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REVIEW

Updates in outcomes of stereotactic radiation therapy in acromegaly

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Abstract *Purpose* Treatment of acromegaly has undergone important progress in the last 20 years mainly due to the development of new medical options and advances in surgical techniques. Pituitary surgery is usually first-line therapy, and medical treatment is indicated for persistent disease, while radiation (RT) is often used as third-line therapy. The benefits of RT (tumor volume control and decreased hormonal secretion) are hampered by the long latency of the effect and the high risk of adverse effects. Stereotactic RT methods have been developed with the aim to provide more precise targeting of the tumor with better control of the radiation dose received by the adjacent brain structures. The purpose of this review is to present the updates in the efficacy and safety of pituitary RT in acromegalic patients, with an emphasis on the new stereotactic radiation techniques. *Methods* A systematic review was performed using PubMed and articles/abstracts and reviews detailing RT in acromegaly from 2000 to 2016 were included. *Results* Stereotactic radiosurgery and fractionated stereotactic RT (FSRT) for patients with persistent active acromegaly after surgery and/or during medical therapy provide comparable high rates of tumor control, i.e. stable or decrease in size of the tumor in 93–100% of patients at 5–10 years and endocrinological remission in 40–60% of patients at 5 years. Hypofractionated RT is an optimal option for tumors located near the optic structures, due to its lower toxicity for the optic nerves compared to single-dose radiosurgery. The rate of new hypopituitarism varies from 10 to 50% at 5 years and increases with the duration of follow-up. The risk for other radiation-induced complications is usually low (0–5% for new visual deficits, cranial nerves damage or brain radionecrosis and 0–1% for secondary brain tumors) and risk of stroke may be higher in FSRT. *Conclusion* Although the use of radiotherapy in patients with acromegaly has decreased with advances in medical treatments, it remains an effective treatment option after unsuccessful surgery and/or resistance or unavailability of medical therapy. Long-term studies evaluating secondary morbidity and mortality rate after the new stereotactic techniques are needed, in order to evaluate their potential brain-sparing effect.

Keywords Acromegaly · Stereotactic radiotherapy · Radiosurgery · Fractionated radiotherapy · Hypofractionated radiosurgery · Hypopituitarism

Introduction

Acromegaly is a severe disease responsible for disabling symptoms, comorbidities and shortened life-span if left untreated [1]. Primary treatment usually involves neurosurgery and, in selected cases, medical therapy. External pituitary irradiation (RT) has been used in the therapy of patients with acromegaly for more than 100 years, initially as an adjuvant to neurosurgery. According to the most recent guidelines, RT is suggested for patients with residual tumor mass following surgery, and if medical therapy is unavailable, unsuccessful, or not tolerated [2].

The method with the longest therapeutical experience is conventional radiotherapy (CRT). CRT is administered by a linear accelerator (4–8 MeV) with a total dose of 40–45 Gy, fractionated in at least 20 sessions. A single rotational field,

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two opposing fields, or a three field technique are generally used, focusing single beams of high-energy radiation onto a small treatment zone area [3]. A five field technique has also been described [4], but is rarely used in clinical practice. CRT achieves long-term tumor growth control in 80–100% of patients and eventually induces GH/IGF1 normalization in 60–80% [5–11]. However its benefits are hampered by the very slow onset of effects (5–15 years until maximal benefit) and the high risk of adverse effects in long-term: hypopituitarism in 30–80% of patients [5, 6, 8–14], radiation-induced optic neuropathy in 0–5%, cranial nerve deficit and brain necrosis in 0–3%, second brain tumors in up to 2% at 10–20 years [14, 15], cerebrovascular accidents in 4% at 5 years up to 21% at 20 years [16], psychocognitive impairments [17, 18]; all leading to an increase in mortality (1.6–2.2 times higher mortality rate [19–22]) in CRT treated patients, mainly due to cerebrovascular disease (standardized mortality ratio 4.4 [23]–7.1 [20]). The adverse consequences of CRT have been attributed to the radiation of healthy surrounding tissues.

Stereotactic techniques have been developed since 1950, including *stereotactic radiosurgery (SRS*) and *fractionated stereotactic radiotherapy (FSRT)*. They deliver a precise high radiation dose to a defined target with a steep dose gradient at the tumor margin, thus limiting the irradiation and the damage to the adjacent brain structures.

Stereotactic radiosurgery is usually performed using photons, as in gamma knife, cyberknife and linear accelerator, or protons.

Gamma knife (GK) consists of an array of 192 or 201 cobalt-60 sources arranged in a hemisphere and focused with a collimator helmet on a single or multiple points named isocenters. The patient wears a rigid metal helmet fixed on the skull and the irradiation is delivered as a single fraction. The dose is usually prescribed at the 50% isodose to obtain the maximum dose at the center of each pinpointed target and the prescribed dose at tumor margins [24]. A mean dose to which each tissue is exposed can also be calculated. Doses delivered to the tumor margin are higher for secreting adenomas (18–35 Gy) than for non-functioning pituitary adenomas (10–20 Gy) [3].

Cyberknife (CK) combines a mobile linear accelerator mounted on a robotic arm with an image-guided robotic system. The patient is fixed in a more comfortable thermoplastic mask and the dose can be delivered as a single-fraction (usually) or in 3–5 fractions, a technique called hypofractionated SRS [25, 26].

Linear accelerator (LINAC) utilizes X-rays which are derived from colliding accelerated electrons with a target metal. The treatment is delivered using multiple arcs or beams shaped with a multileaf collimator. *Modified LINAC* have an improved frameless stereotactic fixation system (infrared and radiographic imaging with a Novalis Tx accelerator or cone-beam CT) and allow single or hypofractionated SRS (3–5 fractions) [27, 28].

Fractionated stereotactic radiotherapy (FSRT) usually denominates an improved conventional RT in which a similar total dose of 45–55 Gy is delivered by a LINAC in 25–33 daily fractions. The patient is immobilized in a frameless stereotactic mask with an accuracy of 1–2 mm and a similar planning system as in SRS is used [3], resulting in more localized irradiation as compared with conventional RT.

The risk of visual complications is proportional with the radiation dose that reaches the optic nerves, and this dose is larger when RT is delivered in a single session, compared to fractionated sessions. Therefore, the use of single-session SRS is usually indicated to relatively small tumors (<3 cm) located more than 3 mm away from the optic structures [2, 29], while hypofractionated SRS can be used in perioptic tumors [28, 30]. CRT and FSRT are usually indicated in large pituitary tumors, including those with invasion of the optic nerves. Currently there is limited experience with hypofractionated SRS as compared to FSRT.

The advances in medical therapy and surgical techniques in acromegaly for the last 20 years were followed by a progressive decline in the use of RT. A recent analysis of the Spanish national registry of acromegaly shows that RT use declined over four decades, from 62.8% of patients treated prior to 1980, to 11.9% in 2000 ($p < 0.001$) [31]. A similar decrease was shown in a Greek center, from 57.8% of patients treated with RT before 1990 to 16.8% after 1990, $p < 0.001$) [32]. Since RT is used more restricted for aggressive or drug resistant tumors, biochemical cure nowadays is potentially lower than previously reported. However, it is important to keep in mind that RT may ultimately lead to cure of GH hypersecretion. The purpose of this review is to present the updates in the efficacy and safety of pituitary RT in acromegalic patients, with an emphasis on the new stereotactic radiation techniques.

Methods

An online search for journal articles relevant to the topic was conducted using the PubMed Database from 2000 up to 2016 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. Cited references within articles were also searched for relevancy to the topic. Combined data from multiple studies are presented as weighted means.

Results

Stereotactic radiosurgery (SRS) in acromegaly

Efficacy

In Table 1, 35 SRS studies including 1868 patients are detailed: 26 studies using GK [33–58], 4 with LINAC SRS [59–62], 3 with CK [25, 26, 63] and 2 with proton SRS [64, 65]. The median doses delivered to the tumor margin ranged from 15 to 35 Gy.

Local tumor control

Tumor control, i.e. stable or reduction in size, is 93–100% in 33 published studies including 1746 patients with acromegaly treated with SRS (Table 1); weighted mean tumor control was 98% at a median follow up (mFU) of 59 months, similar to CRT-induced tumor control (Table 4); tumor shrinkage occured in about 50–75% of cases [35, 41, 43, 45].

Biochemical control

In SRS, the remission rate is most probably 44–52% at 5 years at a median dose of 23.5 Gy. In 35 studies on SRS (Table 1) including 1868 acromegalic patients, the weighted mean biochemical control rate of the disease was 44.3% at a mFU of 59 months (18–114 months) [25, 26, 33–65]. In ten studies (including 700 patients) [35, 38, 40, 41, 43, 45, 49, 53, 61, 64] where a Kaplan Meyer estimate of disease control was available and more stringent criteria for normalization were used (i.e. GH < 1 ng/mL and normal age-corrected IGF-1), at 5 years the biochemical control reached 52% [24] and median time to normalization ranged from 12 to 144 months (median weighted 41.5 months).

Even in studies with ≥5 years of mFU there is a large variability of the normalization rate for GH and IGF-1 serum levels, from 12 to 68% of patients (weighted mean 47.4%), increasing up to 47–86% at 10 years [35, 41, 49, 55] (Table 1). This variability may be due to different criteria used to define GH/IGF-1 normalization, different FU duration, pre-irradiation levels of GH /IGF-1, tumor size, use of RT as primary or post-surgery therapy and use of concomitant medical therapies in some of the studies. Overall, biochemical control may seem higher in SRS than in CRT (52% versus 36% at 5 years in a recent meta-analysis), but it did not reach statistical significance, possibly due to a shorter follow up [66] (Table 3).

In addition, 10 to 30% of the patients who were uncontrolled on medical therapy prior to SRS reach GH/IGF1 normalization with medical therapy after SRS [38, 57].

Favorable prognostic factors for hormonal remission after SRS include a higher margin radiation dose, higher maximum dose, and lower initial GH/IGF-1 level [41, 43]. Densely granulated GH-secreting tumors have a similar response to SRS as sparsely granulated tumors [67].

At similar mFU of 55–60 months, a median dose <20 Gy achieved remission in 31% of 216 patients, doses of 20–25 Gy in 47% of 1196 patients and doses >25 Gy in 33% of 390 patients [24].

Some authors [40, 47, 68], but not all [41, 42, 56, 59] have shown that use of somatostatin analogs may decrease the success of SRS (eg, remission rate was 59% in patients off suppressive medications compared with 37% in patients receiving a suppressive medication, most commonly octreotide, at the time of GK treatment) [47]. Therefore temporary withdrawal of the medical treatment before and during RT was suggested [2].

After RT, the use of medical treatment is recommended [1], with yearly interruptions of 1–3 months (depending on the type of medication) to monitor the efficacy of radiation therapy [56].

Recurrence after GK SRS was evaluated in a retrospective analysis of 272 patients with nonfunctioning pituitary adenoma (NFPA) and 271 patients with a hormone secreting-pituitary adenoma, including 148 with GH-secreting adenomas [69]. The mFU after GK was 78 months and disease recurrence occurred in 2.7% of acromegalic patients, less frequent than in patients with NFPA and other hormone secreting adenomas (10% and 5%). In smaller studies, endocrine relapse was described in 1.2–6% of patients with acromegaly [41, 47] at 26–50 months after SRS-induced remission [47].

Repeated SRS irradiation after CRT or FSRT is possible in selected cases, leading to hormonal normalization in 45–90% of 23 published cases with acromegaly [70, 71]. A higher rate of neurological complications (16%) [70], of visual defects (in 3 of 5 re-irradiated patients) [47] and of hypopituitarism occurred in re-treated patients [70]. It was suggested that 50% of the original radiation dose, recalculated as a single-fraction dose, remains active in occulomotor nerve [70] and 40% in the optic nerve [72].

SRS side effects

Radiation-induced hypopituitarism is the main side-effect of SRS, occurring in 0–66% of patients with acromegaly (weighted mean 22%) at mFU of 60.5 months (around 20–40% in half of the studies with a mFU ≥ 4 years and <20% in a third of those studies) (Table 1). The risk is apparently lower than in CRT treated patients (33%) [66]

Table 1 Radiosurgery long-term studies in patients with acromegaly

Authors	Patients	RT Type	Dose (Gy) median margin dose	Follow-up (median, months)	Remission criteria	Tumor control (%)	Hormonal remission (%)	Time to remission (median, months)	New hypopituitarism (%)	Visual deficit (%)	Cranial nerve deficit (%)	Brain radionecrosis (%)	Second brain tumor (%)	Cerebrovascular disease (%)
Jane et al. [46]	64	GK	15	>18	Normal IGF-1	100	36	28	28	0	0	ND	ND	ND
Kobayashi et al. [44]	67	GK	18.9[a]	63[a]	GH < 1 ng/mL/ GH < 2 ng/mL	100	4.8/11.9	NA	14.6	11	ND	ND	ND	0
Attanasio et al. [58]	30	GK	20	46	GH < 2 ng/mL & normal IGF-1	100	23	24	6.3	0	0	ND	ND	0
Pollock et al. [40]	46	GK	20	63	GH < 2 ng/mL & normal IGF-1	100	50 (11 at 2 y, 60 at 5 y)	36	36 (11 at 2 y, 33 at 5 y)	0	ND	2.2	ND	2.2 carotid artery stenosis
Ronchi et al. [38]	35	GK	20	114	GH < 2.5 ng/mL & GH in OGTT < 1 ng/mL & normal IGF-1	100	52 (46 at 10 y)	144	50	0	0	0	0	5.7 (2 transient ischaemic attacks at 72 & 132 months)
Iwai et al. [49]	26	GK	20	84	GH < 2 ng/mL or GH < 1 in OGTT & normal IGF-1	96	38 (17 at 6 y, 47 at 10 y)	NA	8	0	0	0	0	0
Liu et al. [42]	40	GK	21	72	GH < 2.5 ng/mL & normal IGF-1	97.5	47.5	45	40	0	0	0	0	0
Wan et al. [34]	103	GK	21.4[a]	67[a]	GH < 1 ng/mL in OGTT & normal IGF-1	95	37	NA	1.9	0	0	2	0	ND
Losa et al. [41]	83	GK	21.5	69	GH < 2.5 ng/mL & normal IGF-1	97	60 (52 at 5 y, 85 at 10 y)	60[a]	8.5 (11.8 at 5 y)	0	0	0	ND	ND
Jagannathan et al. [47]	95	GK	22[a]	49	Normal IGF-1	98	53	23.5	34	4.2	0	1	0	0
Franzin et al. [53]	103	GK	22.5[a]	71	GH < 2.5 ng/mL & normal IGF-1	97.3	60.7 (58.3 at 5 y)	NA	7.8	0	0	ND	ND	ND
Gutt et al. [51]	44	GK	23	23	Normal IGF-1	100	48	NA	NA	0	0	NA	NA	NA

Table 1 (continued)

Authors	Patients	RT Type	Dose (Gy) median margin dose	Follow-up (median, months)	Remission criteria	Tumor control (%)	Hormonal remission (%)	Time to remission (median, months)	New hypopituitarism (%)	Visual deficit (%)	Cranial nerve deficit (%)	Brain radionecrosis (%)	Second brain tumor (%)	Cerebrovascular disease (%)
Erdur et al. [54]	22	GK	23.8[a]	60	GH < 1 ng/mL & normal IGF-1	95.2	54.5	NA	28.6	0	0	0	0	0
Izawa et al. [48]	29	GK	23.8[a]	26[a]	Normal GH	100	41	NA	NA	0	0	ND	ND	ND
Sheehan et al. [37]	130	GK	24	31	Normal IGF-1	93	53	29.8	34	2	1.2[b] (0.7 transient)	0	0	0
Hayashi et al. [50]	25	GK	25	36	Normal GH	100	40	NA	0	0	0	0	0	ND
Sicignano et al. [36]	39	GK	25	60	NA	97.7	54	NA	12.3	NA	NA	NA	NA	NA
Lee et al. [43]	136	GK	25	61.5	GH < 1 ng/mL & normal IGF-1	98.5	65.4 (32, 64, 73, 83 at 2, 4, 6, 8 y)	NA	31.6	3	0.7	0.7	0	0
Cohen-Inbar et al. [55]	24	GK	25	159.5[c]	GH < 1 ng/mL in OGTT & normal IGF-1	93.3[c]	75	NA	58.3[c]	NA	NA	NA	NA	NA
Vik-Mo et al. [35]	53	GK	26.5[a]	66[a]	GH < 2.5 ng/mL & normal IGF-1	100	38 (58 at 5 y, 86 at 10 y)	NA	23	3.8 (asymptom)	0	0	0	0
			26.5[a]		GH < 1 ng/mL in OGTT & normal IGF-1		17							
Castinetti et al. [56]	82	GK	28.5[d]	49.5[a]	GH < 2 ng/mL & normal IGF-1	NA	17 at 3 y	35	17	1.2	1.2 (transient)	ND	ND	ND
Castinetti et al. [57]	43	GK	28.5[d]	96[a]	GH < 2 ng/mL &/or GH < 1 ng/mL in OGTT & normal IGF-1	100	42	42.6[a]	21	1.3[b]	5.2[b]	0	0	0
Poon et al. [39]	40	GK	29	73.8	GH < 2 ng/mL & normal IGF-1	NA	17	NA	11.4	0	ND	ND	ND	ND
Zhang et al. [33]	68	GK	31	34	Normal GH	100	40	NA	0	1.5	1.5 (transient)	0	0	0
Jezkova et al. [45]	96	GK	35	54	GH < 1 ng/mL in OGTT & normal IGF-1	100	50 (44 at 5 y; 57 at 8 y)	66	27.1	0	0	0	0	0

Table 1 (continued)

Authors	Patients	RT Type	Dose (Gy) median margin dose	Follow-up (median, months)	Remission criteria	Tumor control (%)	Hormonal remission (%)	Time to remission (median, months)	New hypopituitarism (%)	Visual deficit (%)	Cranial nerve deficit (%)	Brain radionecrosis (%)	Second brain tumor (%)	Cerebrovascular disease (%)
Grant et al. [52]	13	GK	35	40[a,b]	Normal IGF-1	100	61	18.4	31	3	0	0	ND	0
Voges et al. [61]	64	LINAC	15.3[e]	54.3	GH < 2 ng/mL & normal IGF-1	97	37.5 (14 at 3 y, 33 at 5 y)	42.8[a]	12.3 (13 at 3 y, 18 at 5 y)	1.4[b]	0	2.8[b]	ND	0
Wilson et al. [60]	86	LINAC	20	66	GH < 2.5 ng/mL normal IGF-1	96	37.5[f] 34.7[f]	12	19.8	2.2 (1.1 transient)	0	4.6 (2.3 clinical)	1.1	0
Bostrom et al. [62]	21	LINAC	20[g]	96	Normal IGF-1	97.1	23	NA	46.4	2.9[h]	2.9[h] (transient)	0	ND	0
Yan et al. [59]	22	LINAC	23[i]	98	GH < 2.5 ng/mL & normal IGF-1 GH < 1 ng/mL	95	68.2 27.3	30	22.7	0	ND	ND	ND	0
Cho et al. [63]	6	CK	20 (1–3 Fr)	35.1[a]	GH < 2.5 ng/mL	92.3[b]	33	NA	0	0	0	0	0	0
Roberts et al. [25]	9	CK	21 (1–3 Fr)	25.4[a]	Normal IGF-1	100	44.4	12	33	0	0	0	0	0
Iwata et al. [26]	52	CK	21/3 Fr; 25/5 Fr	60	GH < 1 ng/mL & normal IGF-1	100	17	NA	2	0 (≥ grade 2)	0	0	ND	ND
Petit et al. [65]	22	Protons	20 CGE	75	Normal IGF-1	95	59 (67.5 at 5 y)	42	38	0	0	0	0	0
Wattson et al. [64]	50	Protons	20 RBE	51.5	Normal IGF-1 + (in some cases) GH < 1 ng/mL in OGTT	100	48 (26 at 3 y, 49 at 5 y)	62	57 (62 at 5 y)	0	0	2	0	0

RT radiotherapy, *GK* gamma knife radiosurgery, *LINAC* linear accelerator radiosurgery, *CK* Cyberknife radiosurgery, *CGE* cobalt gray equivalents, *RBE* relative biological effectiveness, *Fr* fractions, *NA* not available, *ND* not described, y years

[a]Mean

[b]In a larger cohort of various pituitary tumors

[c]In a cohort of 24 patients with acromegaly and 35 with Cushing's disease with a follow-up > 6 0 months.

[d]Mean isodose 50

[e]Mean dose of the radiation that covers the tumor surface

[f]Calculated in patients with hormonal follow-up (32 and 46 patients, respectively)

[g]Median single dose at the isocenter

[h]In a cohort of 21 patients treated with SRS and 14 with FSRT

[i]Median maximal dose

(Tables 3, 4), but shows the same increasing occurrence over time as in patients treated with CRT [55]. Since hypopituitarism can appear anytime between 1 and 10–15 years after RT [40], yearly assessment of pituitary function is recommended in RT treated patients [2].

Predictive factors reported for SRS-induced hypopituitarism are: margin dose, suprasellar extension, invasion in the cavernous sinus, prior craniotomy, pretreatment pituitary gland function, tumour volume and the rigorousness and length of endocrine FU [37, 40, 55, 57, 73]. Hypophysopexy, a surgical pituitary transposition, may reduce the radiation dose to the normal pituitary gland in cases of residual tumor within the cavernous sinus [74].

Radiation-induced optic neuropathy occurs in 0–4.2% of patients usually during the first 3 years after SRS [35, 47]. Maximum point doses <8–10 Gy to the optic nerves and chiasm are recommended for single-fraction SR [75]. However, in most patients without pre-existing cranial nerve injury, systemic comorbidities (e.g., diabetes and hypertension) or prior irradiation, the maximum dose tolerated by the optic apparatus is likely 10–12 Gy, if applied to small portions (2–4%) of the optic pathways [76].

Cranial neuropathies and brain radionecrosis have been reported in 0–5% of patients when marginal doses ≥20 Gy are used [57, 60].

The risk to develop a *new brain tumor* after SRS appears to be low after mFU of 60 months (0% in the large majority of studies) (Table 1), but longer FU studies are needed to elucidate this effect.

Cerebrovascular disease and mortality after SRS have not been systematically studied, but in 35 SRS studies (Table 1) [25, 26, 33–65], cerebrovascular events have been described in only two studies and consisted of one case of coronary artery stenosis (2.2% of the patients) and 2 transient ischaemic attacks at 72 and 132 months (5.7% of the patient series). In a retrospective series of 42 acromegalic patients cured after CRT (31) or GK (11) compared to 56 patients cured by surgery alone, no difference was observed between irradiated and non-irradiated groups regarding major cardio or cerebrovascular events (10% vs 6% after mFU 16.5 years). In these cured patients, no differences were found between CRT and GK subgroups [77].

These data support the expected brain-sparring effect of SRS, compared to CRT with up to 21% cerebrovascular events reported after 20 years, but longer FU prospective studies are still needed. The cerebrovascular disease rate in CRT treated patients was influenced by the radiation dose and related to atherogenesis in the vascular lining due to radiotoxicity [16]. Published studies support the potential for SRS to cause less vasculopathy than CRT since it irradiates less healthy brain tissue.

More recent studies on mortality failed to confirm an increased risk in patients irradiated with newer techniques [78, 79]. Data from the Danish National registry show that the elevated mortality risk in patients with acromegaly (HR= 1.3, 95% CI: 1.0-1.7) is uninfluenced by treatment modality [80]. Furthermore, a study including 806 patients with a non-functioning pituitary adenoma from the Dutch National Registry of Growth Hormone Treatment in Adults reported that the frequency of secondary intracranial tumors and mortality did not differ between irradiated and non-irradiated subjects [81]. It is plausible that modern RT techniques, medical treatments which improve the biochemical control, a more careful management of comorbidities or all of the above might influence the life expectancy and the cerebrovascular morbidity in acromegalic patients, even in the irradiated ones [20, 79].

Other effects on *neuropsychological performance* and *quality of life* in patients with acromegaly treated with stereotactic RT have not been studied.

Types of SRS

GammaKnife

Most published studies used GK in patients with acromegaly [33–58] with a reported tumor control of 93–100% and biochemical normalization of 46% (17–65%) of 1536 patients, at a mFU of 58 months. New hypopituitarism occured in 22% of patients (2–58%). In a large retrospective study of 136 acromegalic patients treated with GK and followed-up for a median of 61.5 months, 65.4% of the patients achieved remission (mean time to remission 27.5 months). The actuarial remission rates at 2, 4, 6, and 8 years after SRS were 32, 64.5, 73, and 83%, respectively, when normalization criteria were normal age- and gender-matched IGF1 or GH in OGTT < 1 ng/mL, off any medication [43]. New pituitary hormone deficiency occurred in 43 patients (32%) [43].

Cyberknife

The results for 67 acromegalic patients (15 radiated in ≤3 fractions and 52 in >3 fractions with a total dose of 20–25 Gy) showed tumor control in 92–100% and biochemical control in 22.5% of patients (17–44%), after a mFU of 33 months [25, 26, 63]. The apparently lower efficacy of CK is due to a recent study (Iwata et al) which included many large perioptic tumors and used stringent criteria (GH < 1 ng/mL and normal IGF-1) [26] (Table 1). The other 2 studies, including 15 patients, had similar control rates with GK. Hypopituitarism occurred in 0–33% of patients, and no grade 2 or more visual deficits were recorded.

Modified LINAC SRS

In 193 patients with acromegaly this technique induced 95–97% tumor control rate and biochemical remission in 39.4% of patients (23–68%) after mFU of 69 months (54–98) [59–62]. Remission criteria were GH < 2–2.5 ng/mL and/or normal IGF-1. Time to remission was 12–43 months and new hypopituitarism occurred in 20.5% (12–46%) of patients. Visual impairment, cranial nerve deficits and symptomatic brain necrosis occurred in up to 3% of cases and only 1 patient with intracranial malignancy was reported, but it was associated with extracranial metastatic malignancy and was not considered induced by RT [60].

The current data suggest that all the photon SRS techniques achieve similar results.

Proton beam SRS

In 70 acromegalic patients it induced tumor control in 95–100% and biochemical remission in about 50–67% of patients at 5 years [64, 65]. Median time to remission was 30.5 months [65]. The actuarial 3-year and 5-year rates of development of new hypopituitarism were 45 and 62%, median time to deficiency was 40 months [64]. There were no radiation-induced tumors or visual defects. These data suggest that proton SRS achieves similar results with photons SRS.

Hypofractionated SRS

This technique has been used with good results and few visual side-effects in patients with perioptic tumors (within 2–3 mm from the optic nerves or chiasm) for which single session SRS is not suitable. Iwata et al [26] administered CK in 52 patients with GH-secreting pituitary adenomas in a schedule of 3 fractions of 7 Gy each (marginal doses 17–27 Gy) or 5 fractions of 5 Gy each (marginal doses 20–32 Gy), with a mFU of 60 months. The 2 radiation schedules had similar efficacy. The 5- year overall survival and local control was 100%, while stringent hormonal control (random GH < 1 ng/mL or <0.4 ng/mL in OGTT and normal age and sex-adjusted IGF1) was achieved in 17.3% of patients. New hypopituitarism occurred in one patient (2%) but no other major complications [26]. Similar radiation regimens applied to 40 various perioptic pituitary tumors showed 97.5% tumor control and no new hypopituitarism or visual defects at a mFU of 38.5 months [30]. Liao [28] applied 3 fractions with a total dose of 21 Gy with a modified LINAC system to 34 various perioptic pituitary tumors and achieved tumor control in 100% at a mean FU of 37 months, with transient post-treatment diplopia in 1 patient (3%).

A dose–response model for visual pathway tolerance to SRS delivered in 1–5 fractions for perioptic tumors has been recently published [82]. Based on a retrospective evaluation of 262 patients with perioptic tumors, the model suggests a less than 1% incidence of radiation induced optic neuropathy in patients treated with an optic apparatus pathway maximum point dose of 12 Gy in one, 19.5 Gy in three, and 25 Gy in five fractions.

Hypofractionated GK in two or three fractions with a mean margin dose of 7.2 Gy (range 5–8 Gy) was used in ten patients with giant pituitary tumors (adenoma size >4 cm, five functional tumors), after failed surgery. Tumor control was achieved in 100% of cases [83]. In 60% a tumor shrinkage occured during the mFU of 31 months. Hypopituitarism occurred in 10% (one patient) after two fractionated SRS in 5 years.

Fractionated stereotactic radiotherapy (FSRT)

Few reports, including 261 patients, studied the outcome of FSRT in acromegaly, using median total dose of 49 Gy (range 45–54 Gy) [84–91] (Table 2).

Efficacy

Local tumor control was achieved in 97% (92–100%) of patients after mFU of 71 months, similar to SRS or CRT. Tumor shrinkage occurred in 48–53% [85, 86]

Biochemical control varied from 18 to 75%, with a weighted mean of 35% at mFU of 71 months in published series, most of them using stringent GH/IGF1 control criteria. Diallo et al [85] reported 34 acromegalic patients treated by FSRT with a total dose of 50 Gy, mean FU of 12 years. Hormonal remission rate was 25% at 5 years, 43% at 10 years, and 50% at 15 years. Mean time to normalization was 28 months.

In a prospective series of 35 patients with acromegaly treated with SRS (21) or FSRT (12) according to the radiation toxicity risk, after a mFU of 8 years biochemical cure (combined methods) was achieved in 23% and the 5-year local control was 97.1% [62].

In a series of 34 giant GH-secreting tumors, none cured after surgery, from 12 patients who were treated with FSRT (5), CRT (5) and SRS (2), only one patient achieved GH/IGF1 control 1 year following SRS. Seven other irradiated patients were controlled after association with medical treatment [92].

Side effects

Hypopituitarism developed in 29.4% of patients at mFU of 71 months [84–91]. Visual defects occurred in 0–5%, secondary brain tumor (meningioma) was recorded in 1 patient

Table 2 Fractionated stereotactic radiotherapy studies in patients with acromegaly

Authors	Patients	RT Type	Dose (Gy) median total dose	Follow-up (median, months)	Remission criteria	Tumor control (%)	Hormonal remission (%)	Time to remission (median, months)	New hypopituitarism (%)	Visual deficit (%)	Cranial nerve deficit (%)	Brain radionecrosis (%)	Second brain tumor (%)	Cerebrovascular disease (%)
Minitti et al. [89]	17	FSRT	45	39	GH < 2.5 ng/mL or GH in OGTT < 1 ng/mL & normal IGF-1	98 at 5 y	35	43	22[b]	4.3[b] (3 transient)	0	0	0	0
Kim et al. [87]	12	FSRT	45	57	GH < 1 ng/mL & normal IGF-1	92	75 at 4.9 y	59	0	0	0	0	0	8.2 (1 at 5.2 y)
Patt et al. [90]	36	HPCFRT	45	59	GH < 1 ng/mL & normal IGF-1	100	55	63	33	0	0	0	0	ND
Gheorghiu et al. [86]	77	FSRT	45–50	73	GH < 1 ng/mL + (when available) normal IGF-1	95	18 (15 at 5 y); 29.5 for IGF-1	NA	32	4	0	NA	1	9
Diallo et al. [85]	34	FSRT	50	152[a]	Normal IGF-1	100	38 (25 at 5 y, 43 at 10 y, 50 at 15 y)	NA	39	0	0	0	0	0
Colin et al. [84]	31	FSRT	50.4	48	Normal basal hormones and in OGTT	99 at 5 y	29	NA	36.7 (28.5 at 4 years)[b]	0	0	0	0	ND
Milker-Zabel et al. [88]	20	FSRT	52.2	61.3	Normal GH & normal IGF-1	100	55	26	10	5	0	0	0	ND
Roug et al. [91]	34	FSRT	54	45	GH in OGTT < 2.6 mU/L & normal IGF-1	91	29	30	29 at 4 years	0	ND	0	0	0

RT radiotherapy, *FSRT* fractionated stereotactic radiotherapy, *HPCFRT* high-precision conformal fractionated radiotherapy, *NA* not available, *ND* not described, *y* years

[a] Mean

[b] In a larger cohort of various pituitary tumors

Table 3 Conventional radiotherapy studies in patients with acromegaly

Authors	Patients	RT Type	Dose (Gy) median total dose	Follow-up (median, months)	Remission criteria	Tumor control (%)	Hormonal remission (%)	Time to remission (median, months)	New hypopituitarism (%)	Visual deficit (%)	Cranial nerve deficit (%)	Brain radionecrosis (%)	Second brain tumor (%)
Biermasz et al. [6]	36	CRT	40	139	GH in OGTT < 0.38 ng/mL & normal IGF-1	NA	40 at 5y, 61 at 10y, 65 at 15y	NA	50 (32 at 5y, 54 at 10y)	ND	0	ND	0
Minitti et al. [10]	47	CRT	45	244	GH in OGTT < 1 ng/mL & normal IGF-1	95	29 at 5y, 42 at 10y, 61 at 15y	NA	49 (24 at 5y, 45 at 10y)	1.3	0	2.7	0
Jenkins et al. [9]	884	CRT	45	84	GH < 2.5 ng/mL	NA	36 at 5y, 60 at 10y, 74 at 15y	NA	> 27 at 10y	0	ND	ND	0
				84	normal IGF-1		50 at 5y, 63 at 10y, 56 at 15y						
Cozzi et al. [14]	49	CRT	45[a]	168	GH < 2.5 ng/mL & normal IGF-1	96	10	120	8	2	4 (2 transient)	2	4 (2 meningiomas 27–30 yrs after CRT)
Powell et al. [11]	32	CRT	47	67[a]	Normal IGF-1	NA	43.7	NA	32	0	ND	0	0
Jallad et al. [12]	89	CRT	50	71	GH < 2.5 ng/mL & normal IGF-1	100	38 (29 at 5y)	45	47	5	0	3	0
Gonzalez et al. [13]	40	CRT	52	72	GH < 1 ng/mL	100	30 at 3y, 46 at 5y, 57 at 10y	NA	> 15 at 5y	2.5	ND	ND	2.5 (1 meningioma 10 yrs after CRT)
				72	Normal IGF-1		33 at 3y, 36 at 5y, 43 at 10y						
Barrande et al. [5]	128	CRT	52[a]	138	GH < 2.5 ng/mL	NA	35 at 5y, 53 at 10y, 66 at 15y	NA	> 32 at 5y, >54 at 10y	3	0	3	0
Epaminonda et al. [8]	67	CRT	53.6[a]	120	GH < 2.5 ng/mL & normal IGF-1	NA	54 (37 at 5y, 65 after 15y)	144	60	0	0	ND	3 (2 meningiomas, 1 pinealoma 9–22 yrs after CRT)

RT radiotherapy, *CRT* conventional fractionated radiotherapy, *NA* not available, *ND* not described, *y* years

[a]Mean

Table 4 Summary of efficacy and side-effects of radiation therapy methods in patients with acromegaly

RT Type	No of studies	Patients	Dose (Gy), median	Follow-up (median, months)	Tumor control (%)	Hormonal remission (%)	Time to remission (median, months)	New hypopituitarism (%)	Visual deficit (%)	Cranial nerve deficit (%)	Brain radionecrosis (%)	Second brain tumor (%)	Cerebrovascular disease (%)
SRS	35	1868	23	59	98	44 (52 at 5y)	41.5	22	1.5 (0–4)	0.45 (0–5)	0.9 (0-4.6)	0.1 (0–1)	0.3 (0-5.7)
CRT	9	1383	46.5	99	98	56 (36 at 5y)	73	33 (35 at 5y)	0.8 (0–5)	0.47 (0–4)	2.5 (0–3)	0–2 in 20 years[a]	4 at 5 y, 11 at 10 y, 21 at 20 y[b] (0–4)
FSRT	8	261	49	71	97	35	57	29	1.8 (0–5)	0	0	0.3 (0–1)	4.5 (0–9)
SRS type													
GK	26	1536	23	58	98	46	44	22	1.5	0.5	0.5	0	0.3
CK	3	67	22.5	33	99	22.5	12	6.5	0	0	0	0	0
LINAC	4	193	19	69	96	39	25	20.5	1.8	0.35	3.3	0–1	0
Proton	2	72	20	58	98.5	51	30.5	51	0	0	1.4	0	0

The results are expressed in weighted means calculated from the published studies, most of the studies include normal IGF-1 as remission criteria, but GH remission criteria, patient populations, tumor characteristics, duration of follow-up and medical treatments vary largely between studies

SRS stereotactic radiosurgery [25, 26, 33–65]; *CRT* conventional fractionated radiotherapy [5, 6, 8–14]; *FSRT* fractionated stereotactic radiotherapy [84–91]; *GK* gamma knife radiosurgery [33–58]; *LINAC* linear accelerator radiosurgery [59–62]; *CK* cyberknife radiosurgery [25, 26, 63]; Proton radiosurgery [64, 65]; *y* years

[a]Evaluated in various pituitary adenomas [7, 15]

[b]Actuarial rates in 331 various pituitary adenomas [16]

(1.8%), no cranial neuropathies or brain necrosis were reported. In our series of 77 acromegalic patients treated with FSRT with a mFU of 73 months (6–264 months), clinical or imaging signs for stroke occurred in 9% of patients [86], similar with the 8.2% rate in the study of Kim et al [87], while in the study of Diallo et al [85] the rate for stroke was 0% at more than 10 years of FU (Table 2).

Overall, FSRT seems to have a similar efficacy with SRS and risk rate for hypopituitarism and neuropathies, but the risk of stroke seems higher and should be further evaluated (Table 4).

Comparison between SRS and fractionated RT

In Table 4 comparative data, expressed as weighted means from published studies, are shown for the RT methods used in acromegaly. Earlier reports suggested that the declining of serum GH concentration after GK SRS is faster compared with fractionated conventional RT [59, 60, 93]; others did not confirm this finding [44, 45, 51, 56, 61]. The greatest effect occurs within the first 2 years from SRS [40, 59].

In a study comparing the results of GK treatment in 32 patients with acromegaly followed at our center (50% isodose 16–22 Gy, mFU 41 months) to those of FSRT in 77 patients (total dose 45–50 Gy, mFU 73 months) [86], the cumulative probability of GH normalization <1 ng/mL was higher in GK treated patients (13% at 2 years and 29% at 4 years, compared with FSRT: 5% at 2 years and 15% at 5 years [86], $p < 0.05$); after SRS the median nadir GH in OGTT was lower after 2 years (2.5 ± 1.8 ng/mL vs 4.8 ± 8.2 ng/mL, $p < 0.05$) and the rate of GH decrease was higher at 6 months ($45 \pm 20\%$ vs $38 \pm 59\%$ respectively, $p < 0.05$), but not afterwards [86].

A recent systematic review and meta-analysis comparing the outcomes of SRS and fractionated RT (including FSRT and CRT) in acromegaly analyzed 30 eligible studies including 2464 patients, with a FU between 12–240 months [66]. Compared to RT, SRS was associated with a nonsignificant trend of higher IGF-I-based remission rate (52 vs 37%, $P = 0.14$) or GH-based remission (49 vs 36%) at the latest FU period. The length of FU did not significantly affect remission rate.

In the RT group, treatment-naïve patients had similar remission rates compared with patients who had received a prior treatment (surgery, SRS, medical). SRS had a lower incidence of hypopituitarism than RT with borderline statistical significance (32 vs 51%, $p = 0.05$), the difference being largely due to hypogonadism. No comparison was reported for brain necrosis, headache, and secondary malignancy outcomes after either intervention. The authors concluded that SRS may be more efficient than fractionated RT, but the strength of evidence was very low due to the noncomparative nature of the research, increased risk of bias, imprecision, and substantial heterogeneity among studies [66].

Indeed, data presented in Table 4 also suggest a slightly increased benefit of SRS compared mainly to CRT, regarding biochemical control and the risk for radiation-induced hypopituitarism and cerebrovascular disease; visual deficits are similar in SRS and both fractionated RT subtypes. The risk for radionecrosis and second brain tumors may be slightly lower after SRS and FSRT than after CRT, but longer FU studies are needed in order to elucidate these effects.

Conclusion

Although the use of radiotherapy in patients with acromegaly has decreased with the advances in medical and surgical treatments, it remains an effective treatment option in patients with unsuccessful surgery and/or with intolerance, lack of response, or unavailability of medical therapy in selected countries. SRS may be potentially more effective than conventional RT regarding biochemical remission. There have been reports that SRS has a lower rate of induced hypopituitarism, but long term FU is limited and the large heterogeneity of the studies makes the comparison difficult. Long-term studies evaluating cerebrovascular disease and mortality rate after the new stereotactic techniques are needed, in order to evaluate their brain-sparing effects.

Compliance with ethical standards

Conflict of interest The author declares that she has no conflict of interest regarding this manuscript. This article does not contain any direct studies with human participants or animals performed by the author, as it was a review

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