Acromegaly : treatment and follow-up : the Leiden studies

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7

Determinants of survival in treated acromegaly in a single center: predictive value of serial insulin-like growth factor I measurements

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J Clin Endocrinol Metab. 2004; 89:2789-2796

ABSTRACT

We evaluated survival after optimal treatment for acromegaly and assessed the predictive effects of different remission criteria for survival in 164 consecutive acromegalic patients, treated by transsphenoidal surgery and adjuvant therapy between 1977 and 2002. The goal of treatment was a mean GH less than 5 mU/liter, a normal glucose-suppressed GH, and a normal IGF-I for age in all patients. Surgery initially cured 108 patients (66%). Adjuvant therapy for persistent disease was given to 49 patients. At the end of follow-up (mean, 12.3 yr), remission rates for surgery and multimodality treatment were 54% and 90%, respectively. In 2033 person-years of follow-up, 28 of 164 patients died, resulting in an observed:expected mortality ratio of 1.3 (confidence interval, 0.87–1.87). Significant predictors for survival were the duration of disease and the postoperative glucose-suppressed GH. The effects of these predictors became less significant with increasing follow-up duration. A time-dependent effect on survival was observed for serial IGF-I concentrations, but not for serial GH concentrations. Of the three remission criteria, IGF-I was the only one to be significantly associated with survival in this study, with a relative risk of 4.78 for an elevated as opposed to a normal IGF-I concentration.

INTRODUCTION

ACROMEGALY IS A CHRONIC debilitating disorder caused by a GH-producing pituitary adenoma. Active acromegaly is associated with a 2- to 4-fold increased mortality risk, mainly from cardiovascular and malignant disease (1, 2). Mortality risk has been related to various GH excess parameters, including serum GH and IGF-I concentrations, and to comorbidity at the time of diagnosis. Generally, mortality is still elevated in cohorts of patients with acromegaly undergoing modern treatment regimens as reviewed by Holdaway et al. (3). After transsphenoidal surgery (and eventual adjuvant treatment), mortality risk equals that of a control population only in selected patients with serum GH concentrations less than 5 μg/liter (~10 mU/liter) at the end of follow-up (4), normal IGF-I (5) or normal IGF-I, normal glucose suppressed serum GH (<1 μg/liter), and random serum GH concentrations less than 5 mU/liter (6). Bates et al. (7) reported a normalized mortality risk when the lowest serum GH level during follow-up was less than 5 mU/liter, which was confirmed by Orme et al. (8). Normalization of serum IGF-I also appears to be associated with a normal life expectancy according to Swearingen et al. (5). A drawback of most studies is that patients were divided between cured and noncured on the basis of their last known biochemical parameters instead of on the basis of direct postoperative values. These studies may be biased due to the increasing chance to achieve remission during longer follow-up.

Transsphenoidal surgery in experienced hands establishes short-term remission in about 60% of patients, whereas after a follow-up of more than 10 yr, only 40% remain in remission by surgery alone due to recurrence of GH excess. Nonetheless, after unsuccessful surgery or recurrence, most patients achieve remission by treatment with somatostatin analogs or radiotherapy (4, 5, 9).

In the present study we evaluated survival in patients with acromegaly initially treated by surgical and, if necessary, subsequent adjuvant treatment between 1977 and 2002. We hypothesized that this cohort of patients has an equal survival risk compared with controls, because the goal of treatment throughout the entire study period was to achieve serum GH concentrations below 5 mU/liter, normal glucose-suppressed GH levels, and normal age- and sex-adjusted IGF-I concentrations. We further investigated whether there were factors influencing survival within this cohort.

SUBJECTS AND METHODS

Treatment protocol

Between 1977 and 2002, 164 consecutive patients were treated at Leiden University Medical Center by transsphenoidal surgery performed in a single specialist neurosurgeon setting. The diagnosis of acromegaly was based on clinical characteristics and was confirmed by insuf-

ficient GH suppression during oral glucose tolerance testing (GTT). All patients had careful preoperative and postoperative biochemical evaluation, followed by yearly assessments by GTT, serum IGF-I (from 1986 onward), and GH day profiles thereafter. In the case of incomplete tumor removal or recurrence of disease, patients received postoperative pituitary irradiation and/or treatment with somatostatin analogs aiming at normal glucose-suppressed serum GH levels [<1 mU/liter (0.38 μg/liter) for the immunofluorometric assay and <2.5 mU/liter (1.25 μg/liter) for the RIA], random serum GH concentrations less than 5 mU/liter (2.5 μg/liter), and/or normal age-adjusted IGF-I concentrations. In all patients, we analyzed the duration of follow-up, the estimated duration of active disease, the date and cause of death, disease activity with yearly measured serum GH, and glucose-suppressed GH and IGF-I concentrations. The study was approved by the medical ethical committee of Leiden University Medical Center.

Clinical follow-up data

We included all consecutive patients with acromegaly (n = 164) who had surgery from 1977 onward, with the date of surgery as the inclusion date. We used the following end points of follow-up: date of death in 28 patients, date of emigration in three patients, and date of most recent contact in 133 patients in time window between November 2002 and April 2003. The causes of death were derived from the charts of the patients or from the general physicians of the patients. A separate analysis was performed in patients who achieved strict biochemical remission after surgery or after adjuvant treatment (n = 148), using the date of remission as the inclusion date and the end of follow-up as the end point.

Biochemical analysis

Serum GH was measured before 1992 by RIA (Biolab, Serona, Coissins, Switzerland) calibrated against WHO International Reference Preparation 66/21 (detection limit, 0.5 mU/liter; interassay coefficient of variation, <5%; for conversion to micrograms per liter, divide by 2). From 1993 onward, we used a sensitive immunofluorometric assay (Wallac, Turku, Finland), specific for the 22-kDa GH protein, calibrated against WHO International Reference Preparation 80/505 (detection limit, 0.03 mU/liter; interassay coefficient of variation, 1.6–8.4% between 0.25 and 40 mU/liter; for conversion to micrograms per liter, divide by 2.6). The serum IGF-I concentration was determined using an RIA available from 1985 onward (Incstar, Inc., Stillwater, MN; detection limit, 1.5 nmol/liter; interassay coefficient of variation, <11%). Normal values were expressed as age-related SD scores from normal values derived from 137 healthy controls (10).

Statistical analysis

SPSS for Windows version 10.0 (SPSS, Inc., Chicago, IL) was used to perform data analysis. Data were expressed as the mean ± SD and as lower and upper 95% confidence intervals unless mentioned otherwise. Values outside the 95% confidence interval range are significant at the

5% level. Survival curves were generated using Kaplan-Meier analysis. Cox regression analysis was used to study determinants of survival, present at the time of surgery, adjusted for age and sex. We also evaluated serum GH and IGF-I measured 0, 2, 5, and 10 yr postoperatively as time-dependent covariates to discriminate between time in remission and active disease.

Normal mortality rates for the Dutch population were obtained from the Dutch Central Bureau of Statistics (The Netherlands) using mortality rates per sex, age groups of 5 yr, and calendar periods of 5 yr (1975, 1980, 1985, 1990, 1995, and 2000). Expected mortality rates were determined based on the person-years follow-up for each sex and age group and each calendar period and compared with the observed mortality rate.

RESULTS

Baseline characteristics

One hundred and sixty-four consecutive patients were included (91 male and 73 female patients). The mean age at the time of surgery was 46.5 ± 12.5 yr (range, 19–77 yr). The mean disease duration before surgery, estimated using onset of characteristic signs and symptoms and facial changes on photographs, was 8.7 ± 7.6 yr. Thirty-six patients had a microadenoma (21%), 93 had a noninvasive macroadenoma (58%), and 35 an invasive macroadenoma (21%). The mean serum GH concentration before surgery was 86.1 ± 103 mU/liter (3.5–600 mU/liter).

Outcome of treatment

The results of postoperative treatment results and the strategies of adjuvant treatment are detailed in Fig. 1. All patients had transsphenoidal surgery as the first treatment, except for two patients who were treated by unsuccessful pituitary irradiation 5 and 15 yr preoperatively. Immediate postoperative remission was achieved in 108 patients (65.8%). Surgical remission rates according to different remission criteria were similar, as shown in Table 1. Remission rates were 81% for microadenoma, 71% for noninvasive macroadenoma, and 37% for invasive macroadenoma. Even in patients with persistent GH excess, GH levels were reduced from 115 ± 127 to 26 ± 33 mU/liter by surgery ($P < 0.001$), reflecting significant tumor debulking.

Of 56 patients with persistent disease, 40 received postoperative radiotherapy, nine patients were treated with somatostatin analogs, and seven patients were followed without additive treatment.

Of the 108 initially cured patients, 13 patients received prophylactic irradiation for suspected incomplete tumor removal and/or a persistent paradoxical reaction of GH to TRH to prevent recurrence. Recurrence of active disease developed in 14 of the 95 patients (15%) initially cured by surgery without prophylactic irradiation, with usually only mild elevations

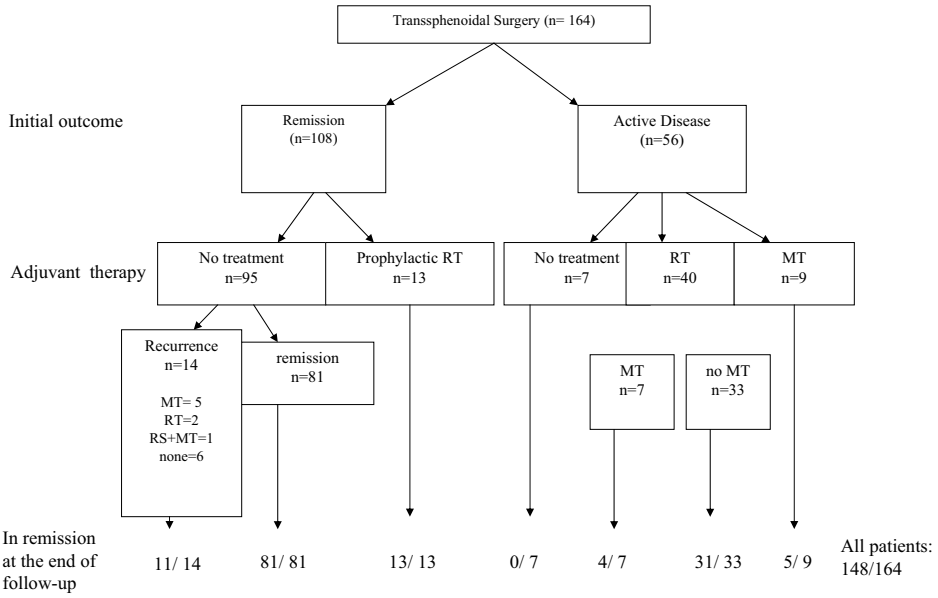

Figure 1. Treatment results and applied adjuvant treatments in 164 patients after transsphenoidal surgery for acromegaly. RT, radiotherapy; MT, medical therapy with somatostatin analogs; RS, repeat surgery. Remission was defined by a normal serum GH (<5 mU/liter), a normal IGF-I for age, and a normal glucose-suppressed serum GH during GTT.

Table 1. Direct postoperative remission rates and risk factors for mortality according to three different biochemical criteria

Criterion	No of patients (remission/total)	% of patients in remission	RR (95% CI)	RR (95% CI) adjusted for age
Serum GH < 5 mU/L	106/164	65	1.69 (0.59 - 2.77)	1.77 (0.80 - 3.94)
Normal glucose- suppressed GH[1]	106/157	67	1.28 (0.56 - 8.93)	1.32 (0.57 - 3.03)
Normal IGF-I for age	60/99	60	1.99 (0.45 - 8.93)	4.78 (1.01 - 22.7)
Remission by all available criteria	108/164	66	1.28 (0.59 - 2.77)	1.34 (0.61 - 2.92)

[1] Normal value for glucose-suppressed GH: for RIA, < 2.5 mU/L; for IFMA, < 1 mU/L.

of serum GH and IGF-I. These 14 patients were followed frequently, and adjuvant treatment was applied in eight patients.

At the end of follow-up (mean follow-up, 12.4 ± 7.3 yr; range, 1–26), 81 of 151 patients (54%) were in long-term remission by surgery alone, excluding for analysis the patients with prophylactic irradiation in long-term remission. The control rates of multimodality treatment were 86% for a serum GH below 5 mU/liter, 85% for a normal serum IGF-I, and 90% as judged by combination of all criteria (see Fig. 1). The overall rate of hypopituitarism, defined as the need for replacement therapy at the end of follow-up, was 31.5%. Eighteen of 107 nonirradiated patients (17%) had one or more pituitary insufficiencies, as did 32 of 57 irradiated patients (56%).

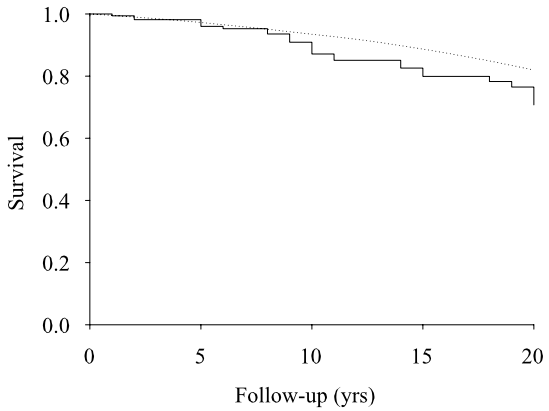

Figure 2. Kaplan-Meier curve for survival in 164 patients after transsphenoidal surgery. *Solid line*, Proportion of surviving patients with acromegaly; *dotted line*, expected survival curve of age-matched Dutch reference population.

Mortality rates in all patients (n = 164)

Twenty-eight patients died 1–21 yr after surgery. There were no perioperative deaths (Fig. 2). Thirteen patients died from malignancy (colon cancer, n = 5), seven from cardiovascular disease, and six from other causes. The cause of death was unknown in two patients. A total of 2033 patient-years of follow-up was available for comparison with normative data of the Dutch population. The observed : expected mortality ratio was 28 : 21.1 [1.33; confidence interval (CI), 0.87–1.87].

We used univariate Cox regression analysis to identify significant predictive factors for survival (Table 2). After adjustment for age and sex, significant predictive factors for survival were the estimated duration of preoperative disease [5–10 vs. < 5 yr; relative risk (RR), 4.97; CI, 1.07–23.08] and the postoperative glucose-suppressed serum GH concentration in milliunits per liter (RR, 1.06; CI, 1.02–1.09).

Three remission criteria, i.e. normal GH, normal glucose-suppressed GH, and normal IGF-I for age, were analyzed separately with Cox regression analysis, adjusted for age. A postoperatively elevated serum IGF-I was associated with decreased survival (RR, 4.779; 95% CI, 1.01–22.70), whereas active disease according to the other remission criteria was not associated with decreased survival (see Table 1).

The 5- and 10-yr survival rates were 96% and 87%, respectively. Age-adjusted determinants of 5-yr postoperative survival were the immediate postoperative serum GH concentration, the glucose-suppressed GH concentration, and the estimated disease duration (Table 3). The predictive effects, i.e. disease duration and postoperative (glucose-suppressed) GH concentration, were strongest in the first 5 yr after surgery and faded with longer follow-up duration.

Serial GH and IGF-I concentrations measured 0, 2, 5, and 10 yr postoperatively were also analyzed in a time-dependent model. There was no time-dependent effect of serial serum

Table 2. Risk factors for mortality in 164 patients treated with transsphenoidal surgery for acromegaly.

	No. of patients or mean ± SD	Univariate		Age- and sex-adjusted	
		RR	CI	RR	CI
Age at surgery (yr)	46.53 ± 12.5	1.119	1.077 - 1.162		
Sex (M/F)	91/73	0.787	0.369 - 1.682		
Preoperative GH (mU/L)	86.1 ± 103	0.999	0.995 - 1.002	1.000	0.996 - 1.005
Tumor classification					
Microadenoma	36				
Macroadenoma	93	0.999	0.325 - 3.071	0.947	0.293 - 3.055
Invasive Macroadenoma	35	3.923	1.244 - 12.372	1.843	0.554 - 6.134
Estimated duration of preoperative disease (yr) [1]	8.74 ± 7.6	1.053	1.019 - 1.089	1.012	0.974 - 1.051
0-5 yr[2]	54				
5-10 yr[2]	50	6.976	1.527 - 31.877	4.974	1.072 - 23.079
>10 yr[2]	60	8.294	1.902 - 36.175	3.172	0.686 - 14.584
Postoperative IGF-I (nmol/L)	30.4 ± 18	0.976	0.917 - 1.038	1.028	0.974 - 1.085
Postoperative glucose- suppressed GH (GTT)	4.60 ± 10	1.026	0.995 - 1.058	1.056	1.022 - 1.090
Postoperative GH (mU/L)	10.5± 22.5	1.008	0.995 - 1.021	1.001	0.989 - 1.013
Postoperative radiotherapy (no/yes)	107/57	1.721	0.808 - 3.662	0.817	0.380 - 1.756

Relative risks (RR) and 95% confidence intervals (CI) for various preoperative and immediate postoperative known factors.

[1] RR's for duration of active disease are shown per year.

[2] RR's are shown for 5-10 and > 10 years compared to 0-5 yr.

GH concentrations on survival. However, in patients with complete IGF-I series (from 1986 onward), a significant effect for the serum IGF-I concentration was observed (RR, 1.107; CI, 1.005–1.220).

Mortality in patients with immediate postoperative remission (n = 108)

Separate analysis was performed on patients in remission after surgery. The mean follow-up after surgery was 13 ± 7.3 yr, and 18 deaths occurred. No predictive values for survival, except age, were identified in this cohort. The observed:expected mortality ratio was 18:14.4 (1.25; CI, 0.74–1.92) in patients with postoperative remission, and 10:6.76 (1.48; CI, 0.69–2.57) in the 56 patients with postoperative active disease.

Mortality in patients in remission after multimodality treatment (n = 148)

Patients achieving remission after surgery or after surgery with adjuvant therapy were analyzed separately. The mean duration of follow-up from the date of remission was 11.9 ± 7.0 yr. Mortality was not significantly increased (24:20.8; ratio, 1.16; CI, 0.73–1.68). Age was the only significant predictor of survival (Table 4).

Table 3. Predictors of survival in different time windows, adjusted for age.

	0 - 5 years	0 - 10 years	2 - 5 years	5 - 10 years	10 years to end
No. of patients	164	164	136	130	85
No. of deaths	6	16	3	10	12
Preoperative factors					
Preoperative disease duration (yr)	1.058 (0.99-0.130)	1.022 (0.975-1.072)	1.104 (1.006-1.211)	0.992 (0.924-1.064)	1.004 (0.944-1.067)
Preoperative GH (mU/L)	0.999 (0.986-1.012)	1.000(0.993-1.007)	1.002 (0.989-1.016)	1.001(0.993-1.009)	1.001 (0.996-1.006)
Postoperative factors					
GH (mU/L)	1.015 (1.002-1.029)	1.009 (0.997-1.022)	1.021(1.005-1.037)	0.990 (0.95-1.032)	0.989 (0.961-1.017)
GH (GTT; mU/L)	1.053 (1.015-1.094)	1.054 (1.018-1.092)	1.078(1.018-1.141)	1.063 (0.944-1.198)	1.048 (0.981-1.120)
2-yr data					
GH (mU/L)			1.098 (1.011-1.192)		
5-yr data					
GH (mU/L)				0.995 (0.86-1.15)	
IGF-I (nmol/L)				1.015 (0.946-1.088)	
10-yr data					
GH (mU/L)					1.021 (0.83-1.255)
IGF-I (nmol/L)					0.985 (0.934-1.038)

Relative risks (RR) and 95% confidence intervals (CI) for various preoperative, postoperative and follow-up parameters.

Table 4. Risk factors for mortality in 148 patients included from date of remission after treatment for acromegaly.

	Number of patients or mean ± SD	Univariate		Age- and sex-adjusted	
		RR	CI	RR	CI
Age at remission(yr)	47.7 ± 12.6	1.162	1.081-1.173		
Sex (M/F)	79/68	0.709	0.31-1.623	0.746	0.323-1.722
Preoperative GH (mU/L)	89.3 ± 107	0.999	0.996-1.003	1.001	0.997-1.005
Tumor classification					
Microadenoma	34				
Macroadenoma	88	1.389	0.395-4.885	1.449	0.409-5.140
Invasive Macroadenoma	26	4.107	1.086-15.537	1.924	0.493-7.506
Estimated duration of preoperative disease (yr)	8.61 ± 7.73	1.051	1.015-1.089	1.005	0.965-1.047
Postoperative GH (mU/L)	7.58 ± 14.89	0.992	0.959-1.026	0.983	0.958-1.010
Postoperative IGF-I (nmol/L)	28.69 ± 17.37	0.981	0.913-1.053	1.048	0.997-1.102
Postoperative glucose- suppressed GH (GTT)	3.41 ± 6.92	1.012	0.958-1.068	1.039	0.971-1.111
Postoperative radiotherapy (no/yes)	97/51	1.733	0.777-3.866	1.169	0.516-2.647

Relative risks (RR) and 95% confidence intervals (CI) for various preoperative and immediate postoperative known factors.

DISCUSSION

In this study we evaluated long-term survival of a consecutive cohort of acromegalic patients treated by surgery and, if necessary, by a subsequent multimodality treatment approach. The immediate postoperative remission rate was 66%. From the start of this study, multimodality treatment was instituted as necessary, aiming at a rapid normalization of (glucose-suppressed) GH and IGF-I levels, which resulted in an overall remission rate of 90% during follow-up. With this treatment strategy, the chance of survival is not different from that of the normal population during a mean follow-up period of 12.3 yr. Apparently, the direct and/or indirect effects of GH causing increased mortality in patients with active acromegaly seem reversible upon biochemical control of GH excess.

In general, acromegalic patients treated with modern multimodality approaches, including transsphenoidal surgery, radiotherapy, and treatment with somatostatin analogs resulting in effective reduction of serum GH levels, still have an approximately 2-fold increased mortality (3, 6, 7). We have summarized these studies in Table 5. After stratification of the patients for normal serum GH and IGF-I concentrations at the end of treatment, successful treatment seems to be associated with an improved mortality risk. Although this is a likely conclusion in view of the clearly reduced life expectancy associated with active acromegaly in the past (1, 2), the use of stratification factors obtained at the end of follow-up may introduce a considerable bias in the analysis (3, 6, 7, 11). We studied a homogenous and unique cohort, as all patients were consecutively treated in a single surgeon setting, and all had similar clinical and biochemical follow-up in our center. Adjuvant treatment decisions were based on the same strict criteria throughout the years. We performed data analysis only with factors available at the moment of inclusion. Consequently, the introduction of bias due to the increasing chance to achieve remission with a longer follow-up was prevented. We found a survival rate not different from that in the general population for all patients after primary transsphenoidal surgery regardless of the biochemical result, although most patients were well controlled in the follow-up using adjuvant treatment. Most series still report an increased mortality risk (3), and our study confirms the normal survival risk for all surgically treated patients reported only by Swearingen et al. (5) and Arita et al. (12). However, it is possible that in larger studies observed:expected ratios 1.2–1.3 times normal would indicate a slightly, but significantly, increased mortality risk.

The immediate postoperative (glucose-suppressed) GH concentrations and preoperative disease duration significantly predicted survival rates in our study. Other characteristics of the severity of GH excess, such as the height of preoperative and postoperative serum GH and IGF-I concentrations, did not predict survival in all patients. Within the first 5 postoperative yr, these predictive effects for survival were strongest. Interestingly, and not reported previously, the negative influences of these perioperative parameters of GH excess disappeared when remission was established and after a follow-up of more than 5 yr.

Factors influencing mortality risk are difficult to distillate from studies in acromegalic patients, as sensitivity to and height of GH and IGF-I concentrations are variable, and cohort sizes are limited due to the low prevalence of the disorder. Moreover, the duration of follow-up may thus affect risk factors. This may explain why other studies with shorter follow-up duration found an even more pronounced impact of duration of preoperative or active disease than we did (13). The finding of a 5-fold, significant increase in mortality with a preoperative disease duration of 5–10 yr compared with a duration of less than 5 yr, and only a 3-fold (nonsignificant) increase with a duration of more than 10 yr is unexplained. Although there might be a relationship between a lower severity of GH excess in those patients with a longer duration of undiagnosed acromegaly, the estimation of disease duration, although carefully examined with photographs and complaints, may be subject to interpretative inaccuracy. However, we believe that the disease duration is a factor of importance for survival because it is also related to significant comorbidity, such as valvular heart disease (14, 15).

The efficacy of adjunctive postoperative therapy in establishing remission in the postoperative follow-up has probably weakened the relationship we found between the postoperative serum GH and IGF-I concentrations and survival and thus improved the outcome of this study. Time-dependent analysis of four successive serum IGF-I concentrations indeed established a relation between the serum IGF-I concentration and survival, notwithstanding that a normal IGF-I concentration was achieved in the majority of patients. Therefore, further research is required to assess which remission criterion should be used with respect to mortality. Bates et al. (7) and Orme et al. (8) both used a mean GH level less than 5 mU/liter (<2.5 μg/liter) at the end of treatment, whereas in the study by Abosch et al. (4) patients with a postoperative serum GH between 2.5 and 5 μg/liter had equal mortality rates. Only Swearingen et al. (5) assessed the effect of disease status as evaluated by a (single) serum IGF-I measurement on survival. Evaluation of different remission criteria in this study suggested that only a normal postoperative serum IGF-I concentration is associated with survival, whereas a normal serum GH level and glucose-suppressed GH concentration were not associated with survival. However, as IGF-I was only measured from 1986 onward, the number of deaths was small for this criterion, as reflected by the broad confidence intervals. In contrast, the present study suggests that the upper limit of a safe GH concentration of 5 mU/liter is probably too high, and this might also be true for the glucose-suppressed GH value. Therefore, confirmation by additional large scale studies with serial GH (and IGF-I) measurements in a time-dependent approach is warranted, and the outcome may lead to more stringent biochemical treatment goals.

Transsphenoidal surgery was the initial treatment for all of our patients with acromegaly diagnosed from 1977 onward. However, an increasing number of acromegalic patients received initial medical treatment since the introduction of somatostatin analog depot preparations. Additional investigation is required to assess whether the survival rates of medically treated

Table 5. Summary of published mortality studies in acromegaly

Author	Date of publication (*study period)*	Design[1]	Number of patients	Follow-up (years)	Number of deaths	Observed : Expected ratio	Predictive factors	Outcome factors
Wright *et al.* (1)	1970	HR	194		55	1.8		
Alexander *et al.* (2)	1980 (1960-1971)	HR (all patients)	164	6.2	45	3.3	Male gender	
Nabarro (15)	1987 *(1963-1983)*	HR	256	6.8	47	1.3	Female gender	
Bengtsson *et al.* (20)	1988 *(1955-1984)*	HR (all patients)	166	15	62	3.2	Calendar year of diagnosis, Surgery vs irradiation	
Raayasoorya *et al.* (12)	1992 *(1964-1989)*	HR (all patients)	151	12	32	3 (cardiovascular) 3.3 (cerebrovascular) 1 (malignancy)	Duration of symptoms Age Presence of hypertension and cardiovascular disease at diagnosis	Last known GH
Etxabe *et al.* (21)	1993 (*1970-1989)*	HR (all patients)	74	15	10	3.2 (1.55-5.93)	Male gender	
Bates *et al.* (7)	1993 *(1967-1991)*	HR (all patients)	79	9-10	28	2.63(1.8-3.9)	not assessed	Lowest GH in follow-up, <5 mU/L , O:E, 1.4; 5-10 mU/L, O:E, 2.0
Orme *et al.* (8)	1998 *(?)*	MC (all patients)	1362		366	1.6 (1.44-1.77)	not assessed	Last known GH <2.5 µg/L, O: E, 1.1; 2.5-10 µg/L:, O: E, 1.4; >10 µg/L, O: E, 2.1
Swearingen *et al.* (5)	1998 *(1978-1996)*	SS (all patients) If in remission	149 86	7.8 ?	12 ?	1.16 (0.66-2.0) 0.84 (0.3-2.2)	Yr in Remission vs yr with active disease (time dependent, age adjusted)	

Author	Date of publication (*study period)*	Design[1]	Number of patients	Follow-up (years)	Number of deaths	Observed : Expected ratio	Predictive factors	Outcome factors
Abosch *et al.* (4)	1998 *(1974-1992)*	SS (all patients) If in remission	214 164		29 20	1.28 1.01	Postoperative persistent disease> 5 µg/L	Last known GH, <5 µg/L, O: E, 1.0; >5 µg/L, O: E, 3.1
Shimatsu *et al.* (22)	1998 *(…-1993)*	MC (all patients)	979	6	84	2.1	not assessed	not assessed
Beauregard *et al.* (6)	2003 *(1970-1999)*	SS (all patients)	91		18	2.14	not assessed	Last known GH< 2.5 µg/L and GH-GTT < 1 µg/L and normal IGF-I, O: E, 0.88
Arita *et al.* (23)	2003 *(1977-2000)*	SS (all patients) If GH <2.5 ng/ml If GH 2.5-5 ng/ml	154 72 51	10	11	1.17 (0.54 - 2.38) 1.09 (0.34 - 3.05) 1.64 (0.48 - 4.97)	not assessed	
Our study	2004 *(1977-2002)*	SS (all patients)	164	12.3	28	1.33 (0.87 - 1.87)	Preoperative disease duration Postoperative glucose-suppressed GH, Normal IGF-I Age	

[1] SS, Surgical (consecutive) series; HR, hospital records/referral series; MC, multicenter study; O: E = observed : expected mortality ratio.

patients are similar to those initially treated by surgery, as no comparative trials between surgery and medical therapy are available.

Cardiovascular disease contributes to the excess mortality in acromegaly, with an average of 33% of deaths and even of 50%, if cerebrovascular deaths are also included (1, 2, 3, 5, 16). Many cardiovascular risk factors are increased in active acromegaly, including hypertension, type 2 diabetes mellitus, dyslipidemia, obesity, insulin resistance, and increased intima media thickness (17). Reduction of serum GH levels improves these risk factors. Additionally, cardiomyopathy, right and left ventricular hypertrophy, and interstitial fibrosis may be present in active acromegaly, which are partially reversed by successful treatment, as assessed especially for somatostatin analogs (18). However, these cardiac effects have not been investigated in surgically cured patients.

There is no consensus as to whether in acromegaly an increased mortality is present for malignant disease. There is evidence for a high incidence of colon polyps and colon malignancy (8, 19, 20). However, the increased life expectancy of the acromegalic patients in treated cohorts and therefore the higher incidence of malignant disease may affect the cancer mortality figures.

In the largest and longest single center mortality study in acromegalic patients (>2000 patient-years) to date, we report an observed:expected mortality ratio of 1.30 for all patients with acromegaly undergoing primary transsphenoidal surgery and in the case of persisting GH excess followed by adjuvant therapy in the form of radiotherapy and treatment with somatostatin analogs. Although not significantly increased due to the small numbers, the data suggest that the mortality risk will still be raised after treatment for acromegaly. Interestingly, of the three remission criteria used in this study, a normal IGF-I level was the only one to be significantly associated with survival. Parameters related to GH excess, i.e. the estimated duration of preoperative disease and the postoperative glucose-suppressed serum GH levels, have a negative predictive effect on survival, especially within the first 5 yr postoperatively. After cure by either surgery alone or surgery plus multimodality treatment, these predictive effects related to GH excess are not present. Therefore, transsphenoidal surgery, in the case of persisting GH excess followed by adjuvant therapy, currently has the best available evidence for reduction of the excessive mortality rate of untreated acromegaly.

Abbreviations: CI, Confidence interval; GTT, glucose tolerance testing; RR, relative risk.

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