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## **Acromegaly: presentation, morbidity and treatment outcomes at a single centre**

Panagiotis Anagnostis, Zoe Efstathiadou, Stergios Polyzos, Fotini Adamidou, Aristidis Slavakis, Michalis Sapranidis, Ioannis Litsas, Simoni Katergari, Despina Selalmatzidou, Marina Kita

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## Acromegaly: presentation, morbidity and treatment outcomes at a single centre

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3 Dr. Graham Jackson  
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5 Editor-in-Chief  
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7 International Journal of Clinical Practice  
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11 Saturday, 19 February 2011  
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13 Re: Revision of manuscript **IJCP-01-11-0015** .....by Anagnostis et al  
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18 Dear Sir,  
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23 We were pleased to hear that the International Journal of Clinical Practice is  
24 interested in a revised version of our work. We are thankful to the reviewers for their  
25 constructive comments. We have addressed all their suggestions in this revised  
26 version. In more detail:  
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32 Reviewer: 1  
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34  
35 1. For the patients who received radiotherapy, it would be useful to know what the  
36 radiation dose was.  
37

38 The radiation dose was the standard 45Gy divided in 25 doses. This is now stated at  
39 the text, p10, 2<sup>nd</sup> paragraph, line 1: "Conventional radiotherapy -at a standard dose of  
40 45 Gy in 25 fractions-..."  
41

42 2. Regarding the morbidity associated with acromegaly at follow up (page 8). Did  
43 these co-morbidities develop during the FU period or they were discovered then  
44 because the patients were not examined for these at presentation?  
45

46 The data presented under the header "***At baseline***" in page 8 refer to morbidity  
47 discovered at baseline. Because there were missing values, for further clarity, we have  
48 added the number of patients who were actually examined for each co-morbidity at  
49 presentation in p8, 2<sup>nd</sup> paragraph, lines 5-8: ".....(data available for 84). Data on  
50 glucose homeostasis were available for 87 patients at presentation and were  
51 diagnostic for DM in 25%, for impaired glucose tolerance (IGT) in another 25%.  
52 Dyslipidemia was present in 35% (data available in 60 subjects)."  
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55

56 3. DA treatment: the authors should explain the abbreviation.  
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58 DA stands for dopamine agonists. We have added the definition the first time it  
59 appears in the text: page 10, 2<sup>nd</sup> paragraph, line 6.  
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Reviewer: 2

General and specific comments to the authors

In this retrospective study are reported the clinical characteristics, the efficacy of treatment, and the morbidity in a cohort of 115 acromegalic patients with mean follow-up 8.8 years from a single center in Greece. These data are valuable though the number of patients is relatively small. However there are some points that should be stressed.

1. The assessment of good disease control is based on targets, which have been set by consensus. However, since epidemiological studies have shown that active acromegaly is associated with increased mortality the targets that establish the remission of the disease have recently changed, as you also have mentioned in the text. For the sake of clarity for the reader I consider that the recent guidelines should follow the previous ones.

We acknowledge that comment and we make a comment about the previous guidelines before the most recent ones in page 5, 1<sup>st</sup> paragraph, lines 2-4: “Till recently, the consensus guidelines for acromegaly cure recommended normal age- and sex-adjusted IGF-I levels, along with a nadir GH<1 µg/L during an OGTT, irrespective of concurrent treatment (6). The latest.....”

2. It is known that the lack of reliable assays for serum GH and IGF-1 measurements is a major issue in the interpretation of the results. Therefore it is important to be presented the characteristics of the assays used regarding at least the used standard and their sensitivity.

We acknowledge the reviewer’s comment and we have inserted a paragraph in the methods section, page 6, 2<sup>nd</sup> paragraph, lines 6-8:

“The detection limits and assay analytical sensitivity for ICMA method are 0.05-40 ng/ml and 0.01 ng/ml respectively for GH and 0.00-1600 ng/ml and 20 ng/ml for IGF-I.”

3. Authors comment on the importance of an experienced surgeon and speculate that the results of their series could be better if they had an experienced pituitary neurosurgeon. This raises a question about the neurosurgeon’s experience and skillful. This lack of clearness should be resolved.

We have added a new reference on the subject and two sentences clarifying the matter in page 14, 2<sup>nd</sup> paragraph, lines 2-6: “A recent review has shown that focused clinical practice and large transsphenoidal surgical volume appear to be important outcome determinants for patients with pituitary tumors (19). The fact that in our country there is no regionalization of care to higher volume pituitary tumor centers of excellence is a major drawback to better surgical outcomes. Consequently.....”

4. The role of SSA therapy in achieving tumor shrinkage is not well defined. Some data in the literature indicate that the presurgical use of SSA may improve surgical outcome. Is there any evidence in your data regarding this issue?

Since there were only 7 patients who received pharmacotherapy prior to surgery, no safe conclusions can be drawn for that matter.

5. Conventional radiotherapy is usually used as an adjuvant therapy in pituitary

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3 adenomas secreting GH. However, its beneficial effect appears progressively over  
4 years. It would be interesting to comment on this in your cohort.  
5

6 We comment that in the discussion session: page16, last paragraph, lines 1-2. To  
7 further clarify that we have added the sentence: “Conventional radiotherapy is usually  
8 used as an adjuvant therapy in pituitary adenomas secreting GH. However, its  
9 beneficial effect appears progressively over years”, at the beginning of the same  
10 paragraph.  
11

12 Furthermore, the time of remission is described in the sentence (lines 7-9): “It must be  
13 noted that radiotherapy outcomes were manifest at 12-34 years of follow-up, except  
14 for 1 patient, who had already achieved remission at 7 years.”  
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17  
18 6. Two inconsistencies are noticed in Table 1; In the second row “surgery alone” it  
19 appears that from the 22 patients, remission was achieved in 9 patients but this  
20 number is not equal to the sum of micro- and macroadenomas in remission (last two  
21 columns). The same inconsistency is also observed in the fourth row  
22 “Surgery/Radiotherapy”  
23

24 This inconsistency is due to the fact that the initial size was not available in 2 patients,  
25 1 treated with surgery alone and 1 with surgery/radiotherapy. Both achieved  
26 remission, as it is stated in the comments at the bottom of the table 1. (We have  
27 corrected surgery/pharmacotherapy to surgery/radiotherapy (comments in table 1).  
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31 We thank you again for the constructive comments, which were contributed to  
32 our manuscript. Having addressed all these comments we hope that the revised  
33 manuscript would be acceptable for publication at the International Journal of Clinical  
34 Practice.  
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39 Sincerely,

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42 Zoe Efstathiadou  
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## Acromegaly: presentation, morbidity and treatment outcomes at a single centre

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**Short title:** Acromegaly: a single centre experience

**Key words:** Acromegaly; Growth hormone; Insulin-like growth factor-1;  
Transsphenoidal surgery; Somatostatin analogues

**Word count:** Abstract 250, Text 3441, Tables 2, Figures 0

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## Abstract

**Objective:** Analysis of patients with acromegaly followed-up at a single centre, focusing on baseline characteristics, morbidity, and efficacy of treatment.

**Design and methods:** Retrospective review of electronic medical records of acromegalics from 1987 to 2009.

**Results:** One-hundred and fifteen patients (45 men), aged  $47\pm 14$  years, with a mean follow-up of  $8.8\pm 0.8$  years were studied. Twenty-five percent had micro- and 75% macroadenomas. Forty-three percent presented with visual field defects, 49% had hypertension, 25% diabetes mellitus and 35% dyslipidemia, 50% myocardial hypertrophy, 55% colon polypoidiasis, 74% nodular thyroid disease and 18% adrenal masses. Surgery was performed in 79% (8% twice), followed by conventional radiotherapy in 27%.

Fifty-two percent of the patients achieved remission. Disease control was reported in 65% of microadenomas and 41% of macroadenomas. Remission rates with surgery alone were 41%. Improvement of remission rates was achieved with subsequent treatment with somatostatin analogues (SSA) (53%), or conventional radiotherapy (63%). Nevertheless, pituitary reserve was compromised with the latter. SSA significantly improved outcomes in microadenomas, even as a monotherapy (remission in 89%), in contrast to macroadenomas (0%), although these agents were associated with impaired glucose metabolism and cholelithiasis in half of the cases.

**Conclusions:** Acromegaly is associated with increased morbidity. About half of the treated patients achieved remission (2/3 of microadenomas). The best outcomes were reported for the combination of surgery with radiotherapy, in spite of a higher risk of hypopituitarism. SSA led to remission in a significant percentage of microadenomas,

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3 but were associated with increased rates of cholelithiasis and impaired glucose  
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5 homeostasis.  
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11 **What's known:**

- 12 • Acromegaly is a rare chronic disease characterized by hypersecretion of GH,  
13 which leads to an increased production of IGF-I.  
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- 15 • Acromegaly is associated with significant morbidity and an increased  
16 mortality rate.  
17
- 18 • Transsphenoidal surgery is the first line treatment for acromegaly. In case of  
19 persisting disease treatment with somatostatin analogues and/or radiotherapy  
20 (conventional or  $\gamma$ -knife) are applied.  
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33 **What's new:**

- 34 • Neurosurgery alone is not effective for disease control in the majority of cases.  
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- 36 • Medical therapy with SSA, either as adjuvant to surgery, or as monotherapy is  
37 effective, but might have unfavourable side-effects, such as impaired glucose  
38 homeostasis and cholelithiasis.  
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- 40 • Remission of the disease is usually achieved by combination of multiple  
41 treatment modalities.  
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## Introduction

Acromegaly is a rare chronic disease characterized by hypersecretion of GH which leads to an increased production of IGF-I (1-2). In the majority of cases (>95%) it results from a GH-secreting pituitary adenoma (1-2).

The incidence of acromegaly is about 3 cases per million persons with an estimated prevalence of 60 per million (3). The disease onset takes place during the 4<sup>th</sup> decade of life with an equal distribution between genders (1-2).

Acromegaly affects almost every organ and is associated with increased morbidity and mortality mainly due to the aggregate of cardiovascular risk factors such as hypertension, diabetes mellitus (DM) and lipid disorders and to the appearance of cardiomyopathy associated with the disease (4). In a recent meta-analysis of 16 series, the mortality ratio of patients with acromegaly was 1.72 compared with the general population, and remained high (1.32) even after surgical management of the disease (5).

Despite the progress that has been made over the years in terms of therapeutic modalities, acromegaly still remains under-diagnosed, with a mean delay of 7-10 years after the estimated onset of symptoms (1-2). The introduction of highly sensitive and specific GH assays has recently led to a re-evaluation of the biochemical criteria needed for the diagnosis of acromegaly. This is based on nadir GH levels >1 µg/L during an oral glucose tolerance test (OGTT) in combination with IGF-I above the upper level of normal for age and sex (1-2).

Although remarkable advances in terms of the medical management of the disease have been made, transsphenoidal surgery (TSS) remains the treatment of choice resulting in disease control in 75-95% of patients harbouring microadenomas and in 40-68% of those with macroadenomas (1-2, 6). In case of persisting disease after

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3 surgical and medical approach, radiotherapy (conventional or  $\gamma$ -knife) is a reasonable  
4 approach (1-2, 6). Till recently, the consensus guidelines for acromegaly cure  
5 recommended normal age- and sex-adjusted IGF-I levels, along with a nadir GH <1  
6  $\mu\text{g/L}$  during an OGTT, irrespective of concurrent treatment (6). The latest guidelines  
7 for acromegaly cure recommend random GH <1  $\mu\text{g/L}$  or nadir GH <0.4  $\mu\text{g/L}$  during  
8 an OGTT combined with age- and sex-adjusted normal IGF-I levels (7). If IGF-I and  
9 GH are elevated, additional therapy should be considered (6-7). In case of discordant  
10 IGF-I and GH measurements –in most cases normal GH and elevated IGF-I (7), the  
11 decision for acromegaly management should be based on clinical judgement (6). In  
12 these cases, multiple GH sampling is also recommended (7).  
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27 The aim of the present study was to describe the clinical characteristics, the  
28 morbidity and the efficacy of treatment in a cohort of patients with acromegaly, who  
29 were followed-up at a single centre.  
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### 36 Patients and methods

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39 This was a retrospective study conducted in the department of Endocrinology in  
40 “Hippokration” General Hospital of Thessaloniki, Greece, a tertiary referral centre for  
41 endocrinology and diabetes. Data from all patients who were diagnosed with  
42 acromegaly or referred to the centre with the diagnosis of acromegaly between 1987  
43 and 2009 were extracted from the department’s electronic database and thoroughly  
44 reviewed. Inclusion criteria were: 1) abnormal nadir GH levels (>1  $\mu\text{g/L}$ ) during a 75-  
45 g OGTT along and/or abnormal IGF-I levels for age and gender 2) imaging  
46 characteristics suggestive of a pituitary adenoma 3) at least 1 complete clinical and  
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3 the criteria for cure of acromegaly changed (8). For the years 1987-1999, a cut-off  
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5 value for nadir GH of 2  $\mu\text{g/L}$  was used. In case of discordant IGF-I and GH results,  
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7  
8 the decision for further therapeutic interventions was based on clinical judgment.  
9

10 The assays used for GH measurement changed over the years. For the period  
11  
12 1987-1999, radioimmunoassay (RIA) was used, while from 2000 and thereafter GH  
13  
14 was measured by an immunochemiluminent assay (ICMA) (Immulite 2500, DPC,  
15  
16 Los Angeles, USA). ICMA was also used for IGF-I assessment from 2000 to 2009,  
17  
18 while before 2000, it was measured using enzyme-linked immunosorbent assay  
19  
20 (ELISA). The detection limits and assay analytical sensitivity for ICMA method are  
21  
22 0.05-40 ng/ml and 0.01 ng/ml respectively for GH and 0.00-1600 ng/ml and 20 ng/ml  
23  
24 for IGF-I.  
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29 All patients underwent physical examination, visual field perimetry and basal  
30  
31 biochemical assessment. In addition, laboratory evaluation of the other pituitary  
32  
33 hormones was performed in order to unmask potential pituitary deficiencies: LH/FSH,  
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35 ACTH, TSH, both before and after surgical intervention. In case of signs and  
36  
37 symptoms of hypopituitarism, stimulation tests were performed. Gonadotrophin  
38  
39 deficiency was defined as low or 'inappropriately normal' LH and FSH levels  
40  
41 combined with serum testosterone and serum oestradiol below the reference range or  
42  
43 inadequate response to (LH-Releasing Hormone) LHRH test. ACTH deficiency was  
44  
45 detected in case of an insufficient increase ( $<18 \mu\text{g/dl}$ ) in cortisol levels during a  
46  
47 cosyntropin-stimulation test or a glucagon-stimulation test. TSH-deficiency was  
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49 determined by low or 'inappropriately normal' TSH with thyroid hormone levels (free  
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51 T4 and/or free T3) below the normal range.  
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57 The patients were reevaluated at 6- to 12-month intervals by clinical, routine  
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59 biochemical laboratory and hormonal (IGF-I and GH levels during an OGTT)  
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3 examination and by MRI. CT was the only means available for pituitary imaging  
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5 before 1993. Shorter intervals between follow-up visits were applied in cases of  
6  
7 significant alterations in clinical status or changes in therapeutic regimen.  
8  
9 Macroadenomas were defined as those with maximum diameter  $>1\text{cm}$ , and  
10  
11 microadenomas when maximum diameter was  $\leq 1\text{cm}$ . The duration of follow-up was  
12  
13 estimated as the time between the first and last GH secretion assessment.  
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### 16 17 **Statistical analysis**

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19 Data for continuous variables are presented as mean  $\pm$  standard error of the mean  
20  
21 (SE). Data for categorical variables are presented as numbers and/or percentages.  
22  
23 Kolmogorov-Smirnov test was used to check the normality of distribution of  
24  
25 continuous variables. Chi-square test or Fischer's exact test were used to identify  
26  
27 differences between categorical variables. Independent-sample T-test or Mann-  
28  
29 Whitney test was used to identify differences between two independent groups of  
30  
31 continuous variables. The analysis of variance (ANOVA) or Kruskal-Wallis test were  
32  
33 used to identify differences among three or more groups of continuous variables. The  
34  
35 General Linear Model (GLM) (repeated measures ANOVA) was used to identify  
36  
37 differences within continuous variables in cases of serial measurements. Adjustment  
38  
39 for violations of the sphericity assumption was performed with the Greenhouse-  
40  
41 Geisser correction. Bivariate correlations were tested by Pearson's (r) or Spearman's  
42  
43 ( $r_s$ ) coefficients of correlation. A  $p$  value less than 0.05 was considered statistically  
44  
45 significant in all the above tests. Statistical analysis was performed with SPSS 13.0  
46  
47 for Windows (SPSS Inc., Chicago, Illinois, USA).  
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## 54 55 **Results**

### 56 57 **Patient characteristics**

Three hundred and ninety-three patients were retrieved from our electronic database with a pituitary adenoma. One hundred and fifteen patients (45 males and 70 females) met the study's criteria.

The mean age at diagnosis was  $47 \pm 1$  years (range 14-84). The mean size of adenomas was  $1.7 \pm 0.1$  cm (range 0.4-4.0); 26% were microadenomas and 74% macroadenomas with extrasellar extension in 44%. In 2 cases acromegaly was detected on radiological examination performed for signs/symptoms unrelated to pituitary disease, that is, head trauma in one case and stroke in the other. There was a strong correlation between GH and nadir GH ( $r=0.961$ ,  $p<0.001$ ) at baseline.

Both GH and nadir GH were also correlated with adenoma size ( $r=0.293$ ,  $p=0.030$  and  $r=0.324$ ,  $p=0.020$ , respectively). The mean duration of follow-up was  $8.8 \pm 0.8$  years (range 0-22). Follow-up data for  $\geq 12$  months were available for 93 patients.

### **Morbidity associated with acromegaly**

#### ***At baseline***

At presentation, visual field defects were detected in 36 of the 84 cases (43%) whose perimetry tests were available. Five patients (14%) with visual disorders were harbouring microadenomas with diameter 0.9-1 cm.

In terms of acromegaly-related morbidity, 46% of the patients presented with arterial hypertension (data available for 84). Data on glucose homeostasis were available for 87 patients at presentation and were diagnostic for DM in 25%, for impaired glucose tolerance (IGT) in another 25%. Dyslipidemia was present in 35% (data available in 60 subjects).

#### ***At follow-up***

Of the 93 acromegalic patients with available follow-up data, 10 (11%) were diagnosed with coronary artery disease and 46 (50%) had cardiac hypertrophy on

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3 echocardiography. Fifty-five percent of those undergoing colonoscopy had  
4 polypodiasis, 74% mono- or multinodular thyroid disease assessed by  
5 ultrasonography and 18% of those submitted to abdominal CT or MRI were  
6 harbouring an adrenal mass.  
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12 Cholelithiasis was detected in 20 of 44 patients examined by ultrasound of the upper  
13 abdomen. Notably, the majority (90%) of patients with gallstones had received SSA  
14 treatment. The frequency of cholelithiasis in patients on SSA treatment was 53% (18  
15 of 34 patients who underwent ultra-sound).  
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22 Glucose homeostasis was assessed in 45 patients who were given SSA  
23 pharmacotherapy. Twenty four patients with abnormal glucose homeostasis (IGT or  
24 DM) at baseline received SSA and glucose control deteriorated in 8, improved in  
25 another 8 and remained stable in the rest. On the other hand, 11 out of 21 euglycaemic  
26 patients at baseline developed IGT or DM after SSA administration. These data for  
27 glucose metabolism were independent of disease remission.  
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### 36 **Treatment**

#### 37 ***Surgical treatment***

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41 Pituitary surgery was performed in 73 patients with follow-up data (79%). Of  
42 these, 6 (8%) were operated twice, due to uncontrolled or recurrent disease. The  
43 majority of the surgical procedures (n=64, 88%) were performed by the  
44 transsphenoidal route. In 10 cases with invasive tumours, transcranial surgery was  
45 selected- in 2 of them secondary to transsphenoidal approach. In 1 case the surgical  
46 approach was not known. Except for the tumour's size and the invasion into  
47 neighbouring structures, the choice of surgical approach was also based on  
48 neurosurgeon's experience.  
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3 Twenty-two patients were exclusively managed with neurosurgery and remission was  
4 reported in 9 (41%). Three had microadenomas and 5 macroadenomas, while initial  
5 size was not available in 1. Interestingly, only 1 in 6 macroadenomas with extrasellar  
6 extension achieved remission after surgery alone. In 1 patient managed successfully  
7 with surgery alone initial size was unknown (table 1).  
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### 10 11 12 13 14 15 **Radiotherapy**

16  
17 Conventional radiotherapy -at a standard dose of 45 Gy in 25 fractions- was  
18 selected for 27 patients (29%) either as monotherapy or adjuvant to either surgery or  
19 SSA. It involved macroadenomas in 24 cases. In general, remission was observed in  
20 14 irradiated patients (52%). Twenty patients (27% of the surgically treated) received  
21 conventional radiotherapy post-surgically, either alone or in combination with  
22 pharmacotherapy [mainly SSA and/or dopamine agonists (DA)], while 1 patient was  
23 managed with  $\gamma$ -knife plus SSA postoperatively.  
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27 Remission was reported in 5 of the 8 patients (63%) who received radiotherapy as  
28 adjuvant to neurosurgery. On the other hand, in a total of 12 patients with refractory  
29 disease, where SSA treatment was necessary after surgery and radiotherapy, only 4  
30 finally responded. (table1).  
31  
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### 33 34 35 36 37 38 39 40 41 42 **Pharmacotherapy**

43  
44 Pharmacotherapy was the exclusive treatment in 13 patients (9 micro- and 4  
45 macroadenomas). SSA were the agents of choice with the exception of 2 patients who  
46 received DA. Lack of compliance and/or patient's refusal was the reason for not  
47 selecting SSA in these patients.  
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51 DA treatment was not successful. On the contrary, SSA treatment led to remission in  
52 8 patients (73% of those exclusively on SSA). It is noteworthy that all the responders  
53 had microadenomas, whereas no macroadenoma achieved remission with SSA alone.  
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3 Additionally, pharmacotherapy alone resulted in a decrease in size in 3 of 13  
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5 adenomas, (2 with SSA and 1 with DA).  
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8 Treatment with pegvisomant either alone or in combination with SSA was  
9  
10 preserved for 4 patients (2 males and 2 females) with refractory disease, after having  
11  
12 undergone surgical therapy, radiotherapy and SSA administration. Two patients  
13  
14 achieved remission at 6-8 months of follow-up, at a daily dose of 10mg as  
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16 monotherapy, whereas the other 2, despite being on a combination regimen with SSA,  
17  
18 have persistently active acromegaly.  
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22 Combination of neurosurgery and pharmacotherapy was reported in 30  
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24 patients: in 7 prior to surgery, in 13 post-surgery and in 10 both pre- and post-  
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26 surgery. Two patients received DA treatment, whereas the rest were treated with SSA.  
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28 Remission was achieved in 16 (53%). In particular, 100% of microadenomas (n=8)  
29  
30 and 43% (n=6) of macroadenomas managed with this approach showed no evidence  
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32 of active disease during follow-up (table 1).  
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### 36 **Effect of different treatment modalities on adenoma size, visual fields and pituitary** 37 38 **function**

#### 39 **Adenoma size and GH/IGF-1 levels**

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42 With respect to adenoma size, 11 of 17 microadenomas (65%) and 21 of 53  
43  
44 macroadenomas (40%) achieved tumour shrinkage after surgery (alone or with  
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46 concomitant radiotherapy or pharmacotherapy) (p= 0.081). Baseline adenoma size  
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48 was not available in 2 cases.  
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53 Disease remission was independent of the tumour invasiveness: remission was  
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55 achieved in 8 cases (38%) with extrasellar extension, compared with 6 cases (38%) in  
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57 which adenoma growth was limited in the sellar space (p=0.97).  
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3 Patients who achieved remission had significantly smaller adenomas at baseline  
4 compared with those who did not ( $1.3\pm 0.2$  vs.  $1.7\pm 0.1$ , respectively,  $p=0.014$ ).  
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8 During the first 5 years, GH, IGF-1 and tumor size decreased significantly. The  
9 changes in GH, GH<sub>nadir</sub>, IGF-I and adenoma size during a 5 year follow-up are  
10 presented in table 2. However, no significant association was observed between  
11 baseline GH ( $p= 0.28$ ), nadir GH ( $p=0.227$ ) or IGF-I ( $p=0.512$ ) and treatment  
12 outcomes.  
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### 15 16 17 18 19 20 **Visual field defects**

21  
22 Twenty-five patients with visual field defects were operated and 14 showed  
23 improvement postoperatively. Another 5 patients received only pharmacotherapy,  
24 which resulted in better perimetry tests in 2. Among the three patients who were  
25 managed exclusively with pituitary irradiation only 1 had a positive response in  
26 vision. Follow-up data regarding changes in visual disorders were absent in 6 patients.  
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### 33 34 **Pituitary reserve**

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36 Post-treatment, partial or total hypopituitarism was detected in 33 cases, in  
37 contrast with the finding of only 8 cases of hypopituitarism at baseline ( $p=0.001$ ).  
38 Post-surgery, after the exclusion of patients submitted to complementary conventional  
39 radiotherapy or radiosurgery, 16 patients developed hypopituitarism. Interestingly,  
40 none of 7 patients treated with radiotherapy alone or plus SSA presented  
41 hypopituitarism during follow-up.  
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### 53 54 **Discussion**

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56 This retrospective study outlines the actual presentation and management of  
57 acromegalic patients at a single endocrine centre in Greece.  
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3 The acromegalics in the present cohort had increased morbidity in keeping  
4 with previous series. However, more patients were reported to have arterial  
5 hypertension than in other European registries: 46% vs. 39% in both the Belgian (9)  
6 and the Spanish (10) studies. In addition, higher rates of cholelithiasis were reported  
7 after SSA treatment: 53% vs. 31% in Acrobel (9) and 15% in REA (10). This  
8 observation might reflect the very strict selection of patients for ultrasound testing.  
9 Furthermore, diabetes onset after SSA was reported in 45%, a little bit higher than in  
10 the REA registry.  
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22 The aims of therapy in acromegaly are suppression of GH hypersecretion,  
23 normalization of IGF-I levels and control of tumor size, as well as preservation of  
24 normal pituitary function. Using the aforementioned criteria, the overall success rate  
25 in our series was 52% -65% for microadenomas and 41% for macroadenomas. These  
26 percentages are in close proximity with the rates presented in Acrobel (49%) (9) and  
27 in West Midlands studies (46%) (11).  
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36 Although the number of patients was small for drawing safe conclusions for  
37 the effectiveness of surgery, this approach was not proven successful as exclusive  
38 therapeutic means for most patients. Remission was achieved in 34 (48%) patients  
39 who underwent surgery. Only 50% of microadenomas and 33% of macroadenomas  
40 (none of those with extrasellar extension) were in remission after surgery. This is in  
41 accordance with other “real life” observational series (9). Surgical series that adopted  
42 the current remission criteria - nadir GH<1 µg/L and/or postoperative random GH  
43 levels ≤2.5 µg/L and normal sex- and age-adjusted IGF-I level- have reported  
44 remission rates of 52-70% (12-14). The timing of post-surgical GH status evaluation  
45 seems to play a capital role on the outcome, since higher cure rates are reported short  
46 term after pituitary surgery and tend to dramatically weaken with time (15). In our  
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3 series, when surgery was followed by medical treatment or radiotherapy the remission  
4 rate increased to 53% and 63% respectively.  
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8 The outcomes of surgical intervention are mainly dependent on initial adenoma size  
9 and preoperative basal GH levels. In particular, an inverse relationship between  
10 surgical outcomes and adenoma size as well as basal GH levels has been described  
11 (14, 16).  
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17 Remission rates have been reported in 75-95% of microadenomas and in 40-71% of  
18 macroadenomas (14, 16). Extrasellar tumour growth and dural invasion by the  
19 adenoma are associated with poor outcomes (about 30%) (14, 16). Regarding the  
20 impact of basal GH levels on surgical outcomes, different thresholds have been used  
21 and, in general, remission rates are about 86-90% in patients with basal GH <10 µg/L,  
22 which may drop to 50% and 25% for GH levels >25 µg/L and >50 µg/L respectively  
23 (14, 17-18). In our series, there was a significant association between surgical  
24 outcomes and initial adenoma size, since we found that patients who achieved  
25 remission had significantly smaller adenomas at baseline in comparison with those  
26 with uncontrolled disease. However, no significant association was observed between  
27 baseline GH nadir GH or IGF-I and treatment outcomes.  
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44 The importance of an experienced surgeon, exclusively for the pituitary, **cannot** be  
45 adequately stressed. **A recent review has shown that focused clinical practice and**  
46 **large transsphenoidal surgical volume appear to be important outcome determinants**  
47 **for patients with pituitary tumors (19). The fact that in our country there is no**  
48 **regionalization of care to higher volume pituitary tumor centers of excellence is a**  
49 **major drawback to better surgical outcomes.** Consequently, the lack of better surgical  
50 outcomes in our study could partly be attributed to the lack of a single efficiently  
51 trained and experienced pituitary surgeon at our region.  
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59 Medical therapy as adjuvant to surgery resulted in remission in about half of the  
60 patients. Interestingly, all microadenomas and less than half of macroadenomas

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3 responded to SSA. Improved outcomes with combination therapy have also been  
4 reported by others (13). It seems that surgical tumor debulking enhances the response  
5 to SSA (20). Moreover, a high proportion of microadenomas (89%) achieved  
6 remission with SSA monotherapy, in contrast to none of macroadenomas. Although  
7 the number of these patients was small, the success rates were higher than usually  
8 demonstrated (6). More specifically, remission has been reported in up to 80% of the  
9 microadenomas (and intrasellar macroadenomas), but in less than 50% for larger  
10 macroadenomas (2, 6, 21-22).

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22 Although, there is a wide consensus that TSS is the first treatment choice for  
23 patients with acromegaly, SSA are increasingly being used as first-line therapy. Of  
24 note, a recent study comparing TSS with octreotide-LAR as first-line therapy in  
25 acromegalics (harbouring mainly macroadenomas) reported similar results in terms of  
26 optimal disease control at 48-week interval (22). Additional data indicate that SSA  
27 monotherapy may offer equivalent biochemical control to secondary treatment after  
28 unsuccessful surgery or radiotherapy (23). Furthermore, in terms of adenoma size,  
29 shrinkage >20% occurs in about 50-75% of acromegalics receiving SSA (2, 6),  
30 although this percentage was lower in the present series.

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42 Interestingly, about half of the patients having received SSA in our study developed  
43 cholelithiasis, as well as IGT or DM. Gallstones are a frequent entity in acromegalics  
44 treated with SSA, may occur at any time, but rarely are symptomatic or require acute  
45 surgery (24). In addition, SSAs exert an unfavourable effect on glucose metabolism,  
46 due to their inhibitory effect on pancreatic insulin secretion (25), which must be taken  
47 into account during therapy.

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**Conventional radiotherapy is usually used as an adjuvant therapy in pituitary  
adenomas secreting GH. However, its beneficial effect appears progressively over**

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3 years. It is reported to lead to biochemical control in about 50-60% of the cases of  
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6 acromegaly (2, 6), which is in line with results of our series. Postoperative  
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8 radiotherapy was more effective than surgery alone, as also shown in other reports  
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10 (13, 26). Radiotherapy as monotherapy or with adjuvant treatment with SSA was  
11  
12 equally successful; however the number of patients was small for safe conclusions. It  
13  
14 must be noted that radiotherapy outcomes were manifest at 12-34 years of follow-up,  
15  
16 except for 1 patient, who had already achieved remission at 7 years. Consequently,  
17  
18 data on radiotherapy can lead to safe conclusions on disease activity (>10 years of  
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20 follow-up).  
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25 Nevertheless, radiotherapy carries some risks that cannot be overlooked such as  
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27 hypopituitarism, and higher incidence of a second intracranial tumour or  
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29 cerebrovascular events (2, 6). Interestingly, with a longer than 10-year follow-up  
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31 interval, none of our patients undergoing radiotherapy alone or with SSA experienced  
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33 hypopituitarism in contrast to 2/3 of those treated with combination of surgery plus  
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35 radiotherapy and to 1/3 of those with surgery alone.  
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39 Successful treatment usually controls the commorbidities associated with  
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41 acromegaly to variable degrees, but some may persist despite biochemical control (1,  
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43 2). However, even partial control of the disease may result in significant improvement  
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45 of these commorbidities, as we have previously reported (27). Both GH and IGF-I  
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47 (mainly GH) correlate with mortality and, when they are controlled, mortality is close  
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49 to the levels expected in the general population (2).  
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53 Despite the meticulous data recorded from our department's database  
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55 throughout the years, we acknowledge the following limitations to our study: 1) it  
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57 constitutes a retrospective study, but it reflects the "real life" approach and problems  
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59 of patients with acromegaly in Greece; 2) the number of patients might look small in  
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3 an era of national acromegaly databases, but it derives from the larger endocrine  
4 centre of northern Greece and, to our knowledge, this is the first report on Greek  
5 population; 3) data on commorbidities were sometimes missing; 4) mortality  
6 assesment was not possible.  
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12 In conclusion, in this series, acromegaly was characterized by a wide range of  
13 systematic complications. Neurosurgery remains the cornerstone of treatment. An  
14 increase in remission rates was achieved with complementary conventional  
15 radiotherapy. However, the longitudinal risk of postoperative hypopituitarism was  
16 higher with this combination. Medical treatment was effective as adjuvant to surgery  
17 for macroadenomas and even as monotherapy for microadenomas. Yet, the  
18 appearance of cholelithiasis and abnormal glucose homeostasis are important  
19 unfavourable events with these agents.  
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### 31 **Conflict of interest**

32 This paper was written independently. The authors did not receive financial or  
33 professional help with the preparation of the manuscript.  
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**Table 1. Outcomes of different therapeutic strategies in acromegaly**

Therapy	Total number of patients	Remission (number of patients)	% of patients with remission	Microadenomas (remission/active disease)	Macroadenomas (remission/active disease)
Surgery alone	22	9	41%	3/3	5/10
Surgery/pharmacotherapy	30	16	53%	8/0	8/14
Surgery/radiotherapy	8	5	63%	0/1	4/2
Surgery/pharmaco- /radiotherapy	12	4	33%	0/2	4/6
Surgery/pharmacotherapy/ $\gamma$ -knife	1	1	100%	0/0	1/0
Radiotherapy alone	4	3	75%	0/0	3/1
Radiotherapy/pharmacotherapy	3	2	67%	0/0	2/1
Pharmacotherapy alone	13	8	62%	8/1	0/4

**Comments:** initial size was not available in 2 patients, 1 of which after surgery alone and 1 after surgery/**radio**therapy achieved remission

**Table 2. Changes in baseline and nadir GH levels, IGF-I levels and adenoma size during follow-up**

	<b>Baseline</b>	<b>1<sup>st</sup> year</b>	<b>3<sup>rd</sup> year</b>	<b>5<sup>th</sup> year</b>
<b>GH (µg/L)</b>	24.4±24.3	12.4±22.1	6.4±17.2	5.1±7.9
<b>GH nadir (µg/L)</b>	22.0±22.1	9.7±17.7	7.2±18.9	4.6±7.1
<b>IGF-I (µg/L)</b>	945±843	609±719	372±278	278±154
<b>Adenoma size (cm)</b>	1.66±0.90	1.2±0.7	1.1±0.6	1.0±0.6