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AME POSITION STATEMENT ON CLINICAL MANAGEMENT OF ACROMEGALY

Guest Editor
E. Papini

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Reviewers
P. Chanson, A. Giustina, E. Ghigo, and C. Strasburger

FOREWORD

The reason for a Clinical Statement on Acromegaly

Acromegaly is a cause of significant morbidity and mortality but, due to its slow progressive course, most patients do not seek a timely consultation and an effective care. Owing to its rarity, most general practitioners hardly meet an affected patient along their long-life professional activity and may not recognize its constellation of symptoms and signs, sometimes apparently unrelated. Even several endocrinologists will meet only few acromegalic patients along their medical activity. Hence, they are not experienced in dealing with the aspects of this fascinating, complex but, very often, chronic and difficult to manage disease.

In the last years, the management of acromegaly has greatly improved and the prognosis of acromegalic patients is deeply changed. First, surgery obtains better results than in the past when performed by neurosurgeons skilled in pituitary disease. Imaging techniques and laboratory tests are continuously improving the monitoring of disease. Last, medical therapy makes currently possible an effective control of the hormonal secretion and the size of tumor in most patients. Hence, nowadays the perspectives for the treatment of acromegaly are dramatically improved, but the therapeutic strategy for the management of this disease is more complex and needs a careful update.

On the basis of these considerations, the decision of the Italian Association of Clinical Endocrinologists (AME) to provide clinicians with the 2009 Position Statement is timely and strategic. The mission of AME, as stated in the home-page of its website (www.associazionemediciendocrinologi.it) is "Aiming to Quality", helping all physicians treating patients affected by endocrine and metabolic diseases to continuously improve their knowledge and skill for clinical assistance. AME has recently signed a strategic alliance with the "Journal of Endocrinological Investigation", which has become its official journal, and this is the first of a series of monographical issues contributing to accomplishing AME mission.

The present Position Statement was written by a group of distinguished colleagues that are experts in the field of clinical neuroendocrinology. They revised thoroughly literature data to provide clinicians with updated and, as far as possible, evidence-based recommendations for the clinical care of acromegalic patients.

As for all rare diseases, the ultimate golden rule for all the clinicians involved in the management of acromegaly should be "suspect, screen, and refer". The panel will be glad to receive comments for a future improvement of the present clinical statement, that is planned to be periodically updated by the writing panel in agreement with the continuous evolution of the medical knowledge.

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AME Position Statement on clinical management of Acromegaly

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DEVELOPMENT AND USE OF THE STATEMENT: LEVELS OF EVIDENCE AND GRADING OF RECOMMENDATIONS

The methodology of the present Position Statement is based upon the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system (1-3).

According to the GRADE system, recommendations are classified into two grades (strong or weak) and the evidence quality is categorized as high, moderate, low, or very low.

Strong recommendation means that benefits clearly outweigh harms and burdens, or vice versa. **Weak recommendation** means that benefits closely balance with harms and burdens.

High quality evidence is defined as consistent evidence from well-performed randomized controlled trials (RCTs) or exceptionally strong evidence from unbiased observational studies.

Moderate quality evidence is evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise evidence), or unusually strong evidence from unbiased observational studies. **Low quality evidence** is evidence for at least one critical outcome from observational studies, from RCTs with serious flaws, or indirect evidence.

Very low quality evidence is evidence for at least one of the critical outcomes from unsystematic clinical observations or very indirect evidence.

When guideline developers are confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects, they will release a strong recommendation. Typically, it will be based on high or moderate quality evidence. Exceptionally, the panel can make strong recommendations based on low to very low quality evidence. This may occur when the values and preferences taken into account by the guideline developers are such that they are confident that the benefits of an intervention outweigh the undesirable outcomes (or *vice versa*). In these cases the panel can make a strong recommendation for (or against) the intervention. *Vice versa*, guideline panel may offer weak recommendations even when high quality evidence is available if evidence clearly demonstrates that the benefits and risks are closely balanced.

ACROMEGALY: THE SCOPE OF THE PROBLEM

Acromegaly is a rare disease: its reported prevalence is 40-70/million and incidence is 2-4/million/year, without significant gender difference (4-9). Prevalence and incidence of the disease are higher than expected in geographic areas close to referral centers for acromegaly (10, 11) and might be greatly underdiagnosed according to Schneider et al. (12).

Patients with acromegaly show increased mortality [relative risk (RR), ranging 1.3-4), mostly due to cardiovascular disease (13-18), that can be reverted with appropriate treatment (19).

The diagnosis of acromegaly is easy in the patient with typical clinical picture: facial disfigurement, enlargement of hands and feet, macroglossia, voice deepening, headache, arthritis. Despite the prominence of these findings at the time of diagnosis, the rate of change is so slow that only few patients seek care because of change in their appearance or other symptoms related to acral enlargement. This is the cause of a diagnostic delay, that is about 12 years from the onset of symptoms until diagnosis (20) but somewhat shorter in aggressive cases and in women due to menstrual disturbances leading to pituitary investigation and ultimately to the diagnosis. The diagnostic delay is, in turn, a main contributor to the development of comorbidities. Some patients with mild typical features or without a clear-cut clinical picture are diagnosed owing to sleep apnea, carpal tunnel syndrome, jaw malocclusion, intractable headache, unexplained dilated cardiomyopathy, diabetes mellitus/ketoacidosis, resistant hypertension (21).

The diagnosis of acromegaly should be ruled out in any patient presenting with pituitary macroadenoma, particularly in macroprolactinoma.

In acromegaly, magnetic resonance imaging (MRI) at diagnosis shows macroadenoma (tumor diameter ≥10 mm) in about 75% of patients (20). The tumor is often large, extending to suprasellar regions, and invasive to sphenoid or cavernous sinus. Visual field defects are present in few patients, mainly young with aggressive disease. Microadenomas are typically located in the infero-lateral portion of pituitary fossa, lined to the sellar floor and close to cavernous sinus, mimicking invasive features. In few patients pituitary MRI is quite negative or shows empty sella.

In very rare patients (<1%) the disease is due to GHRH production, either ectopic (mainly bronchial carcinoid, pancreatic islet-cell tumor, small cell lung cancer) or eutopic (hypothalamic hamartoma, choristoma, ganglioneuroma). In anedoctic cases ectopic GH secretion [lymphoma (22)] or GH-secreting pituitary carcinoma were reported (20). Acromegaly may also be part of multiple endocrine neoplasm type 1 (23), familiar isolated pituitary adenoma syndrome (24), McCune-Albright syndrome (25) or Carney complex (26).

DIAGNOSTIC EVALUATION

Acromegaly results from persistent and unrestrained hypersecretion of GH (20). Excess of GH stimulates the secretion of IGF-I in all tissues with GH receptors. Circulating IGF-I stems mostly (70%) from the liver and its levels are correlated to the disease's activity (27). The clinical suspicion of acromegaly must be confirmed biochemically.

IGF-I

Serum IGF-I clearly differentiates between patients with and without acromegaly. **High age-matched IGF-I coupled to high GH values** (see below) **allows to diagnose acromegaly** and makes diagnostic dynamic tests for GH secretion redundant when the clinical context is clear-cut.

Serum IGF-I shows a semilinear correlation with serum GH, reaching a plateau when GH is close to 20-30 µg/l (28). IGF-I levels are stable and do not fluctuate throughout the day. In normal subjects, serum IGF-I decreases with age, so IGF-I levels must be carefully matched to age-adjusted values. There are no significant differences in IGF-I levels between genders during adult period, whereas gender-related discrepancies in normative data in puberty can be accounted for to the fact that females enter puberty on the average at younger age.

IGF-I assay is the most sensitive lab tool in the diagnosis of acromegaly: high values can be found also in patients with "normal" or very low

GH secretion (*vide-infra*); on the contrary, exceptionally rare patients with clinically clear-cut acromegaly have normal IGF-I levels.

Pitfalls: High serum IGF-I occurs in puberty, postpubertal period and pregnancy (29). The differentiation of pathological GH hypersecretion in tall boys/girls or pregnancy may be difficult. Prolonged fasting, acute intercurrent illnesses, malnutrition, and systemic diseases (liver or renal failure, diabetes mellitus Type 1) lower IGF-I values (30). The effect of exogenous estrogens must be taken into account, because oral estrogens or selective estrogen receptor modulators decrease IGF-I levels (31, 32).

Limitations: The results of IGF-I assessment must be interpreted with caution due to biological variability and specific technical difficulties (even in the best hands) (33). Several technical criteria are required for successful estimation of IGF-I values, such as eliminations of interference of binding proteins, adequate numbers of normal subjects to define normal ranges, use of high affinity, high specificity antisera that allow precise and reproducible measurements (34). Cross comparisons between commercial assays depend on the IGF-I standard reference used for calibration. It is important to underline that within-assay results are still valid and reflect relative changes in IGF-I levels but it may not be appropriate to compare or pool IGF-I values based on different assay (35, 36).

GH

Serum GH levels are elevated in acromegaly. However, random high GH levels *per se* do not make diagnosis of acromegaly due to the pulsatile nature of its secretion (37). Only **values higher than 40 µg/l can be considered pathognomonic for acromegaly**, whereas GH levels below 0.3-0.4 µg/l rule out the diagnosis of acromegaly in most cases (38, 39). High serum GH occurs in physiological conditions (healthy subjects during bursts of episodic secretion, after fasting, exercise, stress, and during sleep, tall boys) and in some pathological conditions beyond acromegaly (Type 1 diabetes mellitus, liver disease, chronic renal failure, depression, malnutrition, disturbances of food intake behavior, hyperthyroidism). In contrast with acromegaly, IGF-I levels are low in most of these conditions (40-45).

In patients with a clinical context suggestive for acromegaly and without a reliable or diagnostic IGF-I assay, a specific dynamic test to differentiate between physiological and pathological GH secretion in the grey zone must be performed. The gold standard is oral glucose tolerance test (OGTT), measuring GH every 30 min over 2 h after the oral administration of 75 g glucose. GH levels after glucose are highly suggestive for acromegaly if >1 µg/l, whereas point to normal GH secretion if <1 µg/l, thus ruling out acromegaly (20). Recently, after the introduction of more sensitive assays (ultrasensitive, chemiluminescent), the adoption of lower GH nadir cut-off (0.3-0.4 µg/l) was suggested. OGTT stimulates GH secretion in about 10% of acromegalic patients.

Whenever GH and IGF-I levels are high within a clinical context of acromegaly, OGTT does not add any further support to the diagnosis. However, this test is clearly helpful in investigating glucose tolerance in acromegalic patients (46). OGTT must not be performed in patients with overt diabetes mellitus. A 3-h spontaneous GH profile during saline infusion has been suggested to be as reliable as OGTT in the diagnosis of active acromegaly (47).

Pitfalls: False positive results during OGTT (i.e. no suppression) are found in tall boys and during adolescence, in liver and chronic renal failure, diabetes mellitus, malnutrition, anorexia nervosa, depression, and heroin addiction (48).

Advantages of GH assay: Due to limitations and difficulties in IGF-I assessment (*vide supra*), GH assay has still a key role in the diagnosis and follow-up of acromegaly, mostly because GH is the direct product of the tumor; in addition, serum GH rapidly reflects the changes in tumor secretory capacity brought about by any (surgical or medical) therapy.

Limitations: Sensitivity of the different commercial kits for GH is widely variable with both radio-immuno assay (RIA) and ultrasensitive methods (49, 50): GH results thus differ widely between different labs. Each endocrinologist should thus know the cut-off OGTT-induced

nadir value of his/her lab's method to avoid mistakes in the diagnosis.

Other tests

In a clinical setting the determination of mean integrated 24-h GH levels is cumbersome and not cost-effective.
TRH and/or GnRH stimulation can increase GH concentrations in some acromegalic patients, but nowadays their use does not have diagnostic value anymore (29) and should be avoided, because they can occasionally cause pituitary apoplexy (51).

Borderline clinical situations

A few patients with a clinical picture of acromegaly and high IGF-I levels show serum GH below 1 µg/l or GH nadir <1 µg/l during OGTT ["micromegaly" (52)]. Thus, recently it has been suggested that, when chemiluminescence or fluorometric assays with very low detection limits are used (0.1 to 0.3 µg/l), the cut-off for GH nadir after OGTT should be lowered to 0.3 µg/l (53). The choice of this new 0.3 µg/l cut-off when using very sensitive GH assays needs still to be ratified.

Pituitary function

Pituitary function should be always evaluated in all patients with acromegaly, looking for associated hypersecretion of other pituitary hormones (mainly PRL) and the presence of pituitary failure. Hypogonadism frequently occurs also in patients with microadenoma, whereas pituitary failure may be present in patients with large macroadenoma. Serum cortisol may be low, mimicking central hypoadrenalism in spite of normal hypothalamus-pituitary-adrenal function (54): low cortisol is due to the inhibitory effect of GH hypersecretion on Type 1 11β-hydroxysteroid-dehydrogenase, that catalyzes the conversion of cortisone to cortisol.

Imaging

Pituitary MRI will show the source of the disease in most (99%) cases. In patients with pituitary enlargement but without clear-cut evidence of adenoma an ectopic GHRH secretion should be suspected. Its location should be looked for by chest X-ray, abdomen ultrasound, and Octreoscan. The proof of an ectopic GHRH secretion is given by GHRH assay, that is not widely available.
MRI can delineate adenoma from normal pituitary tissue and the macroscopic invasion of surrounding tissues. MRI is unable to identify the microinvasivity of the adenoma.
Computerized tomography is nowadays an ancillary method. It has to be used in patients that cannot undergo magnetic fields (pace-maker or metallic prosthesis) or to delineate bone structures for surgery planning.
Patients bearing macroadenoma close to optic chiasm must undergo **ophthalmologic** evaluation for the integrity of visual fields.

Conclusions

We recommend to assess both GH and IGF-I levels to make diagnosis of acromegaly (high quality).
Pathophysiological conditions associated to false positive and false negative results for both GH and IGF-I should be excluded (low quality).
We recommend to perform OGTT for GH levels to diagnose acromegaly only if the combination of GH, IGF-I levels and clinical picture is not clear-cut (low quality).
We recommend to perform MRI at diagnosis (high quality) and to assess PRL levels and other pituitary axes function (moderate quality).
We recommend to evaluate visual fields in patients with macroadenoma close to optic nerves (moderate quality).
We recommend against the use of dynamic tests beyond OGTT in diagnosis or follow-up (very low quality).

COMORBIDITIES

Mortality in acromegaly is increased mostly because of cardiovascular and respiratory involvement, while neoplastic complication role is still uncertain (14, 16, 55). The most important comorbidity impairing quality of life is arthropathy: in contrast with cardiomiopathy and respiratory

complications it is reported to improve less after treatment.

The cardiovascular complications

Cardiovascular involvement occurs commonly in most acromegalic patients.

The most common feature of the acromegalic cardiomyopathy is **concentric biventricular hypertrophy** (56). Ageing and long duration of GH/IGF-I excess are main determinants of cardiac derangement: nevertheless, also young patients are involved. The acromegalic cardiomyopathy progresses in overt cardiac hypertrophy with signs of diastolic dysfunction and/or insufficient systolic performance on effort if the disease is left untreated (56). In some patients systolic dysfunction at rest and overt heart failure with signs of dilative cardiomyopathy may occur (56).

Rhythm disturbances, such as ectopic beats, paroxysmal atrial fibrillation, paroxysmal supraventricular tachycardia, sick sinus syndrome, ventricular tachycardia, and bundle branch blocks, might also be recorded mainly during physical exercise (56). Arrhythmia may be so severe to be an absolute contraindication to neurosurgery or to lead patients to sudden death.

Cardiac valve disease is frequent, even though the echocardiographic alterations do not always have a clinical counterpart, and is associated with left ventricular hypertrophy (57, 58).

Hypertension affects more than one third of the patients, is prevalently diastolic, and begins approximately ten years earlier than in the control population (59).

Increase of the carotid intima-media thickness associated with **endothelial dysfunction** (60, 61) was also described.

Cardiovascular involvement, in particular diastolic dysfunction and arrhythmias, improves after successful treatment of acromegaly (56, 62).

Since the presence and severity of cardiomyopathy and respiratory dysfunction (see below) may influence the treatment choice, **we recommend** that an electrocardiogram (ECG) (to document the presence of arrhythmias, low quality) and an echocardiogram (to document left ventricular dysfunction and valvulopathies, high quality) be performed in the initial work-up. Twenty-four hour ECG should be reserved to patients showing arrhythmias in basal ECG.

The metabolic complications

Impaired glucose tolerance and overt **diabetes mellitus** are frequently **associated** with acromegaly (56). The prevalence of diabetes mellitus in acromegaly ranges between 19 and 56% likely due to different patient series and ethnicity, with a positive association with higher GH levels, higher age and longer disease duration, family history of diabetes and with the concomitant presence of arterial hypertension (63).

The prevalence of **hypercholesterolemia** is similar to that of the general population, whereas the prevalence of type IV **hyperlipidemia** is almost three times higher than in controls (64).

Glomerular hyperfiltration is characteristic: creatinine clearance is higher in patients than in controls (56) as well as microalbuminuria, a marker of cardiovascular risk, suggesting a microvascular involvement (65).

Disease control usually markedly improves glucose tolerance and diabetes (56). Somatostatin analogs (SA), by suppressing insulin secretion, can slightly impair glucose tolerance in some patients, but this is seldom of clinical significance (66, 67) whereas GH receptor (GHR) antagonist influences positively glucose metabolism.

Based on these findings, **we recommend** to perform an OGTT in all patients (high quality) apart from those with overt diabetes at baseline. The glucose tolerance should be checked serially in patients carrying on SA treatment to verify changes.

The respiratory complications

Patients with acromegaly develop several respiratory alterations, as a consequence of anatomical changes affecting cranio-facial bones and soft tissues, respiratory mucosa/cartilages, lung volumes, rib cage geometry, as well as activity of respiratory muscles (56). This range of abnormalities results in two main respiratory dysfunctions, namely **sleep apnea** and **impaired respiratory function**.

Sleep apnea is a common cause of snoring and daytime sleepiness, affecting as many as 60% of unselected acromegalic patients (56). Sleep ap-

nea may be obstructive, due to anatomical narrowing of the upper respiratory airways linked to macroglossia, or central. Sleep apnea is a well-known risk factor for the cardiovascular disease leading to severe decrease in arterial oxygen saturation, arrhythmias and worse control of blood pressure.
Control of acromegaly usually improves sleep breathing disorders.
There is no consensus on how to diagnose and monitor respiratory disorders in acromegaly (low quality). At first patients can be screened by interviewing relatives about night-time sleeping habits of the patient (snoring/apnea) and thereafter the diagnosis is made by using polysomnography, that is a rather difficult method to perform, not routinely used, and not available in every center. An easier method to screen for sleep apnea is the use of Epworth sleepiness scale, providing a measurement of the patients' general level of daytime sleepiness (68).

The neoplastic complications

Cancer does not seem to be a major cause of death in patients with acromegaly (69). A large UK study (14) revealed only a slight increase in **colon cancers** [standard incidence ratio (SIR) 1.68, 95% confidence intervals 0.87-2.93] and a lower than expected incidence of bronchial tumors (SIR 0.33, 95% confidence intervals 0.12-0.72). Digestive tumors constitute the most frequent malignancies; nearly 27% of all tumors and 18% of them are colorectal carcinomas (56). Acromegaly especially stimulates the development of **colon adenomatous polyps** (56).
Because of this finding, **we recommend** a pancolonoscopy at least once in patients with acromegaly (moderate quality). Uncontrolled disease and presence of at least one lesion on first examination, **suggest** repeating colonoscopy after 1-3 years, according to histological pattern (moderate quality). Follow-up should be adapted to the presence of other risk factors to develop colon cancer (familiarity, male gender, presence of skin tags, insulin levels, *etc.*). There is no consensus, however, as to when repeat colonoscopy in patients with controlled disease (very low quality).
Additionally, whilst goiter is a common phenomenon in acromegaly, the occurrence of thyroid tumors constitutes a relatively rare event. There is also no evidence for an increase in breast, lung or prostate cancer.

The complications at the skeletal system

The osteo-articular manifestations are pathognomonic features. Symptoms or signs referable to articular joint disorders occur in the great majority of patients at diagnosis (56). Manifestations include **articular involvement** and **enthesopathy** and are a leading cause of morbidity and functional disability in these patients (56). The acromegalic arthropathy affects both axial and peripheral sites in up to 74% of patients with moderate to severe involvement (56).
Symptomatic **carpal tunnel syndrome** is a common condition, with a prevalence of 20-64% at presentation (56).
Whether controlling GH and IGF-I levels can reverse the acromegalic arthropathy is still questioned. The extensive structural changes occurring at the joints and the limited reparative ability of chondrocytes appear to prevent a significant improvement of acromegalic arthropathy. However, disease remission by surgery or SA markedly ameliorates symptoms and signs of arthropathy and of carpal tunnel syndrome (56).
There is no agreement on how to diagnose and follow the acromegalic arthropathy (very low quality). Standard X-ray is required to study the spine, while ultrasonography have been used to image joints (56).
The relationship between bone mineral density and acromegaly is complex, due to the contrasting effect of GH hypersecretion and hypogonadism (70), but osteoporotic fractures are frequent both in post-menopausal women (71) and males (72) and should be looked for by standard X-ray of the spine.

TREATMENT

The goal of treatment should be the cure of the disease, i.e. the reversal to the normal pattern of physiological pulsatile GH secretion. This is not obtained by any treatment, thus the term re-

mission is commonly used, implying the normalization of GH/IGF-I levels. Both GH and IGF-I levels accepted as normal have been lowered progressively. Normal IGF-I levels must be age-adjusted.

Neurosurgery

Neurosurgery is the only option to definitively cure acromegaly. Its effects are immediate. The end-point for surgery is the complete resection of GH-secreting adenoma with preservation or subsequent restoration of physiological pituitary function. The current goal is a serum IGF-I concentration normal for age and gender and a normal suppression of serum GH concentration (vide infra) after OGTT.

The **transsphenoidal** route should be almost exclusively used, but the surgical technique to be used [microsurgery or endoscopy (73)] remains a preference of the single surgeon.

Surgical results are evaluated by assaying GH levels after OGTT and IGF-I. The currently accepted GH nadir after OGTT for normalcy is less than 1 µg/l (29), but Freda et al. (74) reported that it should be lowered below 0.3 µg/l. Indeed they reported recurrence of the disease in patients with GH nadir after surgery between 0.3 and 1 µg/l (even if faced to normal IGF-I), but their data were not confirmed (75). This discrepancy in the assessment of biochemical criteria for cure is strictly dependent on the sensitivity of the used GH assay.

The **success rate** of surgery is quite variable: it ranges between 15 and 60% in different series. Success rate is related to:

- criteria used to define cure of the disease,
- size and invasiveness of tumor,
- GH levels,
- surgeon's skill and experience (i.e. yearly load of pituitary operations).

In the best hands (76) success rate drops from 85% for microadenomas to 50% for extrasellar macroadenomas, and to 10% for giant adenomas. Moreover, it declines from 86% to 51% in patients whose GH levels are lower than 10 µg/l or higher than 25 µg/l, respectively (77). Recently, UK register (78) showed that surgical success rate may be so low as 10%, according to the operating center, regardless of tumor size or GH levels.

The timing of GH/IGF-I **evaluation after surgery** is clearly dependent on the administration of any GH suppressive treatment before operation as well as its duration. In patients not pre-treated, GH assessment during OGTT is reliable already at 1 week after surgery (79); in pre-treated patients the evaluation must be postponed (up to 6-12 weeks after surgery). In patients undergoing surgical remission, the time to IGF-I normalization may take up to 3 months.

Up to 30% of patients show **discrepancy** between GH nadir and IGF-I values after surgery (80, 81). Patients with GH nadir below 1 µg/l and high IGF-I should be considered still active, whereas in patients with clearly normal IGF-I and GH nadir above 1 µg/l the reason of discrepancy is unexplained: methodological problem in GH assay may be suspected, and a role for GHR polymorphism has been recently claimed (82).

Pituitary function may improve or worsen after surgery, thus it must be evaluated.

MRI should be done in each patient at 3-4 months after surgery: this lag time is required owing to surgical edema, fibrosis, and scarring that would not allow to correctly visualize earlier the result of surgery. Serial MRI is useless when the patient is biochemically cured post-operatively (83).

The overall **recurrence rate** is low and recurrences are uncommon when biochemical remission is clearly documented post-operatively by the adoption of the most recent cut-offs. In cases of recurrence, a second surgery is usually unable to provide long-term remission and may cause pituitary failure and/or permanent diabetes insipidus.

It is still debated if **pre-surgical medical treatment** with SA improves the results of surgery, by reducing tumor size and lowering GH levels. No consensus has yet been reached about improvement of surgical outcome (GH/IGF-I normalization) (84, 85). At variance, SA can clearly improve clinical picture, metabolic (i.e. diabetes mellitus) derangements, and comorbidities (heart and respiratory involvement), favoring anesthesiological procedures and lessening surgical risk, provided that urgent decompressive maneuvers are not required. Severe comorbidities and metabolic derangement, when reverted or ameliorated by GH-

suppressive medical therapy, are thus not permanent contraindications to surgery.
In experienced hands, **mortality** should approach 0 (and should be 0 for microadenomas) and **complications** rate should not be >2% altogether (86, 87). Pituitary function improves or normalizes in 35-45% of those previously impaired, is unaffected in half, and can worsen in 2-6% of those previously unimpaired (76, 88). In young patients with intact pituitary function fertility preservation must be considered.
Given the complexity of the disease and of its presentation, **an interdisciplinary approach is strongly recommended**.
Since the surgical option can be regarded as an only one-shot gun, it is mandatory to assure that the shot is fired timely and by the best available "shooter". **We recommend** that patients are operated by a trans-sphenoidal approach by an experienced pituitary surgeon (at least 25 operations/year), in a dedicated pituitary center, as results and complications are greatly influenced by the surgeon's and the center's experience (89).
We recommend against neurosurgery in patients without any evidence of pituitary adenoma and of ectopic GHRH secretion (low quality).
We recommend to evaluate gonadal function and to assay cortisol and FT_4 levels before and after surgery (moderate quality).
We recommend to evaluate surgical outcome assessing GH levels after OGTT (high quality). The test should be performed at 7 days or at 60-90 days after operation, in patients not pre-treated with GH suppressive treatment before surgery or pre-treated, respectively (low quality). IGF-I should be assayed 30-90 days after surgery (low quality).
We recommend to perform MRI at 3-4 months after surgery (moderate quality).
We suggest that patients in remission repeat only a yearly IGF-I assessment (very low quality).

Medical treatment

At variance with the goal required for remission in post-surgical evaluation, the control of disease during medical treatment is defined by hormonal values associated in epidemiological studies to the normalization of increased mortality of the acromegalic patient, i.e. normal age-and sex-matched IGF-I values and GH levels less than 2 or 2.5 µg/l, defined as "safe" (19, 55, 90, 91). This GH cut-off was obtained by using an old competitive RIA method which is no longer applied nowadays and therefore these cut-off criteria also are not applicable to the more sensitive modern assays.
Presently available drugs for the medical treatment of acromegaly act either by suppressing GH hypersecretion, such as dopaminergic drugs (DA) and SA, or at the peripheral level by blocking IGF-I synthesis, such as Pegvisomant (Peg), a GHR antagonist (GHRA).
GH should be assayed by multiple sampling during saline infusion. Even though the independent association of IGF-I levels to mortality has still supporters (18, 55, 92, 93) and oppositors (94), serum IGF-I correlates better to clinical picture (23), and thus its monitoring is mandatory.
MRI is usually checked in the follow-up of medical treatment to assure tumor size control.

Dopamine-agonist drugs

Bromocriptine, the first employed DA, normalized IGF-I levels in a few patients only (95).
It has been replaced by cabergoline (Cab), an ergolinic compound endowed with powerful, prolonged and selective action at the type 2 dopaminergic receptor, that has been reported to normalize IGF-I levels in up to 25-35% of patients, mainly in those with lower GH and IGF-I levels (96, 97).
PRL hypersecretion is not a prerequisite for Cab effectiveness (97, 98).
Tumor shrinkage is reported in occasional patients (97).
Cab is an oral compound that can be easily administered during dinner. In acromegaly dosages are far greater and schedule administration is more frequent than in PRL-secreting adenomas. In this setting Cab has to be given on a daily schedule, at a progressively escalating dosage (starting from 0.25 mg once/twice weekly up to 0.25-0.5 mg/day).

Adverse effects

Despite high doses, Cab is usually well tolerated: drowsiness, nausea, anorexia are reported at high doses and sometimes may limit the use of

this drug. Recently, the report of cardiac valve deterioration, observed in patients with Parkinson's disease after prolonged Cab treatment at high dosage (3 mg/day), raised concern (99, 100). However, the first observational studies in prolactinoma patients are reassuring (101). **We recommend** echocardiographic monitoring, mainly in patients with acromegalic valve disease (low quality).

Somatostatin analogs

Octreotide and lanreotide are the presently available SA, mimicking the GH secretion block of native somatostatin with more prolonged duration of action at the level of somatostatin receptor subtype 2 (and 5) on the adenomatous cells. Also a direct peripheral IGF-I inhibitory effect of SA on the liver was shown (102, 103).

SA effectively inhibit hormonal hypersecretion:

- achieving safe GH and normal IGF-I levels in at least 50% of patients (104), and considerable decrease of GH and IGF-I secretion in another 40% (105-107);
- without any tachyphylaxis during up to 18 years of continuative administration (108);
- obtaining a progressive amelioration of hormonal control (109).

Clinical amelioration parallels hormonal control: clinical symptoms (headache, swelling, hyperhydrosis, snoring) markedly improve or disappear (110), as well as systemic comorbidities (cardiac involvement, sleep apnea, diabetes mellitus) (56, 62).

Adjuvant medical treatment improves the patients' outcome after unsuccessful surgery (111, 112).

SA induce **tumor shrinkage** (105, 113, 114). The occurrence and degree of shrinkage are more impressive when SA are used as primary treatment (greater than 50% *vs* baseline in over half of patients) than as adjuvant (20%) and with octreotide *vs* lanreotide (80% *vs* 35% of primarily treated patients, respectively) (105). Tumor shrinkage occurs in the first months of treatment, may be quick, and progressive during the prolongation of treatment (115), up to empty sella or disappearance of the tumor.

Predictive role of acute octreotide test is not commonly accepted (11, 116, 117). The lack of response to an acute test (i.e. no or minimal GH decrease) may allow identifying fully unresponsive patients. Final outcome can be reliably predicted by early (3-6 months) results obtained during chronic treatment, at least with octreotide long-acting repeatable (LAR), suggesting clinicians whether it is worthwhile to prolong ongoing treatment that has a high probability to achieve hormonal targets, or it is better to switch patients to alternative treatments (109, 115).

High GH levels and huge adenoma volume are not negative predictors of SA effectiveness according to some (109, 115), but not all authors (102).

In up to 30% of patients, discrepancy between GH and IGF-I levels may occur (80, 81): since IGF-I is more correlated to clinical picture, in these cases **we suggest** to pursue the goal of IGF-I normalization (low quality).

Only a few head-to-head comparative studies between octreotide and lanreotide have been published. Even though Freda et al. (102) suggested that "octreotide LAR is more efficacious than lanreotide Slow Release (SR) when potential preselection effects are removed", this statement is no longer tenable after the availability of lanreotide Autogel (118). A change from one SA to the other one may be beneficial in some patients with partial resistance or adverse effects (119).

SA are parenteral drugs to be injected im (octreotide LAR) or sc (lanreotide Autogel) every 4 weeks, starting with the intermediate strength commercially available dosage (20 and 90 mg, respectively). After 3 injections to allow the reaching of steady state, the dosage has to be individually tailored, according to results (increasing to 30 or 120 mg, or decreasing to 10 or 60 mg, respectively). Serum samples should be taken before the next administration of the drug at 3-month intervals during the titration phase, and at 6-12-month intervals thereafter. OGTT is probably unable to obtain further GH suppression beyond that obtained by any GH suppressive treatment (120-122), but data on this topic are scanty.

In a few very sensitive patients, the interval between injections can be safely lengthened in a stepwise fashion (by 1 week at a time, finding the minimal effective dose, reportedly up to 8 weeks),

thus increasing compliance and saving money (125). Further increase of dosage can sometimes improve results (123, 124), whereas the shortening of interval between injections in partially sensitive patients does not (125).

Adverse effects

Local: discomfort, erythema or swelling, pain and itching at injection site, in 10-20% of patients (112).

Gastroenteric: diarrhea, abdominal pain, flatulence, steatorrhea, nausea, and vomiting in 5-15%, but usually transient and mild to moderate in severity.

Metabolic: the suppressive effect of SA on insulin secretion is usually counterbalanced by the decrease in insulin resistance that follows GH lowering. The net effects on carbohydrate metabolism are widely variable, but seldom of clinical significance (67): in diabetic patients glucose metabolism improves in most cases, even until the withdrawal of any hypoglycemic agents, but may require rarely dose escalation of insulin or glucose-lowering drugs. In previously euglycemic patients, glycated hemoglobin may increase (126, 127) or remain unchanged (115). **We recommend** monitoring of glucose metabolism during SA treatment (moderate quality).

Gallstones are a frequent occurrence in acromegalic patients treated with SA (1 out of 3 altogether), may occur at any time, but they are seldom symptomatic or prompt acute surgery (128). Obesity and dyslipidemia appear to play a major role. **We suggest** ultrasound monitoring (moderate quality).

GHRA

Peg is the presently available GHRA. It is a partially modified GH molecule capable of binding GHR but inhibiting its activation and IGF-I synthesis (129). Serum GH increases during GHRA treatment, but cannot anyway be measured reliably by commonly employed assays due to Peg interference.

Peg is effective in normalizing IGF-I levels (130, 131). In the largest reported series, IGF-I levels normalized in 76% of 177 acromegalic patients resistant/intolerant to SA (132). The higher the basal IGF-I levels and the greater the patients weight, the higher the needed Peg doses; women need higher dose than men for the same weight (133).

In Europe, Peg can be employed only in SA-resistant/intolerant patients after neurosurgical failure or awaiting the effects of radiotherapy. Its primary use might be envisaged also in SA-resistant/intolerant patients without any neuroradiological evidence of pituitary adenoma.

Even though tumor growth remains uncontrolled during Peg treatment, "true" tumor size increase was noticed only in few patients, mainly with aggressive disease, whereas tumor volume reportedly increased in a few cases after the withdrawal of previous SA treatment that had shrunk tumor (134). **We recommend** MRI monitoring before starting and during treatment at 6-month intervals in the first year and yearly thereafter (moderate quality).

Peg ameliorates glucose metabolism in acromegaly, therefore its use can be particularly indicated in patients who experience overt glucose metabolism derangement during SA treatment (135, 136).

Peg is a parenteral drug to be injected sc daily, starting with the 10 mg dose, to be stepwise increased at monthly intervals up to IGF-I normalization. IGF-I suppression can be maintained also by injecting the drug at longer intervals (once-twice/week). A risk to be avoided is overtreatment, i.e. IGF-I lowering below normal age-matched range.

Adverse effects

Injection site reactions in 7.4% (erythema and swelling, lipo-hypertrophy, that in some cases may be worrisome and impair drug absorption), headache in 1.7%, liver toxicity [transaminases x 3 upper limit of normal range (ULN)] in 5.2% (137). Liver toxicity in most cases normalizes after transient drug withdrawal or despite continued treatment (138, 139). Withdrawal due to serious adverse events is reported in 7.9%.

We recommend:

- liver function test monitoring at monthly interval during titration, thereafter at 3-month intervals during chronic treatment at stable Peg dosage (low quality);

- withdrawal of the drug if transaminases levels increase more than × 3 ULN persists or worsens (moderate quality). In patients showing lesser transaminases increase, Peg dosage may be maintained stable or slightly decreased;
- the rotation of drug injection site to avoid lipohypertrophy.

Combined pharmacological treatments

Drugs can be combined to take advantage of different mechanism of action and possible synergies. The combined use of **SA and Cab** reportedly obtained hormonal targets in 20% of patients partially sensitive to SA, irrespective of hyperprolactinemia (140). **We suggest** this combination as a second medical approach in all acromegalic patients achieving hormonal levels close to the target (IGF-I<1.5 ULN) while on SA treatment (low quality).

The combined use of **SA and Peg** (141) is a promising therapeutic option, since it concomitantly controls tumor growth and hormonal hypersecretion, normalizes IGF-I levels in virtually each patient and affords sparing Peg (at least the number of week injections, administered once per week or on alternate days, if not the cumulative dose), improving compliance (142-144) and quality of life. This treatment should be envisaged in all patients with aggressive disease showing tumor shrinkage without the achievement of hormone targets on SA. However, more data are needed and at present it cannot yet be recommended routinely (low quality).

The choice of pharmacological treatment

In patients with mild disease, **we suggest** a trial with Cab (low quality) regardless of PRL levels. Cab may be particularly effective in patients with "true" mixed GH/PRL hypersecretion.

In the majority of patients, mostly if requiring a quick control of the disease, **we recommend** to start with SA (moderate quality). **We suggest** to immediately start with the highest SA dose in patients with aggressive disease (particularly high GH levels and/or huge tumor). **We recommend** starting SA at intermediate dose in all the others (moderate quality), individually tailoring the dose at 28 days after the 3rd monthly injection (i.e. uptitrating if targets are not yet reached, or downtitrating if IGF-I is below the 3rd percentile or –2 SD score).

In patients experiencing troubling adverse events with one SA, **we suggest** a cautious trial with the other molecule (low quality).

In patients with partial sensitivity to SA, we suggest a 3-6-month trial of combined therapy with Cab (low quality).

We recommend to use Peg in patients resistant/intolerant to SA only after unsuccessful surgery or after radiotherapy. Its use might be envisaged also in patients:

- previously fully unresponsive to SA, after unsuccessful surgery;
- resistant/intolerant to SA without any visible tumor;
- with diabetes mellitus linked to SA treatment.

The combined administration of SA and Peg cannot be recommended at present, except in patients with aggressive disease or tumor re-enlargement after SA withdrawal.

Radiotherapy

Presently, two groups of radiation-delivering devices are available (145, 146): fractionated radiotherapy (FRT) and radiosurgery (RS).

FRT delivers radiation in multiple refracted doses that aim to inhibit tissue proliferation by interfering with the cell cycle, theoretically taking advantage of the quicker replication velocity of tumor cells.

RS delivers in a single session a highly collimated dose conformated to the shape of the target aiming to obtain radionecrosis and sparing normal brain tissues.

Interstitial irradiation (by the stereotactic implantation of radioactive seeds, usually ^{90}Yttrium, directly into the target) is no longer employed (due to heavy adverse effects).

Some retrospective studies reported that the administration of GH-suppressive treatment during irradiation counteracts its efficacy (147, 148). However, at present there is no consensus on the radioprotective effect of GH suppressive treatment.

A sound prospective comparison between results obtained by FRT and RS is not feasible for the different indications of the two techniques and the different clinical conditions in which they are used.

Since radiotherapy was shown to impair the orderliness of GH secretion (149), **we recommend** to assess disease's activity in the follow-up after irradiation by IGF-I assay (low quality).

Fractionated radiotherapy

Technique

At present, radiation is delivered by linear accelerators in multiple fractions, with a total dose of 40-45 Grays (Gy) (not to be overcome to avoid damage to normal nervous tissues) fractionated in 4-5 sessions per week over a 4-6 week period. The multiple field strategy maximizes the dose given to the tumor, while relatively sparing the surrounding normal tissue.

Efficacy

Radiation effect is slow. Conflicting results about success rate are reported in different series (5-78%) (150, 151). Differences may be due to techniques and radiation dose, criteria to evaluate results, as well as length of follow-up. IGF-I is normalized in <10%, 23-60%, 16-74%, 61-84% at 2, 5, 10, and 15 years, respectively [reviewed in (145, 146)].

The achievement of hormonal targets depends critically on the initial hormonal values, i.e. the higher GH levels, the slower their normalization (152-154).

Local tumor control is obtained in virtually all patients [reviewed in (146)].

Adverse events

Toxicity may be severe. It is directly related to total dose as well as to dose per fraction, i.e. the highest the dose the greatest the damage.

Hypopituitarism is the commonest complication of radiation. It occurs in an increasingly fraction of patients throughout the years (37-57%, 50-78%, and 75-85% at 5, 10, and 15 years, respectively) (155, 156): gonadotropins first fail, followed by TSH and ACTH; even GH deficiency can occur.

Small but significant risk of visual loss is reported (up to 2%) (157).

An increased risk (RR 4.1, 95% confidence intervals 2.7-5.5) of cerebro-vascular disease was recently reported in several retrospective studies, leading to increased mortality risk (RR 1.6-2.7) in previously irradiated acromegalic patients *vs* not irradiated patients (9, 16, 17, 93, 158, 159).

Impairment in quality of life was reported in previously irradiated patients, even after adjustment for age and hypopituitarism (160, 161).

The occurrence of secondary intracranial neoplasm (meningiomas, sarcomas, gliomas: total risk of 2% at 20 years, with a 10-24 RR *vs* control population) was reported (162-166). Data on the effects of newer focused techniques are not yet available.

Several patients complain of neurocognitive dysfunction after radiotherapy, such as loss of memory and amnesia: its evaluation is difficult due to the lack of appropriate controls, however it needs further study.

Radiosurgery

Technique

RS can be performed by equipments employing different radiation sources: gamma-knife (GK, gamma photons from ^{60}Cobalt), linear accelerator and cyber-knife (X photons) (167, 168), proton beam (protons) (169), but only the first has reached a relatively wide diffusion nowadays.

Owing to high energy delivered in a single session (usually 15-20 Gy), a perfect head immobilization is mandatory: in the case of GK it is obtained by Leksell stereotactic frame that is invasively fixed to patient's skull.

To avoid optic chiasm damage, a safety margin of at least 3 mm has to be left and local dose must not exceed 8 Gy (170, 171).

Efficacy

Few good-quality studies reported results of GK in acromegaly (172-177). Remission of disease evaluated with modern criteria was obtained in 28-53% and 54-75% of patients at 5 and 10 years after GK, respectively.

Adverse events

Cases of vision injury have been reported even with low doses (as low as 0.7 Gy) (178). It is important to underline that radiation-related neural tissue injury is stochastic, meaning that the risk decreases with lower doses, but with no true threshold below which it is entirely safe. Cav-

ernous sinus nerves are more radioresistant and no injury was reported up to now (170). Patients with prior irradiation or with co-morbidities, such as baseline cranial nerve injury, diabetes mellitus, and vascular disease likely define an inherently higher risk population for nerve injury.

Hypopituitarism occurs in 5-60% and its figure seems to be inversely related to the efficacy of treatment. Neurocognitive dysfunction was not evaluated up to now.

Duration of follow-up after GK is probably still too short to confidently evaluate the occurrence of hypopituitarism, cerebrovascular disease, and secondary tumors (179).

<u>Who, when, how to irradiate</u>

Radiotherapy is burdened by slow efficacy, side effects and serious concern on long-term safety (mostly in young patients with long life expectancy, i.e. >30 years). The present availability of very effective antisecretive drugs with a good safety profile is lessening more and more its role.

We recommend that radiotherapy, irrespective of the technique, be performed in reference centers with expertise in treating small benign intracranial lesions in which pros and cons have to be tightly balanced in each patient (low quality).

We recommend against radiotherapy as primary treatment of acromegaly, regardless of the technique (moderate quality).

We suggest that radiotherapy be used only as adjuvant treatment (i.e. after unsuccessful neurosurgery) (moderate quality) in those patients in whom medical therapy is unable to control hormonal hypersecretion and/or tumor growth or is not tolerated.

The choice between FRT and RS depends on tumor characteristics: localization (proximity to optic pathways), size, and shape of residual tumor.

In the event the decision for radiotherapy is established:

- **we suggest** FRT for large remnants (low quality);
- **we recommend** GK for small remnants with at least a 3-mm gap from optic pathways (moderate quality).

In the event FRT is chosen, **we recommend** stereotactic devices to better delineate target (moderate quality).

In the event GK is chosen, **we recommend** that dose of radiation to the optic chiasm does not exceed 8-10 Gy (moderate quality).

At present, no clear data support the withdrawal of any GH-suppressive treatments before and during irradiation.

We recommend medical GH-suppressive treatment after irradiation, while waiting for its effects (moderate quality).

<u>How to monitor radiation effects</u>

We recommend the periodical evaluation of radiation effects on GH and IGF-I levels after the procedure (moderate quality).

In patients achieving IGF-I normalization on GH-suppressive treatment, **we recommend** off treatment GH/IGF-I evaluation every 12-24 months (after 3-month and 1-month withdrawal for long-acting SA, and Cab and Peg, respectively) (low quality). In patients with uncontrolled disease, **we recommend** that the evaluation of disease activity be periodically performed as during any GH suppressive treatment (moderate quality).

We recommend the evaluation of pituitary function after irradiation (moderate quality): this should be performed every 6 months in the first year and thereafter at yearly intervals forever, by assaying morning plasma cortisol and FT_4. Gonadal function should be evaluated in males by assaying testosterone and in females complaining new menstrual disorders by assaying gonadotropins (low quality). **We suggest** to start replacement therapy not only in patients whose target hormones fall clearly below the reference values (high quality), but also in those showing a continuous decline of their values even if still within the low-normal range (very low quality).

After achieving remission of disease, i.e. normal age-matched IGF-I levels, **we recommend** to continue follow-up with yearly assay of IGF-I levels to evaluate whether testing for the occurrence of GH deficiency (low quality).

We suggest pituitary MRI monitoring at first at yearly intervals to evaluate tumor size changes after radiotherapy (moderate quality) and brain MRI at 5-year intervals to screen for secondary tumors (low quality).

We suggest performing periodically neuropsychological evaluation in patients complaining neu-

ropsychological disorders (even though patients seldom complain of) (low quality).

Therapeutic algorithm

A number of factors should be taken into account to select the right strategy of treatment, with the awareness that it seldom will be concluded in one step. The decision making should be influenced by:

- patient's clinical conditions, risk factors (such as comorbidities and age) and personal preference;
- the presence of severe and progressive visual field defect and/or neurological involvement;
- MRI features of the adenoma and GH levels.

Neurosurgery is the only treatment that can induce quick remission of the disease. However, this goal is achieved in near half of patients of the best neurosurgical series only (76). On the other hand, medical treatment dramatically improved the outcome of the disease and several reports have shown that SA adjuvant treatment after unsuccessful surgery obtains GH/IGF-I suppressive effects similar to primary treatment (109, 180-182).

Altogether, these findings have modified the therapeutic strategy in acromegaly and this is the reason why the approach to the acromegalic patient must be individually tailored (183).

First-line treatment

Recently an Italian multicenter study group involving endocrine and neurosurgeons expert in acromegaly issued a document addressing an up-to-date approach to acromegaly (183).

Accordingly, **we recommend first-line neurosurgery** in patients with:

1. clinically significant deterioration of visual field and neurological involvement and/or emergency conditions such as endocranic hypertension and tumor apoplexy, even though surgical cure cannot be achieved (high quality);
2. not invasive adenoma regardless of its dimensions (i.e. both micro- and macroadenoma) and without active invalidating comorbidities (moderate quality), with a high probability to undergo a definitive remission of the disease.

We recommend first-line medical therapy in all the patients who are not amenable to the primary neurosurgical treatment for:

- poor clinical conditions linked to severe comorbidities (cardiomyopathy, sleep apnea, arrhythmias) or metabolic derangements;
- unlikely benefit of surgery for poor surgical prognosis (invasive adenoma, high GH levels) (moderate quality);
- refusal of surgery.

The possibility to indefinitely prolong first-line medical treatment may be considered in patients that achieve a good disease control on ongoing treatment if they have either likely poor surgical prognosis or poor clinical conditions or still refuse surgery.

Depot preparations of SA are **recommended** as the first choice of pharmacotherapy (184, 185). Primary treatment with Cab is suggested very rarely, mainly in patients with mild hypersecretion or refusing injections (183). Peg, though expected to normalize IGF-I secretion in over 80% of the patients (132), is not considered suitable for first-line therapy at present for regulatory problems.

We recommend against first-line radiotherapy in GH-secreting pituitary adenomas (moderate quality) unless the patient refuses surgery and is intolerant to medical therapy and decides for this approach.

Second-line treatment

The decision upon a first-line medical treatment never excludes a second-line surgical treatment.

We recommend second-line surgery if:

- IGF-I is not normalized during SA therapy (moderate quality);
- contraindications to operation have been overcome and patients have a high probability to undergo a definitive remission of the disease (moderate quality).

We recommend adjuvant drug treatment in patients with persistence of disease activity after surgery (moderate quality). **We suggest** to try Cab first in patients with mild disease (low quality), and we recommend to use SA in the others (moderate quality). **We recommend** Peg in patients who are resistant/intolerant to SA or show new glucose metabolism abnormalities during SA (moderate quality).

We recommend against a second surgery in pa-

tients with persistent disease activity and/or remnant of the tumor after the first operation (low quality), since medical therapy (SA, Peg alone or in combination with SA) is able to control residual GH/IGF-I hypersecretion and tumor volume in almost all patients without any serious side effects.
We suggest reoperation in patients who had a first poor surgical outcome and still have a huge remnant of the adenoma, and in those who, despite radiotherapy, show resistance, tachyphylaxis to pharmacological treatment or regrowth of the tumor (low quality).
We suggest that radiotherapy be employed only as adjuvant treatment (i.e. after unsuccessful neurosurgery) (moderate quality) in those patients in whom medical therapy does not control hormonal hypersecretion and/or tumor growth (aggressive cases) or is not tolerated.
In recurrences, **we suggest** that the therapeutic decision is taken according to clinical picture, evaluating patient's age and clinical conditions, residual pituitary function and patient's perspectives, neuroradiological features of the recurrence, sensitivity to medical treatment, taking into account that reoperation aiming to radical removal of the recurrence may be followed more easily by severe and permanent side effects.

Fertility and pregnancy

We recommend that *de novo* patients with perspectives of fertility and normal gonadal function should be operated on exclusively by an experienced neurosurgeon, aiming to preservation of normal pituitary tissue (high quality). At variance, in *de novo* young patients with hypogonadism, **we suggest** to evaluate the severity of the disease, check the possible restoration of gonadal function after pharmacological GH control, and decide thereafter on the basis of the individual clinical picture (very low quality).
Only limited data are available for pregnancy in acromegaly (186). In patients with persistent disease activity after surgery, **we suggest** the withdrawal of any GH suppressive treatment at the beginning of pregnancy and a careful clinical, biochemical and ophthalmologic monitoring throughout pregnancy (low quality), starting again treatment after delivery or even before in case of clinical relapse (with thorough information about risks).

COST OF DISEASE, COMPLICATIONS, AND TREATMENT MODALITIES OF DISEASE

There is little evidence supporting the different therapeutic options in terms of economic costs (187-189). It is well established that, at diagnosis, macroadenomas represent about 70-80% of GH-secreting pituitary adenomas, and near 25-30% among these are clearly macroscopically invasive with poor surgical prognosis. This is the reason why many acromegalic patients often need several different therapeutic approaches (190).
Moreover, important health resource consumption related to comorbidities is to be added to the raw costs related to diagnosis and initial treatment of the disease (14, 187).
Two recent studies (188, 191) evaluated the pharmacoeconomy of treatment for acromegaly, concluding that the cost associated with multimodal treatment is no more expensive than therapy for other chronic diseases and is not excessive due to the low prevalence of acromegaly and can thus be supported by healthcare services. Furthermore, early diagnosis resulted in better outcomes able to extremely reduce the costs.
Lack of epidemiological data suggested to perform a retrospective study in Italy (189), aiming to assess the health resource consumption for the care of acromegaly and its co-morbidities, in order to estimate the amount of the direct costs of acromegalic patients disease management. The reported results support the hypothesis that patients with well-controlled disease cost less to the National Health Service. In fact, the saved expenses were approximately 4,564.61 €/patient (–36.4%) in comparison with poorly or inadequately controlled acromegalic patients.
According to the mean reported prevalence of acromegaly (60 patients/10^6 population), in Italy there should be near 3600 affected patients.
If a first-line surgery for all policy is applied, 1000-2050 (28-57%) patients should be cured, according to results obtained in a real-life situation [UK register (78)] or in the best surgical series (76), respectively. In "cured" patients, a simple yearly assessment of IGF-I allows to establish enduring remission of the disease. As for complications, we can assume that follow-up in these patients is not different *vs* the control reference population when

acromegaly is diagnosed early, whereas patients diagnosed late, whether in remission or still active, require a closer follow-up. Two-10% of surgically treated patients (i.e. 72-360) will develop some kind of complications, transient in most cases, requiring either imaging or reintervention, or replacement therapy and monitoring of doses of substitutive treatment, all items representing additional costs. Patients with recurring/relapsing disease (4% within 10-15 years, i.e. 40-80) need a thorough updated GH assessment and MRI.
On the other hand 1550-2600 patients have still active disease after surgery and need adjunctive treatment.
Among these, up to 5% (i.e. 75-130) can be controlled with DA only (i.e. Cab 1-3.5 mg/week), up to 80% (i.e. 1300-2100) can be controlled with SA, and up to 15% (i.e. 225-390) require Peg. In the SA-treated group, control can be achieved by using the lowest, intermediate, and highest SA dose in 10, 20, and 60%, respectively, and by adding cabergoline in a further 10%. In the SA and/or DA controlled group, the cost of monitoring disease (GH and IGF-I at 3-month intervals during the titration phase, and at 6-12 month intervals thereafter, MRI at 6-month intervals for the first year, at 1-2 year intervals thereafter, and at more prolonged intervals later) adds to the pure cost of drugs (and nurse in the case of injections). Peg can achieve control in 72% of patients, requiring IGF-I evaluation at monthly intervals in the titration period, and at 3-month intervals thereafter, as well as MRI control at 6-12-month intervals.
Monitoring side effects of medical treatment is another cost to be accounted for: glucose metabolism and abdominal ultrasound at yearly intervals during SA; transaminases at monthly intervals during the titration period and fortnightly thereafter during Peg. Basically, a yearly evaluation of glucose and lipid parameters is suggested in all not complicated patients. In patients with specific complications of the disease (diabetes mellitus, hypertension, cardiomyopathy, sleep-apnea, colonic polyps, neoplasms, arthritis, osteoporosis), the work-up has to be individually and specifically tailored.
In patients needing radiotherapy, anti-secretory treatment must be still administered, while biochemical monitoring of disease and complications will be required for 10-20 years, as well as yearly evaluation of pituitary function for the timely start of replacement therapies, and periodic MRI follow-up checking tumor size changes and looking for the development of secondary brain neoplasms, all items adding to the total cost.
This raw calculation of costs does not clearly consider the poor quality of life of the patient (due to severe arthritis, headache, facial disfigurement, social relations, loss of memory or impairment in the superior brain functions in radiotreated patients), complications that cannot be easily evaluated and quantified by any clinical score, but that are clearly evident in the everyday clinical practice.

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