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The choice of therapy in acromegaly. Results of treatment at a tertiary care hospital

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Abstract

OBJECTIVE: The aim of our study was to investigate the characteristics of acromegalic patients diagnosed at a tertiary University Hospital and to evaluate the results of the recommended treatment protocols.
PATIENTS AND METHODS: All our acromegalic patients were included (n=48; 27 women). Demographic, hormonal, visual and imaging data at diagnosis and during follow-up were recorded, as well as the treatments applied.
RESULTS: In 73.0% of the patients, acromegaly was due to a pituitary macroadenoma. From those under periodic surveillance, 68.2% underwent surgery and 36.4% had radiotherapy. At the time of the study 88.6% of the patients were receiving medical therapy, 28.2% of them as first-line treatment. Applying current criteria, only one patient was cured by surgery. Considering normal age and sex-matched concentrations of IGF-I as a control criteria, surgery resulted in disease control in 10% of the patients who had surgery, while medical treatment controlled the disease in 76.9% ($p<0.05$). Of those who receive medical therapy as first-line treatment, tumour size decreased in 45.5%, while in the rest no significant changes were observed during follow-up.
CONCLUSIONS: Not all centres obtain the results reported in the literature in terms of disease control and morbidity after surgical treatment of growth hormone-secreting tumours. It is possible that in some hospitals first-line medical treatment should be chosen, unless the patient has visual disturbances, as long as it is not clear that partial surgical removal of the tumour significantly improves response to medical therapy or reduces its costs.

INTRODUCTION

Active acromegaly leads to increased morbi-mortality. The goal of treatment is to reduce the increased morbi-mortality associated with the disease by: a) reducing GH and IGF-I production, b) decreasing or stabilizing the tumour size, c) preserving normal pituitary function and, d) treating the associated comorbidities**.** Guidelines for acromegaly management have recently been published (Melmed *et al.* 2005; Melmed *et al.* 2002; Colao *et al.* 2006a; Bolanowski *et al.* 2008). The criteria for cure and monitoring the response to treatment are more controversial (Melmed *et al.* 2005; Colao *et al.* 2006a; Giustina *et al.* 2000; Freda *et al.* 1998; Serri *et al.* 2004; Gullu *et al.* 2004; Shalet 2004). Different therapeutic algorithms have been suggested (Melmed *et al.* 2002; Shimon & Melmed

Abbreviations:

SA:	somatostatin analogs
DA:	dopaminergic agonists
aGH:	GH antagonist

1998), although neurosurgical treatment has traditionally been regarded as the first-line therapeutic approach (Melmed *et al.* 2002), with few exceptions, given its supposed high cure rate, low morbi-mortality, low recurrences rates and immediate control of hormone hypersecretion. Medical therapy has been considered as a second-line treatment. Somatostatin analogs (SA) are the medical treatment of choice (Freda *et al.* 2005). If the patient does not tolerate SA, or control is not achieved with SA plus dopaminergic agonists, treatment with the GH antagonist *pegvisomant* should be tried (Colao *et al.* 2003; Trainer 2003; Clemmons *et al.* 2003). First-line medical treatment with SA has already been claimed by some authors (Cozzi *et al.* 2003; Newman *et al.* 1998; Sheppard 2003) and has gained support in recent years (Colao *et al.* 2006a; Cozzi *et al.* 2006; Lorenzo-Solar *et al.* 2005; Petersenn 2005; Burt & Ho 2006).

The aim of our study was to investigate the characteristics of acromegalic patients diagnosed at a tertiary University Hospital, the *Complejo Hospitalario Universitario Juan Canalejo*, and to evaluate the results of the recommended treatment protocols.

PATIENTS AND METHODS

This transversal study included all the acromegalic patients followed at the Endocrine Department of our hospital. At the time of the study we had registered 48 acromegalic patients (27 women), with a mean age of 61.5± 1.7 years. Diagnosis was performed on the basis of suggestive clinical data, elevated IGF-I for age and sex, and absence of GH suppression after an oral glucose tolerance test (OGTT). We examined the following variables: gender, age at diagnosis, months of follow-up, hormonal and visual status as well as imaging studies before and after treatment and the treatments applied.

Studies of hormone and visual function. Imaging tests

The methods used to determine GH and IGF-I, as well as conversion factors from the International to the Conventional System, have changed over time. Nowadays GH is measured by a solid-phase, two-site chemiluminescent enzyme immunometric assay (Immulite, EURO/DPC) with a sensitivity of 0.01 µg/L (conversion factor for SI units, µg/L × 2.6 = mUI/L) and intra-assay variation coefficients of 5.3%, 6.0% and 6.5% for low, medium and high GH concentrations respectively. IGF-I is measured by a chemiluminescence assay (Nichols Institute, San Clemente, CA, USA) with a sensitivity of 20 ng/mL and intra-assay variation coefficients of 3.9%, 2.9% and 2.4% for low, medium and high IGF-I concentrations, respectively. The OGTT was performed with 75g of oral glucose, and GH was measured after 0, 30, 60, 90 and 120 min. The diagnosis of hypopituitarism was based on basal hormone studies, or after the appropriate stimulation tests when considered necessary.

In patients with macroadenomas with suprasellar extension, we recorded the results of tests of visual acuity and visual fields, performed at diagnosis and during follow-up.

The results of imaging studies of the pituitary-hypothalamic area (magnetic resonance imaging, or computerized tomography in the cases first studied before 1994) performed at diagnosis and at regular intervals during follow-up were also recorded. Specifically we recorded information about tumour size and extension (intrasellar, or suprasellar/cavernous/sphenoidal extensions).

In defining the cure, we used the most recently accepted criteria (1): normal IGF-I for age and sex and GH < 0.4 µg/L during an OGTT with 75g of glucose. We considered that the disease was "controlled" if the patient had IGF-I levels in the normal range for age and gender, but GH > 0.4 µg/L during the OGTT.

We considered that medical treatment caused a "reduction in tumour size" when a decrease ≥ 20% of the maximum diameter of the tumour was observed between the MRI performed before medical treatment was initiated and the last MRI.

Statistical Analysis.

The SPSS 14.0 software program (Chicago, IL, USA) was used for statistical analysis. The Mann-Whitney test was used for the comparison of quantitative variables between groups. For qualitative variables, the exact Fisher statistic was applied. Data are expressed as mean ±SEM. p values ≤ 0.05 were considered to be significant.

RESULTS

Patients

At the time of the study we had 48 acromegalic patients recorded in our Department (27 women). Four of them had been lost for follow-up before their response to any type of treatment could be evaluated, and 44 were under periodic surveillance. Mean age at diagnosis was 51.0 ± 2.5 years, and mean time of follow-up 132.0 ± 13.2 months.

Etiology

The disease was due to a pituitary microadenoma in 10.4% of the cases (n=5); a macroadenoma in 73.0%, (n=35); one patient had a gangliocytoma in the suprasellar area; in 4.2% of the patients (n=2) the hypothalamic-pituitary MRI was reported as normal and in the rest of the cases (n=5) information about the imaging studies at diagnosis was not available. In the group of the patients with a macroadenoma, 31.4% (n=11) had

visual disturbances and 42.8% (n=15) had some degree of hypopituitarism (Table 1).

Table 1: Clinical data of the 48 patients at diagnosis.

	nº / %
Sex (women)	27 / 56.2
Age at diagnosis (Years. Mean ± SEM)	51.0 ± 2.0
GH (μg/L. Mean ± SEM)	23.1 ± 4.6
IGF1 (ng/mL. Mean ± SEM)	998.4 ± 79.9
Hyperprolactinemia #	2 / 4.1
Magnetic Resonance Imaging	
Microadenomas	5 / 10.4
Macroadenomas	35 / 72.9
Intrasellar	6 / 12.5∫
Extrasellar extension	29 / 60.4∫
Normal	2 / 4.1
Unknown	5 / 10.4
Others	1 / 2.0
Hypopituitarism	15 / 42.8*
Visual Disturbances	11 / 31.4*

∫ – % of the total of patients.
– PRL ≥200 ng/ml.
* – % of the total of patients with a macroadenoma.

TREATMENT

Surgical treatment

68.2% of the patients (n=30) were treated surgically (12 in other hospitals and 18 in our centre). 90.0% of them were operated on via transsphenoidal. 20.0% of the patients who were operated on had been undergoing SA therapy prior to surgery. After surgery 13 patients were treated with radiotherapy.

31.8% of the patients (n = 14) were not treated surgically, in half of the cases because they refused the operation, and in the other half either because they were not considered **as** good candidates (due to age or comorbidities) or because a good response to medical treatment was observed while waiting for surgery.

Radiotherapy

36.4% of the patients (n =16) received radiotherapy, most (n=14) with conventional radiotherapy. Three of them had not undergone surgery.

Medical treatment

At the time of carrying out this study, 39 patients were undergoing medical therapy: 31 were being treated with somatostatin analogs (SA); 1 patient with SA plus dopaminergic agonists (DA); 1 patient with SA plus GH antagonist (aGH); and 6 patients with aGH.

Medical therapy was used as first-line treatment in 11 patients, and all were treated with SA in monotherapy.

Medical therapy was used as an adjuvant to other treatments in 28 patients: after surgery in 14 cases, after radiotherapy in 3 cases, and after surgery plus radiotherapy in 11 patients.

The treatment schedules applied are summarized in Figure 1 and Figure 2.

RESULTS OF TREATMENT

Surgical treatment

Surgical mortality was 0%. 3.3% of the patients developed cerebrospinal liquid fistula, 3.3% had transient diabetes insipidus and 10.0% had intratumoral bleeding during the operation, which hindered tumoral resection and/or complicated the postoperative period.

If we apply the recently accepted criteria for cure (normal IGF-I for age and sex and GH <0.4 μg/L during the OGTT), after surgery only 1 patient was cured; 2 had IGF-I concentrations within the normal range, although GH did not suppress below 0.4 during the OGTT, and IGF-I concentrations remained high in 27 patients. Therefore surgery controlled the disease in only 10% of our patients (Figure 3a).

After surgery, visual function improved in 6 patients, hypopituitarism improved in 6, and some degree of "de novo" hypopituitarism developed in 5.

The results for surgical treatment in patients operated in our hospital were similar to the results obtained with patients operated in other hospitals.

Radiotherapy treatment

16 patients were given radiotherapy treatment. After a mean follow-up of 138.4 ± 17.6 months, only 2 had normal IGF-I concentrations; in 13 cases the disease was controlled with medical adjuvant therapy, and in 1 IGF-I persisted elevated in spite of medical treatment.

Medical treatment

39 patients received medical treatment, controlling the disease in 76.9% (n=30) of the cases. This percentage was 75.0% in the group of patients who received medical therapy as adjuvant to surgery and/or radiotherapy, and 81.8% in the group of patients who received medical treatment as first-line treatment (p=NS) (Figures 3b and 3c). The percentage of patients with controlled disease was clearly higher with medical therapy than with surgical therapy (81.8% *vs* 10.0%, $p< 0.05$). In all of the cases in which IGF-I persisted elevated despite medical therapy, there was still the chance of increasing the SA dose, of adding DA to SA, changing SA for aGH, or adding aGH to SA.

We found no correlation between GH or IGF-I concentrations at diagnosis and probability of control with medical therapy (GH: 22.1 ± 4.0 μg/L for patients in

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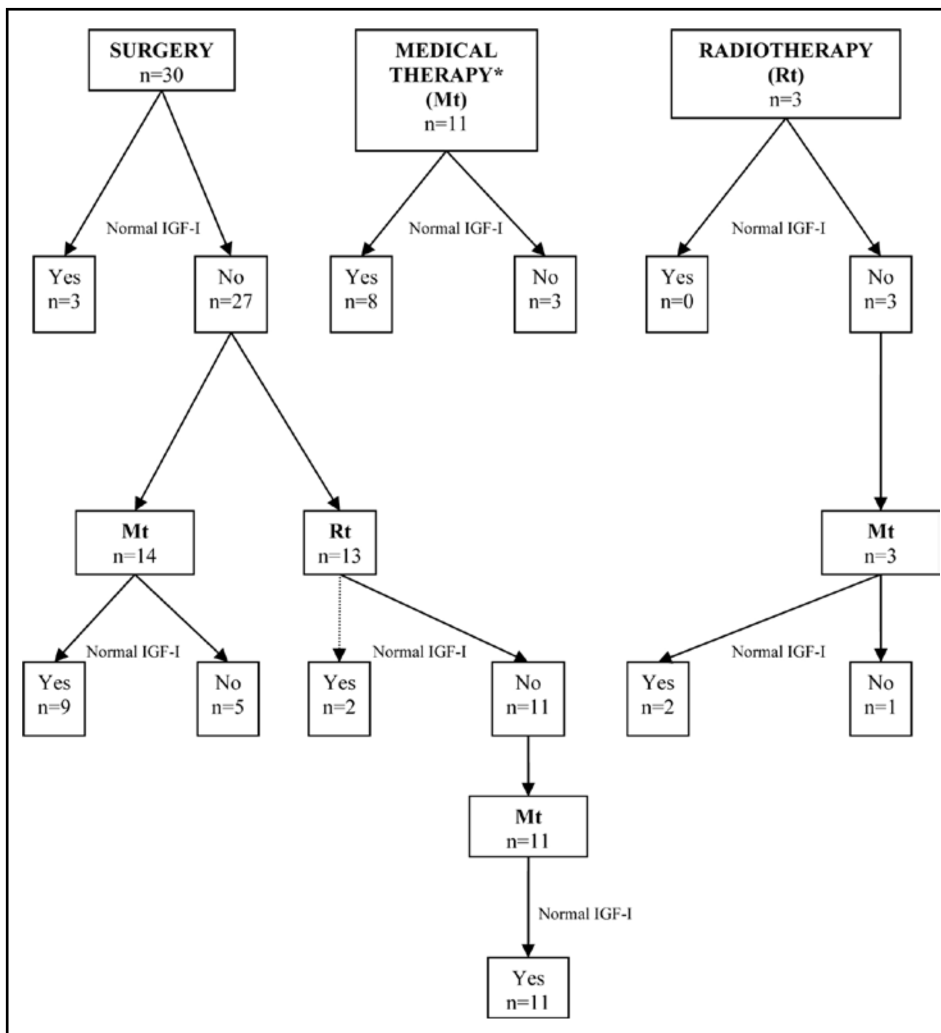

Figure 1: Treatment algorithm and its outcomes in the 44 patients under follow-up.
*Medical treatment = somatostatin analogs, GH receptor antagonist, or both.

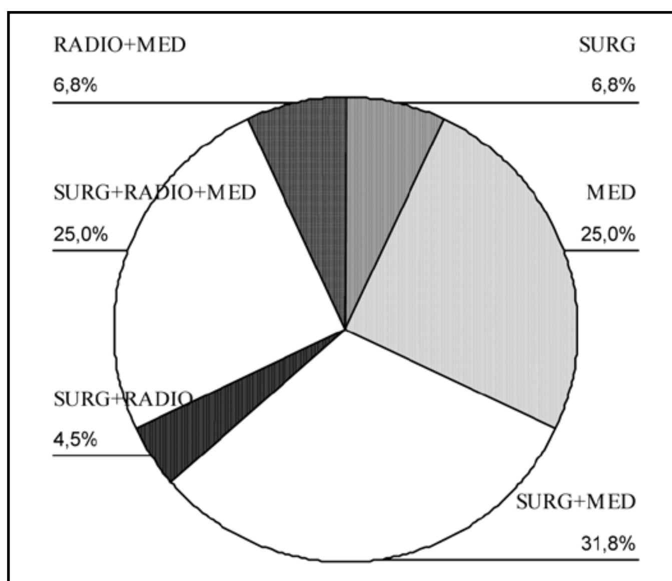

Figure 2: Percentage of patients that received a given treatment or combination of treatments. SURG: surgery. MED: medical treatment. SURG+MED: surgery followed by medical treatment. SURG+RADIO: surgery followed by radiotherapy. SURG+RADIO+MED: surgery followed by radiotherapy plus medical treatment. RADIO+MED: radiotherapy plus medical treatment

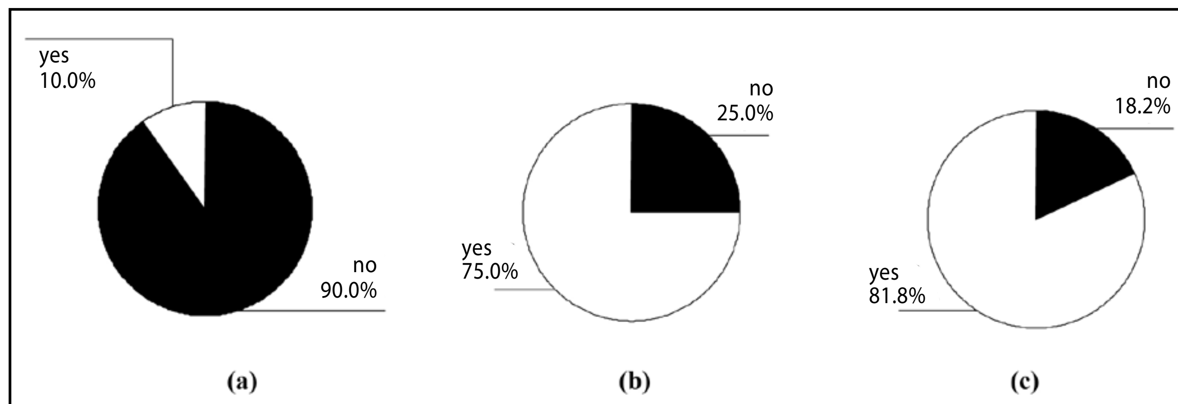

Figure 3: Percentage of patients with controlled disease after surgery **(a)**, with medical therapy when used as adjuvant therapy **(b)**, and with medical therapy when used as first-line treatment **(c)**.

whom the disease was controlled, *vs* 33.3 ± 18.1 μg/L for patients in whom the disease was not controlled, *p*=NS; IGF-I: 1030.6 ± 109.2 ng/mL for patients in whom the disease was controlled, *vs* 959.4 ± 120.0 ng/mL for patients in whom the disease was not controlled, *p*=NS). We could find no correlation between partial surgical removal of the tumour mass and eventual disease control with medical treatment.

In the group of patients that received SA as first-line treatment (1 microadenoma, 10 macroadenomas) we observed significant reductions in tumour size in 45.5%, while in the rest no significant changes in tumour size were observed during follow-up.

DISCUSSION

In our series of acromegalic patients, only one was cured by surgery, and the number of subjects with controlled disease was clearly higher with medical rather than surgical therapy.

Neurosurgical treatment has traditionally been regarded as the first-line therapeutic approach (Melmed *et al.* 2002), with few exceptions. The results of surgery vary among different centres, but if the new and more strict criteria are applied (Melmed *et al.* 2005), the surgical cure rates will probably be lower than those previously reported, which estimated that 80% of patients with microadenomas and "less than" 50% of patients with macroadenomas were cured after surgery (Bolanowski *et al.* 2006). Some authors have reported much more unfavourable results, even when using criteria for cure that would be considered inadequate at present (Erturk *et al.* 2005; Jenkins *et al.* 1995; Yamada *et al.* 1996; Lissett *et al.* 1998). It is possible that the results obtained with the new endoscopic transsphenoidal surgical procedures are different from those obtained with the non-endoscopic approach (Rudnik *et al.* 2007). If we use the new criteria (Melmed *et al.* 2005), only one of our patients may be considered as cured after surgery. If normal IGF-I levels for age and sex are used to define disease control, surgical treatment controlled the disease in 10% of the cases. As ours is a reference centre, not all of the patients operated in our hospital are being followed-up by our department; however, we see no reason to believe that the results are significantly better in those patients that underwent surgery here and were followed-up elsewhere. It is also possible that some of the patients lost for follow-up were cured after surgery. In any event, the surgical outcomes of the patients followed-up at our centre are very poor, but maybe similar to those of other hospitals (Mestrón *et al.* 2004). Several reasons may, at least partly, explain our results: a) a high percentage (at least 60.4%) had tumours whose size/extensions hindered complete surgical removal (Bourdelot *et al.* 2004), b) in our centre we do not have any neurosurgeons specifically dedicated to pituitary surgery, and c) pituitary tumour disease is uncommon, meaning it is difficult to obtain enough experience (Erturk *et al.* 2005; Lissett *et al.* 1998; De P *et al.* 2003). It is worth mentioning that 40% of our surgically treated patients were operated on in other hospitals and the results were similar to ours. Ideally, surgical treatment should preserve, or even restore, normal pituitary and visual function. Few authors take this issue into account when reporting their results. If we consider pituitary function, our results may not be considered **as** good, although the outcomes of visual function are somewhat better.

It is possible that the partial surgical removal of GH-secreting pituitary tumour mass enhances the response to somatostatin analogues (Colao *et al.* 2006b; Petrossians *et al.* 2005; Wass 2005). We could not find any correlation between previous surgery and response to medical therapy, although the small size of our sample, or small degrees of tumour resection, may have influenced our results. Other beneficial effects of partial surgical removal of the tumour mass have been reported (Damjanivic *et al.* 2005; Sze *et al.* 2007) although these effects, with the possible exception of glucose homeostasis, have also been achieved after medical control of acromegaly (Ronchi *et al.* 2006; Colao *et al.* 2006c; Maison *et al.* 2007).

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SA are the medical treatment of choice in patients with acromegaly (Freda *et al.* 2005); if the tumour does not respond to SA, or the patients cannot tolerate them, other medical options are still available. In our series, 76.9% of the patients that were receiving medical therapy had normal IGF-I levels for age and sex. This percentage was 75.0% in the group of patients who received medical treatment as adjuvant of surgery and/or radiotherapy, and 81.8% in the group of patients who received medical treatment as first-line treatment. None of them had been selected on the basis of responsiveness to medical therapy; they were placed on medical treatment if they were not operated on, if surgery failed to decrease IGF-I to normal levels, or while waiting for radiotherapy to normalize IGF-I levels. The percentage of patients with controlled disease was clearly higher with medical treatment than with surgical therapy.

As far as tumour size is concerned, several studies have shown that it decreases in a percentage of those receiving treatment with SA, especially among those in which they are used as first-line treatment (Jallad *et al.* 2005; Bevan 2005; Melmed *et al.* 2005; Bevan *et al.* 2002). Moreover, arrest of tumour growth can be a reasonable target in some cases. We did not observe tumour growth in any of our patients treated with SA as primary treatment, and in fact, in 45.5% the tumour volume actually decreased during follow-up.

We believe all these data support choosing medical therapy as the first-line treatment in a significant proportion of the patients attending our centre, especially as it neither precludes nor hinders subsequent surgery, in the event of it being required at a later stage (Losa *et al.* 2006). SA are effective in controlling the disease and avoiding tumour growth in a considerable number of patients, and have the advantage of preserving normal pituitary function. Moreover, response to medical therapy only depends on the biological characteristics of the tumour, and not on personal experience (Resmini *et al.* 2007).

An important issue when deciding on treatment for any disease is its cost. When successful, neurosurgery is less expensive than lifelong medical treatment, whose costs are high, but perhaps no more than the treatment required for other chronic diseases (Wilson *et al.* 2001). Individual tailoring of therapy can reduce injection frequency and improve its cost-effectiveness (Turner *et al.* 2004). When it is highly improbable that the patient will be cured by surgery, and therefore very likely that they will need medical adjuvant therapy, it has to be shown that partial surgical debulking improves cost-effectiveness, taking into account the possible additional costs induced by the surgical procedure, for example, by "de novo" hypopituitarism.

In summary, not all centres obtain the results reported in the literature in terms of cure and morbidity following surgical treatment of acromegaly. It is essential to evaluate one's own results before deciding the therapeutic approach for each individual patient, in order to avoid unnecessary morbidities and costs. In some centres, first-line medical treatment should be chosen, unless the patient has visual disturbances, while it is unclear whether partial surgical removal of the tumour would significantly improve response to medical therapy or reduce its costs.

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REFERENCES

1 Bevan JS (2005). Clinical review: The antitumoral effects of somatostatin analog therapy in acromegaly. *J Clin Endocrinol Metab.* **90**: 1856–1863.
2 Bevan JS, Atkin SL, Atkinson AB, Bouloux PM, Hanna F, Harris PE, *et al* (2002). Primary medical therapy for acromegaly: an open, prospective, multicenter study of the effects of subcutaneous and intramuscular slow-release octreotide on growth hormone, insulin-like growth factor-I, and tumor size. *J Clin Endocrinol Metab.* **87**: 4554–4563.
3 Bolanowski M, Bar-Andziak E, Kos-Kudła B, Krzyzanowska-Swiniarska B, Lewiński A, Łomna-Bogdanov E, *et al* (2008). Consensus statement of the Polish Society for Endocrinology: presurgical somatostatin analogs therapy in acromegaly. *Neuro Endocrinol Lett.* **29**: 59–62.
4 Bolanowski M, Zatonska K, Kaluzny M, Zielinski G, Bednarek-Tupikowska G, Bohdanowicz-Pawlak A *et al* (2006). A follow-up of 130 patients with acromegaly in a single centre. *Neuro Endocrinol Lett.* **27**: 828–832.
5 Bourdelot A, Coste J, Hazebroucq V, Gaillard S, Cazabat L, Bertagna X, *et al* (2004). Clinical, hormonal and magnetic resonance imaging (MRI) predictors of transsphenoidal surgery outcome in acromegaly. *Eur J Endocrinol.* **150**: 763–771.
6 Burt MG, Ho KK (2006). Newer options in the management of acromegaly. *Intern Med J.* **36**: 437–444.
7 Clemmons DR, Chihara K, Freda PU, Ho KK, Klibanski A, Melmed S, *et al* (2003). Optimizing control of acromegaly: integrating a growth hormone receptor antagonist into the treatment algorithm. *J Clin Endocrinol Metab.* **88**: 4759–4767.
8 Colao A, Attanasio R, Pivonello R, Cappabianca P, Cavallo LM, Lasio G, *et al* (2006b). Partial surgical removal of GH-secreting pituitary tumors enhances the response to somatostatin analogues in acromegaly. J Clin Endocrinol Metab. **91**: 85–92.
9 Colao A, Martino E, Cappabianca P, Cozzi R, Scanarini M, Ghigo E (2006a). First-line therapy of acromegaly: A statement of the A.L.I.C.E. (Acromegaly primary medical treatment Learning and Improvement with Continuous Medical Education) Study Group. *J Endocrinol Invest.* **29**: 1017–1020
10 Colao A, Pivonello R, Auriemma RS, De Martino MC, Bidlingmaier M, Briganti F, *et al* (2006c). Efficacy of 12-month treatment with the GH receptor antagonist pegvisomant in patients with acromegaly resistant to long-term, high-dose somatostatin analog treatment: effect on IGF-I levels, tumor mass, hypertension and glucose tolerance. *Eur J Endocrinol.* **154**: 467–477.
11 Colao A, Pivonello R, Cappabianca P, Auriemma RS, De Martino MC, Ciccarelli A, *et al* (2003). The use of a GH receptor antagonist in patients with acromegaly resistant to somatostatin analogs. *J Endocrinol Invest.* **26**(10 Suppl):53–56.
12 Cozzi R, Attanasio R, Montini M, Pagani G, Lasio G, Lodrini S, *et al* (2003). Four-year treatment with octreotide-long-acting repeatable in 110 acromegalic patients: predictive value of short-term results?. *J Clin Endocrinol Metab.* **88**:3090–3098.

13 Cozzi R, Montini M, Attanasio R, Albizzi M, Lasio G, Lodrini S, *et al* (2006). Primary treatment of acromegaly with octreotide LAR: a long-term (up to nine years) prospective study of its efficacy in the control of disease activity and tumor shrinkage. *J Clin Endocrinol Metab.* **91**:1397–1403.

14 Damjanovic SS, Neskovic AN, Petakov MS, Popovic V, Macut D, Vukojevic P, *et al* (2005). Clinical indicators of biochemical remission in acromegaly: does incomplete disease control always mean therapeutic faliure?. *Clin Endocrinol (Oxf).* **62**: 410–417.

15 De P, Rees DA, Davies N, John R, Neal, J, Mills RG, *et al* (2003). Transsphenoidal surgery for acromegaly in Wales: results based on stringent criteria of remission. *J Clin Endocrinol Metab*. **88**: 3567–3572.

16 Erturk E, Tuncel E, Kiyici S, Ersoy C, Duran C, Imamoglu S (2005). Outcome of surgery for acromegaly performed by different surgeons: importance of surgical experience. *Pituitary.* **8**: 93–97.

17 Freda PU, Katznelson L, van der Lely AJ, Reyes CM, Zhao S, Rabinowitz D (2005). Long acting somatostatin analog therapy of acromegaly. *J Clin Endocrinol Metab.* **90**: 4465–4473.

18 Freda PU, Post KD, Powell JS, Wardlaw SL (1998). Evaluation of disease status with sensitive measures of growth hormone secretion in 60 postoperative patients with acromegaly. *J Clin Endocrinol Metab.* **83**: 3808–3816.

19 Giustina A, Barkan A, Casanueva FF, Cavagnini F, Frohman L, Ho K, *et al* (2000). Criteria for cure of acromegaly: a consensus statement. *J Clin Endocrinol Metab.* **85**: 526–529.

20 Gullu S, Keles H, Delibasi T, Tonyukuk V, Kamel N, Endorgan G (2004). Remission criteria for the follow-up of patients with acromegaly. *Eur J Endocrinol.* **150**: 465–471.

21 Jallad RS, Musolino NR, Salgado NR, Bronstein MD (2005). Treatment of acromegaly with octreotide-LAR: extensive experience in a Brazilian institution. *Clin Endocrinol (Oxf).* **63**:168–175.

22 Jenkins D, O´Brien I, Jonhson A, Shakespear R, Sheppard MC, Stewart PM (1995). The Birmingham pituitary database: auditing the outcome of the treatment of acromegaly. *Clin Endocrinol (Oxf).* **43**: 517–522.

23 Lissett CA, Pearcey SR, Laing I, Tetlow L, Davis JR, Shalet SM (1998). The outcome of surgery for acromegaly: the need for a specialist pituitary surgeon for all types of growth hormone (GH) secreting adenoma. *Clin Endocrinol (Oxf).* **49**: 653–657.

24 Lorenzo-Solar M, Castro A, Peino R, Fernandez-Alvarez J, Dieguez C, Casanueva FF (2005). Can treatment with somatostatin analogs replace neurosurgery?. *J Endocrinol Invest.* **28** (11 Suppl): 48–52.

25 Losa M, Mortini P, Urbaz L, Ribotto P, Castrignano T, Giovanelli M. (2006). Presurgical treatment with somatostatin analogs in patients with acromegaly: effects on the remission and complication rates. *J Neurosurg.* **104**: 899–906.

26 Maison P, Tropeano AI, Macquin-Mavier I, Guistina A, Chanson P (2007). Impact of somatostatin analogs on the heart in acromegaly: a metaanalysis. *J Clin Endocrinol Metab.* **92**: 1743–1747.

27 Melmed S, Casanueva F, Cavagnini F, Chanson P, Frohman LA, Gaillard R, *et al* (2005). Consensus statement: medical management of acromegaly. *Eur J Endocrinol.* **153**: 737–740.

28 Melmed S, Casanueva F, Cavagnini F, Chanson P, Frohman L, Grossman A, *et al* (2002). Guidelines for acromegaly management. *J Clin Endocrinol Metab.* **87**: 4054–4058.

29 Melmed S, Sternberg R, Cook D, Klibanski A, Chanson P, Bonert V, *et al* (2005). A critical analysis of pituitary tumor shrinkage during primary medical therapy in acromegaly. J Clin Endocrinol Metab. **90**: 4405–4410.

30 Mestrón A, Webb SM, Astorga R, Benito P, Catalá M, Gaztambide S, *et al* (2004). Epidemiology, clinical characteristics, outcome, morbidity and mortality in acromegaly based on the Spanish Acromegaly Registry (Registro Español de Acromegalia, REA). Eur J Endocrinol. **151**: 439–446.

31 Newman C, Melmed S, George A, Torigian D, Duhaney M, Snyder P, *et al* (1998). Octreotide as a primary therapy for acromegaly. *J Clin Endocrinol Metab.* **83**: 3034–3040.

32 Petersenn S (2005). Efficacy and limits of somatostatin analogs. *J Endocrinol Invest.* **28** (11 Suppl): 53–57.

33 Petrossians P, Borges-Martins L, Espinoza C, Daly A, Betea D, Valdes-Socin H, *et al* (2005). Gross total resection or debulking of pituitary adenomas improves hormonal control of acromegaly by somatostatin analogs. *Eur J Endocrinol.* **152**: 61–66.

34 Resmini E, Dadati P, Ravetti JL, Zona G, Spaziante R, Saveanu A, *et al* (2007). Rapid pituitary tumor shrinkage with dissociation between antiproliferative and antisecretory effects of a long-acting octreotide in an acromegalic patients. *J Clin Endocrinol Metab.* **92**: 1592–1599.

35 Ronchi CL, Varca V, Beck-Peccoz P, Orsi E, Donadio F, Baccarelli A, *et al* (2006). Comparison between six-year therapy with long-acting somatostatin analogs and successful surgery in acromegaly: effects on cardiovascular risk factors. *J Clin Endocrinol Metab.* **91**: 121–128.

36 Rudnik A, Kos-Kudła B, Larysz D, Zawadzki T, Bazowski P (2007). Endoscopic transsphenoidal treatment of hormonally active pituitary adenomas. *Neuro Endocrinol Lett.* **28**: 438–444.

37 Serri O, Beauregard C, Hardy J (2004). Long-term biochemical status and disease-related morbidity in 53 postoperative patients with acromegegaly. *J Clin Endocrinol Metab.* **89**: 658–661.

38 Shalet SM (2004). Biochemical monitoring of disease activity after surgery for acromegaly. *J Clin Endocrinol Metab.* **89**: 492–494.

39 Sheppard MC (2003). Primary medical therapy for acromegaly. *Clin Endocrinol (Oxf).* **58**: 387–399.

40 Shimon I, Melmed S (1998). Management of pituitary tumors. *Ann Intern Med.* **129**: 472–483.

41 Sze L, Schmid C, Bloch KE, Bernays R, Brandle M. (2007). Effect of transsphenoidal surgery on sleep apnoea in acromegaly. *Eur J Endocrinol.* **156**: 321–329.

42 Trainer PJ (2003). Lessons from 6 years of GH receptor antagonist therapy for acromegaly. *J Endocrinol Invest.* **26**(10 Suppl): 44–52.

43 Turner HE, Thorton-Jones VA, Wass JA. (2004). Systematic dose-extension of octreotide LAR: the importance of individual tailoring of treatment in patients with acromegaly. *Clin Endocrinol (Oxf).* **61**: 224–231.

44 Wass J. (2005). Debulking of pituitary adenomas improves hormonal control of acromegaly by somatostatin analogues. *Eur J Endocrinol.* **152**: 693–694.

45 Wilson LS, Shin JL, Ezzat S (2001). Longitudinal assessment of economic burden and clinical outcomes in acromegaly. *Endocr Pract.* **7**: 170–180.

46 Yamada S, Aiba T, Takada K, Ozawa Y, Shimizu T, Sawano S, *et al* (1996). Retrospective analysis of long-term surgical results in acromegaly: preoperative and postoperative factors predicting outcome. Clin Endocrinol (Oxf). **45**: 291–298.

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