Stereotactic Radiosurgery for Acromegaly

Cheng-Chia Lee, Mary Lee Vance, Zhiyuan Xu, Chun-Po Yen, David Schlesinger, Blair Dodson, and Jason Sheehan

Departments of Neurological Surgery (C.-C.L., M.L.V., Z.X., C.-P.Y., D.S., B.D., J.S.), Radiation Oncology (J.S.), and Medicine (M.L.V.), University of Virginia, Charlottesville, Virginia 22908; and Department of Neurosurgery, Neurological Institute, Taipei Veterans General Hospital (C.-C.L.), and School of Medicine, National Yang-Ming University (C.-C.L.), Taipei, Taiwan 11217, Republic of China

Context: The role of stereotactic radiosurgery (SRS) in acromegaly is being assessed.

Objective: We evaluated the efficacy and safety of SRS for patients with acromegaly. Prognostic factors related to outcomes were also analyzed.

Design: This was a retrospective study of patients treated with SRS at the University of Virginia; the data were collected from 1989 to 2012, with a median follow-up of 61.5 months.

Patients: A total of 136 patients underwent SRS for acromegaly. Diagnosis of acromegaly was based on the combination of clinical features and biochemical assessment, including the serum GH level and age- and gender-matched serum IGF-1 level. All patients underwent a complete endocrine evaluation, neuroimaging study, and ophthalmic examinations before SRS.

Main Outcome Measures: After withdrawal of GH- or IGF-1-altering medications, patients who had an oral glucose tolerance test GH of < 1.0 ng/mL or normal IGF-1 were considered in remission. Post-radiosurgical hypopituitarism was defined as a decrease in one or more hormones below normal.

Results: With a median follow-up of 61.5 months, 65.4% of the patients achieved remission. The mean time to remission was 27.5 months. The actuarial remission rates at 2, 4, 6, and 8 years after radiosurgery were 31.7, 64.5, 73.4, and 82.6%, respectively. Favorable prognostic factors for remission included a higher margin radiation dose, higher maximum dose, and lower initial IGF-1 level. New pituitary hormone deficiency occurred in 43 patients (31.6%); two patients (1.5%) developed panhypopituitarism. Corresponding risk factors for new pituitary hormone deficiency were a margin dose > 25 Gy and tumor volume > 2.5 mL. Other complications included an adverse radiation effect in one patient, visual deterioration in four, and new oculomotor nerve palsy in one.

Conclusion: SRS affords a reasonable rate of endocrine remission in patients with acromegaly and generally does so with a low rate of adverse effects. **(*J Clin Endocrinol Metab* 99: 1273–1281, 2014)**

Although surgical resection is the usual initial treatment for patients with acromegaly, resection does not always lead to a remission. For residual tumors and hormone overproduction, adjuvant therapies including medications to lower GH and/or IGF-1 also play important roles. Radiation therapy and, more recently, stereotactic radiosurgery (SRS) are used to treat patients with persistent acromegaly after failed resection with the goal of achieving remission.

Gamma-knife radiosurgery is a type of SRS that uses radioactive ^{60}Cobalt to deliver a high dose of radiation to the target with a steep radiation fall-off to surrounding critical structures in the brain. Although SRS and traditional fractionated radiation therapy for acromegaly have not been compared in a prospective fashion, a review of the literature by Loeffler and Shih (1) demonstrated a role for SRS in the management of patients with acromegaly. SRS may provide a faster rate of endocrine remission than

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

Received October 9, 2013. Accepted January 16, 2014.
First Published Online January 28, 2014

Abbreviations: MR, magnetic resonance; MRI, MR imaging; OGTT, oral glucose tolerance test; SRS, stereotactic radiosurgery.

traditional fractionated radiation therapy. To date, several studies have included patients who received SRS for acromegaly (2–15). In this study, we evaluated the results of SRS in patients with acromegaly. In particular, we evaluated the rate and timing of endocrine remission as well as the rate, pattern, and timing of development of new pituitary hormone deficiency.

Patients and Methods

Patients

This study was a retrospective review of a prospectively collected gamma-knife database between 1989 and 2012. A consecutive series of 136 patients with acromegaly underwent SRS at the University of Virginia. The study was approved by the Institutional Review Board of the University of Virginia. Initial diagnosis of acromegaly was based on the combination of clinical features of acromegaly and biochemical assessment according to recommended endocrine guidelines (16).

All patients underwent a comprehensive endocrine evaluation, neuroimaging study, and neuro-ophthalmic examination before SRS. Endocrine studies included GH, IGF-1, ACTH, serum cortisol, prolactin, T_4 or free T_4, TSH, LH, FSH, and T (men) levels. In women of premenopausal age (<50 y), the history of menstrual cycles was used to assess gonadal function. Only two patients (1.5%) underwent an insulin tolerance test or ACTH stimulation test to assess cortisol response, and 46 patients (33.8%) had an oral glucose tolerance test (OGTT) before SRS. At the University of Virginia, both GH and IGF-1 were assessed by solid-phase, enzyme-labeled chemiluminescent immunometric assays on the Immulite 2000 (Siemens) until August, 2012; thereafter, the Quest (Nichols) IGF-1 (tandem mass spectrometry) assay was used.

Imaging studies consisted of magnetic resonance imaging (MRI) with and without contrast using thin slices and volume acquisition through the region of the sella turcica. All patients were evaluated by a neuro-ophthalmologist at the University of Virginia before SRS. The ophthalmological evaluation included visual acuity and visual field testing, which includes not only confrontational field testing but also automated perimetry.

Surgical treatment

Patients who had a confirmed diagnosis of acromegaly underwent transsphenoidal surgery as the first treatment. Other treatments, including medications to lower GH and/or IGF-1 and SRS, were recommended for those with persistent acromegaly and a demonstrable tumor on MRI after at least one prior resection. In two patients who had significant comorbidities precluding a resection, SRS was the initial treatment.

Medical treatment

Medications for acromegaly including a somatostatin analog (octreotide), a dopamine agonist (cabergoline or bromocriptine), or a GH antagonist (pegvisomant) were used to lower GH production or block the action of GH. Endocrinologists prescribed these medications at their discretion, but typically in concert with discussion with a neuro-endocrinologist at our center (M.L.V.). In this series, a total of 34 patients (25%) received anti-GH medications before SRS: 26 patients took octreotide-LAR, three took pegvisomant, one took bromocriptine, one took both octreotide-LAR and pegvisomant, one took both octreotide-LAR and cabergoline, and two took both pegvisomant and bromocriptine.

Inclusion criteria

Patients were included in the study if they had a diagnosis of acromegaly and had a minimum of 12 months of clinical, endocrine, and radiographic follow-up. Based on these requirements, 14 (9.3%) patients were excluded due to insufficient follow-up.

Gamma-knife radiosurgery

The procedure for gamma-knife surgery has been previously described (2, 5, 8, 17). Informed consent was obtained for the SRS. In brief, all patients underwent stereotactic frame placement in the operating room with iv-monitored anesthesia and then had MRI stereotactic treatment planning neuroimaging. Radiosurgery was performed using the Leksell Gamma Unit Model 4C (Elekta AB) between 2001 and 2007 and the Perfexion model (Elekta AB) thereafter. Treatment parameters and dose planning varied according to the patient's clinical presentation, neurological and ophthalmological examination, and tumor location as delineated on the planning MRI study. In general, the prescription dose was placed at an isodose level of 50%, and the median margin dose was 25 Gy (range, 18–30 Gy). Any identifiable portion of the optic nerve was generally constrained to receive a dose of 8 Gy or less. Factors considered in dose planning included tumor size, the distance between the tumor and the optic apparatus, previous treatments (eg, prior radiation therapy), and pre-SRS visual deficits.

Clinical, hormone, and imaging evaluations

After SRS, all patients underwent clinical evaluation, comprehensive endocrine evaluation, and MRI studies at 6-month intervals for the first 2 years and then yearly thereafter. Remission was defined as a normal age- and gender-matched serum IGF-1 level and, in some patients, a GH level less than 1 ng/mL after OGTT off of any medication to lower GH and/or IGF-1. Because our institution is a tertiary referral center with patents drawn from afar, not all patients were able to return for an OGTT.

Patients receiving long-acting GH suppressive medications (octreotide-LAR,) were tested after stopping the medication for 2 months (long-acting somatostatin analogs, while given once a month, have been shown to suppress GH and IGF-1 production for 6–8 wk). Thus, a 2-month discontinuation of a somatostatin analog was believed to be adequate to assess the response to gamma-knife treatment. Patients treated with the GH receptor antagonist, pegvisomant, were tested after stopping the drug for 2–3 weeks, as were patients treated with cabergoline or bromocriptine; given the half-life of these drugs, it was believed that this was an adequate amount of time off of medication to assess the effect of SRS. All endocrine testing used to ascertain whether endocrine remission was achieved was performed off suppressive medications. Patients who were symptomatic or incompletely controlled on suppressive medications did not have their medical therapy halted during testing so as not to worsen their condition. However, test results obtained on medical therapy were not used to define an endocrine remission.

New pituitary hormone deficiency was defined as follows. Thyrotroph deficiency was defined by a low free T_4 level with

normal or diminished TSH. ACTH deficiency was defined as a subnormal serum cortisol level with a concomitant low ACTH level. Gonadotroph deficiency was defined by a low plasma T with nonelevated gonadotropin levels in men, amenorrhea with low plasma estradiol and low or normal gonadotropins in premenopausal women, and a lack of increased gonadotropins in postmenopausal women. Although these patients had GH oversecretion, somatotroph deficiency was found several years after SRS. It was defined by a subnormal response of GH to an insulin tolerance test (peak GH $<$ 5 ng/mL).

Because some of the follow-up information came from referring endocrinologists, and because those followed at the University of Virginia were seen at variable times, it was not practical to obtain early morning values in most patients. Thus, interpretation of total T and serum cortisol levels was problematic. In men who had a free T level measured, this and the clinical history of libido and erectile function were used to determine whether a man developed hypogonadism (total T levels decline during the day; if the free T level was normal, this was considered sufficient in the light of normal libido and erectile function). Regarding cortisol levels, patients seen at the University of Virginia also had an ACTH measured, and both cortisol and ACTH, as well as the clinical history, weight, and blood pressure, were used to assess the need for glucocorticoid replacement.

Regarding the radiographic assessment, the aim of imaging follow-up was to determine whether or not there were any volume changes in the adenoma and to detect the presence of any adverse radiation changes. Tumor control was defined as no change in tumor volume or a decrease in the size of the adenoma. Tumor growth was defined as an increase in the adenoma volume by more than 10%. Tumor regression was defined as a decrease in the adenoma volume by more than 10% (18).

Ophthalmological assessments were typically performed at yearly intervals. Follow-up ophthalmology examinations were usually conducted by the patient's local ophthalmologist. If a patient developed any visual symptoms after SRS and returned to the University of Virginia for follow-up, that patient was seen by the neuro-ophthalmologist for evaluation and treatment.

Statistics

Descriptive statistics for all data were presented as the median and range for continuous variables and as frequency and percentages for categorical variables. Prognostic variables associated with remission (eg, age, gender, margin radiation dose, maximum radiation dose, tumor volume, tumor extension, pre-SRS management, and prior endocrine function) were evaluated using binary logistic regression. Prognostic variables associated with time to remission were evaluated using Cox univariate and multivariate analysis. Actuarial time to remission was analyzed using the Kaplan-Meier method.

Prognostic variables related with time to post-SRS new pituitary hormone deficiency (eg, gender, margin radiation dose, maximum radiation dose, tumor volume, tumor extension, or pre-existing hypopituitarism) were evaluated using Cox univariate and multivariate analysis. Actuarial time to development of new hormone deficiency was analyzed using the Kaplan-Meier method. Statistical significance was a P value less than .05. All analyses were completed using commercial statistical software (version 20.0; IBM SPSS).

Results

Patient and tumor characteristics

The median age of the patients was 44 years (range, 14–93 y), and the number of female patients was higher than males (74 females, 62 males). The median pre-SRS tumor volume was 2.3 mL (range, 0.3–16.0 mL), based on volumetric calculations from magnetic resonance (MR) images. Fifty-six (41.2%) patients had an adenoma extending into the cavernous sinus, and 12 tumors (8.8%) extended to the suprasellar region. All but two patients who underwent SRS had undergone transsphenoidal surgery. These two patients were deemed to be at high risk for surgery because of extensive comorbidities. Ten patients (7.4%) had received previous fractionated radiation therapy. The median interval between conventional radiotherapy and SRS was 5 years (range, 2.8–25.3 y). Patients were only treated with SRS if they did not achieve remission from prior radiation therapy. Pretreatment hormone deficits were present in 40 patients (29.4%), and 34 of them (85%) had regular endocrine replacement. The most common pre-existing hormone deficiencies were hypothyroidism (n = 22) and hypogonadism (n = 17), and then hypocortisolism (n = 11). In this series, a total of 34 patients received anti-GH medications before SRS: 15 patients were taking medication at the time of SRS, and 19 patients were instructed to temporarily cease the use of these medications 6 to 8 weeks before radiosurgery and resume medical therapy 2–6 weeks afterward. Sixty-nine patients (50.7%) had follow-up longer than 5 years and 24 patients (17.6%) longer than 10 years (Table 1).

Imaging outcomes

The median imaging follow-up after SRS was 43.5 months (range, 12–191 mo). In all, 84, 34, 23, and 12 patients had two or more, four or more, six or more, and eight or more years of follow-up. On their last available MRI studies, a decrease in tumor volume was observed in 64 patients (47.0%), 70 patients (51.5%) had no change in tumor size, and two patients (1.5%) experienced tumor enlargement. Thus, the overall tumor control rate was 98.5%. The actuarial tumor control rates at 2, 4, 6, and 8 years after radiosurgery were 100, 98.1, 98.1, and 97.5%. The typical post-SRS tumor volume and endocrine changes in acromegaly patients are illustrated in Figure 1.

A decrease in tumor size and endocrine remission occurred in 41 patients (64.1%). No patient who exhibited tumor enlargement achieved endocrine remission.

Endocrine remission

All endocrine testing used to ascertain whether endocrine remission was achieved was performed off medical therapy that suppressed IGF-1 or GH. At last follow-up,

Table 1. Characteristics in 136 Patients With Acromegaly Treated With SRS

Characteristics	Value	Range	%
Median age, y	44	14–93	
Sex (F:M), n	74:62		
Median tumor volume, mL	2.3	0.3–16.0	
No. of patients with CS extension	56		41.2
No. of patients with suprasellar extension	12		8.8
No. of prior TSS	134		98.5
0	2		
1	114		
2	18		
3	2		
No. of prior craniotomy	8		5.9
No. of prior RT	10		7.4
Median pre-SRS IGF-1 level, pg/mL	528.5	181–1800	
Median pre-SRS GH level, pg/mL	4.3	0.6–108.0	
Pretreatment hormone deficiency	40		29.4
Hypothyroidism	22		
Hypogonadism	17		
Hypoadrenalism	11		
Pre-SRS endocrine replacement	34		85.0[a]
Median imaging FU, mo	43.5	12–191	
Median endocrine FU, mo	61.5	12–191	
SRS treatment parameters			
Median margin radiation dose, Gy	25.0	8.8–30.0	
Median maximal radiation dose, Gy	50.0	20.0–62.5	
Median isodose level, %	50.0	25–70	
Median treatment volume, mL	3.0	0.3–16.0	

Abbreviations: CS, cavernous sinus; F, female; FU, follow-up; M, male; RT, radiotherapy; TSS, transsphenoidal surgery.

[a] 85% of patients who had pre-SRS hormone deficiency were receiving hormone replacement at time of SRS.

18 of 27 patients (66.7%) had both normal age- and gender-adjusted IGF-1 and suppression of GH < 1.0 μg/L during an OGTT; 73 of 109 patients (67.0%) had normal age- and gender-adjusted IGF-1 after a median follow-up of 61.5 months (range, 12–191 mo). Thus, a total of 91 patients (66.9%) achieved endocrine remission. The median time from radiosurgery to remission was 29 months based on IGF-1 plus OGTT and 24 months based on IGF-1 alone (Tables 2 and 3). The actuarial remission rates at 2, 4, 6, and 8 years after radiosurgery were 31.7, 64.5, 73.4, and 82.6% (Figure 2A).

Radiation dose, including margin dose or maximum dose, and pre-SRS IGF-1 levels were statistically significant factors portending endocrine remission (Table 4). The *P* values for margin dose, maximum dose, and pre-SRS IGF-1 level were .05, .05, and .011 with Cox univariate regression analysis, respectively. The median margin and maximum doses were 25 and 50 Gy, respectively. Those treated with a margin dose $>$ 25 Gy and a maximum dose $>$ 50 Gy were likely to achieve remission more rapidly (Figure 2, B and D). The pre-SRS IGF-1 level also correlated with endocrine outcome: the patients who had the elevated IGF-1 $\leqq$ two times normal for age and gender before SRS were likely to achieve remission more rapidly (Figure 2C). With Cox multiple analysis, the pre-SRS IGF-1 level was a strong predictor of endocrine outcome ($P = .002$) (Table 4).

Seven patients (7 of 89; 7.9%) who achieved remission after SRS had a recurrence. The median interval between normalized IGF-1 and recurrence (elevated IGF-1 level) was 42 months (Tables 2 and 3). In those patients with recurrence, the median tumor volume before SRS was 4.1 mL, and the median prescribed margin dose was 25 Gy. However, in those patients with and without recurrence, there was no statistically significant difference in tumor volume, radiation dose, or pre-radiosurgical clinical parameters ($P > .050$ for each parameter). One patient underwent repeat SRS after recurrence; that patient exhibited an out of field tumor recurrence on a follow-up MRI; after a second SRS, remission was again achieved, and the patient remains in remission 78 months after the second SRS. The other six patients were treated medically.

New hormone deficiency after SRS

New hormone deficiencies after SRS developed in 43 patients (31.6%). The median time to development of the new hormone deficits was 50.5 months (range, 8–127 mo) after SRS. In Kaplan-Meier analysis, the actuarial rates of post-SRS hormone loss at 2, 4, 6, and 8 years after radiosurgery were 2.5, 10.7, 29.0, and 44.3% (Figure 2E). The distribution of new hormone deficits is illustrated in Figure 2F. The most common new hormone deficiencies were hypothyroidism and hypogonadism, and they typically occurred 4–5 years after SRS. Among these 43 patients, two (1.5%) eventually developed panhypopituitarism, at a median time of 58 months (range, 22–64 mo).

Higher margin dose and larger tumor volume were the most important prognostic factors for development of new hormone deficiency (Table 5). The hazard ratios of margin dose $>$ 25 Gy were 2.84 in Cox univariate analysis and 2.68 in Cox multivariate analysis. The *P* values for the difference were .015 and .021, respectively. The hazard ratios of tumor volume $>$ 2.5 mL were 2.34 in Cox univariate analysis and 2.22 in multivariate analysis. The *P* values for an adenoma $>$ 2.5 mL related to post-SRS hypopituitarism were .016 in univariate and .025 in multivariate analysis, respectively. Other factors including gender, maximum dose, tumor extension to the suprasellar region or tumor present in the cavernous sinus, and pre-

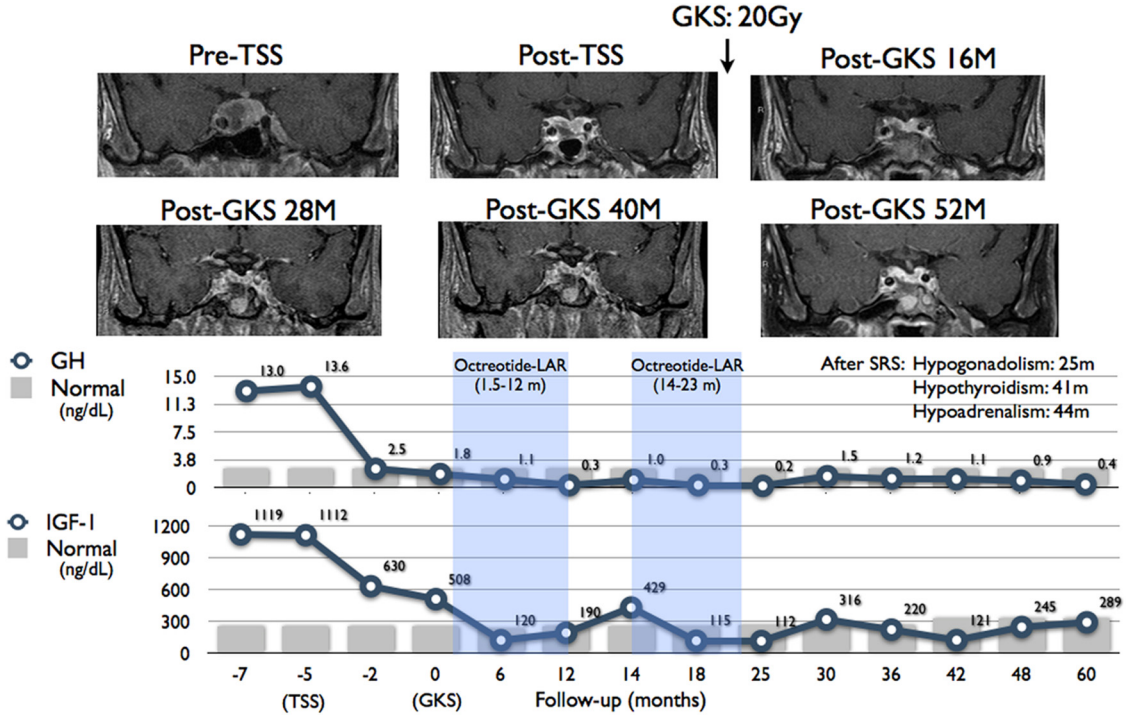

Figure 1. SRS was performed for a 39-year-old man with residual adenoma after surgical resection. Although the patient failed to discontinue the long-acting octreotide once, endocrine remission was achieved 23 months after SRS. He developed new hormone deficiencies, including hypogonadism at 25 months, hypothyroidism at 41 months, and hypoadrenalism at 44 months after SRS. TSS, transsphenoidal surgery; GKS, gamma-knife surgery.

existing hypopituitarism were not the prognostic factors related to the development of new hormone deficiency (Table 5).

Other radiosurgical complications

Four patients developed visual field deficits after SRS. All of these patients had tumor extension to the suprasellar or cavernous sinus region at the time of treatment. One patient had an asymptomatic adverse radiation effect with mild T2 changes in the right medial temporal lobe. The radiation effect resolved on subsequent MR scans; no intervention was required. New oculomotor cranial nerve palsy occurred in one patient at the 79th month of follow-up. No cerebrovascular accident or radiation-induced tumor was demonstrated in this series.

Discussion

Surgical resection is typically the primary treatment for patients with acromegaly. The rates of endocrine remission after a resection are related to the tumor size, the degree of invasiveness, and the surgical expertise (19, 20). Surgical resection led to a remission rate of 42 to 90% after a transsphenoidal surgery (21). For patients with residual disease, adjuvant therapy such as medication or radiation therapy is necessary. Although the effect of conventional external-beam radiation therapy has been well documented, it carries a risk of hypopituitarism for up to 70% of treated patients and much lower risks of visual disturbances, secondary malignancy, and cerebrovascular insults (22). Remission after conventional radiation therapy may require more than 5 years (23). As an alternative to radiation therapy, radiosurgery has been used to treat patients with pituitary adenomas. Acromegaly patients treated with SRS had a shorter time to remission when compared historically with those treated with fractionated radiation therapy (1). In one small series, the mean time to IGF-1 normalization was 1.03 years for those treated with SRS and 6.53 years for those treated with fractionated radiation therapy (23). From the perspective of time to

Table 2. Initial Hormone Outcomes in 136 Patients

Remission Criteria	No. of Patients	Remission, n (%)[a]	Median Time to Remission (Range), mo
IGF-1 normalization and OGTT GH <1 μg/dL	27	18 (66.7)	29 (11–102)
IGF-1 normalization	109	73 (67.0)	24 (5–142)

[a] Combined IGF-1 and OGTT GH data: 91 patients achieved remission after SRS.

Table 3. Acromegaly Recurrence after Initial Remission

Case No.	Tumor Volume, mL	Dose, Gy	Time to Remission After SRS, mo	Time to Recurrence After Remission, mo	Subsequent Treatment
1	3.5	20	27	41	Medication
2	4.1	25	16	32	Medication
3	5.4	25	35	43	Medication
4	1.5	25	26	47	Medication
5	4.4	25	19	42	Medication
6	6.8	25	10	22	Repeated GKS (16.2 Gy)
7	0.5	20	50	72	Medication
Median	4.1	25	26	42	

Abbreviation: GSK, gamma-knife surgery.

achieving remission, radiosurgery may afford better outcome compared with conventional radiotherapy (1).

To date, there are at least 25 published series that have included patients who received SRS for acromegaly (3, 4, 7–9, 11, 12, 24–26). Although the accuracy of a systematic analysis of SRS treatment is limited due to variation in patient selection, radiosurgical technique, length of follow-up, and endocrine criteria, a 17–65% remission rate has been reported to occur within 3–4 years. The current series has the largest (n = 136) and longest follow-up, showing that the actuarial remission rates 2, 4, 6, and 8 years after radiosurgery were 31.7, 64.5, 73.4, and 82.6%, respectively. The neurological complication rate including adverse radiation effects, visual deterioration, and new-onset cranial nerve palsy was 4.3%. The overall rate of new hypopituitarism after SRS was 31.6%. The use of SRS in treating patients with acromegaly after prior failed resection, therefore, seems reasonable.

Favorable factors for remission after radiosurgery have also been documented in prior reports. These factors include higher radiation dose and smaller tumor volume (2, 15). However, recent reports found that the radiation dose did not affect the rate of remission in patients, nor did tumor volume or tumor extension (7, 11, 27). However, initial serum GH and IGF-1 levels were significant predictive factors of outcome (7, 11, 28). Our series demonstrated that remission was not related to smaller tumor volume ($P = .931$), but remission was significantly related

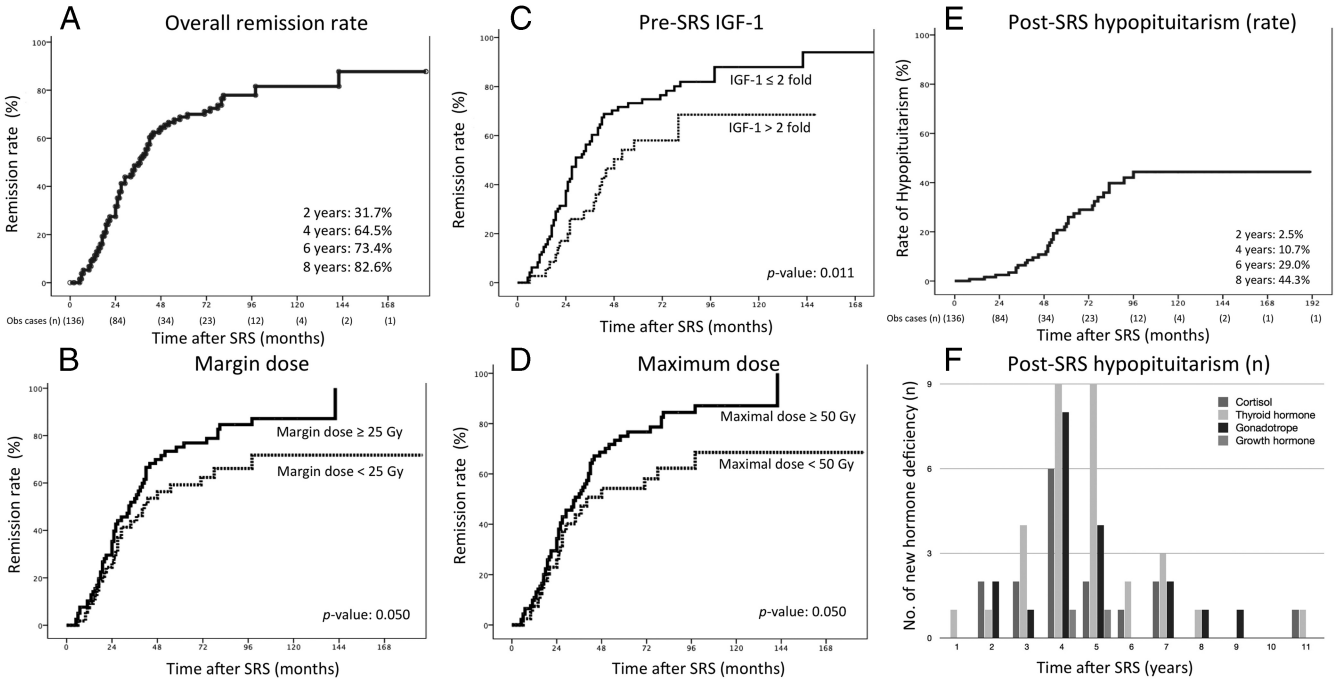

Figure 2. A, Kaplan-Meier analysis for endocrine remission after SRS. The number of patients having two or more, four or more, six or more, and eight or more years of follow-up were 84, 34, 23, and 12, respectively. The actuarial remission rates at 2, 4, 6, and 8 years after radiosurgery were 31.7, 64.5, 73.4, and 82.6%, respectively. B–D, Higher margin dose (B), a pre-radiosurgical IGF-1 level that was less than or equal to two times normal for age and gender (C), and higher maximum margin dose (D) were significantly related to the rate of endocrine remission ($P = .05$, .011, and .05, respectively). E, The incidence of hypopituitarism after SRS for acromegaly. The actuarial incidence rates at 2, 4, 6, and 8 years after radiosurgery were 2.5, 10.7, 29.0, and 44.3%, respectively. F, The distribution of specific hormone deficits after SRS. The highest incidence of hormone deficits occurred 4 to 5 years after SRS. Thyroid hormone was the most common deficiency.

Table 4. Prognostic Factors for Endocrine Remission

	Remission	Nonremission	Cox Univariate	Cox Multivariate
n	91	45		
Age, y	45.5 ± 12.9	44.0 ± 25.8	0.893	-
Gender (females)	51 (56.0)	23 (51.1)	0.408	-
Margin dose, Gy	22.9 ± 3.8	21.0 ± 4.9	**0.050**	0.706
Maximal dose, Gy	47.8 ± 6.4	44.6 ± 8.5	**0.050**	0.113
Tumor volume, mL	2.8 ± 2.3	3.5 ± 3.1	0.931	-
Tumor extension				
CS invasion	34 (39.5)	23 (51.1)	0.915	-
Suparsellar expansion	8 (8.8)	4 (8.9)	0.834	-
Pre-SRS radiotherapy	5 (7.7)	5 (11.1)	0.740	-
Initial IGF-1, ng/dL	531 ± 276	673 ± 351	**0.011**	**0.002**
Initial GH, ng/dL	5.8 ± 13.0	8.0 ± 14.4	0.453	-
Medication during SRS	15 (16.5)	10 (22.2)	0.218	

Abbreviation: CS, cavernous sinus. Data are expressed as number (percentage) or mean ± SD. Dashes are factors not tested as described in the statistical methods section. Bold *P* values are deemed statistically significant ($P \leq .05$).

to a higher margin radiation dose ($P = .05$), higher maximum dose ($P = .05$), and lower pre-SRS IGF-1 levels ($P = .011$). In multivariate analysis, a lower pre-SRS IGF-1 was the strongest prognostic factor for remission ($P = .002$).

Recurrence of acromegaly after a prior resection or radiation therapy has been described. Thus, recurrence after radiosurgery is not surprising. Recurrence of acromegaly after an initial SRS-induced remission appears rare, but the latency of such recurrence means that the true long-term rate of recurrence is likely underestimated. In this study, we noted 7.9% recurrence after initial SRS-induced remission. The fact that seven patients had a recurrence of acromegaly at a median time of 42 months after SRS emphasizes the importance of close and long-term follow-up of these, and all, patients with a pituitary tumor. It is well known that a pituitary adenoma may recur 20 or 25 years after treatment. In clinical practice, it is reasonable to see these patients every 6 months, with measurement of serum IGF-1. If the IGF-1 level is elevated, the patient should undergo an OGTT and MRI study.

The negative effect of somatostatin analogs on the results of SRS for acromegaly was first reported in 2000 (14, 29). Landolt et al (29) detailed the influence of octreotide on the results of SRS in 31 patients. They found that patients treated with octreotide at the time of SRS achieved a normal level of GH and IGF-1 after a significantly longer interval than patients who did not receive the drug (29). Pollock et al (14) reported similar results in 2002. As a result of these studies, we discontinued anti-GH medications for 6 to 8 weeks before SRS and resumed them 2–6 weeks after SRS. Larger, randomized clinical trials are still necessary to confirm the negative relationship between GH-suppressive medications and outcome of radiosurgery.

Hypothalamic-pituitary dysfunction is the most common intermediate to late complication of SRS of pituitary adenomas. In our series, 31.6% of patients developed a new hormone deficiency at a median of 50.5 months after radiosurgery. From the SRS experience in the literature, 30–50% of patients developed a delayed onset of hypopituitarism around 3 years after SRS (2, 8, 30–32). The thyroid function was affected most, and then gonadotropic hormone, ACTH, and GH (33). There appeared to be fairly consistent variables, including margin dose to the tumor and tumor volume, resulting in loss of pituitary function. Although an ideal radiosurgical dose plan has a

Table 5. Prognostic Factors for Development of New Hormone Deficiency After SRS

	Cox Univariate Analysis		Cox Multivariate Analysis	
	P Value	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)
Gender (female vs male)	.528	0.802 (0.404–1.591)	-	-
Margin dose (>25 vs <25 Gy)	.015	2.836 (1.229–6.545)	.021	2.683 (1.160–6.205)
Maximum dose (>50 vs <50 Gy)	.231	1.669 (0.722–3.858)	-	-
Tumor volume (>2.5 vs <2.5 mL)	.016	2.341 (1.174–4.665)	.025	2.200 (1.103–4.387)
Tumor extension				
Suprasellar extension (yes vs no)	.839	1.131 (0.345–3.708)	-	-
Cavernous sinus extension (yes vs no)	.483	0.775 (0.380–1.581)	-	-
Prior hormone deficiency	.613	0.821 (0.382–1.763)	-	-

Abbreviation: CI, confidence interval. Dashes are factors not tested as described in the statistical methods section.

steep gradient index that minimizes the dose to normal pituitary tissue, a true "safe dose" below which the patient avoids hypopituitarism does not exist. Furthermore, an optimal radiosurgical dose to the target lesion seems unwise to reduce for the sake of avoiding hypopituitarism. The clinical consequences of macroscopic tumor progression or recurrence or persistent hormone hypersecretion in acromegaly far outweigh those of radiosurgery-induced hypopituitarism that can readily be managed with hormone replacement therapies.

Very few patients have new-onset neurological deficits after SRS. The study did not include objective studies of neurocognitive function, although there were no reports by patients or referring physicians of memory or cognitive difficulties. We recently began to follow patients' cognitive function in a prospective fashion (34). The preliminary data suggest that SRS does not impair neurocognitive function after SRS for pituitary disease. We are continuing this study. Clearly, delayed complications, including effects on cognitive function, radiation-induced tumors, and cerebrovascular accidents, should be meticulously evaluated for in SRS patients.

Study limitations

This is a retrospective study, with several limitations, that involved a large number of patients treated at the University of Virginia, many of whom came long distances and were subsequently followed by their local endocrinologists. We relied on follow-up laboratory results, clinical notes, and MRI studies from these referring endocrinologists to assess the effect of gamma-knife treatment. Although this is not as rigorous as a controlled study because of the use of different laboratories and dependence upon information from referring endocrinologists, the information provided is as precise and extensive as possible for such a study in a large number of patients. Additionally, over the time period of the study, more sophisticated MR sequences (eg, dynamic studies) and higher field strength magnets have improved the detection rate of recurrence. Last but not least, for patients who underwent conventional radiotherapy before SRS, some adverse events could have been related to prior radiotherapy. We attributed them to the SRS if they occurred after the SRS was performed. Thus, the adverse events attributed to SRS may be an overestimate.

Conclusion

Acromegaly represents a challenging neuroendocrine disorder. Although resection represents the initial treatment for most patients, remission is not always afforded by microsurgery. SRS appears to be a reasonable management option for patients with persistent acromegaly. Loss of pituitary function remains the greatest complication after SRS. Longitudinal follow-up is required to detect latent effects from SRS and the possibility of recurrence after initial remission.

Acknowledgments

Address all correspondence and requests for reprints to: Jason Sheehan, MD, PhD, Department of Neurological Surgery, University of Virginia Health System, PO Box 800212, Charlottesville, VA 22908. E-mail: jsheehan@virginia.edu.

Disclosure Summary: The authors in this research have no relevant disclosures.

References

1. **Loeffler JS, Shih HA.** Radiation therapy in the management of pituitary adenomas. *J Clin Endocrinol Metab*. 2011;96:1992–2003.
2. **Sheehan JP, Pouratian N, Steiner L, Laws ER, Vance ML.** Gamma knife surgery for pituitary adenomas: factors related to radiological and endocrine outcomes. *J Neurosurg*. 2011;114:303–309.
3. **Yang I, Kim W, De Salles A, Bergsneider M.** A systematic analysis of disease control in acromegaly treated with radiosurgery. *Neurosurg Focus*. 2010;29:E13.
4. **Kobayashi T.** Long-term results of stereotactic gamma knife radiosurgery for pituitary adenomas. Specific strategies for different types of adenoma. *Prog Neurol Surg*. 2009;22:77–95.
5. **Jagannathan J, Yen CP, Pouratian N, Laws ER, Sheehan JP.** Stereotactic radiosurgery for pituitary adenomas: a comprehensive review of indications, techniques and long-term results using the gamma knife. *J Neurooncol*. 2009;92:345–356.
6. **Pollock BE, Brown PD, Nippoldt TB, Young WF Jr.** Pituitary tumor type affects the chance of biochemical remission after radiosurgery of hormone-secreting pituitary adenomas. *Neurosurgery*. 2008;62:1271–1276; discussion 1276–1278.
7. **Losa M, Gioia L, Picozzi P, et al.** The role of stereotactic radiotherapy in patients with growth hormone-secreting pituitary adenoma. *J Clin Endocrinol Metab*. 2008;93:2546–2552.
8. **Jagannathan J, Sheehan JP, Pouratian N, Laws ER Jr, Steiner L, Vance ML.** Gamma knife radiosurgery for acromegaly: outcomes after failed transsphenoidal surgery. *Neurosurgery*. 2008;62:1262–1269; discussion 1269–1270.
9. **Vik-Mo EO, Oksnes M, Pedersen PH, et al.** Gamma knife stereotactic radiosurgery for acromegaly. *Eur J Endocrinol*. 2007;157:255–263.
10. **Sheehan JP, Jagannathan J, Pouratian N, Steiner L.** Stereotactic radiosurgery for pituitary adenomas: a review of the literature and our experience. *Front Horm Res*. 2006;34:185–205.
11. **Jezková J, Marek J, Hána V, et al.** Gamma knife radiosurgery for acromegaly–long-term experience. *Clin Endocrinol (Oxf)*. 2006;64:588–595.
12. **Castinetti F, Taieb D, Kuhn JM, et al.** Outcome of gamma knife radiosurgery in 82 patients with acromegaly: correlation with initial hypersecretion. *J Clin Endocrinol Metab*. 2005;90:4483–4488.
13. **Attanasio R, Epaminonda P, Motti E, et al.** Gamma-knife radiosurgery in acromegaly: a 4-year follow-up study. *J Clin Endocrinol Metab*. 2003;88:3105–3112.
14. **Pollock BE, Nippoldt TB, Stafford SL, Foote RL, Abboud CF.** Results of stereotactic radiosurgery in patients with hormone-producing pituitary adenomas: factors associated with endocrine normalization. *J Neurosurg*. 2002;97:525–530.
15. **Zhang N, Pan L, Wang EM, Dai JZ, Wang BJ, Cai PW.** Radiosur-

gery for growth hormone-producing pituitary adenomas. *J Neurosurg*. 2000;93(suppl 3):6–9.
16. **Katznelson L, Atkinson JL, Cook DM, Ezzat SZ, Hamrahian AH, Miller KK.** American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of acromegaly–2011 update. *Endocr Pract*. 2011;17(suppl 4):1–44.
17. **Sheehan JP, Niranjan A, Sheehan JM, et al.** Stereotactic radiosurgery for pituitary adenomas: an intermediate review of its safety, efficacy, and role in the neurosurgical treatment armamentarium. *J Neurosurg*. 2005;102:678–691.
18. **Snell JW, Sheehan J, Stroila M, Steiner L.** Assessment of imaging studies used with radiosurgery: a volumetric algorithm and an estimation of its error. Technical note. *J Neurosurg*. 2006;104:157–162.
19. **Laws ER.** Surgery for acromegaly: evolution of the techniques and outcomes. *Rev Endocr Metab Disord*. 2008;9:67–70.
20. **Theodosopoulos PV, Leach J, Kerr RG, et al.** Maximizing the extent of tumor resection during transsphenoidal surgery for pituitary macroadenomas: can endoscopy replace intraoperative magnetic resonance imaging? *J Neurosurg*. 2010;112:736–743.
21. **Campbell PG, Kenning E, Andrews DW, Yadla S, Rosen M, Evans JJ.** Outcomes after a purely endoscopic transsphenoidal resection of growth hormone-secreting pituitary adenomas. *Neurosurg Focus*. 2010;29:E5.
22. **Melmed S.** Medical progress: acromegaly. *N Engl J Med*. 2006;355:2558–2573.
23. **Landolt AM, Haller D, Lomax N, et al.** Stereotactic radiosurgery for recurrent surgically treated acromegaly: comparison with fractionated radiotherapy. *J Neurosurg*. 1998;88:1002–1008.
24. **Ikeda H, Jokura H, Yoshimoto T.** Transsphenoidal surgery and adjuvant gamma knife treatment for growth hormone-secreting pituitary adenoma. *J Neurosurg*. 2001;95:285–291.
25. **Kobayashi T, Mori Y, Uchiyama Y, Kida Y, Fujitani S.** Long-term results of gamma knife surgery for growth hormone-producing pituitary adenoma: is the disease difficult to cure? *J Neurosurg*. 2005;102(suppl):119–123.
26. **Wan H, Chihiro O, Yuan S.** MASEP gamma knife radiosurgery for secretory pituitary adenomas: experience in 347 consecutive cases. *J Exp Clin Cancer Res*. 2009;28:36.
27. **Iwai Y, Yamanaka K, Yoshimura M, Kawasaki I, Yamagami K, Yoshioka K.** Gamma knife radiosurgery for growth hormone-producing adenomas. *J Clin Neurosci*. 2010;17:299–304.
28. **Motti ED, Losa M, Pieralli S, et al.** Stereotactic radiosurgery of pituitary adenomas. *Metabolism*. 1996;45:111–114.
29. **Landolt AM, Haller D, Lomax N, et al.** Octreotide may act as a radioprotective agent in acromegaly. *J Clin Endocrinol Metab*. 2000;85:1287–1289.
30. **Gutt B, Wowra B, Alexandrov R, et al.** Gamma-knife surgery is effective in normalising plasma insulin-like growth factor I in patients with acromegaly. *Exp Clin Endocrinol Diabetes*. 2005;113:219–224.
31. **Jagannathan J, Sheehan JP, Pouratian N, Laws ER, Steiner L, Vance ML.** Gamma knife surgery for Cushing's disease. *J Neurosurg*. 2007;106:980–987.
32. **Sheehan JP, Starke RM, Mathieu D, et al.** Gamma knife radiosurgery for the management of nonfunctioning pituitary adenomas: a multicenter study. *J Neurosurg*. 2013;119:446–456.
33. **Xu Z, Lee Vance M, Schlesinger D, Sheehan JP.** Hypopituitarism after stereotactic radiosurgery for pituitary adenomas. *Neurosurgery*. 2013;72:630–637; 636–637.
34. **Tooze A, Hiles CL, Sheehan JP.** Neurocognitive changes in pituitary adenoma patients after gamma knife radiosurgery: a preliminary study. *World Neurosurg*. 2012;78:122–128.