Radiation Therapy in the Management of Pituitary Adenomas

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Context: Optimal management of pituitary adenomas involves consideration of the roles of medical therapy, surgery, and radiation therapy. The different forms of radiation therapy and their results are reviewed here.

Evidence Acquisition: A literature search through the U.S. National Library of Medicine was used to identify and review clinical experiences of radiation therapy in the management of pituitary adenomas. Emphasis was placed on studies within the last 5–10 yr, with 5 or more years of follow-up data, and of reasonable quality of data. Older studies with larger numbers or particular significance are also highlighted.

Evidence Synthesis: Success of radiation therapy in controlling tumor growth is high, 90–100% in most series, regardless of radiation technique and adenoma subtype. Success in achieving hormonal normalization in secretory tumors is more variable because of differences in patient population, radiation technique, and doses employed and variation of the definition of success. Complete biochemical remission is generally achieved in 50% of patients at 10 yr after treatment for most adenomas. Higher rates of normalization can be achieved with additional medical therapy. Hypopituitarism is an expectant result of radiation therapy. Overall rate of other treatment-related adverse effects is low.

Conclusions: Radiation therapy should be considered in the management of patients with pituitary adenomas, particularly when medical and surgical options have been exhausted. Because response evolves slowly over many years and because hypopituitarism is likely to occur, patients should be counseled on the importance of continued endocrinological surveillance and medical management. **(*J Clin Endocrinol Metab* 96: 1992–2003, 2011)**

Modern radiation therapy involves the sophisticated delivery of ionizing radiation to target tissues. In pituitary adenomas that are refractory or not amenable to surgery or medical therapy, radiation therapy offers a valuable option as curative treatment. Herein, we review the common forms of radiation therapeutic techniques used in the management of patients with pituitary adenomas followed by a summary of the literature on the success of radiation therapy in the management of pituitary adenomas. Lastly, the potential adverse effects of radiation therapy are discussed.

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Radiation Therapy Schedules: Stereotactic Radiosurgery (SRS) *vs.* Fractionated Radiation

Radiation therapy can be delivered in two primary schedules. SRS is the delivery of high-dose radiation typically in a single treatment visit. When feasible, this is generally the preferred technique based upon equivalence in efficacy of treatment and patient convenience. For tumor targets that approximate radiation-sensitive normal tissues that cannot be safely spared from the radiation, fractionated ra-

Abbreviations: GK, Gamma knife; HPA, hypothalamic-pituitary axis; SRS, stereotactic radiosurgery.

diation therapy is preferred. Fractionated treatment involves the delivery of small doses of radiation given daily, typically 5 d/wk over 5–6 wk. Whereas fractionated therapy has a lower risk of normal tissue injury, it is less convenient for patients and may be slower to achieve biochemical normalization in secretory adenomas (1–3).

Forms of Radiation Therapy

Gamma knife

Gamma knife (GK; Elekta, Stockholm, Sweden) was the first technology designed to deliver photon SRS. Originally designed by a neurosurgeon to treat trigeminal neuralgia, it quickly became adapted to treat a number of other intracranial targets such as pituitary adenomas. The radiation source is radioactive isotope cobalt-60, which is housed within the machine. Patients are held in place by a metal head frame, and the machinery has the capacity of aiming multiple beams of radiation of defined width at the desired intracranial target. Treatments are typically limited to one visit because the head frame is attached to the scalp with pins that are minimally invasive. Dose delivery with a low-energy source such as cobalt-60 requires a large dose gradient such that the dose delivered to the periphery of a target is approximately half the dose delivered to the geometric center of the target. Doses with GK discussed herein will refer to the margin dose delivered to the target because this is the expected minimum therapeutic dose. The greatest experience of radiation therapy in the management of pituitary adenomas has been with SRS delivered by GK.

Linear accelerator

The linear accelerator is the most common form of therapeutic delivery of radiation today. It is a unit that accelerates electrons to high speed and then converts this energy to high-energy x-rays, also known as photons. The radiation beam is shaped and attenuated to the desired specification and then directed to the clinical target. These machines have varying degrees of sophistication to ensure accurate set-up and radiation delivery. Multiple beams are used for treatment, and sometimes arcs (active radiation delivery as the machine sweeps in an arc around the target) may be implemented. Linear accelerators have been adapted to achieve highly precise targeting with the use of external stereotactic localization systems that can be used to facilitate treatment of pituitary adenomas. Three-dimensional conformal therapy is the most common method of radiation planning and treatment by the linear accelerator and is often used to treat pituitary adenomas. This is interchangeably termed "conventional" radiation. More advanced techniques that reduce excess high dose to surrounding tissues include intensity-modulated radiation therapy, fractionated stereotactic radiotherapy, and single fraction SRS. Both invasive and noninvasive immobilization techniques have been developed for SRS delivery. Noninvasive immobilization, that is, the patient set-up, is used for all fractionated treatments.

CyberKnife

CyberKnife (Accuray, Sunnyvale, CA) is another relatively new technology that can be adapted to either SRS or fractionated therapy. It uses a small linear accelerator attached to a robotic arm and provides frameless image-guided treatment. The robotic arm moves around the patient and applies real-time adjustments to treatment delivery based upon variation in patient set-up. Numerous small beams are used such that the radiation delivered is highly conformal, but the overall length of time of treatment is typically longer compared with other radiation therapy modalities.

Proton radiation

Proton therapy used accelerated proton particles to deliver radiation to targets. Because of the physical properties of protons, these beams allow for more sparing of surrounding normal tissue to exposure of ionizing radiation compared with the other mentioned technologies. The minimization of radiation exposure to normal tissues may decrease the risks of potential radiation-associated adverse effects. In a benign condition in which normal life expectancy with treatment can be maintained, this benefit of proton therapy has made it an increasingly attractive option for treating pituitary adenomas where available and when indicated for radiation therapy. Although early experiences of proton therapy in the management of pituitary adenomas date back to the 1950s, the resources of proton therapy facilities have been relatively scarce because of the complexity and capital cost of these centers. In the last decade, the compelling clinical benefits of proton therapy and the technological advancements of commercial proton therapy units have resulted in a significant rise in proton centers across the United States and the world.

Radiation Therapy of Pituitary Adenomas

Current use of radiation therapy in the management of pituitary adenomas arises from the collective experiences of multiple centers that have explored the use of SRS and fractionated radiation therapy. SRS has been used extensively, yet the success rate of treatment is difficult to quantify because of varying techniques, doses, and biochemical

TABLE 1. Radiation therapy for nonfunctioning pituitary adenomas

First author, year (Ref.)	Study years	RT type	RT dose (Gy), median (range)	No. of patients	Follow-up, median	LC (%)	LC median (yr)
Iwai, 2005 (21)	1994–1999	GK	14	34	5 yr	93	5
Mingione, 2006 (20)	1989–2004	GK	18.5 mean (5–25)	90	3.7 yr	92	
Voges, 2006 (22)	1990–2004	L-SRS	15.3 mean (8–20)	37	6.8 yr, mean	100	
Liscak, 2007 (23)	1993–2003	GK	20 (12–35)	140	5 yr	100	
Pollock, 2008 (9)	1992–2004	GK	16 (11–20)	62	5.3 yr	95	7
Sheehan, 2011 (5)	1989–2006	GK	24 (9–30)	152	31 months (min, 6 months)	90.3	
Brada, 1993 (24)	1962–1986	Conv	45 (45–50)	252		97	10
						88	20
Tsang, 1994 (25)	1972–1986	Conv	45	128	8.3 yr	91	10
Colin, 2005 (26)	1990–1999	SRT	50.4	63	6.8 yr (mean, 4 yr)	100	6.8
Ronson, 2006 (27)	1991–2001	Protons	54 (50.4–55.94)	24	3.9 yr	100	
Van den Bergh, 2007 (14)	1979–1998	Conv	45 (45–55.8)	76	7.8 yr	95	10
Chang, 2008 (18)	1975–1995	Conv	45 (45–54)	340	8.4 yr	93	5
						87	10
						81	15
						74	20
Snead, 2008 (28)	1983–2003	Conv	45 (43–50.4)	59	6.7 yr	98	10
Erridge, 2009 (29)	1974–2003	Conv	45 (35–60)	189	9.1 yr	95	10

RT, Radiation; LC, local control; L-SRS, linear accelerator-based SRS; Conv, conventional fractionated radiation; SRT, fractionated stereotactic radiotherapy; min, minimum.

definitions of cure (4). Conventional fractionated treatment suffers from the same variability and has undergone an even larger leap in technological advancements over the last several decades.

A few treatment principles have been seen consistently across multiple institutional series. There is an increase in biochemical response in secretory adenomas irradiated while off of hormonal medical therapy (5–8). This finding was consistent across ACTH-, GH-, and prolactin-secreting adenomas, and in fact one report suggests that the rate of new hypopituitarism is higher if treated while on medical therapy (5). Thus, it is advisable to discontinue medical therapy for 1 month before radiation therapy and not to resume medical therapy until after radiation treatment is completed. Another consistent observation is that smaller tumors are associated with both higher response to radiation and lower risk of new hypopituitarism, supporting the role for debulking surgery when possible (5, 6, 8–11).

Nonfunctioning pituitary adenoma

Radiation therapy in the management of nonfunctioning adenomas is given adjuvant to subtotal resection or as primary therapy in the setting of surgical inaccessibility, medical inoperability, or by patient choice. The role for radiation is perhaps best demonstrated in inoperable cases or in incomplete resections. From surgical-alone series, the rate of tumor progression or recurrence is approximately 50% for subtotally resected tumors and as high as 10–25% for gross totally resected adenomas at 10 yr (12–17). Not all series suggest an elevated risk of recurrence of gross totally resected tumors. Excellent local control of 95% or greater at 5 yr with gross total resections alone has been documented (18, 19). One prognostic indicator of recurrence may be tumor involvement of the cavernous sinus, which has been associated with tumor progression (12, 16, 18).

The goal of radiation therapy in nonfunctioning adenomas is to arrest tumor growth. Partial shrinkage and less commonly complete resolution may occur in approximately two thirds of cases (9, 20) but is secondary in intent. Radiation can be delivered either by single fraction SRS (GK, linear accelerator SRS, or proton SRS) or by any of a number of fractionated radiation therapy modalities (linear accelerator-based therapies of stereotactic radiotherapy, three-dimensional conformal radiation therapy, intensity-modulated radiation therapy, or proton therapy). Common SRS doses are 12–20 Gy, with a more optimal dose range being 14–18 Gy (Table 1). Common fractionated doses are 45–54 Gy at 1.8 Gy per fraction, with adequate doses being 45–50.4 Gy (Table 1). Choice of radiation therapy is dependent upon safety of delivering single fraction radiosurgery. If tumor extension toward the optic chiasm or optic nerves prohibits therapeutic dose delivery to the adenoma without risk of injury to the optic system, fractionated radiation therapy should be used. Adjuvant radiation therapy, whether by fractionated therapy or SRS, has been found to reduce the rate of recurrence to 10% or less at 5–10 yr in numerous series (Table 1). Although radiation therapy does clearly reduce the risk of recurrence of nonfunctioning adenomas, this decision

TABLE 2. Radiation therapy for ACTH-secreting pituitary adenomas

First author, year (Ref.)	Study years	RT type	RT dose (Gy), median (range)	No. of patients	Patient type
Mitsumori, 1998 (2)	1989–1995	SRT	45	30	ACTH
		SRS	15 (10–18)	18	
Höybye, 2001 (32)	1976–1985	GK	30–100/each, 1–4 tx	18	ACTH
Kobayashi, 2002 (11)	1991–1999	GK	28.7 (15–70)	20	ACTH/all
				5	NS subset
Devin, 2004 (33)	1991–2002	L-SRS	15	35	ACTH
			14.7, mean (7–33)		
Voges, 2006 (22)	1990–2004	L-SRS	15.3, mean (8–20)	17	ACTH/CD
Castinetti, 2007 (6)	1993–2003	GK	29.5 (15–40)	40	ACTH
Jagannathan, 2007 (34)	1990–2005	GK	25	90	ACTH
Petit, 2008 (35)	1992–2005	Protons	20 (15–20)	38	ACTH/all
				33	CD
				5	NS
Castinetti, 2009 (36)	1993–2003	GK	28, mean (24–27)	18	ACTH
Sheehan, 2011 (5)	1989–2006	GK	24 (9–30)	82	ACTH/CD
				22	ACTH/NS
Estrada, 1997 (37)	1980–1993	Conv	50, mean (48–54)	30	ACTH
Colin, 2005 (26)	1990–1999	SRT	50.4	10	ACTH
Ronson, 2006 (27)	1991–2001	Protons	54, iso (50.4–55.94)	4	ACTH
Minniti, 2007 (38)	1988–2002	Conv	45 (45–50)	40	ACTH

RT, Radiation; LC, local control; L-SRS, linear accelerator-based stereotactic radiosurgery; Conv, conventional fractionated radiation; SRT, fractionated stereotactic radiotherapy; min, minimum; tx, treatment; CD, Cushing's disease; NS, Nelson's syndrome; CR, complete response; PR, partial response; NL, normalization with medication; H nl, hormonal normalization; iso, isocenter.

must be made with consideration of potential adverse effects, primarily that of hypopituitarism. Histological and molecular analyses of tumors such as tumor proliferative index may lead to the ability to predict those tumors most likely to recur and may be useful to guide the choice of adjuvant radiation therapy in the future (30, 31).

ACTH-secreting pituitary adenoma

When surgery and medical therapy fail to cure ACTH-secreting adenomas, the source of Cushing's disease, radiation therapy should be considered. Radiation can be delivered in fractionated form or as single fraction SRS. Dose ranges used for SRS are 15–30 Gy, with optimal doses being 20–25 Gy. For fractionated radiation, 45–60 Gy is commonly used, with the optimal dose range being 45–50.4 Gy (Table 2). The benefit of SRS, in addition to patient convenience, is a faster biochemical response to treatment (2). SRS achieves normalization of ACTH levels in a median time of approximately 7.5–33 months (Table 2). The actual success rate of hormone normalization by SRS is quite variable in the literature, and many studies do not clearly specify whether medical therapy may be used in their remission figures. Recent literature of SRS series including 15 or more patients suggests remission rates between 35 and 80%. With the addition of medical therapy, remission rates are 85–100% (Table 2). Treatment success appears equivalent across the different methods of SRS of GK (6, 11, 32, 34), linear accelerator-based SRS (2, 33), or proton radiosurgery (35) (Table 2). Fractionated radiation therapy experiences from multiple series report remission rates of 0–84%, but with a tighter range of 50–80% likely to be more representative of response with modern therapy. The median time to ACTH normalization appears to range between 18 and 42 months.

The second goal of radiotherapy in the management of Cushing's disease is the control of tumor growth. Similar to nonfunctioning tumors, excellent results are achieved with typical local control rates of 90–100%, whether by SRS or fractionated therapy (Table 2).

The experience with managing Nelson's syndrome is far more scarce and conflicting with some series suggesting that it is less responsive to radiation than Cushing's disease (5, 11, 22), whereas others report up to 100% remission, albeit always with few patient numbers (35).

GH-secreting pituitary adenoma

Acromegaly is another disease for which radiation therapy can be used when first-line treatment of surgery fails. Medical therapy is typically the second-line therapy, but even effective treatment can often become lifelong. Radiation offers the potential for cure or for reducing the dose of maintenance medical therapy. Both SRS and fractionated radiation can be considered in the management of GH-secreting pituitary adenomas. Similar to ACTH-se-

TABLE 2. Continued

Follow-up, median	LC (%)	LC median	Hormone normalization	Hormone normalization time (months)
34 months	85.3	3 yr	54% CR, 62% PR	18, mean
47 months	100	3 yr	33% CR, 50% PR	8.5, mean
17 yr, mean	100		83% all, 44% 1 tx, 39% 2 tx	
5.3 yr, mean	100		85% CR/PR, 35% CR	
2.5 yr, min			33% CR/PR	
23 months	91	22 months, median	37% CR, 11% NL, 49% all	7.5, mean
42 months, mean				
82 months, mean; 12 months, min	97		78.3% CR, 100% NL	28.9; 27.7, mean
48 months; 54.7 months, mean			42.5% CR	22, mean
45 months, mean	95.2		54%	13, mean
62 months	100		89% CR/PR	
			58% CR	18, median
			52% CR	14, median
			36% NL	
			100% CR	22, median
96 months, mean; 5 yr, min	100		50% CR	33, estimate
31 months; 6 months, min	90.3		54% CR	13.0
			20% CR	50.0
55 months, mean			83%	
82 months; 4 yr, mean	100	6.8 yr	0% CR	
47 months imaging; 83 months H nl	100		25% CR, 25% PR	
9 yr	93	5 yr	78%	
	93	10 yr	84%	

creting pituitary adenomas, the decision for one radiation treatment type over another typically lies in the eligibility of the patient for SRS. The primary limiting factor is tumor abutment or approximation to the optic apparatus such that a therapeutic dose could not be delivered without risk of harming vision. Unusually large tumors may also have a higher risk of SRS-related toxicity. Typical doses for SRS have ranged between 10 and 35 Gy (Table 3). The dose range that appears to be optimally both efficacious and safe is 20–25 Gy. When using fractionated radiation, evaluated dose schedules vary between 40 and 75 Gy (Table 3). Optimal dose range is similar to other adenomas at 45–50.4 Gy at 1.8 Gy daily fractions.

Response to therapy is difficult to assess across studies because of the varying definitions of hormonal normalization and varying endpoints of whether complete remission permits additional medical therapy to achieve hormonal normalization. GH threshold for complete remission commonly varies between 5 and 1.7 ng/ml, with or without the inclusion of age-matched, sex-matched IGF-I normalization and variable inclusion of an oral glucose tolerance test. The difference of remission definition is demonstrated in a recent systematic analysis of SRS for acromegaly including 26 studies and several hundred patients. Complete response rate accepting each investigators' definition was 48–53%, and overall disease control rate that includes medical therapy to achieve hormonal normalization was 73% (50). It is unclear whether many patients may have been counted multiple times because several studies are from the same institution and may represent updates of prior studies, but the reported rate of response would still be expected to be a good estimate. Applying a stricter definition for remission across these studies lowers the complete remission rates after SRS to 45% and SRS with medical therapy to 60.3%. Efficacy of SRS is equivalent regardless of technical modality (Table 3). Whereas most experience has been with GK (5, 7, 13, 41, 43), there are similar successes seen with the use of linear accelerator-based SRS (1, 22, 39), CyberKnife (10), and proton radiosurgery (40). Median time to complete remission after SRS ranges between 3 and 10 yr. Regardless of SRS modality, local control of tumor is high at 95–100% (Table 3).

The rate of remission with fractionated radiation is similar to that of SRS, with most reports ranging between 16 and 100% at 5–10 yr, with a more realistic estimate of 50–60% based on modern treatment techniques. Remission increases to 65–87% at 15 yr, demonstrating that response after radiation may require several years to evolve (Table 3). Overall time to remission appears to be longer than that of SRS, with mean time to complete remission between 6 and 10 yr from multiple studies. The variable definition of remission contributes to this wide range of time. A baseline GH of less than 2.5 ng/ml is more readily

TABLE 3. Radiation therapy for GH-secreting pituitary adenomas

First author, year (Ref.)	Study years	RT type	RT dose (Gy), median (range)	No. of patients
Landolt, 1998 (3)	1973–1992	Conv	40 (40–56)	50
	1994–1996	GK	25	16
Powell, 2000 (1)	1981–1999	Mix		43
		Conv	47.4 (45–54)	32
			5 × 6 Gy	
		L-SRS	18	5
			48 (44–53)	1
		GK		4
		Protons		1
Jezkova, 2006 (39)	1993–2003	GK 1–2 tx	35 (10–42)	96
Voges, 2006 (22)	1990–2004	L-SRS	15.3, mean (8–20)	64
Petit, 2007 (40)	1992–2003	Protons-SRS	20 (15–24)	22
Pollock, 2007 (7)	1991–2004	GK	20	46
Roberts, 2007 (10)	1998–2005	CK–SRS	21 (18–24), 1–3 tx	9
Vik-Mo, 2007 (41)	1989–2002	GK	26.5 (12–35)	53
Losa, 2008 (13)	1994–2006	GK	21.5 (20–25)	83
Castinetti, 2009 (36)	1993–2003	GK	28, mean (24–27)	43
Ronchi, 2009 (42)	1995–2004	GK	20 (15–35)	35
Iwai, 2010 (43)	1995–2005	GK	20, median (14–30)	26
Sheehan, 2011 (5)	1989–2006	GK	24 (9–30)	130
Barrande, 2000 (44)	1951–1998	Conv	52 (43.5–60.5)	128
Cozzi, 2001 (45)	1971–1993	Conv	46 (19–75)	49
Epaminonda, 2001 (46)	1969–1996	Conv	53.6, mean (40–75)	67
				26 subset
Colin, 2005 (26)	1990–1999	SRT	50.4	31
Minniti, 2005 (47)	1982–1994	Conv	45 (45–50)	47
Jenkins, 2006 (48)	1970–2004	Conv	45 (10–55)	656
Ronson, 2006 (27)	1991–2001	Protons	54, iso (50.4–55.94)	11
Jallad, 2007 (49)	1978–2003	Conv	50, mean (32.4–60)	99

RT, Radiation; LC, local control; L-SRS, linear accelerator-based SRS; CK-SRS, Cyber Knife SRS; Conv, conventional fractionated radiation; SRT, fractionated stereotactic radiotherapy; min, minimum; tx, treatment; CD, Cushing's disease; NS, Nelson's syndrome; CR, complete response; PR, partial response; NL, normalization with medication; H nl, hormonal normalization; ?, not stated in paper.

achieved than single or combination requirements of lower baseline GH level, normalized IGF-I, and normal oral glucose tolerance test (39). Those patients with a lower GH level before receiving radiation therapy appear to have a more favorable response to treatment (44, 48). Again, local tumor control rates are excellent at 95–100% in most series (Table 3).

Prolactinoma

Medical therapy is the standard first-line treatment for prolactinomas that are indicated for treatment. Dopamine agonists provide normalization of prolactin levels in 90% of microadenomas and slightly less for macroadenomas (51). When medical therapy provides incomplete response, surgery or radiation therapy can be considered.

TABLE 3. *Continued*

Follow-up, Median	LC (%)	LC median	Hormone normalization (%)	Hormone normalization time
7.5 yr, mean	100		50%	7.1 yr, mean
?	100			1.4 yr, mean
5.2 yr, mean				
			43.7%	5.6 yr, mean
			50%	2.9 yr, mean
			0%	1.2 yr
			0%	3.6 yr
53.7 months, mean	100		67.4%	5 yr
			85.7%	8 yr
82 months, mean	97		33.0% CR	42.8 months
12 months, min			49.8% NL	36.1 months
6.3 yr	100		95% any	
			59% CR	
			36% PR	
			67% CR	5 yr
63 months	100		11%	2 yr
			60%	5 yr
			50%	36 months, mean
25.4 months, mean			44.4% CR, 11.1% PR	12 months, mean
5.5 yr, mean	100		58%	5 yr
			86%	10 yr
69 months	97.6		52.6%	5 yr
		5 yr	84.8%	10 yr
96 months, mean	100		42% CR	42.6 months, mean (mix)
5 yr, min				48 months, estimate
114 months	100	10 yr	43%	130 months, mean
104 months, mean				7 yr
			64% CR/NL	10 yr
			46% CR	10 yr
			82% CR/NL	
84 months	96		16.9%	5 yr
24 months, min			47.4%	10 yr
31 months	90.3		53% CR	29.8 months
6 months, min				
11.5 yr, mean			35%	5 yr
			53%	10 yr
			66%	15 yr
14 yr	96?		16%	10 yr
10 yr			58%	8 yr
15 yr, min			65%	15 yr
82 months; 4 yr, mean	100	82 months, median	29% CR	6.7 yr
12 yr	95	5 yr	31%	5 yr
	95	10 yr	55%	10 yr
	95	15 yr	83%	15 yr
7 yr			60%	10 yr
			74%	15 yr
			77%	20 yr
47 months, imaging	100		45% CR	5 yr
83 months, H nl			36% PR	
4 yr; 5.9 yr, mean	100		54%	Raw
			40%	5 yr
			63%	10 yr
			67%	15 yr

Radiation therapy is more often considered in patients with persistent disease without further surgical options. Radiation offers a potential for curative treatment. Similar to treatment of other pituitary adenomas, both single fraction SRS and fractionated radiation maybe considered. When technically feasible, most patients receive SRS; however, the majority of surgical failures are macroadenomas with extrasellar extension that are often not amendable to SRS.

Success of radiotherapy in managing prolactinomas spans a wide range and often involves medical therapy

TABLE 4. Radiation therapy for prolactin-secreting pituitary adenomas

First author, year (Ref.)	Study years	RT type	RT dose (Gy), median (range)	No. of patients
Pan, 2000 (52)	1993–1997	GK	Mean, 31.2 (9–35)	128
Pouratian, 2006 (8)	1990–2003	GK	18.6 (0.3–25) 18.9 (0.3–25)	23 endo f/u 28 image f/u
Voges, 2006 (22)	1990–2004	L-SRS	Mean, 15.3 (8–20)	13
Jezkova, 2009 (53)	1993–2005	GK	34 (20–49)	35
Castinetti, 2009 (36)	1993–2003	GK	Mean, 28 (24–27)	15
Sheehan, 2011 (5)	1989–2006	GK	24 (9–30)	32
Tsagarakis, 1991 (54)	1972–1981	Conv	45	36
Tsang, 1996 (55)	1972–1986	Conv	50 (40–52)	64
Sasaki, 2000 (56)	1969–1994	Conv	51 (44–70)	5
Colin, 2005 (26)	1990–1999	SRT	50.4	4
Ronson, 2006 (27)	1991–2001	Protons	54 iso (50.4–55.94)	6
Erridge, 2009 (29)	1974–2003	Conv	45 (35–60)	58

RT, Radiation; LC, local control; L-SRS, linear accelerator-based SRS; Conv, conventional fractionated radiation; SRT, fractionated stereotactic radiotherapy; min, minimum; tx, treatment; PRL, prolactin; CR, complete response; PR, partial response; NL, normalization with medication; H nl, hormonal normalization; iso, isocenter; endo f/u, endocrine follow-up; image f/u, imagine follow-up.

to achieve normalization of prolactin levels. For SRS, recent published series suggest complete remission rates of 15–50% and normalization with medical therapy rates of 40–80% at median times of 2–8 yr, with most studies centering around a median time of 2 yr (Table 4).

There are limited reports of fractionated radiation used to manage prolactinomas, but those that do also show similar outcomes of remission with doses most commonly delivered between 45 and 54 Gy (Table 4). Complete normalization with radiation alone occurs in approximately 25–50% of patients. With the addition of medical therapy, normalization approaches 80–100% of patients over a median time to response between 1 and 10 yr, with higher doses seeming to achieve a faster response (27, 54, 56).

Again, local control is excellent by either SRS (8, 22, 36, 53) or fractionated radiation (27, 29), with rates of 89–100% in recent series. A clinically useful endpoint is difficult to assess in prolactinomas because biochemically elevated prolactin does not always require treatment.

Other pituitary adenomas

Experience with radiation therapy in the management of other types of pituitary adenomas is far more limited, with less than 10 patients reported within any given series. Overall, success of hormonal normalization will occur in about half of treated patients, whereas local control is generally excellent (22, 57). Treatment approaches are generally extrapolated from management of other secretory adenomas.

Summary of radiation treatment approaches for pituitary adenomas

Indication for radiation

- Nonfunctioning pituitary adenoma: 1) nonsurgical candidate; 2) recurrence or progression of tumor after surgery; and 3) surgically inaccessible tumor (*e.g.* cavernous sinus).
- Functioning pituitary adenoma: 1) hormonally uncontrolled after maximal surgical and medical therapy; 2) tumor growth or extension that cannot be surgically addressed because of patient being a nonsurgical candidate, tumor recurrence or progression, or surgical inaccessibility.

Type of radiation

- SRS: Tumor target should be at least 3–5 mm removed from the chiasm and less than 3 cm in diameter. Final evaluation and confirmation should be made by a radiation oncologist because the actual determinant is the dose that is delivered to the normal tissues.
- Fractionated radiation therapy: Suitable for any adenoma. This may be the only option if a tumor target is less than 5 mm removed from the chiasm and larger than 3 cm in diameter. Final evaluation and confirmation should be made by a radiation oncologist because the actual determinant is the dose that is delivered to the normal tissues.

Dose of radiation (authors' recommendation)

- SRS: For nonfunctioning pituitary adenomas, 18 Gy; for functioning pituitary adenomas, 20 Gy.

TABLE 4. Continued

Follow-up median	LC (%)	LC median	Hormone normalization (%)	Hormone normalization time
33.2 months, mean	98.4		52.3% CR, most NL	
55 months	89		26% CR	24.5 months, mean
48 months, >1 yr min				
82 months, mean	100		16.7% CR	48.3 months
12 months, min			42.7% NL	40.4 months, mean
75.5 months, mean	97.1		80% all, 37.1% CR, 42.9% NL	8 yr
96 months mean, 5 yr min	100		47% CR	23 months, estimate
31 months, 6 months min	90.3		26% CR	24.5 months, median
			50% CR, 28% PR	7.3 yr, mean
7.3 yr	96	10 yr	25% CR	10 yr
8.2 yr	82.8		40% CR PRL	3 yr, raw
>2 yr min			40% PR PRL	
82 months, 4 yr mean	100	6.8 yr	29% CR	6.7 yr
47 months, imaging	100		33% CR	5 yr
83 months, H nl			66% PR	
9.1 yr	95	10 yr		

- Fractionated radiation therapy: For nonfunctioning pituitary adenomas, 45–50.4 Gy delivered at 1.8 Gy daily fractions; for functioning pituitary adenomas, 50.4–54 Gy delivered at 1.8 Gy daily fractions.

Radiation-Associated Adverse Effects

When successful, radiation therapy can provide a definitive cure for many patients with pituitary adenomas, yet it is almost never first-line therapy. Medical therapy is typically a long-term treatment in secretory adenomas, with withdrawal of therapy often associated with recurrence of the biochemical disorder. The reason for the secondary or tertiary use of radiation therapy is largely due to the potential adverse effects of radiation, most of which are not reversible.

By far the most common toxicity of pituitary irradiation is hypopituitarism of single or multiple axes. This occurs in virtually all patients when followed over many years. Five-year incidence of radiation-associated hypopituitarism is approximately 20% with either fractionated (14, 29, 38, 47, 48, 49) or single fraction radiation (5, 7, 9, 13, 20, 22, 35, 36, 40, 53). In some series, this increases to about 80% by 10–15 yr and likely represents the net result of surgical and radiation intervention (14, 38).

Few studies are dedicated to the evaluation of radiation-associated hypopituitarism. Definitions and assays vary by institution and change with time. Because hypopituitarism is a late effect of irradiation that evolves over years from treatment, accurate assessment of its incidence requires many years of follow-up, whereas most published reports average less than 10 yr of follow-up data. Nonetheless, one of the noteworthy studies to address this issue was a report on 251 patients treated for a variety of cranial irradiation indications, of which 227 cases were pituitary adenomas (58). Low doses of fractionated radiation of 12 Gy or less did not incur detectable hypothalamic-pituitary axis (HPA) deficiency, whereas doses of 20 Gy and higher did result in detectable deficits in thyroid, cortisol, and gonadotropin levels and elevation in prolactin. The severity of HPA dysfunction trended with radiation dose most notably with thyroid function in which 52% of patients treated with 42–45 Gy developed hormonal deficiency. Time to onset of the hormonal effect was also shorter with higher doses. Similar findings of hypopituitarism are reported after SRS. Castinetti *et al.* (36) reported on 76 patients with mixed types of pituitary adenomas that received GK radiosurgery. With a minimum follow-up of 5 yr and one third of patients followed for over 10 yr, these investigators found that 21% of their patients developed hypopituitarism at a mean time of 48 months, which again reinforces the importance of long-term surveillance for HPA dysfunction. Sensitivity of individual hormonal axes varies among patients, with the exception of GH which is consistently the most sensitive with regard to time to deficit (59). GH is not evaluated in many series because replacement in adults is typically not indicated. Similarly, hyperprolactinemia often occurs early but rarely requires intervention and thus is variably measured (60). Data regarding the sensitivity of individual hormonal axes vary greatly, with factors such as dose, fractionation, age, and gender affecting this (59, 60). LH, FSH, ACTH, and TSH are all susceptible to radiation effects, with panhypopitu-

itarism occurring in approximately 5–10% of patients at 5 yr from treatment (6, 35, 36, 40, 49).

Awareness of risk factors for pituitary dysfunction is useful in weighing optimal timing of radiation therapy and in counseling patients. Because pituitary adenomas are by nature juxtaposed to the normal pituitary gland, irradiation and subsequent impact to its function is almost always unavoidable. However, dosimetric data suggest that any avoidance of dose to the normal gland and to the hypothalamus may reduce the incidence of radiation-associated hypopituitarism (60, 61). Thus, it is not surprising that a larger baseline tumor volume of nonfunctioning adenomas has been shown to be predictive of increased secondary hypopituitarism (9). Surgical manipulation before irradiation increased the risk of HPA dysfunction (59). Similarly, patients with preexisting pituitary deficiency, most commonly related to prior surgical intervention, are also more susceptible to further pituitary hormonal deficits after radiation therapy (44, 62). With the high rate of pituitary dysfunction after radiation therapy, all patients should be counseled on the importance of neuroendocrine evaluation and surveillance because most deficits can be pharmacologically corrected.

Fortunately, other potential adverse effects occur at a far lower frequency and generally do not arise within the first 5 yr after treatment. Unfortunately, risks do not decline with time from irradiation but rather slowly increase with each decade from radiation treatment. Injury to the visual system may arise from irradiation of the chiasm or optic nerves. Fractionated radiation is associated with substantially lower risk of optic pathway injury than SRS, with an estimate of 0.8–1.3% at 10 yr and 1.5% at 20 yr based upon two large series of 796 patients (24, 29). Risk of radiation-related optic pathway injury is correlated with single doses to these structures exceeding 8–10 Gy (63, 64). Thus, it is not SRS as a technique that harbors risk of complication but rather the dose that the normal tissues receive. When a therapeutic dose cannot be delivered to an adenoma without exceeding safe tissue tolerance to the optic structures, fractionated radiation should be considered. Secondary tumors are a late risk with an incidence of 1.9% at 20 yr in the same two large studies (24, 29). These large series include data spanning treatment over several decades and largely include antiquated treatment methods in which the volume of normal tissue treated with radiation was far greater than what would be typically used in current practice of the last 10 yr. Visual complications, neurological symptoms, strokes, or secondary tumors are seen very rarely in smaller series and there are even current findings that patients treated with radiation therapy may fair better in general and mental health compared with equivalent patients who do not receive radiation (65). The true incidence of these complications would be expected to be less than 1% and will not be fully realized for several decades when adequate follow-up data using current treatment methods are available.

Conclusion

Radiation can achieve local control rates of 90–100% across all pituitary adenoma types and biochemical complete response in approximately 50% of patients, with even more achieving hormonal normalization with the addition of medical therapy. Modern modalities of radiation therapy permit for highly targeted irradiation of pituitary adenomas with significant reduction of normal tissue irradiation compared with care given even a decade ago. Clinical data to date provide useful results to guide refinement of radiation dose and dose schedules to optimize therapeutic efficacy while minimizing potential treatment-related complications.

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