. As higher doses are used for those with functioning adenomas, these patients may be at greater risk for post-operative complications. With the exception of delayed hypopituitarism, the risk of post-radiosurgical complications for pituitary adenoma patients is fortunately quite rare.

Hypopituitarism occurs in approximately 20-40% of pituitary adenoma patients following radiosurgery. Usually, the decrease occurs in one or two pituitary hormones although theoretically the entire normally functioning gland is at risk of radiation injury. Hormonal replacement may be prudent in patients that demonstrate delayed hypopituitarism following radiosurgery.

Cranial nerve dysfunction is much rarer and appears to occur in less than 1% of patients. Temporary and permanent damage to the optic apparatus and to nerves in the cavernous sinus following radiosurgical treatment of a pituitary adenoma has been reported. Other reported complications have included radiation injury to the hypothalamus and temporal lobe. Injury to the carotid artery and radiosurgical induced neoplasia although possible is exceedingly rare.

V. Conclusions

Although not usually an initial treatment for patients with pituitary adenomas, stereotactic radiosurgery has been proven to be a safe and highly effective treatment for patients with recurrent or residual pituitary adenomas. Radiosurgery affords effective growth control and hormonal normalization for pituitary adenoma patients. Generally, radiosurgery does so with a shorter latency period than that of fractionated radiotherapy. This short latency period before remission can usually be bridged with suppressive medications.

The complications (e.g. radiation induced neoplasia, cerebral vasculopathy, etc.) associated with radiosurgery are infrequent. Radiosurgery can sometimes be used as a primary treatment for those patients deemed unfit for microsurgical resection as a result of other comorbidities or with demonstrable a pituitary adenoma in a surgically difficult to assess location (e.g. the cavernous sinus).

Table 1

Tumor	# Treated	# Evaluable	Remission	Time (months)	Pituitary Deficiency
Acromegaly	137	91	53%	29.8	34%
Cushing's	113	90	54%	13	22%
Nelson's	27	23	20%	50	28%
Prolactinoma	28	23	26%	24.5	38%

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