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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

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Abstract

Criteria to define the biochemical remission of acromegaly following surgery have changed over the years, and the current use of stringent criteria needs a critical re-evaluation of the surgical results. On the other hand, few data are currently available concerning the possible impact of pituitary surgery on the quality of life of operated acromegalic patients. In this prospective study, we wished to evaluate the initial outcome and long-term recurrence rate in a large series of acromegalic patients operated on by transsphenoidal surgery (TSS), to carefully analyse predictive factors for surgical outcome and to point out possible additional effects of surgery in these patients. Ninety-two out of 98 operated patients could be considered for follow-up. Biochemical remission was strictly defined as plasma GH levels < 1 ng/ml during an oral glucose tolerance test (OGTT) and normalisation of age-related IGF-I levels. Hormonal assessment, including an OGTT, was performed 6 months following surgery and then annually to evaluate pituitary function. Fifty-five per cent of patients achieved a biochemical remission of acromegaly. The remission rate at 6 months was 80% for patients with microadenoma and 50% for macroadenoma. Univariate analysis showed that a large extrasellar extension, preoperative high GH levels and dural invasion were correlated with a poor outcome of surgery while, according to multivariate analysis, only invasion of cavernous sinus and preoperative GH levels > 10 ng/ml were independent negative predictors. Mortality was 0% and the overall complication rate was about 10%. Pituitary function worsened in five patients but improved in 16 out of 30 patients with preoperative pituitary defects. No recurrence was observed during a median follow-up of about 8 years. We conclude that TSS is able to achieve a biochemical remission in more than half of acromegalic patients, and that the current criteria for remission seem to indicate a cure in most cases.

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Introduction

Acromegaly is a systemic disease caused by a pituitary growth hormone (GH)-producing tumour in more than 99% of cases (Melmed 1990). It is associated with an increase in mortality and morbidity, especially due to cardiovascular complications (Rajasoorya *et al*. 1994, Colao *et al*. 1997*a*). Transsphenoidal surgery (TSS) remains the first choice treatment for acromegaly (Melmed *et al*. 2002). It is effective and safe (Ross & Wilson 1988, Tindall *et al*. 1993, Davis *et al*. 1993, Van Lindert *et al*. 1997, Abosch *et al*. 1998, Freda *et al*. 1998, Ahmed *et al*. 1999, Laws *et al*. 2000, Shimon *et*

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al. 2001), even in elderly patients (Minniti *et al*. 2001*a*), and it is able to reverse metabolic and cardiovascular complications related to the disease (Colao *et al*. 2001, Minniti *et al*. 2001*b*, Jaffrain-Rea *et al*. 2002). However, complete removal is not always possible and evolutive acromegaly may continue. Medical therapy with somatostatin analogues (Lamberts *et al*. 1992, Freda 2002) or radiotherapy (Barrande *et al*. 2000, Powell *et al*. 2000) are usually administered as post-operative adjuvant treatments for acromegaly. Surgical cure rates range from 40 to 80% in most surgical series, depending on the criteria used to define the biochemical remission of the disease (Ross & Wilson 1988, Losa *et al*. 1989, Tindall *et al*. 1993, Van Lindert *et al*. 1997, Abosch *et al*. 1998, Freda *et al*. 1998, Ahmed *et al*. 1999, Laws *et al*. 2000, Kreutzer *et al*. 2001, Shimon *et al*. 2001). Indeed, the concept of biochemical remission of the disease has changed noticeably over the past two decades, so that basal GH < 2.5 ng/ml or GH < 1 ng/ml during the oral glucose tolerance test (OGTT), and the normalisation of age-related insulin-like growth factor-I (IGF-I) are now widely accepted as modern criteria to define the biochemical remission of the disease (Giustina *et al*. 2000, Melmed *et al*. 2002). According to such stringent criteria, normalisation of GH hypersecretion after surgery is achieved in about 40–60% of patients in the few recently published series (Laws *et al*. 2000, Kreutzer *et al*. 2001), in contrast with older series reporting a surgical success, as defined by plasma GH levels < 5 ng/ml, in more than 75% of patients (Ross & Wilson 1988, Tindall *et al*. 1993), but similar to series considering a glucose-suppressed GH < 2 ng/ml (Falbusch *et al*. 1992, Sheaves *et al*. 1996, Van Lindert *et al*. 1997, Freda *et al*. 1998, Shimon *et al*. 2001).

Although recurrence of acromegaly is commonly estimated to occur in 5–10% of successfully operated patients (Ross & Wilson 1988, Buchfelder *et al*. 1991, Valdemarsson *et al*. 1991, Tindall *et al*. 1993, Abosch *et al*. 1998, Freda *et al*. 1998), a lower incidence has been reported in the most recent series (Laws *et al*. 2000, Kreutzer *et al*. 2001). It is clear that the use of different criteria to define the biochemical remission of acromegaly and the duration of follow-up may account for such differences, and that the use of stringent criteria may reduce the recurrence rate of disease. A re-evaluation of post-operative recurrence rate over a significant follow-up period is therefore mandatory.

We here present the results of a long-term prospective follow-up evaluation conducted in a large series of acromegalic patients who underwent TSS. The clinical outcome and tumour recurrence rate have been evaluated according to the more recent stringent criteria of cure, and both univariate and multivariate analyses have been used to determine the significance of patient and tumour characteristics as prognostic factors, i.e. predictive of post-operative disease persistence. In addition, because normalisation of GH/IGF-I hypersecretion is the main but not the sole objective to achieve when treating acromegaly, we wished to consider some objective parameters concerning the patients' quality of life during the immediate post-surgical period and long-term follow-up.

Patients and methods

In order to evaluate the long-term evolution of the disease, 98 consecutive patients with active acromegaly who underwent surgery between 1990 and 1997 in the Neurosurgical Department of 'La Sapienza' University in Rome were considered for this prospective study. Six patients with insufficient post-operative data were considered lost to follow-up, so that 92 patients (45 males and 47 females), aged 42.3 ± 14.2 years (means $\pm$ S.D.) were finally studied. Acromegaly was diagnosed on the basis of typical clinical features and elevated fasting plasma GH levels, not suppressible to less than 2 ng/ml during an OGTT with 75 g glucose, and plasma IGF-I levels, adjusted for age, above the high normal limit. Tumours were classified into macroadenomas (> 10 mm) or microadenomas (< 10 mm) on the basis of magnetic resonance imaging (MRI). Adenomas were also classified by extension according to Wilson's criteria as follows: stage 0: intrasellar; stage A: suprasellar growth into the cistern; stage B: suprasellar extension, third ventricle recesses obliterated; stage C: suprasellar extension, third ventricle grossly displaced; stage D: intracranial/intradural extension; stage E: cavernous sinus/extradural extension (Wilson 1984). Invasive features of the tumour were diagnosed on the basis of preoperative MRI completed by intra-operative findings. Although campimetric studies were not systematically performed in all patients, they were available for all those with a suprasellar extension adenoma. Twenty-six patients had received preoperative medical treatment with somatostatin analogues (octreotide 200–600 µg/24 h s.c.) for a period of 3–6 months; medical therapy was not randomised but decided case-by-case on the basis of either medical criteria (such as high GH/IGF-I levels, presence of a large tumour and/or cardiovascular complications at the time of diagnosis) or the patient's choice (i.e. delayed surgery). Hypopituitarism was diagnosed according to basal plasma hormone values as follows: low testosterone levels in men, secondary amenorrhea in premenopausal women or inadequately low gonadotrophins in postmenopausal women, low free thyroxine in the presence of low or inadequately normal thyrotrophin values, and low morning cortisol in the presence of low or inadequately normal adrenocorticotrophin levels. According to such criteria, 30 patients had evidence of hypogonadism at the time of the diagnosis, which was associated with central hypothyroidism and hypocortisolism in six and three cases respectively. Prolactin (PRL) levels were high (> 20 ng/ml in men and > 25 ng/ml in women) in 34 patients. TSS surgery was performed by two experienced surgeons (V E and A S) and an immunohistochemical examination of the

tumour was performed in all cases for GH and PRL detection. A complete basal hormonal assessment and OGTT were performed 6 months after surgery and then annually by the same medical staff. Biochemical cure was strictly defined by glucose-suppressed plasma GH levels < 1 ng/ml and normal age-corrected IGF-I values. Patients who did not meet both criteria were considered to have persistent active disease. Recurrence was defined as a secondary increase of IGF-I above normal age-related levels and/or a failure of GH to drop to < 1 ng/ml after OGTT during the yearly follow-up.

Hormone assays

Plasma GH concentrations were determined by an immunoradiometric assay (Biodata Diagnostic, Rome, Italy) with a detection limit of 0.1 ng/ml, and plasma IGF-I concentration by a radioimmunoassay after acid–ethanol extraction (Biochem Immunosystem, Freiburg, Germany). The following age-corrected IGF-I plasma levels were considered normal: $\leqslant 440$ ng/ml (20–30 years), $\leqslant 360$ ng/ml (31–40 years), $\leqslant 310$ ng/ml (41–50 years) and $\leqslant 260$ ng/ml (> 50 years).

Statistical analysis

Data are expressed as means ± S.D., and statistical analysis was performed using the Statview 5.0 software (SAS Institute, USA). Univariate and multivariate analyses by logistic regression analysis were used to examine the outcome of surgery in relation to preoperative bioclinical parameters. Percentages were compared by the Chi-square test. $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

Bioclinical and tumour characteristics of acromegalic patients are shown in Table 1. Note that pretreatment GH, IGF-I and PRL levels were considered in patients who had received preoperative treatment with somatostatin analogues – at the time of surgery, normal GH and/or IGF-I levels were achieved in 18 and 15 out of the 26 patients who received preoperative medical therapy respectively.

Sixteen adenomas were microadenomas (17%) and 76 were macroadenomas (83%), visual field defects being present in only 12 cases. Among macroadenomas, most were intrasellar or extending up to the chiasmatic cistern (stages O/A), a large suprasellar extension being present in 22% of cases (stages B/C). Invasion of cavernous and/or sphenoid sinus could be recognised in 25% and 9% of the tumours respectively. Macroscopic evidence of dural invasion at the time of surgery occurred in 51% of cases. Immunohistochemical examination was positive for GH in all cases, and revealed mixed GH/PRL secretion in 29 cases (31%).

Table 1 Preoperative characteristics of 92 acromegalic patients. Some data are means ± S.D. (range within parentheses)

Parameter	Values
Sex	45M/47F
Age (years)	42.3 ± 14.2
Duration of disease (years)	7.5 ± 3.1
Preoperative medical therapy	26 (28%)
GH	41.7 ± 36.3 (4.3–170)
<10 ng/ml	21 (22%)
>10 ng/ml	71 (78%)
>50 ng/ml	23 (20%)
Mean IGF-I (ng/ml)	622.7 ± 218.5 (346–1493)
Hyperprolactinaemia	34 (37%)
Mean PRL (ng/ml)*	43.3 ± 14.9 (24.7–93.4)
Pituitary dysfunction	30 (32%)
Hypogonadism	30 (32%)
Central hypothyroidism	6 (6.5%)
Secondary adrenal failure	3 (3.2%)
Tumour volume	76 M
Tumour extension†	16 m
Stage 0	26 (28%)
Stage A	46 (50%)
Stage B	13 (14%)
Stage C	7 (8%)
Stage E	23 (25%)
Visual field defects	12 (13%)

*In hyperprolactinaemic patients only; †according to Wilson's classification. M, macroadenoma; m, microadenoma.

Preoperative hyperprolactinaemia was present in 21 mixed adenomas.

Biochemical evaluation of GH/IGF-I secretion 6 months after TSS

Biochemical remission, as defined by mean GH levels < 1 ng/ml during an OGTT and normal IGF-I plasma levels, was achieved in 55% of patients (Table 2). In five cases (5.4%) discrepancies were observed between GH and IGF-I levels: three patients had normal IGF-I but GH levels > 1 ng/ml during an OGTT, whereas two had elevated IGF-I with normal glucose-suppressed GH levels. According to the above criteria, they were not considered to be in remission, but entered the post-operative follow-up study as 'borderline' acromegalic patients.

The overall remission rate at 6 months was 80% and 50% for patients with micro- and macroadenomas respectively. Noteworthy, early post-operative GH levels < 2.5 ng/ml, obtained in 22 cured patients 3 days after surgery, were associated with a 91% chance of biochemical normalisation 6 months after TSS ($P = 0.0001$). In contrast, where a second surgical procedure was performed for the presence of a recurrent or residual tumor ($n = 8$), remission was achieved in only three patients (37%).

Table 2 Surgical outcome and postoperative follow-up in 92 acromegalic patients operated on by TSS

Outcome criteria	No. of patients
Surgical results	
Biochemical remission	51 (55%)
Visual improvement	7/12 (58%)
Improvement of pituitary function	16 (53%)
Surgical complications	
Worsening of pituitary function	5 (5.5%)
Visual worsening	0
Diabetes insipidus	7 (7.6%)
Transient	5 (5.5%)
Definitive	2 (2.2%)
CFS leaks	4 (4.4%)
Lumbar drainage	2 (2.2%)
Surgery	2 (2.2%)
Meningitis	1 (1.1%)
Follow-up of patients in remission ($n = 51$)	
Mean follow-up duration (years)	7.9 ± 2.8
(Range)	(4.4–12.8)
Recurrences	0/51

CSF, cerebrospinal fluid.

Long-term evolution of GH/IGF-I secretion in patients with apparently successful surgery

All the 51 patients who achieved a biochemical remission of acromegaly at 6 months are still alive and could be followed-up yearly for a mean duration of 7.9 ± 2.8 years (range 4.4–12.8 years). In all cases, the measurement of IGF-I and glucose-suppressed GH levels continued to be concordant with the 6-month post-operative evaluation, so that no recurrence of disease was observed.

Noteworthy, among the five 'borderline' patients cited hitherto who were followed-up without any further therapy, one recurrence was observed after 18 months among the three patients with normalised IGF-I but not glucose-suppressed GH levels, whereas in the two patients with only slightly elevated IGF-I levels, adequate glucose-suppressed GH levels (< 1 ng/ml) persisted throughout the follow-up period (7 and 5 years after TSS respectively).

Analysis of prognostic factors influencing post-operative GH/IGF-I normalisation

Analysis of prognostic factors is summarised in Tables 3 and 4. Results from statistical analysis performed 6 months after surgery are shown in Table 3. Note that, because no recurrence was observed during long-term follow-up of patients who were considered in remission 6 months after surgery, this analysis refers to long-term follow-up as well. In addition, because pre-operative medical treatment with somatostatin analogues was not randomised in this study, prognostic factors have been compared between treated and untreated patients (Table 4), indicating that no significant statistical bias has been introduced in the interpretation of this parameter.

Using univariate analysis, tumour size, GH levels and the presence of a dural invasion were the only significant differences between patients whose acromegaly was controlled by surgery and those whose acromegaly was not, whereas age, sex, preoperative medical therapy and IGF-I values were not. The presence of a microadenoma was a slight but significant predictor of good outcome ($P = 0.03$ versus macroadenoma), although no statistical difference could be found between microadenomas and medium-sized macroadenomas (stages O/A) ($P = 0.1$). On the contrary, the presence of a huge adenoma (stage B/C) and/or cavernous sinus invasion (stage E) were strong predictors of post-operative disease persistence. Similarly, the presence of intraoperative evidence of dural invasion was significantly associated with a poor surgical outcome. High preoperative GH levels were also found to negatively influence post-operative outcome: the remission rate was 76% for patients with preoperative GH levels < 10 ng/ml and decreased to 49% and 26% for those with preoperative GH levels > 10 ng/ml or > 50 ng/ml respectively. The presence of a mixed GH/PRL-secreting adenoma was only a borderline predictor ($P = 0.08$).

According to multivariate analysis, only invasion of the cavernous sinus and preoperative GH levels > 10 ng/ml were significant independent predictors of poor surgical outcome ($P = 0.001$ and $P = 0.03$ respectively).

Additional considerations: impact of TSS on the quality of life in acromegalic patients

No post-operative mortality or immediate major complications were observed; however, some minor complications did occur (Table 2). Post-operative diabetes insipidus was observed in seven patients, requiring long-term medical therapy for definitive disease in two cases. In four patients, the presence of post-operative CSF leak required lumbar drainage ($n = 2$) or a new surgical procedure ($n = 2$), requiring prolonged hospitalisation without further mortality; in addition, meningitis occurred in one patient; this was promptly resolved with antibiotics.

The impact of TSS on pituitary function was variable. Out of the 30 patients with preoperative hypopituitarism, 16 experienced an improvement of pituitary function (53%), with a normalisation of gonadal and/or thyroid function in 16 and three patients respectively. Overall, long-term remission of acromegaly was associated with a normal pituitary function in 92% of patients (Table 5). In contrast, pituitary function worsened in five patients, two of them with a normal pre-operative evaluation, requiring definitive post-operative hormone replacement with gonadal steroids ($n = 5$), thyroxine ($n = 4$) and cortisone acetate ($n = 3$). PRL normalised in 22 out of 34 patients with preoperative hyperprolactinaemia

Table 3 Analysis of prognostic factors associated with a poor surgical outcome in 92 acromegalic patients operated on by TSS

	Remission rate	Univariate analysis (*P* value)	Multivariate analysis (*P* value)
Plasma GH		0.009	NS
Plasma GH >10 ng/ml	35/71 (49%)	0.002	0.04
Stage E adenomas	1/23 (4%)	0.0001	0.001
Stage B/C adenomas	5/20 (25%)	0.003	NS
Microadenomas*	13/16 (81%)	0.03*	NS
Dural invasion	18/47 (38%)	0.015	NS
Preoperative medical therapy	15/26 (58%)	NS	NS
GH/PRL-secreting adenomas	11/29 (38%)	NS	NS

*The presence of a microadenoma was associated with a good surgical outcome.
NS, not significant.

Table 4 Analysis of initial prognostic factors according to preoperative medical therapy. Some values are means ± S.D.

	Treated ($n = 26$)	Untreated ($n = 66$)	*P*
Age	42.7±13.8	42.1±14.9	NS
Sex	11M/15F	34M/32F	NS
Plasma GH	44.7±41.9	40.2±30.9	NS
Plasma GH >10 ng/ml	22 (85%)	49 (74%)	NS
Plasma IGF-I	671.5±244.5	607.0±208.8	NS
Stage E adenomas	7 (27%)	16 (24%)	NS
Stage B/C adenomas	7 (27%)	13 (20%)	NS
Microadenomas	3 (12%)	13 (20%)	NS
Dural invasion	15 (58%)	32 (48%)	NS
GH/PRL-secreting adenomas	11 (57%)	18 (27%)	NS

NS, not significant.

(65%), 12 of them with a mixed GH/PRL adenoma. Finally, visual field defects improved in seven out of 12 patients, with a complete normalisation in two cases, and were unchanged in the remaining patients.

Discussion

The first aim of this study was to re-evaluate the efficacy of TSS in acromegaly using current stringent criteria. Indeed, the definition of biochemical remission of acromegaly has changed noticeably over the past two decades. Throughout the 1980s, post-operative GH levels < 5 ng/ml were considered as criteria of biochemical remission of disease, allowing a surgical success in more than 75% of patients in some large series (Ross & Wilson 1988, Tindall *et al*. 1993, Abosch *et al*. 1998). Based on epidemiologic evidence that mortality rates among treated acromegalic patients are higher than those of the normal population until GH and IGF-I levels are normalised (Bates *et al*. 1993, Rajasoorya *et al*. 1994, Swearingen *et al*. 1998, Beauregard *et al*. 2003), more stringent criteria to define the biochemical remission of acromegaly have been proposed in recent years. Using a mean GH < 2 ng/ml during OGTT and normal IGF-I levels, biochemical remission of acromegaly has been reported in 55–70% of patients (Falbusch *et al*. 1992, Van Lindert *et al*. 1997, Freda *et al*. 1998, Shimon *et al*. 2001). More recently, a GH < 1 ng/ml during an OGTT and normal IGF-I levels have been considered to be the leading criteria for the cure of acromegaly (Giustina *et al*. 2000, Melmed *et al*. 2002). Following such criteria, we achieved a normalisation of GH secretion in 55% of patients, similar to that recently reported in some series (Laws *et al*. 2000, Kreutzer *et al*. 2001). Even if the surgical remission of acromegaly is apparently lower than in previous series, it has a dramatic impact on disease-related mortality and morbidity (Beauregard *et al*. 2003). Noteworthy, Lissett *et al*. (1998) reported a lower cure rate

Table 5 Endocrinological outcome in 51 successfully operated acromegalic patients

Preoperative status	Patients (*n*)	Long-term remission with normal pituitary function	Long-term remission with pituitary dysfunction
Normal pituitary function			
Microadenomas	10	9	1 GT
Macroadenomas stage 0/A	21	20	1 GTA
Macroadenomas stage B/C	2	2	
Pituitary dysfunction			
Microadenomas	3 G	3	
Macroadenomas stage 0/A	11 G, 1 GT	11	1 GTA
Macroadenomas stage B/C	2 GT, 1 GTA	2	1 GTA

Macroadenomas were classified according to Wilson's classification. G, gonadal insufficiency; T, thyroid insufficiency; A, adrenal insufficiency.

in a series of 73 patients who were operated on by a large number of neurosurgeons. This observation points out the importance of dedicated specialist pituitary surgeons to improve the success of TSS in acromegaly (Ahmed *et al.* 1999).

An important finding of the present study was the absence of tumour recurrence after a mean follow-up of 8 years. Our results compare favourably with previous series reporting recurrence rates ranging from 0 up to 10% of successfully operated patients (Ross & Wilson 1988, Buschfelder *et al*. 1991, Valdemarsson *et al*. 1991, Falbusch *et al*. 1992, Tindall *et al*. 1993, Van Lindert *et al*. 1997, Abosch *et al*. 1998, Freda *et al*. 1998, Shimon *et al*. 2001). Analysis of these series clearly indicates that such variations mainly depend on the criteria used to define surgical cure and on the duration of follow-up (see Table 6). However, where normalised IGF-I and glucose-suppressed GH < 2 ng/ml have been considered, recurrence rates were less than 5.5%. In fact, Losa *et al*. (1989) reported no recurrences and Kreutzer *et al*. (2001) reported only one recurrence among 42 patients – though in the later series a subset of patients who met only one criterion of cure was considered to be in remission. Overall, these data indicate that, even after a long follow-up, recurrence of acromegaly is extremely rare when stringent criteria of cure are used, so that successful TSS can be definitive for these patients.

Interestingly, discrepancies between the glucose-suppressed GH and IGF-I levels were present in about 5% of our patients, represented by not suppressible GH or elevated IGF-I levels in three and two cases respectively, with a recurrence occurring in one patient from the first group. High discordant rates between these two criteria, exceeding 20%, have been reported recently (Espinosa-de-los-Monteros *et al*. 2002, Kristof *et al*. 2002). High IGF-I levels can be observed even in the presence of normal GH levels in patients with active disease (Dimaraky *et al*. 2002), and IGF-I is considered by most authors to best correlate with disease activity (Arafah *et al*. 1987, Melmed *et al*. 1995). In contrast, other authors consider that GH suppression during OGTT is more reliable than IGF-I to exclude the presence of active acromegaly (Bates *et al*. 1995, Stoffel-Wagner *et al*. 1997, Peacey & Shalet 2001, Kristof *et al*. 2002). So far, it remains to be determined whether patients with normalised IGF-I or a glucose-suppressed GH < 1 ng/ml as the sole criteria of remission are at higher risk for recurrence of active disease, and the use of both parameters represents, at the moment, the most accurate criteria to define biochemical control of the disease. It should be noted, however, that GH/IGF-I discrepancies have been more frequently reported in the immediate post-operative period (Espinosa-de-los-Monteros *et al*. 2002, Kristof *et al*. 2002), so that a 6-month evaluation may be more reliable for the identification of 'borderline' patients.

In this study, we also wished to revise the prognostic significance of several factors on surgical outcome according to stringent criteria of remission. Statistical analysis showed that tumour size, GH levels and dural invasion were the most important predictors of poor outcome. By univariate analysis, high preoperative GH levels, the presence of a large extrasellar extension (stage B/C) and/or cavernous sinus invasion (stage E), as well as the presence of dural invasion at surgery

Table 6 Recurrence rate of acromegaly after successful TSS according to different criteria to define the biochemical remission of disease

Reference	No.	Criteria	Median follow-up (months)	Recurrence rate (%)
Ross & Wilson (1988)	131	GH < 5 ng/ml	76	4.3
Losa *et al.* (1989)	16	GH <1 ng/ml during OGTT and normalised IGF-I	42	0
Buchfelder *et al.* (1991)	61	GH < 2 ng/ml during OGTT	72	6.5
Valdemarsson *et al.* (1991)	28	GH < 3 ng/ml during OGTT	35	10
Tindall *et al.* (1993)	83	GH < 5 ng/ml	102*	11
Van Lindert *et al.* (1997)	33	GH < 2 ng/ml during OGTT and normalised IGF-I	34*	0
Abosch *et al.* (1998)	128	GH < 5 ng/ml	95	7
	101	GH < 2 ng/ml during OGTT		
Freda *et al.* (1998)	70	GH < 2 ng/ml during OGTT and normalised IGF-I	64*	5.4
Ahmed *et al.* (1999)	93	GH < 2.5 ng/ml	60	7.4
Kreutzer *et al.* (2001)	42	GH < 1 ng/ml during OGTT and normalised IGF-I	37.7*	2.4
Shimon *et al.* (2001)	72	GH < 2 ng/ml during OGTT and normalised IGF-I	42	1.3
Present series (2003)	51	GH < 1 ng/ml during OGTT and normalised IGF-I	93*	0

*Mean instead of median follow-up was reported in these series.

were significantly associated with a poor surgical outcome, whereas low GH levels and the presence of a microadenoma were associated with a good surgical outcome. However, multivariate analysis showed that only GH values and invasion of the cavernous sinus were independent predictors of surgical failure. Such data largely support findings from previous studies (Ross & Wilson 1988, Tindall *et al*. 1993, Abosch *et al*. 1998, Kreutzer *et al*. 2001) and indicate that such patients usually require a multidisciplinary and more aggressive approach to control GH hypersecretion. In agreement with previous series (Kristof *et al*. 1999, Losa *et al*. 1999) but in contrast to others (Colao *et al*. 1997*b*, Abe & Ludescke 2001) preoperative medical treatment with somatostatin analogues was not significantly associated with a better surgical outcome in this series. Because we commonly propose preoperative medical treatment according to individual parameters – in the presence of cardiovascular complications in order to improve the patient's preoperative conditions (Colao *et al*. 1997*b*), in the presence of more aggressive tumours hoping for some preoperative shrinkage (Bevan *et al*. 2002), or just waiting for surgery according to the patient's choice – we have retrospectively made sure that no important statistical bias was introduced in the analysis of this parameter. However, treated patients represented less than 30% of the whole series, and all received daily injections of octreotide because of the study period patient's inclusion before 1997. Thus, no definitive conclusions can be drawn from these data, and the possible effects of the currently used long-acting somatostatin analogues should be further studied.

The third goal of this study was to better evaluate the impact of TSS on the quality of life of operated patients. Although TSS is commonly considered as a safe procedure in the hands of experienced surgeons (Lisset *et al*. 1998, Ahmed *et al*. 1999), a minimal rate of surgical complications seems unavoidable. In agreement with previous large series (Abosch *et al*. 1998, Freda *et al*. 1998, Ahmed *et al*. 1999, Laws *et al*. 2000, Shimon *et al*. 2001) operative mortality was absent and, although no major complications occurred, minor complications were observed in 10% of patients, including CSF leak, diabetes insipidus and hypopituitarism. However, additional benefits from surgery were represented by an improvement of neurological symptoms and pituitary function. In this series, TSS was able to improve visual field defects in about 60% of patients and to restore a normal pituitary function in more than 50% of patients with some preoperative pituitary deficit, with a long-term stabilisation of pituitary function. This is of special importance since, despite the fact that it has been well described for non-secreting pituitary adenomas (Arafah *et al*. 1994, Webb *et al*. 1999), post-operative improvement in pituitary function has not been systematically considered for acromegaly. It is therefore worth noting that the chance of improving pituitary function exceeded the risk of its worsening, so that, overall, the large majority of patients with successful surgery had normal post-operative pituitary function.

In conclusion, this study and the revision of the recent literature indicate that TSS in experienced hands is able to induce a long-term remission of acromegaly according to current stringent criteria, with an extremely low risk of recurrence, and in association with a normal pituitary function in almost all successfully operated cases. The present data suggest that current criteria are able to disclose true surgical cure rather than surgical remission in most cases. Additional studies should determine whether current advances in microsurgical techniques, such as endoscopy-assisted microsurgery and neuronavigation, could further improve surgical success and decrease the rate of minor post-operative complications. On the other hand, the well-recognised impact of GH/IGF-I normalisation on disease-associated morbidity and mortality should further emphasise the need for post-surgical complementary treatment – based on medical treatment and/or radiotherapy – in all patients who do not meet the stringent criteria of remission.

References

Abe T & Ludecke DK 2001 Effects of preoperative octreotide treatment on different subtypes of 90 GH-secreting pituitary adenomas and outcome in one surgical centre. *European Journal of Endocrinology* **145** 137–145.

Abosch A, Tyrrel JB, Lamborn KR, Hannegan LT, Applebury CB & Wilson CB 1998 Transsphenoidal microsurgery for growth hormone-secreting pituitary adenomas: initial outcome and long-term results. *Journal of Clinical Endocrinology and Metabolism* **83** 3411–3418.

Ahmed S, Elsheikh M, Stratton IM, Page RCL, Adams CBT & Wass JAH 1999 Outcome of transsphenoidal surgery for acromegaly and its relationship to surgical experience. *Clinical Endocrinology* **50** 561–567.

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 1) levels in predicting the long-term benefit after transsphenoidal surgery for acromegaly. *Journal of Laboratory and Clinical Medicine* **109** 346–354.

Arafah BM, Kailani SH, Nekl KE, Gold RS & Selman WR 1994 Immediate recovery of pituitary function after transsphenoidal resection of pituitary macroadenomas. *Journal of Clinical Endocrinology and Metabolism* **79** 348–354.

Barrande G, Pittino-Lungo M, Coste J, Ponvert D, Bertagna X, Luton JP & Bertherat J 2000 Hormonal and metabolic effects of radiotherapy in acromegaly: long-term results in 128 patients followed in a single center. *Journal of Clinical Endocrinology and Metabolism* **85** 3779–3785.

Bates A, Van't Hoff W, Jones J & Clayton R 1993 An audit of the outcome of acromegaly. *Quarterly Journal of Medicine* **86** 293–299.

Bates AS, Van't Hoff W, Jones JM & Clayton RN 1995 Assessment of GH status in acromegaly using serum growth hormone, serum insulin-like growth factor-1 and urinary growth hormone excretion. *Clinical Endocrinology* **42** 417–423.

Beauregard C, Truong U, Hardy J & Serri O 2003 Long-term outcome and mortality after transsphenoidal adenomectomy for acromegaly. *Clinical Endocrinology* **58** 86–91.

Bevan JS, Atkin SL, Atkinson AB, Bouloux PM, Hanna F, Harris PE, James RA, McConnell M, Roberts GA, Scanlon MF, Stewart PM, Teasdale E, Turner HE, Wass JA & Wardlaw JM 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. *Journal of Clinical Endocrinology and Metabolism* **87** 4554–4563.

Buchfelder M, Brockmeier S, Fahlbusch R, Honegger J, Pichl J & Manzl M 1991 Recurrence following transsphenoidal surgery for acromegaly. *Hormone Research* **35** 113–118.

Colao A, Merola B, Ferone D & Lombardi G. 1997*a* Acromegaly. *Journal of Clinical Endocrinology and Metabolism* **8** 2777–2781.

Colao A, Ferone D, Cappabianca P, del Basso, De Caro ML, Marzullo P, Monticelli A, Alfieri A, Merola B, Cali A, de Divitiis E & Lombardi G 1997*b* Effect of octreotide pretreatment on surgical outcome in acromegaly. *Journal of Clinical Endocrinology and Metabolism* **82** 3308–3314.

Colao A, Cuocolo A, Marzullo P, Nicolai E, Ferone D, Della Morte AM, Pivonello R, Salvatore M & Lombardi G 2001 Is the acromegalic cardiomyopathy reversible? Effect of 5-year normalisation of growth hormone and insulin-like growth factor I levels on cardiac performance. *Journal of Clinical Endocrinology and Metabolism* **86** 1551–1557.

Davis DH, Laws ER Jr, Ilstrup DM, Speed JK, Caruso M, Shaw EG, Abboud CF, Scheithauer BW, Root LM & Schleck C 1993 Results of surgical treatment for growth hormone-secreting pituitary adenomas. *Journal of Neurosurgery* **79** 70–75.

Dimaraky EV, Jaffe CA, DeMott-Friberg R, Chandler WF & Barkan AL 2002 Acromegaly with apparently normal GH secretion: implications for diagnosis and follow-up. *Journal of Clinical Endocrinology and Metabolism* **87** 3537–3542.

Espinosa-de-los-Monteros AL, Mercado M, Sosa E, Lizama O, Guinto G, Lopez-Felix B, Garcia O, Hernandez I, Ovalle A & Mendoza V 2002 Changing patterns of insulin-like growth factor-I and glucose-suppressed growth hormone levels after pituitary surgery in patients with acromegaly. *Journal of Neurosurgery* **97** 287–292.

Fahlbusch R, Honegger J & Buchfelder M 1992 Surgical management of acromegaly. *Endocrinology and Metabolism Clinics of North America* **21** 669–692.

Freda PU 2002 Somatostatin analogs in acromegaly. *Journal of Clinical Endocrinology and Metabolism* **87** 3013–3018.

Freda PU, Wardlaw SL & Post KD 1998 Long-term endocrinological follow-up evaluation in 115 patients who underwent transsphenoidal surgery for acromegaly. *Journal of Neurosurgery* **89** 353–358.

Giustina A, Barkan A, Casanueva FF, Cavagnini F, Frohman L, Ho K, Veldhuis J, Wass J, Von Werder K & Melmed S 2000 Criteria for cure of acromegaly: a consensus statement. *Journal of Clinical Endocrinology and Metabolism* **85** 526–529.

Jaffrain-Rea ML, Minniti G, Moroni C, Esposito V, Ferretti E, Santoro A, Infusino T, Tamburrano G, Cantore G & Cassone R 2003 Impact of successful transsphenoidal surgery on cardiovascular risk factors in acromegaly. *European Journal of Endocrinology* **148** 193–120.

Kreutzer J, Vance ML, Lopes MBS & Laws ER 2001 Surgical management of GH-secreting pituitary adenomas: an outcome study using modern remission criteria. *Journal of Clinical Endocrinology and Metabolism* **86** 4072–4077.

Kristof RA, Stoffel-Wagner B, Klingmuller D & Schramm J 1999 Does octreotide treatment improve the surgical results of macro-adenomas in acromegaly? A randomized study. *Acta Neurochirurgica* **141** 399–405.

Kristof RA, Neuloh G, Redel L, Klingmuller D & Schramm J 2002 Reliability of the oral glucose tolerance test in the early postoperative assessment of acromegaly remission. *Journal of Neurosurgery* **97** 1282–1286.

Lamberts SW, Reubi JC & Krenning EP 1992 Somatostatin analogs in the treatment of acromegaly. *Endocrinology and Metabolism Clinics of North America* **21** 737–752.

Laws ER, Vance ML & Thapar K 2000 Pituitary surgery for the management of acromegaly. *Hormone Research* **53** 71–75.

Lissett CA, Peacey SR, Laing I, Tetlow L, David JRE & Shalet SM 1998 The outcome of surgery for acromegaly: the need for a specialist pituitary surgeon for all types of growth hormone (GH) secreting adenomas. *Clinical Endocrinology* **49** 658–667.

Losa M, Oeckler R, Schopohl J, Muller O, Alba-Lopez J & von Werder K 1989 Evaluation of selective transsphenoidal adenomectomy by endocrinological testing and somatomedin-C measurement in acromegaly. *Journal of Neurosurgery* **70** 561–567.

Losa M, Mortini P & Giovanelli M 1999 Is presurgical treatment with somatostatin analogs necessary in acromegalic patients? *Journal of Clinical Investigation* **22** 871–873.

Melmed S 1990 Acromegaly. *The New England Journal of Medicine* **322** 966–977.

Melmed S, Ho K, Klibanski A, Reichlin S & Thorner M 1995 Clinical review 75: Recent advances in pathogenesis, diagnosis, and management of acromegaly. *Journal of Clinical Endocrinology and Metabolism* **80** 3395–3402.

Melmed S, Casanueva FF, Cavagnini F, Chanson P, Frohman L, Grossman A, Ho K, Kleimberg D, Lamberts S, Laws E, Lombardi G, Vance ML, Werder KW, Wass J & Giustina A 2002 Guidelines for acromegaly management. *Journal of Clinical Endocrinology and Metabolism* **87** 4054–4058.

Minniti G, Jaffrain-Rea ML, Esposito V, Santoro A, Moroni C, Lenzi J, Tamburrano G, Cassone R & Cantore G 2001*a* Surgical treatment and clinical outcome of GH-secreting adenomas in elderly patients. *Acta Neurochirurgica* **143** 1205–1211.

Minniti G, Moroni C, Jaffrain-Rea ML, Esposito V, Santoro A, Affricano C, Cantore G, Tamburrano G & Cassone R 2001*b* Marked improvement of cardiovascular function after successful transsphenoidal surgery in acromegalic patients. *Clinical Endocrinology* **55** 307–313.

Peacey S & Shalet SM 2001 Insulin-like growth factor measurement in diagnosis and management of acromegaly. *Annals of Clinical Biochemistry* **38** 297–303.

Powell JS, Wardlaw SL, Post KD & Freda PU 2000 Outcome of radiotherapy for acromegaly using normalisation of insulin-like growth factor to define cure. *Journal of Clinical Endocrinology and Metabolism* **85** 2068–2071.

Rajasoorya C, Holdaway IM, Wrightson P, Scott DJ & Ibbertson HK 1994 Determinants of clinical outcome and survival in acromegaly. *Clinical Endocrinology* **41** 95–102.

Ross DA & Wilson CB 1988 Results of transsphenoidal microsurgery for growth hormone-secreting pituitary adenomas in a series of 214 patients. *Journal of Neurosurgery* **68** 854–867.

Sheaves R, Jenkins P, Blackburn P, Huneidi AH, Afshar F, Medbak S, Grossman AB, Besser GM & Wass JA 1996 Outcome of transsphenoidal surgery for acromegaly using strict criteria for surgical cure. *Clinical Endocrinology* **45** 407–413.

Shimon I, Cohen ZR, Ram Z & Hadani M 2001 Transsphenoidal surgery for acromegaly: endocrinological follow-up of 98 patients. *Neurosurgery* **48** 1239–1243.

Stoffel-Wagner B, Springer W, Bidlingmaier F & Klingmueller D 1997 Investigation of the criteria for assessing the outcome of treatment in acromegaly. *Clinical Endocrinology* **46** 531–537.

Swearingen B, Barker FG II, Katznelson L, Biller BMK, Grinspoon S, Klibanski A, Moayeri N, Black PM & Zervas NT 1998 Long-term mortality after transsphenoidal surgery and adjunctive therapy for acromegaly. *Journal of Clinical Endocrinology and Metabolism* **83** 3419–3426.

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. *Journal of Neurosurgery* **78** 205–215.

Valdemarsson S, Bramnert M, Cronquist S, Elner A, Eneroth CM, Hedner P, Lindvall-Axelsson M, Nordstrom CH & Stromblad LG 1991 Early postoperative basal GH level and the GH response to TRH in relation to the long-term outcome of surgical treatment for acromegaly: a report of 39 patients. *Journal of Internal Medicine* **230** 49–54.

Van Lindert E, Hey O, Boecher-Schwarz H & Perceczky A 1997 Treatment results of acromegaly as analyzed by different criteria. *Acta Neurochirurgica* **139** 905–913.

Webb SM, Rigla M, Wagner A, Oliver B & Bartumeus F 1999 Recovery of hypopituitarism after neurosurgical treatment of pituitary adenomas. *Journal of Clinical Endocrinology and Metabolism* **84** 3696–3700.

Wilson CB 1984 A decade of pituitary microsurgery: the Herbert Olivecrona Lecture. *Journal of Neurosurgery* **61** 814–833.