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Clinical Article

Treatment outcomes and mortality of 94 patients with acromegaly

R. Trepp[1], **C. Stettler**[1], **M. Zwahlen**[2], **R. Seiler**[3], **P. Diem**[1], and **E. R. Christ**[1]

[1] Division of Endocrinology and Diabetes, University Hospital of Bern, Inselspital, Bern, Switzerland
[2] Department of Social and Preventive Medicine, University of Bern, Bern, Switzerland
[3] Department of Neurosurgery, University Hospital of Bern, Inselspital, Bern, Switzerland

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Summary

Background. Due to new therapeutic modalities and modified therapeutic goals outcome of patients with acromegaly may change over time and differ by centre. We analysed treatment outcomes and mortality of our patients with acromegaly seen between 1971 and 2003.

Method. The cohort consisted of 94 patients who had been followed for 0.3–31 years (mean 10.6 years). Remission criteria were a normalized IGF-I concentration, a nadir GH level during oral glucose load of $<1.0\,\mu g/l$ and a random GH value of $<2.5\,\mu g/l$.

Findings. Transsphenoidal surgery achieved remission in 80% of patients with micro-adenomas (<1 cm), 65% with meso-adenomas (≥1 cm to <2 cm) and 27% with macro-adenomas (≥2 cm). Patients with meso-adenomas operated on after 1995 tended to have a better outcome compared to those operated on before 1995 (Remission in 83% *vs.* 38%). Radiotherapy resulted in disease control in 22 of 47 patients (47%). Intramuscular depot formulation of octreotide (Sandostatin® LAR®) led to disease control in 17 of 26 patients (65%). After multimodal therapy persistent acromegalic activity remained in 18% of the patients; only one of them had an adenoma of <2 cm. The standardized mortality ratio was 1.30 (95% CI 0.52–2.67) for patients in remission and 1.38 (95% CI 0.51–3.00) for patients with persistent acromegalic activity.

Conclusions. Most patients with adenomas of <2 cm can be expected to achieve remission by transsphenoidal surgery alone. Furthermore, virtually all patients with adenomas of <2 cm and more than 80% of patients with adenomas of ≥2 cm can be expected to achieve remission by adjuvant treatment. Aggressive multimodal therapy is critical in the management of acromegaly reducing mortality risk close to that of the general population.

Keywords: Acromegaly; transsphenoidal surgery; radiotherapy; outcome; mortality.

Introduction

Acromegaly is a rare disorder with an annual incidence of 3–4/million and a prevalence of 40–60/million population [3, 35]. The underlying pathology is a growth hormone (GH)-secreting pituitary adenoma [30]. Apart from cosmetic and orthopaedic deformities, uncontrolled acromegaly has been reported to lead to a 2–4.8 fold increased mortality rate, primarily caused by cardiovascular and respiratory diseases [1, 8–11, 26, 33, 38].

Despite recent advances in medical treatment transsphenoidal surgery is still the initial procedure of choice in most patients with acromegaly. Persisting disease can be controlled by conventional and stereotactic radiotherapy, somatostatin receptor ligands, dopamine agonists and the GH receptor antagonist pegvisomant [15].

The aims of treatment are to relieve clinical signs and symptoms, to normalize biochemical disease markers, to reduce tumour size while preserving pituitary function, and to restore life expectancy to that of the general population. Until the early 1990s patients with a post-therapeutic GH level of $<5.0\,\mu g/l$ were considered to be cured [28, 42]. Epidemiological long term studies however showed that a more rigorous biochemical control is required to normalize the elevated mortality rate [1, 8, 9, 26, 33, 38]. Based on these data and due to the development of more sensitive GH assays and the introduction of IGF-I measurement, increasingly stricter remission criteria have been defined over the last decade [24, 31, 32]. At present a nadir GH level of $<1.0\,\mu g/l$ during oral glucose tolerance test and a normal age- and gender-matched IGF-I concentration represent the biochemical treatment goal [24].

Acromegaly is a slowly evolving disease. Long-term follow-up studies are needed in order to assess disease control based on the new remission criteria. Due to new

therapeutic modalities and their availability in the corresponding countries outcome may change with time and may be dissimilar at different centres. Most previous studies focused on some particular aspects of the clinical course of acromegaly and its treatment, without reporting comprehensive detailed long-term data containing outcome results of all applied therapeutic modalities and analysis of mortality. Therefore, we aimed to determine the long-term remission following transsphenoidal surgery, radiotherapy and medical treatment in patients with acromegaly at the University Hospital of Bern. Secondly, mortality of acromegaly was assessed in this cohort.

Patients and methods

Study protocol

A retrospective chart review was performed on all patients with acromegaly seen at the Division of Endocrinology and Diabetes of the University Hospital of Bern, Switzerland, between December 1971 and December 2003. The investigation resulted in a cohort of 94 patients who had been followed for 0.3–31 years (mean 10.6 years).

Endocrine evaluation and outcomes

Typical signs and symptoms associated with biochemical evidence of GH hypersecretion led to the diagnosis of acromegaly in all patients.

Until 1994 GH was measured by radio-immuno assay (RIA) (Serono Diagnostics, Freiburg, Germany). Between 1994 and 2002 GH was measured by immunoradiometric assay (IRMA) (HGH MAIAclone Serono Diagnostics, Freiburg, Germany). The intra-assay coefficient of variation (CV) was 1.8–2.5%, the interassay CV was 2.4–2.9%, and the sensitivity was 0.02 ng/ml. From December 2002 GH was measured by enzyme-linked immuno-absorbent assay (ELISA) (DSL-10-1900 Active kit, Diagnostic System Laboratories, Webster, TX, USA). The intra-assay CV was 3.3–4.3%, the interassay CV was 6.3–6.5%, and the sensitivity was 0.03 ng/mL. From March 1995 to December 1997 IGF-I was measured by hydrochloride acid-ethanol extraction RIA (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). The intra- and interassay CVs were 5.0–9.5% and 8.8–10.8%, respectively. The sensitivity was 0.1 ng/ml. From January 1998 IGF-I was measured by IRMA (Nichols Institute, San Juan Capistrano, CA, USA). The intra-assay CV was 3.3–4.3%, the interassay CV was 9.3–15.8%, and the sensitivity limit was 6 ng/ml.

Current remission status of patients was determined by reviewing the most recent follow-up visit. Remission criteria were a normal age- and gender-matched IGF-I concentration and either a nadir GH level during oral glucose load of $<1.0\,\mu g/l$ or a random GH value of $<2.5\,\mu g/l$. Patients with discordant remission status are reported only for final outcome after multimodal therapy. For analysis of different therapeutic modalities patients with discordant remission status were considered to be in remission. In 58 patients remission status was based on nadir/random GH and IGF-I levels, in 29 patients on IGF-I concentrations only and in 6 patients on nadir/random GH levels only. Remission status could not be assessed in 1 patient who refused follow-up surveillance.

Concurrent impairments of other pituitary hormone axis were assessed on the basis of laboratory evaluations and medication provided.

The second outcome in this study was vital status and cause of death of the whole cohort. The information obtained from the medical charts were confirmed or corrected by contacting the patients' general practitioner.

Tumour classification

Pituitary adenomas were classified by size on magnetic resonance imaging, computer tomography or intraoperative findings: tumour size of <1 cm was defined as micro-adenoma, ≥ 1 cm and <2 cm as meso-adenoma, and ≥ 2 cm as macro-adenoma consistent with earlier reports [2, 37].

Treatment protocol

All but seven patients underwent transsphenoidal surgery at the University Hospital of Bern. All operations were performed or supervised by the same neurosurgeon (R.S.). Adjuvant treatment for those patients with insufficient disease control was individualized on the basis of size and localization of residual tumour, biochemical parameters, available medical therapy and patient medical condition and preference.

Statistical analysis and analysis of mortality rate

Differences in proportions in achieved outcome in relation to tumour size and other factors were investigated by calculating Fisher's exact two-sided P-values. A P-value of <0.05 was considered significant. Analyses were performed using GraphPad InStat version 3.00, GraphPad Software, San Diego, California, USA.

For the analysis of all-cause mortality, survival probabilities of all 94 patients after diagnosis were calculated using the exact dates and accounting for censored observations (Kaplan-Meier survival analysis). Date of outcome was date of death or date of last follow-up for censored individuals. As certain patients were seen at the University Hospital only after the diagnosis had been made elsewhere, these patients provided denominator information only after they first came under observation at the University hospital (staggered entry). Age-specific person-years of follow-up (in 5-year age groups) were calculated and age-specific Swiss mortality rates (in 5-year age groups) for the year 1990 were used to calculate the expected number of deaths in this patient cohort. By dividing the expected by the observed number of deaths we obtained the standardized mortality ratios (with 95% confidence intervals) of patients in remission, patients with persistent disease and the whole cohort [13]. This part of the analysis was performed using Stata 8.2, Stata Corporation, College Station, Texas, USA.

Results

Patient characteristics before treatment (Table 1)

Forty-eight percent were male; mean age at diagnosis was 43.7 years (range 19.6–80.4 years). The mean time interval between occurrence of acromegaly-specific symptoms and the date of diagnosis was 6 years (range 1–25 years). Of those patients with known size of adenoma, 8 percent ($n = 6$) had a micro-adenoma (<1 cm), 29% ($n = 21$) a meso-adenoma (≥ 1 cm to <2 cm) and 63% ($n = 45$) a macro-adenoma (≥ 2 cm). Reliable classification to micro-, meso- or macro-adenoma was not possible in 22 patients mainly because magnetic resonance imaging technology for exact measurement

Table 1. *Patient characteristics, treatment modalities and remission at last follow-up*

	Number of patients	%
Total	94	100
Gender		
Men	45	48
Women	49	52
Age at diagnosis		
20–29 years	13	14
30–39 years	23	24
40–49 years	27	29
50–59 years	18	19
60–69 years	10	11
60–80 years	3	3
Size of adenoma		
Micro-adenoma (<1 cm)	6	8
Meso-adenoma (≥1 cm to <2 cm)	21	29
Macro-adenoma (≥2 cm)	45	63
Exact size unknown	22	–
Therapy		
Surgery only	35	37.5
Surgery and radiotherapy	14	15
Surgery and medical therapy	8	8.5
Surgery, radiotherapy and medical treatment	30	32
Radiotherapy only	2	2
Radiotherapy and medical treatment	1	1
Medical treatment only	3	3
No therapy	1	1
Remission at last follow-up (after multimodal therapy)		
In remission	64	68.8
Persistent disease	17	18.3
Discordant	12	12.9
Unknown	1	–

of tumour size was not yet introduced at the time of diagnosis.

Therapy (Table 1)

Ninety-three percent of the patients (n = 87) had initial pituitary surgery. Three patients, diagnosed in 1951, 1963 and 1968, were treated by conventional radiotherapy without prior pituitary surgery. One patient with a principally prolactin-secreting pituitary adenoma with only moderately elevated IGF-I levels was controlled by a dopamine agonist only. Because of advanced age 2 other patients were treated with a dopamine agonist only. One patient refused treatment.

Radiotherapy was used in 50% (n = 47) and medical treatment in 44.5% (n = 42) of the patients. 37.5% of the patients (n = 35) were treated by transsphenoidal surgery alone (without adjuvant therapy). Fifteen percent (n = 14) received surgery combined with radiotherapy and 8.5% (n = 8) surgery and medical intervention (dopamine agonists and/or somatostatin analogues). Thirty-two percent (n = 30) needed combination of all three modalities (surgery, radiotherapy and medical therapy) including one patient who was treated with the GH receptor antagonist pegvisomant. Radiotherapy and/or medical treatment without pituitary surgery were given in 6% (n = 6).

Mode of radiotherapy was conventional (three-field, total dose of 45–50 Gy in 25 fractions) in 43 patients. Three of them received additional stereotactic radiotherapy [27]. Stereotactic radiotherapy without prior conventional radiotherapy was performed in 4 patients.

Dose of long-acting release preparation of octreotide (Sandostatin® LAR®) ranged from 10 to 40 mg and was adjusted every 2–3 months based on the response of GH and IGF-I levels.

Remission after initial pituitary surgery (Table 2)

The success of initial transsphenoidal pituitary surgery was related to tumour size. At last follow-up 80% of patients with micro-adenomas (4/5), 65% with meso-adenomas (13/20) and 27% with macro-adenomas (12/44) were in remission after initial surgery. The proportion of patients in remission was significantly higher in patients with adenomas <2 cm compared to patients with macro-adenomas (≥2 cm) ($P = 0.02$). For the total cohort postoperative remission without additional adjuvant therapy was achieved in 42%. Considering 18 patients with unknown tumour size did not change overall remission. Mean follow-up after transsphenoidal surgery was 7 years (range 0.3–18.2 years) for micro-adenomas, 6.9 years (range 1.0–24.1 years) for meso-adenomas, 10.6 years (range 0.5–31 years) for macro-adenomas and

Table 2. *Remission after pituitary surgery in relation to tumour size and time period of surgery (brackets show number of patients in remission out of total number of patients of the respective subgroup)*

	Micro-adenoma	Meso-adenoma	Macro-adenoma	Total
1972–1995	66% (2/3)	38% (3/8)	26% (7/27)	33% (12/38)
1996–2002	100% (2/2)	83% (10/12)	29% (5/17)	55% (17/31)
Total	80% (4/5)	65% (13/20)	27% (12/44)	42% (29/69)

9.3 years for the whole cohort. Proportion of patients in remission reached 100%, 83%, 29% and 55% for micro-adenomas, meso-adenomas, macro-adenomas and the total cohort, respectively, during the period between 1996 and 2002. Compared to the previously (between 1972 and 1995) surgically treated patients a trend towards improved outcome was seen for meso-adenomas (38% *vs.* 83%, $P = 0.06$) and the total cohort (33% *vs.* 55%, $P = 0.09$).

Remission after radiotherapy

Radiotherapy achieved remission in 47% (22/47) of the patients after a mean follow-up of 10.1 years (median 8.0 years, range 0.3–30 years). Of those with more than 10 years follow-up after radiotherapy 57% (12/21) were in remission. Difference between these two proportions was not statistically significant ($P = 0.60$). Patients in remission after radiotherapy but still on medical treatment were considered to have persistent disease. This group consisted of 5 patients treated with dopamine agonist, 1 patient treated with octreotide LAR and 13 patients treated with octreotide LAR and dopamine agonist.

Seven patients were treated by stereotactic radiotherapy. Three of them already had conventional radiotherapy before: one achieved remission one year after stereotactic radiotherapy, the other two still needed further medical treatment 4 and 7 years after the intervention. Of the four patients without prior conventional irradiation, stereotactic radiotherapy achieved remission in one patient. Mean follow-up in this group was 13 months (range 4–16 months).

All three patients treated by initial conventional radiotherapy without pituitary surgery achieved remission. One of them was transiently treated with bromocriptine.

Remission with octreotide therapy

Twenty-six patients were treated with intramuscular depot formulation of octreotide (Sandostatin® LAR®). Sixty-five percent (n = 17) achieved remission. Nineteen patients had prior radiotherapy and 20 patients were concomitantly treated with a dopamine agonist. Four patients had octreotide as the only adjuvant treatment (without radiotherapy or dopamine agonist); three of them achieved remission.

Remission at last follow-up after multimodal therapy (Table 1)

Overall, 69% of the patients were classified as in remission at the last follow-up. 45.2% achieved complete remission in terms of a normal age- and gender-matched IGF-I concentration and either a nadir GH level during oral glucose load of $<1.0\,\mu g/l$ or a random GH value of $<2.5\,\mu g/l$. In 20.4% IGF-I levels were normalized, but oGTT was not performed; and in 3.2% IGF-I concentrations were not available but a sufficient suppression of GH after glucose load was achieved. 12.9% had discordant results: 3.2% had elevated IGF-I levels but normal GH suppression during oral glucose load and 9.7% had non-suppressible GH but normal IGF-I concentrations. Of the remaining 18.3% who did not achieve remission (5.4% defined by elevated IGF-I and pathological oGTT, 9.7% by elevated IGF-I concentrations, 3.2% by elevated random GH), only one patient had an adenoma of $<2\,cm$. Remission status could not be assessed in 1 patient who refused follow-up surveillance.

Concurrent pituitary function abnormalities (Tables 3 and 4)

At the time of diagnosis, 34% of the patients had concomitant hyperprolactinemia. Forty-five percent of the patients had partial or complete pituitary insufficiency. Most commonly the gonadal axis was affected (in 34%) followed by secondary hypothyroidism (17%) and ACTH deficiency (7%). No patient with diabetes

Table 3. *Concurrent function abnormalities of pituitary hormone axes (brackets show number of patients with respective pituitary function abnormality out of total number of patients)*

	Pretreatment	Posttreatment
Hyperprolactinemia	34% (24/71)	9% (8/91)
Partial or complete hypopituitarism	45% (32/71)	74% (67/91)
LH/FSH deficiency	34% (24/71)	60% (55/91)
TSH deficiency	17% (12/71)	53% (48/91)
ACTH deficiency	7% (5/71)	41% (37/91)
GH deficiency	–	5% (5/91)
Permanent diabetes insipidus	0% (0/71)	4% (6/91)
Unknown	23 patients	3 patients

Table 4. *Presence of hypopituitarism after adjuvant radiotherapy and/or medical treatment (brackets show number of patients in remission out of total number of patients of the respective subgroup)*

Adjuvant treatment modality (after transsphenoidal surgery)	Presence of hypopituitarism
Medical therapy only	88% (7/8)
Radiotherapy only	100% (14/14)
Radiotherapy and medical treatment	83% (25/30)
Total (radiotherapy and/or medical treatment)	88% (46/52)

insipidus was recorded prior to surgery. Posttreatment, 74% of the patients had partial or complete hypopituitarism. With a prevalence of 60%, gonadal insufficiency was the most common pituitary axis failure following treatment. Secondary hypothyroidism was found in 53%, ACTH deficiency in 41% of patients. Five percent developed severe growth hormone deficiency and 4% suffered from permanent diabetes insipidus. Status of other pituitary hormone axes was not recorded in 23 patients before and in 3 patients after therapy.

Patients requiring adjuvant therapy (medical treatment and/or radiotherapy) after pituitary surgery had a prevalence of pituitary insufficiency of 88%. 100% of patients adjuvantly treated by radiotherapy only and 88% managed on adjuvant medical treatment only developed hypopituitarism. Adjunctive treatment using both modalities was associated with hypopituitarism in 83% of patients.

Mortality (Fig. 1, Tables 5 and 6)

Thirteen of the 94 patients died during the follow-up period (5 men and 8 women) at a mean age at death of 70.5 years. Six patients died from heart disease, four from malignant disease and one in a traffic accident.

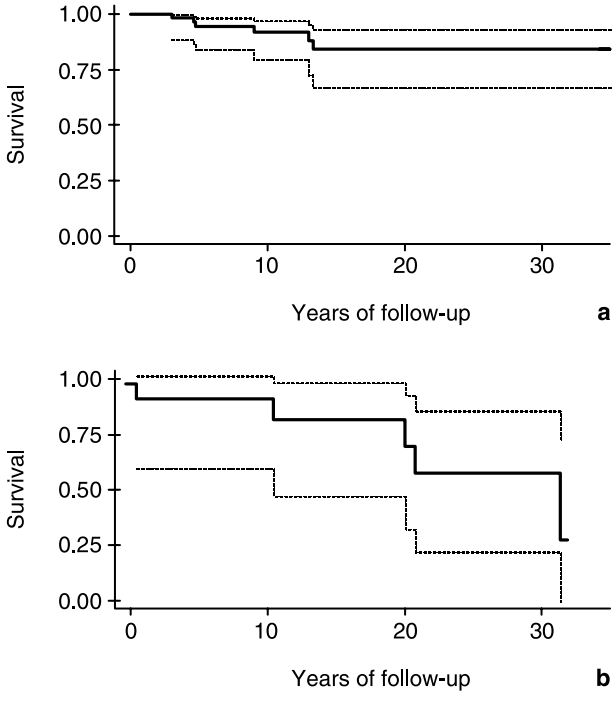

Fig. 1. Kaplan-Meier survival probabilities of patients in remission (a) and patients with persistent acromegalic disease activity (b). Dotted lines indicate 95% confidence limits

Table 5. *Characteristics of deceased patients with acromegaly*

Gender	Age at death	Cause of death	Remission status at last follow-up
Male	56 years	traffic accident	in remission
	68 years	unknown	in remission
	73 years	colorectal carcinoma	in remission
	75 years	myocardial infarction	persistent disease
	82 years	heart failure	in remission
Female	53 years	multiple myeloma	persistent disease
	55 years	heart failure	persistent disease
	60 years	colorectal carcinoma	in remission
	61 years	ovarian carcinoma	persistent disease
	72 years	heart failure	in remission
	80 years	heart failure	in remission
	91 years	unknown	persistent disease
	92 years	heart failure	persistent disease

Table 6. *Standardized mortality ratios according to status of remission at last follow-up*

Remission status at last follow-up	Observed deaths	Expected deaths	Standardized mortality ratio (95% confidence interval)
In remission	7	5.40	1.30 (0.52–2.67)
Persistent disease	6	4.35	1.38 (0.51–3.00)
Whole cohort	13	9.72	1.34 (0.71–2.29)

Direct cause of death was unknown in two patients. Seven patients who died were in remission at last follow-up (mean age at death of 70.0 years). Six patients had persistent disease at last follow-up (mean age at death 71.1 years). Compared to the 1990 Swiss population, the standardized mortality ratio (SMR) for the whole cohort was 1.34 (95% CI 0.71–2.29). The SMR for patients in remission was 1.30 (95% CI 0.52–2.67) and the SMR for those with persistent disease at last follow-up was 1.38 (95% CI 0.51–3.00). Survival in patients in remission tended to be improved compared with patients with persistent disease (Logrank test for equality of survivor functions of $P = 0.09$).

Discussion

The catchment area of our centre in Switzerland includes about 1 million people. The incidence of newly-diagnosed cases of acromegaly was about 3–4 per year which corresponds to previous reports from other countries [3, 10, 19, 35]. Gender distribution, age at diagnosis and time interval of symptoms until diagnosis of the present cohort were similar to earlier reports [2, 9, 17, 23, 37]. Interestingly, our cohort consisted of a

notably larger proportion of patients with a macro-adenoma and only relatively few patients with a micro-adenoma. This may be due to the fact that biochemical assays and pituitary imaging techniques were less reliable 20–30 years ago, and therefore, the diagnosis of a GH-secreting micro-adenoma was more difficult at that time. Furthermore, the awareness of primary health physicians may have improved over the last decades resulting in an earlier diagnosis of the disease. The fact that all but one GH-secreting micro-adenoma were diagnosed during the last ten years supports this hypothesis.

Epidemiological long term studies showed that a reduction of mean GH day curve or random GH to $<2.5\,\mu g/l$ measured by RIA is required to normalize the elevated mortality rate [1, 8, 33, 38]. The newer more sensitive GH assays yield lower results compared to the formerly used RIA [21]. For analysis of different therapeutic modalities patients with discordant remission status were considered to be in remission. No patient had discordant results in terms of a random GH $<2.5\,\mu g/l$ measured by IRMA or ELISA and an elevated IGF-I. Therefore, treatment outcome results were not falsely improved by using the same cut-off GH value as for measurements by RIA.

Remission after pituitary surgery as initial treatment was significantly dependant on tumour size. Eighty percent of patients with micro-adenomas, 65% with meso-adenomas and 27% with macro-adenomas achieved remission after surgery only. Despite lower numbers of performed operations per year the outcome of transsphenoidal surgery in our cohort was comparable with earlier reports of specialized centres with a single dedicated neurosurgeon [2, 9, 17, 23, 37]. However, reliable comparisons between centres are difficult to make since differences in patient populations, tumour classifications and criteria of postoperative remission complicate comparisons between studies. Our results show that the cut-off of tumour size above which surgical cure becomes considerably less likely is around 2 cm rather than around 1 cm, in keeping with a recently published report [11]. Pituitary adenomas of more than 2 cm almost always invade surrounding structures. Some of these tumours are *a priori* not completely removable by neurosurgery, especially when vital structures such as the carotid arteries are enclosed.

More recent surgical procedures showed a trend towards better outcomes. Notably, our results do not represent early postoperative remission, but remission after a mean follow-up of 10.5 years, thereby including the patients with recurrent disease. Impending disease recurrence might slightly deteriorate more recent surgical results but using the current stringent remission criteria substantial impact is unlikely [40]. The improvement of surgical results over time in our cohort was mainly due to a higher remission rate for meso-adenomas during the last seven years. Meso-adenomas are often just confined to the sella or only moderately invading surrounding structures. In these situations the experience of the performing neurosurgeon is likely to be critical for success or failure. Although the time periods were chosen to contain a similar number of patients according to tumour size, firm conclusion is limited by the relatively small number of patients in the subgroups. Moreover, the arrangement resulted in notably different length of time periods. Nevertheless, the suspected improvement is in keeping with earlier reports and possibly due to the growing surgical experience and expertise over time [2, 23, 29, 38]. In addition, improvements in preoperative imaging studies and surgical equipment may have contributed to these findings.

Radiotherapy resulted in disease control in 22 (47%) of 47 patients after a mean follow-up of 10.1 years (median 8 years, range 0.3–30 years). Patients receiving medical treatment with octreotide or dopamine agonist at last follow-up were considered to have persistent disease. As the effects of radiotherapy can occur years after treatment it is conceivable that some patients received unnecessary medical treatment. However, since we try to omit medical treatment at least every second year following radiotherapy substantial impact on the present results is unlikely. Three recently published reports questioned the efficacy of radiotherapy when assessed by strict biochemical remission criteria [5, 16, 43]. Our results however are more in line with other studies that showed achievement of remission in a substantial proportion of patients (34–79%) albeit after a considerable time interval (mean or median follow-up 5–15 years) [7, 12, 18, 25, 34].

In seven patients stereotactic radiotherapy was performed [27] and control of disease was obtained after one year in 2 patients suggesting a more rapid achievement of safe GH levels compared with conventional radiotherapy [4, 6, 39, 41, 44]. The small sample size with a relatively short period of observation and the heterogeneity of the group (i.e. three patients with previous conventional radiotherapy) do not allow firm conclusions about efficiency of stereotactic radiotherapy compared to conventional radiotherapy.

Sixty-five percent of our patients treated with octreotide LAR achieved remission, in keeping with previous reports [20]. Most of the patients had prior radiotherapy and were concomitantly treated with a dopamine agonist; therefore the actual effect of octreotide LAR itself might be somewhat lower.

Administrating multimodal therapy all patients with micro-adenomas and all but one patient with meso-adenomas achieved remission. Uncontrollable acromegalic activity remained a problem in 18% of patients; virtually all of them had invasive macro-adenomas. These results are consistent with the results of other specialized centres [1, 9, 11, 12, 38].

Thirteen percent of our patients showed discordant results (i.e. adequate GH suppression and elevated IGF-I concentrations or vice versa); 30% were assessed by IGF-I measurement only. Taking into account other conditions that are associated with decreased IGF-I levels (i.e. cachexia) [21], we generally give more weight to IGF-I levels as they reflect the integrated effect of growth hormone secretion. Depending on the assay methods and cut-off values used, disagreement between random/nadir GH and IGF-I levels occurs in up to one third of patients [21]. In some patients, discordant results may express slight persistent disease activity, which may lead to increased morbidity and possibly mortality [22, 36].

Partial or complete pituitary insufficiency was encountered in 45% before and in 74% after treatment. The gonadal axis was the most common affected, followed by the thyroidal and the adrenocortical. In the present study a high prevalence of pituitary insufficiency was observed in patients requiring adjuvant treatment after transsphenoidal surgery irrespective of the used adjunctive treatment modalities. However, the retrospective design, the relatively small number of patients and the overlapping treatment with both adjunctive therapeutic modalities hinder reliable comparison. More long-term data comparing morbidity and mortality of acromegalic patients managed on adjuvant medical treatment with *versus* without (stereotactic) radiotherapy are warranted.

Thirteen deaths occurred in our cohort, mainly due to cardiovascular disease and neoplasia. Standardized mortality ratio was 1.30 for patients in remission, 1.38 for patients with persistent disease and 1.34 for the whole cohort. Considering the low number of patients and the resulting large confidence interval, the relatively low mortality ratio in our patients with persistent disease does not necessarily disagree with previous observations that reported up to 4.8 fold increased mortality rates in patients with persistent acromegalic activity [1, 8, 9, 11, 26, 33, 38]. However, the increase in mortality rate is dependent on the degree of GH hypersecretion [26] and most of our patients with persistent disease had only moderate residual GH hypersecretion possibly reflecting a more aggressive treatment approach and/or a more comprehensive availability of adjuvant therapeutic modalities.

Conclusions

This study suggests that most patients with adenomas of <2 cm can be expected to achieve remission by transsphenoidal surgery alone. Furthermore, virtually all patients with adenomas of <2 cm and more than 80% of patients with adenomas of ≥ 2 cm can be expected to achieve remission by adjuvant treatment. The effect of radiotherapy is similar to somatostatin analogues in terms of biochemical disease control albeit after a long time interval. Cardiovascular disease and neoplasia are the most common causes of death in acromegalic patients. Aggressive multimodal therapy is critical in the management of the disease reducing mortality risk close to that of the general population. Advances in pharmacological treatment (i.e. use of pegvisomant and selective somatostatin receptor agonists) and radiotherapy (radiosurgery) may result in further improvement of disease control.

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Comments

This paper presents a series of 94 patients with Acromegaly who were treated by different treatment modalities during a period of 30 years. Although this is a surgical series (only 7 out of 94 patients were not

operated on), the adjuvant treatments such as irradiation and Octreotide treatments are well analysed with a long period of follow-up.

The article is well written and is original in the approach to analyse the various treatment modalities. Analysis of the rate of mortality in acromegalic patients adds to our body of knowledge of this disease.

There are a few limitations to the study as mentioned by the authors in the Discussion section. These are:

1. Medical treatment without surgery was given to only a few patients
2. The cohort in this study included a higher proportion than usual of Macro-adenomas >2 cm, which may influence the rate of remission.
3. Only a few patients received Stereotactic irradiation. This is a modern treatment modality that is not well presented among the various options studied in this paper.

In conclusion, this is an important work that may contribute to the understanding of the overall management of Acromegaly.

M. Hadani
Tel-Aviv

This paper is a clearly written audit of acromegaly care in a single Swiss centre.

J. S. Bevan
Aberdeen

Correspondence: Emanuel Christ, Division of Endocrinology and Diabetes, University Hospital of Bern, Inselspital, 3010 Bern, Switzerland. e-mail: emanuel.christ@insel.ch