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Long-term follow-up results of postoperative radiotherapy in 36 patients with acromegaly

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ABSTRACT

In acromegaly, pituitary irradiation is a slow, but effective, intervention in decreasing GH concentration. Few studies addressing the outcome of radiotherapy have used the currently accepted strict criteria for remission in the analysis of data. These studies report a low percentage of remission after radiotherapy. Doubt has especially been raised as to whether radiotherapy is effective in normalizing serum insulin-like growth factor (IGF)-I concentration. We analyzed the long-term follow-up data of postoperatively administered radiotherapy in 36 patients with postoperative persistent acromegaly, using both the normalization of GH suppression during oral glucose loading (GTT) and the normalization of IGF-I concentration as criteria for remission. Before radiotherapy, mean suppressed GH was 9.8 ± 1.9 mU/L ($n = 31$), and mean IGF-I concentration was 44.3 ± 3.9 nmol/L, equivalent to $+ 4.76 \pm 0.78$ age-related IGF-I SD score ($n = 13$). The median radiation dose was 40 Gray (range, 25–50 Gray).

At 5, 10, and 15 yr follow-up, 18 out of 30 patients (60%), 23 out of 31 patients (74%), and 16 out of 19 patients (84%), respectively, achieved normal serum IGF-I concentration. At the last assessment of all patients, after a mean follow-up period of 139 ± 12 months, 27 out of 36 (75%) patients had a normal IGF-I concentration without additional medication, whereas 5 patients still required treatment with octreotide. Remission, as judged by normalization of GH suppression during GTT, was documented in 65% of patients from 2–5 yr after radiotherapy ($n = 34$); in 69% of patients, up to 10 yr after radiotherapy ($n = 29$); and in 71% of patients, up to 15 yr post irradiation ($n = 17$). At the latest assessment, a mean of 125 ± 11 months after radiotherapy, 71% of patients ($n = 35$) were in remission, as defined by normal suppression of serum GH during GTT. Remission, as judged by normalization of both GTT and IGF-I, was found in 40% of patients 3–5 yr after radiotherapy ($n = 30$); in 61% of patients, 6–10 yr after radiotherapy ($n = 28$); in 65%, after 11–15 yr after radiotherapy ($n = 17$); and in 63% of patients, at the end of the follow-up period ($n = 35$). Substitution of one or more pituitary hormone deficiencies was required in 11% of patients postoperatively; in 29%, 5 yr after radiotherapy; in 54%, 10 yr after radiotherapy; and in 58%, more than 15 yr after radiotherapy. Our findings support the use of radiotherapy as an effective intervention in the treatment of residual clinical activity of disease after surgery for acromegaly.

INTRODUCTION

EXTERNAL IRRADIATION OF GH-SECRETING pituitary adenoma is effective in decreasing serum GH levels, but the process is slow. In different retrospective studies, a decline in GH levels of 23–29% of pretreatment GH concentrations per year is reported in the first 5 yr after radiotherapy (1–5). According to a review by Eastman et al. (1), a serum GH concentration below 10 mU/L is achieved in about 80% of patients 15 yr after radiotherapy. Disadvantages of radiotherapy include the long interval it takes before serum GH levels fall within an acceptable range and also the significant number of patients developing hypopituitarism post irradiation. Other complications, such as loss of vision, brain damage, or development of an epileptic disorder are rarely observed (1).

With changes in the definition of remission for acromegaly, most retrospective studies addressing radiotherapy results have to be placed into perspective (6). So far, only a few of these studies have focused on the recently proposed criteria, namely the normalization of the insulin-like growth factor (IGF)-I concentration, as an integrated marker for GH production and the normalization of GH suppression after oral glucose loading (GTT) (7, 8). These studies raise serious doubts as to whether radiotherapy is effective in normalizing GH hypersecretion. For example, Barkan et al. (8) report normalized IGF-I levels in only 2 of 38 patients studied.

It is widely accepted that the first-choice treatment option for patients with acromegaly is transsphenoidal microsurgery, resulting in an immediate decline of serum GH concentration in nearly all patients. Reported remission rates range from 50–81% and depend on various parameters, including preoperative GH concentration (9–11), tumor classification (10, 11), and experience of the neurosurgeon (12).

Radiotherapy is reserved for those patients with postoperative residual disease or those with recurrent disease (13). In these cases, the choice between radiotherapy, with its possible side effects, and the cost of increasingly efficacious medical therapies has to be weighed carefully. We retrospectively analyzed follow-up data of patients treated with adjuvant postoperative radiotherapy. Our aim was to identify the remission rates of postoperative irradiation in acromegaly using the generally accepted criteria, i.e. a normal glucose-suppressed GH concentration and normal serum IGF-I concentration.

SUBJECTS AND METHODS

Patients

Between 1977 and 1996, 129 patients with acromegaly underwent transsphenoidal microsurgery in the Leiden University Medical Center. Acromegaly was diagnosed on the basis of the characteristic clinical features of acromegaly and confirmed by insufficient suppression of GH concentration during GTT and the presence of a pituitary adenoma on radiological

imaging. Fifty of the 129 operated patients received adjuvant radiotherapy for residual disease. Thirty-six of these patients were selected for further analysis. The remaining 14 patients were excluded for the following reasons: prophylactic irradiation (before 1985) for invasive tumor growth (4 patients) and/or unchanged paradoxical reaction to TRH in the presence of a normal serum GH concentrations postoperatively and throughout follow-up (6 patients), or lack of IGF-I data in follow-up (4 patients). The group of 36 patients studied consisted of 23 males and 13 females. Mean age at surgery was 43.4 ± 2.1 (range, 21–68) yr. Mean age at irradiation was 44.3 ± 2.1 (range, 22–69) yr and was 46.2 ± 3 yr for male patients and 41 ± 3 yr for female patients. Radiotherapy was administered within 1 yr of surgery, except in 4 patients, who were irradiated 2, 3, 5, and 9 yr postoperatively. Five patients (14%) had microadenomas, 21 patients (58%) had noninvasive macroadenomas, and 10 patients (28%) had invasive macroadenomas. Four patients were lost to follow-up, and 4 patients died. All other patients visited the outpatients' clinic once yearly.

Treatment

All patients underwent transsphenoidal surgery as primary therapy. Surgery was performed in the Leiden University Medical Center by the same neurosurgeon (H. van Dulken). Radiotherapy was administered by a linear accelerator (4–8 mega electron volt). In the majority of patients (75%), a dose of 40 Gray (Gy), fractionated in doses of 2–2.5 Gy at 4–5 sessions a week, was used. The other patients received 25 Gy ($n = 1$), 36 Gy ($n = 2$), 45–46 Gy ($n = 5$), and 50 Gy ($n = 1$). In 28 patients (78%), rotational fields were used; and in 8 patients (22%), a 2-field technique with laterally opposed fields was used. Additional (temporary) GH-suppressive medical treatment was given to 12 patients. At the latest follow-up visit, 5 patients still required octreotide (27, 59, 108, 182, and 190 months after radiotherapy).

Hormonal evaluation

After oral ingestion of 75 g glucose, measurements of GH, insulin, and glucose were taken at 0, 30, 60, 90, and 120 min. The lowest GH concentration achieved during this test (GTT) was used as the suppressed serum GH concentration. Serum IGF-I concentration was measured from 1985 onward. GTT testing and IGF-I measurements were performed yearly. Substitution with cortisol, sex-hormones, and/or T_4 was based on clinical findings, supported by decreased hormone concentrations, and abnormal stimulation tests, as performed on a yearly basis. In this study, the start of substitution with T_4 , cortisol, and/or testosterone was taken as the endpoint of adequate pituitary functioning. Premenopausal women were considered LH/FSH-deficient when a menstrual cycle was absent. Postmenopausal women were considered gonadotropin-deficient when LH was less than 20 U/L. Somatotrope axis reserve was judged inadequate by insufficient increase (<7 mU/L) in GH concentration after insulin-induced hypoglycemia (ITT) or after iv administration of GHRH. After radiotherapy, patients using octreotide were considered not to be in remission.

Assays

Before 1992, serum GH concentration was measured with an RIA (Biolab, Serono Laboratories, Inc., Coissins, Switzerland), calibrated against World Health Organization International Reference Preparation (WHO-IRP) 66/21. Detection limit of this assay was 0.5 mU/L (0.25 µg/L). The interassay coefficient was less than 5%. The normal value of minimal suppressed serum GH concentration was below 2.5 mU/L (1.25 µg/L), as determined in 40 healthy controls, 20–70 yr old. An immuno-fluorometric assay (Wallac, Inc. Oy, Turku, Finland), specific for the 22-kDa GH protein, was used after 1992. Human biosynthetic GH (Pharmacia & Upjohn, Inc., Uppsala, Sweden) was used as standard, calibrated against WHO-IRP 80–505, with a detection limit of 0.03 mU/L and an intraassay variation coefficient of 1.6–8.4%, between 0.25 and 40 mU/L. For this assay, the normal value of glucose-suppressed minimal serum GH concentration was below 1 mU/L (<0.38 µg/L), as validated in 35 healthy controls in the same age range as our patients.

Serum IGF-I concentration was determined by RIA (INCSTAR Corp., Stillwater, MN), with an interassay variation coefficient of less than 11% and a detection limit of 1.5 nmol/L. Age-related normal values of 137 healthy controls were used to calculate an SD score, as used before in our center (14). Mean IGF-I concentrations (\pm SD) in those 137 healthy controls were 22.8 ± 5.5 nmol/L (20–40 yr), 18.3 ± 5.2 nmol/L (40–60 yr), and 14.9 ± 5.0 nmol/L (>60 yr). In this study, we used an SD score of +1.5 as the upper limit for normal values, i.e. normal values for serum IGF-I were below 31.0 nmol/L for patients between 20 and 40 yr, below 26.0 nmol/L for patients between 40 and 60 yr, and below 22.4 nmol/L for patients over 60 yr. PRL was measured using WHO-IRP 75/504 as calibration preparation. The interassay variation was 10.6%, and the detection limit was 0.2 µg/L (Serono Laboratories, Inc., Amersfoort, The Netherlands). More recently, with an immunofluorometric assay using WHO-IRP 84/500, the interassay variation coefficient was 3.4–6.2%, and the detection limit was 0.04 µg/L (Wallac, Inc. Oy). Normal values for basal PRL were less than 10 µg/L for both assays.

Statistical analysis

Data are expressed as mean \pm SEM, unless otherwise mentioned. Statistics (Student's t test, ANOVA, and chi-square test) were calculated using Statistical Package version 8.0 (SPSS, Inc., Chicago, IL). Logistic regression was performed using the JMP Statistical Package (SAS Institute, Inc., Cary, NC). P-values less than 0.05 were considered significant.

RESULTS

Preoperatively, serum IGF-I concentration was 54.3 ± 4.12 nmol/L ($+ 6.59$ SD ± 0.79 , measured in 12 patients), and minimal GH concentration during GTT was 56.9 ± 9.5 mU/L. Before radiotherapy, IGF-I concentration decreased, as a result of surgery, to 44.3 ± 3.9 nmol/L (equivalent

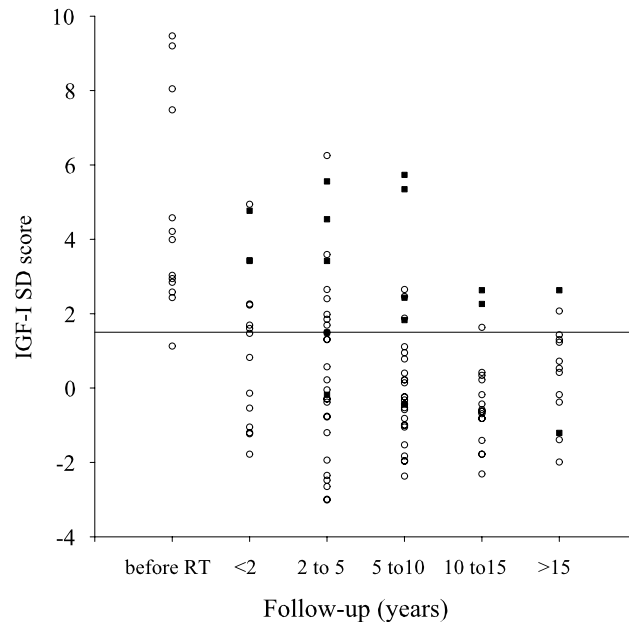


Figure 1. Serum IGF-I concentrations (expressed as age-related SD score), in relation to time after radiotherapy. An age-related IGF-I SD score less than +1.5 SD (*reference line*) is considered normal. The used follow-up assessments are 2 yr after radiotherapy and those closest to 5, 10, 15, and 20 yr of follow-up. ○, Patients not using GH-suppressive medical treatment; ■, patients using octreotide.

to $+4.76 \text{ SD} \pm 0.78$, $n = 13$); and the minimal suppressed GH concentration, to $9.8 \pm 1.9 \text{ mU/L}$ ($P = 0.008$ and $P < 0.001$, respectively). The mean follow-up period after radiotherapy was 130 ± 10 months (range, 27–243 months).

Sequential serum IGF-I concentrations are expressed as age-related SD scores and are plotted in Fig. 1. IGF-I measurements (obtained at the latest assessment, in the following intervals: before radiotherapy; at 0–2 yr, 2–5 yr, 5–10 yr, and 10–15 yr; and more than 15 yr after radiotherapy) were used in the analysis. Serum IGF-I concentrations were elevated before radiotherapy in 12 of the 13 patients in whom it was measured. One patient, with an IGF-I SD score within the normal range before radiotherapy, had insufficient suppression during GTT and also elevated IGF-I levels in the first year after radiotherapy. Because IGF-I concentrations were measured from 1985 onwards, the other patients had only IGF-I data after irradiation. In 10 patients, the first measured IGF-I was elevated; and in the other 14 patients, the first measured IGF-I was normal. Up to 2 yr after radiotherapy, 47% of patients had normal IGF-I concentrations; 2–5 yr after radiotherapy, 60%; and 5–10 yr after radiotherapy, 74% (without adjuvant medical therapy). When considering the most recent IGF-I measurements of all patients (mean follow-up, 139 ± 12 months), 75% of patients had a normal serum IGF-I concentration at the end of follow-up (Table 1). At the end of each time interval, serum IGF-I concentrations (nmol/L) were plotted against IGF-I data obtained in healthy controls (Fig. 2). Six patients had IGF-I levels below the control data 2–5 yr after radiotherapy, but only 2 had

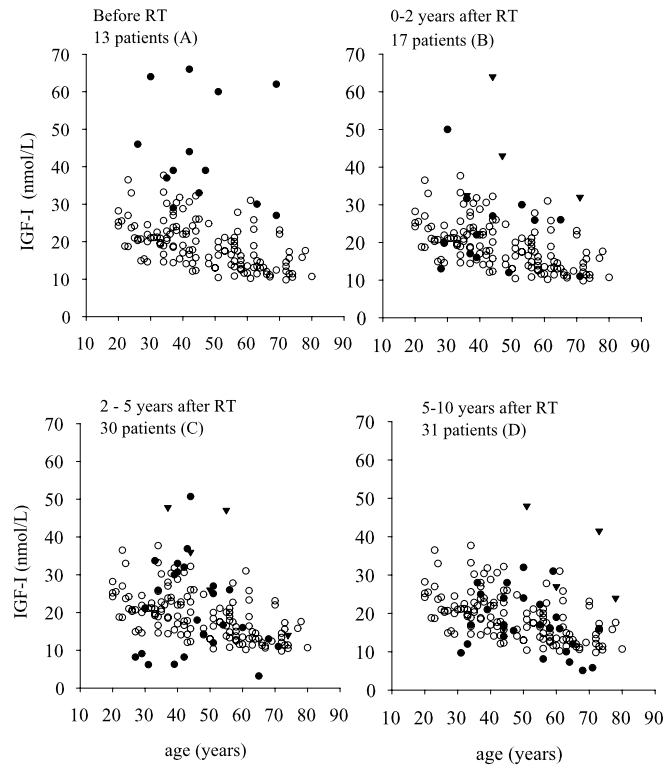


Figure 2. Serum IGF-I concentrations of patients without medication (*closed circles*) and patients using octreotide (*closed triangles*), compared with 137 normal controls (*open circles*). A, IGF-I concentrations before radiotherapy (13 patients); B, IGF-I concentrations 2 yr after radiotherapy (17 patients); C, IGF-I data 3–5 yr after radiotherapy (30 patients); D, IGF-I concentrations 6–10 yr after radiotherapy (31 patients).

Table 1. Radiotherapy results in acromegaly. Patients with normal IGF-I concentration.

Follow-up ¹	Mean follow-up (months)	No. of patients with IGF-I data	No. of patients with medical treatment	Mean IGF-I SD score (no medication)	No. of patients with normal IGF-I ²
0-2 yr	20 ± 2	17	4 (24%)	0.70 ± 0.5 SD	8 / 17 (47%)
2-5 yr	51 ± 2	30	5 (17%)	0.24 ± 0.45 SD	18 / 30 (60%)
5-10 yr	105 ± 3	31	5 (16%)	-0.27 ± 0.26 SD	23 / 31 (74%)
10-15 yr	166 ± 4	19	2 (11%)	-0.60 ± 0.23 SD	16 / 19 (84%)
> 15 yr	209 ± 6	13	2 (15%)	0.34 ± 0.37 SD	10 / 13 (77%)
Final follow-up	139 ± 12	36	5 (14%)	-0.31 ± 0.26 SD	27 / 36 (75%)

¹ Data used for each interval were the results closest to the end of the interval of 0-2, 2-5, 5-10, 10-15 years and the most recent result for final follow-up.

² Patients with normal IGF-I without octreotide/total number of patients (percentage of patients with normal IGF-I)

Table 2. Radiotherapy results in acromegaly. Patients with normal GH suppression during GTT.

Follow-up ¹	Mean follow-up (months)	No. of patients followed	No. of patients with medical treatment	Mean suppressed GH (mU/L)	No. of patients with normal suppression
0-2 yr	18 ± 1	36	6 (17%)	2.8 ± 0.7	17 / 34 (50%)
2-5 yr	50 ± 2	36	6 (17%)	1.5 ± 0.3	22 / 34 (65%)
5-10 yr	105 ± 3	29	4 (14%)	1.3 ± 0.3	20 / 29 (69%)
10-15 yr	164 ± 4	17	2 (12%)	1.2 ± 0.4	12 / 17 (71%)
> 15 yr	195 ± 6	9	2 (22%)	1.0 ± 0.3	5 / 9 (56%)
Final follow-up	125 ± 11	36	5 (14%)	1.1 ± 0.2	25 / 35 (71%)

¹ Data used for each interval were the results closest to the end of the interval of 0-2, 2-5, 5-10, 10-15 years and the most recent result for final follow-up.

² Patients with normal GH suppression (GTT) without octreotide/total number of patients (percentage of patients with normal GH suppression (GTT)).

accompanied insufficient increase of GH after ITT, whereas the other 4 patients had normal IGF-I concentrations at more recent follow-up.

The results for normalization of GH suppression during GTT are detailed in Table 2. Patients using medication were not considered to be in remission. When considering the latest available glucose suppressed GH, 25 out of 35 patients had normal GH suppression (71%).

Both normal IGF-I concentration and normal GH suppression during GTT were present in 40% of patients (n = 30) up to 5 yr after irradiation. Up to 10 yr after irradiation, 61% of patients (n = 28) were in remission, as judged by both tests; and up to 15 yr after radiotherapy, 65% of patients (n = 17) were in remission. At the latest follow-up assessment, 63% of patients had both normal IGF-I concentration and normal GH suppression during GTT (n = 35); see Table 3. Discrepancies between IGF-I and suppressed GH concentration were present in 23% of patients at the end of follow-up and are further detailed in Table 3.

Table 3. Concordance of GH suppression during GTT and IGF-I concentration.

Follow-up	No. of patients no medication/ both tests available	No. of patients on medication	Normal IGF-I and normal GH suppression ¹	Normal IGF-I and insufficient suppression	Normal suppression and IGF-I elevated	Both (IGF-I and suppressed GH) abnormal
2-5 yr	23	7	12 / 30 (40%)	4	5	2
5-10 yr	24	4	17 / 28 (61%)	4	3	
10-15 yr	15	2	11 / 17 (65%)	3	1	
Final follow-up	30	5	22 / 35 (63%)	4	3	1

¹ Percentage of remission expressed as number of patients with both normal tests without medical treatment divided by the total group, including those on medication.

In 6 patients with PRL-cosecretion, as defined by immunohistochemistry, mean basal PRL levels decreased from 13.0 ± 2.2 $\mu\text{g/L}$ before radiotherapy to 6.7 ± 1.0 $\mu\text{g/L}$ at the latest follow-up examination,

Using logistic regression analysis, attainment of both normal suppressed GH and serum IGF-I concentration was significantly related to a lower mean GH concentration before radiotherapy ($P = 0.04$), but not to sex, age, tumor class, or duration of follow-up.

Development of one or more pituitary deficiencies is detailed in Table 4. Substitution therapy was required in 11% of patients postoperatively. After exclusion of patients with postoperative deficiency, substitution therapy was further required in 29% of patients within 5 yr of radiotherapy; in 54%, between 5 and 10 yr after radiotherapy; in 56%, between 10 and 15 yr after radiotherapy; and in 58% of patients, more than 15 yr after radiotherapy. At the end of follow-up, 51% of patients required substitution therapy: 35% for TSH deficiency, 31% for ACTH deficiency, and 50% of male patients for LH/FSH deficiency. Fifteen percent of female patients had LH/FSH deficiency postoperatively, and 50% of female patients developed LH/FSH deficiency during follow-up, as judged by low LH and FSH ($n = 4$). Gonadal status was not assessed after radiotherapy in 3 premenopausal women, because of the use of contraceptive drugs. Insufficient increase of GH after ITT, as defined by a maximal concentration of GH of less than 7 mU/L, was observed in 13 patients (36%) at the end of follow-up. Decreased GH reserve during ITT was associated with normal IGF-I levels in 7 patients; and low normal IGF-I levels (between -1.5 SD and -2 SD below the mean), in 6 patients.

Table 4. Development of hypopituitarism in patients with acromegaly up to 139 ± 12 months after radiotherapy.

Follow-up	TSH-axis substitution No. of patients ¹	ACTH-axis substitution No. of patients ¹	LH/FSH-axis substitution No. of male patients ¹	LH/FSH-axis deficiency No. of female patients ²	GH-reserve (ITT) Insufficient No. of patients	Substitution ³ No. of patients
Postoperative	2 / 36 (6%)	4 / 36 (11%)	1 / 23 (4%)	2 / 13 (15%)	-	4 / 36 (11%)
0–5 yr after radiotherapy	3 / 34 (9%)	5 / 32 (16%)	8 / 22 (36%)		8 / 36 (22%)	10 / 35 (29%)
6–10 yr after radiotherapy	9 / 27 (33%)	8 / 27 (30%)	9 / 17 (53%)		12 / 29 (41%)	15 / 28 (54%)
11–15 yr after radiotherapy	7 / 18 (39%)	6 / 18 (33%)	7 / 9 (78%)		9 / 19 (47%)	10 / 18 (56%)
> 15 yr after radiotherapy	5 / 11 (45%)	5 / 11 (45%)	5 / 6 (83%)		7 / 13 (54%)	7 / 12 (58%)
Final follow-up	12 / 34 (35%)	10 / 32 (31%)	11 / 22 (50%)	4 / 8 (50%)	13 / 36 (36%)	18 / 35 (51%)

¹ Development of substitution after radiotherapy is analyzed after exclusion of patients with postoperative deficiency.

² Female LH/FSH deficiency is evaluated dependent on pre/postmenopausal status (see Subjects and Methods) and only assessed at the end of follow-up and postoperatively. Three female patients not evaluated because of use of contraceptive drugs.

³ Requirement of substitution for one or more pituitary deficiencies after radiotherapy. One patient substituted completely after surgery is excluded.

DISCUSSION

This retrospective study was primarily conducted to evaluate the efficacy of radiotherapy in normalizing serum IGF-I concentrations in postoperative persistent acromegaly. Normalization of IGF-I concentration, after treatment, was recently related to the return of mortality risk to normal (15), which has already been correlated to a GH concentration below 5 mU/L. IGF-I, an integrated marker of GH-production, is currently used as an important criterion for remission in many studies addressing the outcome of surgical and medical interventions in acromegaly. However, follow-up data for IGF-I after radiotherapy are scarce and demonstrate discrepancies (7).

The first-choice treatment in acromegaly, transsphenoidal surgery, establishes remission in 50–81% of patients (16, 10, 17–19). In patients with postoperative persistent disease, adjuvant therapy is required in the form of radiotherapy and/or medical therapy, such as long-acting somatostatin-analogs, dopaminergic drugs, and (in the future) probably receptor antagonists (20, 21). Radiotherapy is currently reserved for the small number of patients with postoperative persistent acromegaly despite medical treatment. It is of clinical importance, therefore, to evaluate the effectiveness of radiotherapy in acromegaly according to the preferred strict criteria for remission.

In our patient group, normal IGF-I concentrations were present in 60% of patients 3–5 yr after radiotherapy, and in more than 75% of patients more than 10 yr after radiotherapy. Published studies, evaluating IGF-I concentrations after radiotherapy (7, 8, 15, 22–26), are summarized in Table 5; and normal IGF-I levels were reached in 5 (8) to 68% (22) of patients. Results from these studies are discrepant and mostly less favorable than the results we are able to present. This lack of consensus between studies might be explained by differences in follow-up duration, disease activity, or therapies administered before irradiation. Another significant cause for the discrepancy between results is the use of various IGF-I assays and different normal values for IGF-I concentration.

Although Speirs et al. (27) reported that the effectiveness of radiotherapy is not influenced by previous ablative treatment, Littley et al. (28) showed a better chance of achieving a GH level of less than 5 mU/L when preradiotherapy GH concentrations were below 30 mU/L. The latter report emphasizes the important role of surgery in reducing serum GH concentration before radiotherapy. In the present study, both suppressed GH and IGF-I concentrations were significantly reduced after transsphenoidal surgery, and only a minority of patients had a serum GH concentration greater than 25 mU/L before radiotherapy. This probably contributes significantly to the favorable results we are able to report. Our results are in keeping with other studies with comparable low GH concentrations before radiotherapy (8, 24), which also show more favorable GH concentrations after irradiation than those with higher GH concentrations before radiotherapy (1). Normalization of glucose-suppressed GH concentrations was found in 65% of patients at the 5 yr follow-up and in 70% of patients with follow-up

Table 5. Overview of studies on radiotherapy results using normalized IGF-I concentration as parameter for remission.

Author	Follow-up (yr)	No. of Patients	Therapy ¹	Preradiotherapy IGF-I	Normal IGF-I
Barkan et al. (8) (1997)	Mean 6.8±0.8 (1-19)	38	33 SURG+RT, 2RT, 3 PB	289 ± 23% ULN ³	2/38 (5%)
Ciccarelli et al (22) (1993)	Range 1-6	19	42RT, 4 SURG+RT	3.22 ± 0.3 mU/mL	13/19 (68%)
Thalassinis et al (7) (1998)	Range >10	14 ²			4/14 (29%)
Freda et al. (26) (1998)		32	32 SURG+RT		10/32 (31%)
Van der Lely (25) (1997)	Mean 7	37	37 SURG+RT		0/37 (0%)
Powell et al (23) (1999, A)	Mean 5.2	48	47 SURG+RT, 1RT		19/48 (44%)
Porretti et al (24) (1999)	Mean 10± 7	70	70 SURG+RT	110.8 ± 48 nmol/L	34/67 (51%)
Swearingen et al (15) (1998)	Mean 6.7	45			19/45 (42%)
Own results	Mean 4.3± 0.2	30	30 SURG+RT		18/30 (60%)
	Mean 8.8 ± 0.2	31	31 SURG+RT		23/31 (74%)
	Mean 13.8± 0.3	19	19 SURG+RT		16/19 (84%)
	Mean 11.3± 1	36	36 SURG+RT		27/36 (75%)

¹ SURG = surgery, mainly transsphenoidal surgery, in few cases transcranially. For exact data, see references. RT, radiotherapy, PB, proton beam irradiation, MED, no. of patients using medication.

² 14 of 21 patients with follow-up > 10 year had IGF-I measured.

³ ULN= upper limit of normal.

for 10 and 15 yr. Few other studies have evaluated radiotherapy results using oral glucose suppression tests (26, 28, 29). The suppressed GH concentration after GTT is considered a sensitive test for follow-up of treated acromegaly (30–32) and might, when using a highly sensitive GH assay, be less variable between centers than IGF-I measurements.

As reported by others, we also found individual discrepancies between criteria for remission (normal IGF-I vs. normal GH suppression) in 20% of patients at the latest follow-up visit after radiotherapy (8, 32–34). In contrast, other studies reported highly correlated relationships between GH and IGF-I concentrations (30, 35–37), but data on the correlation between IGF-I and clinical disease activity or morbidity are limited (38); and therefore, the clinically relevant question concerning the value of serum IGF-I in the follow-up of treated acromegaly remains, as yet, unanswered.

In six patients with mixed GH-cell and PRL-cell adenomas, we observed a tendency toward normalization in PRL concentrations in the long-term follow-up after radiotherapy associated with normalization of IGF-I levels. This is in agreement with a report of Ciccarelli et al. (39), in which acromegalic patients with high PRL levels, before radiotherapy, showed a decline in PRL levels post irradiation.

Hypopituitarism is an important unwanted side-effect of irradiation, developing in agreement with others in at least 50% of our patients (40). A single study by Little et al. (41)

reported a lower incidence of hypopituitarism in low-dose (20 Gy) pituitary irradiation, with equivalent reduction of GH concentration, compared with results with higher-dose irradiation (40 Gy). It should be mentioned, however, that Sheline et al. (42) previously reported a high relapse rate of chromophobe adenomas after low-dose irradiation. A mean irradiation dose of 40 Gy was applied in our patients, a dose slightly lower than that used in other studies in which the dose range was 37.5 Gy (2, 3) up to a maximum of 50 Gy (7, 8, 43). Nevertheless, our present dose regimen of 40 Gy apparently effectively normalizes suppressed GH and IGF-I levels. Prospective (multicenter) studies, comparing currently used schemes of 40–50 Gy with lower-dose schemes and using highly sensitive GH and IGF-I assays, are certainly required to address this important issue.

At the end of the follow-up period, 36% of patients had diminished response of GH during ITT. In about 50% of cases, low GH reserve during ITT was accompanied by low normal IGF-I concentrations (<1.5 SD below the age-related mean). We also observed low IGF-I concentrations (<-2 SD) in some patients, 5 and 10 yr after radiotherapy (Fig. 2). The meaning of these low values is unclear; but, as Hoffman et al. (44) demonstrated, IGF-I is a poor diagnostic parameter for evaluating GH deficiency. It is important to note that none of the patients had clinical evidence for GH deficiency and, so far, only one treated acromegalic patient (not part of this study) receives GH replacement therapy in our clinic.

An interesting recent study by Landolt et al. (45), reporting the short-term results of γ -knife radiosurgery in acromegaly, suggests that normalization of GH concentration occurs faster than after conventional fractionated radiotherapy, a finding also reported by others (46, 47). In these short-term follow-up studies, hypopituitarism is observed in only 0–16% of patients (45, 48), but long-term follow-up data on pituitary damage are not available.

We conclude that radiotherapy, used after unsuccessful surgery without additional medical treatment, is effective in normalizing both suppressed GH concentrations during a GTT and IGF-I concentrations, in about 60% of patients with acromegaly after 5 yr of follow-up, and in about 70% at the end of follow-up. Although hypopituitarism develops in about 50% of patients, we believe that radiotherapy remains an important adjuvant therapy used alone or in combination with medical therapy in unsuccessfully operated patients.

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