Radiation treatment strategies for acromegaly

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The high morbidity and mortality associated with acromegaly can be addressed with multiple treatment modalities, including surgery, medicines, and radiation therapy. Radiation was initially delivered through conventional fractionated radiotherapy, which targets a wide area over many treatment sessions and has been shown to induce remission in 50%–60% of patients with acromegaly. However, conventional fractionated radiotherapy takes several years to achieve remission in patients with acromegaly and carries a risk of hypopituitarism that may limit its use. Stereotactic radiosurgery, of which there are several forms, including Gamma Knife surgery, CyberKnife therapy, and proton beam therapy, offers slightly attenuated efficacy but achieves remission in less time and provides more precise targeting of the adenoma with better control of the dose of radiation received by adjacent structures such as the pituitary stalk, pituitary gland, optic chiasm, and cranial nerves in the cavernous sinus. Of the forms of stereotactic radiosurgery, Gamma Knife surgery is the most widely used and, because of its long-term follow-up in clinical studies, is the most likely to compete with medical therapy for first-line adjuvant use after resection. In this review, the authors outline the major modes of radiation therapies in clinical use today, and they critically assess the feasibility of these modalities for acromegaly treatment. Acromegaly is a multisystem disorder that demands highly specialized treatment protocols including neurosurgical and endocrinological intervention. As more efficient forms of pituitary radiation develop, acromegaly treatment options may continue to change with radiation therapies playing a more prominent role. (DOI: 10.3171/2010.7.FOCUS10124)

KEY WORDS • growth hormone • pituitary adenoma • radiotherapy • radiosurgery • Gamma Knife surgery • CyberKnife therapy

TRANSPHENOIDAL microsurgery to resect the causative GH-secreting pituitary adenoma remains the initial treatment of choice in the majority of patients with acromegaly.^{10,25,48,52,53,74,90} However, the optimal management of the 10%–50% of patients who do not enter remission after transsphenoidal surgery^{13,52} and the 20% of patients who experience recurrence of acromegaly after transsphenoidal surgery¹³ remains less clear. Radiation represents an evolving treatment modality for acromegaly that warrants consideration as an alternative to medical therapy for tumors refractory to transsphenoidal surgery.

The conceptual groundwork for focused irradiation of GH-secreting pituitary adenomas while avoiding damage to surrounding neural structures was established more than 50 years ago.^{2,56,97} Since that time, substantial advances in radiation technology have yielded increasingly precise pituitary adenoma-targeting capability and consequently an

expanded set of treatment options for acromegaly to supplement resection and hormonal suppression with medical management. A complex array of factors dictate treatment decisions for acromegaly in the modern era, including adenoma size, degree of secretory hyperactivity, invasion of surrounding structures, and therapeutic side effects and their particular impact in the patient in question. For these reasons, contemporary treatment of patients with acromegaly now routinely involves multiple disciplines, including neurosurgery, endocrinology, and radiation oncology.^{1,3,27,34,47,62,64,65,76,78} Indeed, in cases of acromegaly, all 3 approaches (surgery, medication, and radiation) can be beneficial and can play a role in management. Thus, an expert panel, the Acromegaly Consensus Group, formed in 2000, publishes guidelines for acromegaly management, most recently in 2009. The recommendations are that tumors deemed completely resectable undergo surgery, with somatostatin analogs used in cases in which remission after surgery is not achieved. Tumors deemed incompletely resectable are treated with somatostatin analogs. Cases in which remission is not achieved with the use of somatostatin analogs are treated with pegvisomant if there is

Abbreviations used in this paper: CFR = conventional fractionated radiotherapy; GH = growth hormone; GKS = Gamma Knife surgery; IGF-I = insulin-like growth factor-I.

no mass effect on MR imaging, because the tumor growth that can occur with pegvisomant would be tolerated, or with radiation if there is mass effect on MR imaging.⁶³ However, because these recommendations are not based on randomized clinical trials, further studies will likely be needed to definitively determine the role of radiation therapy in achieving the best long-term outcome for patients with acromegaly. Here, we review the results to date with radiation as a treatment modality for acromegaly, and we outline future directions that might get us closer to a definitive understanding of the role of radiation in acromegaly management.

Methods

An online search for journal articles relevant to the topic was conducted using the PubMed Database by entering combinations of the MeSH terms “acromegaly,” “radiosurgery,” “radiation,” “radiotherapy,” “fractionated,” “Gamma Knife,” “Cyberknife,” and “proton beam.” Articles were limited to the English language. Captured articles were indexed by content using an electronic citation manager. Cited references within articles were also searched for relevancy to the topic. Articles describing independent retrospective studies of CFR and radiosurgery for acromegaly were detailed in table format (Tables 1 and 2).

Results

Conventional Fractionated Radiotherapy

Conventional fractionated radiotherapy is a direct descendant of the radiography devices first used by Bécélère and Gramagna in 1909 to irradiate pituitary tumors in patients with acromegaly.²⁹ Today, CFR has been modified to deliver megavoltage doses of radiation in fractions separated over time to increasingly smaller intracranial target volumes. In the case of pituitary adenomas, a standard dose of 160–180 cGy 4–5 times per week over 5–6 weeks for a total dose of 45–50 Gy is typically performed (Table 1).⁶⁹ Using strict remission definitions that began to be adapted in the mid-1990s of GH level below 2 ng/ml and/or normalized IGF-I levels, most studies from the period 1997–2007 have reported remission rates of 35%–75% with CFR (Table 1). These remission rates typically take 10 years to achieve. The main factors identified in these studies that was predictive of achieving remission were the initial GH and IGF-I levels, as patients with higher levels have been shown to take longer to achieve remission and have lower remission rates.¹³ Radiotherapy is typically followed by a maximal decrease in GH during the first 2 years, with the mean GH decreasing to 50%–70% of its initial value during this time, followed by a progressive slow decrease over the ensuing 10–20 years.¹³

Conventional fractionated radiotherapy treatment of acromegaly has been associated with high rates of hypopituitarism, ranging from 50% to 80% (Table 1).^{50,51,66,83,96} The development of hypopituitarism after CFR has a similar time course as the development of remission, typical-

ly occurring 10 years after treatment (Table 1).^{50,51,66,83,96} The overall incidence of new pituitary deficits after CFR is greater when pituitary function was already impaired prior to CFR.⁷⁹ Visual deficits after CFR occur in 5% of patients with acromegaly 7–12 months after treatment,³⁸ with many patients who suffer visual deficits having suprasellar tumor needing radiation treatment, suggesting that aggressive tumor debulking before CFR, using surgery to remove suprasellar tumor, will be vital to reduce the rate of visual deficits after CFR. Other toxicities, such as radiation necrosis and radiation-induced cerebral tumors occur in less than 1% of CFR-treated patients, with a mean latency of 7–24 years.⁶⁷ Vascular injury has been reported with a 1.7- to 2.8-fold increased risk for patients treated with CFR for pituitary adenomas, with the risk directly proportional to the total CFR dose and higher in patients treated previously with surgery and in patients with hypopituitarism.²⁴

The pituitary dysfunction rate and time to remission has improved with the most recent study, published in 2007, in which a remission rate of 38% was achieved in a mean time of 6 years and an associated hypopituitarism rate of 47%.³⁸ However, the radiosurgical techniques described below still are associated with a much shorter time to remission and a lower rate of hypopituitarism, causing some to question the usefulness of CFR in the contemporary management of acromegaly.^{5,68,87} Conventional fractionated radiotherapy could still prove useful in treating particularly large, aggressive GH-secreting adenomas with significant residual tumor after surgery due to invasion of bilateral cavernous sinuses or extension into the temporal lobe that cannot be safely treated with radiosurgery because adjacent elegant structures would be affected by the high-dose precise targeting of radiosurgery.^{13,38}

Introduction to Stereotactic Radiosurgery

In contrast to CFR, which focuses single beams of high-energy radiation onto a small treatment field, radiosurgery, conceived in the 1950s,⁵⁵ delivers multiple low-energy beams toward a target with improved stereotactic accuracy and a suprathreshold integral dose. The principal advantage of radiosurgery is that it reduces the dose of radiation received by transirradiated tissue close to the target because the multiple low-energy beams converge at the target to create a dosimetry map in which the target receives a dose high enough to inactivate or kill tissue in the target, but a sharp falloff of radioactivity near the target lowers the dose received by adjacent structures compared with CFR. Stereotactic radiosurgery accomplishes this precise targeting in a single or few fractions, and the radiation can be delivered as photons using devices such as the Gamma Knife or CyberKnife or as charged particles using proton-beam radiosurgery.

In the 1990s, neurosurgeons began to use stereotactic radiosurgery to treat pituitary adenomas to improve on the remission rate, time to remission, and hypopituitarism rate associated with CFR.^{19,28,32,39,43,44,57,61,71,72,77,82,89} The beam trajectories were calculated to spare critical structures near the pituitary adenoma, such as the optic chiasm.

Gamma Knife Surgery. Gamma Knife surgery is a

TABLE 1: Results of published series studying conventional fractionated radiotherapy in the treatment of acromegaly*

Authors & Year	No. of Patients	FU Time (yrs)	Mean Total Dose in Gy (range)	Mean No. of Fractions (range)	Remission Criteria	Remission Rate (%)	New Posttreatment Hormone Deficiency		
							Mean Time to Remission (yrs)	% Patients	Mean Time to Deficit (yrs)
Barkan et al., 1997	38	mean 6.8	46 (45–50)	24	normal IGF-I	5	5	NE	NE
Powell et al., 2000	47	mean 5.2	47 (45–54)	26 (25–30)	normal IGF-I	60	10	32	NE
Biermasz et al., 2000	0	mean 11.3	40 (25–50)	19	normal IGF-I	74	10	50	10
Epaminonda et al., 2001	67	median 10	54 (40–75)	33 (30–35)	GH <2.5 ng/ml & normal IGF-I	65	15	60	NE
Barrande et al., 2000	128	mean 11.5	52	29	GH <2.5 ng/ml & normal IGF-I	53	10	80	10
Cozzi et al., 2001	49	median 14	45	22	GH <2.5 ng/ml & normal IGF-I	10	10	8	10
Minniti et al., 2005	74	median 12	45	25	GH <1.0 ng/ml & normal IGF-I	47	10	80	10
Jenkins et al., 2006	884	median 7	45 (10–55)	25	GH <2.5 ng/ml or normal IGF-I	60	10	60	10
Jallad et al., 2007	89	mean 5.9	50 (32.4–60)						

* NE = not evaluated.

TABLE 2: Results of series reported in 2007–2009 studying radiosurgery for the treatment of acromegaly*

Authors & Year	No. of Patients	FU Time (yrs)	Modality (targeted field of treatment)	Dose	Remission Criteria	Remission Rate (%)	Mean Time to Remission (mos)			New Posttreatment Hormone Deficiency	
										% Patients	Time to Deficit (yrs)
Roberts et al., 2007	9	mean 2.1†	CyberKnife therapy (NR)	21 Gy‡	normal IGF-I	44	12	33	NR		
Petit et al., 2007	22	median 6.3	PBRS (sella)	median 20 CGE	normal IGF-I	59	42	38	median 3–4.7†§		
Pollock et al., 2007	48	median 5.3†	GKS (tumor margins)	20 Gy¶	normal IGF-I & GH <2 ng/ml	50	36	33	median 2.7†		
Vik-Mo et al., 2007	53	mean 5.5	GKS (tumor margins)	25 Gy‡	normal IGF-I	17	not stated	13	NR		
Jagannathan et al., 2008	95	mean 4.8†	GKS (various)	22 Gy‡	normal IGF-I	53	29.8	34 (1.6)	mean 1.6†		
Losa et al., 2008	83	median 5.8†	GKS (tumor margins)	25 Gy‡	normal IGF-I & GH <2.5 ng/ml	60	60	10	3.3%–4.9% cumulative risk at 5 yrs		
Imran et al., 2009	12	median 2.4†	LINAC-based (tumor margins)	NE	normal IGF-I	33	NR	8	2 (in 1 patient)†		
Swords et al., 2009	10	median 3.0†,**	GKS (tumor margins)	NE	normal IGF-I	80	NR	NR	NR		
Cho et al., 2009	6	median 3.0†,**	CyberKnife therapy (tumor margins)	1983 cGy††	GH <5 mIU/L	33	15	0			
Ronchi et al., 2009	35	median 9.5†	GKS (tumor margins)	20 Gy¶	GH <2.5 ng/ml, normal IGF-I, & postglucose GH nadir <1 ng/ml	46	120	50	median 8.3†		
Castinetti et al., 2009	43	mean 8.5 remission†; mean 8.2 uncured†	GKS (tumor margins)	24 Gy‡‡	GH <2 ng/ml &/or postglucose GH <1 ng/ml & normal IGF-I	42	50	NR for acro cohort	NR for acro cohort		
Kobayashi, 2009	71	mean 5.3†	GKS (NR)	18.9 Gy‡	GH <1 ng/ml	4.8	NR	14.6	NR		

* acro = acromegaly; CGE = cobalt Gray equivalents; NR = not reported; PBRS = proton-beam radiosurgery.

† Conversion from months.

‡ Mean margin dose.

§ Depending on the hormone deficit.

¶ Median margin dose.

** Calculated median from raw data to nearest tenth.

†† Mean total dose.

‡‡ Mean isodose 50.

Radiation for acromegaly

neurosurgical technique using a source of ^{60}Co to deliver narrow beams in a single session with stereotactic precision and accuracy to destroy or inactivate a target with minimal damage to the surrounding brain. In acromegaly, mean doses of 20 to 25 Gy are delivered to the tumor margin, higher than the 10–20 Gy mean margin doses used for GKS of endocrine inactive adenomas, because the goal when using radiosurgery to treat acromegaly or other endocrine active adenomas is to completely disrupt hormonal hypersecretion, while the goal with GKS for endocrine inactive adenomas is to prevent adenoma growth. Gamma Knife surgery is the most extensively studied radiosurgery method in the treatment of acromegaly (representative case shown in Fig. 1). A landmark 1998 study compared GKS with CFR for acromegaly at a single institution and found that stereotactic radiosurgery had a mean time to normalization of GH and IGF-I of 1.4 years, far less than the mean time to normalization of 7.1 years seen with CFR ($p < 0.0001$).⁵⁰ In addition, the rate of new pituitary deficits was 16% in the CFR-treated group, while no patient treated with GKS developed a new pituitary deficit.⁵⁰ While this study did not specify the remission rates achieved in the 2 groups, around the time of this 1998 study, 6 other studies of GKS for acromegaly reported a wide range of remission rates of 31%–58%. These rates are slightly below rates seen in CFR, but they increased somewhat in ra-

diology studies published in the latter portion of the next decade (Table 2). While it does still appear that the published remission rates seen with CFR (Table 1) may be higher than the acromegaly remission rates seen with GKS (Table 2), it should be emphasized that the CFR series in the literature tend to be slightly older studies that preceded the recent increasing use of medical treatments for acromegaly, while the GKS studies tend to be more recent studies occurring at a time when patients receiving radiation are those with partial or total resistance to medical treatments. All of these follow-up studies have consistently confirmed a faster remission and lower rate of hypopituitarism with GKS (Table 2) than with CFR (Table 1).^{4,16,30,35–37,41,46,58,60,81,85,91–93,95,98} Gamma Knife surgery is typically followed by a maximal decrease of GH secretion during the 1st year, followed by progressive slow decrease over the next 5 years.¹³ Achieving timely remission of acromegaly is vital because, like Cushing disease,²¹ the mortality remains elevated in patients with acromegaly even after hormonal normalization,²² possibly due to irreversible physiological effects of elevated GH. And achieving timely remission with reduced risk of hypopituitarism is also important because of studies showing increased long-term mortality associated with hypopituitarism.⁹⁴

Several groups have identified the following 4 factors predictive of achieving remission in patients undergo-

FIG. 1. Case example. A 55-year-old woman presented with acromegaly (GH level 36 ng/ml [reference level < 11 ng/ml] and IGF-I = 1200 $\mu\text{g/L}$ [reference range 81–225 $\mu\text{g/L}$]) and a 15 × 22 × 18-mm adenoma with left cavernous sinus invasion, seen on T1-weighted Gd-enhanced sagittal (A) and coronal (B) images. The patient underwent transsphenoidal surgery for the adenoma 2 weeks after the MR images were obtained. Six weeks after surgery, postoperative MR imaging revealed residual tumor in the left cavernous sinus, seen again on T1-weighted Gd-enhanced sagittal (C) and coronal (D) images. Six weeks after surgery, her postsurgical GH and IGF-I levels were 2 ng/ml and 344 $\mu\text{g/L}$, respectively. The latter value, along with MR imaging showing residual adenoma, was indicative of persistent postoperative acromegaly. Four months after transsphenoidal surgery, the patient underwent GKS to target residual adenoma in the left cavernous sinus, prescribed to a dose of 25 Gy to the 54% isodose line (E). Twenty months after radiosurgery and 2 years after diagnosis, the IGF-I level normalized to 200 $\mu\text{g/L}$, the GH level remained normalized to 1 ng/ml, and T1-weighted Gd-enhanced sagittal (F) and coronal (G) images showed no residual enhancing tissue, consistent with remission of acromegaly.

ing GKS for acromegaly: 1) discontinuation of antiacromegaly medications at the time of radiosurgery, namely dopamine agonists, somatostatin analogs, and/or the GH antagonist pegvisomant; 2) lower pretreatment GH and IGF-I levels; 3) higher total integral radiation dose; and 4) higher maximal dose to the adenoma.¹⁵

Several groups have found that patients who are off all acromegaly medications at the time of radiosurgery achieve greater biochemical remission,^{81,95} with the most comprehensive study reporting a hazard ratio of 4.2 in patients who had not been on medications 1 month prior to radiosurgery.⁸¹ Antiacromegaly medications could inhibit radiosurgery efficacy for 3 possible reasons as follows: 1) patients unable to wean off antiacromegaly medications prior to radiosurgery may have tumors more resistant to treatment, regardless of modality; 2) medical therapy for acromegaly reduces metabolic activity in pituitary adenoma cells, making these cells less proliferative and therefore less responsive to radiation therapy, which causes DNA damage in rapidly replicating cells at the time of treatment;⁴⁹ and/or 3) the somatostatin analogs, for example, octreotide, contain disulfide bonds that are reduced to expose free thiols, which help to scavenge DNA-disrupting oxygen-free radicals that arise from ionizing radiation and cause the DNA damage that precedes radiation-induced cell death. Although these explanations are indirectly substantiated by recent data, they remain speculative at this point, and other studies have found no effect of antiacromegaly medications on remission, such as a 2005 study from a French group that failed to find any correlation between the probability of remission and the discontinuation of antiacromegaly medications for at least 3 months at the time of radiosurgery.¹³

Several other groups have found that lower pretreatment IGF-I levels are predictive of likelihood of remission, while adenoma size is not.^{58,81} A 2007 study demonstrated IGF-I levels less than 2.25 times the upper limit of normal (hazard ratio 2.9) as predictive of remission in a multivariate analysis.⁸¹ Another group found that initial GH and IGF-I levels while off somatostatin analogs were significantly higher in patients who did not achieve remission than in patients with biochemical remission,¹³ which suggests that, even if being off antiacromegaly medications at the time of radiosurgery does not improve the chances of remission, another benefit of being off medications at the time of GKS is that the pretreatment hormone levels provide a better understanding of the likelihood of achieving remission with radiosurgery.⁸⁵

A study of 42 patients with endocrine active adenomas identified 2 other factors predicting remission in a multivariate analysis, higher total integral dose ($p = 0.005$), and maximum dosage ($p = 0.001$).¹⁹ The integral dose represents the total energy absorbed by the adenoma during radiosurgery in gram rad units (1 g rad unit represents 100 ergs/g), while the maximum dosage represents the highest dose any part of the adenoma receives in Gray units.

As with CFR, hypopituitarism is the primary adverse effect associated with GKS, but, as stated above, its occurrence seems to be less frequent with GKS than with CFR. The risk of hypopituitarism in patients with acromegaly undergoing GKS seems to be higher in 1) those

who have undergone previous transsphenoidal surgery; 2) those who have undergone previous CFR; 3) the degree of target definition, as lack of an enhancing abnormality on MR imaging causes the hypopituitarism risk with GKS to be as high as it is with CFR; and 4) the dose to the pituitary stalk. In identifying factors predicting the development of hypopituitarism in patients with pituitary adenomas who are undergoing radiosurgery, a German group retrospectively reviewed 92 cases (of which 9 had acromegaly) and found that the pituitary stalk in patients who went on to lose pituitary function received 7.7 Gy, compared with 5.5 Gy in those without subsequent loss of pituitary function ($p = 0.03$),²⁶ suggesting that the pituitary stalk may be even more radiosensitive than the overlying optic chiasm, where doses are typically kept below 10 Gy.⁸¹

Optic neuropathy is the second most frequent adverse event seen with GKS for patients with acromegaly, but it occurs far less often than hypopituitarism, occurring in less than 1% of patients with acromegaly treated with GKS. Other rare side effects that have been reported with CFR, such as radiation necrosis, vascular injury, and the development of secondary tumors, appear to be even less common with radiosurgery than with CFR, but CFR has been studied with longer-term follow-up than radiosurgery, and these adverse effects take 10–25 years to develop. A recent review reported 13 cases of radiation necrosis in 1567 patients with pituitary adenomas treated with radiosurgery, but half of the patients who developed radiation necrosis had received prior CFR, making the etiology of the necrosis difficult to definitively determine.¹¹

As the number of studies showing the efficacy of GKS in treating acromegaly continues to grow, it will be important to account for differences in remission criteria, the frequency with which antiacromegaly medications are used, and variations in laboratory assays. For example, a 2009 study of GKS by Ronchi et al.⁸⁵ found a 10-year time to remission, which is significantly slower than the times to remission reported with other series (Table 2). But these results reflect the fact that Ronchi et al. reported remission rates in patients who were off somatostatin analog therapy at the time of radiosurgery using a strict 3 criteria must be met definition of remission (normal oral glucose tolerance test, “safe” GH levels, and normal IGF-I level), whereas other studies with faster times to remission included patients on medical therapy at the time of treatment and used only 1 or 2 criteria for remission. Furthermore, rates of hypopituitarism can be underestimated in the absence of adequately sensitive assays.⁸⁵ In the future, it is hoped that conflicting results with regard to time to remission, remission rates, factors predicting remission, and factors predicting adverse effects like hypopituitarism may be addressed through large multicenter trials with central review, in which patients are ideally randomized according to variables of interest, such as those on or off acromegaly medications for specific durations of time at the time of treatment.

CyberKnife Therapy

The CyberKnife system is a frameless, image-guided, robotic radiosurgical device that delivers linear accelera-

tor (LINAC)-based x-ray radiation in one or a few sessions with accuracy comparable to frame-based methods such as the Gamma Knife. To date, however, few studies have been published on the efficacy of CyberKnife treatment of GH-secreting pituitary adenomas. The Stanford University group reported the largest series of 9 patients with acromegaly treated with CyberKnife from 1998 to 2005. The group achieved remission in 44% of patients, with a 1-year mean time to remission and a 33% rate of new hormone deficiency.⁸⁴ Two other reports noted similar efficacy using the CyberKnife, although a larger series is needed to confirm these results.^{17,42} The CyberKnife has several potential advantages over the Gamma Knife in that it can treat intracranial and extracranial tumor sites. One particularly significant advance with regard to treatment of acromegaly is the potential to reduce rates of hypopituitarism even further by using dose hypofractions rather than single fraction-based therapy.³¹

Proton-Beam Radiosurgery

Proton-beam radiosurgery takes advantage of the superior dose distribution of protons versus photons, resulting from the peak in the energy distribution of protons (that is, the Bragg-peak) before they come to rest at the treatment depth. This method of irradiation was widely used for treatment of acromegaly in the 1960s and 1970s.^{33,45,56} Its popularity, however, waned as more advanced technologies, such as GKS, were optimized for less frequent side effects.^{6,59,83} Still, interest in this modality remains, and the treatment continues to be studied at the 7 proton beam centers in the US. A 2007 study of proton-beam radiosurgery in treating acromegaly found a 59% remission rate, among the highest reported for acromegaly radiosurgery, and a 33% rate of hypopituitarism,⁷⁹ suggesting the benefit of the superior dose distribution in the region of the target must be weighed against a greater dose being delivered to the normal gland or pituitary stalk as well.

Comparison of Radiation With Medical Management

Medical management of acromegaly has a mean time to achieve remission of 6 months with octreotide⁷³ and 9 months with pegvisomant.¹² These numbers are less than the 30- to 60-month time to remission reported in most studies of radiosurgery. However, the cost of medical management is \$20,000–\$25,000 US dollars per year for short-acting octreotide,⁶⁶ \$29,000–\$35,000 per year for long-acting formulations like Sandostatin LAR,⁸ and \$40,000–\$65,000 per year for pegvisomant,⁷⁰ far more than the \$8,000–\$16,000 cost of a single radiosurgery treatment.^{18,54,88} Thus, as radiosurgical techniques continue to improve, thereby lowering the morbidity and increasing the efficacy of radiosurgery for acromegaly, clinicians caring for patients with acromegaly will need to consider the cost effectiveness of a single radiosurgery treatment followed by medical management that can be discontinued if remission is achieved, compared with not doing radiosurgery and being committed to the cost of lifelong medical management, as most,⁸⁰ but not all,⁸⁶ studies have suggested the need for lifelong continuation of medicines in medically treated acromegaly.

Conclusions

These results from studies of multiple modalities of radiosurgical treatment of acromegaly will require verification in larger series conducted over a longer period of time. Future experimental directions designed to improve the remission rates with radiosurgery for acromegaly could include use of somatostatin receptor scintigraphy to localize adenoma cells⁷⁵ and better define a target for radiosurgery. Another goal of future studies will be to document the long-term recurrence rates in patients with acromegaly who achieve remission after radiosurgery. Overall, GKS, present in 109 centers in the US and 30 centers in Europe, is so far the most extensively studied modality with several reports involving 10-year patient follow-up data. Large single-fraction and high-precision doses of radiation with steep falloff are features of radiosurgery that make it an attractive option for adjuvant therapy for refractory acromegaly after transsphenoidal surgery. Its use may be optimally effective in patients who have discontinued their antiacromegaly medication at the time of treatment, have low basal GH and IGF-I levels, and receive higher total integral radiation doses and higher maximal doses. Future multicenter clinical trials that are currently under development such as the Phase II Radiation Therapy Oncology Group (RTOG) trial 0930 will study radiosurgery for the treatment of persistent acromegaly after transsphenoidal surgery and will be poised to confirm the findings to date from smaller studies and to address the other as yet unanswered questions described in this review.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Aghi. Acquisition of data: Rowland. Analysis and interpretation of data: both authors. Drafting the article: Rowland. Critically revising the article: both authors. Reviewed final version of the manuscript and approved it for submission: Aghi. Study supervision: Aghi.

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