CLINICAL STUDY

Fractionated stereotactic radiotherapy in patients with acromegaly: an interim single-centre audit

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Abstract

Aim: To evaluate the effect of fractionated stereotactic radiotherapy (FSRT) in acromegaly in a retrospective analysis.

Patients and methods: Thirty-four patients (17 females, median 43 years (range 30–74)) with acromegaly were treated with FSRT (conformal dynamic arcing, dose 54 Gy, 27–30 fractions) between January 1998 and April 2007. Of the 34 patients, 32 had undergone transsphenoidal adenotomy, and 28 were on medical therapy before FSRT. Patients on medical therapy continued this during and after the irradiation. The treatment was gradually decreased/withdrawn after careful assessment.

Results: Magnetic resonance scanning of the pituitary gland 34 months (median, range 11–95) after irradiation showed stable or reduced volume of the remaining tumour tissue in 31 of 34 patients (91%). Seventeen patients (50%) were biochemically controlled (normalised nadir GH during oral glucose tolerance test and IGF1 < +2 s.d.) 30 months after FSRT (median, range 6–60), and ten of them had true biochemical remission (off medical therapy) 30 months after FSRT (median, range 12–69). Of 28 patients with one or more functioning pituitary axes before irradiation, 8 (29%) developed further deficit of one or two pituitary axes 48 months (median, range 6–102) after FSRT. Of 34 patients, 20 still required medical treatment for acromegaly at the end of this study, mainly those with a short follow-up period after irradiation.

Conclusion: The FSRT seems promising in terms of treatment of acromegaly. Longer follow-up is, however, needed to assess the overall efficacy and safety of FSRT for acromegaly.

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Introduction

Acromegaly, GH hypersecretion, is associated with increased morbidity and mortality, and therefore treatment is needed (1, 2). Conventional treatment of GH-secreting pituitary adenoma is primarily transsphenoidal surgery where cure or adequate control can be expected in >80% of cases when the tumour is within the sella (3). Besides the size and location of the tumour, the expertise of the surgeon is a determinant of the outcome of the surgery (4). Medical therapy, mostly as somatostatin analogues and/or GH receptor antagonist, is an alternative treatment option (4). Even though medical therapy is efficient in controlling acromegaly, radiotherapy (RT) may still have a role both on the hormonal level and on tumour mass control (3) in a subgroup of acromegalic patients. RT is mainly performed in patients with an inoperable tumour, unacceptable hormone level despite surgery and medical therapy, or progressive tumour growth (4, 5).

Stereotactic techniques have improved RT of acromegaly – mainly due to the high accuracy in the radiation delivery (6). Only stereotactic radiosurgery (SRS) has

documented faster hormonal effect than conventional RT (3), but overall SRS and fractionated stereotactic RT (FSRT) result in the same local control (6). FSRT, though, is recommended when the tumour is close to critical structures (6, 7).

FSRT is being used as a treatment modality for acromegaly at Rigshospitalet, Copenhagen, since January 1998. The aim of this study was to evaluate, in a retrospective analysis of a consecutive cohort of patients with FSRT-treated acromegaly, the effect of FSRT on control of GH overproduction/insulin-like growth factor 1 (IGF1) with (controlled acromegaly) or without medical therapy (true remission), magnetic resonance (MR) scan control of tumour size, persistent medical treatment with somatostatin analogues (Sandostatin LAR, Novartis, Basel, Switzerland) and/or a GH receptor antagonist (Somavert, Pfizer, New York, USA), and function of other pituitary axes.

Patients and methods

Thirty-four consecutive patients (17 females, median 43 years (range 30–74)) with GH-secreting pituitary

adenomas treated with FSRT at Rigshospitalet, Copenhagen, between January 1998 and April 2007 entered the study. The indication for irradiation was persistent acromegaly after surgery and/or medical treatment, or intolerance to the medical treatment. No patients were excluded from the study, and no patient was lost during follow-up.

Time between diagnosis of acromegaly and FSRT was 35 months (median, range 5–346). Of the 34 patients, 31 (91%) had undergone primary transsphenoidal adenotomy. Nine patients had undergone surgery more than once. Time between operation and FSRT was median 16 months (range 4–345). Three patients were treated primarily with FSRT since the location of the adenoma made FSRT more suitable than surgery. One of these patients, however, had to undergo surgery 37 months after FSRT due to lack of response and intolerance to both somatostatin analogue and GH receptor antagonist therapy. The other two patients were not biochemically controlled despite treatment with somatostatin (Tables 1 and 2).

The patients were treated according to ethics described in the Helsinki II declaration, and the study has been listed in ClinicalTrials.gov (ID NCT00934271). There is no requirement in Denmark for informed consent and approval from the ethical committee of an audit.

Biochemical acromegaly status (IGF1 and nadir GH)

The criteria for biochemical success were nadir GH <2.6 mU/l by oral glucose tolerance test and IGF1 below +2 s.d. of gender- and age-matched normal healthy individuals. Biochemical control was defined as above biochemical success irrespective of medical therapy status. True biochemical remission was defined as biochemical control as defined above without adjunctive medical therapy. IGF1 and nadir GH were measured every 6 months after FSRT.

Two patients were biochemically controlled on medical therapy pre FSRT, and were treated with FSRT due to serious side effects of medical therapy (Sandostatin LAR 20 mg i.m./month) or to severe symptoms of headache and impaired vision despite medical therapy (Sandostatin LAR 30 mg i.m./month and Somavert 15 mg s.c./day), which were considered to be local symptoms from the remaining tumour tissue.

Ten patients had discordant measurements of IGF1 and nadir GH prior to FSRT, two of them with elevated IGF1 and normal nadir GH, and eight with elevated nadir GH and normal IGF1 (Table 2).

MR scan

By an individual estimate, pituitary MR scan was done every 12–24 months, and was evaluated by the same radiologist to avoid interpersonal variation. Tumour volume was evaluated in three diameters: anterior–posterior, cranial–caudal and side–side. Median

tumour volume before FSRT was 4.5 cm³ (range 0.9–38.6). Tumour tissue that had a growth <2 mm was considered stable tumour tissue. Tumour control was defined as regression or stable (remaining) tumour tissue. The expansion of the tumour was divided into intra- and extrasellar extension (Table 3).

Medical therapy

Of 34 patients, 28 (82%) had been on medical therapy prior to FSRT for 21.5 months (median, range 4–126). The medically treated patients had been on either somatostatin analogue (Sandostatin LAR) or GH receptor antagonist (Somavert), or a combination of both for variable periods of time from 4 to 126 months (Tables 1 and 2).

No patients were advised to stop medical therapy during the period of FSRT. The need for continued medical therapy was estimated individually, and all patients were assessed at least every 6 months after FSRT based on clinical side effects and biochemical acromegaly status.

Pituitary function

ACTH deficiency was diagnosed if basal or stimulated (synacthen or insulin tolerance test) cortisol levels did not reach 500 nmol/l. All blood tests were performed in a fasting state between 0900 and 1100 h (8). TSH deficiency was defined when free thyroxine (FT₄) was low (below or in the low normal range) with an inappropriately low TSH. LH/FSH deficiency was defined when testosterone or oestradiol concentrations were low combined with inappropriately low FSH and LH, and/or the FSH and LH response to GnRH was less than twofold. Panhypopituitarism was defined as deficiencies of all three axes. Replacement therapy was initiated when clinical signs and/or biochemistry indicated the need. Of the 34 patients, 30 (88%) had hypopituitarism before FSRT, 6 of them with panhypopituitarism (Table 4). Time intervals for evaluation of the pituitary function were estimated individually, and the evaluation was performed at least every 6 months in all 34 patients.

Twenty-two patients (65%) had received hormone replacement therapy prior to FSRT for a median of 22 months (range 2–165). Three patients were substituted on three axes (L-T₄, hydrocortisone and testosterone), and ten patients on two axes (L-T₄ and hydrocortisone), while nine patients were substituted on only one axis (seven with hydrocortisone and two with testosterone). Two women were on oral contraceptives.

Assays

GH was analysed by a fluoroimmunoassay (AutoDelfia, Perkin-Elmer, Wellesley, MA, USA) calibrated against the International RP 80/505

Table 1 Patients' characteristics before and after fractionated stereotactic radiotherapy.

Patient	Sex	Age (years)	Total dose (Gy)	Follow-up (months)	Pre-FSRT tumour volume (cm ³)	Pre-FSRT biochemical status	Pre-FSRT medical status ^a	Post-FSRT tumour volume (cm ³)	Post-FSRT biochemical status	Post-FSRT medical status ^a
1	F	44	54	102	8.5		On	8.5	BR	Off
2	M	33	54	66	18.9		On	12.6		On
3	F	32	54	60	12.2		On	9.8	BC	On
4	F	55	54	30	38.6		On	30.9		On
5	F	33	54	84	4.6		Off	4.2	BR	Off
6	M	74	54	54	1.4		On	1.4	BR	Off
7	F	37	54	72	11.2		On	14.5	BR	Off
8	M	63	54	72	1.4		Off	1.4	BR	Off
9	M	51	54	72	10.8		Off	10.5	Discordant	Off
10	F	57	54	66	11.6		Off	9.9	BR	Off
11	M	35	54	66	6.3	Discordant	On	6.0	Discordant	Off
12	F	41	54	72	4.6		On	4.4	BR	Off
13	F	60	54	102	4.4	Discordant	Off	3.9	Discordant	Off
14	F	47	54	54	6.4	Discordant	On	2.2	Discordant	Off
15	M	53	54	54	0.9	BC	On	0.9	BR	Off
16	M	38	54	42	2.9		On	1.0	Discordant	On
17	M	34	54	60	6.7	Discordant	On	5.9	Discordant	On
18	M	47	54	48	2.7	Discordant	On	1.9		Off
19	F	53	54	42	2.3		On	1.8	BC	On
20	M	32	54	36	4.7	Discordant	On	3.1	BC	On
21	F	46	54	36	2.2	BC	On	1.8	BC	On
22	M	50	54	42	3.6		On	0.08		On
23	F	42	54	36	3.8		On	2.6	Discordant	On
24	M	35	54	30	3.9		On	1.6	BC	On
25	F	37	54	36	2.9	Discordant	On	0.7	BR	Off
26	M	61	54	54	2.3	Discordant	Off	4.1	BC	On
27	F	30	54	36	13.0		On	7.1		On
28	F	39	54	12	3.4		On	2.0		On
29	M	36	54	6	30.0		On	16.0		On
30	F	49	54	24	2.8	Discordant	On	2.8	Discordant	On
31	M	45	54	18	3.3	Discordant	On	4.1	BC	On
32	F	30	54	18	11.6		On	8.1		On
33	M	47	54	22	30.4		On	334.9		On
34	M	30	54	42	3.2		On	2.3		On

BC, biochemical control with or without GH-reducing drugs; BR, true biochemical remission; BC, without any GH-controlling drugs.

^a'On' and 'off' refer to GH-regulating therapy.

Table 2 Biochemical insulin-like growth factor 1 (IGF1 and nadir GH) and medical therapy status before and after fractionated stereotactic radiotherapy (FSRT) in 34 acromegalic patients.

	Before FSRT			After FSRT		
	Number of patients on medical therapy		Number of patients off medical therapy	Number of patients on medical therapy		Number of patients off medical therapy
	Sandostatin	Somavert		Sandostatin	Somavert	
Biochemical remission						
Biochemical control	1		10			
Elevated IGF1 and normal nadir GH	6	1	10	5		2
Elevated nadir GH and normal IGF1	2		3	1		1
Elevated IGF1 and nadir GH	12	2	1	2	1	6

(1 mg = 2.6 IU). Intra- and interassay coefficients of variations (CV) were 2.2–5.1 and 1.4–2.5% respectively.

IGF1 was initially analysed by a RIA with intra- and interassay CV of 3.1 and 10% respectively. After January 2008, IGF1 was analysed by a solid-phase enzyme-labelled chemiluminescent immunometric assay with intra- and interassay CV of 2.3–3.9 and 3.7–8.1% respectively. Calculations of age- and gender-adjusted SDS for IGF1 (IGF1-SDS) were published previously together with the reference data used in the calculation (9).

Fractionated stereotactic radiotherapy

The patients were treated with accelerator-based irradiation in normally conformal dynamic arcs. An individual mask of the head was made during the planning process, and was used during all the treatments. The mask was fixed to the board during the radiation, thereby creating immobilisation. A fusion of MR and computed tomography (CT) scans was used as a visual treatment plan, whereby the gross target volume (GTV) was estimated. A 3-mm margin was added to account for set-up uncertainties and penumbra. All dose planning was done in BrainLab (Munich, Germany) dose planning system. All patients were treated with 54 Gy in 27–30 fractions prescribed to the periphery of the GTV during 5.5–6 weeks.

Statistical analysis

All calculations were made in GraphPad Software. Fisher's exact test and paired *t*-test were used, and a level of 0.05 was considered significant.

Results

Biochemical acromegaly status (IGF1 and nadir GH)

Biochemical follow-up was available in all 34 patients 45 months after FSRT (median, range 6–102; Tables 1 and 2). Seventeen patients were biochemically controlled (50%) 30 months after FSRT (median, range 6–60), and none of the 17 patients had biochemical relapse during the subsequent follow-up period of 18 months (median, range 6–72). Of the 17 patients, ten even had true biochemical remission (biochemical control off medical therapy) 30 months after FSRT (median, range 12–69). Seven patients withdrew medical therapy after FSRT, and three patients, who tried medical therapy before FSRT, were intolerant to both drugs. None of the ten patients in true remission had biochemical relapse during the subsequent follow-up period of 26 months (median, range 6–72).

Of the 17 biochemically controlled patients, 2 were biochemically controlled already before FSRT, and both remained in this state during follow-up. One stopped

Table 3 Tumour expansion in 34 acromegalic patients before and after fractionated stereotactic radiotherapy (FSRT).

	Before FSRT	After FSRT
Intrasellar extension total	5 (15%)	6 (18%)
Extrasellar extension (E) total	29 (85%)	28 (82%)
E – suprasellar	12 (35%)	10 (29%)
E – infrasellar	13 (38%)	15 (44%)
E – anterior	1 (3%)	0 (0%)
E – posterior	3 (9%)	4 (12%)
E – parasellar bilateral	5 (15%)	5 (15%)
E – parasellar dex	11 (32%)	11 (32%)
E – parasellar sin	12 (35%)	11 (32%)

medical therapy, and was therefore also considered in true biochemical remission 27 months after FSRT and for the following 27 months, while the other patient remained on medical therapy (Sandostatin LAR and Somavert) during the follow-up period of 36 months.

IGF1 (SDS) was $+0.5$ (median, range -1.85 ± 1.8) in the 17 biochemically controlled patients 54 months after FSRT (median, range 18–102), and it was $+0.64$ (median, range -1.77 ± 1.8) in the ten patients in true biochemical remission 69 months after FSRT (median, range 36–102).

True biochemical remission rate was 50% (3 of 6 patients) in the group of patients off medical therapy during FSRT compared with 25% (7 of 28 patients) in the group of patients treated with somatostatin analogues and/or GH receptor antagonist.

The biochemical control rate after 1 year was 24% ($n=8/34$; with seven of the eight on medical therapy), after 3 years was 38% ($n=10/26$; with six of the ten on medical therapy) and after 5 years was 64% ($n=7/11$; with three of the seven on medical therapy).

Eight patients (24%) had at the last follow-up measurement discordant IGF1 and nadir GH concentrations, three of whom had elevated nadir GH with normal IGF1, and five had elevated IGF1 with normal nadir GH (one of the five patients had FSRT before surgery). Nine patients (26%) did not normalise nadir GH or normalise IGF1 during follow-up (two of these nine patients were treated primarily with FSRT combined with medical therapy).

IGF1 (SDS) in the 17 patients who did not normalise both IGF1 and nadir GH was $+3.12$ (median, range

-0.77 ± 5.5) 42 months after FSRT (median, range 6–102).

Mean nadir GH ($n=34$) dropped from 12.8 mU/l (range 1.3–149) pre FSRT to 6.4 mU/l (range 0.1–96.5) 45 months (median, range 6–102, 95% confidence interval (CI) 2.6–10.2) after FSRT ($P=0.0016$), while mean IGF1 ($n=34$) decreased from 510 $\mu\text{g/l}$ (range 193–974) pre FSRT to 261 $\mu\text{g/l}$ (range 97–605) 45 months (median, range 6–102, 95% CI 190–309) after FSRT ($P=0.0001$).

MR scan

Radiographic follow-up was available in all 34 patients 34 months (median, range 11–95) after FSRT. Thirty-one patients (91%) had tumour control, 17 of them (55%) with regression of the tumour tissue at a median follow-up time of 32 months (range 12–95; 1 of the 17 patients was treated primarily with FSRT), while 14 patients (45%) had stable tumour tissue after a median of 43 months (range 11–70; 2 of the 14 patients had primary FSRT and 1 of the 2 patients was operated afterwards).

The remaining three patients (9%) had progression of the tumour tissue in median 23 months (range 20–27) after FSRT. One of them was known with malignant metastases from the pituitary tumour, and progression was found in all three diameters. The remaining two patients had progression of both the cranial–caudal and side–side diameters.

Median tumour volume after FSRT was 4.0 cm³ (range 0.08–334.9). Without the one patient known with malignant pituitary tumour, median tumour volume was 3.9 cm³ (range 0.08–30.9) after FSRT. There was no statistical difference between tumour volume before and after FSRT ($P=0.4$).

No statistical difference was found in tumour volume expansion between the numbers of patients with intrasellar and extrasellar tumour extension before and after FSRT ($P=1$; Table 3). There was no evidence of secondary tumour development, cerebral necrosis or vascular changes during the follow-up on MR scan.

Medical therapy

The medical therapy was withdrawn in 9 of 28 patients (32%) after 33 months (median, range 23–72), and 7 of them remained biochemically controlled and therefore were considered in true biochemical remission. Two patients started the medical treatment after FSRT, one patient for a period of 66 months with a discordant biochemical value subsequent to withdrawal of the medication, and one patient was still on medical therapy at the end of this study, but had normal levels of IGF1 and nadir GH and was considered biochemically controlled.

Thus, 20 patients (59%) were still on medical treatment at the end of this study compared with 28 patients (82%) before FSRT. Follow-up time for these 20 patients was 36 months (median, range 6–66; Tables 1 and 2).

Table 4 Pituitary function in 34 acromegalic patients before and after fractionated stereotactic radiotherapy (FSRT) in four categories: normal function and deficiency of 1, 2 and 3 axes respectively.

	Before FSRT	After FSRT
Normal pituitary function	4 (12%)	1 (3%)
One axis deficient	19 (56%)	15 (47%)
Two axes deficient	5 (15%)	10 (29%)
Three axes deficient (panhypopituitarism)	6 (17%)	8 (21%)

Pituitary function

Follow-up time for the 34 patients was 45 months (median, range 6–102). Three of four patients (75%) with completely normal function of the three pituitary axes before FSRT developed deficiency of two axes 27 months after FSRT (median, range 12–42). Of 24 patients with hypopituitarism before FSRT, 5 (21%) experienced worsening of the pituitary function by new deficiencies 30 months (median, range 12–42) after FSRT, while 8 of 34 patients (21%) had panhypopituitarism at the end of the study (Table 4).

New hormone replacement therapy was initiated in 16 patients 27.5 months (median, range 2–70) after FSRT, 7 of whom (44%) had to replace an additional axis 26 months (median, range 8–53) after FSRT.

No significant difference was found in the incidence of hormone deficits at the latest follow-up between the group of patients with a normal pituitary function prior to FSRT and the group of patients with hypopituitarism (deficits less than three axes) prior to FSRT ($P=0.35$).

Mortality

One patient (3%) died 22 months after FSRT due to metastatic GH-producing pituitary tumour. The tumour had an aggressive invasive behaviour before FSRT.

Discussion

The traditional algorithm for acromegaly advocates surgery and medical therapy as the first-line therapy, but between 10 and 30% (3, 5) of patients with acromegaly still need additional treatment such as RT. Most publications on RT have reported results on fractionated conventional RT (10–12), and FSRT can therefore still be considered a new RT modality, which is also partly the reason why few studies have evaluated the role of FSRT in patients with acromegaly.

In the present study, 34 consecutive and prospective patients with acromegaly were evaluated retrospectively after treatment with FSRT between January 1998 and April 2007. The study was a single-centre audit, and as all patients irrespective of prior treatment and tumour size and growth were included, the patient population was very mixed. Seventeen patients were biochemically controlled and 15 of these 17 patients (88%) also had tumour control. In total, ten patients were in true biochemical remission 30 months after FSRT (median, range 12–72). Tumour control was achieved in 31 of 34 patients (91%) after a median of 34 months (range 11–95), and 17 of the tumours (55%) even regressed.

It is difficult to compare the present study to existing papers when it comes to tumour control in acromegalic patients after FSRT, since most papers evaluated the

Table 5 Status at the latest follow-up after fractionated stereotactic radiotherapy (FSRT) for acromegaly in different series.

Authors (year)	Total dose (Gy)	Fraction dose (Gy)	Number of patients overall/acromegalic	Median radiological follow-up (months)	Number of patients with tumour control (%)	Median biochemical follow-up (months)	Number of patients in biochemical control (BC)	Number of patients in true biochemical remission	Number of patients developing new pituitary axes deficiency (%)
Present series (2009)	54	1.8–2.0	34/34	34	31 (91%)	45	17 (50%)	10 (29%)	8 (29%)
Imran <i>et al.</i> (2009)	50 (25 ^a)	2.0 (5 ^a)	12/12	28.5	11 (92%)	28.5	4 (33)	1 (8%)	1 (8%)
Selch <i>et al.</i> (2006)	45–50.4	<2.0	39/2	32	39 (100%)	32	0 (0%)	0 (0%)	6 (15%)
Minniti <i>et al.</i> (2006)	45	1.8	92/18	32	90 (98%)	39	–	6 (35%)	16 (22%)
Colin <i>et al.</i> (2004)	50.4	1.8	110 (75)/31	82	74 (99%)	80	–	9 (29%)	36 (37%)
Milker-Zabel (2003)	52.2	1.8	20/20	61.3	20 (100%)	59.8	11 (55%)	11 (55%)	2 (10%)

^aOf 12 patients, 1 had 25 Gy in five fractions.

efficacy on a mixture of pituitary tumours, not confined to GH-producing adenomas (13–15), and the patients with acromegaly were difficult to identify from the other groups. Also, the criteria for biochemical success were not clear in some papers (13, 15). The present study thus brings new data on efficacy of both hormonal and radiological controls of acromegaly after FSRT, and also has the highest number of patients in which FSRT on acromegaly was evaluated ($n = 34$) (13–17).

Longer follow-up is expected to strengthen results in regard to control of the remaining tumour mass, since the time of follow-up for the radiological evaluation was limited to 34 months (median, range 11–95), and the effect of RT is known to develop years later (3) (Table 5). One of the three patients who had progression of the tumour mass died of metastases from the malignant tumour, which is a very rare occurrence (18). However, no secondary tumours, cerebral necrosis or vascular changes were identified in any of the other patients after FSRT.

Seventeen of our patients (50%) were biochemically controlled by both IGF1 and nadir GH, and eight patients (24%) had discordant values at the end. Biochemical control rate after 1 year was 24%, 3 years was 38% and 5 years was 64%. Of the 17 biochemically controlled patients, ten were considered to be in true biochemical remission since they were off medical therapy. Acceptable concentrations of both GH/nadir GH and IGF1 are important goals in the treatment of acromegaly in order to reduce morbidity and mortality (19), which is why we chose to include both IGF1 and nadir GH in the criteria for biochemical success in this study, even though normalisation of IGF1 with patients off medical therapy is often used as the sole criterion for true biochemical remission (20, 21).

Discordance between normalisation of the biochemical acromegaly status in regard to IGF1 and GH/nadir GH can be useful in the treatment and follow-up strategies, since elevated IGF1 alone seems to have a different prognosis compared with elevated GH/nadir GH alone (22, 23). Patients with elevated IGF1 and normal GH/nadir GH are at risk of having persisting clinical manifestations of acromegaly and can therefore indeed benefit from the treatment with a GH receptor antagonist (24, 25), while patients with elevated GH/nadir GH and normal IGF1 are at a risk of relapse of the tumour (22, 23). The origin of discordance is likely to be that IGF1 and GH/nadir GH seem to represent two different aspects of acromegaly (26), and RT in general reduces rather than cures the hypersecretion of GH (3, 24). Discordance is seen in up to 27% of acromegalic patients (22). This makes the discussion about criteria for cure relevant, and probably also substantiates a need for age-related limits in regard to GH/nadir GH and consensus regarding methods of analysis (27–29).

In general, we found results that were comparable to those of the existing papers on efficacy (13–17)

Table 6 Status at the last follow-up after stereotactic radiosurgery (SRS) for acromegaly in different series.

Authors (year)	Form of radiation (SRS)	Total dose (Gy)	Number of acromegalic patients	Median radiological follow-up (months)	Number of patients with tumour control	Median biochemical follow-up (months)	Number of patients in biochemical control (BC)	Number of patients in true biochemical remission	Number of patients developing new pituitary axes deficiency
Ronchi <i>et al.</i> (2009)	201-source 60 Co gammaknife	40	35	114	35 (100%)	114	23 (66%)	15 (43%)	16 (50%)
Losa <i>et al.</i> (2008)	201-source 60 Co gammaknife	25	83	69	81 (98%)	69	70 (84%)	49 (59%)	7 (9%)
Pollock <i>et al.</i> (2008)	201-source 60 Co gammaknife	20	27	46.9	27 (100%)	46.9	–	18 (67%)	–
Roberts <i>et al.</i> (2007)	201-source 60 Co gammaknife	21	9	25.4	9 (100%)	25.4	5 (56%)	4 (44%)	3 (33%)
Vik-Mo <i>et al.</i> (2007)	201-source 60 Co gammaknife	53.4	53	66	47 (100%)	66	20 (38%)	11 (21%)	8 (13%)
Petit <i>et al.</i> (2007)	Proton beam	20	22	75.6	22 (100%)	75.6	21 (95%)	13 (59%)	8 (38%)
Swords <i>et al.</i> (2003)	Linac (SMART)	8–15	13	20.1	13 (100%)	25	6 (55%)	5 (45%)	–

(Table 5). However, the present study has added knowledge about biochemical discordance between IGF1 and GH/nadir GH, which was not evaluated in most existing papers regarding acromegalic patients treated with FSRT, probably because the acromegalic patients were a subgroup of patients with various pituitary tumours (13–15).

Comparison between patients treated with FSRT and SRS is complicated since allocation to the different stereotactic treatment modalities is different based on tumour size, shape and location (6, 7, 30, 31). By combining the high radiation precision known from SRS and the radiobiological advantages of fractionated radiation, FSRT is preferred over SRS when the target is close to a critical structure as, for example, the optic pathway (13, 32). Also, FSRT is performed mostly using a dental or head mask, thereby avoiding the invasive pins used during SRS (the Cyberknife is an exception) (6). However, SRS is more convenient for patients than FSRT, requiring 1 day versus 6 weeks of treatment (33).

Most series regarding FSRT to acromegalic patients have a follow-up time shorter than those for SRS (13–17, 20, 30, 32, 34–37) (Tables 5 and 6), which complicates the comparison since the effect of FSRT is known to appear later than the effect of SRS (6). However, the biochemical remission after SRS seems to vary between 21 and 67% (follow-up median 66 months, range 25–114) compared with 0 and 55% after FSRT (follow-up median 42 months, range 28.5–59.8) (13–17, 20, 30, 32, 34–37) (Tables 5 and 6), but the criteria for biochemical remission in both the SRS and FSRT series were not identical. When allocated to the different stereotactic radiation methods by taking the limitations and advantages into consideration, the efficacy seemed equal (Tables 5 and 6).

Hypopituitarism is a serious side effect of RT of the pituitary gland in general (4, 24), and the incidence of new anterior pituitary hormonal deficiencies varies from 0% in the first years to 66% after a median follow-up of up to 17 years (38). Due to a slowly progressing effect of radiation on the pituitary gland, the highest incidence of hypopituitarism has been reported in the series of patients with the longest follow-up (38, 39). Risk of deficiency, though, seems maximal during the first 96 months after radiation (40). Evaluation of post-radiation hypopituitarism is difficult because of confounding factors such as previous surgery and/or radiation and differences in radiation of the tumour margin (38). The radiation dose in general, and to the pituitary stalk and the hypothalamus in particular, increased the incidence of hypopituitarism (6). This could be the reason why SRS of the pituitary gland compared with FSRT seemed to have a lower incidence of newly onset hypopituitarism (Tables 5 and 6). However, future studies are needed to clarify this. Also, deficiency prior to radiation has been reported to increase the vulnerability of the

pituitary gland to radiation, and can therefore by itself increase the incidence (39). Yet, no statistical difference was found between the incidence of hypopituitarism in the patients with normal function of the pituitary gland and those with hormonal deficiencies prior to FSRT in this study.

The higher radiation precision by stereotactic techniques has not been proven to improve the cumulative incidence in long-term follow-up studies compared with conventional RT (38). Hypopituitarism is, like acromegaly, combined with increased mortality (41), which is an important reason for evaluating this side effect during the development of new radiation techniques. In the present series, 29% of the patients had a new deficit of one or two axes 48 months (median, range 6–102) after FSRT. Sixteen patients had hormone replacement therapy after FSRT, seven of whom (44%) had to replace two axes. Compared with existing papers, we chose a high total radiation dose, although the fraction doses appeared alike (Table 5). Therefore, the low incidence of hypopituitarism ($n=8$) is very interesting, and could indicate a high precision of radiation (6) in the present series.

Despite some indications that somatostatin analogues and the GH receptor antagonist could be radioprotective (39, 42), we chose to continue medical therapy during the period of radiation in order to limit the time of seriously elevated GH/IGF1. The present study has thus demonstrated that an acceptable treatment outcome can be achieved with FSRT, while the patients were still on medication, which is also in keeping with a demonstrated lack of significant difference between patients treated or not treated with somatostatin analogues (40). Current recommendations, however, seem to advise withholding medication during the radiation (6), and evaluation of biochemical measurements pre radiation without medical therapy seems to be a predictive factor of remission (40). However, only a prospective randomised study with sufficient power can clarify this issue.

In conclusion, FSRT may be used in acromegalic patients who have persistent or recurrent tumour growth or who are resistant/intolerant to medical therapy. Longer follow-up is, however, needed to assess the long-term efficacy and safety of FSRT for acromegaly. Since most of the patients had pituitary insufficiency before FSRT already, the main issue for follow-up that should be focused upon is the other long-term effects of irradiation, such as impaired cognition, morbidity and mortality, although the fertility issue should also be taken into account.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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