Stereotactic radiosurgery for Cushing disease

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The most common cause of Cushing syndrome is Cushing disease, in which hypercortisolism is produced by a functional adrenocorticotrophic hormone–producing adenoma of the anterior pituitary gland. The common therapies available include microsurgical resection, conventional fractionated radiotherapy, and stereotactic radiosurgery (SRS). In this article the authors review the indications, results, and complications associated with SRS in the treatment of Cushing disease.

In as many as 90% of patients SRS results in disease remission, which is defined as a normal 24-hour urinary free cortisol level and a normal or subnormal morning serum cortisol level. Although in most patients who are subsequently cured a marked decrease in the serum cortisol level is demonstrated within 3 months after treatment, a biochemical cure may be delayed up to 3 years in some cases. Complications following SRS for pituitary adenomas are uncommon, particularly in patients with microadenomas, which are most commonly seen in Cushing disease. The most common complication is hypopituitarism, which occurs in up to 50% of patients with a mean latency period of 5 years. Radiation-induced optic neuropathy has been reported in less than 2% of cases and induction of a secondary neoplasm in less than 1% of cases.

For patients with Cushing disease, the rate of endocrinological cure following SRS appears to be similar to that attained using microsurgical resection. In contrast to surgery, SRS has the benefit of being noninvasive and associated with a very low incidence of diabetes insipidus, although hypopituitarism may be more common with SRS. With continued follow-up patient reviews and additional experience with SRS, it may become possible to make more definitive statements regarding SRS as the initial treatment for patients with Cushing disease.

KEY WORDS • Cushing disease • pituitary adenoma • stereotactic radiosurgery

Cushing syndrome is a well-known constellation of signs and symptoms produced by an excessive level of cortisol that is either endogenously secreted or exogenously administered. The most common cause of this syndrome is Cushing disease, in which an adenoma of the anterior pituitary gland that secretes ACTH stimulates the synthesis of cortisol by the adrenal gland; this accounts for up to 80% of all cases of Cushing syndrome (Fig. 1).²⁴ The morbidity associated with Cushing syndrome may be severe with multiple organ systems affected; the mortality rate associated with this syndrome, if left untreated, has been reported to be 50% within 5 years.³⁸

Therapeutic options include microsurgical resection, conventional radiotherapy, chemotherapy, and SRS. Microsurgical resection remains the proven primary therapy; it has a long-term cure potential and a low incidence of complications when current microneurosurgical techniques are used. Nevertheless, cures following resection range between 64 and 93% of cases and surgical cures for invasive adenomas are infrequent.^{2,16,24,29,43,45} Although conventional fractionated radiotherapy is also effective in reducing the hypercortisolemia of Cushing disease, there may be a significant delay of up to several years follow-

ing radiotherapy for a beneficial clinical and biochemical effect. Conventional radiotherapy also results in irradiation of critical intracranial structures, such as the temporal lobes and optic apparatus and is associated with at least a 50% long-term incidence of hypopituitarism.^{27,37} Because agents such as bromocriptine or inhibitors of steroidogenesis are used, chemotherapy is reserved for adjuvant therapy of treatment-resistant Cushing disease or for the occasional mild form of the disease, which responds to these medications.

Stereotactic radiosurgery was developed in Sweden in 1969 by Lars Leksell and has been used in the treatment of ACTH-producing adenomas since that time. Despite its widespread use in Sweden, this technique did not become a viable therapeutic option in many other countries until the 1980s.

STEREOTACTIC RADIOSURGERY

Stereotactic radiosurgery can be administered using either a linear accelerator or gamma knife system. Both forms of radiosurgery are based on similar principles of delivering focused radiation to intracranial targets while sparing normal structures, but they differ in the type of radiation that is delivered and in their targeting technologies. Radiosurgery has become a valuable option as a primary therapy for many neurosurgical problems because it is minimally invasive, takes relatively little time to admin-

Abbreviations used in this paper: ACTH = adrenocorticotrophic hormone; CT = computerized tomography; MR = magnetic resonance; RON = radiation-induced optic neuropathy; SRS = stereotactic radiosurgery.

Fig. 1. Coronal contrast-enhanced MR image of the sella turcica in a patient with recurrent Cushing disease. There is a well-circumscribed 7-mm-wide lesion in the left lateral aspect of the pituitary gland. This lesion is suitable for SRS treatment.

ister (often in only one session), can be performed in an outpatient setting, and has few acute side effects. As experience with radiosurgery continues to grow, questions regarding long-term efficacy and potential complications, such as the induction of secondary neoplasms, will be answered.

Several problems, both practical and theoretical, face the radiosurgeon. Although some of these problems apply to radiosurgery in general, others are specific to the treatment of Cushing disease (Table 1). In most of the oncology literature regarding the relative success of radiosurgery the authors rely on tumor control as the primary measure, which means that a lack of increase in tumor size is indicative of successful treatment. Absence of tumor growth for ACTH-producing adenomas is not an appropriate measure of successful therapy because persistent hypercortisolemia may cause ongoing morbidity. Thus, cure rather than control is the goal of therapy in patients with Cushing disease and this is measured by biochemical means. In the older literature on this disease, definitions of “cure” or “remission” were not standardized. Normal or subnormal levels of 24-hour urinary free cortisol and morning serum cortisol are probably the most appropriate and practical measures of a cure, although a normal plasma level of ACTH or a normal response to the dexamethasone suppression test have been added by some authors.^{18,32,40,46}

Deciding the most appropriate dose of radiation can be confusing, and the choices physicians make complicate a comparison of patient outcomes from different centers. Older studies of SRS focused on maximal tumor doses. Evidence from nonpituitary lesions treated with SRS has indicated that the radiation dose directed to the tumor margin is more important in determining the relative treatment

TABLE 1
Problems facing the radiosurgeon when treating patients with Cushing disease

No.	Problem
1	What is the appropriate measure of success? Is it growth control? Is it biochemical cure?
2	What is the definition of cure for Cushing disease?
3	What is the appropriate radiosurgical dose? Is it the maximal dose or the dose to the tumor margin that is important?
4	What if no lesion is seen on the imaging study?

success,^{11,19} but this has not been shown conclusively for pituitary adenomas. In patients with Cushing disease, both maximal⁴⁰ and margin²² radiation doses have been reported to be statistically significant predictors of success.

Finally, targeting of ACTH-producing adenomas by using CT-guided technology may not provide enough resolution to identify the microadenomas typical of Cushing disease. The distinct identification of the radiosurgical target may require fusion with MR images or an MR imaging–based targeting system, both of which may introduce inaccuracies in targeting. In addition, in up to 17% of patients with Cushing disease no demonstrable intrasellar abnormality is apparent, even on high-resolution MR images.⁴³ The radiosurgical literature contains no study of the utility of SRS in the treatment of patients with occult adenomas, that is, those patients in whom no abnormality appears on imaging to be targeted. Nevertheless, there have been reports of radiosurgery-induced hypophysectomy for the treatment of cancer pain in patients in whom doses in the range of 150 to 200 Gy were administered with one or two isocenters targeting the pituitary stalk.¹⁷ As a result of the morbidity associated with persistent hypercortisolemia, radiosurgical hypophysectomy may be a viable option in patients with severe Cushing disease in whom definite imaging abnormality is lacking and the disease has been refractory to standard therapies (Fig. 2). In this circumstance in particular, the correct diagnosis and the appropriate biochemical demonstration of a pituitary source of hypercortisolemia are critical before embarking on any treatment for Cushing disease.

Results of SRS

As mentioned previously, biochemical remission without associated complications is the goal of therapy in patients with Cushing disease. Remission rates after surgery have been reported and microsurgical resection remains the proven primary therapy because it produces an immediate beneficial effect following successful surgery. Surgical cures for recurrent or invasive adenomas are less common than those for typical ACTH-producing adenomas, however, prompting a need for effective adjuvant therapies. Although conventional radiotherapy results in up to a 90% remission rate by 5 years posttreatment,⁸ if followed long enough a large proportion of patients begin to experience hypopituitarism and approximately 5% of patients experience an RON, which is very difficult to treat effectively.^{1,27,48} Stereotactic radiosurgery has the advantages of a rapid onset of therapeutic benefit, similar to surgery, and a minimally invasive nature, similar to radio-

Fig. 2. Coronal contrast-enhanced MR image obtained in a patient with recurrent Cushing disease, which previously was treated with transsphenoidal resection and fractionated radiotherapy. No discrete adenoma is seen, but the patient may be a candidate for SRS if the Cushing disease is severe and the biochemical workup indicates that the sella turcica is the source of ACTH hypersecretion.

therapy. Table 2 provides some details in the literature on the cures, complications, and latency periods for microsurgical resection, conventional radiotherapy, and SRS.

Early results of radiosurgical treatment of ACTH-producing adenomas were encouraging, even though until approximately 1980 neurosurgeons were limited to using pneumoencephalography for outlining the lesions to be treated. Degerblad, et al.,⁷ reported their results in 35 patients with Cushing disease who were treated between 1975 and 1982 at Karolinska Hospital by using pneumoencephalography-based radiosurgery. Treatment was administered using an early version of the Gamma Knife.⁷ Of the 29 patients who were followed up for longer than 3 years, disease remission was achieved in 14 (48%) after a single maximal dose of radiosurgery, which ranged between 70 and 100 Gy. An additional eight patients experienced remission of their disease after undergoing between one and three radiosurgical procedures, for a total of 22 patients (76%) in biochemical remission. Disease remissions 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.

Hoybye, et al.,¹⁸ provided additional long-term follow-up data on patients with ACTH-producing adenomas who were treated at Karolinska Hospital between 1976 and 1985. Unfortunately, of the 89 patients treated with SRS for Cushing disease, detailed data were only available in 18. Overall, 83% of patients experienced remission of their disease after a mean follow-up period of 17 years, with 44% enjoying remission after one session of SRS and

TABLE 2
Literature review for incidence of endocrinological cure and hypopituitarism following resection, conventional radiotherapy, and SRS for ACTH-producing adenomas

Therapy, Authors & Year	Cure		Hypopituitarism	
	Rate (%)	Latency Period	Rate (%)	Latency Period
surgery	64–93	immediate	2–48	early
Guilhaume, et al., 1988				
Mampalam et al., 1988				
Burke, et al., 1990				
Trainer, et al., 1993				
Bochicchio, et al., 1995				
Ciric, et al., 1997				
Laws, et al., 2002				
conventional radiotherapy	90	≤5 yrs	50	months–many years
Littley, et al., 1989				
Estrada, et al., 1997				
Petrovich, et al., 2003				
radiosurgery	35–90	3 mos–3 yrs	16–55	50–60 months (median)
Degerblad, et al., 1986				
Hoybye, et al., 2001				
Feigl, et al., 2002				
Kobayashi, et al., 2002				
Pollock, et al., 2002				
Vladyka, et al., 2003				

39% after between two and four treatments in which a dose of 30 to 35 Gy was delivered to the tumor margin. Again, there were no instances of recurrence. Significantly, it was found that the most marked decrease in cortisol occurred within 3 months after treatment; if the urinary free cortisol level was not less than 500 nmol/L by 3 months, a subsequent remission was unlikely. In this study, 69% of patients experienced hypothyroidism and all patients had growth hormone deficiency, but no other morbid state was reported.

In a study from Japan, Kobayashi, et al.,²² reported on 20 of 25 patients with Cushing disease who underwent gamma knife surgery. These authors evaluated both tumor size and endocrine results posttreatment with a mean follow-up period of 64 months. The mean dose to the tumor margin was 29 Gy and there was a mean of 3.8 isocenters per patient. Among the 20 patients, there was complete resolution of the tumor on MR images in six patients (30%), a greater than 50% of decrease in the size of the lesion in 11 (55%), a 25 to 50% decrease in the size of the lesion in two (10%), and no change in one patient (5%). Levels of ACTH and cortisol became normal in seven patients (35%), were significantly decreased in five (25%), were somewhat decreased in five (25%), and did not change in three (15%). No mention was made of morbidity, although an unfavorable outcome was reported for five patients (25%), including one who died. In this study, the predictors of a complete tumor response (disappearance of the lesion on MR images) were a radiosurgical target lower than 10 mm in diameter and a radiation dose greater than 40 Gy directed to the tumor margin.

In a series of 59 patients with functional pituitary adenomas, which included nine patients with Cushing disease treated at the Mayo Clinic, Pollock, et al.,⁴⁰ found that 78% of patients with ACTH-producing adenomas were

cured following gamma knife surgery; the cure was established by findings of a 24-hour urinary free cortisol level lower than 90 μg during a mean follow-up period of 40 months. Predictors of failure determined by a multivariate analysis included the use of preoperative hormone-suppressive medications and a maximal (as opposed to margin) radiosurgical dose lower than 40 Gy. This maximal dose of 40 Gy likely represents a dose of 20 Gy to the tumor margin, which is substantially less than that reported by the groups from Sweden.^{7,18} Nevertheless, it is probable that the good outcomes attained by Pollock, et al.,⁴⁰ were related to significantly better targeting capabilities afforded by CT and MR imaging than existed with pneumoencephalography. Also in contrast to the studies discussed previously, this group rigorously reported incidences of morbidity. The overall incidence of morbidity was 26%, with 16% of patients having new hormonal deficits, 3% harboring radionecrosis of the temporal lobe, and 2% experiencing visual loss. These morbidity rates were reported for the whole group of patients with functional pituitary adenomas and not just for those with ACTH-producing adenomas.

Other authors have recommended SRS for the treatment of ACTH-producing adenomas that persist after noncurative surgical treatment and for recurrent Cushing disease.^{24,46} In a study of 65 patients with Cushing disease in whom surgery failed to produce a cure, 40 patients were followed up for more than 12 months; Laws, et al.,²⁴ found that 24-hour urinary free cortisol and morning cortisol levels normalized in 74% of these patients a mean of 16 months after radiosurgical treatment. In this study, there was an 8% recurrence rate between 19 and 38 months after therapy, and a 24% incidence of new endocrine deficits. The dose of radiation did not correlate with the biochemical outcome, nor was there any correlation between the preoperative size of the tumor and the endocrine outcome.^{14,39,46}

Complications of SRS

Complications after SRS for pituitary adenomas do occur, but are less common in patients with microadenomas. The most significant complications following irradiation of the pituitary region are RON, temporal lobe necrosis, induction of a secondary neoplasm, and hypopituitarism. In contrast to surgery, in which the risk of diabetes insipidus is approximately 18%,⁵ this risk appears to be negligible with SRS. The incidence of RON following conventional radiotherapy is 5%,^{13,27} but it is less than 2% after SRS when all tumors, including macroadenomas, are included.^{42,49} Girkin, et al.,¹⁵ reported four cases of RON following SRS, two of which occurred in patients treated for pituitary adenoma, of 2400 radiosurgical cases; it is unclear how many patients in the treatment group had pituitary tumors. Three of the four patients received more than 8 Gy to the anterior optic apparatus, prompting the authors to agree with previous reports that the optic nerves and chiasm can tolerate a maximal radiation dose of 8 Gy,^{15,31,52} although others have reported safe doses in the range of 10 to 12 Gy.^{26,34,36,49} Other risk factors for the development of RON include previous radiation therapy,¹⁰ pretherapy visual loss,²⁵ tumor size greater than 10 mm,^{12,50} and isocenters within 5 mm of the visual path-

ways.⁵⁰ Stafford, et al.,⁴⁹ have estimated that the incidence of RON following SRS is 1.7% if the dose to the chiasm is less than 8 Gy, 1.8% if it is between 8 and 10 Gy, and 6.9% if it is greater than 12 Gy. The proximity of the optic chiasm to the tumor is not an issue in radiosurgical planning, because the typical microadenoma of Cushing disease is well separated from the optic chiasm. Thus, limiting the exposure of the optic structures to radiation in such patients is usually not difficult (Fig. 3).

The incidence of temporal lobe necrosis following conventional radiation therapy for pituitary adenomas is difficult to determine based on the literature, but it is likely to be between 1 and 5%.⁴⁰ In a rigorous discussion of induction of a secondary neoplasm in normal tissues within the irradiated field, an appropriate definition should be used. Radiation-induced neoplasms must meet the following criteria. 1) The tumor must be within the previous field of irradiation. 2) There must be a sufficient interval between the irradiation and the development of the new tumor (typically ranging from many months to years). 3) The histological characteristics of the new tumor must differ from that of the original lesion. 4) The patient must not have a disease associated with the development of new tumors, such as neurofibromatosis, Li-Fraumeni syndrome, or tuberous sclerosis.⁴ The incidence of such a neoplasm induction is approximately 1 or 2% following conventional radiation therapy for pituitary tumors.³⁷ This risk accumulates with time; the actuarial risk is 1.7% at 10 years and 2.7% at 15 years.⁵⁴ To our knowledge, two cases of radiation-induced neoplasms have been reported following SRS for pituitary tumors, both in patients with acromegaly; in one of these patients a meningioma developed and in the other a vestibular schwannoma within the field of radiation.²⁸ In addition, four patients with radiation-

Fig. 3. Radiosurgical dose planning for the patient whose MR image is shown in Fig. 1. Coronal (A) and axial (B) contrast-enhanced MR images include an overlay of the isodose curves (300–2000 cGy). The maximum radiation dose was 2284 cGy and the dose prescribed to the tumor margin was 1800 cGy (at the 80% isodose line). The optic nerves, optic chiasm, and brainstem were outside the 300-cGy isodose line. The relationship of the 80% isodose line (with its associated dosecloud) to critical structures, particularly the optic chiasm and brainstem, is apparent (C).

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induced neoplasms have been reported following SRS in other regions of the brain.^{20,44,47,56}

A 50% rate of hypopituitarism at 20 years after conventional radiotherapy has been reported for those patients with normal pretreatment endocrine function.^{27,37} Early experience with SRS in which pneumoencephalography was used for targeting produced similar results with respect to pituitary function.¹⁸ Somatotrophs of the anterior pituitary constitute the cell type most sensitive to the effects of radiation, followed by gonadotrophs, corticotrophs, and thyrotrophs.^{6,18,27} In contemporary series the incidence of new-onset hypopituitarism requiring replacement therapy following SRS has been reported to range between 16 and 55% with a median period of between 50 and 60 months.^{7,9,33,51,55} In two of the most recent studies the incidence was reported to be less than 20%,^{33,55} although in another recent study the incidence was determined to be 41%.⁹ Feigl, et al.,⁹ found that the pituitary stalk received a higher dose of radiation in patients in whom hypopituitarism developed than in those in whom it did not (7.7 Gy compared with 5.5 Gy). Another study found that the safe mean dose of radiation to the hypophysis was 15 Gy for gonadotropic and thyrotropic function and 18 Gy for adrenocorticotrophic function.⁵⁵

Nelson Syndrome

The development of a particularly aggressive ACTH-producing adenoma following bilateral adrenalectomy has been termed "Nelson syndrome" and deserves a separate mention.^{30,35,41} For these tumors, which tend to be more invasive, transsphenoidal microsurgery is unlikely to be as successful in obtaining a biochemical cure than it is for typical Cushing disease. Indeed, only five (45%) of 11 patients with Nelson syndrome experienced disease remission after surgery in one study.²¹ Pollock, et al.,⁴¹ have recently reported their experience with 11 patients who underwent SRS for Nelson syndrome. In this series, tumor growth was controlled in nine patients (82%). In addition, ACTH levels decreased a median of 66% and in four patients (36%) there was normalization of ACTH levels. The median radiation dose was 20 Gy. Three patients (27%) experienced a complication, including visual loss and asymptomatic temporal lobe necrosis; because all these patients had been previously treated with conventional radiotherapy, it is difficult to determine the relative contributions of the SRS and standard radiotherapy to these complications. Based on results such as these, it appears that SRS may be an effective treatment for patients with Nelson syndrome.^{30,41}

QUESTIONS FOR FURTHER STUDY

Many questions require thoughtful answers in the growing field of SRS. Obviously, a longer follow-up period and greater experience are required before definitive statements can be made regarding long-term outcomes and complications following SRS. Important questions regarding this therapy of pituitary adenomas need to be clarified before SRS can be definitively recommended as a viable primary therapy for all patients. It is still not clear what is the most appropriate radiation dose, nor whether the maximal dose or that directed to the tumor margin is more important. It does appear, however, that the dose to

the tumor margin needs to be greater to achieve an endocrinological cure than it does to attain control of tumor growth.⁵⁵ The margin dose for growth control lies in the range of 18 to 25 Gy,^{23,55} whereas that required for endocrinological control may need to be as high as 35 Gy.^{7,18,55} This has important implications for treating functional adenomas with SRS, because a high rate of tumor cure may be achieved only at the expense of hypopituitarism. In addition, the quality of follow-up data reported for patients treated with SRS in clinical series is poor. The SRS literature is replete with papers containing follow-up results for only a fraction of the actual number of patients treated. In the strictest sense, a report that 45 (90%) of 50 patients were cured with a particular therapy, when in fact 150 patients were treated and 100 were lost to follow up, actually represents 45 (30%) of 150 patients proven to be cured. In addition, the role of repeated treatment with SRS for persistent or recurrent Cushing disease needs to be clarified. Limited initial evidence suggests that repeated treatment is both effective and safe, but further experience is required.^{7,18} Finally, the role of fractionated stereotactic radiotherapy should be addressed. Although fractionation may make biological sense for malignant neoplasms, this is not the case for benign tumors.²³ It may not make sense to reduce the tumor control rate to achieve a potential decrease in a complication rate when that rate is already so low (particularly for microadenomas).

CONCLUSIONS

Stereotactic radiosurgery is becoming an increasingly valuable option in the treatment of many patients with diseases suited to neurosurgery. For patients with Cushing disease, the rate of endocrinological cure following SRS appears to be similar to that attained using microsurgical resection. Although the incidence of hypopituitarism post-SRS may be higher than that following resection, the incidence of diabetes insipidus is negligible and the treatment is not as invasive. Complications such as RON, temporal lobe necrosis, and induction of a secondary neoplasm are rare following SRS. With some standardization within the radiosurgical literature regarding appropriate dosing and criteria for cure, along with more rigorous follow-up review of all treated patients, it may be possible in the near future to make more definitive statements regarding the use of SRS as an initial treatment for patients with Cushing disease.

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