# Acromegaly : treatment and follow-up : the Leiden studies

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# Postoperative radiotherapy in acromegaly is effective in reducing GH concentration to safe levels

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## SUMMARY

OBJECTIVE Several studies have established that in treated acromegaly mortality is only normalized in patients achieving a serum GH concentration below 5 mU/l. Few studies however, have addressed results of radiotherapy using this strict criterion. The aim of our study was to assess the efficacy of postoperative radiotherapy in reducing serum GH concentration below 5 mU/l.

PATIENTS AND METHODS Forty acromegalic patients who underwent radiotherapy for postoperative persistent disease after transsphenoidal surgery were studied. Mean time of follow-up after radiotherapy was 123 ± 11.1 months. A serum GH concentration of <5 mU/l was used to define remission.

RESULTS Following surgery mean GH concentration decreased from 120.8 ± 21 mU/l to 24.4 ± 5.2 mU/l and mean GH concentration prior to radiotherapy, administered after a mean of 8.2 ± 2.7 (0.5 – 96) months postoperatively was 26.0 ± 5.1 mU/l. Using individual regression plots, GH was reduced to 50% by radiotherapy after a mean of 27 ± 5 months (range 3 – 105 months). The observed mean GH concentration as measured at follow-up visits was reduced by 55% (-36 – 95%) after the first year, by 65% (-29 – 97.3%) after 2 years and by 78% (-29 – 99%) after 5 years. We could not demonstrate a significant correlation between a normalized GH concentration on the one hand and tumour size, preradiotherapy GH concentration or duration of follow-up on the other hand. During follow-up, GH-suppressive medical therapy was used in 11 patients, five of whom were still using medication at the end of follow-up. Eight patients had a follow-up of less than 5 years and three of them had a serum GH concentration of <5 mU/l at their latest follow-up visit (38%). At 5 years of follow-up after radiotherapy, 24 out of 32 patients had a GH level of <5 mU/l without medication (75%). At 10 years following irradiation, 16 of 21 patients (76%) had a GH level of <5 mU/l without medical treatment. At 15 years follow-up, a serum GH concentration of <5 mU/l was observed in 13 out of 15 patients (87%) without GH suppressive medication. At the latest follow-up visit, serum GH concentration below 5 mU/l was present in 75% of patients (30 out of 40) without medical therapy after a mean of 10.4 ± 0.9 years, but five patients required octreotide up to the end of follow-up. Twenty-seven out of 37 patients with available IGF-I data had normal IGF-I at the end of follow-up (73%). Fifty percent of patients needed substitution therapy for (partial) hypopituitarism after 10 years and 75% after 15 years of radiotherapy.

CONCLUSION In our group of patients who were incompletely cured by surgery, but had a significant postoperative decrease of serum GH concentrations, radiotherapy was able to achieve 'safe' serum GH concentrations in the majority in the long term.

## INTRODUCTION

UNTREATED ACROMEGALY IS ASSOCIATED with considerable morbidity and an elevated mortality risk (1,2). Normalized mortality risk is restored when GH levels are reduced to 5 mU/l or less (3,4) or serum IGF-I concentrations are normalized (5).

Using the criterion of a serum GH concentration of 5 mU/l or less, transsphenoidal surgery, the treatment of choice, is successful in about 42 – 81% of patients (6 – 13). Remission rates are dependent on tumour size and preoperative GH concentration (7,9,12,14) but also, as recently emphasized, on the experience of the neurosurgeon in performing pituitary surgery (10,15,16). Recurrence after transsphenoidal surgery occurs in 3 – 18% of cases (9,17) after long-term follow-up. Adjuvant therapy in the form of pituitary irradiation and/or medical GH-suppressive treatment should be considered in patients with persistent disease postoperatively, in those who develop recurrence of disease and also in these patients with elevated postoperative GH levels (>5 mU/l) without symptomatic acromegaly. Disadvantages of radiotherapy are the time it takes to reduce GH levels and the high rate of postradiation hypopituitarism. Although most recent studies regarding results of transsphenoidal surgery and those of medical therapy have used the above mentioned strict criterion of a serum GH concentration below 5 mU/l to define remission, only few reports address radiotherapy results using this criterion. Thalassinos et al. (18) reported a 'safe' GH level of <5 mU/l in only 20% of their patients a mean of 7.6 years after radiotherapy. Recent advances in medical therapy, using long-acting depot preparations of octreotide, although expensive and mostly required life-long, report remission according to achieving a stricter GH level < 2 µg/l (≈ 4 mU/l) in 55 out of 101 patients (54.6%) (19). We retrospectively analysed the long-term follow-up data of 40 patients treated with postoperative radiotherapy after incompletely successful surgery. Our aim was to assess the efficacy of radiotherapy in reducing GH concentration, using the currently accepted strict criterion of a GH of <5 mU/l.

## PATIENTS AND METHODS

### Patients

One hundred and twenty-nine acromegalic patients underwent transsphenoidal surgery in the Leiden University Medical Centre between 1977 and 1996. Fifty of these patients received adjuvant radiotherapy postoperatively. Ten patients were excluded because they received prophylactic irradiation for invasive tumour growth (three patients), had an unchanged paradoxical reaction to TRH administration in the presence of normal serum GH concentrations postoperatively and throughout follow-up (6 patients) or because of loss to follow-up (1 patient). There were 24 male and 16 female patients. Mean age at surgery was 45.4 ± 2.1 years (range: 21 – 68) and mean age at radiotherapy was 46.2 ± 2.1 years (range: 22 – 69). Mi-

croadenomas were present in six patients (15%), noninvasive macroadenomas in 21 patients (52.5%) and invasive macroadenomas in 13 patients (32.5%).

### Treatment

Transsphenoidal surgery as primary therapy was performed by the same neurosurgeon (HvD) at the Leiden University Medical Centre in all patients. Radiotherapy was administered by a linear accelerator (4 – 8 MeV), mostly 40 Gy divided in doses of 2 – 2.5 Gy given in 4 – 5 sessions a week (mean irradiation dose 40.75 ± 0.63 Gy). Rotational fields were used in 31 patients and a two-field technique in nine patients. Additional (temporary) GH-suppressive medical treatment was given to 11 patients. At the latest follow-up visit five patients were still using octreotide (27, 59, 108, 182 and 190 months after radiotherapy).

### Hormonal evaluation

Preoperative and early postoperative (7 – 10 days postoperative) hormonal assessment used in this study included the mean serum GH concentration of samples taken at 0800, 1130, 1630 and 2300 hours. The need for substitution of cortisol, testosterone and thyroxine was based on clinical findings supported by decreased hormone concentrations and abnormal stimulation tests. The start of substitution therapy was taken as the time of failure of adequate pituitary function. The last evaluation before irradiation was used as the baseline for evaluation of the effect of radiotherapy. In most patients, data before radiotherapy were derived from the postoperative evaluation. Yearly follow-up data used were mean serum GH concentrations (from either the day-profile or from the mean of basal fasting values of different stimulation or suppression tests generally performed within a 1 – 2-week period). At the latest follow-up examination we also evaluated the suppressed GH concentration following 75 g oral glucose loading. Serum GH concentration was measured at 30 minutes intervals (0, 30, 60, 90, 120 minutes). The minimal GH concentration measured during this test was used for analysis of the data. We also used IGF-I concentrations obtained at the last follow-up visit.

Mean GH concentration from a day-curve and that from the mean of the different tests pre- and postoperatively were compared in the total group of 129 acromegalic patients in whom surgery was performed. The correlation coefficient of 191 data sets was highly significant ($r = 0.917$, $P < 0.001$). Mean GH concentrations, as defined above, also significantly correlated with a single fasting serum GH concentration (fasting sample obtained during the GTT or isolated sample) ($r = 0.85$, $P < 0.001$, $n = 191$). We therefore used an isolated GH value if a day-curve and/or a mean of basal values of tests were not available. The 15 years evaluation and the latest follow-up assessment are mostly based on a single GH value. Follow-up duration was expressed in months after irradiation or as a 5, 10 or 15 years follow-up visit.

### Assays

Before 1992, serum GH concentrations were measured with a radioimmunoassay (RIA; Biolab, Serono, Coissins, Switzerland) calibrated against WHO-IRP 66/21. Detection limit of this assay was 0.5 mU/l. The interassay coefficient was less than 5% (1.0 µg/l = 2.0 mU/l). Normal values of mean or random GH-concentration were <5 mU/l and of suppressed serum GH concentration <2.5 mU/l, as determined in 40 healthy controls aged 20 – 70 years. After 1992 an immunofluorometric assay (IFMA; Wallac, Turku, Finland) specific for the 22-kDaA GH protein was used. Human biosynthetic GH (Pharmacia-Upjohn, Uppsala, Sweden) was used as standard calibrated against WHO-IRP 80-505, with a detection limit of 0.03 mU/l and an intra-assay variation coefficient of 1.6 – 8.4% between 0.25 and 40 mU/l (1 µg/l = 2.6 mU/l). Normal values of mean or random serum GH concentration were <5 mU/l in this assay. Normal values for GH suppression after oral glucose loading were 2.5 mU/l (RIA) and <1 mU/l (IFMA). IGF-I concentration was determined by RIA (Incstar, Stillwater, MN, USA), interassay variation was <11%, detection limit was 1.5 nmol/l. Normal reference-values were age-dependent and derived from healthy controls, as previously reported (20,21).

### Statistical analysis

Data are expressed as mean ± SEM or median and range.

Follow-up data for mean serum GH concentration were plotted for each patient and individual data were fitted exponentially, using SPSS Windows, version 7.0 and Sigma Plot for Windows, 4.0 (SPSS Inc., Chicago, IL, USA).

Logistic regression and survival curves were calculated using the KaplanMeier method with JMP (SAS Institute Inc. Cary, NC, USA).

The study was performed in accordance with the guidelines of the Declaration of Helsinki for human experimental studies.

## RESULTS

Preoperative mean serum GH concentration was 120.8 ± 21 mU/l. Postoperatively, mean GH concentration decreased to 24.4 ± 5.2 mU/l ($P < 0.001$, $n = 40$). At the latest assessment before radiotherapy mean serum GH concentration was 26.0 ± 5.1 mU/l ($n = 40$). At this assessment, 14 patients (35%) had a serum GH concentration above 25 mU/l, with a mean GH concentration of 54.5 ± 11.1 mU/l (range 25.8 – 167.5 mU/l). Eleven patients had a serum GH concentration between 10 and 25 mU/l (28%), 13 patients between 5 and 10 mU/l (33%) and two patients had a mean serum GH concentration below 5 mU/l before radiotherapy, but insufficient suppression of serum GH concentration during GTT and persistent clinical activity.

The mean follow-up period after radiotherapy was 123.5 ± 11 months (range 12 – 243 months). Regression plots were fitted for each patient individually, using the formula

$y = ae^{-bt}$

for expressing the estimated decrease in serum GH concentration during follow-up. Twelve patients were excluded from this analysis because of insufficient data points for calculating the coefficient a and the exponent b (four patients) or for receiving additional GH suppressive therapy for several years (eight patients). Three patients receiving short-term medical treatment in the form of octreotide (less than 1 year) were included, omitting the data obtained during medical therapy. Coefficient a, expressing the estimated GH concentration before radiotherapy, varied between 2.4 and 99.8 with a mean of 18.7 ± 3.8 and the exponent b between 0.01 and 0.27 with a mean of 0.08 ± 0.01. The estimated time to reduction to half of the preradiotherapy GH concentration following radiotherapy was calculated using the formula

$t\,½ = \ln 2/b$

Mean time to 50% reduction of GH level was 27 ± 5 months with a minimum of 3 months and a maximum of 105 months (n = 28 patients).

In the 28 patients used in the regression analysis, serum GH concentrations measured at the yearly follow-up visits were also expressed as percentage of the GH concentration before irradiation. At 1 year, the mean GH concentration was reduced by 54.9% ± 6.3% (range: -35.8% – 94.7%, n = 27) of the initial value and at 2 years by 64.5 ± 6.2% (range: -29.0 – 97.3%, n = 24) of the initial value. At 5 years GH was reduced by 77.6 ± 5.8% (range: -28.7 – 99.1%, n = 25), at 10 years by 84.3 ± 3.5% (range: 42.9 – 96.0%, n = 16) and at 15 years by 84.1 ± 5.4% (range: 41.7 – 99.6%, n = 11).



A survival plot showing the probability of maintaining an elevated serum GH concentration during follow-up was performed in all patients. The five patients medically treated at the end of follow-up were considered not to have achieved remission (Fig. 1). At 24 months after radiotherapy a proportion of 0.56 of patients had elevated serum GH concentrations, this was 0.29 at 60 months and 0.25 at 120 months.

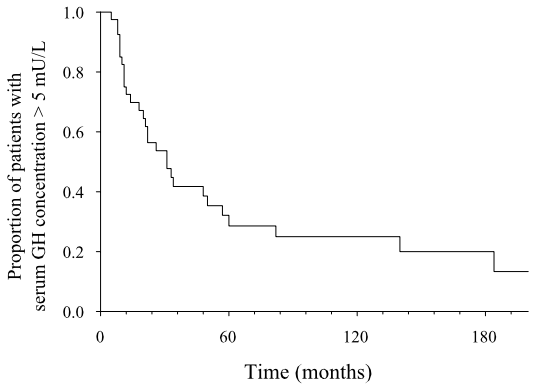


**Figure 1.** Life table plot showing the chance of persistent elevation of serum GH concentrations during follow-up (months). Patients using octreotide until the end of follow-up are considered not in remission.

**Table 1.** Follow-up data of serum GH concentration at 5, 10 and 15 year's follow-up in 40 patients irradiated for postoperatively persistent acromegaly.

| Follow-up | No. of patients | Remission No. (%) [1] | No remission No. (%) | | Serum GH (mU/l) [3] |
|---|---|---|---|---|---|
| | | | Medication | No medication | |
| 5 years | 32 | 24 (75%) | 4 (16%) | 4 (16%) | 1.8 (0.5 - 19) |
| 10 years | 21 | 16 (76%) | 4 (24%) | 1 (5%) | 1.9 (0.5 - 6.0) |
| 15 years | 15 | 13 (87%) | 2 (13%) | - | 1.4 (0.05 - 12.7) |
| Final Visit [2] | 40 | 30 (75%) | 5 (13%) | 5 (13%) | 1.14 (0.05 - 43.5) |

[1] Remission defined by serum GH concentration < 5 mU/L.

[2] Final follow-up examination, a mean of 10.4 ± 0.9 years (range 1-20 years) after radiotherapy.

[3] Median with range of serum GH concentration of all patients with follow-up data.

The follow-up results for attainment of normal serum GH concentration are listed in Table 1. Eight patients, of whom only three had a serum GH concentration <5 mU/l (38%) without additional medical therapy had a follow-up of less than 5 years. At the 5 years follow-up visit, serum GH concentration was normalized in 24 out of 32 patients (75%). Twenty-one patients had 10 years of follow-up after radiotherapy. Normalization of GH concentration was present in 16 patients without medication (76%). Fifteen patients had follow-up data 15 years after irradiation, of whom 13 had a serum GH concentration <5 mU/l (87%) without medication. At the final follow-up visit, 30 out of 40 patients (75%) had a serum GH concentration below 5 mU/l. Five patients were treated with octreotide at the end of follow-up.

In addition, we compared the evaluation criteria in 37 patients who had both a serum GH concentration and an IGF-I concentration measured at the latest follow-up visit. Thirty out of 37 patients had a GH <5 mU/l and 27 out of 37 a normal IGF-I concentration. Twenty-five patients (68%) patients were in remission according to both tests and did not use medical therapy. Five patients were not in remission according to both criteria or used medical therapy. Five patients had normal GH concentrations but elevated IGF-I and two other patients had normal IGF-I but slightly elevated GH concentrations (5.39 and 5.27 mU/l, respectively).

We also compared normalization of GH suppression during GTT at the latest visit with the attainment of a GH concentration <5 mU/l in 37 patients in whom both tests were performed. In this group, 30 patients had a GH concentration of <5 mU/l and 26 patients had normal GH suppression during GTT. Remission according to both criteria was achieved in 25 patients (68%) and six patients had both elevated GH concentration and insufficient suppression, or were using GH suppressive medication. Insufficient suppression together with a GH concentration below 5 mU/l was present in five patients and one patient had normal GH suppression but elevated basal GH concentration (i.e. 5.39 mU/l).

Using logistic regression analysis there was no significant correlation between the attainment of a serum GH concentration <5 mU/l and sex, age, tumour size, GH concentration before irradiation or duration of follow-up in months.

**Table 2.** Number of patients with substitution requirement for hypopituitarism at 5, 10 and 15 years follow-up.

| Follow-up | No. of patients | TSH deficiency | ACTH deficiency | LH/FSH deficiency (male patients)[1] | Deficiencies for one or more axes[2] |
|---|---|---|---|---|---|
| Postoperative | 40 | 3 | 5 | 2/24 | 6/40 (15%) |
| 5 years | 32 | 5 | 10 | 9/14 | 12/32 (37%) |
| 10 years | 22 | 10 | 9 | 8/12 | 11/22 (50%) |
| 15 years | 16 | 9 | 8 | 8/9 | 12/16 (75%) |

[1] LH/FSH axis only described for male patients. [2] No. of patients (%) deficient for one or more pituitary hormones.

The number of patients using substitution therapy at 5, 10 and 15 years's follow-up is detailed in Table 2, showing an increasing number of hormone deficiencies with time after radiotherapy.

## DISCUSSION

This study was undertaken to assess the efficacy of radiotherapy in reducing serum GH concentrations to below 5 mU/l, one of the currently accepted strict goals to achieve in the treatment of acromegaly (22 – 24) as few reports have addressed the results of radiotherapy in acromegaly using this criterion. Thalassinos et al. (18) reported that only 20% of their patients achieved this safe level after a mean follow-up of 7.6 years. Littley et al. (25) reported that 26% of 70 patients reached a GH level <5 mU/l and estimated a remission rate of 49% at 10 years follow-up. In line with the present study, more promising results were reported by Porretti et al. (26) who observed a GH of <5 mU/l in 60% (n = 70) of postoperatively irradiated patients. We found a serum GH concentration <5 mU/l in 75% of patients 5 and 10 years after radiotherapy and in 87% of patients after a follow-up of 15 years.

Most studies reporting results of radiotherapy have used less strict criteria of serum GH concentration <10 mU/l or even <20 mU/l. In these studies a GH <10 mU/l is reached in 25% to 83% of patients after 5 years and in 29 – 75% of patients 10 years after radiotherapy (27 – 31). Recently, IGF-I concentration was also introduced as a criterion for remission in acromegaly following radiotherapy. Reported remission percentages according to this parameter vary between 0 and 51% in follow-up (5,12,18,26,32 – 34). In the present long-term follow-up study normal serum IGF-I concentrations were present in 73% of patients, which is more favourable than reported by others.

Most studies included both primarily irradiated patients and patients in whom radiotherapy was applied as treatment for persistent disease after surgery. We included only patients who received radiotherapy when transsphenoidal surgery did not succeed in reducing GH levels to below 5 mU/l. In our institution, transsphenoidal surgery as performed by one specialist neurosurgeon, is successful in reducing GH levels to below 5 mU/l in 60% of all patients (6).

This remission rate is in the upper range of other reports addressing results of transsphenoidal surgery (7 – 13, 15). In patients with persistent disease postoperatively, serum GH levels were, however, significantly reduced by surgery resulting in a minority of patients with serum GH concentration >25 mU/l. The low serum GH levels before radiotherapy will probably have had a favourable impact on the remission percentage found in our population, as was also found by Littley et al. (25) comparing results in patients with GH <30 mU/l and >30 mU/l. In our patients we were unable to demonstrate significant differences in respect to preradiotherapy GH levels and outcome, probably because all patients studied had relatively low preradiotherapy GH levels. Theoretically, the early postoperative treatment results could have been positively or negatively affected by oedema at the site of surgery, stress or perioperative medication as was suggested in a recent consensus statement (35). However, our data on recently operated acromegalics obtained 9 – 10 days after surgery show besides normalized GTT and IGF-I levels in the cured patients, also normalized parameters of GH secretion including 24 h basal, pulsatile and total GH production and number of secretory events as analysed by deconvolution analysis (36). In addition early postoperative regularity of GH secretion, as measured by approximate entropy, is restored in many patients even shortly after surgery (37). We therefore believe that generally outcome of surgery can be established in this time period, at least in our hands. Nowadays, decisions for radiotherapy are not based on a single assessment anymore, taking into account the high incidence of hypopituitarism and other available treatment options.

Radiotherapy is not a primary treatment option and is currently reserved for patients in whom surgery is unsuccessful, for those with an insufficient response to medical therapy and for patients with contraindications for medication and/or surgery (38,39). In acromegaly, reports on radiotherapy should thus focus on reporting postoperative radiotherapy results, with fairly low starting serum GH levels.

Although there is still controversy about the best way to define remission in acromegaly, many favour and use a basal or random serum GH concentration below 5 mU/l (23). Measuring a single GH concentration is convenient and can be used to compare treatment results.

We used mean GH concentration of a day-profile or a mean of basal values (<5 mU/l) in the first years of follow-up in this study. In recent years however, due to logistic restrictions, yearly follow-up has been performed in the outpatient clinic by performing a GTT and/or measuring a random GH and IGF-I concentration. We found a good correlation between mean GH concentration and random GH ($r = 0.91$), although there were individual discrepancies. Other criteria, as a normal suppression of GH during oral glucose loading and normalization of IGF-I concentration, were assessed at the latest follow-up examination. When comparing remission percentages of random GH concentration <5 mU/l with either normal minimal suppressed GH concentration or normal IGF-I concentration discordant remission percentages were present in 16 and 19% of patients, respectively. Good correlation of mean and random

or basal GH was also reported by others, using a single GH value in reports of their follow-up results (8,33).

The time to 50% reduction of the preradiotherapy GH concentration of 28 months with a wide range from 3 to 105 months, as was estimated using individual regression plots, is in agreement with data from others (31), who found a 50% decrease of serum GH concentration 2 years after radiotherapy and a 75% decrease at 5 years follow-up. In our patients, the measured GH concentration at follow-up visits was already reduced to a mean of 50% of the preradiotherapy value after 1 year, a figure somewhat earlier than expected from the regression analysis.

Temporary medical GH suppressive therapy was given to a minority of our patients and was based on the presence of clinical symptoms related to GH-hypersecretion, while awaiting the decline of GH following radiotherapy.

Hypopituitarism developed in 37% of patients after 5 years, in 50% of patients 10 years after radiotherapy and in an even greater percentage of patients thereafter. These figures correspond to other reports (31). Only one report of Littley et al. (40) comparing low-dose with high-dose irradiation found a lower incidence of hypopituitarism in patients treated with low-dose radiotherapy. Other complications, such as secondary brain tumours, have been reported but are rarely observed (41). The choice for adjuvant therapy following unsuccessful surgery should be made individually, taking into account the high incidence of hypopituitarism following radiotherapy on the one hand and costs of medical therapy with the usual need for life-long treatment on the other hand. No studies comparing the efficacy of both adjuvant therapies have been performed. However, it is important to evaluate results of both medical treatment and radiotherapy with respect to the currently used strict criterion of a GH concentration below 5 mU/l.

We conclude that although we believe that radiotherapy should be used only after unsuccessful surgery and/or treatment with somatostatin-analogues, in acromegaly, this intervention is effective in reducing GH concentration to <5 mU/l in 75% of patients in the long-term after transsphenoidal surgery.



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