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Efficacy and Safety of Higher Dose Stereotactic Radiosurgery for Functional Pituitary Adenomas: A Preliminary Report

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Key words
- 35 Gy
- Gamma-knife surgery
- Optic apparatus
- Optic nerves
- Pituitary adenoma
- Stereotactic radiosurgery

Abbreviations and Acronyms
ACTH: Adrenocorticotropic hormone
GH: Growth hormone
MRI: Magnetic resonance imaging
SRS: Stereotactic radiosurgery
TSH: Thyroid stimulating hormone


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OBJECTIVE: **Single fraction stereotactic radiosurgery (SRS) is a common adjuvant therapy for hormonally active pituitary adenomas when surgical resection fails to control tumor growth or normalize hypersecretory activity. Marginal doses of 20–24 Gy are used at many centers and here we report our outcome data in patients treated with a higher marginal dose of 35 Gy.**

METHODS: **Thirty-one patients with secretory pituitary adenomas (adrenocorticotropic hormone, $n = 15$; growth hormone, $n = 13$; prolactin, $n = 2$; thyroid-stimulating hormone, $n = 1$) were treated with 35 Gy to the 50% isodose line, and had a mean follow-up time of 40.2 months (range = 12–96). All patients were evaluated post-SRS for time to hormonal normalization, time to relapse, as well as incidence and time course of radiation-induced hypopituitarism and cranial neuropathies.**

RESULTS: **Initial normalization of hypersecretion was achieved in 22 patients (70%) with a median time to remission of 17.7 months. After initial hormonal remission, 7 patients (32%) experienced an endocrine relapse, with a mean time to relapse of 21 months. New endocrine deficiency within any of the five major hormonal axes occurred in 10 patients (32%). One patient (3%) developed new-onset unilateral optic nerve pallor within the temporal field 3 years after SRS. Three patients (10%) reported transient new or increasing frontal headaches of unclear etiology following their procedures.**

CONCLUSION: **Time to endocrine remission was more rapid in patients treated with 35 Gy, as compared to previously reported literature using marginal doses of 20–24 Gy. Rates of endocrine remission and relapse, post-SRS hypopituitarism, and radiation-induced sequelae were not increased following higher dose treatment.**

INTRODUCTION

Tumor shrinkage following fractionated radiotherapy for pituitary adenomas has been shown to be slow and incomplete, associated with a high rate of hypopituitarism and secondary tumor development, and implicated in the development of neuropsychiatric side effects related to temporal lobe radiation (7, 21). Gamma Knife radiosurgical treatment of secretory pituitary adenomas results in normalization of hormone levels faster than fractionated radiotherapy, and can normalize

hormone levels in patients who have failed prior fractionated radiotherapy (13, 15). The additional benefit of limiting radiation to extrapituitary tissues has therefore resulted in single-fraction stereotactic radiosurgery (SRS) becoming a common adjuvant to surgery for hormonally active pituitary adenomas (42). This is particularly the case when surgical resection fails to control tumor growth or normalize hypersecretory activity. However, success in achieving hormonal normalization in these secretory tumors has been highly variable, with reported rates of 10%–100% for Cushing disease, 0%–100% for acromegaly, and 0%–84% for prolactinomas (10). Retrospective reviews have yielded more reproducible rates of 35%–83% for Cushing disease, 42%–60% for acromegaly, and 26%–43% for prolactinomas (3, 10). Relapse rates have been reported of 20%–48% for Cushing disease (2, 9, 45), but have been relatively unreported for the remaining hormones.

The literature is varied with regards to the effect of prescription dose, tumor volume, secretory type, and/or initial hormonal levels as predictors of treatment outcome (3). Regardless, it is not unreasonable to presume that higher treatment doses might achieve both more rapid endocrine responses as well as a higher rate of hormonal normalization. Indeed, there are some reports to suggest that higher marginal doses may result in faster tumor shrinkage, with Sheehan et al. recently demonstrating that tumor margin dose is inversely correlated with time to endocrine remission (43).

Single-fraction marginal doses of 20 Gy were calculated to be radiobiologically equivalent to 50–110 Gy delivered in 2-Gy fractions, and therefore marginal doses of 20–24 Gy are often chosen for treating patients with functional pituitary adenomas (6, 28, 31, 46). Concern about radiation-induced optic neuropathy (18, 29, 44, 48) has lead most centers to limit the dose to the optic apparatus to 8–10 Gy. This dose constraint is usually attainable with marginal doses of 20–24 Gy, but can limit the ability to employ higher doses in many patients.

At the time of starting the Gamma Knife radiosurgery program at Yale–New Haven Hospital, a decision was made, based upon prior institutional experience with linear accelerator radiosurgery for functional adenomas, to prospectively escalate the marginal dose to 35 Gy to try to improve outcome. We now report our retrospectively evaluated outcome data for patients with functional adenomas, treated at our single institution under this prospectively established policy, in order to determine the safety and efficacy of using a marginal dose of 35 Gy.

METHODS

Patient Population

We performed an institutional review board–approved retrospective review of medical records at the Yale–New Haven Hospital Gamma Knife Center for all patients ($n = 54$) who underwent SRS for secretory pituitary adenomas between January 1, 1998, and December 31, 2009. Data on patient demographics (age and sex), initial disease state (magnetic resonance imaging [MRI] characteristics, neuroendocrine status, clinical symptoms, and use of hormonal antisecretory or replacement medications), surgical history, tumor pathology, and Gamma Knife radiation treatment (dose, volume) were tabulated. Posttreatment data on hormonal status, medication requirements, MRI characteristics, clinical symptoms, and complications were also extracted. Only patients with a minimum of 12 months of follow-up after SRS were included in our analyses. All patients were evaluated for time to cure, time to endocrine relapse, and time course of any radiation-induced sequelae.

SRS Treatment Protocol and Follow-Up

All SRS procedures were performed using the Leksell Gamma Knife 4C radiosurgery machine with the associated Gamma Plan software (Elekta, Stockholm, Sweden). All study patients were prescribed 35 Gy to the tumor margin defined as the 50% isodose line in a single fraction. Tumor dosing adjacent to the optic apparatus was adjusted using shot selection, shot weighting, and shot plugging to reduce the dose to less than 8–10 Gy in all cases. Additionally, all patients had their suppressive hormone therapy withdrawn prior to the initiation of SRS given a reported counterproductive effect of antisecretory medications on the rate of hormone normalization following radiosurgery (14, 16, 36). The patients were followed with standard MRI at 6 months, 12 months, and every 1 year after. There is no capability to analyze follow-up imaging data by volumetrics at our institution and therefore standard length, width, and height measurements were used to assess tumor size change following treatment.

Hormonal Evaluations and Definitions

Assessment of each patient as hypersecretory, hyposecretory, or normal in all four pituitary-controlled axes (growth hormone [GH], cortisol, prolactin, and thyroid) was performed at all follow-up time points. Two independent researchers performed assignment of hormone status with conflicts resolved by committee discussion. Remission of hypersecretory states were defined by normalization of hormone levels at any follow-up time point, with the first follow-up starting 3 months post-SRS. Patients who continued to require suppressive medications or required an additional radiosurgical or surgical intervention were not considered to have achieved remission, regardless of hormone status. Of note, the time interval between discontinuation of suppressive medications and hormonal testing was always at least 6 months in length. Specifically, remission in acromegalic patients was defined as age and sex normalized serum insulin-like growth factor 1 levels off of any dopamine agonists, somatostatin analogues, and/or GH receptor antagonists. Cushing disease remission was defined as normalization of 24-hour urinary free cortisol excretion off any adrenolytic therapy. In patients rendered hypoadrenal, the clinical documentation of this condition based on serum cortisol levels and replacement therapy with exogenous glucocorticoids was accepted as remission. Prolactinoma remission was defined as normalization of serum prolactin levels off of any dopamine agonists. Thyrotropinoma remission was defined as a thyroid-stimulating hormone (TSH) level within the normal range in addition to a normalized free T4 level off somatostatin analogues. Of note, patients whose hormonal levels initially normalized off suppressive medications, but then subsequently required reinitiation of these medications secondary to rising hormone levels, were included in the relapse category.

Conversely, for hormonal hyposecretion, GH deficiency was defined as a post–pharmacologic stimulation GH level >5 ng/mL or >10 ng/mL if the stimulus consisted of the combination of GH-releasing hormone and arginine, or insulin-like growth factor 1 levels below the