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To cite this version:

Frédérique Albarel, Frederic Castinetti, Isabelle Morange, Bernard Conte-Devolx, Jean Gaudart, et al.. Outcome of multimodal therapy in operated acromegalic patients, a study in 115 patients. Clinical Endocrinology, 2013, 78 (2), pp.263-270. 10.1111/j.1365-2265.2012.04492.x . hal-01307697

HAL Id: hal-01307697

https://amu.hal.science/hal-01307697v1

Submitted on 26 Apr 2016

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Clinical Endocrinology (2013) **78**, 263–270 doi: 10.1111/j.1365-2265.2012.04492.x

ORIGINAL ARTICLE

Outcome of multimodal therapy in operated acromegalic patients, a study in 115 patients

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Summary

Introduction Given the new therapeutic options in acromegaly, it seemed important to evaluate the outcome of operated acromegalic patients today.

Objective To analyse the characteristics and short- and long-term surgical outcome of patients who underwent transsphenoidal surgery for a growth hormone (GH)-secreting adenoma in our centre and to determine predictive factors of remission.

Design and patients This retrospective 10-year study included 115 newly diagnosed acromegalic patients operated on at Timone University Hospital, Marseille, France, between 1997 and 2007.

Measurements Initial and long-term outcomes were evaluated using stringent and current remission criteria, associating GH nadir after oral glucose tolerance test <0·4 μg/l and normal insulin-like growth factor-1 (IGF-1) at 3 months, and a normal IGF-1 at the end of follow-up (52·4 ± 36·8 months, median 41 months, range 6·7–135·4 months, $n = 99$).

Results At the end of follow-up, 90·9% of patients had controlled disease. Overall, 49·5% of patients were in long-term remission after surgery alone, and only 2·0% of patients experienced recurrent disease. Multivariate predictors of 3-month remission included mean GH at diagnosis ($P = 0{\cdot}033$), tumour invasion ($P = 0{\cdot}013$) and surgeon report of incomplete or uncertain macroscopic resection ($P = 0{\cdot}003$ and $P = 0{\cdot}047$, respectively). Multivariate predictors at diagnosis of long-term remission included mean GH level ($P = 0{\cdot}048$), adenoma size ($P = 0{\cdot}007$) and absence of pituitary deficit ($P = 0{\cdot}026$).

Conclusions In long-term follow-up after surgery of acromegaly, half of the patients achieved remission after surgery alone and more than 90% had their disease controlled. With stringent 3-month remission criteria, recurrence was rare.

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(Received 24 April 2012; returned for revision 15 May 2012; finally revised 28 June 2012; accepted 4 July 2012)

Introduction

Acromegaly is a rare chronic endocrine disease associated with excessive production of growth hormone (GH).[1] In most cases, the condition is related to a pituitary adenoma, which develops from somatotroph cells.[2] Acromegaly is characterized by a dysmorphic syndrome with disproportionate growth of skeletal tissues and organs, accompanied by metabolic disturbances.[3,4] Large retrospective studies showed patients with acromegaly had on average a 10-year lower life expectancy than the general population, mainly due to cardiovascular disease.[5,6]

Treatment for acromegaly is aimed at reducing the tumour volume, normalizing GH and insulin-like growth factor (IGF-1) and improving symptoms and long-term morbidity and mortality.[7–9] For this, transsphenoidal microsurgery is widely accepted as the first-line therapy.[4,10]

Data show that acromegalic patients with IGF-1 levels above normal and final GH levels above 2·5 μg/l continue to have significantly higher mortality rates than the general population.[5] As the levels of these variables are lowered, the mortality rate begins to improve. However, only patients with normal IGF-1 levels and GH levels around 1 μg/l will have a mortality rate similar to the normal population.[5] Although GH and IGF-1 levels are usually closely correlated, discrepancies can occur. In most cases, the reason for discrepancy is not clear and a close follow-up of both parameters is necessary.[11]

Given the recent progress in the management of acromegaly (including emerging knowledge and increased sensitivity of GH assays), experts have proposed new evidence-based consensus guidelines. Acromegaly is now considered 'controlled' in case of age- and sex-normalized levels of IGF-1, associated with a random GH level <1 μg/l or nadir GH after an oral glucose tolerance test (OGTT) <0·4 μg/l.[8] Note that previous studies had different remission criteria, which makes efficacy comparison difficult.[7]

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In this 10-year retrospective study, we first analysed the characteristics of patients who had surgery for a GH-secreting adenoma. We then evaluated their initial and long-term surgical outcome using updated criteria for remission.[8] We also tried to identify factors linked to surgical remission, with the overall aim of individualizing treatment and follow-up.

Patients and methods

Design and patients

A total of 155 patients with acromegaly were operated on between 1997 and 2007 by two neurosurgeons at the Timone University Hospital. Of these patients, 40 were excluded from the current analysis for incomplete data (25 not followed in our centre and 15 with <3 months postsurgery follow-up). We thus collected and analysed retrospectively pre-, per- and post-operative data for 115 patients during their regular follow-up (3 months after surgery and then yearly) including clinical, biological, radiological, surgical and anatomopathological (including immunohistochemistry) results, and details concerning complications and treatment. Written informed consent was obtained from all patients.

The diagnosis of acromegaly was made on the association of clinical symptoms, elevated IGF-1 levels for patient's age and gender associated with failure of GH suppression during an OGTT (GH $\geq$ 1 μg/l).[7–9]

Hormonal, ophthalmological and imaging evaluation

During the OGTT, GH levels were determined at 0, 30, 60, 90 and 120 min after ingestion of 75 g of glucose, and GH nadir was used for analysis. Mean GH level (GHm) was calculated by averaging nine hourly measurements (from 0800 to 1600 h). Serum GH levels were determined by radioimmunoassay {Immunotech, Marseille, France [1997–2002; Cisbio, Marseille, France [2003 onwards)]}. Intra- and inter-assay coefficients of variation were 0·66–1·5% and 13·1–14%, respectively, and sensitivity was 0·05 μg/l. Levels of GH were expressed in μg/l or in mIU/l (1 μg/l = 3 mIU/l).[12]

IGF-1 was 'normalized' using the upper limit of normal (ULN), which was set as the age- and gender-adjusted 95th percentile in our laboratory. Plasma IGF-1 was measured by radioimmunoassay (Immunotech) and standardized according to normal values for age, gender and, if needed, pubertal status. Intra- and inter-assay coefficients of variation were 2·6–7·4% and 7·8–15·5%, respectively, and sensitivity was 3 ng/ml.

Thyroid-stimulating hormone (TSH) deficiency was defined as a low free T4 level (free T4 <12 pM) with low or inappropriately normal TSH level. Adrenocorticotropic hormone (ACTH) deficiency was diagnosed if there was a low cortisol level (<200 nM) with low or inappropriately normal ACTH level at 0800 h; an insulin tolerance test was performed if cortisol was in the low-to-normal range or in the presence of clinical symptoms. The response was considered adequate if the cortisol peak was above 550 nM (with blood glucose nadir <2·2 mM). Gonadotrophin deficiency was defined by low plasma sex steroids with inappropriate gonadotrophin levels (normal or low) and amenorrhoea in nonmenopausal women, or a lack of increase in gonadotrophins in menopausal women. Hyperprolactinaemia was defined as a basal plasma prolactin level >25 ng/ml. Posterior pituitary function was assessed by clinical features, urinary volume, and plasma and urinary osmolality.

Ophthalmologic evaluations using Goldman's campimetry were conducted in our ophthalmological centre.

Pituitary MRI was performed using sagittal and coronal sections and interpreted by neuroradiologists (Neuroradiology Department, Timone Hospital). The sequences were spin echo T1- and T2-weighted images, followed by postgadolinium T1-weighted images. Microadenomas were defined by a largest tumour size <10 mm, and macroadenoma, $\geq$ 10 mm. MRI was performed before surgery, 3 months postsurgery and regularly during follow-up.

Surgery and remission criteria

All patients underwent sublabial or nasal transsphenoidal microsurgery, with the exception of two who were operated on by the transfrontal route. Four patients had a second surgery: one scheduled, one for air in the sella and two because of a GH-secreting residue. Endoscopic transsphenoidal surgery was performed in 24 patients. For all patients, the two neurosurgeons specified whether macroscopic tumour resection was complete, incomplete or uncertainly complete. Any surgical complication was noted, as were the anatomopathological and immunohistochemical characteristics of each tumour.

Patients were considered to be in short-term remission when they had normal IGF-1 levels for their age and gender and a GH nadir <0·4 μg/l after an OGTT 3 months postsurgery. For diabetic patients (unreliable GH values after an OGTT, n = 9), only IGF-1 measurement was taken into account. Patients who received a medical treatment at the time of surgery or who did not stop this treatment at least 3 months before surgery had their IGF-1 immediately postsurgery excluded from analysis (n = 53). Values of mean GH and nadir of GH after OGTT immediately after surgery of patients who received a medical treatment that was not interrupted at least 2 months before surgery were excluded from analysis (n = 9). Patients who received adjuvant treatment immediately after surgery (n = 14) were not considered to be in remission (3-month GH and IGF-1 values were excluded). Patients with discordant results [normal IGF-1 but GH nadir after OGTT $\geq$0·4 μg/l (n = 17), elevated IGF-1 but GH nadir after OGTT <0·4 μg/l (n = 10)] were considered to be in 'uncertain remission'. Ninety-nine patients who had a follow-up superior to 6 months were considered for long-term evaluation. Recurrence was defined as elevated IGF-1 levels or inadequate GH suppression ($\geq$0·4 μg/l) after an OGTT during follow-up. Patients were considered to be in long-term remission if they had normal IGF-1 levels with no medication at last visit (only patients in remission after surgery alone were considered for statistical evaluation of long-term remission after surgery, n = 49). If IGF-1 was normalized with ongoing treatment, they

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were considered 'controlled', and if IGF-1 was elevated, 'uncontrolled'.

Statistical analyses

Descriptive statistics with quantitative variables were expressed as mean ± standard deviation (SD) and, for long-term follow-up in median with ranges (minimum–maximum). Univariate comparisons between groups were made by two-tailed Student's unpaired *t*-test or ANOVA for continuous variables (variance equality was verified by the Lévéné test and Welch correction was applied if necessary). Two-tailed Pearson's chi-square or Fisher's exact test were used for comparison of qualitative data. Variables with P-value < 0·25 were selected (following Mickey and Greenland recommendations[13]) for the multivariate analysis as well as interactions between covariates. Forward stepwise logistic regression analysis was used for multivariate studies, with selection based on likelihood ratio. The remaining covariates were considered significant if P-value < 0·05.

The following variables were considered for analysis: clinical data (age at diagnosis, age at surgery, blood pressure: systolic and diastolic, body mass index), biological data (GHm, IGF-1, GH after OGTT at diagnosis), imaging data (size of adenoma, invasiveness, characteristics: micro *vs* macroadenoma at diagnosis), visual field abnormalities and hormonal data at diagnosis (hyperprolactinaemia, pituitary deficits), anatomo-pathological data (pure GH-secreting adenoma or not), surgery (endoscopic way, surgeon report of macroscopic resection). Furthermore, biological data (GHm, IGF-1 and GH nadir after OGTT) immediately postsurgery were considered for short-term remission and the same parameters at 3 months postsurgery for long-term remission.

Results

Table 1 shows the general characteristics of the 115 acromegalic patients at diagnosis. Table 2 shows hormonal and imaging data. Patients were followed up for a mean period of 45·6 ± 38·1 months, median 35·8 months, range 2·9–135·4 months. Seventy patients (60·9%) received medical treatment before surgery (somatostatin analogues or dopamine agonists) for a mean duration of 9·1 ± 13·8 months (1–108). Most of the patients received somatostatin analogues alone (55 patients, or 78·6%, who received Octreotide, n = 30 or Lanreotide, n = 25), a few of them dopamine agonists alone (two patients, 2·9%, Cabergoline) and some patients an association of both treatment (13 patients, 18·5%).

Surgery and early postoperative results

Anatomopathological analysis and immunohistochemistry found 56 pure GH adenomas and 58 mixed adenomas (GH-prolactin, GH-α-subunit and GH-prolactin-α-subunit), one was not interpretable. Staining for Ki-67/MIB-1 was not available. Severe surgical complications were reported in nine patients (7·8%) (3 permanent diabetes insipidus, 2 cerebrospinal fluid rhinorrhea, 1 sphenoid sinusitis, 1 repeat surgery for air in the sella, 1 V2 neuralgia, and 1 severe adrenal insufficiency). Transient mild hyponatraemia was reported in 17 (14·8%) patients. There was no postoperative mortality. The evolution of GHm level (n = 106), standardized IGF-1 (n = 57) and GH nadir after OGTT (n = 85) just after surgery are summarized in Table 2 and Fig. 1. Fourteen patients who were obviously not in remission (high GH levels postsurgery, incomplete macroscopic surgical resection) immediately received an adjunctive treatment, including somatostatin analogues (n = 11), dopaminergic agonists (n = 2) or pegvisomant (n = 1). One patient was scheduled to undergo further surgery.

Table 1. Characteristics at diagnosis of 115 acromegalic patients who underwent surgery between 1997 and 2007 at Timone Hospital, Marseille

Characteristics at diagnosis (n = 115)	Values (range)
Age at diagnosis, years	44·6 ± 12·1 (10·7–69)
Age at surgery, years	45·5 ± 12·5 (10·8–72·8)
Sex ratio, women/men	1·2/1
Tumor characteristics, *n* (%)	
Adenoma size, mm	17·7 ± 9·9 (3–82)
Microadenoma	20 (17·4)
Macroadenoma	95 (82·6)
Invasive	64 (55·7)
Impact on the visual field*	26 (28·3)
Pure growth hormone-secreting adenoma	56 (48·7)
Pituitary function, *n* (%)	
Deficits	51 (44·3)
One deficit	46 (40·0)
Two deficits	4 (3·5)
Three deficits	1 (<1)
Hyperprolactinemia	36 (31·3)
Macroscopic surgical resection, *n* (%)	
Complete	48 (41·7)
Incomplete	34 (29·6)
Uncertain	33 (28·7)

SD, standard deviation.
Unless otherwise stated, values are mean ± SD (range) or number of patients (%).
*Assessed in 92 patients.

Three-month postoperative results

All patients included had 3-month evaluation (performed between 2·9 and 4 months after surgery). Three months postsurgery, GHm (n = 88), standardized IGF-1 (n = 97) and GH nadir after OGTT (n = 88) values are represented in Table 2 and Fig. 1. Three-month and immediate postsurgery IGF-1 values differed significantly (Table 2, Fig. 1).

Overall, 43 patients (37·4%) were in remission at 3 months: 65% of patients with a microadenoma and 31·6% of patients with a macroadenoma; 45 patients (39·1%) were not in remission. Remission was considered uncertain in 27 patients (23·5%) because of discrepant results of IGF-1 and GH nadir after OGTT (Fig. 2). MRI was performed in 110 patients at 3 months; it was considered normal for 71 patients (64·5%). Visual field defects were also significantly improved by surgery (Table 2).

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Table 2. Hormonal and imaging characteristics of 115 operated acromegalic patients at diagnosis and during follow-up

Characteristics	Presurgery, at diagnosis	Immediately postsurgery	Three months postsurgery	Last visit
BMI (kg/m^2)	26·1 ± 3·9		26·1 ± 4·0	
GHm (μg/l)	31·1 ± 36·2	4·4 ± 10·3*	4 ± 9·9*	1·1 ± 1·4‡
IGF-1 (×ULN)	3·3 ± 1·5	1·7 ± 1·1*	1·1 ± 0·8†	0·8 ± 0·6‡
GH nadir/OGTT (μg/l)	25·8 ± 32	2·6 ± 5·6*	1·2 ± 2·5*	0·2 ± 0·3‡
Hyperprolactinaemia (% patients)	31·3	2·6*		2·6*
Pituitary hormone deficit (% patients)	44·3	47·0		23·0*
Visual field defect (% patients)	28·3	5·8*	10·3*	5·8*

BMI, body mass index; GHm, mean growth hormone; IGF, insulin-like growth factor; OGTT, oral glucose tolerance test; SD, standard deviation, ULN, upper limit of normal.
Significant difference ($P < 0·05$): *comparison between data after and before surgery; †comparison with immediate postsurgery data; ‡comparison between data at last visit and at three months postsurgery.

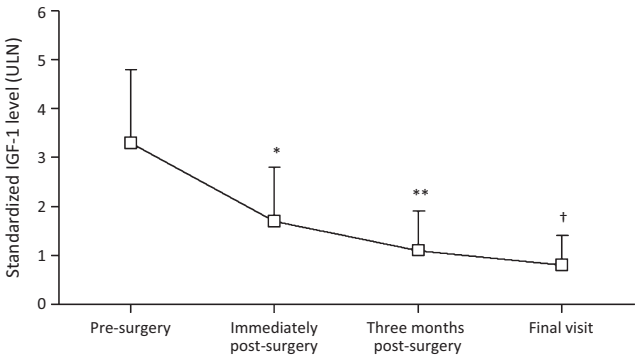

Fig. 1 Levels of normalized IGF-1 at diagnosis, immediately postsurgery, 3 months postsurgery and at final visit. Data are shown as mean ± upper standard deviation. *$P < 0·01$ *vs* presurgery value; **$P < 0·01$ *vs* immediately postsurgery value; †$P < 0·01$ *vs* 3-month postsurgery value.

Predictive factors of short-term remission and recurrence

Univariate analysis demonstrated a significant relationship between 3-month postoperative remission and a number of factors (Table 3). No significant relationship was observed between 3-month postoperative remission and levels of standardized IGF-1 or GH nadir after OGTT at diagnosis. There was also no significant relationship between remission and the use of endoscopic technique, tumour immunohistochemical findings (pure GH-secreting or mixed), hyperprolactinaemia or pituitary deficits at diagnosis.

In multivariate analyses, low GHm at diagnosis [OR = 0·98 (0·96–0·99), $P = 0·033$] remained a significant predictor of 3-month postsurgical remission, as did tumour invasion [OR = 0·22 (0·065–0·722), $P = 0·013$] and surgeon report of incomplete or uncertain macroscopic tumour removal [OR = 0·11 (0·03–0·48), $P = 0·003$ and OR = 0·25 (0·064–0·979), $P = 0·047$, respectively].

The group of patients with uncertain remission at 3 months appeared to be a distinct intermediate group. In addition to discordant values for IGF-1 and GH nadir after OGTT, these patients presented with intermediary results, between those of patients in remission and those not in remission for a number of other clinical and biochemical variables, including age at diagnosis (44·1 years), age at surgery (44·6 years), GHm at diagnosis (22·9 μg/l) and adenoma size (17 mm).

During the course of the study, two patients (2%) experienced recurrence at 11 and 114 months of follow-up. Among the 23 patients considered to be in uncertain remission who were followed for more than 6 months, 10 (43·5%) had finally a persistent disease, with an average delay of diagnosis of 11·7 months, 6 had insufficiently suppressed GH after OGTT and four had an elevated IGF-1 level. For these patients, an adjuvant treatment was proposed. Among these 10 patients, at the end of follow-up, 2 received no treatment and still had an active disease, 5 had their disease controlled by medical treatment (3 on somatostatin analogues, 1 on pegvisomant and 1 on dopamine agonists) and 3 were considered in remission (among them 2 had gamma knife).

Long-term follow-up

The majority of patients not in remission or presenting a recurrence were treated by adjunctive treatment. As first-line treatment, 40 patients received a medical treatment for a mean duration of 27·3 ± 26·5 months (29 of them, somatostatin analogues), 4 had radiotherapy (1 gamma knife and 3 conventional radiotherapy) and 3 experienced repeated surgery. Twenty-six patients had a second-line therapy: 17 received medical treatment for a mean duration of 17·1 ± 14·6 months (pegvisomant, 6) and 9 radiotherapy (7 gamma knife and 2 conventional). Eighteen patients needed a third-line therapy: 15 received medical treatment for a mean duration of 28·6 ± 24 months (somatostatin analogues, 7, and pegvisomant, 5) and 3 radiotherapy (1 gamma knife, 2 conventional). Nine patients had fourth-line therapy, consisting in seven medical treatments for a mean duration of 26·7 ± 14·6 months (pegvisomant in 4) and 2 radiotherapy (1 gamma knife, 1 conventional). Finally, only two patients had fifth-line therapy, two medical treatments, for 12 and 61 months, respectively. Characteristics of postsurgical treatments are detailed in Table 4.

At the last follow-up visit (excluding 16 patients who had only 3-month assessment data), GHm ($n = 49$), standardized IGF-1 ($n = 98$) and GH nadir after OGTT ($n = 45$) were all sig-

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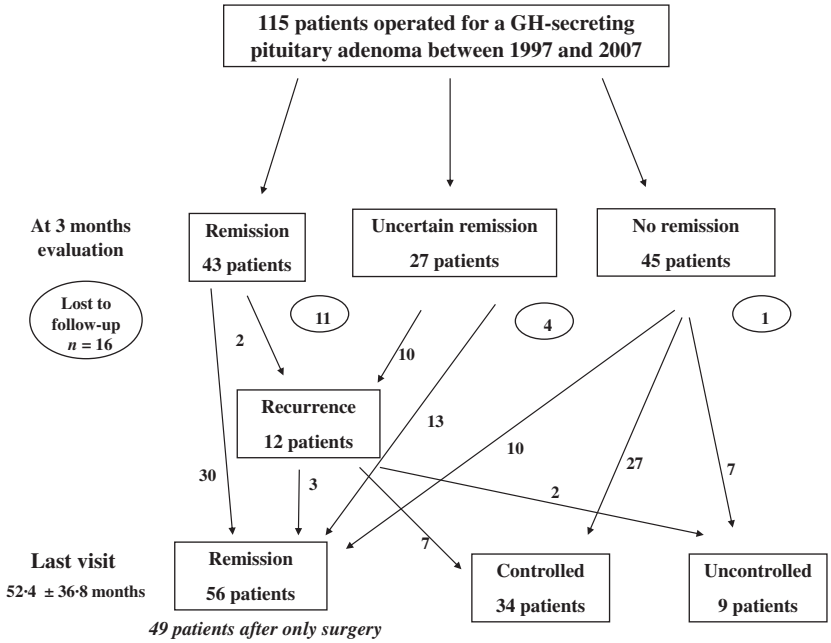

Fig. 2 Short- and long-term evolution of 115 acromegalic patients who underwent surgery in Timone Hospital, Marseille, France. Uncertain remission = discrepancy between results of GH after OGTT and IGF-1 (normal IGF-1 and elevated suppressed GH, $n = 17$; elevated IGF-1 and normally suppressed GH, $n = 10$). GH, growth hormone; OGTT, oral glucose tolerance test.

Table 3. Significant predictive factors of 3-month remission in univariate analysis

Predictive factor	3-month remission ($n = 43$)	3-month no remission ($n = 45$)	Significance (P-value)
Age at diagnosis (years)	48·4 ± 10·9	42·0 ± 13·4	<0·05
Age at surgery (years)	49·0 ± 10·8	42·7 ± 13·1	<0·05
GHm at diagnosis (μg/l)	20·7 ± 26·7	45·7 ± 44·7	<0·01
Adenoma size (mm)	13·7 ± 5·6	22·0 ± 12·3	<0·001
Macro/microadenoma (% patients)	69·8	93·3	<0·01
Local invasiveness (% patients)	27·96	82·2	<0·001
Surgeon report of complete macroscopic resection (% patients)	62·8	20·0	<0·001
Postoperative GHm (μg/l)	1·1 ± 1·5	8·7 ± 15·1	<0·01
Postoperative GH nadir/OGTT (μg/l)	1·1 ± 2·6	6·1 ± 8·4	<0·01
Postoperative IGF-1(xULN)	0·7 ± 0·2	1·9 ± 1·1	<0·001

GH, growth hormone; GHm, mean GH; IGF-1, insulin-like growth factor; NS, not significant; OGTT, oral glucose tolerance test; ULN, upper limit of normal.

nificantly decreased from their corresponding 3-month values (Table 2, Fig. 1). A pituitary deficit was reported in only 23 patients, which was a significant improvement: 12 patients presented with one deficit, 4 with two deficits and 7 had more than two deficits. The frequency of hyperprolactinaemia was also significantly improved by surgery (Table 2).

Long-term remission status was determined after an average follow-up of 52·4 ± 36·8 months in 99 patients who were followed for more than 6 months, with a median of 41 months, range 6·7–135·4 months. Of these, 56 (56·6%) had long-term remission (normal laboratory values without treatment at the last consultation) and 49 (49·5%) had achieved this after surgery alone. Among the 56 patients who were in long-term remission, at 3-month evaluation, 30 were considered in remission, 16 were in uncertain remission (among them 3 had persistent disease) and 10 were not considered in remission (Fig. 2). Furthermore, in these patients, four received radiotherapy during follow-up [conventional ($n = 1$) and gamma knife ($n = 3$)].

At last visit, acromegaly was controlled by medical treatment in 34/43 patients not cured by surgery. In nine patients, disease was still uncontrolled. Among them, 6 received at least one treatment during follow-up (4 were adjusting their treatment, 2 were waiting for a gamma-knife procedure), while 1 wished to undergo *in vitro* fertilization, 1 had nearly normalized laboratory parameters with no clinical symptoms and one patient was lost to follow-up.

In multivariate analyses, prognostic factors of long-term remission, at diagnosis, were GHm levels [OR = 0·940 (0·883–0·999), $P = 0·048$], adenoma size [OR = 0·773 (0·640–0·933), $P = 0·007$] and absence of pituitary deficit [OR = 0·123 (0·019–0·780), $P = 0·026$]. Three-month postsurgery, GH nadir after OGTT [OR = 0·195 (0·060–0·634), $P = 0·007$] and IGF-1 [OR = 0·69 (0·07–0·674), $P = 0·021$] were also found to be predictive of long-term remission.

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Table 4. Postsurgical treatment administered to patients not in 3-month remission or with a recurrence

	Treatment after surgery				
	First-line (n = 47)	Second-line (n = 26)	Third-line (n = 18)	Fourth-line (n = 9)	Fifth-line (n = 2)
Medical treatment, n	40	17	15	7	2
Duration of treatment, months (mean ± SD)	27·3 ± 26·5	17·1 ± 14·6	28·6 ± 24	26·7 ± 14·6	*
Regimen, n					
SA	29	5	7	1	1
DA	5	2	1	1	–
Pegvisomant	5	6	5	4	–
SA + DA	1	1	–	–	–
SA + Pegvisomant	–	3	2	1	1
Repeat surgery, n	4	–	–	–	–
Gamma knife radiosurgery, n	1	7	1	1	–
Conventional radiotherapy, n	3	2	2	1	–

SA, somatostatin analog; DA, dopamine agonist; SD, standard deviation.
*Treatment was received for 12 and 61 months, respectively, in the two patients who received fifth-line treatment.

Discussion

In this study, which reflects the evolution of acromegalic patients operated on nowadays in a reference centre by dedicated neurosurgeons, almost 91% of operated patients followed for more than 6 months were in control of their disease after a mean long-term follow-up of 52·4 months. Among them, 49·5% were in remission after only surgery. Note that with the current remission criteria, only 37·4% of patients were considered in 3-month remission (65% for microadenomas and 31·6% for macroadenomas), but only 2% of patients experienced recurrent disease.

The results of the current study are comparable to those of the few long-term studies in the literature, with 56·6% of patients in remission at the end of follow-up and 49·5% after only surgery. Long-term remission rates of 44% (16 years of follow-up), 52% (13·4 years of follow-up) and 61% (mean follow-up of 5·4 years) were reported in studies after only surgery.[14–16] When all patients in remission and those controlled by treatment in the current study are considered, more than 90% had controlled disease at the end of follow-up, which is comparable with results obtained in long-term studies of the last decade, in which results increased from 82% to 94%, with a mean follow-up of 7·8–13·4 years.[14,16,17] In this long-term follow-up, note that, as in many other studies, we considered IGF-1 levels to be a determinant of remission. The main reason was that during medical treatment, GH nadir after OGTT and, even basal GH are not a good reflection of biochemical control.[18] Furthermore, epidemiological studies have demonstrated that acromegalic patients with postsurgical IGF-1 normalization have a reduced disease-related morbidity and a life expectancy overlapping that of the general population.[5,12]

One of the main aims of this study was to evaluate the efficacy of surgery for achieving remission in acromegaly using the current stringent criteria first defined by a 2005 international consensus group[9] and confirmed by updated guidelines.[8] Indeed, in our study, an overall remission rate of 37·4% was observed at 3 months postsurgery. This rate reflected that our criteria for remission were more stringent than those used in other studies and, additionally, that only 17·4% of patients had a microadenoma, which is known to be associated with better surgical outcome. When we took adenoma size into account, the remission rate was comparable to those in the literature: 65% of patients with microadenoma were in remission at 3 months in the current study, compared with 68% (GH nadir after OGTT $\leq$ 2 μg/l),[19] 67% (GHm < 2·5 μg/l)[15] and 59% (GHm < 2 μg/l),[20] despite less stringent criteria. Our 31·6% remission rate for patients presenting macroadenomas was also comparable to others in the literature: 25% (GHm < 2 μg/l), 26% (normal IGF-1)[20] and 27% (random GH < 2·5 μg/l with nadir GH after OGTT < 1 μg/l and normal IGF-1).[21] But Jane *et al.* recently published on a series of 60 acromegalic patients who had endoscopic transsphenoidal surgery, with an overall rate of remission of 70%, using the 2010 criteria. This difference could be explained by the proportion of macroadenomas (76·7% *vs* 82·6% in our study), the proportion of tumour invasion (25% Knosp grade 3 or 4 *vs* 55·7% invasive tumour in our series), a different study design (elevated IGF-1 levels 2 months after surgery were drawn again 6 months later to consider remission) or the surgical approach.[22] The only other study using current remission criteria found an overall postsurgery remission rate of 38% on 24 acromegalic patients (83% macroadenomas) operated on by endoscopic approach.[23]

Furthermore, the frequency of tumour recurrence is strongly associated with accuracy of remission criteria; the more stringent they are, the lower the short-term remission rate should be, but also the long-term recurrence rate.[24] Indeed, during follow-up, only 2·0% of our patients considered in 3 months remission experienced a recurrence. Higher recurrence rates were reported in studies using less stringent short-term remission criteria:

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5·4% (normal IGF-1 and/or a basal or glucose-suppressed GH $\leq$ 2 ng/ml),[25] or even 19% (GH < 2·5 ng/ml with glucose-suppressed GH < 1 μg/l).[15]

Long-term follow-up studies have shown that changes in biochemical status are most likely to occur within the first postoperative year, and if initial GH postglucose and IGF-1 levels are discordant.[26] In our study, discordant biochemical results at 3 months postsurgery further revealed an intermediary class of patients considered in 'uncertain remission' (23·5%), who were at greater risk of recurrence, in fact persistence, presenting intermediary results in terms of GH levels, adenoma and patient characteristics. Among the 23 patients in 'uncertain remission' with long-term follow-up, 10 (43·5%) were diagnosed as having persistent disease, with a mean delay of 11·7 months postsurgery. This increased risk has been reported in other studies, with several groups demonstrating that an abnormal pattern of postoperative GH suppression was associated with recurrence in some, but not all, patients.[15,27,28] The clinical significance of this initial discrepancy is still unknown, and management of such patients should be individualized,[11] with more intensive assessments and adapted treatment strategies, especially during the first year of follow-up.

Finally, this study allowed the identification of the current prognostic factors particularly linked to remission. Short-term predictive factors of remission included GHm level at diagnosis, degree of tumour invasion and surgeon observation of total macroscopic resection; these findings agreed with those of other studies[15,20,27,29–31] and emphasized the importance of having dedicated neurosurgeons for such interventions. Their macroscopic surgical report was a strong predictor for 3-month remission, but note also that there was no postsurgical mortality and only 7·2% of patients experienced severe surgery complications. Furthermore, pituitary deficiency and hyperprolactinaemia improved significantly after surgery (44·3–23%, $P < 0{\cdot}01$ and 31·3–2·6%, $P < 0{\cdot}01$, respectively). These are data to take into account because hypopituitarism affects patients' quality of life and can lead to increased mortality.[32] Concerning long-term remission, multivariate analysis showed the predictive factors at diagnosis were GHm levels and adenoma size, as well as lack of a pituitary deficit. Interestingly, 3 months postsurgery GH nadir after OGTT and IGF-1 were both significant predictors of long-term remission, as we used these particular data for 3-month remission criteria, as currently recommended.[8] Identifying such predictive factors should allow physicians to better predict the postsurgery outcome of acromegalic patients and to adapt their therapeutic strategy.

Overall, this study is an actualized picture of what should be expected after surgery when acromegalic patients are followed up in an expert centre with dedicated neurosurgeons. At long-term, more than 90% of patients should have their disease controlled, and almost 50% after surgery alone. Also note that recurrence of acromegaly was rare when we implemented the current criteria of short-term remission and that prognostic remission factors at diagnosis included mean growth hormone level and size and invasion characteristics of adenomas. Furthermore, patients with discrepant 3-month remission criteria seemed to be at higher risk of developing early recurrence, which we considered as persistent disease and should undergo a close initial follow-up. Ongoing research should now focus on developing treatments[33,34] to control disease in all patients and on improving quality of life in patients not achieving surgical remission.

Acknowledgements

We thank Claire Pouwels of *in*Science Communications, Springer Healthcare, who provided English language assistance. This assistance was funded by Pfizer, France. This work was supported by the "Association pour le Développement de la Recherche Médicale au Centre Hospitalier Universitaire de Marseille" (ADEREM).

Conflict of interest

Thierry Brue is a member of advisory boards and has received conference fees and research grants from Ipsen, Novartis and Pfizer.

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