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

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# Ten-year follow-up results of transsphenoidal microsurgery in acromegaly

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## ABSTRACT

Fifty-nine acromegalic patients, transsphenoidally operated by a single neurosurgeon (H.v.D.) were followed for at least 10 yr to assess the late outcome of surgery. Mean follow-up was 16 ± 0.4 yr (range, 10–22). Criteria for remission were a serum GH concentration below 2.5 μg/L, a normal glucose-suppressed GH (oral glucose tolerance test), and a normal serum insulin-like growth factor I (IGF-I) concentration. Mean serum GH concentration decreased from 59 ± 8.7 μg/L to 5.6 ± 1.4 μg/L after surgery. Early postoperative remission rates were 61% (GH, <2.5 μg/L), 67% (suppressed GH), and 60% (both GH <2.5 μg/L and suppressed GH). Early postoperative remission was significantly related to preoperative serum GH concentration (P = 0.023), but not to tumor size. Of 36 patients with postoperative remission (GH, <2.5 μg/L), 9 patients received (prophylactic) radiotherapy for persistent paradoxical reaction to TRH or probable invasive tumor growth. All nine patients are in remission at the end of follow-up. Of the other 27 patients with postoperative remission, 5 (19%) developed recurrence, becoming evident within 5 yr in 4 patients and after 10 yr in 1 patient. Of these 27 patients, surgical remission rates at the end of follow-up are 78% (random GH, <2.5 μg/L), 73% (normal glucose-suppressed GH), 74% (normal IGF-I), and 65% (normal IGF-I and GH suppression). Of the patients with postoperative persistent disease, 18 patients were irradiated and 5 patients were followed without further treatment. Two of five nontreated patients had spontaneous normalization of GH concentration at the 6 months visit and remained in remission by surgery only. The long-term efficacy of multimodality treatment was evaluated after exclusion of the prophylactically irradiated patients. At the end of follow-up, 48% of patients had not required adjuvant therapy and the rest received radiotherapy (34%), octreotide (10%), or both (8%). Remission rates of multimodality therapy were 96% (serum GH, <2.5 μg/L) and 94% (normal serum IGF-I concentration). Remission rates of transsphenoidal surgery alone were 46% (serum GH, <2.5 μg/L), 44% (normal IGF-I concentration), 41% (suppressed serum GH), and 37% (normal serum IGF-I and suppressed GH). In this first report on separate 10 or more years results of transsphenoidal surgery for acromegaly, using strict criteria for remission, 19% of patients with postoperative remission developed recurrence. Nevertheless, about 40% of patients remain in remission after only surgical intervention, even after a mean follow-up of 16 yr.

## INTRODUCTION

FOR OVER 20 YEARS, transsphenoidal microsurgery has been the treatment of choice for acromegalic patients with micro- and macroadenomas, and it continues to be the preferred therapy, although advances in medical therapy are increasingly effective in decreasing and normalizing serum GH and insulin-like growth factor I (IGF-I) concentrations (1, 2). The recent finding that the increased mortality associated with active acromegaly is decreased to normal in a population of cured acromegalics (3, 4) supports the use of transsphenoidal surgery, which is able to achieve immediate normalization of GH concentration in 42–67% of all patients, when using the criterion of a serum GH concentration below 5 mU/L (4 – 8). Transsphenoidal surgery removes the tumor mass, thereby eliminating local mass effects, and has a low incidence of complications, including the development of hypopituitarism. Outcome of surgery, logically largely dependent on the criteria used in defining cure, is inversely correlated to preoperative serum GH concentration (5, 9), tumor size (4, 5, 8), and tumor stage (10) and is positively affected by the experience of the neurosurgeon (11, 12).

After unsuccessful surgery, adjuvant pituitary irradiation, and/or medical GH-suppressive treatment with depot preparations of long-acting somatostatin analogs additionally achieves clinical control in most patients. Secondary transsphenoidal surgery has a low success rate (13). Longer-term follow-up studies of transsphenoidal surgery clearly show that recurrences are seen in about 2–5% of patients within 5 yr (4, 5, 8) and provide a fairly good image of 5-yr results by now. Summarizing only studies using the generally accepted strict criteria for cure of a GH concentration below 2.5 μg/L, a suppressed GH concentration during glucose-suppressed GH [oral glucose tolerance test (GTT)] below 1 μg/L, and/or a normal IGF-I concentration, long-term surgical remission rates range from 42–62% (4, 6, 8, 14, 15), and multimodality remission rates vary between 52% and 83% (4, 8, 14, 16). The studies mentioned above included patients with even up to 20 yr of follow-up, but no study has been reported in which all patients were followed more than 10 yr postoperatively. We retrospectively analyzed data of all acromegalic patients who were operated before 1988 and were followed for at least 10 yr to investigate whether the effectiveness of surgery is maintained in the long-term in initially cured patients and whether multimodality therapy is able to achieve and maintain normalization in the noncured or in those with recurrence of disease.

## PATIENTS AND METHODS

### Patients

Seventy-five patients underwent primary transsphenoidal microsurgery for acromegaly between 1977 and 1988. Diagnosis of acromegaly was based on clinical symptoms, an elevated GH day-profile, and insufficient GH suppression during the GTT. Sixteen patients with less

than 10 yr of follow-up data were excluded from the study: nine patients died, four were lost to follow-up, and three patients had more than 10 yr of follow-up but failed to attend yearly follow-up visits. At the final follow-up visit (mean, 7.2 ± 1 yr after surgery), 88% of the excluded patients had a normal mean serum GH and 11 patients (70%) had normalized GH suppression and were considered in remission, 4 after radiotherapy and 7 without. The remaining 59 patients were studied: 34 males and 25 females with at least 10 yr of follow-up results. The mean age at surgery was 44.2 ± 1.4 yr (range, 21–67).

### Treatment

All patients underwent transsphenoidal microsurgery performed by a single neurosurgeon (H.v.D.) as first line of therapy. Adjuvant radiotherapy (40 Gy) was given for elevated GH concentration, and, before 1985, it was also administered prophylactically to nine patients. Medical therapy, in the form of bromocriptine or octreotide was given instead of radiotherapy (on the patients' or doctors' preferences) or in combination with radiotherapy awaiting the effects of radiotherapy. Choice of adjuvant therapy for recurrence was made individually.

### Hormonal evaluation

The preoperative, postoperative, and yearly assessments during a short hospital admission consisted of a GH day-profile (0800, 1130, 1600, and 2300 h), a 75-g oral GTT (serum GH and glucose measured at 0, 30, 60, 90, and 120 min), a 200-µg iv TRH test, and a serum IGF-I concentration from 1986 onward (17). Other pituitary hormone functions were evaluated by stimulation tests and measurements of serum levels of $T_4$, cortisol or testosterone, and estradiol levels. In recent years, patients were evaluated in the outpatients' clinic and a GTT, a random/fasting serum GH concentration, and IGF-I determination were measured yearly, followed by more extensive testing when a possible recurrence of disease activity or pituitary failure was suspected.



### Tumor classification

Tumor classification was determined at surgical exploration by the neurosurgeon according to Hardy et al. (18). For this study, the classification was simplified to microadenoma ($pI^{0}$), noninvasive macroadenoma ($pII^{0,\ A,\ B,\ C}$), and invasive macroadenomas (with suprasellar or parasellar invasive growth; i.e. $pII^{D,E}$, $pIII^{0\text{-}E}$, and $pIV^{0\text{-}E}$).

### Assays and normal values

GH was measured by RIA up to 1993 and thereafter by immunofluorometric assay (IFMA). The RIA assay (Biolab/Serono, Coinsins Switzerland) was calibrated against WHO-IRP 66/21, with an interassay coefficient below 5% and a detection limit of 0.5 mU/L. The IFMA assay (Wallac,Turku Finland), specific for the 22-kDA GH protein, was calibrated against WHO-IRP 80–505, had an intra-assay coefficient of 1.6–8.4% between 0.25 and 40 mU/L, a detection

limit of 0.03 mU/L, and used human biosynthetic GH (Pharmacia-Upjohn, Uppsala, Sweden) as a standard. GH concentrations originally expressed in mU/L, were converted into µg/L using the division factor 2 for the samples analyzed by RIA and a factor 2.6 for the samples analyzed by IFMA. Normal mean values for GH day-profile, fasting, or random GH measurements, as determined in healthy controls, were less than 5 mU/L for both assays, equal to less than 2.5 µg/L (RIA, before 1993) and 1.9 µg/L (IFMA, from 1993 onward) (6, 19, 20, 21). When a GH day-profile was not available, we used the mean of the basal values from the different dynamic tests usually obtained within a week. In recent years, we used a single GH measurement (random or fasting) for the GH concentration in most cases. Suppressed normal values during the GTT were less than 1.25 µg/L (RIA, before 1993) and less than 0.38 µg/L (IFMA, from 1993 onward (20, 21). A doubling of serum GH during TRH test was considered paradoxical.

The IGF-I concentration determination was performed by RIA (INCSTAR Corp., Stillwater, MN), with an interassay variation of less than 11% and a detection limit of 1.5 nmol/L. Normal values for IGF-I were calculated using in-house data obtained from 137 healthy controls in the same age range as our patients expressed as SD score, as used before (20 – 25). A SD score of less than +2 SD was considered normal in this study. Other hormones were measured by commercially available RIA or enzyme-linked immunosorbent assay kits.

### Statistics

Data analysis was performed using SSPS statistical package (8.0 for Windows; SPSS, Inc., Chicago, IL), JMP statistics (SAS Institute, Inc., Cary, NC), and Sigma Plot for Windows 4.0 (SPSS Inc., Chicago, IL). We used Student's t tests for paired and unpaired data, $\chi^2$ tests, ANOVA, and logistic regression analysis. A P value less than 0.05 was considered significant. Descriptive data were expressed in mean ± SEM, unless otherwise stated.

## RESULTS

### Preoperative results

The mean preoperative GH concentration was 59 ± 8.7 µg/L (3–300 µg/L). The mean GH of a day-profile (60 ± 9.6 µg/L), and the mean of the basal value of tests (49 ± 8.6 µg/L) in 53 patients with both measured preoperatively were highly correlated ($r = 0.894$, $P < 0.001$) (Fig. 1A). Also, a single fasting GH concentration and mean GH concentration (day-profile) correlated significantly ($r = 0.841$, $P < 0.001$) (Fig. 1C). The mean minimal GH concentration during the GTT was 35 ± 7.6 µg/L (range, 1–325).

### Early postoperative results

Postoperatively, the mean serum GH concentration (day-profile) decreased to 5.6 ± 1.4 µg/L (range, 0.25–62) and 36 patients (61%) achieved a normal mean GH concentration. Correla-

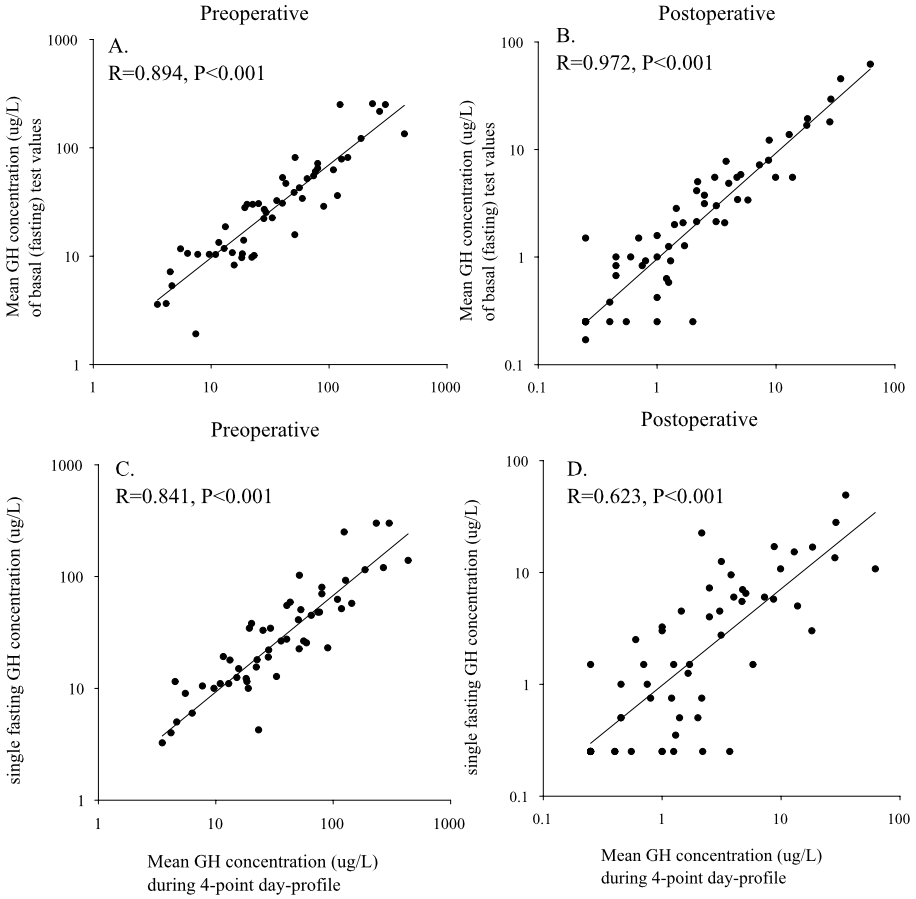


**Figure 1.** Scatterplot showing the correlation between mean serum GH concentration from a four-point day-profile and the mean of fasting GH concentrations (A and B) and the mean GH concentration and a single fasting GH concentration (C and D). A and C, Preoperative situation. B and D, Postoperative situation.



tion between mean GH (day-profile) and mean GH (basal of tests) was high ($r = 0.972$, $P < 0.001$) (Fig. 1B). The correlation of a single fasting sample with the postoperative mean GH day-profile is plotted in Fig. 1D. When a mean GH of a day-profile below 2.5 µg/L was used to exclude active disease, a random GH sample (both preoperatively and postoperatively) had a sensitivity of 79% and a specificity of 95%. Positive predictive value of a random serum GH concentration was 88%, and the negative predictive value was 91%.

A postoperative GTT was performed in 58 patients (1 patient had overt diabetes mellitus). The mean suppressed GH concentration during the GTT was 2.6 ± 0.6 µg/L (range, 0.25–21.0), and normal GH suppression was achieved in 39 patients (67%). Normalization of both mean serum GH and glucose-suppressed GH concentrations occurred in 35 patients (60%), and 19 patients (33%) had both elevated serum GH and suppressed GH concentrations. The patient with diabetes mellitus had normal mean serum GH concentrations and was considered in

**Table 1.** Direct postoperative results in relation to tumor class.

| Tumor class | No of patients | Normal GH concentration | Normal suppressed GH concentration |
|---|---|---|---|
| Microadenoma | 9 | 6/9 (67%) | 6/8 (75%) [1] |
| Macroadenoma | 42 | 24/42 (57%) | 27/42 (64%) |
| Invasive adenoma | 8 | 6/8 (75%) | 6/8 (75%) |

[1] one patient not tested because of diabetes mellitus.

**Table 2.** Pre- and postoperative characteristics of 59 acromegalic patients of four treatment subgroups (A-D).

| | Group A (n=27) | Group B (n=9) | Group C (n=18) | Group D (n=5) |
|---|---|---|---|---|
| Preoperative mean GH (µg/L) | 36.8 ± 9.2 | 78.7 ± 23.1 | 82.2 ± 19.4 | 54.6 ± 33.6 |
| Preoperative glucose-suppressed GH (µg/L) | 20.5 ± 5.7 | 54.2 ± 24.2 | 50.2 ± 21.7 | 36.5 ± 17.0 |
| Postoperative mean GH (µg/L) | 0.89 ± 0.1 | 1.1 ± 0.2 | 14.9 ± 3.6 | 5.5 ± 1.1 |
| Postoperative glucose-suppressed GH (µg/L) | 0.41 ± 0.1 | 0.5 ± 0.1 | 6.4 ± 1.4 | 4.6 ± 2.7 |

Groupcharacteristics: group A: cured patients, 5 microadenomas, 19 macroadenomas and 3 invasive macroadenomas; group B: prophylactically irradiated patients, 1 microadenoma, 5 macroadenomas and 3 invasive adenomas; group C: non-cured irradiated patients, 1 microadenoma, 15 macroadenomas, 2 invasive adenomas; group D: noncured and nonirradiated patients, 2 microadenoma and 3 macroadenoma.

remission. Four patients had normalized suppression of GH concentration during GTT early postoperative, but their mean serum GH concentration remained (slightly) elevated, being 3.1, 3.2, 3.7, and 5.8 µg/L, respectively, and they were considered not to be in remission. Remission rates according to tumor class are shown in Table 1. The incidence of (partial) hypopituitarism following transsphenoidal surgery was 5%.

Using logistic regression analysis, there was no significant relationship between early postoperative outcome and tumor classification, year of surgery, sex, or age at operation. There was, however, a significant relationship between early postoperative outcome and preoperative mean GH concentration ($P = 0.023$), with more patients in remission with lower preoperative GH concentration.

Patients were divided into four groups based on the early postoperative evaluation and consequent treatment decisions, which are detailed in the flow diagram (Fig. 2). The 36 patients in remission, according to both normal mean GH and suppressed GH, were divided between groups A and B: 27 patients were not adjuvantly treated (group A), and 9 patients received prophylactical radiotherapy (group B) for persistent paradoxical reaction to TRH (n = 7) and/or invasive tumor growth or suspected incomplete tumor removal (n = 4). Patients with persistent disease were divided between groups C and D: 18 patients underwent pituitary irradiation for persistent disease postoperatively (group C), and 5 other patients not in remission early postoperatively were followed without further treatment (group D). Group characteristics are summarized in Table 2.

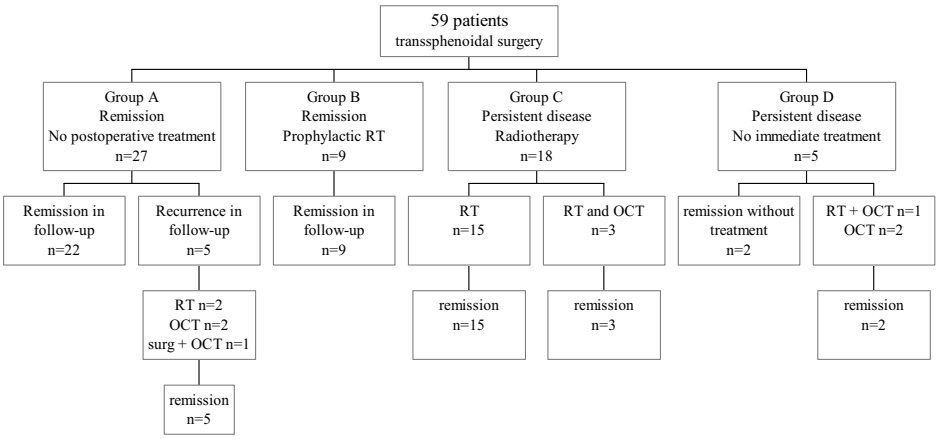


**Figure 2.** Flow diagram of postoperative adjuvant therapy and treatment results in 59 patients who underwent transsphenoidal surgery for acromegaly. RT, Radiotherapy; OCT, octreotide.

### Follow-up results of initially cured patients (group A)

Of the 27 patients early postoperatively in remission and not adjuvantly treated, 5 patients (18.5%) were treated for recurrent acromegaly in the course of follow-up. Two patients developed recurrence within 6 months and after 3 yr, respectively, and received radiotherapy. Two other patients developed recurrence with mild elevations of GH concentration and insufficient suppression of GH after glucose load after 3 yr and 4 yr, respectively, without clinical activity, and were recently started on a long-acting formulation of octreotide (Sandostatine LAR) (10 and 12 yr postoperatively). Another patient underwent a second transsphenoidal operation 17 yr after primary surgery for recurrent disease, becoming apparent 10 yr postoperatively, and was treated with octreotide after unsuccessful secondary surgery. Figure 3 details the development of the five recurrences regarding serum mean GH concentration (Fig. 3A) and GH suppression during the GTT (Fig. 3B).

At 5 yr postoperatively, 2 patients were treated for recurrence, and of the 25 remaining patients, 21 had a normal mean serum GH concentration (84%) and 20 of 24 patients had normal suppression of GH during the GTT (not performed in 1 patient). Both tests were normal in 18 patients, and both tests were elevated in 2 patients. Two patients had a normal mean GH but insufficient suppression during the GTT, and two other patients had only normal GH suppression. Eleven of 13 patients with available IGF-I had a normal IGF-I SD score.

Ten years postoperatively, 2 patients were treated for recurrence, and of the other 25 patients, 21 (84%) had a normal serum GH, 17 of 24 (71%) had normal glucose- suppressed GH, and 20 of 24 patients (83%) had normal IGF-I concentration.

At the end of this study, a mean 16.0 ± 0.8 yr after surgery, 5 patients are treated for recurrence, and of the other patients, 21 of 22 have a normal serum GH, 19 of 21 have normal GH suppression (GTT), and 20 of 22 have normal IGF-I SD scores.

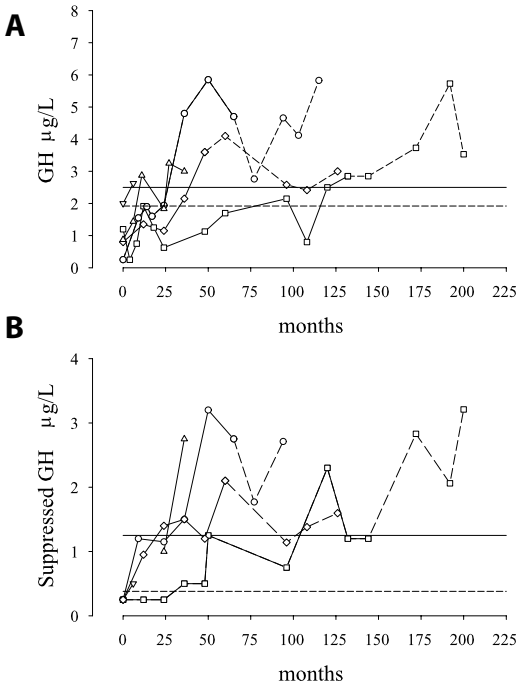


**Figure 3.** Follow-up of GH concentration (A) and suppressed GH concentration during GTT (B) in five patients who developed recurrence of disease. *Continuous line*, RIA data; *interrupted line*, IFMA data.

Remission at final follow-up in the 27 patients initially in remission (group A) was not significantly related to sex, tumor class, year of operation, or age of the patient. There was a significant relationship between the preoperative mean GH concentration (P = 0.04) and remission according to the most recent random GH concentration.

### Follow-up results of multimodality therapy

Remission rates of multimodality therapy, applied as specified in the flow diagram (Fig. 2), were 96% (serum GH, < 2.5 µg/L) and 94% (normal serum IGF-I). Figure 4 (A–D) shows the follow-up data of the mean serum GH concentration of all patients and patients of groups A, B, and C. All nine prophylactically irradiated patients remained in remission. Two patients with early postoperative persistent disease who were not treated further (group D) showed spontaneous normalization of GH concentrations and GH dynamics without additional treatment at the 6-month evaluation and remained in remission according to all parameters in the long term. The remission rates at the last visit of two criteria, a normal serum IGF-I and a normal GH suppression, were compared. Both IGF-I and GH suppression were normal in 43 of 51 patients with available data (84%). Discordant results were present in two patients (normal GH suppression and abnormal IGF-I) and six patients (insufficient GH-suppression and normal IGF-I).

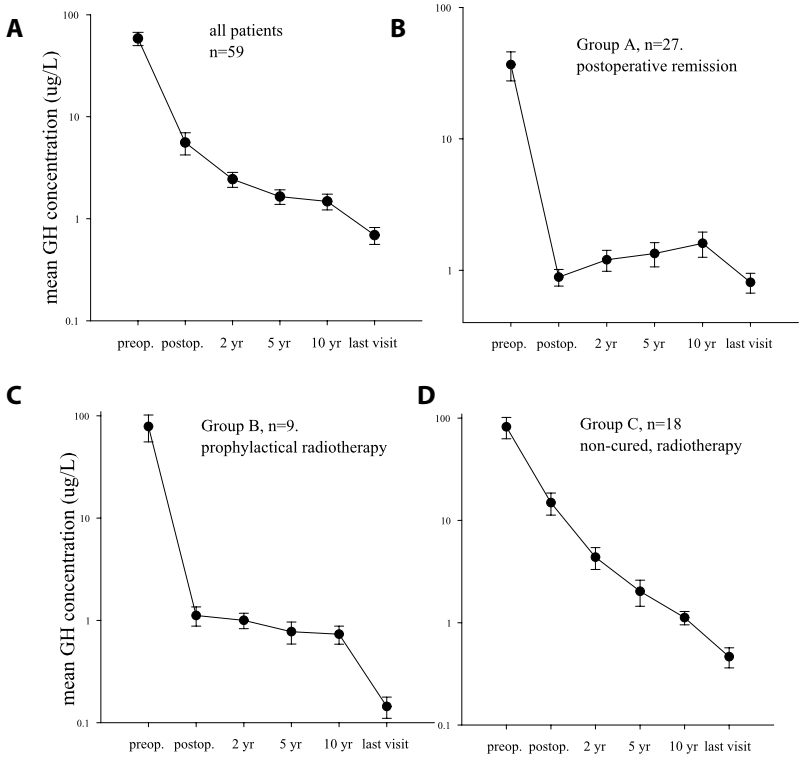


**Figure 4.** Follow-up of mean GH concentration (mean ± SEM) of all patients (A), patients initially in remission and not adjuvantly treated (B), patients with initial remission and prophylactical radiotherapy (C), and patients irradiated for persistent disease (D).



## DISCUSSION

We retrospectively analyzed the long-term outcome of transsphenoidal surgery in acromegaly by focusing on those patients with biochemical and clinical follow-up data ranging from 10–22 yr. Here, we report results of surgery as performed before 1988. Preoperative data such as age and sex distribution, tumor class, and preoperative GH concentration were comparable with other studies (5, 8, 10, 26, 27). Of all 75 patients who underwent surgery before 1988, 16 patients with a follow-up duration shorter than 10 yr because of mortality or loss to follow-up were excluded. Their mean GH concentration at the end of follow-up was not significantly different to the GH level of the 59 patients included in this study ($P = 0.595$), which makes it unlikely that the exclusion of patients followed for less than 10 yr affected the outcome of this study. The number of patients with early postoperative remission (i.e. 61% as defined by a mean serum GH concentration of <2.5 μg/L and 67% when using normalization of GH suppression during the GTT) is comparable to others (4, 8, 14, 16). Although others reported late follow-up data up to 20 yr (4), this is the first study in which all patients were followed more than 10 yr after surgery. In the present study, we have observed a considerably

lower success rate in the long-term follow-up than in the short-term follow-up. The relatively short-term successful results of others should be, therefore, cautiously interpreted.

There is still no consensus as to which criterion is best to use to define remission, some using suppressed GH concentration during the GTT (11, 15), others using mean serum GH concentration of day-profiles (5, 7, 28), and many using random or fasting GH samples or serum IGF-I concentrations (4, 8, 16, 29). The mean serum GH concentration indicating disease control has currently decreased in various studies from less than 10 μg/L to less than 2.5 μg/L.

In this study, mean GH concentrations and random GH samples correlated well, both in untreated and in treated acromegaly. Because both positive and negative predictive values of a random serum GH concentration were high (88% and 91%, respectively), we measured only random/fasting GH samples in recent years instead of the mean GH concentration of a day-profile as used in the first years postoperatively. Glucose-suppressed GH concentrations results are described separately, and they are concordant with random GH concentration in most cases, although there were some discrepancies. For instance, two patients had normal GH suppression after the GTT but elevated GH concentration, and two patients had normal GH levels but insufficient GH suppression after the GTT at the 10-yr follow-up visit.

Although in many studies biochemical cut-off levels for normalization of disease activity are arbitrarily set, all our normal values of GH concentration, glucose-suppressed GH concentration, and IGF-I concentration for all used assays are derived from normal controls measured in our laboratory. IGF-I and suppressed GH were both normal in most patients, although discordant results were present in 16% of patients at the end of follow-up. A similar discrepancy was also present in our recent data on radiotherapy results for acromegaly (25) in which both decline of IGF-I and GH was observed over time after irradiation, although there was a small percentage of discrepant data, which was also reported by others (30, 31).

Some studies have confirmed the logical idea that surgical results improve with time, and with experience of the neurosurgeon and improvement of neurosurgical techniques (4, 7, 11). Although the generally accepted criteria for remission were less strict 1 or 2 decades ago, the criteria of a mean serum GH concentration of less than 2.5 μg/L (as measured by RIA) was already used in all our patients to define postoperative remission, and adjuvant treatment decisions also were based on this criterion, as has been described before (6). Whether the early postoperative evaluation at 7–10 days after surgery provides an adequate view of surgical results can be challenged by data of the two patients of group D, who showed persistent GH hypersecretion at the first evaluation and met both all used criteria for remission at the 6-month evaluation and required no further treatment. This interesting observation is probably due to late tumor necrosis induced by surgery, which was also reported by others (14, 32).

Nine patients underwent prophylactic radiotherapy for invasive tumor growth and/or paradoxical reaction to TRH. None of these patients, formerly believed to be at high-risk for development of recurrence, developed biochemical recurrent disease at follow-up. Prophy-

lactic radiotherapy is no longer used in our institution, because the value of the TRH test in predicting recurrences is questioned and also because of the high incidence of hypopituitarism following irradiation.

Follow-up of the 27 patients, not adjuvantly treated patients in remission, revealed five recurrences (19%), and although four recurred within the first 5 postoperative years, 1 patient showed the first signs of recurrence of acromegaly as evidenced by slightly elevated GH concentration and insufficient suppression more than 10 yr postoperatively. The incidence of recurrences might have been higher had no prophylactic radiotherapy been applied. This question can, however, only be addressed when follow-up results of more recently surgically treated patients with invasive tumor growth and/or paradoxical reaction to TRH, who did not receive prophylactical radiotherapy, become available. At the most recent assessments ranging from 10–22 yr, some patients have repeatedly or incidentally abnormal serum GH or IGF-I concentrations or insufficiently suppressed serum GH concentrations. Whether the elevated concentrations of one or more parameters indicate variation within the normal range of control of treated acromegaly or are the first signs of biochemical recurrence is not known and requires even longer follow-up to become clear. In all recurrences, the minor elevation of GH concentration and inadequate GH suppression during the GTT, as shown in Fig. 3, preceded the development of clinical disease activity. In the three well-documented recurrences in this report, we observed mild biochemical disturbances several years before clinical symptoms developed. From this clinical observation, we suggest that the process of recurrence can take up to 10 yr and abnormal and normal biochemical results may be present for many years, making the diagnosis of recurrence difficult. Repeated follow-up assessments are, therefore, required to establish with certainty the diagnosis of recurrence.



The incidence of recurrence of acromegaly of 19% in patients with at least 10 yr of follow-up and a mean follow-up of 16 yr we report here is higher than the 4 of 38 recurrences within 5 yr of follow-up described by Truong et al. (33) in an abstract on separate 10 yr outcome of surgery. All other long-term follow-up studies of transsphenoidal surgery in acromegaly also included patients with a shorter duration of follow-up, making the evaluation of long-term results difficult. Swearingen et al. (4) reported a recurrence rate of 6% at 10 yr of follow-up and 10% at 15 yr of follow-up and a mean follow-up duration of 7.8 yr (1–19 yr). Freda et al. (8) found a recurrence rate of 5.4% after a mean follow-up of 5.4 yr (1 week to 15.7 yr).

In accordance with previous reports, both early postoperative outcome for all patients and latest outcome for patients of group A (remission, not further treated) were significantly related to preoperative mean GH concentration using logistic regression analysis (5, 15). Consistent with a former publication of transsphenoidal surgery in our hospital (6), we could not demonstrate a significant relationship between outcome and tumor class, which was reported by many others (5, 8, 15).

In summary, 24 of 59 patients (41%) are still in remission following only transsphenoidal surgery, without need for adjuvant therapy after a mean follow-up period of 15.9 yr (range,

10–22). Multimodality therapy, in the form of primary surgery, followed by radiotherapy and/or medical therapy, achieved normalization of serum GH concentration in 57 of 59 patients (97%) and normalization of serum IGF-I concentration in 56 of 59 patients (95%) at long-term follow-up.

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