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

Biermasz, N.R.

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## I. TREATMENT OF ACROMEGALY

Acromegaly is associated with increased morbidity and mortality. Therefore, all patients with biochemical growth hormone excess require treatment, aiming at swift and strict normalization of serum GH secretion and IGF-I concentrations (1, 2).

Transsphenoidal surgery has traditionally been the first choice treatment in most centers. It is the only treatment modality by which a normal physiological GH secretion can be restored (3). Results of surgical treatment are dependent on the experience of the neurosurgeon, and by tumor size and extension (4). Since the introduction of effective medical treatments in the form of somatostatin analogs, these are being used as preferred secondary treatment but in recent years also as first treatment option (5, 6). The introduction of effective drugs including Pegvisomant has obviated the need for conventional pituitary irradiation in most patients. New developments are present for all treatment modalities. Transsphenoidal endoscopy may improve visualization of adenomas especially those with parasellar tumor extension. Gamma knife irradiation is potentially able to reduce excess GH secretion more rapidly with a potential smaller negative effect of hypopituitarism, but long-term effects of this treatment are lacking (7, 8). GH receptor antagonists are now available for clinical practice and they are able to control GH excess in almost all patients (9). New somatostatin analogs, with high binding affinity for all or for specific SSTR subtypes, are promising drugs for the treatment of octreotide insensitive patients and phase 2 trials will start soon (10).

This thesis describes the long-term treatment results of the various therapies separately. Most patients were primarily treated by transsphenoidal surgery although in recent years an increasing number of patients started treatment with somatostatin analogs. In the adjuvant treatment setting nowadays the vast majority will receive somatostatin analogs instead of radiotherapy. The change in treatment approach in the Leiden University Medical Center is summarized in Figs. 1a and 1b, showing the applied primary and secondary treatments against the years of first treatment.

### Transsphenoidal Surgery

In ***Chapter 2*** we describe the follow-up results of transsphenoidal surgery focusing on patients with a follow-up of more than 10 years. We report an immediate postoperative remission rate of 61%. Patients with a lower preoperative GH concentration had better surgical results, but surgical outcome was not associated with tumor class or year of surgery. In surgically cured patients a recurrence rate of 19% (5/27 patients) was observed in this long-term study. After incomplete tumor removal, multimodality treatment was effective in inducing remission in almost all patients.

Our short-term surgical results are comparable with other centers (11 – 26), as summarized in Table 1 a-b. However, reports use different initial remission criteria, and vary in the duration and mode of biochemical follow-up. All these factors may contribute to differences in

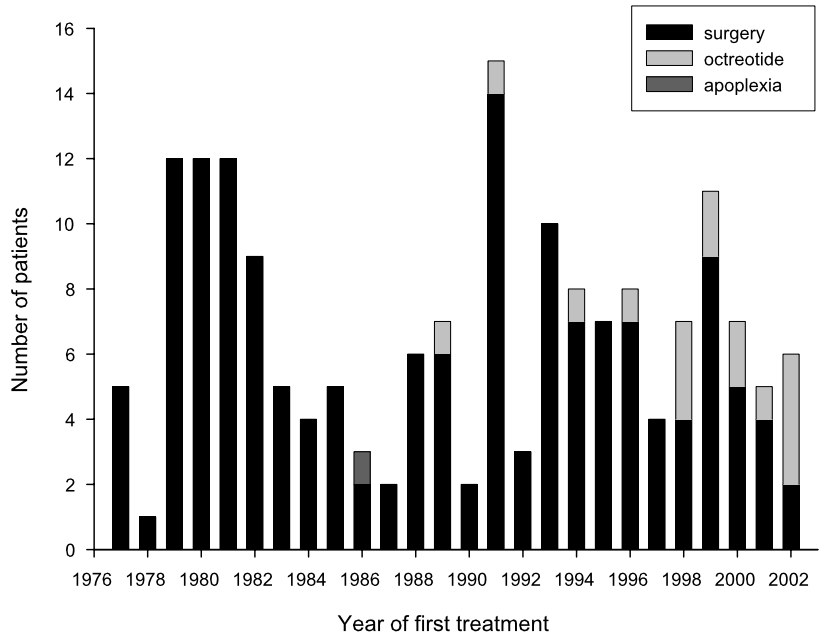


**Figure 1a.** [illegible]



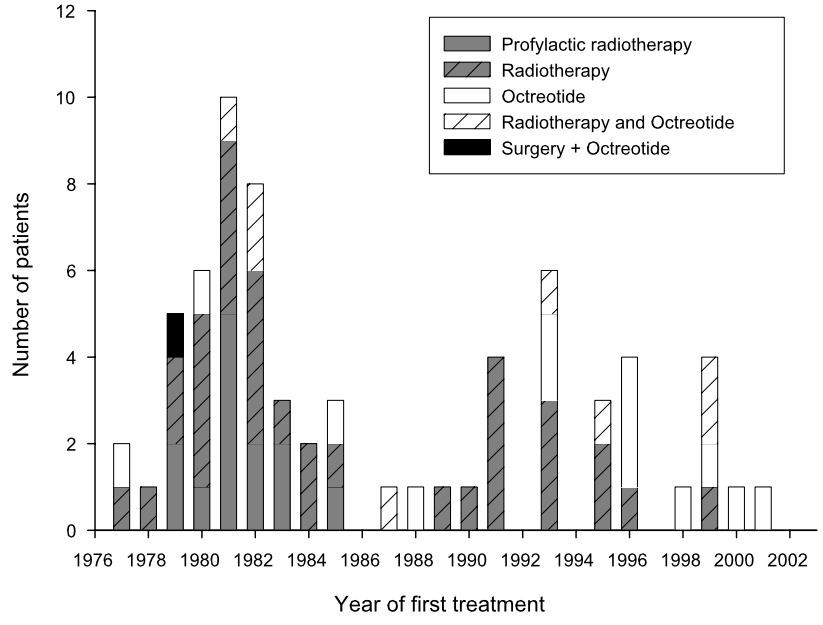


**Figure 1b.** [illegible]

initial remission and recurrence rates. Interestingly, in our center microadenomas have an unexplained tendency for a lower remission rate and macroadenomas for a higher remission rate than reported in other studies.

**Table 1A.** Results of transsphenoidal surgery in patients with acromegaly in studies in which GTT is used to define cure.

| Author (yr) | No of patients | Criteria for remission GTT | Remission rates (%) All (micro/macro) | Follow-up duration Mean (range) yr | Recurrence rate (%) | 10 yrs follow-up |
|---|---|---|---|---|---|---|
| Roelfsema (1985) | 60 | < 2.5 mU/L | 62 | 3.3 (0.5-7) | 0 | - |
| Losa (1989) | 29 | < 1 µg/L | 55 | 2.9 (0.5-11) | 0 | - |
| Osman (1994) | 79 | <2mU/L | 49 (67/27) | 7.1 | 6.5[1] | - |
| Biermasz (2000) | 59 | <1.25/0.38 µg/L | 67 (75/66)[2] | 16 (10-22) | 19[2] | 41% surgical remission<br>96% multimodality control |
| Laws (2000) | 86 | <1 µg/L | 56 | 6.8 | 1 | - |
| Kreutzer (2001) | 57 | <1 µg/L | 51.4 | 3.1 | 1 | - |
| De (2003) | 90 | <1 µg/L | 63 (79/56) | 10.9 (0.5-20) | 0 | - |
| Beauregard (2003) | 103 | <1 µg/L | 54 (82/47) | 12 | 7 | 52% surgical remission<br>80% multimodality control |
| Minniti (2003) | 51 | <1 µg/L | 55 (80/50) | 7.8 | 0 | - |
| Update Leiden Studies (IFMA)[3] | 59 | <0.38 µg/L | 56 | 4.3 (1-9) | 0 | - |

[1] no glucose-suppression < 2 mU/L in patients cured at the immediate postoperative evaluation.

[2] early postoperative evaluation GTT < 1.25 µg/L (RIA), late outome GTT < 0.38 µg/L (IFMA).

[3] Only patients with postoperative evaluation by IFMA were included.

**Table 1B.** Results of transsphenoidal surgery in patients with acromegaly in studies in which IGF-I is used to define cure.

| Author (yr) | No of patients | % with normal IGF-I |
|---|---|---|
| Arafah (1987) | 43 | 65% |
| Oyen (1988) | 25 | 36% |
| Tindall (1993) | 25 | 76% |
| Swearingen (1998) | 162 | 71% |
| Freda (1998) | 115 | 61% |
| Laws (2000) | 117 | 67% |
| Shimon (2001) | 98 | 74% |
| Kreutzer (2001) | 57 | 70% |
| Beauregard (2003) | 99 | 56% |
| Biermasz (2004) | 99 | 60% |

Direct postoperative remission rates in the more recently treated cohort of our center (between 1993 and 2002, see Table 1), were similar to those reported in ***Chapter 2,*** representing results before 1989. The high recurrence rate of 19%, has not been confirmed by other studies focusing on follow-up results of more than 10 years. Two studies with equal long-term follow-up reported recurrence rates of 6 and 10% (18, 23).

In the 10-years study, the less sensitive GH radioimmunoassay (RIA) was used in the postoperative assessment of all patients. From 1993 onwards, postoperative remission is defined by a normal glucose-suppressed GH of < 1 mU/L as measured by the more sensitive immunofluorometric assay (IFMA). No recurrences were observed in those 33 patients that were strictly cured according to this criterion, although mean duration of follow-up is only 4.3 (range 1 – 9) years. Therefore, the sensitive IFMA assay might discriminate better between patients with long-term remission and those at risk for recurrence than the RIA assay, which was used in the 10-years study. The finding of a very low incidence of recurrences in those with a postoperatively normal glucose-suppression according to the IFMA criteria has potential implications for the follow-up of patients with surgical remission. Less frequent biochemical follow-up could suffice for these patients. Nonetheless, we recommend life-long follow-up of patients cured of acromegaly by surgery because of the risk of recurrent disease.



### Radiotherapy

In ***Chapters 3 and 4,*** we report the results of postoperative radiotherapy. In our post-surgical series, the proportion of patients in remission increases with time to a total of ~75% after 15 years of follow-up irrespective of the criterion for remission used. However, the biochemical success is accompanied by an increasing incidence of hypopituitarism up to a similar rate after 15 years. For serum GH concentrations, but not for IGF-I, we were able to estimate the rate of normalization following radiotherapy.

After the report by Barkan et al. (27), suggesting that radiotherapy is ineffective in normalizing serum IGF-I levels, the question why and whether serum IGF-I is less likely to normalize than GH following radiotherapy has been addressed by several other reports, summarized in Table 2 (23, 27 – 38). The differential effects of radiotherapy on serum GH and IGF-I are unexplained and illogical, as plasma IGF-I levels are determined to a large extent by GH. After pituitary irradiation there is altered GH secretion (39, 40) with decreased regularity, high pulse frequency and increased basal secretion. However, there is no evidence that these alterations lead to increased GH sensitivity of the liver. In agreement with other recent reports, our conclusion is that serum IGF-I levels normalize in the long-term follow-up after radiotherapy. Thus, radiotherapy is an effective therapy for acromegaly. The discrepant results between studies may be caused by patient selection bias, different baseline serum GH concentrations prior to treatment, different assay characteristics and/or different radiotherapeutic techniques.

**Table 2.** Outcome of Radiotherapy

| Author (yr) | No of patients | Treatment | Technique | Follow-up Years | Normal IGF-I (%) | Normal GTT(mU/L) | Normal GH (mU/L) | Hypopi-tuitarism | Comment |
|---|---|---|---|---|---|---|---|---|---|
| Ciccarelli (1993) | 19 | 42 prim RT<br>4 postop RT | | Range 1-6 | 68% | | | | |
| Barkan (1997) | 38 | 33 postop RT<br>2 prim RT<br>3 proton beam | Median 46 Gy | 6.8 ±0.8 | 5% | | | | Different IGF-I assays<br>Follow-up < 5 yr<br>Different radiation techniques |
| Van der Lelij (1997) | 37 | Postop RT | | 7 | 0% | | | | Comment |
| Powell (2000) | 48 | 47 postop RT (6 stereotact/ gamma knife, 1 PB)<br>1 prim RT | 47.4 Gy 28/48 | 5.2 | 44% | | | | RT given at different centers<br>>6yr post RT 69% nl IGF-I<br>26 prert IGF 268% ULN, GH unknown |
| Porretti (1999) | 70 | Postop RT | | 10 ± 7 | 51% | | | | 110.8 ± 48 nmol/L |
| Swearingen (1998) | 45 | Postop RT | | 6.7 | 42% | | | | |
| Biermasz (2000) | 37 | Postop RT | 40 Gy | 5 yr<br>10 yr<br>15 yr<br>mean 11.5 | 60%<br>74%<br>84%<br>75% | 65%<br>69%<br>71%<br>71% | | 29%<br>54%<br>56%<br>51% | |
| Gutt (2001) | 41 | 35 postop RT<br>6 prim RT | Median 50 Gy | Median 12.8 (3.7-43.4) | 34% | | 34% | | PreRT GH 31 µg/L (7-210) |
| Barrande (2000) | 128 | 104 postop RT<br>24 prim RT | Median 52Gy | 2<br>5<br>10<br>15<br>15.0 ± 11.3 | <br><br><br><br>79% | | 7%<br>35%<br>53%<br>66% | <br><br><br><br>80% | PreRT GH 36.5 ± 70 µg/L |
| Cozzi (2001) | 49 | 34 postop<br>15 prim RT | Mean 45 gy | 10 yr | 16% | 12% | | | Many patients excluded, preRT GH 22-22 µg/L |
| Epaminonda (2001) | 67 | Postop RT | 40-75 Gy | Mean 12<br>Mean 8 | 55% | <br>61% | | | PreRT GH 20.2 ± 27<br>IGF-I 110.8 ± 48 nmol/L |
| Thalassinos (1998) | 46 | 42 prim RT<br>4 postop RT | 45-50 Gy | 7.6 | 4/14 (29%) | 20.8% | | 50% | PreRT GH 30.9 µg/L |
| Jenkins (1995) | 372 (13 centers) | | | 10yr | 56% | 59% | | | |

**Table 3.** Discordance between GH and IGF-I assessment of remission in acromegaly

| GH < 2-2.5 µg/L and raised IGF-I (% of patients) | | Normal IGF-I, but GH above remission range (% of patients) | |
|---|---|---|---|
| Jenkins (1995) | 29% | Freda (1998) | 10% |
| Freda (1998) | 18% | Biermasz (2000) | 13% |
| Abosch (1998) | 13% | Kaltsas (2001) | 18% |
| Ahmed (1999) | 3% | Holdaway (2003) | 19% |
| Biermasz (2000) | 10% | | |
| Kaltsas (2001) | 13% | | |
| Holdaway (2003) | 16% | | |

It is of note that discrepancies between GH and IGF-I criteria are not unique for radiotherapy, but are also observed within many clinical studies following surgery and during medical treatment (see Table 3) (4, 14, 38, 41 – 44). The clinical management of patients with discordant results remains difficult. However, it is likely that patients with normal (glucose-suppressed) serum GH concentrations, but repeatedly elevated serum IGF-I concentrations, have excessive GH production, and therefore should receive adjuvant treatment.

A third of irradiated patients had diminished GH reserve as measured by insulin tolerance testing, and a sixth of them had also low serum IGF-I concentrations for age in the long-term after radiotherapy. Further research is therefore required to assess as to whether the low serum IGF-I levels and/or the disturbed GH reserve after insulin tolerance testing following radiotherapy, signifies a clinically relevant GH deficiency requiring treatment with recombinant human GH.



In The Netherlands and many other countries, in which somatostatin analog and GH receptor antagonist treatment is available for adjuvant treatment in acromegaly, radiotherapy is not routinely used for residual disease anymore. At present, most if not all patients that were studied in ***Chapter 3 and 4*** would have been treated with somatostatin analogs for residual disease after surgery. If necessary combination treatment with Pegvisomant and somatostatin analogs should be offered in patients with elevated IGF-I concentrations despite somatostatin analog treatment. However, the place of radiotherapy in the treatment algorithms of acromegaly might require re-evaluation in the future and will be dependent on cost-efficacy studies, health care strategies, results of radiosurgery and longer-term efficacy and safety data of Pegvisomant.

### Pre-surgical somatostatin analog treatment

Preoperative somatostatin analog treatment did not improve our surgical results as discussed in ***Chapter 5*****.** Up to now no new randomized controlled trials of (depot preparations) of somatostatin analogs addressing this issue have been performed. In a recent review of the performed uncontrolled studies on preoperative somatostatin analog treatment, it was concluded that there is no significant effect on surgical outcome. There may be a slight improved

remission rate in pre-treated macroadenomas (45). Recent studies on primary treatment with depot preparations of octreotide LAR suggest tumor shrinkage of 30 – 50% in the majority of patients (80 – 100%) after 6 to 12 months of treatment (6;46 – 48). Further investigation is required to assess whether this octreotide-induced tumor shrinkage will improve the surgical outcome in macroadenomas expanding into the cavernous sinus. However, the design of a potential randomized trial assessing this topic in this rare disease will be very complicated.

Perioperative morbidity was not a study parameter in our study, although there was a very low complication rate and no mortality after transsphenoidal surgery. Nevertheless, as many cardiovascular risk factors respond well to somatostatin analog treatment, it may be advantageous to reduce risks before anesthesia and (transsphenoidal) surgery using somatostatin analogs. Pretreatment may thus be favorable for these patients with increased surgical risk and co-morbidity. One should realize that in patients pretreated with depot preparations, the postoperative evaluation should be postponed to at least 3 months postoperatively (see also ***Chapter 6***), as octreotide levels remain detectable for at least 8 weeks, and probably much longer, following an intramuscular injection.

### Somatostatin analog treatment

In ***Chapter 6***, we performed a long-term (44 weeks) study to assess whether the interval of a somatostatin analog depot preparation (octreotide- LAR) in well-controlled patients can be enlarged. The hypothesis was derived from the characteristic pharmacokinetic release pattern of the depot preparation leading to therapeutic drug levels for at least 42 days after the first injection. In addition short-term withdrawal studies suggested that the injection interval could be enlarged (49, 50). In our study, most patients, well-controlled on a 4- weekly regimen, were also well-controlled at a 6- weekly scheme. However, in one third of patients serum IGF-I levels started to rise at the end of the study (after 44 weeks) without accompanying increase in mean serum GH levels. This increase may probably reflect a less effectively suppressed GH-IGF-I system. We therefore suggested that patients should remain under frequent control (e.g. twice a year) by measurement of serum IGF-I and GH profiles, when treated with a 6 weekly schedule.

In our study, the random or fasting GH samples correlated well with the morning profile of eight GH samples. Therefore, also random GH values in combination with serum IGF-I levels are probably sufficient to justify dose (interval) change decisions.

Long-term dose extension to 6 weekly injections was thus possible in ~60% of patients that were well controlled on a 4 weekly scheme. Thus, an individual cost reduction of 30% may be achievable in 60% of well- controlled patients (~70% of all patients). The estimated cost saving of this treatment strategy for acromegalic patients in the Netherlands may be in the range 15% – 25% of the yearly cost for octreotide treatment in acromegaly.

A recent study by Turner *et al.* confirmed the advantages of controlled dose-extension of octreotide LAR leading to a cost reduction of even ~50% in their study (51). They extended

doses to 12 weeks and 50% of included patients were treated by 6 weekly, 27% by 8 weekly and 14% by 12 weekly injections. They did not report an increase in IGF-I concentrations in some patients at the end of the study. However, the follow-up duration once an individual dose scheme was established is not described. Our dose extension results were supported by stable octreotide concentrations during long-term treatment on a 6 weekly scheme, while this was not a study parameter in the study by Turner et al.

A dose-dependent effect of octreotide concentrations on GH and IGF-I suppression is observed, although there appears to be an individual maximal suppression, and thereafter, higher octreotide concentrations do not further suppress GH concentrations. This is probably due to somatostatin subtype pattern of the adenoma and reflects octreotide sensitivity.

For dose increments, a higher monthly dose is probably more convenient than dose intensification. In well-controlled patients, we favor dose interval increase to 6 weeks or even longer, because of the costs and the advantage of less frequent injections.

It is important to note that no mortality studies have been performed in patients treated by somatostatin analogs and it is not sure whether a "safe" GH level of < 5 mU/L is a good criterion to aim for during medical treatment. A serum GH of less than 5 mU/L could still indicate significant GH hypersecretion during medical therapy, especially when accompanied by elevated serum IGF-I concentrations. Further investigation is required to assess which GH levels should be aimed for during octreotide LAR treatment, but a lower level than 5 mU/L (for example 2.5 mU/L) may reflect better control of GH excess in patients well-sensitive to octreotide eligible for dose interval extension of octreotide LAR.



### Current pharmacotherapy for acromegaly

In ***Chapter 15*** we reviewed the results of pharmacotherapy in patients with acromegaly. Of both somatostatin analogs, octreotide LAR has increased efficacy when compared to lanreotide SR (52), while insufficient data are available to compare octreotide LAR and lanreotide Autogel (53 – 55). Many pharmacotherapeutic trials included patients with a known good response to octreotide. The recent meta-analysis of Freda et al. (52) recognizes pre-selection to be a bias in trials, although efficacy of octreotide LAR is still present after correction for pre-selection.

Pegvisomant treatment is very effective in reducing IGF-I concentrations, and combination treatment of weekly Pegvisomant with somatostatin analog treatment may reduce some costs, while equally effective (9, 56, 57). In our opinion, transsphenoidal surgery and somatostatin analog treatment can both be considered as primary treatment for acromegaly. The choice can be individualized depending on several factors, such as age, experience of the center, presence of contra-indications or co-morbidity, size and extension of the tumor and octreotide sensitivity. The extremely high costs of life-long medical treatment for acromegaly, especially for Pegvisomant, have to be considered against the other treatment options.

### Biochemical criteria for cure

Criteria for cure have been tightened throughout the years. At present, generally accepted criteria are a normal serum IGF-I concentration and a normal glucose-suppressed serum GH concentrations (<0.38 – 1 µg/L) for postoperative follow-up and a normal IGF-I and a mean serum GH < 5 mU/L during medical treatment.

We used strict biochemical criteria throughout the whole follow-up span from 1977 –2003, in which only the GH assay was changed from RIA to the more sensitive IFMA in 1993 and serum IGF- I measurements were introduced in 1986. Normal glucose-suppression of GH levels was determined in controls for both assays in our institution. Moreover, we collected our own normal data for IGF-I. These two parameters were used to assess physiological restoration of the GH-IGF-I axis. The third criterion was a random or mean (of 4-point day-curve or of 4 fasting samples on consecutive days) GH concentration with an arbitrary cut-off level of 5 mU/L. Although this criterion does not reflect physiological restoration of the GH – IGF-I axis, this parameter is most frequently related to a normalized mortality risk (58). Furthermore, a single GH measurement is convenient for follow-up assessment and can be reliably measured in an assay with low variation coefficients.

In untreated, in surgically treated, in radiotherapy treated and in somatostatin analog treated patients there was a high correlation between random and mean serum GH concentrations and glucose-suppressed GH concentrations (***Chapters 2 – 6***). Nevertheless, IGF-I and (glucose-suppressed) serum GH concentrations were discrepant in a significant proportion (20 to 30%) of patients. These findings are supported by others, see Table 3, (2, 59).

To evaluate various criteria for cure, we analyzed the early postoperative assessments since the IFMA has been used. Postoperative criteria for cure, (random) serum GH and serum IGF-I measurements (in nmol/L and SD score for age) were compared using ROC curve analysis using the glucose-suppressed serum GH concentration below 1 mU/L as the gold standard in 59 patients (Fig. 2). GH instead of IGF-I measurements better approximated the GTT with respective areas under the curve of 0.96 ± 0.02 (95% CI 0.92 – 1.00) and 0.77 ± 0.06 (0.65 – 0.89). When a cut-off GH concentration of < 2.5 mU/L was used, a sensitivity of 100% and a specificity of 76% are achieved to detect active disease, while with a cut off GH value of < 6.8 mU/L, a sensitivity of 54% and a specificity of 100% are achieved. This analysis supports the use of a single serum GH measurement for the evaluation of remission in treated acromegaly.

Intra-individual variation in IGF-I concentrations during clinical follow-up was higher than 10% in our series, in stable disease situations. For both random serum GH concentrations and glucose suppressed GH concentrations intra-individual variation was < 5%. Therefore, we recommend re-evaluation of serum IGF-I measurements in case of an unexpected normal or high value and discrepant GH and IGF-I results. When discrepant results persist, elevated serum IGF-I concentrations probably justify adjuvant treatment also in the case of normal serum GH concentrations.

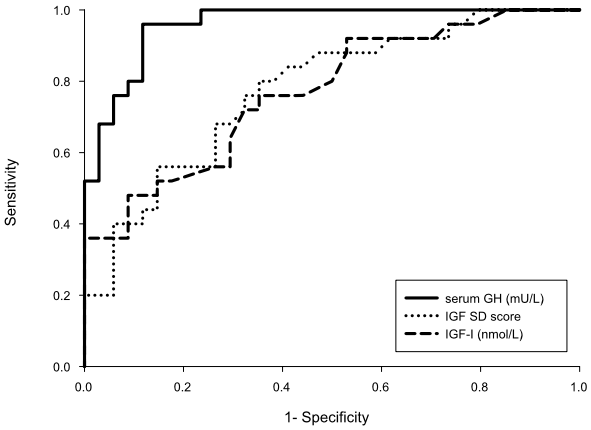


**Figure 2.** ROC curve analysis of postoperative biochemical serum GH and IGF-I measurements, using a normal glucose suppression (GH < 1 mU/L) as the gold standard.

In summary, remission rates for transsphenoidal surgery in our single-surgeon setting are in the range of 60% for all GH producing adenomas, 80% for microadenomas and 50% for macroadenomas. The recurrence rate after biochemically successful surgery is 19% in the cohort that was followed for 10 years, and this figure will probably decrease substantially when remission is defined by normal glucose- induced GH suppression according to the IFMA assay. Following unsuccessful surgery, multimodality treatment is able to establish control of disease in most patients. Treatment with somatostatin analogs is nowadays preferred over radiotherapy, because of the side effects. However, both are efficacious in an equal number of patients. Short-term treatment results of Pegvisomant suggest normalization of serum IGF-I levels in almost all patients, and this modality will probably further limit the use of radiotherapy when long-term Pegvisomant treatment will appear to be safe.

Further research is required to establish a cost- effective follow-up regimen in acromegalic patients but re-analysis of data in the present cohort suggest that a less frequent than yearly biochemical evaluation in patients cured after transsphenoidal surgery may suffice as no recurrences were observed in patients cured according to the IFMA assay. High linear correlation coefficients were found between random and mean serum GH samples, and between random GH and glucose-suppressed GH values. Follow-up of acromegaly in remission may thus be performed with random serum GH measurements and IGF-I concentrations, if necessary supported by GTT. Although serum IGF-I concentrations reflect the bioactivity of GH secretion, there is a high intra-individual variation in IGF-I results also in stable disease situations, either by assay variation or by other causes and therefore its value in discriminating between active and inactive disease in treated acromegaly still requires further investigation. Age-related normal values should be established for each laboratory. This is of importance

especially for the follow-up of GH receptor antagonist treatment during which IGF-I is the only available biochemical parameter for evaluation of treatment efficacy.

## II. CLINICAL ASPECTS OF WELL-CONTROLLED ACROMEGALY

As described in ***Chapters 2 – 6***, the multimodality treatment approach as applied in our center is able to normalize biochemical parameters in the majority of patients. The long-term outcome of these well-treated patients with acromegaly was studied in ***Chapters 7 – 10*** focusing on survival, quality of life, co-morbidity and bone mineral density (BMD).

### Survival

Reduction of the increased mortality risk due to GH excess in acromegaly is a major aim of treatment. At present, it is unclear to which extent treatment improves survival in acromegaly. In ***Chapter 7,*** we studied survival in surgically treated acromegalic patients. The majority of these patients was cured immediately after surgery, and in the others adjuvant therapy in the form of radiotherapy and/or somatostatin analog treatment was instituted immediately aiming at swift normalization of GH and IGF-I levels. We report a near-normal mortality risk, a finding that is supported by other studies (18, 23, 42, 58, 60 – 63). In summary, consecutive surgical series report standardized mortality ratios (SMR) of 1.16 to 2.14, while subsets of patients who attain remission have a SMR of ≈ 1.0. In large enough series, the mortality risk of well-treated acromegaly will probably remain slightly but significantly increased (1.2 to 1.3 fold higher than normal), because the "normalized mortality" can partly be attributed to the broad confidence intervals in small studies.

Bates *et al.* was the first to relate a normalized mortality risk to a serum GH below 5 mU/L(58). Thereafter, others also suggested "safe" serum GH and IGF-I concentrations below which a normalized mortality risk is restored. A normal survival was found in patients with a normal IGF-I (23, 26), a serum GH ≈ < 10 mU/L (< 5 µg/L) (42), serum GH < 5 mU/L (or < 2.5 µg/L) (18, 60, 64), ≈ < 4 mU/L (< 2 µg/L) (61) and ≈ < 2 mU/L (<1 µg/L) (62). However, there is a methodological concern with the interpretation of most studies (18, 58, 61, 62). The use of serum GH and IGF-I concentrations, obtained at the end of the observation period instead of at entry, does not truly predict survival and may lead to considerable bias in the analysis. The aim of treatment is to achieve remission and therefore the likelihood to achieve lower GH or IGF-I concentrations increases with a longer duration of follow-up. Patients living longer during follow up are more prone to achieve normalization of GH excess, in contrast with those who die early during follow up. Consequently, it is unsure whether patients die due to causes related to GH excess or due to causes unrelated to GH excess but before their GH levels have decreased sufficiently. The importance of inclusion of patients at a well-defined and similar point in the course of the disease in prognostic studies was stressed for example

by Laupacis et al. (65). This potential bias in mortality analysis for acromegaly was previously discussed by Swearingen *et al* (23). The impact of the bias introduced by the use of biochemical parameters at the end of follow-up may be negligible in patients with stable disease in follow-up, when GH and IGF-I levels at the end of treatment reflect levels at the inclusion in the analysis. However, the vast majority of patients in the various reports received pituitary irradiation leading supposedly to a gradual lowering of serum GH and IGF-I levels instead of stable levels. Therefore, the assumption of stable levels during follow-up cannot be made. Analysis of predictive "safe" cut-off levels for survival should therefore be performed with patients followed after inclusion at a similar point in the course of the disease (i.e. at diagnosis, *n* years post radiotherapy, or the moment a certain serum GH was achieved), using the GH and IGF-I values at inclusion. Preferentially, with the changing exposure to GH in the years after radiotherapy, serial measurements could be considered using a time-dependent Cox regression model.

In ***Chapter 7***, we report a significant improved survival for patients with a normal IGF-I as opposed to an elevated IGF-I concentration immediately postoperatively (relative risk (RR) 4.78), but we were not able to identify a safe cut-off value for the serum GH or glucose-suppressed GH concentration. However, there was a significant effect for the immediate postoperative glucose-suppressed GH concentration in mU/L, especially in the first years following surgery (RR 1.06). At present, only few other studies used biochemical parameters at entry or time-dependent analysis of sequential data to predict mortality in acromegaly. Thus, the only evidence for normalized mortality in relation to biochemical parameters is available for a normal postoperative IGF-I reported by Swearingen *et al* supported by our data and a postoperative serum GH < 5 µg/L reported by Abosch *et al* (23, 42).



In our study, another predictive factor influencing mortality was the estimated duration of preoperative disease, also found by Rayasoorya et al. (66). Recently, Ayuk *et al* found a significant negative survival outcome for patients who underwent radiotherapy compared to those who did not (61) and this finding was also suggested by Mestron et al. (63). The negative relation between survival and radiotherapy reported by Ayuk *et al.* will probably be due to the slow decrease in GH concentration and less likely to radiation damage.

All three well-designed survival studies in acromegaly are derived from consecutive surgical series (23, 26, 42). In these and in other available studies showing improved overall survival, most patients were treated by surgery and/or radiotherapy and only few by somatostatin analogs. Thus, the improved survival in treated acromegaly compared to active acromegaly can especially be attributed to normalization of GH excess by surgery and radiotherapy. Somatostatin analog treatment has not yet been associated with improved survival, but it is likely that the effective decrease of GH and IGF-I excess will lead to improved survival. The biochemical treatment goal during medical treatment with respect to survival requires further investigation. With the availability of Pegvisomant, it will be possible to normalize GH excess quicker in more patients than in the present survival studies. Together with earlier diagnosis

of acromegaly, new treatment algorithms with medical treatment instead of radiotherapy may lead to a further normalization of the excess mortality associated with acromegaly also in large cohorts. However, it will take many years before the outcome in survival of medical treatment can be evaluated.

In conclusion, the currently widely accepted 'safe' GH concentration with respect to mortality may well not be reproducible in large well-designed epidemiological studies. At present, the only well-designed survival studies are performed in primarily surgically treated patients with eventual adjuvant treatment and suggest a survival benefit when serum IGF-I is normal post-surgery (23, 26) and when serum GH postoperatively is below 5 µg/L (≈10 mU/L) (42). It is of note that at present there is no evidence to support any "safe" serum GH or IGF-I concentration with respect to mortality for patients treated by medical therapy, as in the reported studies the majority of patients received either surgical or radiotherapeutic treatment.

### Quality of life

Quality of life and patients' perceived well being are important parameters in today's clinical research. Quality of life is likely to be reduced in all patients with a chronic disorder. For doctors, the assessment of quality of life is generally not a priority. Moreover, in clinical practice we lack the tools to quantify quality of life. Nevertheless, the selection of questionnaires and appropriate controls is of vital importance for the interpretation of results. In our patients treated for acromegaly, described in ***Chapter 8***, we studied quality of life using disease-specific and several other health-related questionnaires. Patients were compared to age- and sex-matched controls obtained from the environment of the patients and also to reference data from the literature. As expected, significant impairments were present for all assessed topics in acromegalic patients. These impairments were less pronounced when compared to reference data from the literature than when compared to own collected control data. Actual disease status in a treated cohort did not affect questionnaire scores (unpublished observations). Importantly, patients with radiotherapy had significantly worse general health and fatigue scores. Somatostatin analogs make patients remember of their chronic illness at a monthly basis and therefore it is of note that well- being was not affected by the use of medical therapy. Patients cured after surgery, without accompanying hypopituitarism and no adjuvant treatment for GH excess had some advantages in quality of life compared to the other patients. Nonetheless, even these patients still had reduced quality of life, indicating irreversible effects of previously active acromegaly.

The effect of radiotherapy on quality of life scores, especially for fatigue and anxiety scales, was previously reported for patients with a non-functioning adenoma by Page *et al*, (67). Further investigation is warranted to address the long-term deleterious effects of this mode of treatment. The lack of correlation with biochemical disease status in treated patients and quality of life and the negative impact of radiotherapy on quality of life scores were recently confirmed by others (68).

Quality of life scores of our well-controlled patients could be compared to a limited number of reports in active acromegaly. Following treatment and after cure, quality of life seems improved compared to active acromegaly as measured by SF-36 and ACRO-QOL. At present, there are no longitudinal data on quality of life during treatment of acromegaly.

### Prevalence of co-morbidity

The symptoms that persist after cure for acromegaly together with the prevalence of co-morbidity are described in ***Chapter 9***. We report a high prevalence of hypertension and a high prevalence of self-reported joint problems in cured acromegaly, whereas the prevalence of diabetes seems not increased compared to population- based reference data. Only a single other study evaluated morbidity data in a cured acromegalic patient series and they report similar figures for hypertension and diabetes like we found (69).

The high prevalence of joint-related problems was not previously reported in cured acromegaly, although clinicians do recognize osteoarthritis as important clinical problem in patients treated for acromegaly. We are the first to report the severe impact of joint problems on quality of life in patients with acromegaly. Only female sex, but not GH/IGF-I concentrations, duration of disease or age, was associated with a higher prevalence of joint problems. It is important to realize that the impact of joint problems on quality of life is also observed in the general population (70). Acromegalic patients without joint problems may even have a normal quality of life, since there was no significant difference in quality of life as measured by SF-36 in acromegalic patients and controls without joint problems (70). Considering the impact of osteoarthritis on quality of life, an important challenge is the early diagnosis and the optimalization of treatment of acromegaly to improve the clinical outcome of cured acromegaly.



### Bone mineral density (BMD)

In ***Chapter 10***, BMD status was assessed in a cross-sectional study of cured patients. The anabolic effect of GH on bone is well established and, therefore, bone turnover and BMD are important efficacy parameters in GH deficient patients. However, the effect of acromegaly on bone is not clear and studies disagree as to whether a normal, increased or decreased bone mass is found. Partly, this is due to the heterogeneous cohorts studied with respect to gonadal and GH status. Moreover, a differential response of trabecular and cortical bone to GH may underlie the discrepant findings. We report increased BMD in our mainly eugonadal patients. Interestingly, the duration of remission and the application of radiotherapy were negatively correlated with bone mass. The negative influence of pituitary irradiation was unexpected and not previously reported in other pituitary diseases, and may reflect some degree of GH deficiency. Unfortunately, we were not able to report longitudinal data on BMD in cured acromegaly and to assess the incidence of vertebral and non-vertebral fractures in this cohort. Although our cross-sectional study suggest maintenance of BMD for up to 15

years after cure for acromegaly, provided that hypogonadism is adequately suppleted, these findings would be strengthened if additional studies demonstrated a stable bone mass and absence of fractures during longitudinal follow-up.

## III. DYNAMIC TESTS IN ACROMEGALY

### The intravenous octreotide test

In general, about 60% of the patients with active acromegaly can be controlled by (primary) somatostatin analog treatment. Therefore, the question has emerged whether the therapeutical response to octreotide can be predicted by a test. In ***Chapter 11,*** we studied the responses to an iv bolus of octreotide. Although other studies previously described a good predictive value of subcutaneous octreotide challenge tests for long-term treatment with subcutaneous octreotide (71), a test for octreotide sensitivity is infrequently used in clinical practice. Since the efficacy of depot preparations of somatostatin analogs can only be evaluated after 3 months when a steady state has been reached, a predictive test has become even more relevant than previously for subcutaneous octreotide treatment.

We evaluated the test characteristics of a 50 µg iv bolus of octreotide and were the first to compare an octreotide sensitivity test with long-term treatment with the depot preparation of octreotide. Although the iv and sc test were not directly compared, we believe that the main advantage of the iv test is the 100% availability and shorter duration of testing as maximal suppressibility of GH levels is quicker achieved.

We observed a decrease in serum GH concentrations in almost all patients, whereas the presence of normalization of GH excess was dependent on the height of the basal GH concentrations and most likely also on the somatostatin-subreceptor status of the GH-producing adenoma. The rate of decrease of GH levels during the test mimics the half-life of GH, suggesting acute and complete blockade in some, but not in all, patients. A nadir GH below 5 mU/L during the octreotide test predicts that chronic treatment is able to achieve serum GH concentrations < 5 mU/L.

Like in ***Chapters 2 – 6,*** discordant findings were present between GH and IGF-I criteria for the control of disease activity. The positive and negative predictive values were less favorable for IGF-I than for GH. The possible explanation for discrepancies has been previously discussed. The value of the octreotide test in patients with discrepant IGF-I and GH requires evaluation in a larger cohort.

Recently, four studies addressed the predictive value of a sc octreotide proof dose of 50 µg (72 – 75). Three of the studies confirm the clinical definition of octreotide sensitivity we used, i.e. achievement of a nadir GH during the test of < 5 – 10 mU/L in stead of a percentage decrease which was used before. The sc octreotide test was also found to be a good predictor of the response to somatostatin depot preparations for normalization of GH concentrations

(73 – 75), although the predictive value for normalization of IGF-I was limited (72). The nadir during the sc test was achieved later than we reported for the iv test. Thus, the sc octreotide test requires longer test duration (up to 6 hours).

### The TRH-test

In ***Chapter 12***, we report the high predictive value of a persisting postoperative paradoxical GH response to TRH for the recurrence of GH excess. Data of this study were predominantly measured by RIA. A TRH-induced GH increase of 3.75 mU/L early postoperatively was associated with recurrence of disease.

As previously discussed, less recurrences were observed when patients were cured according to glucose suppressed GH measured by IFMA. A persistent paradoxical rise after TRH injection, was indeed rarely seen in patients with glucose suppressed GH below 1 mU/L. Further research is required to assess whether the TRH test remains of value in patients cured according to IFMA criteria.

So far, the molecular or pathophysiological basis is not established for the TRH induced GH increase present in some patients with acromegaly. TRH-induced GH release is observed in many other conditions, e.g. depression, anorexia nervosa, hypothyroidism, diabetes mellitus, and is frequently observed in children and in other species (76).

In conclusion, although the mechanism of the TRH-induced GH increase remains to be elucidated, a postoperative persistent response was a good predictor of recurrence. After the introduction of the more sensitive IFMA and reassessment of the normal values for glucose suppression it is likely that there will be fewer patients with normal glucose suppression but persistent responsiveness for TRH. The threshold for paradoxical responsiveness during IFMA requires further investigation. We nevertheless advise frequent follow-up in those patients in remission by GTT with postoperative persistent GH responsiveness to TRH as they are at risk for developing a recurrence.



## IV. GH REGULATION DURING TREATMENT AND IN GHRH PRODUCING CARCINOIDS

### GH regulation during Octreotide LAR treatment

Transsphenoidal surgery is able to completely restore the physiological GH production and secretion with respect to the diurnal variation and the regularity as a measure for normalized feedback and feedforward control in selected patients early and late after successful surgery (3, 77). In contrast, radiotherapy disturbs GH secretion and detailed studies show increased pulse frequency, decreased pulse amplitude and irregularity. GH production is dependent on the efficacy of radiotherapeutic treatment and may be still increased or subnormal in the long-term (39, 40).

In ***Chapter 13***, we studied to which extent the abnormal secretory characteristics of active acromegaly, i.e. increased pulse frequency and burst mass, increased basal GH secretion and secretion irregularity could be reversed by chronic octreotide therapy via depot preparation. Although octreotide LAR was able to decrease serum GH secretion by 70 – 96% and the secretion abnormalities of active acromegaly improved, none of the patients – not even the most octreotide sensitive patients - showed normalization of any of the secretion abnormalities. This suggests that tumoral autonomy persist for event frequency, regularity and increased basal secretion, despite octreotide treatment. Moreover, even in the most octreotide sensitive patients excessive GH secretion persists during octreotide LAR treatment. In accordance, also during lanreotide Autogel treatment these abnormal secretory characteristics persist (53).

Successful transsphenoidal surgery is therefore the only therapeutic option for acromegaly that has been associated with physiological restoration of the abnormal secretory characteristics and normalization of the increased GH production (3;77). Radiotherapeutic treatment is associated with disturbed secretory characteristics, but the total 24 GH production will eventually normalize after many years or even lead to decreased GH production (39, 78). This may even lead to GH deficiency. Further research is required to assess the biological impact of the persistently increased total 24 hour production during somatostatin analog treatment, even in the case of normalized IGF-I levels, on morbidity and mortality in medically treated patients.

### GH regulation in patients with GHRH producing carcinoids

In ***Chapter 14***, we describe the presentation, clinical follow-up and detailed GH secretory studies in three patients with the rare condition of a GHRH carcinoid causing acromegaly. The diagnosis in two of the patients was only made after transsphenoidal surgery. Few data are available on the long-term results of treatment with somatostatin analogs in these patients. The two non-cured patients following carcinoid resection in our study remained both well-controlled by somatostatin analog treatment in the long-term.

Detailed analysis of the 24 hour GH secretory profiles reveals the abnormalities in secretory characteristics that are also found in pituitary derived acromegaly. Thus, pituitary derived acromegaly and acromegaly due to excessive GHRH production can not be distinguished using GH secretory characteristics. Interestingly, there was a highly significant co-pulsatility between GH and GHRH.

## V. CONCLUDING REMARKS

### Treatment algorithms

The present thesis describes treatment results from 1977 to 2003. In this period transsphenoidal surgery was the first choice of treatment. After incomplete removal, radiotherapy was applied before the availability of somatostatin analogs, and from 1996 onwards most patient with residual or recurrent disease were treated by medical treatment. Since the availability of octreotide LAR (in 1998), new patients are treated by primary surgery or primary medical therapy. This treatment approach resulted in high control rates (95%) according to strict biochemical criteria after long-term follow-up.

Immediate remission rates of primary transsphenoidal surgery were 66% for all patients and 56% for patients evaluated by IFMA. Patients with a lower preoperative GH had better surgical results. The incidence of hypopituitarism after surgery is low (< 10%) and the complication rate is very low. A high recurrence rate of 19% was present in our cohort studied for at least 10 years. These recurrences developed gradually during many years, were partly predicted by GH increase to TRH response, and effective treatment was instituted when clinical GH excess developed. It is likely that the recurrence rate is considerably lower in patients with postoperative remission according to IFMA criteria.

Postoperative radiotherapy is an effective treatment for residual disease leading to gradual normalization of GH excess in 70 – 80% after many years and normalization of serum IGF-I concentrations in an equal number of patients. The rate of radiotherapy-induced hypopituitarism is high (75% after 15 years). The time to normalization of GH excess following radiotherapy is largely dependent on the pre-radiotherapy GH and IGF-I levels. Gamma knife radiotherapy may be associated with earlier normalization of GH excess and a lower incidence of hypopituitarism, but no long-term data are available.

Octreotide LAR was effective in 70% of patients with residual or recurrent disease in our surgical cohort. The same response rate is reported for primary octreotide treatment in literature, however, many of these studies used patients pre-selected for octreotide sensitivity. During an iv octreotide test, 50% of consecutive untreated patients, unselected for octreotide sensitivity, achieved a GH < 5 mU/L, especially those with a basal serum GH < 50 mU/L. The iv octreotide test was a good predictor of the response to long-term treatment. Thus, primary octreotide LAR treatment may result in strict disease control in less than 60% of patients. Indeed, a normal GH was achieved in only 54% (octreotide LAR) and 48% (lanreotide SR) of patients unselected for octreotide sensitivity according to the recent meta analysis by Freda et al. (52).

In patients with a good response to octreotide LAR treatment, a dose interval extension can be attempted and will succeed in about 60% of patients well-controlled on a 4 weekly scheme. The significant tumor shrinkage after primary treatment with octreotide LAR may

improve the surgical results of adenomas with parasellar extension and a trial to assess this important issue is warranted.

The introduction of Pegvisomant, normalizing serum IGF-I levels in almost all patients and the development of universal or more selective somatostatin analogs will open new perspectives and will change the treatment algorithm of acromegaly. The lack of long-term safety and efficacy data for Pegvisomant at present, the extremely high costs of (newer) medical therapies and its life-long need, have to be considered against the risk of hypopituitarism following radiotherapy.

In conclusion, we recommend transsphenoidal surgery by a specialized neurosurgeon as first treatment option. Primary somatostatin analog treatment is a suitable alternative, especially in patients with lower GH levels, with contraindications for surgery or in patients with a good response to an octreotide bolus. In case of persisting GH excess, despite somatostatin analog treatment, we advise surgery or treatment with Pegvisomant (see treatment algorithm in ***Chapter 15***.

In patients with postoperative persistent GH excess, somatostatin analog treatment is the first adjuvant treatment option, followed by (combination) treatment with Pegvisomant. In patients with insufficient reaction to primary somatostatin analog treatment, transsphenoidal surgery and/or Pegvisomant treatment can be offered. Radiotherapy will be reserved for selected cases, but will not be routinely applied.

### Follow-up strategies and criteria for cure

Evidence is present that a normal survival is restored when IGF-I is normal and GH is < 5 µg/L (10 mU/L) as assessed in patients who underwent primary transsphenoidal surgery. However, it is likely that these criteria are also applicable for medical treatment (and radiotherapy). The glucose-suppressed GH is not yet related to survival; however, it is a standardized test, independent on the pulsatile nature of GH and without the difficult assay characteristics of IGF-I. For all criteria, normal values should be determined depending on the assay used.

The remission rates for IGF-I, GH (< 5 mU/L) and glucose-suppressed serum GH concentrations (< 1 mU/L) were comparable in our treatment studies, although there were individual discrepancies. These discrepancies are also found by others, and their meaning for clinical practice is not yet clear. Sequential IGF-I concentrations have a higher intra-individual variation than serum GH concentrations. However, repeatedly elevated serum IGF-I measurements probably reflect excessive GH production, also in the presence of normalized GH and suppressed GH levels. Therefore, patients with high IGF-I should be offered treatment.

The criteria of glucose suppression and normal IGF-I used in the present thesis are generally accepted. In our studies, also random GH concentrations were well correlated to glucose-suppressed values. We recommend the use of glucose-suppressed GH, (random) GH and IGF-I for surgical (and radiotherapy) treated patients and the use of (random) GH and IGF-I for somatostatin analog treatment. For Pegvisomant we recommend repeated IGF-I samples.

Postoperative follow-up was performed yearly in the studied cohort. Because of the gradual development of recurrences and the probably lower recurrence rate with IFMA, biochemical follow-up by glucose tolerance testing on a 2 to 5 year basis may suffice. Random GH and IGF-I could be measured on a yearly basis. Following radiotherapy, the risk of recurrent GH excess is negligible. However, the high incidence of hypopituitarism requires yearly evaluation of pituitary function.

During medical treatment, random measurement of GH and IGF-I every 6 to 12 months should suffice, in stable situations. However, we recommend more frequent monitoring in patients with recent dose change, because of the observed elevation of IGF-I in the long-term in some patients in the dose interval extension study.

### Clinical outcome of well-controlled acromegaly

A near-normalized survival (SMR 1.3) was achieved in acromegaly patients treated between 1977 and 2002, and survival was influenced by parameters of GH excess, i.e. preoperative disease duration and postoperative (glucose-suppressed) GH and IGF-I. However, only a normal IGF-I and not a normal GH or suppressed GH was associated with a normalized survival.

After successful biochemical treatment of acromegaly, quality of life remains impaired. Some of the quality of life parameters were significantly influenced by radiotherapy and duration of active disease. Moreover, the presence of joint-related complaints were associated with an impaired quality of life.

Whether an earlier diagnosis and earlier success of adjuvant therapies (using somatostatin analogs and Pegvisomant will further improve survival, quality of life and the incidence of arthropathy, and resolve the deleterious effects of GH excess is yet unknown.

## REFERENCES


1. Giustina A, Barkan A, Casanueva FF, et al. 2000 Criteria for cure of acromegaly: a consensus statement. J Clin Endocrinol Metab 85:526-529
2. Freda PU 2003 Current concepts in the biochemical assessment of the patient with acromegaly. Growth Horm IGF Res 13:171-184
3. van den Berg G, Frolich M, Veldhuis JD, Roelfsema F 1994 Growth hormone secretion in recently operated acromegalic patients. J Clin Endocrinol Metab 79:1706-1715
4. Ahmed S, Elsheikh M, Stratton IM, Page RC, Adams CB, Wass JA 1999 Outcome of transphenoidal surgery for acromegaly and its relationship to surgical experience. Clin Endocrinol (Oxf) 50:561-567
5. Newman CB, Melmed S, George A, et al. 1998 Octreotide as primary therapy for acromegaly. J Clin Endocrinol Metab 83:3034-3040
6. Bevan JS, Atkin SL, Atkinson AB, et al. 2002 Primary medical therapy for acromegaly: an open, prospective, multicenter study of the effects of subcutaneous and intramuscular slow-release octreotide on growth hormone, insulin-like growth factor-I, and tumor size. J Clin Endocrinol Metab 87:4554-4563
7. Mahmoud-Ahmed AS, Suh JH, Mayberg MR 2001 Gamma knife radiosurgery in the management of patients with acromegaly: a review. Pituitary 4:223-230
8. Attanasio R, Epaminonda P, Motti E, et al. 2003 Gamma-Knife Radiosurgery in Acromegaly: A 4-Year Follow-Up Study. J Clin Endocrinol Metab 88:3105-3112
9. Trainer PJ, Drake WM, Katznelson L, et al. 2000 Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant. N Engl J Med 342:1171-1177
10. Lamberts SW, van der Lely AJ, Hofland LJ 2002 New somatostatin analogs: will they fulfil old promises? Eur J Endocrinol 146:701-705
11. Roelfsema F, van Dulken H, Frolich M 1985 Long-term results of transsphenoidal pituitary microsurgery in 60 acromegalic patients. Clin Endocrinol (Oxf) 23:555-565
12. Losa M, Oeckler R, Schopohl J, Muller OA, Alba-Lopez J, von Werder K 1989 Evaluation of selective transsphenoidal adenomectomy by endocrinological testing and somatomedin-C measurement in acromegaly. J Neurosurg 70:561-567
13. Osman IA, James RA, Chatterjee S, Mathias D, Kendall-Taylor P 1994 Factors determining the long-term outcome of surgery for acromegaly. QJM 87:617-623
14. Biermasz NR, van Dulken H, Roelfsema F 2000 Ten-year follow-up results of transsphenoidal microsurgery in acromegaly. J Clin Endocrinol Metab 85:4596-4602
15. Laws ER, Vance ML, Thapar K 2000 Pituitary surgery for the management of acromegaly. Horm Res 53 Suppl 3:71-5.:71-75
16. Kreutzer J, Vance ML, Lopes MB, Laws ER, Jr. 2001 Surgical management of GH-secreting pituitary adenomas: an outcome study using modern remission criteria. J Clin Endocrinol Metab 86:4072-4077
17. De P, Rees DA, Davies N, et al. 2003 Transsphenoidal surgery for acromegaly in wales: results based on stringent criteria of remission. J Clin Endocrinol Metab 88:3567-3572
18. Beauregard C, Truong U, Hardy J, Serri O 2003 Long-term outcome and mortality after transsphenoidal adenomectomy for acromegaly. Clin Endocrinol (Oxf) 58:86-91
19. Minniti G, Jaffrain-Rea ML, Esposito V, Santoro A, Tamburrano G, Cantore G 2003 Evolving criteria for post-operative biochemical remission of acromegaly: can we achieve a definitive cure? An audit of surgical results on a large series and a review of the literature. Endocr Relat Cancer 10:611-619
20. Arafah BM, Rosenzweig JL, Fenstermaker R, Salazar R, McBride CE, Selman W 1987 Value of growth hormone dynamics and somatomedin C (insulin-like growth factor I) levels in predicting the long-term benefit after transsphenoidal surgery for acromegaly. J Lab Clin Med 109:346-354
21. Oyen WJ, Pieters GF, Meijer E, Laarhoven J, Smals AG, Kloppenborg PW 1988 Which factors predict the results of pituitary surgery in acromegaly? Acta Endocrinol (Copenh) 117:491-496

22. Tindall GT, Oyesiku NM, Watts NB, Clark RV, Christy JH, Adams DA 1993 Transsphenoidal adenomectomy for growth hormone-secreting pituitary adenomas in acromegaly: outcome analysis and determinants of failure. J Neurosurg 78:205-215
23. Swearingen B, Barker FG, Katznelson L, et al. 1998 Long-term mortality after transsphenoidal surgery and adjunctive therapy for acromegaly. J Clin Endocrinol Metab 83:3419-3426
24. Freda PU, Wardlaw SL, Post KD 1998 Long-term endocrinological follow-up evaluation in 115 patients who underwent transsphenoidal surgery for acromegaly [see comments]. J Neurosurg 89: 353-358
25. Shimon I, Cohen ZR, Ram Z, Hadani M 2001 Transsphenoidal surgery for acromegaly: endocrinological follow-up of 98 patients. Neurosurgery 48:1239-1243
26. Biermasz NR, Dekker FW, Pereira AM, et al. 2004 Determinants of survival in treated acromegaly in a single center: predictive value of serial insulin-like growth factor I measurements. J Clin Endocrinol Metab 89:2789-2796
27. Barkan AL, Halasz I, Dornfeld KJ, et al 1997 Pituitary irradiation is ineffective in normalizing plasma insulin-like growth factor I in patients with acromegaly. J Clin Endocrinol Metab 82:3187-3191
28. Ciccarelli E, Valetto MR, Vasario E, Avataneo T, Grottoli S, Camanni F 1993 Hormonal and radiological effects of megavoltage radiotherapy in patients with growth hormone-secreting pituitary adenoma. J Endocrinol Invest 16:565-572
29. van der Lely AJ, de Herder WW, Lamberts SW 1997 The role of radiotherapy in acromegaly. J Clin Endocrinol Metab 82:3185-3186
30. Powell JS, Wardlaw SL, Post KD, Freda PU 2000 Outcome of radiotherapy for acromegaly using normalization of insulin-like growth factor I to define cure. J Clin Endocrinol Metab 85:2068-2071
31. Porretti S, Epaminonda P, Cappielo V, Palmieri E, Faglia G, Arosio M, Efficacy of radiotherapy in normalizing IGF-I levels in acromegalic patients. p 578 (Abstract)
32. Biermasz NR, van Dulken H, Roelfsema F 2000 Long-term follow-up results of postoperative radiotherapy in 36 patients with acromegaly. J Clin Endocrinol Metab 85:2476-2482
33. Gutt B, Hatzack C, Morrison K, Pollinger B, Schopohl J 2001 Conventional pituitary irradiation is effective in normalising plasma IGF-I in patients with acromegaly. Eur J Endocrinol 144:109-116
34. Barrande G, Pittino-Lungo M, Coste J, et al. 2000 Hormonal and metabolic effects of radiotherapy in acromegaly: long-term results in 128 patients followed in a single center. J Clin Endocrinol Metab 85:3779-3785
35. Cozzi R, Barausse M, Asnaghi D, Dallabonzana D, Lodrini S, Attanasio R 2001 Failure of radiotherapy in acromegaly. Eur J Endocrinol 145:717-726
36. Epaminonda P, Porretti S, Cappiello V, Beck-Peccoz P, Faglia G, Arosio M 2001 Efficacy of radiotherapy in normalizing serum IGF-I, acid-labile subunit (ALS) and IGFBP-3 levels in acromegaly. Clin Endocrinol (Oxf) 55:183-189
37. Thalassinos NC, Tsagarakis S, Ioannides G, Tzavara I, Papavasiliou C 1998 Megavoltage pituitary irradiation lowers but seldom leads to safe GH levels in acromegaly: a long-term follow-up study. Eur J Endocrinol 138:160-163
38. Jenkins D, O'Brien I, Johnson A, Shakespear R, Sheppard MC, Stewart PM 1995 The Birmingham pituitary database: auditing the outcome of the treatment of acromegaly. Clin Endocrinol (Oxf) 43:517-522
39. Peacey SR, Shalet SM 1999 Growth hormone pulsatility in acromegaly following radiotherapy. Pituitary 2:63-69
40. Peacey SR, Toogood AA, Veldhuis JD, Thorner MO, Shalet SM 2001 The relationship between 24-hour growth hormone secretion and insulin- like growth factor I in patients with successfully treated acromegaly: impact of surgery or radiotherapy. J Clin Endocrinol Metab 86:259-266
41. Freda PU, Post KD, Powell JS, Wardlaw SL 1998 Evaluation of disease status with sensitive measures of growth hormone secretion in 60 postoperative patients with acromegaly. J Clin Endocrinol Metab 83:3808-3816
42. Abosch A, Tyrrell JB, Lamborn KR, Hannegan LT, Applebury CB, Wilson CB 1998 Transsphenoidal microsurgery for growth hormone-secreting pituitary adenomas: initial outcome and long-term results. J Clin Endocrinol Metab 83:3411-3418

43. Kaltsas GA, Isidori AM, Florakis D, et al. 2001 Predictors of the outcome of surgical treatment in acromegaly and the value of the mean growth hormone day curve in assessing postoperative disease activity. J Clin Endocrinol Metab 86:1645-1652
44. Holdaway IM, Rajasoorya CR, Gamble GD, Stewart AW 2003 Long-term treatment outcome in acromegaly. Growth Horm IGF Res 13:185-192
45. Ben Shlomo A, Melmed S 2003 The Role of Pharmacotherapy in Perioperative Management of Patients with Acromegaly. J Clin Endocrinol Metab 88:963-968
46. Jenkins PJ, Emery M, Howling SJ, Evanson J, Besser GM, Monson JP 2004 Predicting therapeutic response and degree of pituitary tumour shrinkage during treatment of acromegaly with octreotide LAR. Horm Res 62:227-232
47. Amato G, Mazziotti G, Rotondi M, et al. 2002 Long-term effects of lanreotide SR and octreotide LAR on tumour shrinkage and GH hypersecretion in patients with previously untreated acromegaly. Clin Endocrinol (Oxf) 56:65-71
48. Colao A, Ferone D, Marzullo P, et al. 2001 Long-term effects of depot long-acting somatostatin analog octreotide on hormone levels and tumor mass in acromegaly. J Clin Endocrinol Metab 86:2779-2786
49. Jenkins PJ, Akker S, Chew SL, Besser GM, Monson JP, Grossman AB 2000 Optimal dosage interval for depot somatostatin analogue therapy in acromegaly requires individual titration. Clin Endocrinol (Oxf) 53:719-724
50. Lorcy Y, Dejager S, Chanson P 2000 Time course of GH and IGF-1 levels following withdrawal of long-acting octreotide in acromegaly. Pituitary 3:193-197
51. Turner HE, Thornton-Jones VA, Wass JA 2004 Systematic dose-extension of octreotide LAR: the importance of individual tailoring of treatment in patients with acromegaly. Clin Endocrinol (Oxf) 61:224-231
52. Freda PU, Katznelson L, van der Lely AJ, Reyes CM, Zhao S, Rabinowitz D 2005 Long-acting somatostatin analogy therapy of acromegaly: a meta- analysis. J Clin Endocrinol Metab
53. Van Thiel SW, Romijn JA, Biermasz NR, et al. 2004 Octreotide long-acting repeatable and lanreotide Autogel are equally effective in controlling growth hormone secretion in acromegalic patients. Eur J Endocrinol 150:489-495
54. Ashwell SG, Bevan JS, Edwards OM, et al. 2004 The efficacy and safety of lanreotide Autogel in patients with acromegaly previously treated with octreotide LAR. Eur J Endocrinol 150:473-480
55. Alexopoulou O, Abrams P, Verhelst J, Poppe K, Velkeniers B, Abs R, Maiter D 2004 Efficacy and tolerability of lanreotide Autogel therapy in acromegalic patients previously treated with octreotide LAR. Eur J Endocrinol 151:317-324
56. van der Lely AJ, Hutson RK, Trainer PJ, et al. 2001 Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist. Lancet 358:1754-1759
57. Feenstra J, de Herder WW, ten Have SMTH, et al. 2005 Combined therapy with somatostatin analogues and weekly pegvisomant in active acromegaly. The Lancet In Press, Corrected Proof:
58. Bates AS, Van't Hoff W, Jones JM, Clayton RN 1993 An audit of outcome of treatment in acromegaly. Q J Med 86:293-299
59. Parfitt VJ, Flanagan D, Wood P, Leatherdale BA 1998 Outpatient assessment of residual growth hormone secretion in treated acromegaly with overnight urinary growth hormone excretion, random serum growth hormone and insulin like growth factor-1. Clin Endocrinol (Oxf) 49:647-652
60. Arita K, Kurisu K, Tominaga A, et al. 2003 Mortality in 154 surgically treated patients with acromegaly--a 10-year follow-up survey. Endocr J 50:163-172
61. Ayuk J, Clayton RN, Holder G, Sheppard MC, Stewart PM, Bates AS 2004 Growth hormone and pituitary radiotherapy, but not serum insulin-like growth factor-I concentrations, predict excess mortality in patients with acromegaly. J Clin Endocrinol Metab 89:1613-1617
62. Holdaway IM, Rajasoorya RC, Gamble GD 2004 Factors Influencing Mortality in Acromegaly. J Clin Endocrinol Metab 89:667-674
63. Mestron A, Webb SM, Astorga R, et al. 2004 Epidemiology, clinical characteristics, outcome, morbidity and mortality in acromegaly based on the Spanish Acromegaly Registry (Registro Espanol de Acromegalia, REA). Eur J Endocrinol 151:439-446

64. Orme SM, McNally RJ, Cartwright RA, Belchetz PE 1998 Mortality and cancer incidence in acromegaly: a retrospective cohort study. United Kingdom Acromegaly Study Group. J Clin Endocrinol Metab 83:2730-2734
65. Laupacis A, Wells G, Richardson WS, Tugwell P 1994 Users' guides to the medical literature. V. How to use an article about prognosis. Evidence-Based Medicine Working Group. JAMA 272:234-237
66. Rajasoorya C, Holdaway IM, Wrightson P, Scott DJ, Ibbertson HK 1994 Determinants of clinical outcome and survival in acromegaly. Clin Endocrinol (Oxf) 41:95-102
67. Page RC, Hammersley MS, Burke CW, Wass JA 1997 An account of the quality of life of patients after treatment for non-functioning pituitary tumours. Clin Endocrinol (Oxf) 46:401-406
68. Rowles SV, Prieto L, Badia X, Shalet SM, Webb SM, Trainer PJ 2005 Quality of life (QOL) in patients with acromegaly is severely impaired: use of a novel measure of QOL: acromegaly quality of life questionnaire. J Clin Endocrinol Metab 90:3337-3341
69. Serri O, Beauregard C, Hardy J 2004 Long-Term Biochemical Status and Disease-Related Morbidity in 53 Postoperative Patients with Acromegaly. J Clin Endocrinol Metab 89:658-661
70. Picavet HSJ, Hoeymans N 2004 Health related quality of life in multiple musculoskeletal diseases: SF-36 and EQ-5D in the DMC3 study. Ann Rheum Dis 63:723-729
71. Lamberts SW, Uitterlinden P, Schuijff PC, Klijn JG 1988 Therapy of acromegaly with sandostatin: the predictive value of an acute test, the value of serum somatomedin-C measurements in dose adjustment and the definition of a biochemical 'cure'. Clin Endocrinol (Oxf) 29:411-420
72. de Herder WW, Taal HR, Uitterlinden P, Feelders RA, Janssen JA, van der Lely AJ 2005 Limited predictive value of an acute test with subcutaneous octreotide for long-term IGF-I normalization with Sandostatin LAR in acromegaly. Eur J Endocrinol 153:67-71
73. Karavitaki N, Botusan I, Radian S, Coculescu M, Turner HE, Wass JA 2005 The value of an acute octreotide suppression test in predicting long-term responses to depot somatostatin analogues in patients with active acromegaly. Clin Endocrinol (Oxf) 62:282-288
74. Gilbert JA, Miell JP, Chambers SM, McGregor AM, Aylwin SJ 2005 The nadir growth hormone after an octreotide test dose predicts the long-term efficacy of somatostatin analogue therapy in acromegaly. Clin Endocrinol (Oxf) 62:742-747
75. Lindsay JR, McConnell EM, Hunter SJ, McCance DR, Sheridan B, Atkinson AB 2005 Poor Responses to a Test Dose of Subcutaneous Octreotide Predict the Need for Adjuvant Therapy to Achieve 'Safe' Growth Hormone Levels. Pituitary .:
76. Harvey S 1990 Thyrotrophin-releasing hormone: a growth hormone-releasing factor. J Endocrinol 125:345-358
77. van den Berg G, Pincus SM, Frolich M, Veldhuis JD, Roelfsema F 1998 Reduced disorderliness of growth hormone release in biochemically inactive acromegaly after pituitary surgery. Eur J Endocrinol 138:164-169
78. Peacey SR, Toogood AA, Shalet SM 1998 Hypothalamic dysfunction in "cured" acromegaly is treatment modality dependent. J Clin Endocrinol Metab 83:1682-1686