CLINICAL STUDY

Conventional pituitary irradiation is effective in normalising plasma IGF-I in patients with acromegaly

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Abstract

Objective: For patients in whom acromegaly persists despite pituitary surgery, conventional pituitary irradiation represents an additional treatment option. A 30–60% cure rate is described in the literature, but these studies did not utilise strict rules of remission, such as 'safe' GH levels <2.5 µg/l, and age-adjusted normal IGF-I levels.

Design and methods: We report the outcome of 41 patients with acromegaly who received pituitary conventional external irradiation. The median follow-up time was 12.8 years (3.7–43.4 years) post-radiotherapy.

Results: The median pre-irradiation GH level was 31.0 µg/l (7.0–210 µg/l). Information on IGF-I levels was only available for 6 patients prior to therapy. Utilising strict rules of remission, one-third (14/41) of our patients had normal biochemical parameters, i.e. 'safe' GH (0.5 µg/l (range 0.2–1.6 µg/l)) and normal age-adjusted IGF-I levels (multiple of upper limit of normal range (×ULN); 0.45 (0.2–1.0)) at the end of the follow-up period. An additional 9 patients achieved normal levels with adjunctive drug therapy. Furthermore, disease activity was reduced in a considerable proportion of the 18 patients who did not achieve normal biochemical levels (GH: 3.6 µg/l (1.9–15.7 µg/l); ×ULN of IGF-I: 1.6 (0.9–2.6)). In retrospect, remission is unlikely in patients who had a GH level greater than 52 µg/l (mean+2 s.d. of cured patients) prior to radiotherapy.

In addition to the 12 patients with pre-irradiation pituitary functional deficiency, another 11 patients developed symptoms of panhypopituitarism during the 3-year period following irradiation. Within a 6-year period, partial pituitary insufficiency was observed in a further 7 patients, thus necessitating hormone substitution treatment.

Conclusion: Using strict rules of remission, in our cohort we found both a normalisation of IGF-I and safe GH levels in 34% of patients treated for acromegaly with conventional irradiation therapy.

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Introduction

Untreated acromegaly invariably leads to disfigurement, disability and shortened life expectancy and, in over 99% of cases, is caused by excessive secretion of growth hormone (GH) from a pituitary adenoma. Importantly, many of the growth-related outcomes of acromegaly are mediated by elevated levels of insulin-like growth factor-I (IGF-I), which is produced in response to GH (1). Thus, one of the primary treatment goals in patients with acromegaly is reduction of these biochemical parameters. The recommended definition for normal biochemical values in patients with acromegaly is normal, age-adjusted IGF-I levels and, because GH levels after therapy are not strictly normal (2), 'safe' GH levels of less than 2.5 µg/l. A further criterion of biochemical cure of acromegaly is the ability to suppress serum GH to <1 µg/l during an oral

glucose tolerance test (OGTT) (3–6). Most previous reports have used only a single GH sampling as the parameter for the efficacy of treatment, and have defined complete remission as a GH level below the arbitrary limit of 5 or 10 µg/l.

Today, the biochemical end-point aimed for is a normal age-adjusted IGF-I level (6). Bates *et al.* (3) have shown that a GH level of <2.5 µg/l is associated with a normalisation of the mortality rate in patients with acromegaly, and is therefore considered 'safe'.

The current primary treatment of choice for acromegaly is trans-sphenoidal surgery (4, 5). For patients not cured by surgery and for those in whom the disorder recurs, medical treatment with dopamine agonists and/or somatostatin analogues is indicated. If there is insufficient response to drug treatment or surgery is contra-indicated, conventional irradiation or new methods such as heavy particle irradiation or

stereotactic radiotherapy/radiosurgery are considered. The disadvantages of radiotherapy are the long duration required to normalise biochemical parameters (up to 20 years), as well as the side-effects.

In 1997, Barkan and co-workers (7) reported that pituitary irradiation appears to be ineffective in normalising plasma IGF-I levels in patients with acromegaly, and therefore discussion of the role of radiotherapy has intensified again (7). Considering the reported benefits, the side-effects and the different reported biochemical outcomes carefully, the point in question is whether radiotherapy continues to have an important role in the treatment of patients with acromegaly.

We report here the outcome of 41 patients with acromegaly whose progress following conventional pituitary radiotherapy was observed in our departments.

Materials and methods

Patients

In this retrospective study, the charts of all patients with acromegaly who were treated in our departments between 1973 and 1999 were examined. Of a total of 201 patients with proven acromegaly, 20 men and 21 women aged 29–79 years (median 56) were treated with external pituitary irradiation. Of these 41 patients, 35 continue to be followed in our outpatient clinic and 7 have died. The hospital charts of all 41 patients were retrieved and the data were analysed. For 23 patients, radiotherapy charts were also retrieved and these included all details of radiotherapy. For the remaining 18 patients, place, date, source and dose could be retrieved from the hospital charts. The clinical notes of these patients were scrutinised.

The patients were irradiated between 1948 and 1996 (median 1981). The majority of patients underwent treatment at one institution (Department of Radiotherapy, Ludwig-Maximilians-University, Munich, Germany). However, 3 patients received radiotherapy at other hospitals. They were irradiated with megavoltage external beam treatments with bilateral opposed fields and photon energy ranging from 18 to 19 MeV. One patient was treated with a cobalt unit for half her treatment course. A total dose of 46–54 Gy (median 50 Gy) was given, usually delivered in 1.8–2.5 Gy (median 2.0 Gy) fractions, five times a week for a total of 5 weeks. The radiation field size was chosen according to X-ray and computed tomography imaging extent with an additional margin of 1 cm.

All patients had a macroadenoma of the pituitary. At the time of irradiation, 6 patients had undergone no previous treatment. Therapy prior to irradiation consisted of surgery in 26 patients, surgery plus a post-operative regime of bromocriptine in 6 patients, and surgery plus post-operative bromocriptine and somatostatin analogue therapy in 3 patients. No patients were re-irradiated for recurrent pituitary adenomas.

Follow-up for evaluation of therapy success and side-effects was usually once to twice a year in the first 5 years, and subsequently every 1 to 2 years. Seven patients died in the follow-up period after a median of 11.5 years (5.7–43.4 years) post-irradiation. Cause of death was cardiovascular disease in 5 patients, stomach cancer in 1 patient and gastroenteral bleeding in another patient.

For analysis, the 41 irradiated patients were divided into two groups based upon treatment used and biochemical parameters at the end of the follow-up time. To determine a patient's biochemical status at their last follow-up, IGF-I and GH samples were evaluated. All IGF-I samplings were single determinations, and all GH samplings were the mean value of three consecutive determinations, conducted over the course of a year. A normal age-adjusted IGF-I in combination with a 'safe' serum GH level ($<2.5 \mu\text{g/l}$) were used as criteria for remission. In our institution, these criteria are used for discontinuation of drug therapy.

The first group included those patients who, after irradiation and using strict criteria of remission, were 'cured'. They were all off drug treatment and had normal age-adjusted IGF-I levels and 'safe' GH levels ($n = 14$). The second group consisted of those patients who still had active acromegaly after irradiation ($n = 27$).

For generating life table analyses (Fig. 3), random IGF-I and GH samplings were used to determine remission. All GH samplings were the mean value of three consecutive determinations, conducted over the course of a year in which the patients received medication (except for the patients of the first group after remission). To preclude transiently normal IGF-I values due to spontaneous fluctuations or assay variability, IGF-I was considered normal when the age-adjusted IGF-I levels remained normal at the two subsequent visits. However, as IGF-I levels were not widely available prior to 1992, when creating life table analyses the ability to suppress serum GH to $<1 \mu\text{g/l}$ during an OGTT was also included in the remission criteria.

Laboratory values

Plasma IGF-I was assayed by an IGF-binding protein-blocked IGF-I radioimmunoassay (RIA) using a commercial IGF-I kit (bioMérieux, Nürtingen, Germany) with standard values (normal range 5th to 95th percentile) for adults depending on the age group (no gender differences in adults). According to the manufacturer's instructions, the lower detection limit was $0.02 \mu\text{g/l}$. The intra-assay coefficient of variance (CV) was below 6.2%, the interassay CV below 7.4% (8).

In all text, table and figures, IGF-I values are given as the multiple of the upper limit of normal ($\times\text{ULN}$) = measured IGF-I value/95th percentile of age- and sex-adjusted normal range. Serum GH measurement was

done with an in-house immunofluorometric assay (sandwich type), using human GH (IRP 80/505) as standard. The lower limit of detection was 0.1 $\mu\text{g/l}$. The intra-assay CV values were 10.3, 2.0 and 2.1% at human GH concentrations of 0.3, 1.2 and 18.6 $\mu\text{g/l}$ respectively. The interassay CV values were 6.7, 2.1 and 8.2% at concentrations of 0.2, 1.6 and 5.2 $\mu\text{g/l}$ respectively. Prior to 1992, serum GH was measured in triplicate using conventional double-antibody RIA (9). The detection limit of the assay was 0.6 $\mu\text{g/l}$ with inter- and intra-assay variations of 7 and 3.8% respectively. There is good comparability between serum GH levels measured with RIA and those measured with the newer assay ($r = 0.99$). All measures were assayed in a single laboratory, which participated in the German external quality assessment scheme for human GH and IGF-I.

Basal pituitary function and, if indicated, dynamic testing after insulin-induced hypoglycaemia were assessed in all patients after irradiation therapy and at regular intervals thereafter during the follow-up period. The diagnosis of secondary adrenal insufficiency was made on the basis of an inadequate response of plasma cortisol to insulin-induced hypoglycaemia. Hypothyroidism was diagnosed on the basis of low plasma free tri-iodothyronine and thyroxine, an inappropriately low thyrotrophin (TSH), and TSH after a thyrotrophin-stimulating hormone stimulation test. Pituitary hypogonadism was diagnosed on the basis of low serum sex steroids, as well as inappropriately low

gonadotrophins and gonadotrophins after stimulation with gonadotrophin-releasing hormone.

Statistical analysis

StatView (for Macintosh; SAS Institute Inc., USA) was used for data analysis. For all GH and IGF-I variables investigated, group values are expressed as median (and range), unless otherwise indicated. Statistical significance in outcome differences was evaluated using non-parametrical statistics with Kruskal–Wallis H test and Wilcoxon–Signed–Rank test (two-tailed). Life table analysis of treatment outcome was determined using Kaplan–Maier analysis. A P value <0.05 was accepted as the nominal level of significance, a P value <0.01 as the nominal level of high significance.

Results

Serum IGF-I and GH concentrations

The IGF-I and GH concentrations in the two groups of patients at their last visit in our departments are shown in Fig. 1. Group 1 consisted of 14 patients (8 women, 6 men) between 37 and 75 years of age (median 59 years) who had normal age-adjusted biochemical values, and who were off medication at the final follow-up. Thirteen of the fourteen had previously undergone pituitary surgery. Nine patients received temporary medical therapy until remission (7 had

Figure 1 IGF-I and GH levels at the patients' last follow-up visit, after a median follow-up time of 12.8 years (3.7–43.4 years). These values, in combination with treatment regimen at last follow-up visit were utilised to divide the groups. To consider the age- and sex-adjustment of IGF-I values, IGF-I is given as $\times$ ULN. The broken and dotted lines indicate the upper limit of the normal IGF-I range (1 ULN) and the normal range of GH ($<2.5 \mu\text{g/l}$).

received bromocriptine and 2 had received daily subcutaneous doses of somatostatin analogues). At the final follow-up, the patients were off medical treatment for a median period of 5 years (3–8 years). The median duration of follow-up was 13.5 years (3.7–26.1 years). The median serum IGF-I level, given as $\times$ ULN, was 0.45 (0.2–1.0) and the median GH level was 0.5 μ g/l (0.2–1.6 μ g/l) at the last visit. The median GH value before irradiation was 13.7 μ g/l (7.0–59.5 μ g/l). In the first 2 years after irradiation mean plasma GH fell by 69.3% (16.6–88.1%) to 4.2 μ g/l (1.3–14.6 μ g/l); $P < 0.01$.

Group 2 was comprised of 27 patients, 15 female and 12 male, of whom 22 had undergone prior pituitary surgery. At the final follow-up, median patient age was 53 years (22–74 years). At the time of their final follow-up, the median $\times$ ULN of serum IGF-I was 1.3 (0.4–2.5) and the median GH level was 3.0 μ g/l (0.5–15.7 μ g/l). Immediately prior to radiotherapy, median GH was 36.5 μ g/l (7.0–210 μ g/l), and it declined by a mean of 74.8% (–1.2% to 95.1%) to 9.2 μ g/l (2.3–96.0 μ g/l); $P < 0.001$ within the first 2 years. Nine patients in this group (6 female and 3 male) reached normal biochemical values with additional drug treatment (bromocriptine in 5 patients and subcutaneous octreotide in 4 patients). At the time of their final follow-up, the median $\times$ ULN of serum IGF-I was 0.6 (0.4–0.9) and median GH was 1.3 μ g/l (0.5–1.9 μ g/l). Immediately prior to radiotherapy, median GH was 32.1 μ g/l (7.1–149.0 μ g/l), and it declined by a mean of 71.4% (–1.2% to 88.5%) to 9.2 μ g/l (3.7–50.0 μ g/l); $P < 0.05$ within the first 2 years. In these 9 patients, short (1–2 days) withdrawal of drug therapy in the last years always led to an immediate increase in GH levels and clinical disease activity.

The remaining 18 patients of group 2 did not achieve normal IGF-I or 'safe' GH values despite irradiation and

drug treatment. At the time of the final follow-up, 17/18 of these patients did not have normal age-adjusted IGF-I levels ($\times$ ULN: 1.6; 0.9–1.6), and none of these patients had a 'safe' random GH (3.8 μ g/l; 1.9–15.7 μ g/l). Since only 6 patients had IGF-I values measured prior to receiving radiotherapy, these were not used in the pre- and post-radiotherapy analysis.

Utilising strict rules of remission, it was noted that when the GH level prior to therapy is greater than 52.2 μ g/l (mean+2 S.D. of group 1), it is less likely that normal biochemical parameters can be obtained. Thirteen of the fourteen patients from group 1, and eight out of the nine patients in group 2 who reached normal biochemical values under additional drug treatment had GH levels below 52.2 μ g/l (in fact below 39.0 μ g/l) prior to radiotherapy. Only 5 of the remaining 18 patients in group 2 whose biochemical values could not be suppressed despite drug therapy had GH levels below that mark immediately prior to radiotherapy.

Additional data characterising these two groups are shown in Table 1.

Development of anterior pituitary failure

Twelve patients had pituitary functional deficiency requiring hormone substitution treatment prior to radiotherapy. Following radiotherapy, there was a progressive failure of normal anterior pituitary function in an additional 7 patients from group 1; losses of gonadotrophin function (6/7), corticotrophin (6/7) and thyrotrophin function (4/7) were noted. Eleven out of twenty-seven patients in group 2 developed pituitary dysfunction, with a loss of gonadotrophin function in 11/11, corticotrophin function in 8/11 and thyrotrophin function in 8/11. The groups did not differ in their development of anterior pituitary failure (Fig. 2), and

Table 1 Clinical features of 41 patients with acromegaly treated with conventional radiotherapy (IGF-I given as $\times$ ULN).

	Group 1 ($n = 14$)	Group 2 ($n = 27$)
Treatment: last visit	Off medication	On medication
Outcome: last visit (normalised IGF-I and GH <2.5 μ g/l)	14/14	9/27
IGF-I: last visit		
Median ($\times$ ULN)	0.45	1.3
Range ($\times$ ULN)	0.2–1.0	0.4–2.5
GH: last visit		
Median (μ g/l)	0.5	3.0
Range (μ g/l)	0.2–1.6	0.5–15.7
GH: pre-radiotherapy		
Median (μ g/l)	13.7	36.5
Range (μ g/l)	7.0–59.5	7.0–210
GH: decline (pre-radiotherapy: last visit)		
Median (%)	97.7	74.8
Range (%)	87.1–99.4	–1.2–95.1
P value	<0.01	<0.01
Hypopituitarism: pre-radiotherapy (%)	14	37
Hypopituitarism: last visit (%)	64	78

Figure 2 Estimated cumulative risk for all 41 patients of developing pituitary functional deficiency requiring hormone substitution treatment in at least one axis after radiotherapy.

there was no significant association between hypopituitarism and biochemical cure. On the other hand, there were 5 patients in the first group and 6 patients in the second group who had no pituitary dysfunction.

Discussion

Conventional external beam irradiation to the pituitary is known to result in a decline in serum GH concentrations in patients with GH-secreting pituitary tumours in the vast majority of patients (5). Up to 90% of patients achieve a reduction of GH levels to under 5 µg/l after irradiation (10–13). Current understanding of the mechanisms of somatic growth implicate GH-dependent IGF-I as the final mediator of the growth-promoting effects of GH (14). Thus, IGF-I, rather than GH, should be monitored as the marker of disease control in acromegaly.

To date, few studies have utilised the normalisation of the IGF-I concentration as a criterion of cure. Barkan *et al.* (7) measured IGF-I instead of GH as the parameter for determining the efficacy of radiotherapy in acromegaly. They did not find a significant decline in plasma IGF-I after irradiation in their patients after a 7-year follow-up period (2/38 achieved normal IGF-I levels). In the editorial to their paper, van der Lely *et al.* (15) confirmed that in their patients ($n = 37$) radiotherapy did not result in normal IGF-I concentrations, even after a 7-year follow-up period. However, they also

noted the methodological weaknesses in the paper by Barkan *et al.* (7) (variability of radiotherapy methods and IGF-I assays). On the other hand, Ciccarelli *et al.* (33) and Biermasz *et al.* (17) demonstrated a high efficacy of radiotherapy in lowering IGF-I in 13/19 patients (68%) and 27/36 patients (75%) respectively. Results from these studies are discrepant. This lack of consensus between studies might be explained by differences in follow-up duration, disease activity before irradiation, the use of various IGF-I assays and the use of different irradiation techniques and radiotherapy sources.

The present retrospective study was performed to determine the rate of normalisation of plasma IGF-I after pituitary irradiation in our patients with acromegaly. Our patients were largely treated in the same radiotherapy unit, and serum IGF-I samples were measured in one laboratory, always using the same IGF-I RIA.

We have shown that pituitary irradiation was effective in lowering both serum GH and serum IGF-I. At the end of the follow-up period, one-third of our patients (14/41) were not on medication and had normal IGF-I levels and 'safe' GH levels less than 2.5 µg/l. Our results are in agreement with the evaluation of Powell *et al.* (18), demonstrating a remission rate of 39% after radiotherapy, and Thallasinos *et al.* (19), who found a normalisation of IGF-I in 4/14 patients (29%). However, because normalisation

Figure 3 Estimated cumulative remission rate of our cohort ($n = 41$) demonstrates the length of time to achieve 'complete' remission (patients from group 1) with normal biochemical parameters following treatment with radiotherapy, defined as 'safe' serum GH levels $<2.5 \mu\text{g/l}$ and age-adjusted normal IGF-I levels. The dashed line indicates patient outcome after 7 years.

of elevated hormone levels may take up to 15 years (20, 21) long follow-up periods are required to assess the outcome of pituitary radiotherapy.

Life table analysis of our cohort showed that, in contrast to Barkan *et al.* (7), after a follow-up period of 7 years, 17% (7/42) of all irradiated patients (60% of patients from group 1 in whom remission occurred) reached 'complete' remission with normal biochemical parameters without additional drug treatment (Fig. 3). Consistent with the literature, which indicates that somatostatin analogues can reduce GH and IGF-I (22–24), a further 22% of our patients achieved normal IGF-I levels when somatostatin and/or bromocriptine were administered after radiotherapy. The remaining 18 of our patients did not achieve a biochemical remission, although they received the same medication and radiotherapy. It is important to note, however, that most of these patients had a significant reduction in GH levels.

As others previously (16), in retrospect we were able to calculate a cut-off of $52 \mu\text{g/l}$ for GH, above which it is less likely to achieve normal biochemical values with radiotherapy. Unfortunately, it is not possible for us to determine a cut-off value for IGF-I at the time of irradiation, because IGF-I measurement with our current RIA kit has only been done since 1992.

The significant side-effects of pituitary irradiation must also be considered. At what cost have we achieved these remissions? Severe side-effects such as cranial nerve paralysis (including loss of vision) or radionecrosis occur in less than 1% of treated patients if

modern techniques are employed (25). A risk of 0–2% for the induction of secondary malignancies after 10–20 years has also been reported (26). The most frequent side-effect of pituitary radiotherapy is hypopituitarism leading to hypocortisolism, hypogonadism and/or hypothyroidism (27, 28). There are few series of pituitary radiotherapy in the literature that report side-effects after 10–20 years of follow-up. Reported data suggest that the risk of pituitary failure increases with late follow-up (29). These data must be cautiously interpreted, however, as the technique, total dose and dose per fraction previously used may be far removed from that which is considered standard radiotherapy today.

We did not demonstrate significant long-term complications such as cranial nerve palsies (including loss of vision), tumour necrosis and the development of secondary brain malignancy in our groups. It must be noted, however, that this retrospective study was not designed to address these questions directly.

Twenty-nine percent of patients had pre-irradiation pituitary insufficiency requiring substitution of at least one axis. Hypopituitarism after radiotherapy occurred in a further 62% of those patients showing an intact hormone axis prior to radiotherapy. Earlier reports have shown an increased frequency of pituitary insufficiency as a result of irradiation correlating to the longest follow-up time (29). This makes a careful life-long follow-up of patients who have received pituitary radiotherapy necessary. Seven of the forty-one patients died during the follow-up period. There

was no indication that death was caused by irradiation, but interestingly, 5/7 patients never achieved safe GH and normal IGF-I levels. (The follow-up period after irradiation in those 5 patients was a median of 25 years, the shortest period was 13 years.) The cause of death was most likely the long-standing active acromegaly.

The current availability of pharmacological agents, especially the long-acting somatostatin analogues (22–24) that are capable of lowering GH hypersecretion, normalising plasma IGF-I and, rarely, shrinking pituitary somatotropinomas, may lower the need for radiotherapy. On the other hand, normalising serum IGF-I levels with somatostatin analogues is only a palliative therapy, and requires life-long therapy. Furthermore, drug therapy – especially with somatostatin analogues – currently results in very high costs.

In light of the high number of side-effects after conventional irradiation (especially hypopituitarism which requires subsequent life-long hormone replacement therapy), and the fact that remission to normal values only occurs after a lengthy time-period (up to 20 years) and only in patients with moderately elevated pre-irradiation GH levels, the indication for conventional radiotherapy must be strictly set. Radiotherapy appears to be a good therapeutic option for patients with relatively low GH levels after exhaustion of all neurosurgical possibilities. However, in these patients, drug treatment is usually very effective, with no risk of hypopituitarism and in most cases radiotherapy is therefore not necessary. Conventional radiotherapy may be considered in patients who display high GH and IGF-I values despite surgery and drug treatment, and where further surgery is not feasible. Furthermore, in those patients who do not tolerate drug treatment or in whom life-long high-dose medical therapy is necessary, radiotherapy may also be an option. In large, non-operable pituitary tumours with no further interventional possibilities, irradiation can be considered for reduction of tumour size. In patients who display high GH and IGF-I after having undergone pituitary surgery, and in whom surgical treatment has led to hypopituitarism, conventional radiotherapy should be considered.

We have shown that radiotherapy does lower IGF-I to age-adjusted normal values in a significant proportion of patients with acromegaly who have previously been treated with surgery. A complete remission to normal biochemical values occurred in 34%, and a further 22% reached these with additional drug treatment. This is accompanied by hypopituitarism in 62% of patients whether they achieve remission or not.

We look forward to improvements in radiotherapy administration (e.g. stereotactic radiotherapy), in the hope that efficacy in reducing IGF-I and GH levels will be improved, and will be accompanied by fewer side-effects (10, 30–32).

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