External Beam Radiation Therapy and Stereotactic Radiosurgery for Pituitary Adenomas

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KEYWORDS

• Pituitary adenoma • Stereotactic radiosurgery • Radiation therapy

KEY POINTS

- Recurrence of pituitary adenomas after microsurgery is reasonably common.
- Stereotactic radiosurgery (SRS) and radiation therapy provide a high rate of tumor control for recurrent or residual pituitary adenomas.
- After radiosurgery and radiation therapy for patients with functional adenomas, endocrine remission occurs in the majority of patients but the rate is not as high as that observed for tumor control.
- Delayed hypopituitarism is the most common complication after radiosurgery or radiation therapy for pituitary adenoma patients.
- Cranial neuropathies after radiosurgery or radiation therapy are fairly rare.

INTRODUCTION

Pituitary adenomas are found in 10% to 27% of the general population.[1,2] Microadenomas (less than 1 cm in maximum dimension) are usually diagnosed either after being discovered incidentally during MRI or due to hormone hypersecretion. Macroadenomas may be discovered as a result of mass effect leading to hypopituitarism, elevation in prolactin output, or a focal neurologic deficit (eg, cranial nerve dysfunction). As a distribution, microadenomas are divided equally between functioning and nonfunctioning lesions. With regard to macroadenomas, nonfunctioning lesions are more common (approximately 80%).[1] At presentation, pituitary adenoma patients often exhibit symptoms of headache (40%–60%), visual disturbance, hypopituitarism, or rarely apoplexy.[1,2]

Pituitary adenomas are some of the most challenging clinical entities that physicians have dealt with over the past century. It has been more than 100 years since Dr Harvey Cushing published his landmark book, *The Pituitary Body and Its Disorders: Clinical States Produced by Disorders of the Hypophysis Cerebri*.[3] Nevertheless, pituitary adenomas remain difficult to cure with microsurgical techniques alone, and they often require multimodality treatment, which includes surgery, radiation therapy, radiosurgery, and medical management. Cushing recognized the limitations of conventional microsurgical approaches for treating intracranial tumors. Cushing and his colleagues used a device called a radium bomb to deliver a radiation therapy to intracranial tumors.[4,5] Since that time, neurosurgeons and radiation oncologists, in conjunction with medical physicists, have used ionizing radiation to treat patients with recurrent or residual pituitary adenomas.

Great attention and effort in the fields of radiation therapy and SRS have been placed on the

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preservation of surrounding neuronal, vascular, and hormonal structures in an effort to improve the therapeutic ratio. Technical refinements for treating pituitary adenoma patients have been achieved through advances in radiobiology, neuroimaging, medical physics, and biomedical engineering. This article reviews the role of radiation therapy and SRS for pituitary adenomas (**Fig. 1**).

EXTERNAL BEAM RADIATION THERAPY CONCEPT AND TECHNIQUE

Fractionation indicates that the total radiation dose is delivered in several smaller doses over time. Beneficial and adverse outcomes are influenced by the dose per fraction and the total number of fractions. Conventional fractionation uses a dose of 1.8 Gy to 2 Gy per day. Most pituitary adenomas are treated with a total external beam radiation dose of 45 Gy to 54 Gy, which translates to 25 to 30 fractions delivered over a 5-week to 6-week treatment period. Treatment planning uses three-dimensional conformal radiation therapy (3D CRT), and various treatment planning software packages can permit this approach. A minimum of 3 unopposed beams is used in 3D CRT plans to minimize dose inhomogeneity and reduce the risk of normal tissue toxicity. Alternatively, inverse planned intensity-modulated radiation therapy can be used for challenging cases where the target is in close proximity to a radiation-sensitive normal tissue structure. Intensity-modulated radiation therapy usually divides the primary radiation beam into 5 mm by 5 mm up to 10 mm by 10 mm beamlets of varying intensities to achieve an acceptable dose plan.

STEREOTACTIC RADIOSURGICAL CONCEPT AND TECHNIQUES

In 1951, SRS was described by Lars Leksell[6] as the "closed skull destruction of an intracranial target using ionizing radiation." Leksell treated the first pituitary adenoma patient with the Gamma Knife in 1968. Since that time, SRS has been used to treat thousands of patients with pituitary adenomas.

SRS used focused, high-dose radiation to the target, while sparing surrounding structures of appreciable doses of radiation. Radiosurgery is traditionally delivered in a single session but may be delivered in up to 5 sessions.[7] It is characterized by a steep dose falloff to the surrounding normal tissues. For cobalt-based SRS devices, the gradient index (ie, steepest falloff) is achieved at

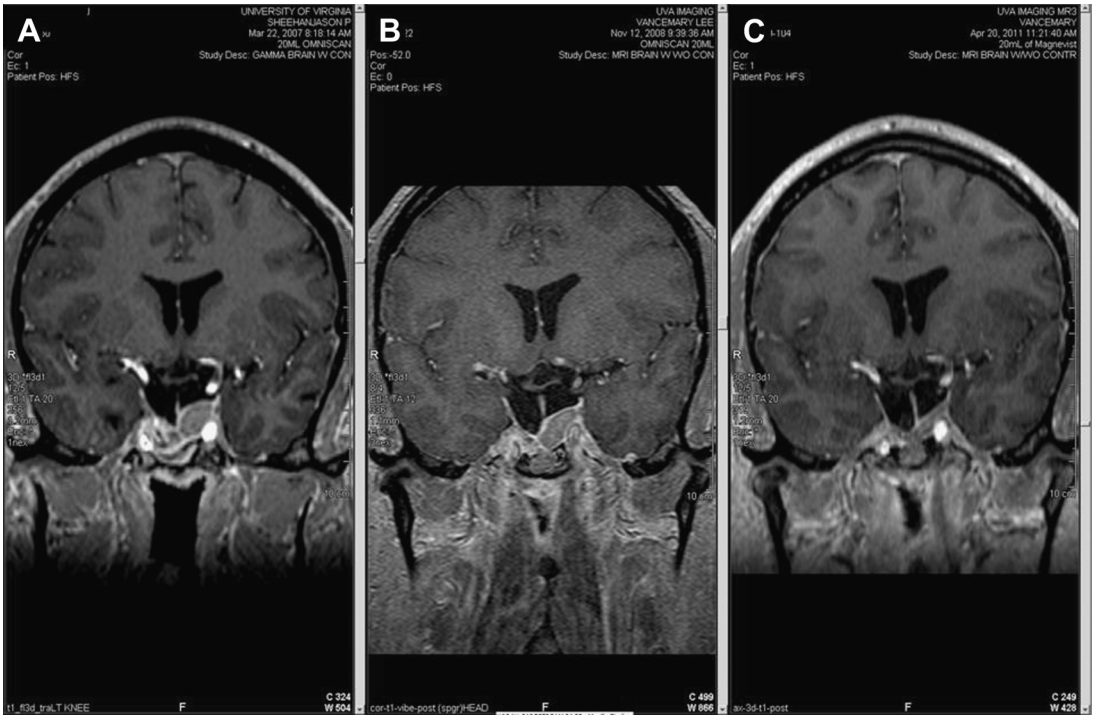

Fig. 1. (*A [left panel]*, *B [middle panel]*, and *C [right panel]*) are postcontrast, coronal MRIs. A 49-year-old man presenting with a recurrent, nonfunctioning pituitary adenoma (*A*). The patient underwent SRS in which 15 Gy was delivered to the tumor margin: 1.5 years later (*B*), the pituitary adenoma had decreased in size, and (*C*) 49 months after radiosurgery, the patient's adenoma continues to regress.

approximately a 50% isodose line, whereas for linear accelerator (LINAC)-based systems, it is usually at the 80% to 90% isodose line. Patients are immobilized using rigid frames fixed to the skull or other immobilization devices (eg, aquaplast masks or bite blocks); each immobilization device has its own stereotactic coordinate system. Radiosurgery is image guided and reliably achieves submillimeter accuracy in intracranial space. Onboard imaging systems may be used to further track and compensate for sources of error (eg, setup error or patient movement).

There are several types of radiosurgical delivery devices, including the Gamma Knife (Elekta AB), modified LINACs, or proton beam units. Single-session radiosurgical margin doses for nonfunctioning adenomas vary from 12 Gy to 18 Gy and 15 Gy to 30 Gy for functioning adenomas. For multisession radiosurgery, these doses may be divided more than 2 to 5 fractions.

Gamma Knife radiosurgery involves the use of multiple isocenters to achieve a dose plan that conforms to the target volume. The number of isocenters varies based on the size, shape, and location of the pituitary adenoma. In the current version of the Gamma Knife Perfexion, each isocenter comprises 8 independent sectors of beams, and each sector comprises no more than 192 simultaneous beams. Beam diameters for the current Gamma Knife Perfexion unit range from 0 mm (ie, blocked) to 16 mm. Other cobalt-based radiosurgical devices are also in use and include the Infini system (MASEP).

LINAC-based radiosurgery (eg, CyberKnife, TrueBeam STx, Trilogy, TomoTherapy, and Axesse) uses multiple radiation arcs to crossfire photon beams at a target.[8] Most systems use nondynamic techniques in which the arc is moved around its radius to deliver radiation that enters from many different vantage points. Technical improvements with LINAC-based radiosurgery include beam shaping, intensity modulation, multileaf collimation, and onboard CT or fluoroscopic imaging.

Proton therapy has been adapted as a radiosurgical tool for intracranial pathology. It takes advantage of the inherently superior dose distribution of protons compared with that of photons because of the Bragg peak phenomenon.[9] Currently, there are just a few centers using proton beam technology to perform radiosurgery (1 session treatment) whereas proton centers perform fractionated stereotactic radiotherapy (FSRT). The number of proton beam centers is increasing as the technology becomes more cost-effective and more compact proton units become available.

CONVENTIONAL FRACTIONATED RADIATION THERAPY VERSUS STEREOTACTIC RADIOSURGERY

For pituitary adenomas, SRS has specific advantages over fractionated external beam radiation therapy (EBRT). It is more convenient for patients and able to better spare normal tissue from appreciable toxicity. As dose is escalated and number of fractions decreased, there is a greater radiobiologic effect on late responding tissues, such as pituitary adenoma cells, compared with early responding tissues. Also, for functioning adenomas, radiosurgery seems to provide a more rapid rate of endocrine remission.[10]

Some patients are not good candidates for SRS secondary to tumor volume, irregular tumor shape, or close proximity of the tumor to radiation-sensitive (ie, critical) structures. In such cases, EBRT may be used to treat such patients. Although each patient must be assessed individually, the advantages and safety of radiosurgery decline when the tumor is greater than 3 cm and when it abuts radiation critical structures, such as the optic apparatus. For pituitary adenomas, the optic apparatus is the most sensitive of the adjacent tissues. Single-session radiosurgical dose to the optic apparatus should generally be kept to below 8 Gy to 10 Gy. Brainstem tolerance for single-session SRS is believed to be 12 Gy to 1 cm^3 or less of tissue.

For EBRT, the 5-year risk of visual deficits is believed to be 5% when 50 Gy is delivered and 50% when 65 Gy is used.[11] Visual complications after EBRT alone, however, have been reported at doses as low as 46 Gy delivered in a 1.8 Gy per fraction scheme. Multimodality treatment, such as patients undergoing treatment with Avastin, can have alteration in the threshold dose of their visual apparatus.

SRS FOR PITUITARY ADENOMAS

SRS and Nonfunctioning Pituitary Adenomas

After a microsurgical resection, control of a pituitary tumor is achieved in 50% to 80% of macroadenomas.[12] SRS provides an excellent treatment approach for patients who have progression or recurrence. It may also be used in cases of residual tumor or presumed tumor progression (eg, patients with silent corticotropin or thyrotropin adenomas). Based on the published literature, radiosurgery affords the vast majority of pituitary adenoma patients with effective, long-term tumor control as well as a low rate of complications.[12]

Table 1 lists the major radiosurgical series since 2002 that detail outcomes in nonfunctioning

Table 1
Summary of the literature review for the radiosurgical management of nonfunctioning pituitary adenomas

Year	Authors	Patients (N)	Mean/Median Follow-Up (Mo)	Mean/Median Margin Dose (Gy)	Radiologic Control of Tumor (%)	Neurologic Deficit (%)	Delayed Hypopituitarism (%)
2002	Feigl et al[14]	61	55.2	15	94	NR	40
2002	Sheehan et al[15]	42	31.2	16	97.6	4.8	0
2002	Wowra and Stummer[16]	30	57.7	16	93.3	0	10
2003	Petrovich et al[17]	52	34	15	100	3	NR
2004	Losa et al[18]	54	41.1	16.6	96.3	0	9.3
2004	Muacevic et al[19]	51	21.7	16.5	95	0	3.9
2005	Kajiwara et al[20]	14	32.1	12.6	92.9	7.1	7.1
2005	Picozzi et al[21]	51	40.6	16.5	96.1	NR	NR
2005	Iwai et al[22]	28	36.4	12.3	93	0	7
2006	Mingione et al[13]	100	46.4	18.5	92.2	0	25
2006	Voges et al[23]	37	56.6	13.4	100	4.2	12.3
2007	Liscak et al[24]	140	60	20	100	0	1.4
2008	Pollock et al[25]	62	64	16	96.8	1.6	27
2009	Höybye & Rähn[12]	23	78	20	100	4.3	0
2009	Kobayashi[26]	71	50.2	NR	96.7	2.8	8.2
2010	Castro et al[27]	14	42	12.5	100	0	0
2010	Hayashi et al[28]	43	36	18.2	100	0	0
2011	Gopalan et al[29]	48	95	18.4	83	6.3	39
2011	Iwata et al[30] (CyberKnife)	100	33	21 Gy/3 Fr 25 Gy/5 Fr	98	1	2
2011	Park et al[31]	125	62	13	90	2.4	24
Total/ average		1146	48.66	15.9	95.7	2.1	12.0

Abbreviations: Fr, fraction; NR, not reported.

adenoma patients (see **Table 1**).[12–31] Single-session radiosurgery margin doses of 12 Gy to 18 Gy are typically used for patients with nonfunctioning adenomas. Tumor control rates range from 83% to 100% (average 95.7%) (see **Table 1**). Neurologic deficits are uncommon (average 2.1%, range 0%–7.1%) as was hypopituitarism (average 12%, range 0%–39%). At the authors' institution, 90% tumor control was reported in a series of 100 patients with nonfunctioning pituitary adenomas.[13] Tumor control was statistically less likely when the margin dose to the adenoma was reduced to below 12 Gy.[13] In a more recent publication from the authors' group, the outcomes of a smaller group of patients with a minimum follow-up of 4 years after radiosurgery were examined. The overall progression-free survival was 83%, with the vast majority of patients (75%) demonstrating marked decrease in the adenoma volume.[29] This same study demonstrated that tumor control was related to adenoma volume and that those patients with an adenoma volume of less than 5 cm^3 were more likely to have tumor control after radiosurgery. This finding underscores the importance of a maximum safe resection prior to radiosurgery.

SRS and Cushing's Disease

In 80% of cases, endogenous Cushing's disease results from overproduction of corticotropin (ACTH), with the vast majority of these secondary to a pituitary adenoma.[32] Although microsurgical resection remains the primary treatment for Cushing's disease, many adenomas show invasion of the surrounding dura and/or cavernous sinus or are difficult to delineate on MRI, thereby making a surgical cure unlikely. Radiosurgery proves an invaluable treatment option for patients with persistent Cushing's disease after a resection.

In **Table 2**, the major radiosurgical series for Cushing patients since 2000 are listed (see **Table 2**).[14,17,20,23,26,28,33–51] Most investigators used 24-hour urinary-free cortisol (UFC) or serum cortisol to define an endocrine remission. In addition, radiosurgical margin doses of 18 Gy to as high as 30 Gy are delivered to the adenomas of patients with persistent Cushing's disease.

Most series demonstrate rates of remission for the majority of patients (ie, >50%) after radiosurgery from 16.7% to 87% (see **Table 2**). Unfortunately, the endocrine remission rates after radiosurgery do not match the excellent rates of radiologic control of purely nonfunctioning adenomas. Based on the authors' experience, endocrine remission of Cushing's disease is achieved on average approximately 12 months after SRS.[39] In most series, after radiosurgery the rates of newly developed or worsened cranial neuropathies, including visual deterioration, are low (average 3.4%; see **Table 2**). The incidence of hypopituitarism after radiosurgery for Cushing's disease seems slightly higher (average 24.9%; see **Table 2**) compared with that of nonfunctioning adenoma series; this may be due to higher margin doses delivered to the adenoma that results in higher doses to collateral structures, such as the normal pituitary gland and stalk. Long-term radiologic and endocrine follow-up is crucial because late recurrences have been seen in several Cushing's disease series.[39,46]

SRS and Acromegaly

Acromegaly occurs with a prevalence of approximately 60 per million.[52] Uncontrolled acromegaly is associated with significant morbidity and even mortality (hypertension, diabetes, cardiomyopathy, and sleep apnea), conveying a standardized mortality ratio of 1.48.[52] Given its nearly immediate endocrine remission effect if successful, surgical resection remains the first-line therapy. Nevertheless, as in Cushing's disease, those cases in which there is invasion of surrounding structures (eg, the dura or the cavernous sinus) are unlikely to achieve a cure. Also, because many patients with acromegaly have macroadenomas, complete resection is not always feasible because these adenomas tend to be large and infiltrative.

Table 3 delineates the major radiosurgical series for acromegalic patients published since 2000 (see **Table 3**).[14,17,20,23,28,34,35,38,43,45–48,50,51,53–69] Similar margin doses of 18 Gy to 30 Gy are routinely delivered to the adenoma as part of single-session radiosurgery. In published series, endocrine remission after radiosurgery is achieved in 43.6% of acromegalic patients (range 0%–82%; see **Table 3**). Neurologic deficits and hypopituitarism occur after radiosurgery in 1.8% (range 0%–11%) and 15.3% (range 0%–40%) of cases, respectively (see **Table 3**). Temporary cessation of antisecretory medications around the time of the authors' center and other centers.[50] Also, patients who had a low-volume adenoma (<3 cm^3) at the time of radiosurgery were more likely to achieve endocrine remission after radiosurgery.[50] Hence, even if there is clear cavernous sinus invasion of the adenoma, maximum safe resection should be attempted; such a resection will likely yield a greater chance of endocrine remission after radiosurgery.

At the authors' center, the mean time to endocrine remission after radiosurgery for acromegalic patients was 24 months. This is nearly twice as

Table 2
Summary of the literature review for the radiosurgical management of Cushing's disease

Year	Author	Patients (N)	Mean/Median Margin Dose (Gy)	Mean/Median Follow-Up (Mo)	Biochemical Remission (%)	Neurologic Deficit (%)	Hypopituitarism (%)
2000	Izawa et al[38]	12	23.8	26.4	16.7	0	0
2000	Sheehan et al[15]	43	20	39.1	63	2.3	16
2000	Shin et al[45]	7	32.3	88.2	50	6.3	16.7
2001	Hoybye et al[37]	18	NR	16.8	44	0	68.8
2002	Feigl et al[14]	4	15	55.2	60	NR	40
2002	Kobayashi[26]	20	28.7	64	23.3	NR	NR
2002	Laws et al[41]	40	20	NR	74	2.5	24
2002	Pollock et al[51]	9	20	42.4	78	22.2	16
2003	Choi et al[35]	7	28.5	42.5	55.6	0	0
2003	Petrovich et al[17]	3	15	34	NR	3	NR
2003	Wong et al[49]	5	NR	38	100	0	20
2003	Witt[48]	8	24	24	0	0	NR
2004	Devin et al[36]	35	14.7	42	49	0	40
2006	Voges et al[23]	17	16.4	58.7	52.9	4.2	12.3
2007	Castinetti et al[33]	40	29.5	54.7	42.5	5	15
2007	Jagannathan et al[39]	90	23	45	54	5	22
2007	Kajiwara et al[101]	2	26	38.5	50	0	50
2007	Petit et al[42]	33	20	62	52	0	52
2008	Pollock et al[25]	8	20	73	87	0	36
2008	Tinnel et al[46]	12	25	37	50	0	50
2009	Castinetti et al[34]	18	28	94	50	5.3	21
2009	Wan et al[47]	68	23	67.3	27.9	2.9	1.7
2009	Kobayashi[26]	30	28.7	64.1	35	NR	NR
2010	Hayashi et al[28]	13	25.2	36	38	15.4	0
2011	Sheehan et al[50]	82	24	31	54	NR	22
Total/ average		624	23	48.9	49.9	3.4	23.6

Abbreviations: Gy, Gray; GKS, Gamma Knife radiosurgery; NR, Not reported.

Table 3
Summary of the literature review for the radiosurgical management of acromegaly

Year	Authors	Patients (N)	Mean/Median Follow-Up (Mo)	Mean/Median Margin Dose (Gy)	Biochemical Remission (%)	Neurologic Deficit (%)	Hypopituitarism (%)
2000	Izawa et al[38]	29	26.4	23.8	41.4	0	0
2000	Shin et al[45]	6	42.7	34.4	66.7	6.3	0
2000	Zhang et al[64]	68	34	31.3	36.8	2.9	0
2001	Fukuoka et al[55]	9	42	20	50	0	0
2001	Ikeda et al[56]	17	55.8	25	82	0	0
2002	Feigl et al[14]	9	55.2	15	60	NR	40
2002	Pollock et al[51]	26	42.4	20	42	0	16
2003	Attanasio et al[53]	30	46	20	23	0	6.6
2003	Choi et al[35]	9	42.5	28.5	50	0	0
2003	Muramatsu et al[61]	4	30	27.5	50	0	0
2003	Petrovich et al[17]	5	34	15	NR	3	NR
2003	Witt[48]	4	24	24	25	0	NR
2005	Castinetti et al[54]	82	49.5	25	17	0	17.1
2005	Gutt et al[65]	44	22.8	18	47.7	0	NR
2005	Kajiwara et al[20]	2	53.5	13.5	0	0	0
2005	Kobayashi et al[59]	67	63.3	18.9	4.8	11.1	14.6
2006	Jezkova et al[58]	96	53.7	35	50	0	26
2006	Voges et al[23]	64	54.3	16.5	37.5	4.2	12.3
2007	Pollock et al[62]	46	63	20	50	2.2	33
2007	Roberts et al[66]	9	25.4	21	44.4	0	33.3
2007	Vik-Mo et al[63]	61	66	26.5	17	3.3	13.1
2008	Jagannathan et al[57]	95	57	22	53	4.2	34
2008	Losa et al[60]	83	69	21.5	60.2	0	8.5
2008	Pollock et al[25,43]	27	46.9	20	67	0	36
2008	Tinnel et al[46]	9	35	25	44.4	11	22
2009	Castinetti et al[34]	43	102	24	42	5.3	21
2009	Wan et al[47] (MASEP GKS)	103	67.3	21.4	36.9	1	1.7
2009	Ronchi et al[67]	35	120	20	46.0	0	40
2010	Iwai et al[68]	26	84	20	38.0	0	8
2010	Hayashi et al[28]	25	36	25.2	40.0	0	0
2010	Poon et al[69]	40	73.8	20–35	75	0	11.4 (GKS1); 27.3 (repeat GKS)
2011	Sheehan et al[50]	130	31	24	53	NR	34
Total/average		1303	51.5	22.6	43.6	1.8	14.9

Abbreviation: NR, not reported.

long as the same milestone for Cushing's disease patients. These and similar findings of differential response of secretory pituitary adenomas to radiosurgery warrant further investigation in terms of the underlying radiobiology and ways to enhance the beneficial effects of radiosurgery on subtypes of secretory pituitary adenomas.[43]

SRS and Prolactinomas

Prolactinomas represent one of the more common types of secretory pituitary adenomas. Unlike patients with acromegaly or Cushing's disease, however, those with prolactinomas are managed first and foremost with medical therapy. For those patients with a prolactinoma that cannot be controlled with medical management or for those unable to tolerate the side effects of medical therapies, radiosurgery can be used for treatment. Considering that most patients are successfully managed with medications, the prolactinoma patients who undergo radiosurgery are likely atypical in their tumor biology and represent some of the most challenging of this cohort of patients.

The radiologic control rate after radiosurgery for a prolactinoma is high in most series and typically is more than 90%. The endocrine remission rates vary substantially, however, after radiosurgery (**Table 4**).[14,17,20,23,26,34,35,38,46,47,51,61,70–76] Biochemical remission off antisecretory medications after radiosurgery ranges from 0% to 83%. In general, biochemical remission for prolactinomas after radiosurgery tends to be worse than for those with Cushing's disease and acromegaly, even when taking into account preradiosurgical patient and tumor attributes.[43] Some of this variation in endocrine remission rates may be a result of selection bias at respective centers. As with acromegaly, however, the rates of endocrine remission seem improved in those patients who were treated with radiosurgery while they were off antisecretory medications.[70,72]

SRS-Induced Biochemical Remission and Late Recurrence

SRS yields hormone normalization within a period of time that is longer than that achieved after surgical extirpation.[77] As such, patients are typically bridged with suppressive medications after radiosurgery. Patients are periodically taken off the antisecretory medication and endocrine testing is performed. Antisecretory medications can be halted at the time when a postradiosurgery endocrine remission has been achieved. The time interval in which remission can occur ranges from 3 months to 8 years.[44,45,62] Most series demonstrate endocrine remission in Cushing's disease and acromegalic patients within 1 to 3 years after radiosurgery.

Several groups have investigated factors that increase the probability of endocrine remission. Castinetti and colleagues[54] demonstrated that preoperative growth hormone (GH) and insulinlike growth factor 1 (IGF-1) levels are significantly associated with the rate of post-SRS remission. Pollock and colleagues[62] evaluated 46 patients with GH-secreting adenomas and identified 2 significant associations. A preradiosurgical IGF-1 level greater than 2.25 times the upper limit of normal range was significantly associated with a lower rate of endocrine remission (hazard ratio 2.9; 95% CI, 1.2–6.9). For patients who had IGF-1 levels less than 2.25 times the upper limit of normal and were not taking somatostatin agonists at radiosurgery, the rates of biochemical remission exceeded 80%. A similar finding was reported by Landolt and colleagues,[78] who demonstrated that the post-SRS remission rates fell from 60% to 11% for those using octreotide during the perioperative period. Potential mechanisms underlying this phenomenon include a decreased radiosensitivity of adenoma cells secondary to decreased cell division when exposed to somatostatin agonists. Additionally, somatostatin agonists, such as octreotide, may serve as free radical scavengers, thereby reducing the DNA damage after ionizing radiation.

This result is not exclusive to acromegaly. Landolt and colleagues[78] found a significant trend toward worse outcomes in patients on dopamine agonist who were treated with radiosurgery for prolactinomas. Pouratian and colleagues[72] analyzed 23 patients with refractory prolactinomas and demonstrated a significant increase in the rates of remission in patients who were not taking dopamine agonists at the time of radiosurgery. The authors observed a similar improvement in endocrine remission in acromegalic patients who were systematically taken off pituitary suppressive medications at the time of radiosurgery.[57]

The effect of pituitary suppressive medications on endocrine outcomes after radiosurgery remains controversial. Reports in the literature have not been consistent regarding the importance of a temporary cessation of suppressive medications at the time of radiosurgery.[51,53,54,62,70,78] Two groups analyzed remission rates after radiosurgery among patients on somatostatin agonists and failed to identify an association between the use of somatostatin agonists and endocrine remission.[53,54] The definition of endocrine remission, however, has not been well defined across series, with GH levels varying from less than 5 ng/mL to (upper limit of remission).[55,79] Second, the follow-up in retrospective series varies widely. Pollock

Table 4
Summary of the literature for the radiosurgical management of prolactinomas

Year	Authors	Patients (N)	Mean/ Median Follow-Up (Mo)	Margin Dose (Gy)	Biochemical Remission (%)	Neurologic Deficit (%)	Hypopituitarism (%)
2000	Izawa et al[38]	15	28	22	20	0	NR
2000	Landolt and Lomax[70]	20	29	25	25	0	NR
2000	Pan et al[71]	128	33	32	41	0	NR
2002	Feigl et al[14]	18	55	15	NR	NR	NR
2002	Pollock et al[51]	7	42	20	29	14	16
2003	Choi et al[35]	21	42.5	28.5	24	0	0
2003	Muramatsu et al[61]	1	30	15	0	7.7	0
2003	Petrovich et al[17]	12	41	15	83	0	NR
2005	Kajiwara et al[20]	3	35.3	17.5	33	4.7	9.5
2006	Pouratian et al[72]	23	55	18.6	26	7	28
2006	Voges et al[23]	13	56	20	15.4	4.2	18.3
2006	Ma et al[76]	51	37	26.1	40	NR	17.6
2008	Pollock et al[25,43]	11	48	30	18	2	45
2008	Tinnel et al[46]	2	19.5	30	50	11	22
2009	Castinetti et al[34]	15	85.5	30	46.6	5.3	21
2009	Jezkova et al[73]	35	75.5	49	37.1	0	14.3
2009	Wan et al[47]	176	67.3	35	23.3	1.7	1.7
2009	Kobayashi[26]	27	37.4	18.4	43.5 in 23 pts	0	0
2010	Tanaka et al[74]	22	60	25	17	8	42
2011	Sun et al[75]	1	48	23	0	0	0
Total/ average		601			29.4	3.6	15.7

Abbreviations: NR, not reported; pts, patients.

and colleagues[62] demonstrated that remission continued to occur up to 5 years after radiosurgery, whereas in the report by Castinetti and colleagues,[54] 44% of their patient population received the final endocrine evaluation less than 36 months after radiosurgery. At the University of Virginia, the authors discontinue the use of suppressive medication around radiosurgery for 6 to 8 weeks, depending on its pharmacokinetics (ie, the drug's half-life). Most patients can tolerate a brief period off suppressive medications during their radiosurgery.

The rates of biochemical remission vary widely across series. There = seems to be a differential radiosensitivity between specific types of secretory pituitary adenomas.[23,26,43] Overall, Cushing's disease demonstrates the highest rates of biochemical remission, followed by acromegaly, prolactinomas, and Nelson syndrome. This sensitivity discrepancy has been attributed to patient selection, tumor volume, radiation dose, use of suppressive medications, and duration of follow-up.[26,43] Pollock and colleagues[43] reviewed a retrospective series of 46 patients. This case-controlled study demonstrated wide variations in endocrine remission after SRS for various types of secretory adenomas. This study and others suggest that different types of secretory adenomas have different radiosensitivities, but an explanation for this remain obscure.

Overall, few cases of recurrence after SRS-induced biochemical remission have been reported.[39,51] In some SRS series, however, recurrence rates of up to 20% have been reported. This serves to underscore the importance of long-term radiographic and endocrine follow-up after SRS for secretary pituitary adenomas.

Adverse Events After SRS

Fortunately, adverse events after radiosurgery for a pituitary adenoma are uncommon. Delayed onset of hypopituitarism is the most frequently occurring unintended effect of radiosurgery. Retrospective series demonstrate that 30% of patients eventually develop some form of anterior pituitary deficiency after radiosurgery. Hypopituitarism has been correlated to the radiosurgical treatment volume, with those patients having a tumor volume less than or equal to 4.0 cm^3 exhibiting an 18% 5-year risk of hypopituitarism versus 58% for those with larger lesions.[43] The incidence of hypopituitarism after radiosurgery is likely related to the preradiosurgical status of the normal pituitary gland, type and timing of prior treatments, the radiosurgical dose per volume delivered to the normal gland, the dose delivered to the pituitary stalk, and the rigorousness and length of the follow-up assessment period. A safe radiosurgical dose or dose per volume below which hypopituitarism will not occur probably does not exist. Some investigators have advocated placement of an inert spacer between the residual adenoma and pituitary gland if postoperative radiosurgery is contemplated.[80] A lower dose achieved in part through a steep gradient index, however, is intuitively pleasing in terms of minimizing the risk of hypopituitarism. Nevertheless, delivery of an optimal dose to the target volume should not be compromised when attempting to avoid hypopituitarism. Adenoma progression or persistence of a hypersecretory state is far more of a threat to longevity and quality of life than is delayed hypopituitarism. Hypopituitarism should be managed with hormone replacement under the care of an experienced neuroendocrinologist.

The second most common toxicity is cranial neuropathy. Cranial nerves II, III, IV, V, and VI are located in the parasellar or suprasellar regions and are at risk of injury from radiosurgery. Such neuropathies after radiosurgery occur in 2% or fewer of all patients. Improved conformality, steeper dose gradients, and adequate shielding may help minimize this risk.[77] Rare toxicities include radiation necrosis of the adjacent parenchyma,[23,43,47,51] internal carotid artery stenosis/occlusion,[51,81] and radiation-induced secondary malignancy.[82] No cases of radiation-induced secondary malignancies have been reported to date after SRS for pituitary tumors. Based on the available literature, the risk of serious and irreversible complications after radiosurgery for a pituitary adenoma is low.

EXTERNAL BEAM RADIATION THERAPY

In the current era, most pituitary adenoma patients in the United States are treated with SRS. For those patients with large or diffusely infiltrative adenomas or with suprasellar or brainstem extension, fractionated EBRT should be considered to minimize the risk of late toxicities.[83] The local tumor control rate after conventional fractionated EBRT for nonfunctioning pituitary adenomas is greater than 90% in most series. Similar to that seen with radiosurgery, however, the rate of biochemical normalization of functioning tumors is lower than the rate of tumor control and is dependent on on adenoma subtype.[84–86]

Radiation therapy planning starts with delineation of the target. The gross tumor volume (GTV) is the full extent of the pituitary adenoma based on neuroimaging (MRI and/or CT). Next, the clinical target volume (CTV) is defined as the GTV and areas of presumed disease extension, such as the cavernous sinus or clivus. The planned

treatment volume is an expansion of the CTV to accommodate for setup error and patient movement. With sellar-based targets, CTV expansion to create a PTV typically requires expansion of 2 mm to 5 mm, although the expansion may be nonuniform. Unlike in radiosurgery, patient immobilization typically uses a thermoplastic mask, which does not afford the same degree of immobilization and leads to a larger PTV expansion than that achieved using stereotactic approaches. It is the sum of the random errors from intrafractional and interfractional positional variation that requires a larger expansion of the CTV than in radiosurgery. This approach is in marked distinction to radiosurgery in which the PTV is usually equivalent to the GTV. Similar to radiosurgery, however, risk structures, such as the brainstem, optic apparatus, pituitary stalk, hypothalamus, and temporal lobes, are defined. Dosimetric constraints are set for the structures at risk and an optimal radiation dose and fractionation scheme is determined for the PTV. Fractionated radiation doses for pituitary adenomas typically vary from 45 Gy to 54 Gy.

EBRT and Nonfunctioning Adenomas

Conventional fractionated EBRT to a dose of 45 Gy to 54 Gy in 1.8 Gy to 2 Gy fractions has demonstrated effectiveness for patients with recurrent or progressive nonfunctioning pituitary adenomas. A retrospective experience of 2 hospitals in the United Kingdom included 126 patients with nonfunctioning pituitary adenomas. The hospitals had different approaches to management.[87] One hospital chose to treat postoperative patients with radiation therapy (45 Gy in 30–33 fractions) whereas the other did not. The progression-free survival at 15 years significantly favored the cohort who underwent EBRT (93% vs 33%, $P<.05$). In a similar study, clinicians from the Netherlands evaluated 76 patients who received postoperative EBRT and a group of 28 patients who were conservatively managed.[88] The 10-year tumor control rate was 95% for the EBRT group compared with 22% for the conservatively managed cohort. Although most radiation therapy approaches for pituitary adenomas have used photons, proton beam–based radiation therapy has also been used to treat patients with nonfunctioning adenomas. The Loma Linda group reported its experience using proton beam to treat 24 patients with nonfunctioning adenomas. In a series with a median dose of 54 cobalt Gy equivalents (CGE) and a median follow-up of 47 months, the group noted tumor control achieved in all patients.[89]

If adequate sparing of normal tissue cannot be attained with a single-fraction SRS, FSRT may be used because it combines the precise immobilization of SRS with the radiobiologic benefits of standard fractionation on normal tissue. FSRT has been used by some centers to treat patients with nonfunctioning adenomas. This approach is a blending of the advantages and disadvantages of radiosurgery and EBRT. Colin and colleagues[90] detailed a series of 63 patients with nonfunctioning adenomas who underwent FRST. At a median follow-up of 82 months after FSRT, tumor control was achieved in all patients. In this same series, hypopituitarism was seen in 28.5% of patients at 4 years and 35% of patients at 8 years post-FSRT.

EBRT and Cushing's Disease

EBRT is commonly used for patients with residual or recurrent tumor after an initial transsphenoidal resection or in patients with no radiographic evidence of disease but endocrine evidence of persistent Cushing's disease. Endocrine remission is usually defined as normalization of the 24-hour UFC, salivary cortisol, and serum corticotropin, but significant differences in remission criteria are used, even at leading centers. Both EBRT and SRS seem to achieve biochemical remission rates of 50% to 80%. The latency period between EBRT and endocrine remission is usually a year or more. EBRT tends to be associated with a longer time to achieve endocrine remission in patients with functioning adenomas. In one series comparing time to endocrine remission, patients undergoing radiosurgery achieved endocrine remission at a mean time of 8.5 months, whereas those treated with EBRT achieved remission in 18 months.[83]

In a group of patients with Cushing's disease, Estrada and colleagues[84] reported endocrine remission rates of 44% at 1 year and 83% at 3 years after EBRT. In a group of 40 patients with Cushing's disease treated with doses between 45 Gy and 100 Gy, Hughes and colleagues[91] reported a 10-year endocrine remission rate of 59%.

Early experiences with charged particles from the Lawrence Berkeley National Laboratory demonstrated 85% endocrine remission rates using helium ions, with doses ranging from 30 CGE to 150 CGE in patients with Cushing's disease. The Massachusetts General Hospital proton group noted 52% of radiographic and endocrine remission, with a median dose of 20 CGE at a median follow-up of 62 months.[92]

EBRT and Acromegaly

EBRT has been used to treat patients with persistent acromegaly. Unlike patients with Cushing's

disease, where the adenoma may be less apparent on neuroimaging studies, patients with persistent acromegaly after transsphenoidal resection tend to have well-demarcated tumors. Tumor control after EBRT is usually quickly achieved radiographically, but endocrine remission typically takes years to attain. Endocrine remission is usually defined as a normalization of IGF-1 (matched for age and gender) and GH level less than 1 ng/mL after an oral glucose challenge.

The largest experience reported to date was a series of 884 patients reported by 14 different centers in the United Kingdom.[93] GH levels less than 2.5 ng/mL were achieved in 22%, 60%, and 77% at 2, 10, and 20 years, respectively. In that same series, normal IGF-1 levels were found in 63% of patients at a median follow-up of 10 years after EBRT. In another series with a median follow-up of 11.5 years, Barrande and colleagues[94] demonstrated that 66% of 128 patients achieved a GH of less than 2.5 ng/mL at 15 years post-EBRT. In that same series, 79% of patients ultimately achieved a normal IGF-1. In a smaller Dutch series of 36 patients treated with EBRT to a median dose of 40 Gy, IGF-1 normalization rates of 60%, 74%, and 84% were observed at 5, 10, and 15 years, respectively.[95]

In a few institutions, proton beam therapy is used to treat acromegalic patients. The Massachusetts General Hospital group reported a 59% endocrine remission rate in a series of 22 patients with a median follow-up of 6.3 years. The median time to endocrine remission in this series was 3.5 years.[42] The Loma Linda experience with proton beam for 11 acromegalic patients demonstrated a rate of endocrine normalization of 45% at a median follow-up period of 3.9 years.

EBRT and Prolactinomas

As is true for radiosurgery, prolactinomas are seldom treated with EBRT. Most prolactinoma patients are treated medically with dopamine agonists or approached via a transsphenoidal resection. Those prolactinoma patients undergoing EBRT likely represent a selected and poorly behaving cohort of patients.

Biochemical remission is defined as a normal serum prolactin level of less than 20 ng/mL depending on gender. EBRT affords endocrine remission off antisecretory medications in approximately 10% to 30% of patients and the latency of effect is usually achieved over many years.[96,97] In 1991, Littley and colleagues[98] reported their results with EBRT for patients with large prolactinomas. They used standard fractionation schemes of 20 Gy to 42.5 Gy in 8 to 15 fractions and followed patients for up to 154 months after treatment. In a total of 58 patients, 71% of patients achieved a normal prolactin level while on a dopamine agonist. When off the dopamine agonist, however, only 21% achieved a normal prolactin level after EBRT. Isobe and colleagues[97] reported on their experience with EBRT (48–60 Gy, median 50 Gy) in prolactinoma patients. They noted that patients with a prolactinoma were less likely to achieve local tumor control after EBRT. Although radiation therapy may be used as a salvage approach for prolactinoma patients refractory and/or ineligible for medical therapy, microsurgery, or radiosurgery, its overall chances of achieving endocrine remission seem lower than with Cushing's disease or acromegalic patients.[91]

ADVERSE EVENTS AFTER EBRT

The most common risk associated with EBRT is delayed hypopituitarism. Risks of hypopituitarism after EBRT range from 50% to 100% depending on the length and rigorousness of endocrine follow-up.[84,98] EBRT carries a 1% to 3% risk of optic neuropathy.[86,99] Other more severe complications include a 2.7% risk of radiation-induced neoplasia at 10 years after EBRT and a 4% risk at 5 years of suffering a cerebrovascular accident after EBRT, presumably from radiation-induced carotid stenosis.[100]

EBRT has had a longer track record for use with pituitary adenoma patients. Although the extended follow-up period for EBRT may explain some differences between the frequency and severity of complications associated with EBRT versus SRS, the true differences in the risk profile of EBRT and SRS have yet to be fully defined. Nevertheless, in the United States, contemporary management of pituitary adenoma patients has largely shifted away from EBRT to SRS because of SRS's improved rates of endocrine remission and the perception, at least, of an improved side-effect profile.

SUMMARY

EBRT and SRS play important roles in the management of pituitary adenomas. SRS or EBRT are typically used in patients with substantial residual tumor or recurrence after resection. They are also used for patients with functioning adenomas that fail to achieve endocrine remission after prior resections. Neurologic function after SRS or EBRT is usually preserved or at times improved, even when the treated adenoma extends into the cavernous sinus. Delayed hypopituitarism is the most common complication but is manageable with hormone replacement. Other

serious complications are rare. Lifelong follow-up for pituitary adenoma patients is recommended.

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