Results of surgical and somatostatin analogue therapy and their combination in acromegaly
– A Retrospective Analysis of the German Acromegaly Register

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Abstract – ECE: maximal 250 Wörter – Ist: 250

Background: Data on surgical and medical treatment outcome in acromegaly mostly originate from specialized centres. We retrospectively analysed data on surgery, primary somatostatin analogue therapy (SSA), surgery preceded by SSA and SSA preceded by surgery in 1485 patients from the German Acromegaly Register. **Methods:** Two trained nurses visited all centres (N=42) for data acquisition. **Results:** Primary surgery: Of 889 patients 554 yielded analyzable data (microadenomas 22.9%, macroadenoms 77.1%). GH and IGF-I normalized in 54.3 and 67.2%. Partial or total pituitary insufficiency occurred in 28.6% initially and 41.2% post surgery. Primary SSA (≥3 months): Of 329 patients 145 yielded analyzable data (microadenomas 26.7%, macroadenoms 73.3%). GH and IGF-I normalized in 36.3 and 30.5%, increasing to 40.8 and 41.5% with longer SSA (≥360 days) in 54 patients. Pituitary function did not change. SSA (≥3 months) prior to surgery: Of 234 patients 93 yielded analyzable data. Post-surgery GH and IGF-I was normalized in 62.9 and 68.4%, significantly more often compared to primary surgery for GH (p<0.05), but not for IGF-I. Surgery followed by SSA: Of 122 patients 34 yielded analyzable data. GH and IGF-I normalized during SSA in 24.1 and 45.5%, Relative GH decrease was significantly larger compared to primary SSA. **Conclusions:** Pituitary surgery was more effective to lower GH and IGF-I concentrations than primary SSA. Primary SSA may be an option in selected patients. SSA prior to surgery only marginally improved surgical outcome. Debulking surgery may result in better final outcome in patients with a high GH concentration and a large tumor.
Introduction

Selective transsphenoidal surgery is the classical treatment option for patients with acromegaly. Success rates vary depending on the experience of the surgeon (1). Secondary – and in some cases primary – medical treatment mostly consists of somatostatin analogues (SSA) (2), although dopamine agonists (DA) may be efficacious in some patients (3). If SSA and DA fail to normalize the GH and IGF-I concentration, the newer GH antagonist pegvisomant (PEG) has been reported to achieve normalization of IGF-I in almost all patients (4).

SSA have also been suggested as primary and long-term treatment of acromegaly (5). However, a randomized study comparing primary surgery and primary medical treatment has not yet been published. SSA treatment prior to surgery has been suggested for reduction of surgical risks (6) and improvement of surgical results. However, the effect of SSA pretreatment on surgical outcome remains at present unclear (7). On the other hand, “debulking” surgery has been suggested to improve the efficacy of subsequent SSA treatment (8, 9) We analyzed data of the first 1485 patients from the German Acromegaly Register for these different treatment options.

Methods

The German Acromegaly Register performs an epidemiological, retrospective study of diagnosis, treatment and follow-up of patients with acromegaly in Germany. Participating centres include university hospitals, non-university hospitals and endocrinologists in private practice (10). Anonymized data are entered into the database. Collected data include estimated date of initial symptoms, date of diagnosis, method and results of pituitary imaging. Random GH values are either single determinations or the first value of a profile or OGTT. IGF-I concentration is complemented by an indication whether it was normal or not with respect to the local reference values. Details of treatment include date and route of surgery, type and periods of medical treatment (dopaminergic drugs, somatostatin analogues, GH-antagonist), as well as method and
dose of radiotherapy. Pituitary insufficiency is recorded as “yes, no, or not known”, supplemented by information on hormone therapy and whether this was a consequence of acromegaly/surgery or given for an unrelated cause.

The protocol of the register was approved by the Ethics Committee of the Charité, Universitätsmedizin Berlin and the Berlin Commissioner for Data Protection and Freedom of Information. Sponsorship is provided by an unrestricted grant from Novartis Oncology, Germany.

Patients were instructed about the use of their data and signed an agreement form. Data were stored in the data bank in anonymized form, using an identification number.

**Data acquisition**

Data are collected and the database is run and developed by a commercial company (Lohmann & Birkner, Health Care Consulting GmbH, Berlin, Germany), under the guidance of the Pituitary Disease Study Group of the German Endocrine Society. The software is based on that of the British Acromegaly Register (as described in (11)) with minor changes made for adaptation to the German situation. Two trained study nurses visit all centres for data collection, using standardized forms to ensure correct and uniform sampling. The nurses discuss their visits regularly with the coordinator of the register (HJQ). Completeness and correctness of data sampling and transfer into the database were randomly checked yearly by a second visit in selected centres by two of the authors (HJQ, RL). The correct data-transfer from the paper forms into the database was counterchecked by personal of the project management firm unrelated to the Register. However, availability of data in the centres varied considerably, due in part to financial restrictions in private practice centres and to differences in disease interest priorities. As a consequence, the number of patient data available for analysis is often smaller than the total number of patients in a treatment category. Details of the structure and working of the Register have been published elsewhere (10).

**Data characterization**
GH and IGF-I concentrations are those reported by case notes. For the purpose of this analysis, control of GH is defined by a concentration <2.5 µg/L (12). Due to variations in assays and reference ranges, normal IGF-I is defined using local criteria. Radiological evaluation of the pituitary tumor is reported using a scoring system as microadenoma (comprising ‘not visible’ (1) and <10 mm in size, (2)) and macroadenoma (comprising intrasellar macroadenoma (3) and macroadenoma with extrasellar extension (4)). MRI, CT and conventional X-ray imaging had been done at diagnosis in 596, 140 and 20 patients, resp. The mode of imaging was not documented in 70 patients and there was no information on tumor size in 659 patients at diagnosis.

Patients

Up to November 2005, 1485 patients with acromegaly (m 45.6%, f 54.4%) had been entered into the database, collected from 42 German centers (20 university hospitals [886 patients], 18 primary care hospitals [158 patients], 14 private practices [441 patients]). Pre-treatment GH-values (median and range) were 15.8 (1.1-620) µg/L (>2.5 µg/L in 94.1%) and IGF-I was elevated (according to age and sex) in 95.3% of the patients. Microadenomas were seen in 21.1% and macroadenomas in 79% of the patients. Tumor size scores 1, 2, 3 and 4 were present in 3.0 / 18.1 / 41.3 and 37.7% of the patients, resp. The analysis includes results of primary surgery and primary SSA treatment, as well as preoperative SSA treatment and SSA treatment as secondary therapy following surgery. Many patients received further – tertiary, quaternary etc. therapy – but this was not included in the present analysis.

Statistical Evaluation

Results are expressed as median (range). GraphPad Prism 4.0 (GraphPad Software Inc., San Diego, USA) was used for statistical analysis. The Wilcoxon signed rank test and the Mann Whitney-U test were performed, where appropriate. Control rates by different treatments were compared using the Chi-square test. Significance was accepted at p<0.05.
**Results**

**Primary treatment by surgery**

In this group 554 patients had analyzable data (for patients’ details see Table 1). Results of surgery were evaluated after a median of 9.8 months (0.03-469.8). Normal GH values (<2.5 µg/L) increased from 6.3% of patients at diagnosis to 54.3% postoperatively and normal IGF-I values from 3.4% to 67.2%. For absolute GH values see Table 2. Insufficiency of at least one pituitary axis was present in 28.6% of patients pre- and in 41.2% postoperatively, a surgically-induced increase of 12.6% (p<0.0001). For details see Table 3. Postoperative secondary treatment included repeat surgery (6.3%), SSA (9.0%), DA (11.0%), radiotherapy (4.2%), and none documented in 69.5%. When different time periods were analyzed, results for GH<2.5 ng/ml improved from 40.7% for operations before 1985 to 58.3% for operations in the period 2000–2005 (Table 4). Little change was noted for IGF-I normalization, which may be due to the low number of IGF-I assessments performed during the early time periods.

**Primary SSA treatment**

In this group 145 patients had analyzable data, had been treated for at least three months and had biochemical data available after a median duration of 7.7 months (range 3.0-143.1). These patients were slightly older than those in the primary surgery group (Table 1, p<0.0001). SSA doses ranged from 100-2500 µg/d (median 300 µg/d) for the octreotide s.c. preparation and from 10-40 mg every 4 weeks (median 20 mg every 4 weeks) for octreotide LAR. However, there was no uniform treatment protocol for these patients. The highest dose of octreotide LAR 40 mg was given in a single patient only.

Normal GH values (<2.5 µg/L) increased from 8.4% of patients at diagnosis to 36.3% during SSA treatment and normal IGF-I values from 3.8% to 30.5%. For absolute GH values see Table 2. With increasing duration of treatment (>180 d [n=96]; >365 d [n=54]), the percentage of patients with GH <2.5µg/l and normal IGF-I increased to 40.0% and 40.8% (GH) and to 36.7% and 43.1%
(IGF-I), resp. (p = ns). There was no significant difference between short-acting octreotide (GH < 2.5 µg/L in 39.4%; IGF-I normal 30.4%; [n=71]) and octreotide LAR (GH < 2.5 µg/L in 32.0% and IGF-I normal in 31.9% [n=50]). The number of patients who had received lanreotide was too small for analysis [n=9].

Insufficiency of at least one pituitary axis was present in 29.4% prior to and in 26.6% during SSA treatment (p = ns compared to pre-treatment). For details see Table 3. When SSA treatment did not normalize GH and/or IGF-I, patients received secondary treatment (surgery [60.0%], DA [2.8%], PEG [0.7%], radiotherapy [2.8%]). No change in treatment was reported in 33.7% of the patients.

**Surgery after SSA pre-treatment (SSA-OP) – comparison with primary surgery**

In this group GH and IGF-I concentrations at diagnosis and postoperatively were available from 93 patients who had received SSA treatment for at least 3 months prior to surgery (median duration 6.7 months, range 3.0-24.4). Before therapy neither their GH nor IGF-I concentrations nor tumor size differed significantly from those of the group with primary surgery (n=554). The patients were re-evaluated 9.8 (0.2-134.8) months after surgery.

In the SSA-OP group normal GH values (< 2.5 µg/L) increased from 6.8% of the patients at diagnosis to 62.9% postoperatively and normal IGF-I values from 1.4% to 68.4% of the patients. These normalization rates were not significantly different from those in the primary surgery group. In absolute terms, GH improvement was slightly but significantly better after SSA-pretreatment (Table 2).

**SSA treatment after primary surgery (OP-SSA) – comparison with primary SSA treatment**

In this group 34 patients who had received secondary SSA treatment within 12 months after primary operation had analyzable data. SSA was started 4.9 (1.0-11.9) months after surgery for 17.5 (3.0-196.8) months. Patients who received postoperative treatment other than SSA as second line treatment were excluded which explains the relatively low number in this group. Compared to
SSA patients (n=145) OP-SSA patients had significantly higher initial GH (p<0.05), and larger tumors (score 4 [2-4], p<0.05), but similar IGF-I concentrations (Table 2).

At the last re-evaluation during postoperative SSA treatment, normal GH values (<2.5 µg/L) had increased from 0.0% to 24.1% of the patients and normal IGF-I values from 4.8 to 45.5% (both p=ns versus primary SSA treatment). Details are given in Table 2. Compared to primary SSA treatment, GH decreased significantly more in OP-SSA (to 13.2% of initial values compared to 40.6%, p<0.005). The normalization rates of GH and IGF-I were not significantly different between primary SSA treatment and OP-SSA.

**Influence of treatment modality on tumor size**

The percentage decrease in tumor size score was 33.3% (25-400%), 100% [33.3-400%], 33.3% (25-200%), and 100% (25.0-100%) for primary surgery, primary SSA, SSA-OP, and OP-SSA, respectively. The distribution of microadenomas (tumor size scores 1 and 2) and macroadenomas (scores 3 and 4) pre- and post-therapy are given in Table 5. As expected, surgery alone - as well as surgery preceded by SSA therapy - reduced the tumor size significantly. Primary SSA-therapy alone did not significantly change the tumor size, and reduction in tumor size after surgery followed by SSA therapy just failed to reach significance. It has to be emphasized, that only major changes in tumor size may be detected with the data available for this analysis.
Discussion

The German Acromegaly Register aims to retrospectively evaluate the quality of diagnosis and treatment of acromegaly under the specific conditions of the German health care system. In Germany, patients with acromegaly are cared for in academic centers – which in the past have published almost exclusively data of their own experience - but also in non-academic hospitals and by endocrinologists in private practice (approximately 40% of patients). The present evaluation is based on approximately one third to one half of all acromegalic patients in Germany (80 Mill. inhabitants) as estimated from published prevalence data (13). Patients diagnosed from 1965 onwards were included.

Primary surgery

The results of primary surgery in our series (postoperative GH concentrations <2.5 µg/L in 54.3% and normal IGF-I concentrations in 67.2%) are compatible with published success rates. These vary between approximately 33% and less in non-specialized centers (1) and up to 70% and more in specialized centers (14) overall success rates being 50 to 60% (15). However, criteria for cure differ (GH <1.0 µg/L in OGTT, random or profile GH <2.5 µg/L, normal IGF-I or combinations there-of) and hence, comparison of results is difficult.

Patients who attain GH concentrations below 2.0/2.5 µg/L, GH suppression below 1.0 µg/L during OGTT or normal IGF-I concentration have a survival rate comparable to that of the normal population (16). In our cohort this amounts to approximately 54% (GH <2.5 µg/L) and 67% (normal IGF-I) of the patients. However, a 15-year recurrence rate of 10% has been reported (15).

Surgical success rates depend on the experience of the surgeon (11), adenoma size (14, 17, 18) and initial GH concentration (17, 19, 20). Because of a relatively large number of surgeons we did not break down the results according to the different surgical centers. The distribution of adenoma sizes (22.9% micro- and 77.1% macro-adenomas) was similar to that described in the literature, varying between approximately 25 to 35% for micro- and accordingly 65 to 75% for
macroadenomas, respectively (18, 21). However, we have not further analyzed this relationship, since only major changes in tumor size can be detected by our scoring system. In accordance with published observations (11, 20) surgical success improved when results from different time periods were compared.

While GH results of OGTT are already highly predictive of cure one week post-operatively, IGF-I values stabilize only after approximately 12 weeks (22). When IGF-I values from 47 patients of our cohort with determinations earlier than 3 months post-operatively were excluded, normal IGF-I values were seen in 54.8 percent, not significantly different from the analysis including immediate samples.

The increase of pituitary insufficiency from 28.6% of patients preoperatively to 41.2% postoperatively – a surgically-induced rate of 12.6% - compares favorably with data in the literature of e.g. 21 or 17.5% (20, 23). However, the methods of detection of pituitary insufficiency varied considerably in the different centers. In the literature, data on pre- and post-operative pituitary insufficiency are either lacking or given only summarily. Numbers range from 2% of 254 patients developing postoperative hypopituitarism (no information on preoperative function and details of hypopituitarism) (19) to 43% rendered panhypopituitary plus an additional 22% with partial anterior pituitary insufficiency (20). For a valid evaluation and comparability, as well as for optimal patient care, pre- and post-operative standardized function tests would be necessary.

**Primary SSA treatment**

In our patients with primary SSA treatment GH- and IGF-I normalization was lower (36.3% and 30.5%, resp.) than in most published studies, although the success rate increased somewhat in the group with a treatment duration longer than 180 days, comparable to the observations of Cozzi et al. (24). Final success rates were similar to those reported by Mercado et al. (25) (GH and IGF-I after 48 weeks 44% and 34%, resp.) However, others have found no or only minor further improvement with prolonged treatment periods (2, 25, 26), or even a loss of efficacy (27).
recent meta-analysis found an overall normalization rate of 57% for GH and of 67% for IGF-I in microadenomas and of 48% and 47% in macroadenomas (2). We excluded patients with less than three months therapy because of evidence that a maximal or near maximal effect on both GH concentration and tumor volume is only achieved after that time period (28). Hence we may have lost information on patients with less than three months treatment time who were transferred to their family physician because of an early excellent response.

Larger GH/IGF-I suppression and tumor volume reduction has been claimed for depot- versus short-acting octreotide (29), but this has not been confirmed (28). In our analysis, GH- and IGF-I-normalization rates did not differ significantly between short- and long-acting preparations. This is only of historical interest, since short-acting SSA are no longer used for long-term treatment of acromegaly. Nevertheless, our data may be biased by lack of a uniform treatment schedule and the inclusion of both s.c. and depot (LAR) octreotide preparations.

Of the patients treated primarily with SSA, 8.4% had normal GH concentrations at diagnosis and this was also seen in 6.8% of the patients in the SSA-OP group. We assume that these patients were nevertheless treated with SSA because of clinically unequivocal acromegaly and the finding of a tumor in their cranial MRI. In all patients who were later treated surgically, the diagnosis of a growth-hormone secreting adenoma was confirmed. Acromegaly in the presence of normal GH values has already been described (30).

Treatment results of primary surgery and primary SSA-therapy were compared. Pre-treatment GH and IGF-I concentrations, initial tumor size, initial rate of pituitary insufficiency and sex distribution were all similar in these groups. Not unexpectedly tumor size was lower following surgery than during SSA (p<0.0001), but conversely the rate of insufficiency was higher (p<0.005). This is in accordance with published data ((31), although there is only little information on the development of pituitary insufficiency. Primary, lifelong SSA treatment has been advocated for patients in whom surgery is highly unlikely to be curative or who have a contraindication for surgery (25, 26). Although our GH- and IGF-I normalization rates were lower
than reported in the literature, they nevertheless confirm that complete normalization is possible in a certain number of patients. One cause of poor or absent response to SSA seems to be a primary or induced absence of the SST-2 subtype of the five SST-receptors (32).

**Preoperative SSA treatment**

The value of preoperative SSA treatment is still a matter of controversy (6, 7, 33). In our group – which included patients with all tumor sizes – normalization rates of GH and IGF-I were not significantly improved by preoperative SSA treatment, although in absolute terms the GH decrease was better than after primary surgery. A better identification of patients who might benefit from preoperative SSA treatment still awaits a large prospective, well designed study. Short-term SSA pretreatment may however be useful to diminish the perioperative risks, caused by glucose intolerance, hypertension, airway difficulties or fluid imbalance (6, 34).

**SSA-treatment preceded by surgery**

The role of “debulking” surgery for the effectiveness of postoperative SSA treatment is unclear (8). In our patients the GH and IGF-I normalization rates were not different from those of the surgery alone group. However, the OP-SSA group had higher initial GH concentrations in accordance with their larger tumors, and their percentagewise GH decrease during postoperative SSA treatment was larger than that of the primary SSA group. Although this observation tends to support “debulking” surgery prior to SSA treatment in patients with large tumors, it must be recognized that the value of our results is compromised not only by the relatively small number of patients in this group, but also by the inclusion of patients with microadenomas. In the literatur improvement of SSA-induced GH-suppression or improvement of IGF-I but not GH have been reported from retrospective studies (35-37). A recent prospective study reported an improvement of the postoperative effect of Lanreotide by prior surgery (9).

**General considerations**
We have not performed an analysis of subgroups matched for age and sex, both of which have been shown to influence GH and IGF-I concentrations and their mutual relationship in healthy individuals and in acromegalic patients (38). This may e.g. influence the comparison of the apparent outcome of female and male patients receiving medical therapy because of different drug doses necessary for control or cure of the disease (39). An unavoidable bias in the outcome analysis may arise when patients are lost to documentation because they have been considered cured and escaped further care by an endocrinologist.

The rate of IGF-I normalization in our population was less than that of GH. In the presence of high GH concentrations the discrepancy between GH and IGF-I is probably due to the known plateau of IGF-I beginning at a GH concentration of approximately 20-30µg/l (40, 41). The percent of GH decrease is therefore expected to be larger than the corresponding percent decrease of IGF-I, especially, when initial GH values are grossly elevated. Moreover, even in the case of low GH concentrations, a dissociation of GH- and IGF-I- concentrations is not uncommon, due to assay variability and the influence of factors other than GH, such as nutrition, estrogens and gender. Whether the GH concentration will be a better indicator of treatment success than the IGF-I value awaits further, long-term observations.

**Limitations**

In view of the retrospective nature of this epidemiological study it is important to be aware of a number of factors that may have introduced a bias in some of the data. These include:

- Non-availability of certain treatment options in earlier years that have appeared over time, such as somatostatin analogues and, more recently, the growth hormone receptor blocker pegvisomant,
- Increased refinement of operative methods and accumulation of surgical experience in large centers,
- Development of diagnostic methods over time, such as magnetic resonance imaging,
• Development of laboratory methods over time, such as the determination of IGF-I and the use of monoclonal antibodies in hormone assays,

• Heightened awareness for the disease due to advances in teaching and requirements of Continuing Medical Education.

• Limited documentation available for a proportion of patients

Moreover, hormone determinations – most importantly GH and IGF-I – were done locally at the different centers and reported values are therefore a mix of different assay systems. It has been shown that GH as well as IGF-I results differ between laboratories and that assignment to a category – “cured” or “normal” – may therefore differ between centers (42-44). Determination of tumor size as well was done at the different centers and was not counterchecked by independent radiologists. Furthermore, criteria for “pituitary insufficiency may very between centers, depending on the methods used (e.g. basal hormone determinations or pituitary function tests). A few patients were diagnosed as having “diabetes insipidus” at the time of initial diagnosis. We have doubts about the correctness of this diagnosis. Possibly these patients had reported symptoms of mild diabetes insipidus, which were accepted as such without further investigation.

We are fully aware, that these unavoidable restrictions of a large, multicenter retrospective observational study are a limitation to any conclusions or recommendations for future treatment options. However, we feel that there will be no improvement without an uncompromising evaluation of the present conditions.

**Conclusions:** In this large cohort of acromegalic patients primary surgery lowered GH and IGF-I values more efficiently than primary SSA treatment, but conversely pituitary function suffered more. Primary medical treatment with SSA nevertheless presents an alternative in selected patients, since 30% of the patients on primary SSA therapy attained GH <2.5 µg/L or normalized their IGF-I concentration. The value of pre-operative SSA therapy, as well as that of debulking surgery remain uncertain and should be further evaluated by prospective controlled studies directed towards specific subgroups of patients.
The large percentage of missing values for essential parameters (GH, IGF-I, pituitary imaging) demands intensified efforts for diagnostically important testing and improved documentation. Follow-up documentation of the patients and use of the analysis for the purpose of Continuing Medical Education are future tasks of the register.
Acknowledgements

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<table>
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<th>Category</th>
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<th>Male/Female (%)</th>
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<td>889</td>
<td>554</td>
<td>46.0 / 54.0</td>
<td>46.0 / 13-73</td>
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<tr>
<td>SSA alone</td>
<td>329</td>
<td>145</td>
<td>48.3 / 51.7</td>
<td>51.0 / 18-78</td>
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<tr>
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<td>234</td>
<td>93</td>
<td>49.5 / 50.5</td>
<td>47.0 / 18-69</td>
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<td>OP-SSA</td>
<td>122</td>
<td>34</td>
<td>35.3 / 64.7</td>
<td>40.5 / 19-67</td>
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Table 2 - Comparison of the four different treatment schemes: Primary surgery, primary SSA therapy, pretreatment with SSA (SSA-OP) and SSA after surgery (OP-SSA). GH concentration is given in µg/L (median and range). In addition, GH and IGF-I are given in percentage of patients who have attained either GH <2.5µg/L or a normal IGF-I concentration.

<table>
<thead>
<tr>
<th>Scheme</th>
<th>Percent of patients</th>
<th>Percent of patients</th>
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<td></td>
<td>GH median/range</td>
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<td>IGF-I normal</td>
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<td></td>
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<tr>
<td>pre-OP</td>
<td>15.8 (0.2-620)</td>
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<td>3.4</td>
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<tr>
<td>post-OP</td>
<td>2.0** (0.01-169)</td>
<td>54.3</td>
<td>67.2</td>
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<td>SSA-OP</td>
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<tr>
<td>pre-SSA</td>
<td>17.7 (1.4-143)</td>
<td>6.8</td>
<td>3.4</td>
</tr>
<tr>
<td>post-OP</td>
<td>1.3*** (0.1-56)</td>
<td>62.9</td>
<td>68.4</td>
</tr>
<tr>
<td>p&lt;sup&gt;2&lt;/sup&gt;</td>
<td>ns / &lt;0.05</td>
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</tr>
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</table>

<sup>1</sup> p-value for comparison of GH concentrations (µg/L): OP alone vs SSA alone

<sup>2</sup> p-value for comparison of pre-Tx values (SSA-OP vs OP alone and OP-SSA vs SSA alone) / p-value for comparison of post/during Tx values (SSA-OP vs OP alone and OP-SSA vs SSA alone)

** p<0.0001 pre-OP vs post-OP and pre-SSA vs during SSA

*** p<0.0001 pre-SSA vs post-SSA-OP and pre-OP vs during OP-SSA
Table 3 – Insufficiency of pituitary functions before and after/during surgery/SSA therapy (% of patients)

<table>
<thead>
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<th>Adrenal</th>
<th>Gonadal</th>
<th>Thyroid</th>
<th>Diab.ins.</th>
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<tr>
<td>Before surgery (N=554)</td>
<td>11.6</td>
<td>17.7</td>
<td>7.4</td>
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<tr>
<td><strong>Post-surgery</strong></td>
<td>19.6</td>
<td>26.8</td>
<td>18.6</td>
<td>7.4</td>
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<tr>
<td>Before SSA (N=145)</td>
<td>12.8</td>
<td>15.6</td>
<td>7.3</td>
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<tr>
<td><strong>during SSA</strong></td>
<td>8.1</td>
<td>16.9</td>
<td>8.1</td>
<td>2.4</td>
</tr>
</tbody>
</table>
Table 4 – Percent of primary surgery patients with postoperative control of biochemical parameters during various time periods

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>81</td>
<td>169</td>
<td>140</td>
<td>139</td>
</tr>
<tr>
<td>GH&lt;2.5 (%)</td>
<td>40.7</td>
<td>55.6</td>
<td>56.4</td>
<td>58.3</td>
</tr>
<tr>
<td>N</td>
<td>33</td>
<td>112</td>
<td>133</td>
<td>130</td>
</tr>
<tr>
<td>IGF norm (%)</td>
<td>66.7</td>
<td>68.8</td>
<td>69.2</td>
<td>63.8</td>
</tr>
</tbody>
</table>
Table 5 - Influence of treatment modality on tumor size scores (microadenoma in % (scores [1+2]) // macroadenoma (scores [3+4]) in %)

<table>
<thead>
<tr>
<th></th>
<th>Surgery alone</th>
<th>SSA alone</th>
<th>SSA-OP</th>
<th>OP-SSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Tx</td>
<td>22.9 // 77.1</td>
<td>26.7 // 73.3</td>
<td>19.1 // 80.9</td>
<td>11.1 // 88.9</td>
</tr>
<tr>
<td>After/during Tx</td>
<td>85.5 // 14.5</td>
<td>31.3 // 68.8</td>
<td>83.9 // 16.1</td>
<td>50.0 // 50.0</td>
</tr>
</tbody>
</table>