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CLINICAL STUDY

Results of surgical and somatostatin analog therapies and their combination in acromegaly: a retrospective analysis of the German Acromegaly Register

S Petersenn, M Buchfelder[1], M Reincke[2], C M Strasburger[3], H Franz[4], R Lohmann[4], H-J Quabbe[5], U Plöckinger[6] and the Participants of the German Acromegaly Register

Division of Endocrinology, Medical Center, University of Duisburg-Essen, Hufelandstreet 55, 45122 Essen, Germany, [1]Department of Neurosurgery, University of Erlangen-Nuremberg, Erlangen, Germany, [2]Klinikum Innenstadt, University of Munich, Munich, Germany, [3]Division of Endocrinology, Charité–Universitätsmedizin Berlin, Campus Mitte, Berlin, Germany, [4]Lohmann and Birkner, Health Care Consulting GmbH, Berlin, Germany, [5]Charité-Universitätsmedizin Berlin, Campus Benjamin Franklin, Berlin, Germany and [6]Interdisziplinäres Stoffwechsel-Centrum, Charité-Universitätsmedizin Berlin, Campus Virchow-Klinikum, Berlin, Germany

(Correspondence should be addressed to S Petersenn; Email: stephan.petersenn@uni-due.de)

Abstract

Background: Data on surgical and medical treatment outcomes in acromegaly mostly originate from specialized centers. We retrospectively analyzed the data on surgery, primary somatostatin analog (SSA) therapy, surgery preceded by SSA, and SSA preceded by surgery in 1485 patients from the German Acromegaly Register.
Methods: Two trained nurses visited all centers ($N=42$) for data acquisition.
Results: Primary surgery: out of 889 patients, 554 yielded analyzable data (microadenomas 22.9%, macroadenomas 77.1%). GH and IGF1 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): out of 329 patients, 145 yielded analyzable data (microadenomas 26.7%, macroadenomas 73.3%). GH and IGF1 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: out of 234 patients, 93 yielded analyzable data. Post-surgery GH and IGF1 was normalized in 62.9 and 68.4%. GH improvement was slightly, but significantly better after SSA pretreatment. Surgery followed by SSA: out of 122 patients, 34 yielded analyzable data. GH and IGF1 normalized during SSA in 24.1 and 45.5%. Relative GH decrease was significantly larger compared with primary SSA.
Conclusions: Pituitary surgery was more effective to lower GH and IGF1 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.

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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 analogs (SSAs) (2), although dopamine agonists (DAs) may be efficacious in some patients (3). If SSAs and DAs fail to normalize the growth hormone (GH) and insulin-like growth factor I (IGF1) concentrations, the newer GH antagonist pegvisomant (PEG) has been reported to achieve normalization of IGF1 in almost all patients (4).

SSAs have also been suggested as primary and long-term treatments of acromegaly (5). However, a randomized study comparing primary surgery and medical treatment has not yet been published. SSA treatment prior to surgery has been suggested for reduction in 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 the data of the first 1485 patients from the German Acromegaly Register for these different treatment options.

Methods

The German Acromegaly Register perform an epidemiological, retrospective study of diagnosis, treatment, and follow-up of patients with acromegaly in Germany. Participating centers include university hospitals,

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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 oral glucose tolerance test (OGTT). IGF1 concentration is complemented by an indication of whether it is normal or not with respect to the local reference values. Details of the treatment include date and route of surgery, type and periods of medical treatment (dopaminergic drugs, SSAs, 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 asked to sign an agreement form. Data were stored in the data bank in anonymized forms, 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 visited all centers for data collection, using standardized forms to ensure correct and uniform sampling. The nurses discussed their visits regularly with the coordinator of the register (H J Q). Completeness and correctness of data sampling and transfer into the database were randomly checked yearly by a second visit to selected centers by two of the authors (H J Q, R L). The correct data transfer from the paper forms into the database was counterchecked by the personnel of the project management firm unrelated to the register. However, availability of data in the centers varied considerably, due in part to financial restrictions in private practice centers 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 IGF1 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 IGF1 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)). Magnetic resonance imaging (MRI), computer tomography (CT), and conventional X-ray imaging had been done at diagnosis in 596, 140, and 20 patients respectively. 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 (males 45.6%, females 54.4%) had been entered into the database, collected from 42 German centers (20 university hospitals (886 patients), 18 primary care hospitals (158 patients), and 14 private practices (441 patients)). Pretreatment GH values (median and range) were 15.8 (1.1–620) μg/l (>2.5 μg/l in 94.1%) and IGF1 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 respectively. The analysis includes results of primary surgery and 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, CA, USA) was used for statistical analysis. The Wilcoxon signed-rank and Mann–Whitney U tests were performed where appropriate. Control rates by different treatments were compared using the χ^2 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 IGF1 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

Table 1 Patients' characteristics.

Category	*N* total	*N* analyzable data	Male/female (%)	Age (median, range)
OP alone	889	554	46.0/54.0	46.0/13–73
SSA alone	329	145	48.3/51.7	51.0/18–78
SSA-OP	234	93	49.5/50.5	47.0/18–69
OP-SSA	122	34	35.3/64.7	40.5/19–67

preoperatively 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 IGF1 normalization, which may be due to the low number of IGF1 assessments performed during the early time periods.

Primary SSA treatment

In this group, 145 patients had analyzable data, had been treated for at least 3 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 to 2500 μg/d (median 300 μg/d) for the octreotide s.c. preparation, and from 10 to 40 mg every 4 weeks (median 20 mg every 4 weeks) for octreotide long acting release (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 IGF1 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 < 2.5 μg/l and normal IGF1 increased to 40.0% and 40.8% (GH) and to 36.7% and 43.1% (IGF1) respectively (P=NS). There was no significant difference between short-acting octreotide (GH < 2.5 μg/l in 39.4%, IGF1 normal 30.4% ($n=71$)) and octreotide LAR (GH < 2.5 μg/l in 32.0% and IGF1 normal in 31.9% ($n=50$)). The number of patients who had received lanreotide was too small to analyze ($n=9$).

Insufficiency of at least one pituitary axis was present in 29.4% prior to and in 26.6% during SSA treatment (P=NS compared with pretreatment). For details, see Table 3. When SSA treatment did not normalize GH and/or IGF1, 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 pretreatment (SSA-OP): comparison with primary surgery

In this group, GH and IGF1 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, their GH, IGF1 concentrations, and tumor size did not differ significantly compared with 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 IGF1 values from

Table 2 Comparison of the four different treatment schemes: primary surgery, primary somatostatin analog (SSA) therapy, pretreatment with SSA (SSA-OP), and SSA after surgery (OP-SSA).

			Percentage of patients					Percentage of patients		
		GH median/range	GH < 2.5	IGF1 normal			GH median/range	GH < 2.5	IGF1 normal	*P*[a]
OP alone	Pre-OP	15.8 (0.2–620)	6.3	3.4	SSA alone	Pre-SSA	14.0 (1.1–184.0)	8.4	3.8	NS
	Post-OP	2.0* (0.01–169)	54.3	67.2		During SSA	4.1* (1.1–624)	36.3	30.5	< 0.0001
SSA-OP	Pre-SSA	17.7 (1.4–143)	6.8	1.4	OP-SSA	Pre-OP	28.7 (2.9–193)	0.0	4.8	–
	Post-OP	1.3† (0.1–56)	62.9	68.4		During SSA	3.5† (0.3–50)	24.1	45.5	–
P[b]		NS/< 0.05	–	–			< 0.05/NS	–	–	

GH concentration is given in μg/l (median and range). In addition, GH and IGF1 are given in percentage of patients who have attained either GH < 2.5 μg/l or a normal IGF1 concentration. *$P<0.0001$ pre-OP versus post-OP and pre-SSA versus during SSA. †$P<0.0001$ pre-SSA versus post-SSA-OP and pre-OP versus during OP-SSA.

[a]*P* value for comparison of GH concentrations (μg/l): OP alone versus SSA alone.

[b]*P* value for comparison of pre-Tx values (SSA-OP versus OP alone and OP-SSA versus SSA alone)/*P* value for comparison of post/during Tx values (SSA-OP versus OP alone and OP-SSA versus SSA alone).

Table 3 Insufficiency of pituitary functions before and after/during surgery/somatostatin analog (SSA) therapy (% of patients).

	Adrenal	Gonadal	Thyroid	Diabetes insipidus
Before surgery ($N=554$)	11.6	17.7	7.4	1.0
Post-surgery	19.6	26.8	18.6	7.4
Before SSA ($N=145$)	12.8	15.6	7.3	0.0
During SSA	8.1	16.9	8.1	2.4

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 with 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 IGF1 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 IGF1 values from 4.8 to 45.5% (both $P=$NS versus primary SSA treatment). Details are given in Table 2. Compared with primary SSA treatment, GH decreased significantly more in OP-SSA (to 13.2% of initial values compared with 40.6%, $P<0.005$). The normalization rates of GH and IGF1 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 distributions 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.

Table 4 Percentage of primary surgery patients with postoperative control of biochemical parameters during various time periods.

Time period	<1985	1985–1994	1995–1999	2000–2005
N	81	169	140	139
GH<2.5 (%)	40.7	55.6	56.4	58.3
N	33	112	133	130
IGF norm (%)	66.7	68.8	69.2	63.8

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 and also in non-academic hospitals and by endocrinologists in private practice (~40% of patients). The present evaluation is based on approximately one-third to one-half of all acromegalic patients in Germany (80 million inhabitants) as estimated from the published prevalence data (13). Patients diagnosed from 1965 onward were included.

Primary surgery

The results of primary surgery in our series (postoperative GH concentrations <2.5 μg/l in 54.3% and normal IGF1 concentrations in 67.2%) are compatible with published success rates. These vary between ~33% and less in non-specialized centers (1), and up to 70% and more in specialized centers (14) overall success rates being 50–60% (15). However, criteria for cure differ (GH<1.0 μg/l in oral glucose tolerance test (OGTT), random or profile GH<2.5 μg/l, normal IGF1 or combinations thereof), 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 IGF1 concentration have a survival rate comparable with that of the normal population (16). In our cohort, this amounts to ~54% (GH< 2.5 μg/l) and 67% (normal IGF1) of the patients.

Table 5 Influence of treatment modality on tumor size scores (microadenoma in % (scores (1+2))//macroadenoma (scores (3+4)) in %).

	Surgery alone	SSA alone	SSA-OP	OP-SSA
Before Tx	22.9//77.1	26.7//73.3	19.1//80.9	11.1//88.9
After/during Tx	85.5//14.5	31.3//68.8	83.9//16.1	50.0//50.0

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% microadenomas and 77.1% macroadenomas) was similar to that described in the literature, varying between ~25–35% for microadenomas and accordingly 65–75% 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 the results from different time periods were compared.

While GH results of OGTT are already highly predictive of cure 1 week postoperatively, IGF1 values stabilize only after ~12 weeks (22). When IGF1 values from 47 patients of our cohort with determinations earlier than 3 months postoperatively were excluded, normal IGF1 values were seen in 54.8%, not significantly different from the analysis including immediate samples.

The increase in 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, for example, 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 postoperative pituitary insufficiency are either lacking or given only summarily. The 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 postoperative standardized function tests would be necessary.

Primary SSA treatment

In our patients with primary SSA treatment, GH and IGF1 normalization was lower (36.3% and 30.5% respectively) than in the most published studies, although the success rate increased somewhat in the group with a treatment duration longer than 180 days, comparable with the observations of Cozzi *et al.* (24). Final success rates were similar to those reported by Mercado *et al.* (25) (GH and IGF1 after 48 weeks 44% and 34% respectively). However, others have found no or only minor further improvement with prolonged treatment periods (2, 25, 26) or even a loss of efficacy (27). A recent meta-analysis found an overall normalization rate of 57% for GH and of 67% for IGF1 in microadenomas and of 48% and 47% in macroadenomas (2). We excluded patients with less than 3 months therapy because of the 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 3 months treatment time, who were transferred to their family physician because of an early excellent response.

Larger GH/IGF1 suppression and tumor volume reduction have been claimed for depot versus short-acting octreotide (29), but this has not been confirmed (28). In our analysis, GH and IGF1 normalization rates did not differ significantly between short- and long-acting preparations. This is only of historical interest, since short-acting SSAs are no longer used for long-term treatment of acromegaly. Nevertheless, our data may be biased by the 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 GH secreting adenoma was confirmed. Acromegaly in the presence of normal GH values has already been described (30).

Treatment results of primary surgery and SSA therapy were compared. Pretreatment GH and IGF1 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 IGF1 normalization rates were lower than those 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 IGF1 were not significantly improved by preoperative SSA treatment, although in absolute terms the GH decrease was better than that 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 IGF1 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 percentage 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 literature, improvement of SSA-induced GH suppression or improvement of IGF1 but not GH has 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 IGF1 concentrations and their mutual relationship in healthy individuals and acromegalic patients (38). This may, for example, 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 IGF1 normalization in our population was less than that of GH. In the presence of high GH concentrations, the discrepancy between GH and IGF1 is probably due to the known plateau of IGF1 beginning at a GH concentration of ~20–30 μg/l (40, 41). The percentage of GH decrease is therefore expected to be larger than the corresponding % decrease in IGF1, especially when initial GH values are grossly elevated. Moreover, even in the case of low GH concentrations, a dissociation of GH and IGF1 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 IGF1 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 the following:

- non-availability of certain treatment options in earlier years that have appeared over time, such as SSAs and, more recently, the GH receptor blocker PEG,
- increased refinement of operative methods and accumulation of surgical experience in large centers,
- development of diagnostic methods over time, such as MRI,
- development of laboratory methods over time, such as the determination of IGF1 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, and,
- limited documentation available for a proportion of patients.

Moreover, hormone determinations, most importantly GH and IGF1, 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 IGF1 results differ between laboratories, and that assignment to a category of 'cured' or 'normal', may therefore differ between centers (42–44). Determination of tumor size was also done at the different centers and was not counterchecked by independent radiologists. Furthermore, criteria for 'pituitary insufficiency, may vary 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 IGF1 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 IGF1

concentrations. The value of preoperative SSA therapy, as well as that of debulking surgery, remains uncertain and should be further evaluated by prospective controlled studies directed toward specific subgroups of patients.

The large percentage of missing values for essential parameters (GH, IGF1, 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 the future tasks of the register.

Declaration of interest

The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.

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