Cushing disease is associated with significant complications including visceral obesity, insulin resistance, hypertension, cardiovascular disease, hypercoagulability, osteoporosis, psychiatric disease, growth hormone deficiency, hypogonadism, and hypothyroidism. These disorders can persist for up to 5 years after resolution of hypercortisolism. Cushing disease is often difficult to diagnose and is critically dependent on hormonal testing to establish the presence of ACTH-dependent hypercortisolism. Adrenocorticotropic hormone adenomas are small lesions, and in 20% of cases they are not visible even on high-resolution dynamic contrast high-field strength MR images. In this scenario, superior petrosal sinus sampling can confirm the presence of pituitary-dependent CD.

The preferred and most effective treatment for CD is selective transsphenoidal adenomectomy to effect immediate remission and and spare pituitary function. Cure rates after resection for Cushing microadenomas vary from 72 to 97%; for obvious reasons the cure rate for macroadenomas is lower, 50–80%. Adrenocorticotropic hormone adenomas are small lesions, and in 20% of cases they are not visible even on high-resolution dynamic contrast high-field strength MR images. In this scenario, superior petrosal sinus sampling can confirm the presence of pituitary-dependent CD.

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Stereotactic radiosurgery was introduced in Sweden in 1969 by Lars Leksell and has since been used successfully in the treatment of ACTH-producing adenomas. The current indications for SRS include the following: 1) a previously failed resection; 2) a lesion not amenable to complete resection by surgery; and 3) use as a primary therapy in patients who are unable to undergo conventional surgery. A major disadvantage to pituitary radiotherapy for CD is the significant delay that exists between radiation delivery and subsequent decline of hypercortisolemia. This delay often necessitates the use of cortisol-lowering medications in the interim.

Stereotactic Radiosurgical Technology

Stereotactic radiosurgery can be performed with either a linear accelerator or the Gamma Knife. Both forms of radiosurgery are based on similar principles of delivering focused radiation to the target while sparing surrounding normal structures, but they differ in the type of radiation delivered and in the targeting technologies used. Multiple radiation fields are used to deliver high-dose radiation to the tumor while delivering a minimal dose to the surrounding normal tissue, thus reducing the patient’s risk of complications. The best results are obtained in well-defined tumors and when precise head fixation is used during the treatment.

Radiotherapy is an excellent primary therapy for many neurosurgical problems because it is minimally invasive, takes relatively little time to administer, can be performed in an outpatient setting, and has few acute side effects. The radiosensitivity of the visual pathways places constraints on dose planning for pituitary tumors, consequently the size and location of the tumor are important factors in deciding on treatment. In patients with CD, both maximal

Abbreviations used in this paper: ACTH = adrenocorticotropic hormone; CD = Cushing disease; GKS = Gamma Knife surgery; MR = magnetic resonance; SRS = stereotactic radiosurgery; UFC = urinary free cortisol.
and margin\textsuperscript{26} radiation doses have been reported to be statistically significant predictors of treatment success.

Application of the stereotactic frame is performed on the morning of the procedure after local anesthesia has been administered. Preoperative MR and computed tomography images are obtained. It is important to note that, in up to 17\% of patients with CD no demonstrable intrasellar abnormality is apparent, even on high-resolution MR images.\textsuperscript{1} Radiosurgical hypophysectomy may be an option in patients with severe CD in whom definite imaging abnormalities are lacking. The decision-making process should incorporate the expertise of the endocrinologist, neurosurgeon, radiation oncologist, and medical physicist. The exact contours of the target are precisely delineated at this stage, and dose prescription takes into consideration the tumor volume, distance to the visual pathways, patient age, and history of prior radiotherapy. There is no verifiable evidence that any of the currently available technologies for delivery of SRS for pituitary adenomas is superior to any other in terms of efficacy, convenience, or risk profile.

**Criteria for Cure**

Currently, there is no consensus concerning the timing, choice of biochemical tests, or threshold values to define remission,\textsuperscript{2} however, postoperative assessment combining clinical evaluation and laboratory measurement of morning plasma cortisol levels, 24-hour UFC measurement, low-dose dexamethasone suppression testing, midnight salivary cortisol, or cortisol response to corticotropin-releasing hormone are necessary to evaluate remission status, and may predict long-term durability of treatment and freedom from recurrence.\textsuperscript{4,10,26,32,37,42,43,47} An absence of tumor growth in ACTH-producing adenomas is not an appropriate measure of successful therapy because persistent hypercortisolemia may cause ongoing complications despite adequate tumor control. In most patients who obtain disease cure or remission, there is a period of severe hypoaldrenism, probably due to the suppression of normal pituitary corticotrophic function by previous hypercortisolism.\textsuperscript{16} These patients often display undetectable or extremely low serum and urine cortisol levels. After a period of hypoaldrenism, the hypothalamic-pituitary-adrenal axis typically recovers, with a time to recovery of \~ 11–14 months.\textsuperscript{3,7,16} Exogenous steroid replacement is required to treat adrenal insufficiency during this recovery phase. Cure for CD is usually accompanied by resolution of the hypercortisolemia phenotype. Furthermore, the normal cortisol response to hypoglycemia and cosyntropin stimulation recovers in most patients, allowing withdrawal of glucocorticoid replacement, and typically there is a return of the diurnal pattern of cortisol secretion.\textsuperscript{14} Immediate postoperative cortisol levels in the first 24 hours after treatment have been used to predict disease cure.\textsuperscript{88} Other authors have suggested that testing after 6–12 weeks prevents misclassification of patients who have a delayed decline in postoperative cortisol level (N M Oyesiku, personal communication). The timing of any definitive assessment must be guided by the fact that long-term follow-up evaluation is essential to understand the true rates of remission, recurrence, and cure. Premature statements as to cure must be viewed skeptically in the absence of long-term data of biochemical cure.

Once it has been determined that the disease is not cured or has recurred based on biochemical and clinical evidence, then MR imaging is necessary to determine whether a definable lesion is present. If the lesion is situated outside of the sella (parasellar location or cavernous sinus) such that a repeated operation is unlikely to be successful, then radiosurgery is clearly the preferred option, provided that tumor size and configuration are favorable. In cases in which partial resection is needed to obtain a more favorable configuration or size appropriate for radiosurgery, then a repeated operation may be warranted even when complete resection is unobtainable. If there is no definable target on MR imaging, then radiosurgery delivered to the area of prior resection or repeated surgical exploration are both reasonable options when there was clear evidence of a prior tumor.

**Results of SRS**

Stereotactic radiosurgery has the advantages of a relatively rapid onset of therapeutic benefit compared with conventional or fractionated stereotactic radiotherapy. Early results with SRS of ACTH-producing adenomas before the advent of computed tomography were encouraging; Degerblad et al.,\textsuperscript{11} reported their results in 35 patients with CD who were treated at Karolinska Hospital between 1975 and 1982. Of the 29 patients who were followed up longer than 3 years, remission was achieved in 14 patients (48\%) after radiosurgery with a single maximal dose of 70–100 Gy. Remission was achieved in an additional 8 patients after 1–3 SRS procedures, for a total of 22 patients (76\%) in biochemical remission. Disease remission occurred in approximately 50\% of the patients within 1 year, and in the other 50\% within 3 years. No recurrences or complications were reported. Pituitary insufficiency eventually developed in 55\% of the patients between 4 months and 7 years post-SRS.

Ganz and colleagues\textsuperscript{37} reported on the results when with GKS with a margin dose of 25 Gy in 4 patients with CD and 3 with Nelson syndrome. They reported that 4 (57\%) of 7 adenomas decreased in size; hormone levels normalized in 2 patients and improved in 4; and remained unchanged in 1 after more than 18 months.

In their retrospective study, Hoybye et al.,\textsuperscript{22} described the long-term outcomes in patients with ACTH-producing pituitary tumors treated with GKS. Eighty-nine patients (range 5–67 years) were treated from 1976 to 1985, but only 18 patients (range 18–68 years; mean 41 years), were followed up in detail. Fifteen of these patients were women. None had previously undergone conventional radiotherapy, but pituitary microsurgery had been performed in 2 patients, and 1 patient had had an adrenalectomy. In the remaining 15 patients, radiosurgery was the primary therapy. Sixty-four patients had 1 stereotactic treatment, and 25 patients had 2 or more treatments. No complications were observed during treatment or in the immediate follow-up period. During follow-up, 17 patients died 1–20 years after the first treatment, although no deaths were related to the treatment. In the 18 patients with the closest follow-up, the follow-up time after the first SRS treatment ranged from 12 to 22 years (mean follow-up period 17 years). Urinary cortisol levels gradually normalized in 83\% of patients; there were no disease recurrences.
observed. Hypopituitarism developed in about two-thirds of patients and arose more than 10 years after treatment. Eight patients had transient hyperprolactinemia. No visual or other radiation-induced side effects were noted in any of the patients.

Kobayashi and associates reported on 20 patients with CD who underwent GKS with a mean follow-up of 64 months. The mean dose to the tumor margin was 29 Gy, and there was a mean 3.8 isocenters per patient. Among these 20 patients, there was complete resolution of the tumor on MR images in 6 patients (30%), > 50% of decrease in lesion size in 11 (55%), a 25–50% decrease in lesion size in 2 (10%), and no change in 1 patient (5%). Levels of ACTH and cortisol normalized in 7 patients (35%), significantly decreased in 5 (25%), somewhat decreased in 5 (25%), and did not change in 3 (15%). Complications were reported in 5 patients (25%), including 1 who died of the disease. Predictors of a complete tumor response to treatment (defined as disappearance of the lesion on MR images) were a < 10-mm-diameter radiosurgical target and a radiation dose > 40 Gy at the tumor margin.

Pollock and associates reported that 78% of their patients with ACTH-producing adenomas were cured after GKS as determined on 24-hour UFC tests with < 90 [mu]g cortisol during a mean follow-up period of 40 months. Predictors of failure determined by multivariate analysis included the use of preoperative hormone-suppressive medications and a maximal radiosurgical dose < 40 Gy. The overall complication rate in their patients was 26%, with new hormonal deficits developing in 16%, radionecrosis of the temporal lobe in 3%, and visual loss in 2%.

Devin et al. reported on their results after linear accelerator SRS for CD in 35 patients with regard to control of hypercortisolism, improvement of clinical features, prevention of tumor progression, and subsequent incidence of hypopituitarism. Seventeen (49%) patients achieved control of their cortisol levels after SRS; the mean time to normalization was 7.5 months (range 1–33 months). Four (19%) patients experienced recurrent hypercortisolism at a mean time of 35.5 months after therapy (range 17–64 months). Control of tumor progression was achieved in 91% of patients. Fourteen patients (40%) demonstrated a new pituitary deficiency after SRS.

In their more recent study, Castinetti et al. prospectively evaluated SRS as both a primary and adjunctive therapy by assessing long-term hormonal effects and tolerance. They performed follow-up in 40 patients with CD treated by GKS over a decade, with a mean follow-up of 54.7 months. Eleven patients were treated with GKS as the primary treatment at a median margin dose of 29.5 Gy. Patients were considered in remission if they had normalized 24-hour free UFC levels, and suppression of plasma cortisol noted after a low-dose dexamethasone suppression test. Seventeen patients (42.5%) were in remission after a mean of 22 months (range 12–48 months). Although they did not differ in terms of initial hormonal levels, the target volume was significantly higher in the uncured group than in the remission group (909.8 compared with 443 mm³, p = 0.038). Castinetti et al. reported that the disease was cured in only 27% of patients in the primary treatment group compared with 48% in the adjunctive treatment group, and also found a significant difference in outcome between patients who were and were not taking anticortisol drugs at the time of GKS (20 compared with 48% patients in remission respectively, p = 0.02).

Equally current is the report by Jagannathan and associates. In their retrospective review, these authors examined the efficacy and safety of GKS in 90 patients with ACTH-secreting pituitary adenomas treated between January 1990 and March 2005. All but 1 patient had undergone prior resection for a pituitary tumor without achieving remission. Successful endocrine outcome after GKS was defined as a normal 24-hour UFC concentration after a minimum of 1 year of follow-up. Patient records were evaluated for tumor volume, development of new hormone deficiencies, visual acuity, cranial nerve neuropathies, and radiation-induced imaging changes. Ninety evaluable patients had undergone GKS, with a mean follow-up duration of 45 months (range 12–132 months). The mean radiation dose to the tumor margin was 23 Gy (median 25 Gy). Normal 24-hour UFC levels were achieved in 49 patients (54%), at an average time of 13 months after treatment (range 2–67 months). In the 49 patients in whom a tumor was visible on the planning MR imaging, tumor size decreased in 39 (80%), there was no visible change in size in 7, and tumor growth occurred in 3 patients. Ten patients (20%) experienced a relapse of CD after an initial remission; the mean time to recurrence was 27 months (range 6–60 months). Seven of the patients who experienced a recurrence underwent repeated GKS, and 3 achieved a second remission. New hormone deficiencies developed in 20 patients (22%), with hypothyroidism being the most common endocrinopathy after GKS. Five patients experienced new visual deficits or third, fourth, or sixth cranial nerve deficits; 2 of these patients had undergone prior conventional fractionated radiation therapy, and 4 had previously undergone GKS. Radiation-induced changes were observed on MR imaging in 3 patients, and 1 patient had symptoms attributable to these changes.

Complications of SRS

The most significant complications of radiation to the pituitary region are hypopituitarism, optic neuropathy, temporal lobe necrosis, and induction of a secondary neoplasm (rare). The incidence of optic neuropathy is less than 2% after SRS if the dose is < 8 Gy. There are other reports of the tolerance of the optic nerves and chiasm to a maximum radiation dose of 8–12 Gy. Furthermore, any prior radiation, proximity of the target of less than 5 mm from the optic nerve, and tumor size must be considered as confounding factors in the risk of neuropathy. The incidence of induction of a secondary neoplasm is very low, and only a few cases have been reported after SRS for pituitary tumors. The incidence of new-onset hypopituitarism requiring replacement therapy after SRS varies between 16 and 55% with a median period of 50–60 months.

Although hypopituitarism should be considered as a possible complication of radiosurgery, thanks to the advances in hormone replacement therapy this condition can be successfully managed in most patients without undue complications. In contrast, however, there can be no tolerance for radiation injury to the optic nerves and chiasm; these struc-
tures must be meticulously factored into the treatment decision and planning.

Conclusions

Stereotactic radiosurgery is a safe and effective therapeutic option for the treatment of CD in carefully selected cases. Improvements in imaging techniques, dose planning, and our understanding of radiobiology will probably yield better results in the future.

References

Stereotactic radiosurgery for Cushing disease


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