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TOPIC REVIEW

Treatment paradigms for pituitary adenomas: defining the roles of radiosurgery and radiation therapy

Dale Ding · Robert M. Starke · Jason P. Sheehan

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Abstract Pituitary adenomas represent one of the most common types of intracranial tumors. While their macroscopic appearance and anatomical location are relatively homogeneous, pituitary tumors have the potential to generate a wide variety of clinical sequelae. Treatment options for pituitary tumors include medical therapy, microscopic or endoscopic surgical resection, radiosurgery, radiation therapy, or observation depending on the biochemical profile and clinical status of the patient. Radiosurgery and external beam radiation therapy (EBRT) are most commonly as adjunctive treatments following incomplete surgical resection leaving residual tumor, tumor recurrence, or failure of medical therapy. We present a comprehensive literature review of the radiosurgery series for pituitary tumors including nonfunctioning adenomas, ACTH- and GH-secreting adenomas, and prolactinomas. While post-radiosurgery radiographic tumor control for nonfunctioning adenomas is excellent, typically around 90 %, the rates of biochemical remission for functioning adenomas are lower than the tumor control rates. The highest endocrine remission rates are achieved patients with Cushing's disease and the lowest in those with prolactinomas. Although EBRT has been largely supplanted by radiosurgery for the vast majority of pituitary adenomas cases, there remains a role for EBRT in select cases involving large tumor volumes in close proximity to critical neural structures. By far the most common complication after radiosurgery or EBRT is delayed hypopituitarism followed by cranial neuropathies. The effect of suppressive medications on radiosurgery outcomes remains controversial. Due to the rare but well-documented occurrence of late recurrence following endocrine remission, long-term and rigorous clinical and radiographic follow-up is necessary for all pituitary adenoma patients treated with radiosurgery or EBRT.

Keywords Pituitary neoplasms · Prolactinoma · Acromegaly · Cushing's disease · Radiotherapy · Radiosurgery

D. Ding · R. M. Starke · J. P. Sheehan (✉)
Department of Neurological Surgery, University of Virginia, P.O. Box 800212, Charlottesville, VA 22908, USA
e-mail: jps2f@virginia.edu

Introduction

Pituitary adenomas are common among the general population, and they comprise 10–20 % of all intracranial tumors [1, 2]. While many anatomic and histological classifications of pituitary adenomas exist, they are classically divided by size, with microadenomas less than 1 cm in size and macroadenomas at least 1 cm in size, and by secretory status, with hormone hypersecretion from functioning lesions and lack of abnormal hormonal production from nonfunctioning lesions. Functioning and nonfunctioning lesions each comprise half of microadenomas whereas macroadenomas are predominantly (approximately 80 %) nonfunctioning. Therefore, microadenomas are more likely to be diagnosed as incidental lesions or due to hormone hypersecretion compared to macroadenomas which are more likely to be diagnosed secondary to mass effect resulting in pituitary insufficiency, hyperprolactinemia, or focal neurological deficit most commonly of the cranial nerves [1]. With the exception of prolactinomas, which are treated primarily with medical therapy, the first-line treatment for symptomatic pituitary adenomas is surgical resection, either microscopic or endoscopic. Despite a multitude of technological advances over the years,

pituitary adenomas remain difficult to cure with surgical resection alone, and, frequently, they require additional treatment including radiation therapy or radiosurgery and antisecretory medications. We review the role of external beam radiation therapy (EBRT) and radiosurgery for treating pituitary adenomas with an emphasis on the radiosurgical literature. A comprehensive literature review was performed using Pubmed to identify all pituitary adenoma radiosurgery series, including both functioning and nonfunctioning lesions, since 2000. Due to the paucity of radiosurgery literature describing Nelson's syndrome, we extended our search for this particular disease back to 1990.

Principles of external beam radiation therapy and radiosurgery

External beam radiation therapy principles

EBRT is a predefined cumulative radiation dose divided into smaller doses, or fractions, which are delivered on a daily basis until the goal total dose is achieved. The primary factors which affect EBRT outcomes are total dose, fractional dose, dose rate, treatment duration and number of fractions. For the treatment of pituitary adenomas, a typical treatment scheme consists of a total radiation dose of 45–54 Gy delivered in 25–30 daily fractions of 1.8–2.0 Gy over a treatment period of 5–6 weeks. Conventional EBRT is planned with three-dimensional conformal radiation therapy (3D CRT) which utilizes a minimum of three separate radiation beams. Intensity-modulated radiation therapy (IMRT) is a relatively newer technology which divides the primary radiation beam into thinner beamlets, usually 5–10 mm in diameter, of varying intensities. IMRT is especially useful for targeting lesions very close to radiation-sensitive normal tissue.

Radiosurgery principles

Initially conceived by Lars Leksell in 1951, stereotactic radiosurgery delivers a single high, concentrated dose of radiation to the target [3]. The Gamma Knife was subsequently employed by Leksell to treat the first pituitary adenoma patient in 1968. Since then, radiosurgical devices and techniques have developed significantly with thousands of pituitary adenomas treated in the interim. While radiosurgery is traditionally delivered in a single session, multisession radiosurgery delivers smaller radiation doses in up to 5 sessions [4]. Radiosurgery is characterized by a steep dose fall-off thereby relatively sparing radiation exposure to surrounding normal tissues. There are several types of radiosurgery systems including cobalt-based systems, such as the Gamma Knife (Elekta AB) and Infini system (MASEP), linear accelerator (LINAC) based systems, such as the CyberKnife, and proton beam units. For cobalt-based radiosurgery devices the optimal gradient index, or steepest radiation dose fall-off, is achieved around the 50 % isodose line whereas for LINAC-based systems it is usually achieved at the 80–90 % isodose line. Single session radiosurgical margin doses vary from 12 to 18 Gy for nonfunctioning adenomas and from 15 to 30 Gy for functioning adenomas. For multi-session radiosurgery, these doses may be divided over 2 to 5 fractions.

Gamma Knife radiosurgery utilizes multiple isocenters to create a dose plan based upon the dimensions, anatomy, and location of the target lesion. The most current version of the Gamma Knife, the Perfexion^{TM} model, consists of eight independent sectors of up to 192 simultaneous radiation beams. The beam width can by adjusted from 0, blocked, to 16 mm. LINAC-based radiosurgery utilizes multiple radiation arcs to crossfire photon beams at the target lesion [5]. Most systems use non-dynamic 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 beam 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 [6]. Currently, there are only a few centers using proton beam technology to perform single session radiosurgery 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.

Outcomes following radiosurgery for pituitary adenomas

Radiosurgery for nonfunctioning pituitary adenomas

Radiosurgery provides an excellent treatment approach for pituitary adenoma patients who have residual tumor or tumor progression or recurrence despite surgical resection which achieves tumor control in 50–80 % of cases [7]. In Table 1, we list the major radiosurgical series since 2002 that detailed outcomes in nonfunctioning adenoma patients [7–31]. Single session radiosurgery margin doses of 12–20 Gy, with a median of 16 Gy, were used for patients with nonfunctioning adenomas. Tumor control rates ranged from 83 to 100 % with a mean of 95.2 %, and new-onset

Table 1 Summary of radiosurgery literature for nonfunctioning pituitary adenomas

Series	Year	Number of patients	Mean/median follow-up (months)	Radiosurgery type	Mean/median margin dose (Gy)	Radiographic tumor control (%)	Post-radiosurgery hypopituitarism (%)
Feigl et al.	2002	61	55.2	Gamma Knife	15	94	40
Sheehan et al.	2002	42	31.2	Gamma Knife	16	97.6	0
Wowra et .al.	2002	30	57.7	Gamma Knife	16	93.3	10
Petrovich et al.	2003	52	34	Gamma Knife	15	100	NR
Losa et al.	2004	54	41.1	Gamma Knife	16.6	96.3	9.3
Muacevic et al.	2004	51	21.7	Gamma Knife	16.5	95	3.9
Kajiwara et al.	2005	14	32.1	CyberKnife	12.6	92.9	7.1
Picozzi et al.	2005	51	40.6	Gamma Knife	16.5	96.1	NR
Iwai et al.	2005	28	36.4	Gamma Knife	12.3	93	7
Mingione et al.	2006	100	46.4	Gamma Knife	18.5	92.2	25
Voges et al.	2006	37	56.6	Linac	13.4	100	12.3
Liscak et al.	2007	140	60	Gamma Knife	20	100	1.4
Pollock et al.	2008	62	64	Gamma Knife	16	96.8	27
Hoybye et al.	2009	23	78	Gamma Knife	20	100	0
Kobayashi et al.	2009	71	50.2	Gamma Knife	NR	96.7	8.2
Castro et al.	2010	14	42	Gamma Knife	12.5	100	0
Hayashi et al.	2010	43	36	Gamma Knife	18.2	100	0
Gopalan et al.	2011	48	95	Gamma Knife	18.4	83	39
Iwata et al.	2011	100	33	CyberKnife	21 Gy/3Fr, 25 Gy/5Fr	98	2
Park et al.	2011	125	62	Gamma Knife	13	90	24
El-Shehaby et al.	2012	21	44	Gamma Knife	12	85	0
Runge et al.	2012	65	83	Linac	13	98.3	9.8
Starke et al.	2012	140	50.4	Gamma Knife	18	90	30.3
Wilson et al.	2012	51	50	Linac	14	100	NR
Sheehan et al.	2013	512	36	Gamma Knife	16	93	21

NR not reported, *Fr* fraction, *LINAC* linear accelerator

hypopituitarism following radiosurgery was observed in 0–40 % with a mean of 8.8 % (Table 1). At our institution, we reported approximately 90 % tumor control and a 30 % occurrence of post-radiosurgery hypopituitarism in a series of 140 patients with nonfunctioning pituitary adenomas (Fig. 1) [29]. New or increased cranial nerve deficit, the vast majority of which was visual decline, was observed in 14 % of patients. The same study demonstrated that tumor control was significantly less common in adenomas greater than 5 cc in volume [29]. This finding underscores the importance of a maximum safe surgical resection prior to radiosurgery.

In a recent multicenter trial evaluating the role of Gamma Knife radiosurgery for 512 patients with nonfunctioning pituitary adenomas and a median follow up of 36 months (range 1–223 months), the authors observed an overall tumor control rate of 93 % [31]. Hypopituitarism following GKRS was noted in 21 % of patients [31]. Favorable outcomes of tumor control and neurological preservation were more commonly seen in patients older than 50 years, those with a tumor volume less than 5 cc, and those without prior radiation. These prognostic factors were integrated into a radiosurgical pituitary score (RPS) [31].

Radiosurgery for cushing's disease

Despite surgical resection of ACTH-secreting pituitary adenomas, which remains the primary treatment for Cushing's disease, invasion of the surrounding dura or neighboring cavernous sinus by many of these tumors decreases the likelihood of cure with surgery alone. Radiosurgery therefore plays a crucial role in the treatment of persistent Cushing's disease refractory to surgical management. Table 2 lists the major radiosurgical series for Cushing's disease since 2000 [8, 11, 14, 18, 21, 23, 32–52]. Endocrine remission was defined, in most series, by 24-hour urinary free cortisol (UFC) or serum cortisol. Radiosurgical margin doses of range 15–35 Gy and median 24 Gy were used to treat persistent Cushing's disease.

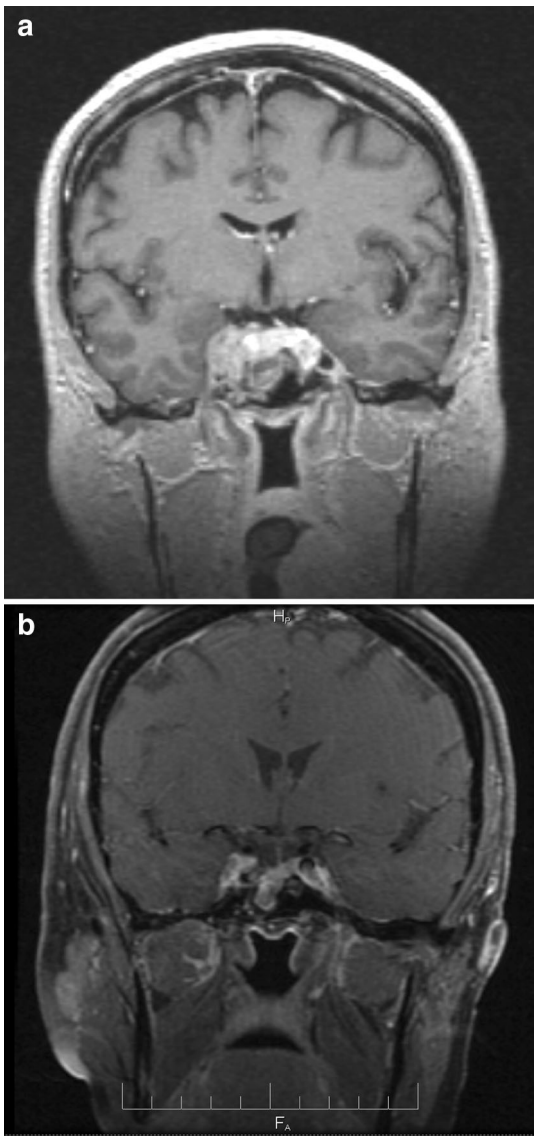

Fig. 1 **a** The patient demonstrates a progressive nonfunctioning pituitary adenoma involving the *right side* of her sella and the cavernous sinus on this coronal view of a T1-weighted post-contrast MRI. Her normal pituitary gland and the stalk are deviated to the *left*. She has had prior resection this tumor via a transsphenoidal approach. The tumor was treated with Gamma Knife radiosurgery using a dose of 15 Gy to the tumor margin. **b** This T1-weighted post-contrast MRI, coronal view, was taken 5 years following Gamma Knife radiosurgery. The patient's adenoma has markedly regressed following the radiosurgery. The patient did not develop hypopituitarism as a result of her radiosurgery

Most series demonstrated endocrine remission for the majority of patients after radiosurgery but the reported rates varied widely from 0–100 % with a mean of 51.1 % (Table 2). The mean time interval after radiosurgery to endocrine remission in successfully treated cases is 12 months [44]. Although the mean rate of neurological deficit was 3 %, the occurrence of post-radiosurgery hypopituitarism was higher in patients treated for Cushing's disease, mean 24.3 % and range 0–69 %, than for nonfunctioning adenomas. The most likely explanation for this finding is the higher radiosurgical doses typically required to attain endocrine remission in Cushing's disease compared to those used to control the growth of nonfunctioning adenomas. Just as is true for microsurgical series, endocrine recurrence can occur after documentation of radiosurgery-induced remission with normal 24-hour UFC. In a series of 90 Cushing's disease patients who underwent radiosurgery with a mean follow up of 45 months, endocrine recurrence occurred in 10 patients at a mean time of 27 months after initial remission [44]. Of these 10 patients, 7 patients were retreated and 3 achieved a second remission [44]. Castinetti et al. [48] noted two Cushing's disease patients with late recurrence 6 and 8 years after initial radiosurgery-induced remission. While the rate of recurrence after an initial remission appears low, these patients do require longitudinal follow-up to detect recurrence amongst other things.

Radiosurgery for acromegaly

Due to the significant resultant morbidities associated with untreated acromegaly, including hypertension, diabetes, cardiomyopathy, and obstructive sleep apnea, rapid endocrine remission achieved via surgical resection is the initial treatment of choice for these patients [53]. Since the initial presentation of acromegaly is relatively insidious, many GH-secreting tumors are not diagnosed until they are macroadenomas. Therefore, complete resection is not always feasible due to the large and infiltrative nature of these tumors. Table 3 delineates the major radiosurgical series for acromegaly since 2000 [8, 11, 14, 18, 20, 23, 32, 34, 38–40, 47–50, 52, 54–73]. The median margin dose used to treat GH-secreting adenomas was 22 Gy with a range of 14–35 Gy. Endocrine remission was achieved in 0–82 % of patients with a mean of 44.7 % whereas post-radiosurgery hypopituitarism occurred in 0–40 % of patients with a mean of 16.4 %.

Patients with an adenoma volume less than 3 cc at the time of radiosurgery have been reported to have significantly higher odds of achieving endocrine remission compared to those with tumor volume greater than 3 cc [50]. Similar to ACTH-secreting adenomas, the case is again made for maximum safe surgical resection prior to radiosurgery in order to maximize the chances of endocrine remission. In our experience, the mean time to endocrine remission after radiosurgery for acromegaly was 24 months which is approximately twice the time interval to remission for Cushing's disease.

Radiosurgery for prolactinomas

Prolactinomas are the most common type of secretory pituitary adenomas. However, unlike ACTH- or GH-secreting adenomas, the initial management of prolactinomas is with

Table 2 Summary of radiosurgery literature for Cushing's disease

Series	Year	Number of patients	Mean/median follow-up (months)	Radiosurgery type	Mean/median margin dose (Gy)	Endocrine remission (%)	Post-radiosurgery hypopituitarism (%)
Izawa et al.	2000	12	26.4	Gamma Knife	23.8	16.7	0
Sheehan et al.	2000	43	39.1	Gamma Knife	20	63	16
Shin et al.	2000	6	88.2	Gamma Knife	32.3	50	16.7
Hoybye et al.	2001	18	16.8	Gamma Knife	NR	44	68.8
Feigl et al.	2002	4	55.2	Gamma Knife	15	60*	40*
Kobayashi et al.	2002	20	64	Gamma Knife	28.7	23.3	NR
Laws et al.	2002	40	NR	Gamma Knife	20	74	24
Pollock et al.	2002	9	42.4	Gamma Knife	20	78	16
Choi et al.	2003	7	42.5	Gamma Knife	28.5	55.6	0
Petrovich et al.	2003	4	34	Gamma Knife	15	NR	NR
Witt et al.	2003	8	24	Gamma Knife	24	0	NR
Wong et al.	2003	5	38	LINAC	NR	100	20
Devin et al.	2004	35	42	LINAC	14.7	49	40
Kajiwara et al.	2005	2	38.5	CyberKnife	26	50	50
Voges et al.	2006	17	58.7	LINAC	16.4	52.9	12.3
Castinetti et al.	2007	40	54.7	Gamma Knife	29.5	42.5	15
Jagannathan et al.	2007	90	45	Gamma Knife	23	54	22
Petit et al.	2008	33	62	Proton Beam	20	52	52
Pollock et al.	2008	8	73	Gamma Knife	20	87	36
Tinnel et al.	2008	12	37	Gamma Knife	25	50	50
Castinetti et al.	2009	18	94	Gamma Knife	28	50	21
Kobayashi et al.	2009	30	64.1	Gamma Knife	28.7	35	NR
Wan et al.	2009	68	67.3	Gamma Knife	23	27.9	1.7
Hayashi et al.	2010	13	36	Gamma Knife	25.2	38	0
Sheehan et al.	2011	82	31	Gamma Knife	24	54	22
Wein et al.	2012	17	23	LINAC	18	58.8	11.8
Grant et al.	2013	15	40.2	Gamma Knife	35	73	40

NR not reported, *LINAC* linear accelerator

medical therapy. Since the majority of prolactinomas can be biochemically suppressed with medical therapy alone, the relatively small proportion of prolactinomas which are refractory to medical therapy and therefore subject to further treatment, such as radiosurgery, represent a very iatrogenically selected and biologically challenging cohort of tumors. Therefore, compared to patients with acromegaly and Cushing's disease, complete endocrine remission rates off suppressive medications in prolactinoma patients are lower. However, it remains unclear as to whether or not prolactinomas are a more radioresistant adenoma subtype. As most prolactinoma patients undergo successful medical therapy in the modern era, selection bias of prolactinoma patients undergoing radiosurgery may be a major cause for the lower published rates of endocrine remission after radiosurgery. In fact, most prolactinoma radiosurgical series are comprised of patients who have failed both medical and microsurgical treatments thereby predisposing this group to be an inherently challenging cohort. However, many patients with prolactinomas benefit from a substantial but incomplete reduction in their hyperprolactinemia following radiosurgery. For example, in a recent series by the UPMC group with a median follow up of 36 months, 27.3 % of patients achieved an endocrine normalization but another 54.5 % had endocrine improvement in their hyperprolactinemia [73]. For patients who are intolerant of high dose medical therapy, an improvement in prolactin levels after radiosurgery may make medical therapy more tolerable and effective. Table 4 summarizes the radiosurgical series for prolactinomas since 2000 [8, 11, 14, 18, 21, 32, 38, 39, 46–49, 58, 74–78]. Endocrine remission off antisecretory medications following radiosurgery ranged from 0 to 100 % with an average of 34.7 %. The margin dose was 15–49 Gy with a median of 24 Gy and the rate of post-radiosurgery hypopituitarism was 0–45 % with a mean of 14.8 %.

Table 3 Summary of radiosurgery literature for acromegaly

Series	Year	Number of patients	Mean/median follow-up (months)	Radiosurgery type	Mean/median margin dose (Gy)	Endocrine remission (%)	Post-radiosurgery hypopituitarism (%)
Izawa et al.	2000	29	26.4	Gamma Knife	23.8	41.4	0
Shin et al.	2000	6	42.7	Gamma Knife	34.4	66.7	0
Zhang et al.	2000	68	34	Gamma Knife	31.3	36.8	0
Fukuoka et al.	2001	9	42	Gamma Knife	20	50	0
Ikeda et al.	2001	17	55.8	Gamma Knife	25	82	0
Feigl et al.	2002	9	55.2	Gamma Knife	15	60	40
Pollock et al.	2002	26	42.4	Gamma Knife	20	42	16
Attanasio et al.	2003	30	46	Gamma Knife	20	23	6.6
Choi et al.	2003	9	42.5	Gamma Knife	28.5	50	0
Muramatsu et al.	2003	4	30	LINAC	27.5	50	0
Petrovich et al.	2003	5	34	Gamma Knife	15	NR	NR
Witt et al.	2003	4	24	Gamma Knife	24	25	NR
Castinetti et al.	2005	82	49.5	Gamma Knife	25	17	17.1
Gutt et al.	2005	44	22.8	Gamma Knife	18	47.7	NR
Kajiwara et al.	2005	2	53.5	CyberKnife	13.5	0	0
Koybayashi et al.	2005	67	63.3	Gamma Knife	18.9	4.8	14.6
Jezkova et al.	2006	96	53.7	Gamma Knife	35	50	26
Voges et al.	2006	64	54.3	LINAC	16.5	37.5	12.3
Pollock et al.	2007	46	63	Gamma Knife	20	50	33
Roberts et al.	2007	9	25.4	CyberKnife	21	44.4	33.3
Vik-Mo et al.	2007	61	66	Gamma Knife	26.5	17	13.1
Jagannathan et al.	2008	95	57	Gamma Knife	22	53	34
Losa et al.	2008	83	69	Gamma Knife	21.5	60.2	8.5
Pollock et al.	2008	27	46.9	Gamma Knife	20	67	36
Tinnel et al.	2008	9	35	Gamma Knife	25	44.4	22
Castinetti et al.	2009	43	102	Gamma Knife	24	42	21
Ronchi et al.	2009	35	120	Gamma Knife	20	46.0	40
Wan et al.	2009	103	67.3	Gamma Knife	21.4	36.9	1.7
Hayashi et al.	2010	25	36	Gamma Knife	25.2	40.0	0
Iwai et al.	2010	26	84	Gamma Knife	20	38.0	8
Poon et al.	2010	40	73.8	Gamma Knife	20–35	75	11.4 % (initial); 27.3 % (repeat)
Sheehan et al.	2011	130	31	Gamma Knife	24	53	34
Franzin et al.	2012	103	71	Gamma Knife	22.5	60.7	7.8
Liu et al.	2012	40	72	Gamma Knife	21	47.5	40
Grant et al.	2013	13	40.2	Gamma Knife	35	61	31

NR not reported, *LINAC* linear accelerator

Radiosurgery for Nelson's syndrome

Far less information is available about the efficacy of radiosurgery for patients with Nelson's syndrome. In patients with ACTH-secreting tumors who have undergone bilateral adrenalectomies, these pituitary adenomas tend to fall on the more aggressive end of the biological spectrum for growth rates. As such, endocrinological cure rates and growth control are critical for Nelson syndrome. The major radiosurgical series for Nelson's syndrome are detailed in Table 5 [36, 79–83]. Mean tumor margin dose varied from 12 to 28.7 Gy. Of these Nelson's syndrome radiosurgical series, only two studies detailed the endocrine criteria utilized to define a remission. Endocrine remission rates varied from 0 to 33 %. In contrast, radiographic control rates of the adenoma were more favorable and ranged from 90 to 100 %.

Table 4 Summary of radiosurgery literature for prolactinomas

Series	Year	Number of patients	Mean/median follow-up (months)	Radiosurgery type	Mean/median margin dose (Gy)	Endocrine remission (%)	Post-radiosurgery hypopituitarism (%)
Izawa et al.	2000	15	28	Gamma Knife	22	20	NR
Landolt et al.	2000	20	29	Gamma Knife	25	25	NR
Pan et al.	2000	128	33	Gamma Knife	32	41	NR
Feigl et al.	2002	18	55	Gamma Knife	15	NR	NR
Pollock et al.	2002	7	42	Gamma Knife	20	29	16
Choi et al.	2003	21	42.5	Gamma Knife	28.5	24	0
Muramatsu et al.	2003	1	30	LINAC	15	0	0
Petrovich et al.	2003	12	41	Gamma Knife	15	83	NR
Kajiwara et al.	2005	3	35.3	CyberKnife	17.5	33	9.5
Pouratian et al.	2006	23	55	Gamma Knife	18.6	26	28
Voges et al.	2006	13	56	LINAC	20	15.4	18.3
Pollock et al.	2008	11	48	Gamma Knife	30	18	45
Tinnel et al.	2008	2	19.5	Gamma Knife	30	50	22
Castinetti et al.	2009	15	85.5	Gamma Knife	30	46.6	21
Jezkova et al.	2009	35	75.5	Gamma Knife	49	37.1	14.3
Wan et al.	2009	176	67.3	Gamma Knife	35	23.3	1.7
Kobayashi et al.	2009	27	37.4	Gamma Knife	18.4	43.5	0
Tanaka et al.	2010	22	60	Gamma Knife	25	17	42
Grant et al.	2013	2	40.2	Gamma Knife	35	100	0
Liu et al.	2013	22	36	Gamma Knife	15	27.3	4.5

NR not reported, *LINAC* linear accelerator

Endocrine remission following radiosurgery

Endocrine remission following successful radiosurgical treatment takes place over a much longer time interval than after complete surgical resection [84]. In order to limit the symptoms caused by secretory pituitary adenomas during this latency period, radiosurgery patients are bridged with antisecretory medications after treatment. Endocrine testing off suppressive medications is performed at regular intervals. These medications are halted after confirmation of endocrine remission following radiosurgery. The time interval between radiosurgical treatment and endocrine remission ranges from 3 months to 8 years; typically remission is achieved within 12 years after radiosurgery [33, 34, 47].

Several reports have described factors associated with increased likelihood of endocrine remission. For patients with acromegaly, lower pre-radiosurgery GH and insulin-like growth factor 1 (IGF-1) levels, pre-radiosurgery IGF-1 levels less than 2.25 times the upper limit of normal, and not taking somatostatin agonists at the time of treatment have associated with increased rates of radiosurgery-induced endocrine remission [59, 63, 66, 85]. The finding that lack of suppressive medication at the time of radiosurgery results in improved outcomes has been corroborated in the cessation of dopamine agonists for prolactinomas [76]. The effect of antisecretory medications on radiosurgery outcomes remains unclear with only single center, retrospective studies addressing this topic. However, some respected groups advocate temporary cessation around the time of treatment and others reporting no effect on outcomes with medication cessation [38, 57, 59, 63, 74, 85]. Our institutional protocol at the University of Virginia is the discontinuation of suppressive medications for 6–8 weeks around the time of radiosurgery. The vast majority of our patients are able to tolerate this brief period of medication cessation well.

Although the rates of endocrine remission vary significantly across different radiosurgery series, there is an overall trend toward differential responses of different types of secretory pituitary adenomas to radiosurgery [18, 21, 46]. In order of decreasing rate of radiosurgery-induced endocrine remission from most to least responsive is Cushing's disease, acromegaly, prolactinoma, and Nelson's syndrome. This differential sensitivity based on biochemical subtype is influenced by patient and tumor characteristics and selection, radiosurgical margin dose, use of antisecretory medications, and duration of follow-up [21, 46]. Currently, a definitive explanation for these findings remains to be determined.

Table 5 Summary of radiosurgery literature for Nelson's syndrome

Series	Year	Number of patients	Mean/median follow-up (months)	Radiosurgery type	Mean/median margin dose (Gy)	Radiographic tumor control (%)	Endocrine remission (%)
Levy et al.	1991	17	NR	Proton and helium beam	NR	94	NR
Ganz et al.	1993	3	18	Gamma Knife	NR	100	0
Wolffenbuttel et al.	1998	1	33	Gamma Knife	12	100	0
Laws et al.	1999	9	NR	Gamma Knife	NR	NR	11
Kobayashi et al.	2002	6	63	Gamma Knife	28.7	100	33
Mauermann et al.	2007	23	50	Gamma Knife	25	90	20

NR not reported

Radiosurgery-induced complications

Delayed pituitary insufficiency is, by far, the most common adverse effect of radiosurgery for pituitary adenomas, occurring in up to 40 % of patients with nonfunctioning lesions and up to nearly 70 % of patients with functioning lesions with wide variation across different radiosurgery series. Factors affecting the rate of post-radiosurgery hypopituitarism include pre-treatment pituitary gland function, the modality and timing of prior treatments, the radiation dose to the normal pituitary gland and stalk, and the rigorousness and length of endocrinological follow-up.

While an ideal radiosurgical dose plan has a steep gradient index which minimizes the dose to normal pituitary tissue and therefore reduces the risk of treatment-induced hypopituitarism, a true 'safe dose' below which the patient is not afflicted with hypopituitarism does not practically exist. Furthermore, the optimal radiosurgical dose to the target lesion should not be compromised under the guise of avoiding hypopituitarism. The clinical consequences of macroscopic tumor progression or recurrence or persistent hormone hypersecretion far outweigh those of radiosurgery-induced hypopituitarism which is readily managed with medical therapy by neuroendocrinologists.

The second most common radiosurgery-related complication following treatment of pituitary adenomas is cranial neuropathies. Multiple cranial nerves, including II, III, IV, V, and VI, by virtue of their location in the parasellar and suprasellar regions are at risk of inadvertent injury from radiosurgical treatment. Most radiosurgery series report neurological deficit rates of less than 5 % with optic neuropathy as the most common owing to its high sensitivity to radiation-induced damage [31]. In a recent study of 217 pituitary adenoma patients who underwent radiosurgery, nine patients (4 %) developed new or worsened cranial nerve dysfunction. Of the those patients with radiosurgery-induced cranial neuropathies, six (67 %) experienced complete resolution over a median follow up period of 32 months [86]. As such, the radiosurgical maximum dose to the optic apparatus should be kept below the limit threshold of 8–12 Gy in order to minimize the risk of optic nerve damage. Careful dose planning with careful contouring of critical structures and shielding of the same can often achieve a solution which yields deliver of an optimal dose to the target and a typically safe dose to the critical structures (Fig. 2). Extremely rare and seldom reported radiosurgery-related complications are radiation-induced parenchymal necrosis and internal carotid artery stenosis or occlusion [18, 38, 46, 49, 87, 88]. There are currently no reported cases of radiation-induced neoplasms following radiosurgery for pituitary tumors.

Late biochemical recurrence

Late biochemical recurrence of secretory pituitary adenomas is fortunately rare after successful radiosurgery-induced endocrine remission. However, in some radiosurgical series, late recurrence rates of up to 20 % have been reported. Several Cushing's disease radiosurgery series have described late biochemical recurrence [44, 47]. The overall incidence of late biochemical recurrence is relatively low [38, 44]. Ultimately, the existence and potential for biochemical recurrence despite successful endocrine remission underscores the critical importance of long-term endocrine follow-up after radiosurgery for functioning pituitary adenomas.

Role of upfront radiosurgery

As a general principle the use of radiosurgery in the management of pituitary adenomas should be reserved for recurrent or residual lesions and for patients with functioning adenomas who remain symptomatic from persistent hormone hypersecretion despite surgical intervention. The literature does not support the routine use of upfront radiosurgery for pituitary adenomas. However, radiosurgery may be used as an upfront treatment in rare and unusual circumstances. These include very old or medically ill patients deemed unfit for

surgical resection with a fairly definitely diagnosis by a combination of neuroimaging and serum endocrine profile. Radiosurgery could also be considered upfront in a patient with an adenoma that residues largely in the cavernous sinus and for whom resection is likely to produce substantial reduction in the overall tumor volume.

Comparison of external beam radiation therapy versus radiosurgery for the management of pituitary adenomas

As a result of the reported higher complications rates as well as the longer and lower success rates particularly for endocrine remission of functioning adenomas after EBRT, the current role of adjuvant, post-surgical management of recurrent or residual pituitary adenomas has largely shifted away from EBRT to radiosurgery. Radiosurgery provides certain advantages over EBRT including increased convenience for the patient due to the relative ease of single session radiosurgery treatment compared with EBRT and a better ability to spare normal pituitary and neural structures due to steeper gradient indices. Additionally, late-responding tissue, such as pituitary adenoma cells, have a greater radiobiologic response than early-responding tissue to higher radiation doses in fewer fractions of which radiosurgery represents the most extreme end of the spectrum as it is usually delivered in one session. Furthermore, the rate of endocrine remission following radiosurgery is unequivocally more rapid than after EBRT [89]. The faster endocrine remission achieved with radiosurgery as compared to EBRT can yield substantial benefits to patients with functioning adenomas.

Just as with radiosurgery, the most frequently encountered complication following EBRT is delayed hypopituitarism although the reported rates, ranging from 50 to 100 % depending on the duration and quality of endocrine follow-up, are significantly higher than in the radiosurgery literature [90, 91]. The rates of optic neuropathy are, in most EBRT series, comparable to than those found in radiosurgery series. However, at a total radiation dose of 65 Gy, the 5-year risk of visual deficits after EBRT is up to 50 % with reports of optic neuropathy at doses as low as 46 Gy in 1.8 Gy fractions [92]. More severe complications, which occur at a reportedly higher frequency following EBRT than radiosurgery, include a 10-year risk of radiation-induced neoplasia of 2.7 % and a 5-year stroke risk of 4 %, presumably from radiation-induced carotid stenosis or occlusion [93]. It is important to note that EBRT, which was developed prior to radiosurgery, has been used to treat pituitary adenoma patients for a longer time period which has resulted in more extended follow-up intervals in the EBRT literature than in the radiosurgery literature. However, the radiosurgical literature has become quite mature as of late, and the severe complications associated with ischemic stroke and radiation induced neoplasia well documented with EBRT do not seem to be observed with radiosurgery. Nevertheless, these severe complications are at least theoretically possible with radiosurgery too.

While radiosurgery has overtaken EBRT as the dominant adjuvant treatment modality, there remain cases in

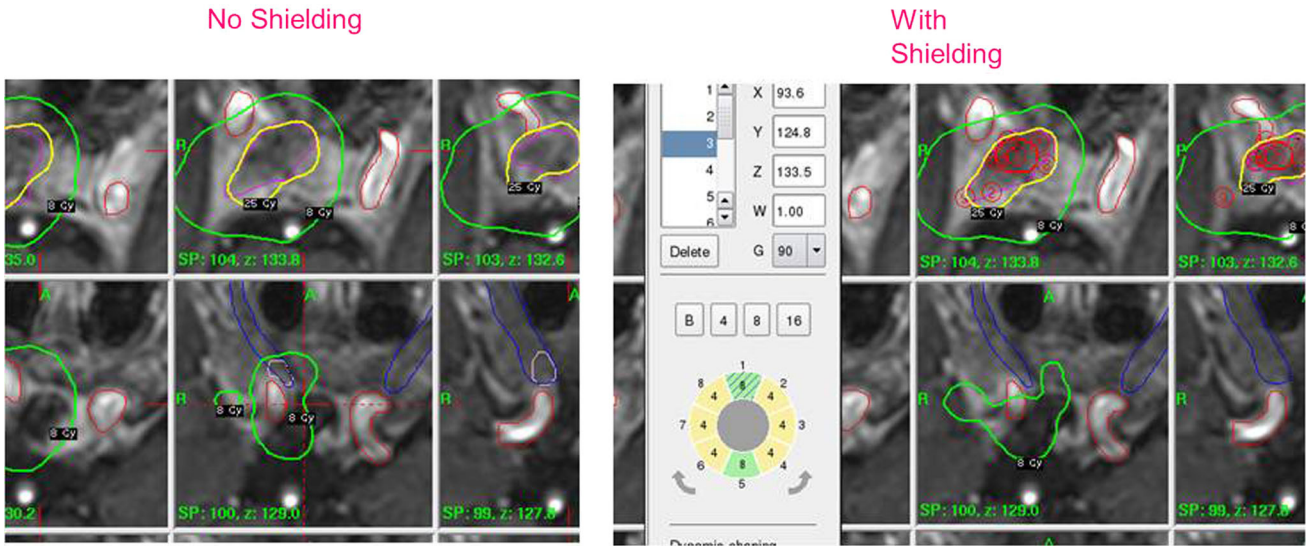

Fig. 2 The optic apparatus is the most radiation sensitive of the cranial nerves. For pituitary adenomas, the optic apparatus must often be shielded. The figure on the *left* depicts the 8 Gy isodose line (*the green line*) contacting the optic nerve (*outlined in blue*). The dose plan on the *right* shows the 8 Gy line no longer contacting the optic nerve. Tumor coverage (*the yellow isodose line*) remains unchanges. Shielding was achieved by blocking one sector of a nearby Gamma Knife isocenter

which EBRT is favored. For large pituitary adenomas, typically greater than 3 cm in diameter, tumors with irregular anatomy, including diffuse local infiltration and suprasellar or brainstem extension, and lesions in very close proximity to neural structures highly sensitive to radiation, most commonly the optic apparatus, EBRT may represent a safer treatment option than radiosurgery [94]. In concordance with radiosurgery, EBRT provides excellent tumor control, which rates exceeding 90 % in most series, for nonfunctioning adenomas but a lower rate of endocrine remission for functioning lesions with a differential response based on the adenoma subtype [90, 95, 96]. EBRT may also be used for patients with pituitary carcinoma.

Conclusions

Radiosurgery and, to a lesser extent, EBRT play important roles in the contemporary management of patients with a pituitary adenoma. Both treatment modalities are typically utilized in patients with substantial residual tumor or recurrence after surgical resection of nonfunctioning adenomas. They are also employed for patients with functioning adenomas that fail to achieve endocrine remission after prior resection. Neurological function after radiosurgery or EBRT is usually preserved or, at times, improved even when the treated adenoma extends into the cavernous sinus. Delayed post-treatment hypopituitarism is the most common complication but is manageable with appropriate hormone replacement. Lifelong neuro-imaging and endocrine follow-up is recommended for pituitary adenoma patients treated with radiosurgery or EBRT.

Conflict of interest The authors have no relevant conflict of interest related to this work.

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