9° Congresso Nazionale AME
Associazione Medici Endocrinologi

Update in Endocrinologia Clinica

Position statement AME
Gestione clinica dell'acromegalia

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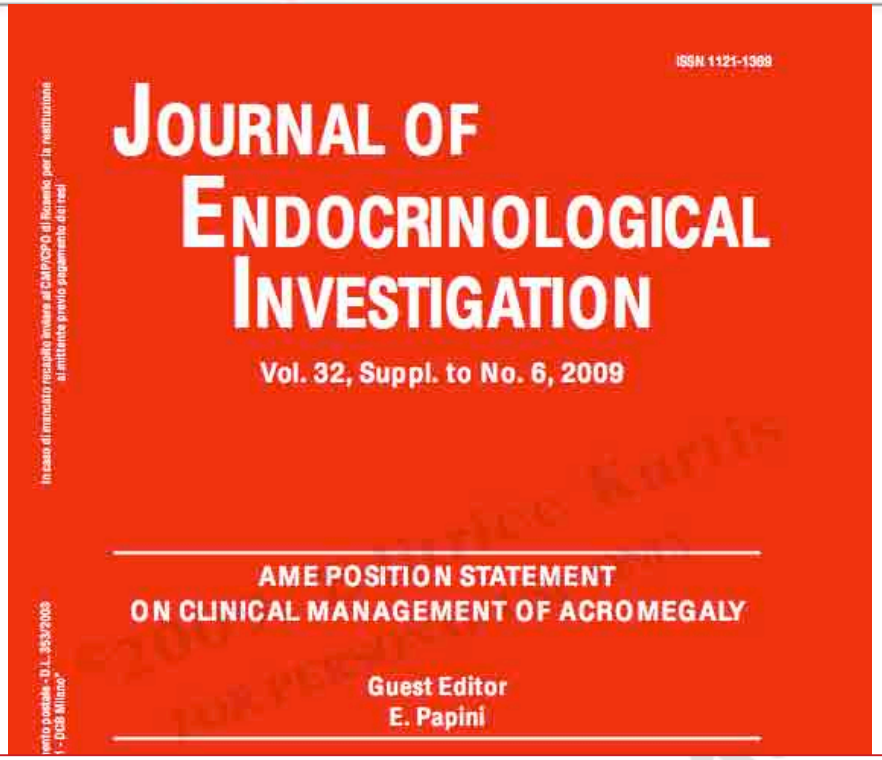

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The scope of the problem

- Prevalence: 40-70/million
- Incidence: 2-4/million/year
- No gender difference
- Prevalence and incidence higher than expected in geographical areas close to referral center
- Underdiagnosis

Why to treat

- Increased mortality (RR 1.34)
- Increased morbidity: cardiovascular diseases
- Treatment reverts the risk

Etiology

- ✓ **Pituitary disease**:
  - ✓ **Macroadenoma** 70-75%
  - ✓ Microadenoma 25-30%
  - ✓ Negative imaging 1-2%

- ✓ Ectopic/eutopic GHRH secretion: < 1%

  bronchial carcinoid, pancreatic islet cell tumor, small cell lung cancer, hypothalamic amartoma, choristoma, ganglioneuroma

- ✓ GH-secreting pituitary carcinoma

- ✓ Familiar diseases:

  MEN 1, FIPA, McCune Albright syndrome, Carney complex

Methodology

GRADE system: **G**rading of **R**ecommendations, **A**ssessment, **D**evelopment, and **E**valuation

Recommendations are classified into two grades:

- **strong** recommendation means that benefits clearly outweigh harms and burdens
- **weak** recommendation means that benefits closely balance with harms and burdens

Methodology-2

The **evidence of quality** is categorized as:

- **High** defined as consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies
- **Moderate** defined as evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise evidence), or unusually strong evidence from unbiased observational studies
- **Low** defined as evidence for at least one critical outcome from observational studies, from RCTs with serious flaws, or indirect evidence
- **Very low** defined as evidence for at least one of the critical outcomes from unsystematic clinical observations or very indirect evidence

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Outline

- When to suspect
- Diagnosis
- Treatment

When to suspect the disease

1. **Typical clinical picture**: facial disfigurement, enlargement of hands and feet, macroglossia, voice deepening, headache, arthritis

2. **Without a clear-cut clinical picture**:
   - ✓ sleep-apnea
   - ✓ carpal tunnel syndrome
   - ✓ intractable headache
   - ✓ jaw malocclusion
   - ✓ unexplained dilated cardiomiopathy
   - ✓ diabetic ketoacidosis, resistant hypertension

3. **All macroadenoma** (macroprolactinoma!)

Outline

- When to suspect
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- Treatment

Diagnostic evaluation

- ✓ **IGF-I**
- ✓ **GH**
- ✓ **MRI**

IGF-I

- **IGF-I assay is the most sensitive lab tool in the diagnosis of acromegaly**
- Serum IGF-I clearly differentiates between patients with and without acromegaly
- High IGF-I values also in patients with “normal” or very low GH secretion
- **High age-matched IGF-I coupled to high GH values allows to diagnose acromegaly** (making redundant dynamic tests for GH secretion)

Pitfalls in IGF-I

- ✓ **High levels**
  - ✓ Puberty
  - ✓ Post-pubertal period
  - ✓ Tall boys-girls
  - ✓ Pregnancy

- ✓ **Low levels**
  - ✓ Acute intercurrent illness
  - ✓ Systemic diseases
  - ✓ Liver or renal failure
  - ✓ Diabetes mellitus type 1
  - ✓ Exogenous estrogens or SERMS
  - ✓ Fasting
  - ✓ Malnutrition

Limitations

- **Biological variability**

- **Technical difficulties**
  - ✓ Definition of normal ranges
  - ✓ Interference of binding proteins
  - ✓ Antisera that allow precise and reproducible measurements
  - ✓ Standard reference

GH

- GH levels are elevated in acromegaly
- Random high GH levels per se do not make diagnosis
- Only GH > 40 ng/mL is pathognomonic
- GH < 0.3-0.4 ng/mL rules out the diagnosis

GH

- GH levels are elevated in acromegaly
- Random high GH levels per se do not make diagnosis

if GH is in the grey zone

(0.4 ÷ 40 ng/mL)

check IGF-I

GH pitfalls

High GH in:

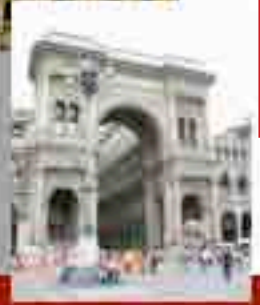
- ✓ **physiological conditions**:
  - spikes
  - fasting
  - exercise
  - stress
  - sleep
  - tall boys

- ✓ **pathological states:**
  - type 1 diabetes,
  - liver disease
  - chronic renal failure
  - depression
  - malnutrition
  - disturbances of food intake behavior
  - hyperthyroidism

GH pitfalls

High GH in:

- ✓ **physiological conditions**:
  - spikes
  - fasting
  - exercise
  - stress
  - sleep
  - tall boys



- ✓ **pathological states:**
  - type 1 diabetes

but in all these pathological conditions

IGF-I is low!!

  - disturbances of food intake behavior
  - hyperthyroidism

Dynamic tests: OGTT

- **When**:
  - ✓ no clear-cut clinical context and single GH level in the grey zone (0.4-40 ng/ml) but without reliable IGF-I assay
  - ✓ not to be performed in overt diabetic patient (saline for 3 h)

- **How**:
  - ✓ 75 g oral glucose
  - ✓ GH samples every 30 minutes over 2 hours

- **Cut-off value**:
  - ✓ 1 ng/ml
  - ✓ 0.3-0.4 ng/ml (ultrasensitive /chemiluminescent assay)

OGTT pitfalls

False positive (no suppression) in:

- ✓ tall boys
- ✓ adolescence
- ✓ diabetes mellitus
- ✓ liver and chronic renal failure
- ✓ malnutrition
- ✓ anorexia nervosa
- ✓ depression
- ✓ heroin addiction

GH

❑ Advantages in GH assaying

- ✓ Direct tumoral production rate
- ✓ Mirroring of pituitary secretion after any therapy
- ✓ Difficulties in IGF-I assays

❑ Limitations

- ✓ Widely variable sensitivity of commercial kits
- ✓ RIA vs ultrasensitive

Imaging

- **Pituitary MRI** will show the source of the disease in 99% of cases

- If no clear-cut evidence of adenoma, look for ectopic GHRH secretion (chest X-ray, abdomen US, Octreoscan)

Pituitary function

Check:

- ✓ **associated hypersecretion** of other pituitary hormones: PRL, TSH
- ✓ **pituitary failure**: sex hormones (testosterone in males, amenorrhea in females), FT_4, cortisol

Diagnostic conclusions

- We **recommend** to assess both GH and IGF-I to make diagnosis *(high quality)*
- Consider false positive and false negative for both GH and IGF-I *(low quality)*
- We **recommend** OGTT for GH only if the combination of GH, IGF-I and clinical picture is not clear-cut *(low quality)*
- We **recommend** MRI at diagnosis (high quality) and to assess PRL and pituitary function *(moderate quality)*
- We **recommend against** dynamic tests beyond OGTT in diagnosis or follow-up *(very low quality)*

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Staging of disease complications

- ✓ Cardiovascular
- ✓ Metabolic
- ✓ Respiratory
- ✓ Neoplastic
- ✓ Skeletal system

Cardiovascular complications

- **Common**
- **Cardiomyopathy**
  - ✓ concentric biventricular hypertrophy
  - ✓ diastolic dysfunction
  - ✓ insufficient systolic performance on effort
  - ✓ systolic dysfunction at rest and overt heart failure with signs of dilative cardiomyopathy
- **Rhythm disturbances**
- **Cardiac valve disease**
- **Hypertension**

- Cardiovascular involvement **improves after successful treatment**

Cardiovascular complications-2

- **We recommend** ECG and echocardiogram in the initial work-up *(high quality)*

- 24h-ECG should be reserved to patients showing arrhythmias in basal ECG

Metabolic complications

- **Impaired glucose tolerance** and overt **diabetes mellitus** are frequent
- Type IV **hyperlipidemia**
- **Disease control** usually **markedly improves** glucose tolerance and diabetes

- We **recommend** to perform an OGTT for glucose assessment 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

Respiratory complications

- **Sleep apnea**
- **Impaired respiratory function**
  - Disease control improves sleep breathing disorders

- There is no consensus on how to diagnose and monitor respiratory disorders in acromegaly *(low quality)*

Neoplastic complications

- Cancer does not seem to be a major cause of death
- Slight increase in **colon cancers** (SIR 1.68)
- **Colon adenomatous polyps**

- **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)*
- There is no consensus as to when repeat colonoscopy in patients with controlled disease *(very low quality)*

Skeletal system complications

- Articular involvement and enthesopathy leading cause of morbidity, functional disability and poor QOL
- Carpal tunnel syndrome
- Osteoporotic fractures are frequent

- There is no agreement on how to diagnose and follow-up the acromegalic arthropathy *(very low quality)*
- Standard X-ray is required to study the spine

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Outline

- When to suspect
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Treatment

- ✓ The goal
- ✓ Neurosurgery
- ✓ Pharmacotherapy
- ✓ Radiotherapy
- ✓ Algorithm

The goal of treatment

- The **cure** of acromegaly, i.e. the reversal to the normal pattern of physiological pulsatile GH secretion, is not obtained by any treatment
- **Remission** implies 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

- Aims to:
  - ✓ complete resection of the adenoma
  - ✓ preservation of pituitary function
- **Only option to definitively cure acromegaly**
- Immediate effects
- In the best hands success rate drops from 85% for micro to 50% for extrasellar macro, and to 10% for giant adenomas

Neurosurgery

- The **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

Outcome of neurosurgery

- PRE-SURGICAL MEDICAL TREATMENT:
  - ✓ on clinical picture
  - ✓ on surgical outcome

- TIMING OF THE EVALUATION:
  - ✓ GH reliable at 7 days after surgery in not pre-treated patients
  - ✓ pre-treated patients: GH 6-12 weeks after surgery
  - ✓ IGF-I: up to 3 months after surgery

Outcome of neurosurgery

CRITERIA FOR REMISSION:

- ✓ IGF-I levels: **normal**
  GH nadir after OGTT:
  - < 1.0 ng/ml
  - 0.3 ÷ 1 ng/ml
  - < 0.3 ng/ml

- ✓ **high** IGF-I levels and high GH: no need for OGTT testing

- ✓ **discrepancy** between GH nadir and IGF-I levels
  - high IGF-I and GH < 1.0 ng/ml: active disease
  - normal IGF-I and GH > 1.0 ng/ml: unknown

RECURRENCE: low (by the modern cut-offs)

Neurosurgery consensus

- An **interdisciplinary approach is strongly recommended**
- **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
- **We recommend against** neurosurgery in patients without any evidence of pituitary adenoma and of ectopic GHRH secretion *(low quality)*

Neurosurgery consensus-2

- **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 pretreated with GH suppressive treatment before surgery or pretreated, respectively *(low quality)*

  IGF-I should be assayed 30-90 days after surgery *(low quality)*

- **We recommend** to evaluate gonadal function, cortisol and FT_4 levels before and after surgery *(moderate 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)*

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Pharmacological treatment

- **Aim**: to control disease, i.e. normal age-matched IGF-I and “safe” GH levels, i.e. < 2-2.5 ng/ml
- **Monitoring**: a single IGF-I and multiple GH sampling (saline infusion)
- **Discrepancy** in GH/IGF-I levels: we **suggest** to pursue the goal of IGF-I normalization *(low quality)*
- **MRI** during follow-up for tumor size control

Drugs

- ✓ Dopamine agonists
- ✓ Somatostatin analogs
- ✓ Pegvisomant
- ✓ Combinations

Dopamine-agonist drugs

- ✓ Bromocriptine
- ✓ Cabergoline: powerful and prolonged activity
- ✓ Cabergoline normalizes IGF-I in 25-35% of patients (with lower GH/IGF-I values)
- ✓ PRL hypersecretion not a prerequisite
- ✓ Oral administration
- ✓ Up to 0.25-0.5 mg/day
- ✓ Cardiac valve deterioration ?

Somatostatin analogs

- ✓ Octreotide
- ✓ Lanreotide

Effects on

- ✓ SS receptors on pituitary tumoral cells
- ✓ peripheral IGF-I synthesis inhibition

- ✓ Monthly im injection
- ✓ Inhibition of hormonal hypersecretion
- ✓ Clinical amelioration
- ✓ Tumor shrinkage

Somatostatin analogs: hormonal levels

- **Normal IGF-I/safe GH in at least 50%**
- Considerable decrease of GH/IGF-I in another 40%
- No tachyphylaxis (up to 18 years)
- Progressive amelioration of hormonal control
- Adjuvant treatment improves patient's outcome after poor surgical result

Somatostatin analogs: clinical amelioration

Improvement/disappearance of clinical symptoms and comorbidities

Somatostatin analogs: tumor shrinkage

- **More impressive in primary vs adjuvant treatment** (>50% vs >20%)
- More frequent with octreotide LAR vs lanreotide in SA primarily treated patients (80% vs 35%)
- Quick
- Progressive
- Sometimes up to empty sella/disappearance of the tumor

Somatostatin analogs: predictors of efficacy

- ✓Early results
- ✓Pretreatment GH levels
- ✓Tumor size

GH receptor antagonist: Pegvisomant

- ✓ Partially modified GH molecule that inhibits IGF-I synthesis and increases GH levels (not assayable by commonly used GH assays)
- ✓ Pituitary tumor growth uncontrolled
- ✓ sc injection (usually daily,10-40 mg)

Pegvisomant: clinical effects

- **IGF-I normalization in 76% of intolerant or resistant SA patients**
- Tumor size may increase in patients with aggressive disease or after SA withdrawal in patients with previous tumor shrinkage on SA
- Glucose metabolism amelioration

The choice of the drug

- We **recommend** to start with SA *(moderate quality)*
- We **suggest** to immediately start with the highest SA dose in patients with aggressive disease. 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
- In patients experiencing adverse events with one SA, we **suggest** a cautious trial with the other molecule *(low quality)*

The choice of the drug-2

- In patients with mild disease, we **suggest** a trial with Cabergoline *(low quality)* regardless of PRL levels (Cab may be particularly effective in patients with mixed GH/PRL hypersecretion)
- We **suggest SA and Cab** 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)*
- We **recommend** to use Pegvisomant in patients resistant/intolerant to SA only after unsuccessful surgery or after radiotherapy
- The combined use of **SA and Peg** cannot be recommended at present, except in patients with aggressive disease or tumor re-enlargement after SA withdrawal *(low quality)*

Monitoring drug adverse events

- **During DA** treatment
  - ✓ we **recommend** echocardiographic monitoring, mainly in patients with acromegalic valve disease *(low quality)*

- **During SA** treatment
  - ✓ we **recommend** monitoring of glucose metabolism *(moderate quality)*
  - ✓ we **suggest** ultrasound monitoring *(moderate quality)*

Monitoring drug adverse events -2

- **During Pegvisomant** treatment we **recommend:**
  - ✓ **liver function test monitoring**:
    - ❖ at monthly interval during titration
    - ❖ at 3-month intervals during chronic treatment at stable dosage (*low quality*)
  - ✓ withdrawal of the drug if transaminases levels increase more than x 3 ULN persists or worsens (*moderate quality*). In patients showing lesser transaminases increase, Peg dosage may be maintained stable or slightly decreased
  - ✓ **MRI monitoring** at 6-month intervals in the first year and yearly thereafter (*moderate quality*)
  - ✓ the **rotation of drug injection site** to avoid lipo-hypertrophy

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Radiotherapy: techniques

❑Fractionated radiotherapy

- ✓ Multiple refracted doses
- ✓ Aim: to inhibit tissue proliferation by interfering with the cell cycle
- ✓ Slow effect
- ✓ Conflicting results about success rate
- ✓ Hormonal values are critical: the higher GH, the slower its normalization
- ✓ Severe toxicity

❑Radiosurgery

- ✓ In a single session a highly collimated dose conformated to the shape of the target
- ✓ Aim: to obtain radionecrosis, sparing normal brain tissues
- ✓ Safety margin of at least 3 mm from optic chiasm
- ✓ Long-term safety still under scrutiny

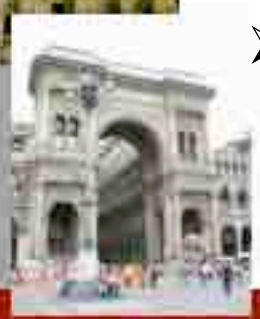
❑**Interstitial irradiation** is no longer employed

Radiotherapy consensus

- 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 *(moderate quality)* in those patients in whom medical therapy is unable to control
  - ✓ hormonal hypersecretion
  - ✓ tumor growth

  or is not tolerated



- We **recommend** that radiotherapy, irrespective of the technique, be performed in reference centers in which pros and cons have to be tightly balanced in each patient *(low quality)*

Radiotherapy consensus – 1a

- 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)*

Radiotherapy consensus -2

- At present no clear data support the withdrawal of any GH-suppressive treatments during irradiation
- We **recommend** medical GH-suppressive treatment after irradiation, while waiting for its effects *(moderate quality)*
- **We recommend** the periodical evaluation of radiation effects and to assess disease's activity by IGF-I assay *(low quality)*

Radiotherapy consensus -2b

- In patients achieving IGF-I normalization on GH-suppressive treatment, we **recommend** off treatment GH/IGF-I evaluation every 12-24 months *(low quality)*

- In patients with uncontrolled disease, we **recommend** that the evaluation of disease activity be performed as during any GH suppressive treatment *(moderate quality)*

- We **recommend** the evaluation of pituitary function (morning plasma cortisol, FT_4 and gonadal function) after irradiation *(moderate quality):*
  - ✓ every 6 months in the first year
  - ✓ thereafter at yearly intervals forever *(low quality)*

- After achieving remission of disease we **recommend** to continue follow-up with yearly assay of IGF-I levels to evaluate the occurrence of GH deficiency *(low quality)*

Radiotherapy consensus -3

- 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** 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)*

- We **suggest** performing periodically neuropsychological evaluation in patients complaining neuropsychological disorders *(low quality)*

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Therapeutic algorithm: first line treatment

- We **recommend first-line neurosurgery** in patients:
  - ✓ with clinically significant deterioration of visual field and neurological involvement and/or emergency conditions (endocranic hypertension and tumor apoplexy), even though surgical cure cannot be achieved *(high quality)*
  - ✓ without active comorbidities and with not invasive adenoma regardless of its dimensions (i.e. both micro- and macroadenoma) with a high probability to undergo a definitive remission of the disease *(moderate quality)*

Therapeutic algorithm: first line treatment - 2

- We **recommend first-line medical therapy** (depot preparations of SA are recommended as the first choice of pharmacotherapy) in all the patients not amenable to the primary neurosurgery for:
  - ✓ poor clinical conditions for severe comorbidities (cardiomyopathy, sleep apnea, arrhythmias)
  - ✓ metabolic derangements
  - ✓ unlikely benefit of surgery for poor surgical prognosis (invasive adenoma, high GH levels) *(moderate quality)*
  - ✓ refusal of surgery
- We **recommend against first-line radiotherapy** *(moderate quality)*

Therapeutic algorithm: second line treatment

- The decision upon a first-line medical treatment never excludes a second-line surgical treatment
- We **recommend second-line neurosurgery** if:
  - ✓ contraindications to operation have been overcome and patients have a high probability to undergo a definitive remission of the disease *(moderate quality)*
  - ✓ IGF-I is not normalized during first line SA therapy *(moderate quality)*

Therapeutic algorithm: second line treatment - 2

- We **recommend adjuvant drug treatment** in patients with persistence of disease activity after surgery *(moderate quality)*
  - ✓ We **suggest** Cab first in patients with mild disease *(low quality)*
  - ✓ We **recommend** SA in the others *(moderate quality)*
  - ✓ We **recommend** Peg in patients resistant/intolerant to SA or showing new glucose metabolism abnormalities during SA *(moderate quality)*

Therapeutic algorithm: second line treatment - 3

- We **recommend against** a second surgery in patients with persistent disease activity and/or remnant of the tumor after the first operation *(low quality)*
- We **suggest** reoperation only in patients who had a first poor surgical outcome with a huge remnant of the adenoma, and in those who, nevertheless radiotherapy, show resistance, tachyphylaxis to pharmacological treatment or regrowth of the tumor *(low quality)*
- We **suggest** radiotherapy only as adjuvant treatment *(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

Ringraziamenti

- Al **Consiglio Direttivo AME** per averci dimostrato la sua fiducia affidandoci questo incarico
- A tutti i **membri del panel** per l'enorme lavoro svolto
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- A **tutti voi** per l'attenzione

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