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Comprehensive review of stereotactic radiosurgery for medically and surgically refractory pituitary adenomas

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Abstract

Despite advances in surgical techniques and medical therapies, a significant proportion of pituitary adenomas remain endocrinologically active, demonstrate persistent radiographic disease, or recur when followed for long periods of time. While surgical intervention remains the first-line therapy, stereotactic radiosurgery is increasingly recognized as a viable treatment option for these often challenging tumors. In this review, we comprehensively review the literature to evaluate both endocrinologic and radiographic outcomes of radiosurgical management of pituitary adenomas. The literature clearly supports the use of radiosurgery, with endocrinologic remission rates and time to remission varying by tumor type [prolactinoma: 20–30%, growth hormone secreting adenomas: ~50%, adrenocorticotrophic hormone (ACTH)-secreting adenomas: 40–65%] and radiographic control rates almost universally greater than 90% with long-term follow-up. We stratify the outcomes by tumor type, review the importance of prognostic factors (particularly, pre-treatment endocrinologic function and tumor size), and discuss the complications of treatment (with special attention to endocrinopathy and visual complications). We conclude that the literature supports the use of radiosurgery for treatment-refractory pituitary adenomas, providing the patient with a minimally invasive, safe, and effective treatment option for an otherwise resistant tumor. As such, we provide literature-based treatment considerations, including radiosurgical dose, endocrinologic, radiographic, and medical considerations for each adenoma type.

Key Words: Pituitary adenoma, radiosurgery, stereotactic

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INTRODUCTION

Pituitary adenomas are relatively common tumors, comprising approximately 10–20% of all primary intracranial lesions, with a reported incidence of up to 20% within the general populace.[25,28] Traditionally, they have been divided into two categories, functioning and nonfunctioning, based on the presence or absence of significant hormone secretion [most commonly, prolactin (PRL), growth hormone (GH), adrenocorticotrophic hormone (ACTH)], respectively. Although one of the primary goals of surgery for both tumor categories is to maximize surgical resection, oftentimes this is not possible due to extrasellar invasion into the dura or

cavernous sinus.[51] Moreover, functioning tumors may continue to produce significant amounts of hormone with deleterious endocrine and systemic effects despite subtotal or perceived gross total resection, adding an additional degree of difficulty to achieving neurosurgical cure. Consequently, rates of tumor control using surgery alone vary from 50 to 90% depending on the functional status and degree of tumor invasion.[4,13,28,48]

For decades, radiation therapy has served as an adjuvant treatment for residual or recurrent adenomas, and even as a primary form of treatment for pituitary lesions in patients who are not candidates for surgery. Initially performed solely with conventional fractionated radiation, this form of radiotherapy has the longest available follow-up and has been demonstrated to aid in tumor control and endocrine normalization following initial surgical resection of nonfunctioning and functioning pituitary adenomas. However, moderate rates of recurrent tumor growth (up to 20%),[3,16,74] high rates of long-term resultant pituitary hormone deficiencies (50–100%),[44,50] and the albeit lower but unacceptable risks of cranial neuropathies, secondary neoplasms, and stroke are some of the criticisms against conventional radiotherapy. Moreover, the time needed to achieve hormone normalization in certain functioning pituitary adenomas can be as long as two or three decades, during which the patient will continue to be subject to the increased morbidity of the adenoma-induced endocrinopathy.[1] Given the above-mentioned deficiencies of conventional radiotherapy, other avenues of adjuvant treatment were pursued.

Stereotactic radiosurgery (SRS) has recently received a great deal of attention in the secondary treatment of pituitary adenomas. SRS for pituitary tumors was first performed using the Leksell Gamma Knife in 1968.[41] The ability to deliver the full treatment dose within one session, and the theoretically reduced risk of injury to nearby neural structures on account of the conformal nature of the beams gained SRS immediate popularity. However, given the relative novelty of this technology compared to conventional radiotherapy, long-term studies on the efficacy and complications of SRS are still being acquired. In this review, we summarize the most pertinent studies regarding SRS for pituitary adenomas over the last decade in order to review its long-term efficacy in terms of tumor control, endocrine remission in functional adenomas, and its associated complications in terms of pituitary function and neurologic deficit.

MATERIALS AND METHODS

A Pubmed search was conducted with the key words "pituitary adenoma," "radiosurgery," "stereotactic," "Gamma Knife," and "Cyberknife," alone and in combination. Search results were reviewed for primary series of nonfunctioning and secretory adenomas treated with single-dose radiosurgery (or up to three fractions for hypofractionated radiosurgery) since the year 1999. Additional studies were obtained through secondary review of references from publications acquired from the initial search results. Studies that published results on a single subset of pituitary adenomas were prioritized for compilation into relevant tables. Other studies that reported combined results on multiple adenoma subtypes were included if they had significant sample sizes or had important contributions to the clinical understanding of adenoma response to radiosurgery.

RESULTS AND DISCUSSION

Nonfunctioning pituitary adenoma

Nonfunctioning pituitary adenomas (NFPAs), as the name suggests, do not secrete excess normal pituitary hormones unlike their functioning counterparts. As such, the resultant presenting symptoms are generally secondary to tumor mass effect on the optic apparatus and pituitary gland, namely visual disturbances and endocrine deficiencies. In line with the presenting problem, first-line therapy remains surgical extirpation with the goal of surgical decompression of the affected adjacent structures while preserving neurologic and endocrine function. Retrospective analyses indicate that with any radiographic evidence of tumor remnant, the progression of tumor growth in nonfunctioning adenomas is typically about 50% at 5–10 years, and that the factors most associated with risk of growth are invasion into parasellar structures such as the cavernous sinus and length of imaging follow-up.[4,58,82,83] A side-by-side comparison of these retrospective series investigating recurrence rates of NFPAs is difficult, as each study includes patients with variable extents of resection, resulting in a wide range of 10-year recurrence risk following surgery alone (20–80%).[55] However, the early use of radiotherapy appears to lead to greater tumor control, supporting the notion of early radiation treatment for tumor control rather than a "wait-and-see" policy.[58,65,83]

Numerous reports to date have assessed the long-term tumor control of SRS in patients with NFPAs [Table 1]. Although the vast majority of the studies have used Gamma Knife radiosurgery (GKRS),[18,21,23,37,43,47,52,54,57,65,76,88] other modalities of radiosurgery including Cyberknife (CK)[10,32,34] and linear accelerator based SRS (LINAC)[86] based radiosurgery, both as single dose treatments and hypofractionated schemes, have also been used. Retrospective GKRS series have the longest follow-up, with median radiographic surveillance ranging from 29 to 80 months, with the majority of studies reporting greater than 60 months. The mean/median margin dose used in the GKRS-based publications ranged from 13 to 24 Gy, with the majority of groups reporting a mean/

Table 1: Nonfunctioning pituitary adenomas

Author	Rx type	N	Median follow-up, months (mean)	RT dose (Gy), median (range)	Local control (%) [decrease]	New pituitary deficit (%)	New visual deficit (%)
Sheehan (2011)[76]	GKRS	152	31	*	90.3	*	*
Park (2011)[57]	GKRS	125	62	13	89.6 [53]	24	0.80
Gopalan (2011)[18]	GKRS	48	80.5	18.4 mean (8–25)	83.3 [75]	38	6.25 (Tumor related)
Kobayashi (2009)[37]	GKRS	71	>36	14.1	96.7 [71.3]	8.2	4.3
Killory (2009)[34]	CK	14	29.3	25/5 Fr	NR	NR	7
Hoybye (2009)[21]	GKRS	23	78	20	100 [78]	0	NR
Cho (2009)[10]	CK	17	27	1900 cGy (1500–2200, 1–3 fractions)	*	0	11.8
Pollock (2008)[65]	GKRS	62	64	16 (11–20)	97 [60]	27	0
Liscak (2007)[43]	GKRS	140	60	20 (12–35)	100 [89]	1.4	0
Voges (2006)[86]	LINAC	37	56.6	15.3 mean (8–20)	100 [40.5]	12.3	NR
Mingione (2006)[52]	GKRS	90	44.9	18.5 mean (5–25)	92.2 [65.6]	19.7	0
Kajiwara (2005)[32]	CK	14	32	12.6	92.9 [7.1]	7.1	0
Iwai (2005)[23]	GKRS	31	59.8	14 (8–20)	87.1 [58.1]	6.5	0
Losa (2004)[47]	GKRS	54	[41.1]	16.6 (12–21)	100 [42.3]	12.5/8.6/2.3¥	0
Wowra (2002)[88]	GKRS	30	55	16 (11–20)	93	10	0
Mokry (1999)[54]	GKRS	31	28.9	13.8	98.3	19.2	0

*Hypogonadism/hypothyroidism/hypoadrenalism, *Data reported from a series including other types of adenomas, GK: Gamma Knife radiosurgery, CK: Cyberknife, LINAC: Linear accelerator based SRS, NR: Not reported

median margin dose of approximately 14–20 Gy. Tumor control ranged from 83 to 100% over the range of follow-up periods. While radiographic control did not appear to be strictly correlated with the median margin dose, there is a trend toward poorer control rates with longer follow-up. While the primary goal of treatment is usually tumor control (or preventing tumor growth), many studies have also reported rates of reduction in tumor size, which is far more variable with rates ranging from 42 to 89%. This wide variability is in part on account of one group requiring greater than 20% reduction in tumor size to classify an adenoma as having shrunk,[47] while all others reported any reduction in total tumor size on magnetic resonance imaging (MRI; range 53–89% without this outlier).

Given the relative novelty of CK in the adjuvant treatment of pituitary adenomas, the literature regarding its use and associated follow-up periods is limited compared to that with Gamma Knife. The few reports regarding its use in NFPAs contain retrospective follow-up periods of approximately 30 months. Although the reported tumor control rate of over 92–93%[10,32] is promising, the limited follow-up period and delivery of therapy in fractions make it difficult to compare with the results from Gamma Knife. Similarly, a report of 100% tumor control rate by a group using LINAC will need further studies to corroborate the findings.[86]

Rates of new anterior pituitary deficits following SRS of nonfunctioning adenomas ranged from 0 to 38% [Table 1]. Interestingly, the group that reported the greatest incidence of new pituitary deficit had the longest follow-up period (80.5 months),[18] with other groups reporting more similar incidences around 10–20%, suggesting that prolonged follow-up is needed before the actual rate of endocrine dysfunction from SRS can be known. New visual deficits ranged from 0 to 12%, with most groups reporting no new deficiencies in visual acuity.[10,23,47,52,54,88]

PRL producing adenoma

The most common pituitary adenoma, prolactinomas, accounts for 45% of pituitary tumors.[12] The first-line treatment for prolactinomas is dopamine agonists, such as bromocriptine or carbergoline, which normalize PRL levels in 80–90%, with higher success rates in the treatment of microadenomas.[36,45] In the remaining 10–20% of patients in whom PRL levels fail to normalize following maximal medical therapy, and in patients who cannot tolerate dopamine agonists due to their side effects, resection and/or radiosurgery is indicated. SRS is generally considered a viable treatment alternative for prolactinomas, although it is usually reserved for use after surgical resection in patients who have persistent disease after resection or tumor recurrence or progression following surgery.

The peripheral radiation dose commonly used for prolactinoma treatment is approximately 25 Gy (median range 13–34 Gy), which is higher than doses used in both nonfunctioning and ACTH/GH secreting tumors. Complete endocrine normalization [when assessed off medical (dopamine agonist) therapy] has been reported

to occur in 11–80% of patients with a mean time to normalization of 2–8 years, although most studies report a remission rate of 20–30% [Table 2]. Although endocrine normalization rates are far from ideal, reduction of PRL levels without complete endocrine normalization following SRS is found and reported in most patients (up to 80%).[80] Remission criteria are generally defined as PRL levels within normal limits (often < 20 ng/ml), although interpretation of outcomes in studies of SRS for prolactinomas is challenging as not all groups publish remission criteria and minimally elevated PRL levels may be due to stalk injury without residual tumor. Tumor control rates approach 100%, but tumor shrinkage occurs in fewer patients (20–50%).[11,19,24,30,35,56,80,87]

Microadenomas appear to be more responsive than

Table 2: Prolactin-secreting adenomas

Author	Rx type	N	Follow-up median, months (mean)	Margin dose (Gy), median (range) [mean]	Initial median PRL level, ng/ml	Biochemical remission criteria	Partial endo response (%)	Complete endo cure (%)	New pituitary deficit (%)	New visual deficit (%)
Sheehan (2011)[76]	GKRS	32	*	*	NR	PRL < 619 mIU/l in non-pregnant women, PRL < 430 mIU/l in post-menopausal women, PRL < 375 mIU/l in men	NR	26	38	*
Marek (2011)[48]	GKRS	10	*	*	NR	PRL < 619 mIU/l in non-pregnant women, PRL < 430 mIU/l in post-menopausal women, PRL < 375 mIU/l in men	NR	37.5–50	*	*
Tanaka (2010)[80]	GKRS	22	60	25 (16–30)	88.4	Men: PRL < 13 ng/ml, women: PRL < 27 ng/ml, off DA	14	18	42	0
Castro (2010)[8]	GKRS	9	*	*	55	Normal serum PRL	33	44	*	0
Wan (2009)[87]	GKRS	176	*	22.4 (15–35)	NR	PRL < 20 μg/l non-pregnant women, <12 μg/l in men	NR	23.3	1.7	0
Jezkova (2009)[30]	GKRS	35	66	34 (20–49)	28,930 mIU/l (mean)	PRL < 619 mIU/l in non-pregnant women, PRL < 430 mIU/l in post-menopausal women, and PRL < 375 mIU/l in men	NR	80	14	*
Castinetti (2009)[6]	GKRS	15	86.2	*	130 (remission) vs. 980 (uncured)	PRL level < 20 ng/ml, off DA	NR	46	*	*
Tinnel (2008)[81]	GKRS	4	19.5	19 (15–30)	NR	Normal serum PRL	25	50	0	0
Pollock (2008)[63]	GKRS	11	48	25 (18–30)	129	PRL < 27 ng/ml women, <13 ng/ml men	NR	18	*	9
Voges (2006)[86]	LINAC	13	(56)	13.5 (10.2–16.9)	NR	NI PRL (range NR)	NR	15.4	*	*
Pouratian (2006)[70]	GKRS	23	55	[18.6]	928	PRL < 20 ng/ml, off DA	NR	26	28	0
Kim (2006)[35]	GKRS	44	*	*	NR	NR	NR	62.5	*	0
Petrovich (2003)[62]	GKRS	12	*	*	219 (mean)	NR	0	83	*	*
Jane (2003)[29]	GKRS	19	*	*	NR	Normal serum PRL	NR	11	21	0
Choi (2003)[11]	GKRS	21	*	*	NR	PRL < 20 ng/ml	61.9	23.8	0	0
Pollock (2002)[67]	GKRS	7	*	*	123	PRL < 23 ng/ml	NR	29	*	0
Pan (2000)[56]	GKRS	128	(33.2)	[31.2] (9–35)	>30	Normal serum PRL	28	52	<1	0
Landolt (2000)[40]	GKRS	20	(28.6)	(20–35)	NR	PRL level < 19 ng/ml in women, <16 ng/ml in men, off DA	55	25	NR	NR

*Data reported from a series including other types of adenomas, GK: Gamma Knife radiosurgery, CK: Cyberknife, LINAC: Linear accelerator based SRS, NR: Not reported

macroadenomas, with remission rates of 70% versus 30%, respectively.[30] Patients with tumors smaller than 3 cm^3 and who are not receiving dopamine agonists at the time of SRS will likely benefit the most from SRS.[29,40,63,70,80] It has been hypothesized that suspending dopamine agonist therapy prior to SRS may increase tumor cell susceptibility to radiosurgery, and various groups have published findings to support this.[40,70] Overall complication rates are low for visual deficits (0–2%), but significantly higher for postoperative pituitary dysfunction (0–42%).

Growth hormone producing adenoma (acromegaly)

The excess production of GH from pituitary adenomas results in acromegaly, an endocrine disorder characterized by progressive somatic disfigurement and increased mortality secondary to the systemic effects of chronically elevated GH and its primary mediator insulin-like growth factor-1 (IGF-1).[9] First-line therapy historically has consisted of surgical resection, with or without medical therapy. Surgical cure of GH-producing microadenomas is favorable, with rates of approximately 75–95%; however, on account of the insidious nature of the disease and oftentimes resultant late diagnosis, most present as macroadenomas, which are cured by surgery alone only 40–68% of the time.[89] Although surgical debulking, even in cases of subtotal resection, can lead to improved medical management,[33] patients are dependent on somatostatin analogs and GH antagonists for life, which can become very costly. Early work with fractionated radiotherapy demonstrated that radiation therapy can result in GH normalization, however, in addition to the typical side effects of pituitary deficits and cranial neuropathies, the time to remission was in the order of decades, an unfavorable delay before treatment effect, given the continued morbidity with elevated GH and IGF-1.[1,39]

Numerous studies have been published regarding the treatment of GH-producing pituitary adenomas with SRS [Table 3]. The vast majority of groups report a median margin dose of 20–25 Gy, with a minority of studies reporting margin doses as high as 35 Gy.[31,77] Tumor control rates range from 92 to 100%. A recent meta-analysis by Yang *et al.*[89] evaluated the rates of remission based on study-specific criteria and found that following SRS the rate of cure was approximately 48–53%. Endocrine normalization improved to 60.3% when also including patients who met the criteria for cure while

Table 3: Growth hormone secreting adenomas

Author	Rx type	N	Follow-up median (months) [mean]	Margin dose (Gy), median (range)	Initial median GH level (ng/ml)	Initial median IGF-1 level (ng/ml)	Biochemical remission criteria	Cure rate without meds (%)	Remission rate with meds (%)	New pituitary deficit (%)	New visual deficit (%)
Sheehan (2011)[76]	GKRS	130	*	*	NR	NR	Normal IGF-1	NR	53	34	*
Poon (2010)[69]	GKRS	40	[73.8]	(20–35)	36.94 (cured), 38.66 (uncured)	NR	GH < 2 ng/ml and normal IGF-1	NR	75	15	0
Iwai (2010)[22]	GKRS	26	84	20	11	790	GH < 2 or GH < 1 after OGTT and IGF-1 normal	4	38	8	0
Wan (2009)[87]	GKRS	103	*	21.4 (12–30)	NR	NR	OGTT GH < 1 ng/ml and normal IGF-1	NR	36.9	1.9	NR
Ronchi (2009)[72]	GKRS	35	114	20 (15–35)	3 (cured), 7.5 (uncured)	NR	GH < 2.5 ng/ml, normal IGF-1, and OGTT GH < 1 ng/ml	46	50	50	0
Cho (2009)[10]	CK	6	[35]	1983 cGy (mean)	NR	NR	GH level below 5 mIU/l	33	NR	0	0
Castinetti (2009)[6]	GKRS	43	[50]	*	7.2 (cured), 43.4 (uncured)	605 (cured), 721 (uncured)	GH < 2 ng/ml and/or OGTT GH < 1 ng/ml, and normal IGF-1	42	NR	*	*
Swords (2009)[79]	GKRS	10	36	10	10	90	GH < 1.8 ng/ml and normal IGF-1**,***	29	43	*	*

Contd...

Table 3: Contd...

Author	Rx type	N	Follow-up median (months) [mean]	Margin dose (Gy), median (range)	Initial median GH level (ng/ml)	Initial median IGF-1 level (ng/ml)	Biochemical remission criteria	Cure rate without meds (%)	Remission rate with meds (%)	New pituitary deficit (%)	New visual deficit (%)
Tinnel (2008)[81]	GKRS	9	35	25 (16–30)	NR	NR	Normal IGF-1	44	NR	22	0
Pollock (2008)[63]	GKRS	27	46.9	20	7.9	591	GH < 2 μg/ml and normal IGF-1	67	NR	*	0
Jagannathan (2008)[26]	GKRS	95	49	22	NR	NR	Normal IGF-1	53	67	34	4
Losa (2008)[46]	GKRS	83	69	21.5	7	540	GH < 2.5 ng/ml and normal IGF-1	60	84	8.5	0
Vik-Mo (2007)[84]	GKRS	53	[66]	26.5 (12–35)	7.69	546	GH < 1 ng/ml and normal IGF-1 or OGTT GH < 1 ng/ml	17	NR	13	4
Petit (2007)[60]	Proton	22	75.6	-	[20CGE]	-	Normal IGF-1	59	NR	38	NR
Pollock (2007)[66]	GKRS	46	63	20 (14.4–30)	8.4	NR	GH < 2 ng/ml and normal IGF-1	50	NR	33	0
Roberts (2007)[71]	CK	9	[25.4]	21 (18–24)	[21BED]	NR	Normal IGF-1	44	56	33	0
Voges (2006)[86]	LINAC	64	[54.3]	16.5			GH < 2 ng/ml and normal IGF-1	37.5	47		
Jezkova (2006)[31]	GKRS	96	54	35 (10–42)	20	944	GH < 1 ng/ml in OGTT and normal IGF-1	57.1	NR	27	0
Castinetti (2005)[7]	GKRS	82	[49.5]	26	22	653	GH < 2 ng/ml and normal IGF-1	17	40	17	0
Gutt (2004)	GKRS	44	22.8	18 (12–23)	NR	NR	Normal IGF-1	48	NR	0	0
Attanasio (2003)	GKRS	30	46	20 (15–35)	10	624	GH < 2.5 ng/ml and normal IGF-1	23	40	7	0
Choi (2003)	GKRS	12	*	*	NR	NR	GH < 1.8 ng/ml	50	NR	*	0
Swords (2003)	LINAC	12	25	*	7	624	GH < 1.7 ng/ml; normal IGF-1	50	58	*	0
Petrovich (2003)	GKRS	6	*	*	22.3	940	GH < 5.0 ng/ml	100	100	*	*
Jane (2003)[29]	GKRS	64	*	*	NR	NR	Normal IGF-1	36	NR	28	0
Pollock (2002)[67]	GKRS	26	*	*	8.3	305	GH < 2 ng/ml and normal IGF-1	42	62	*	*
Ikeda (2001)	GKRS	90	[58.8]	25	51.2	NR	Cure: OGTT GH < 2 ng/ml and normal IGF-1; remission: normal IGF-1****	57	NR	0	0
Fukuoka (2001)	GKRS	9	36	20	17	NR	GH < 5 ng/ml and normal IGF-1	50	NR	0	0
Landolt (2000)	GKRS	31	[19.2]	24.5	NR	NR	GH < 5 ng/ml and normal IGF-1	45	NR	NR	NR
Shin (2000)	GKRS	6	[42.7]	34.4	8.5	781.5	GH < 3.8 ng/ml and IGF-1 < 450 ng/ml	67	NR	0	0
Zhang (2000)	GKRS	68	[34]	31.3	NR	NR	GH < 12 ng/ml	96	NR	Incomplete	1.5

*Data reported from a series including other types of adenomas, **Patients on pegvisomant subtracted from total patients in cure analysis as GH could not be reliably analyzed, ***Includes pegvisomant patients as well (n = 10), ****Extrapolated as only 42 of 60 pts with normal IGF-1 had OGTT tested, -Unable to access information, GK: Gamma Knife radiosurgery, CK: Cyberknife, LINAC: Linear accelerator based SRS, NR: Not reported, BED: biologically effective dose, CGE: Cobalt Gray equivalents

on hormone suppressive medications. However, given the variable definitions of endocrinologic remission between each study, and incomplete information as GH-producing tumors were often combined with other functional and nonfunctional pituitary adenomas in reported analyses, it is difficult to make an accurate assessment of the results to date.[45] This is especially true with the definitions of endocrinologic cure as defined by the Acromegaly Consensus Group,[17] as these criteria have become increasingly more stringent within the last decade.

The limited number of studies reporting CK treatment of GH-producing adenomas show a comparable tumor control rate of 92–100%.[10,71] Rates of endocrine cure without medication ranged from 33 to 44% based on study-dependent criteria. However, the relatively short mean follow-up time of 25–35 months suggests a favorable response of GH pituitary adenomas to CK therapy. Similarly, studies investigating the use of LINAC to treat acromegaly have small patient sizes and are components of larger series including other types of adenomas. Endocrine cure without medication ranged from 37.5 to 50%, with tumor control rates ranging from 97 to 100%.[78,86] One report using proton beam SRS showed a cure rate of 59%.[60] However, similar to the studies using CK, due to limited patient size and follow-up, future studies with longer analyses will be necessary to compare the above-mentioned modalities to GKRS.

Despite the disparate study designs, radiation dosing, and criteria for endocrine remission, a few prognostic trends have emerged as predictors of endocrine response to SRS in acromegaly. Multiple groups have reported that lower baseline levels of GH[6,7,31,46,72] and/or IGF-1[6,7,31,46,66] at the time of radiosurgery were a positive predictor of endocrine response to SRS, with IGF-1 levels less than 2.25 times the upper limit of normal being the most commonly cited prognostic threshold. Other groups reported that the cessation of somatostatin analogs or GH antagonists prior to radiosurgery resulted in a beneficial response.[26,67] The mechanism behind the medication status is unclear; however, it may be related to the fact that adenoma cells not being suppressed by medications will be actively proliferating, and thus are more sensitive to the effects of radiation. Alternatively, it could be that in the retrospective studies that report these relationships, patients who could actually tolerate being off medications may have a less aggressive form of the disease.[73] Still, others have found no effect of being on or off medications at the time of radiosurgery,[6,46,72] arguing that further studies may be needed to elucidate the presence of a true effect.

Rates of complications including new anterior pituitary deficits (0–50%) and worsening of visual acuity or fields (0–4%) were comparable to other tumor types receiving SRS. Similar to NFPAs, the group reporting the greatest incidence of new pituitary dysfunction had the longest follow-up time.[72]

Adrenocorticotrophic hormone-producing adenoma (Cushing's disease)

Radiosurgery for Cushing's disease is often an adjuvant to surgical resection of ACTH-secreting adenomas. Failure to achieve remission or tumor recurrence occurs in up to 30% following initial successful transsphenoidal resection of ACTH-secreting tumors in Cushing's disease patients.[2,59] Margin doses used for SRS range from 15 to 30 Gy, with an optimal dosing of approximately 20 Gy. SRS may accelerate clinical and endocrinologic response to treatment.[53]

SRS achieves normalization of ACTH levels in a median time of approximately 7.5–58 months [Table 4]. Success rates of hormone normalization by SRS are variable and difficult to interpret, given the lack of standardized criteria for postoperative hormone control (e.g. 24-h urinary free cortisol vs. serum ACTH, vs. basal serum cortisol) and many studies do not specify whether medical therapy is ongoing during the postoperative period. Complete endocrine normalization has been reported in 10–87% of patients, with most reports showing remission rates of approximately 40–65% [Table 4]. Tumor control is achieved in 80–100% of patients, with decreased adenoma volume in 10–70% of patients [Table 4]. Similar to other functioning adenomas, microadenomas are associated with better response rate than macroadenomas[37,38] and remission rates may be improved by continuing medical therapy in the postoperative period. Tumor recurrence can present late,[6,14,27,75] with recurrent hypercortisolism being reported as late as 8 years postoperatively.[6] In the largest study to date involving 90 evaluable Cushing's patients undergoing SRS with a mean dose of 23 Gy (median 25 Gy) and a mean endocrine follow-up of 45 months, Jagannathan and colleagues reported normalization of 24-h urinary free cortisol in 54% of patients with an average time to remission of 13 months (range 2–67 months).[27] While the average time to remission was 8.9 months, 20% of patients demonstrated tumor recurrence between 6 and 60 months after SRS.[27] These findings suggest that despite evidence of endocrine remission following SRS, Cushing's patients require lifelong follow-up in order to monitor for tumor recurrence. In all studies, rates of complication are similar to those of other functioning adenomas, with new anterior pituitary deficits reported in 0–66% of patients, visual deficits in 0–27% of patients, and cranial nerve deficits in <5% of patients [Table 4].

Bilateral adrenalectomy for the treatment of Cushing's syndrome may lead to uncontrolled growth of any preexisting pituitary adenoma due to the lack of negative feedback from endogenous cortisol. Resulting tumors of Nelson's syndrome are often aggressive and difficult to control. SRS has been reported to be less effective

Table 4: Adrenocorticotrophic hormone secreting adenomas

Author	Rx type	N	Follow-up median, months [mean]	Margin dose (Gy), median (range) [mean]	Biochemical remission criteria	Partial endo response (%)	Complete endo cure (%)	New pituitary deficit (%)	New visual deficit (%)
Sheehan (2011)[76]	GKRS	82	*	*	NR	NR	54	22	*
Hayashi (2010)	GKRS	13	[36]	25.2 (12–35)	NR	38	38	0	2
Castro (2010)[8]	GKRS	9	*	*	Normal ACTH	11	66	*	0
Wan (2009)[87]	GKRS	68	*	21.9 (15–35)	24-h UFC < 200 μg/dl (550 nmol/dl) + plasma cortisol <2.5 μg/dl (69 nmol/dl)	NR	27.9	1.5	0
Castinetti (2009)[6]	GKRS	18	[96]	*	Normal 24-h UFC + cortisol <50 nmol/l after low-dose dexamethasone suppression test	NR	50	*	*
Tinnel (2008)[81]	GKRS	12	[37]	25 (16–30)	24-h UFC within normal	17	50	50%	0
Pollock (2008)[63]	GKRS	8	73	20 (18–30)	24-h UFC within normal	NR	87	*	0
Petit (2008)[61]	Proton	33	62	20 CGE (15–20)	Normal 24-h UFC >3 months	36	52	52	0
Jagannathan (2007)[25]	GKRS	90	[45]	25 (8–30)	Normal 24-h UFC	NR	54	22%	<1
Castinetti (2007)[5]	GKRS	40	48	29.5 (15-40)	Normal 24-h UFC with suppressible plasma cortisol level after low-dose dexamethasone suppression test	NR	42.5	15%	0
Voges (2006)[86]	LINAC	17	[58.7]	[16.4] (13.2-19.6)	Serum cortisol <25 μg/dl or normal 24-h UFC	11.8	64.7	12.30%	NR
Devin (2004)[14]	LINAC	35	[42]	[14.7] (10.7–18.7)	Require steroid replacement therapy at some point after SRS + no evidence of recurrent hypercortisolism	NR	49	40%	NR
Petrovich (2003)[62]	GKRS	4	*	*	NR	0	50	*	*
Jane (2003)[29]	GKRS	45	*	*	UFC < ULN	NR	73	31	2.2
Choi (2003)[11]	GKRS	9	*	*	Daily UFC < 90 mg	11.1	55.6	0	0
Kobayashi (2002)[38]	GKRS	25	[63.6]	28.7 (15–70)	ACTH < 50 pg/ml + cortisol ≤10 mg/dl	50	35	NR	NR
Pollock (2002)[68]	GKRS	11	37	20 (12–25)	Normal ACTH	54	36	9	27
Sheehan (2000)[75]	GKRS	43	44	20 (3.6–30)	Normal/low 24-h UFC	NR	63	16%	2.3
Hoybye (2001)[20]	GKRS	18	[204]	NR	UFC normalization, normal/low serum ACTH (2–11 pmol/l), nl dexa suppression test	NR	83	66%	0
Shin (2000)[77]	GKRS	6	[88.2]	[32.3] (20–49)	24-h UFC <90 mg/d	0	50	0	0

*Data reported from a series including other types of adenomas, GK: Gamma Knife radiosurgery, CK: Cyberknife, LINAC: Linear accelerator based SRS, UFC: Urinary free cortisol, ULN: Upper limits of normal, NR: Not reported

in Nelson's syndrome than Cushing's disease, with cure rates in less than 36% of patients despite lower ACTH levels in approximately 70% of patients and tumor growth control in up to 90% of patients.[38,49,76,86]

Complications and follow-up

Despite the varying median margin doses, the rates of new anterior pituitary deficits following SRS are relatively comparable across all pituitary adenoma subtypes. Radiation dose to the normal pituitary gland,[42,48,64,85] dose to the infundibulum,[15,48] poor MRI appreciation of the normal gland,[8,43] size of the tumor,[65] previous conventional radiation therapy,[46,57] and previous

surgery[43] are some of the more consistently reported risk factors amongst the published series. Retrospective analyses have indicated that to minimize the risk of anterior pituitary deficit, the dose should be kept less than 15 Gy to the normal gland[42,48,85] and less than 17 Gy to the distal infundibulum.[48] Additionally, the 5-year risk of developing new anterior pituitary deficits was considerably higher in one study for tumors >4 cm^3 (58% vs. 18%).[65] These findings suggest that maximum safe surgical resection, especially in the case of macroadenomas greater than 4 cm^3, should be considered prior to SRS and that radiosurgical planning should specifically limit dosing of the normal gland and infundibulum in order avoid post-SRS endocrine deficits.

With the availability of long-term follow-up data following SRS for pituitary adenomas, it has become increasingly clear that the disease course is still uncertain even after years of clinical stability and that lifetime observation is required. Tumor progression, for example, has been noted to recur as far as 120 months following radiosurgery, even after a decade of radiographic tumor control.[18] In addition to radiographic tumor control, endocrine control has also been found to relapse, with patients exhibiting hypersecretory pituitary states even as long as 8 years after endocrine remission through SRS.[6] This seems to be more problematic within the subset of ACTH-secreting adenomas, with the above-mentioned series by Jagannathan *et al*. demonstrating up to 20% recurrence of hypercortisolism in patients who were thought to be in endocrine remission.[27] Conversely, median time to biochemical remission for ACTH-secreting adenomas seems to be shorter than that for GH- or PRL-secreting tumors, with one series demonstrating the time required for approximately 80% remission to be 2 years for ACTH-producing adenomas and over 5 years for GH-producing ones (PRL-producing tumors plateaued at 18% at approximately 18 months).[63] Moreover, new pituitary deficits following SRS have been shown to occur even beyond 10 years following SRS treatment.[6,20] Given the possibility of tumor growth, recurrent endocrinopathy, or new pituitary deficit even a decade following radiosurgery, it is evident that patients will likely require lifetime radiographic and endocrine follow-up in order to monitor for disease progression and radiation-associated complications.

Recommendations

Despite advances in endoscopic techniques, intraoperative imaging, and surgical methods, there is still a moderate incidence of subtotal resection of pituitary adenomas on account of invasion into parasellar structures and difficulty appreciating smaller functional tumors radiographically and intraoperatively. Patients who have undergone maximal safe surgical resection with residual, recurrent, or progressive endocrinologic or radiographic disease should be considered for radiotherapy. Patients who choose not to have further surgical resection or are medically unfavorable surgical candidates should be considered for radiation treatment as well. However, not all patients with residual adenomas following extirpation are candidates for radiosurgery. Pituitary lesions greater than 4–4.5 cm^3 should be evaluated for repeat surgical resection as these macroadenomas have been found to have higher rates of recurrence[57] and anterior pituitary deficits[65] following SRS. Moreover, lesions that are less than 3 mm away from the optic apparatus are at significantly increased risk for vision loss following most stereotactic radiosurgical modalities. Although some reports indicate that CK may be an acceptable alternative in such cases of tumor apposition with visual structures,[34] longer follow-up is required to determine its true safety. Therefore, residual or recurrent pituitary lesions that have undergone maximal safe surgical resection, that are less than 4 cm^3, and are more than 3 mm away from the optic apparatus should be recommended for radiosurgery.

Dosing for nonfunctional adenomas should range from 18 to 20 Gy as tolerated and able. Dosing for functioning adenomas should range from 23 to 25 Gy as tolerated and able. In order to maximize treatment efficacy and minimize the risk of new anterior pituitary deficits following SRS, it is critical to be able to define the normal gland and infundibulum and minimize the dose delivered to these structures. Additionally, in the case of functioning adenomas, endocrine suppressive medications should be discontinued at least 2 months prior to radiosurgery if tolerated by the patient, as preliminary evidence suggests the rates of remission are greater with this treatment protocol. Importantly, long-term follow-up (at least 10 years) is crucial to assess for endocrine remission, new pituitary deficits, and tumor or endocrine recurrence.

CONCLUSION

SRS has been demonstrated to be a suitable adjuvant therapy in patients with pituitary adenomas should they have residual or recurrent tumor, persistent or recurrent hormone hypersecretion, or medical comorbidities that make them unsuitable surgical candidates. The single treatment dosing is far more convenient than previously performed fractionated radiotherapies, which require daily visits for multiple weeks. In addition, SRS has been shown to have lower rates of endocrinopathies and faster times to remission than conventional radiotherapy. Although outcomes are not perfect and future studies with longer follow-up are needed, SRS serves as an excellent treatment consideration in patients with pituitary adenomas.

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