

Preoperative octreotide treatment in newly diagnosed acromegalic patients with macroadenomas increases cure short-term postoperative rates: a prospective, randomized trial.

Sven M. Carlsen ^{a,b}, Morten Lund-Johansen ^{c,d}, Thomas Schreiner ^e, Sylvi Aanderud ^f, Øivind Johannesen ^g, Johan Svartberg ^{h,i}, John G. Cooper ^j, John K. Hald ^k, Stine L. Fougner ^{e,l}, Jens Bollerslev ^{e,l}, on behalf of the POTA study group.

^aDepartment of Laboratory Medicine, Childrens and Womens Health, Norwegian University for Science and Technology, Trondheim, ^bDepartment of Endocrinology, St. Olavs Hospital, Trondheim, ^cDepartment of Neurosurgery, Haukeland University Hospital, Bergen, ^dNeurosurgery Unit, Institute of Surgical Sciences, University of Bergen, Bergen, ^eEndocrinology Unit, Department of Medicine, Rikshospitalet-Radiumhospitalet Medical Center, Oslo, ^fEndocrinology Unit, Department of Medicine, Haukeland University Hospital and Institute of Medicine, University of Bergen, ^gEndocrinology Unit, Department of Medicine, Aker University Hospital, Oslo, ^hEndocrinology Unit, Department of Medicine, University Hospital of North Norway, ⁱInstitute of Clinical Medicine, University of Tromsø, ^jEndocrinology Unit, Department of Medicine, Stavanger University Hospital, Stavanger, ^kDepartment of Radiology, Rikshospitalet-Radiumhospitalet Medical Center, Oslo, , and ^lResearch Institute for Internal Medicine, University of Oslo, Oslo, Norway.

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Corresponding author:

Sven M. Carlsen, Department of Endocrinology, St. Olavs Hospital, University Hospital of Trondheim, 7006 Trondheim, Norway.

E-mail: sven.carlsen@ntnu.no

Reprint request:

Sven M. Carlsen, Department of Endocrinology, St. Olavs Hospital, University Hospital of Trondheim, 7006 Trondheim, Norway.

E-mail: sven.carlsen@ntnu.no

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Summary

Context: Surgery is the primary treatment of acromegaly. However it often fails to cure the patient. New strategies that improve surgical outcome are needed.

Objective: To investigate whether six months preoperative treatment with octreotide improves the surgical outcome in newly diagnosed acromegalic patients.

Patients: During a five year period (1999 – 2004) all newly diagnosed acromegalic patients between 18 and 80 years of age in Norway were screened and invited to participate in the study. Sixty-two patients were included in the Preoperative Octreotide Treatment of Acromegaly (POTA) study.

Research design and methods: After a baseline evaluation patients were randomized directly to transsphenoidal surgery (n=30) or to pre-treatment with octreotide (n=32) 20 mg im. every 28th day for six months prior to transsphenoidal surgery. Cure was evaluated three months postoperatively primarily by Insulin like Growth Factor-1 levels (IGF-1).

Results: According to the IGF-1 criteria 14 out of 31 (45%) pretreated patients vs. 7 out of 30 (23%) patients with direct surgery were cured by surgery (p=0.11). In patients with microadenomas (≤ 10 mm) 1 out of 5 (20%) pretreated vs. 3 out of 5 (60%) with direct surgery were cured (p=0.52). In patients with macroadenomas 13 out of 26 (50%) pretreated vs. 4 out of 25 (16%) with direct surgery were cured (p=0.017).

Conclusion: Six months preoperative octreotide treatment might improve surgical cure rate in newly diagnosed acromegalic patients with macroadenomas. These results have to be confirmed in future studies.

Introduction:

In the majority (98%) of cases, acromegaly is caused by a growth hormone (GH) producing pituitary adenoma. Retrospective cohort studies suggest that mortality in acromegaly is at least doubled compared to the general population (1-3). Morbidity and mortality are associated with elevated levels of growth hormone (GH) and Insulin-like Growth Factor-1 (IGF-1) (1,2,4). The aim of treatment is to relieve symptoms, control tumour growth and ensure biochemical cure.

Neurosurgery is the accepted first-line treatment of acromegaly. Outcome predictors include tumour size, extrasellar extension, dural invasion, pre-treatment GH levels and the experience of the neurosurgeon (5,6). The best reported cure rates for micro- and macroadenomas are 80-90% and 50-60%, respectively (5-7), whereas overall cure rates as low as 18% (39% in microadenomas and 12% in macroadenomas) have been reported (8). It is possible that studies with low cure rates remain unpublished.

Medical treatment of acromegaly with somatostatin analogues (SSA) can lead to normalized GH and IGF-1 levels (9) and relief of symptoms (10). SSA treatment may cause shrinkage of GH-secreting pituitary adenomas (9,11). Theoretically, this could improve the likelihood of a radical resection, particularly in macroadenomas.

Furthermore, it has been suggested that SSA treatment softens the tumour parenchyma and thereby facilitates tumour removal (12,13). Finally, it has been reported that SSA pre-treatment leads to a shortening of postoperative hospital stay (14).

Previous studies addressing preoperative SSA treatment and subsequent surgical cure rates are conflicting, reporting a benefit (12,14,15), or no difference between groups (13,16,17). Most of these studies were retrospective in design.

Between 1999 and 2004, we included patients in the randomized Preoperative Octreotide Treatment of Acromegaly (POTA) study to investigate whether six months

pre-treatment with the SSA octreotide would improve the surgical cure rate of newly diagnosed acromegalic patients.

Material and methods:

Study population: In Norway all pituitary surgery is performed by one dedicated neurosurgeon at each of the five university hospitals. All five neurosurgical departments participated in the POTA study. All acromegalic patients in Norway diagnosed between September 1th 1999 and October 31th 2004 were invited to participate in the study.

Inclusion criteria were: a) newly diagnosed, previously untreated patients with GH nadir > 2.5 mcg/L during a standard 75 gram 2 hour oral glucose tolerance test (OGTT), b) pituitary adenoma verified by a pituitary MRI scan, and c) age between 18 and 80 years.

Exclusion criteria were; a) immediate surgery indicated by clinical criteria, b) pregnancy, c) contraindications to MRI scan, and d) patients judged not suitable to participate in the study for other reasons such as personality disorders and alcohol abuse. Power calculations indicated that 31 patients had to be included in each group in order to have an 80% probability of demonstrating an increase in overall cure rate from 40% to 75%.

Eighty-three consecutive patients with previously undiagnosed acromegaly were identified during the inclusion period of five years and two months. Twenty-one of these were not included due to contraindications, unwillingness to participate or because the diagnosis of acromegaly was established after surgery. The present study presents data from the 62 (75% of eligible) included in the POTA study.

Written informed consent was obtained from each patient before inclusion and the declaration of Helsinki was followed throughout the study. The study was approved by the Committee for Medical Research Ethics in each of the five health regions in Norway, and The Norwegian Medicines Agency.

Investigations: The diagnosis of acromegaly was made in each participating center based on a GH nadir > 2.5 mcg/L during a two hour 75 g OGTT which was performed according to the WHO procedure. Samples for GH measurements were drawn at baseline and every half hour for 2 hours. The presence of a pituitary adenoma was confirmed by a pituitary MRI scan (T1-weighted coronal and/or sagittal and/or axial scans, 3-5 mm slice thickness at 1.5T).

Fasting serum samples for IGF-1 analysis were drawn at baseline and three months postoperatively and stored at -70°C until assayed. The samples were analyzed after the last patient had completed the study schedule, as single measurements in one run using an ELISA kit from R&D. The upper limit of normal (ULN) was set as the age adjusted 95 percentile by regression based on 40 samples run in parallel with a commercial kit from CisBio with given reference interval (18). The intra- and interassay coefficient of variation were 3.8 % and 7.2 %, accordingly. In two patients, sera from the postoperative evaluation were missing and the locally measured IGF-1 values against local ULN were used instead. GH analyses were performed consecutively by standard laboratory procedures at each of the participating study centers. In Norway GH-values are given in mIU/L. We chose to use a “conservative” conversion factor of 2.0 for conversion between mcg/L and mIU/L.

MRI scans were examined retrospectively in a blinded fashion by two physicians (JKH & SLF), one being an experienced neuroradiologist. Adenomas measuring ten mm or less on MRI in the largest dimension were classified as microadenomas, and larger tumors as macroadenomas. No distinction between enclosed, suprasellar and invasive macroadenomas was made as this was not predefined in the protocol. The longest anterior-posterior, vertical and transverse diameters were measured, and tumor volume calculated by the formula $\text{height} \times \text{width} \times \text{length} \times 0.5$ (19).

Treatment: After a baseline evaluation, patients were randomized separately for each study center in blocks of four directly to transsphenoidal surgery (direct surgery group, n = 30) or to six months of preoperative treatment with octreotide (pre-treatment group, n = 32). Randomization was completely balanced between the two study groups at the three centers that included an equal number of patients. One more patient was randomized to pre-treatment with octreotide at each of the two remaining study centers that included an odd number of patients.

To reduce the risk of gastrointestinal adverse effects in the pre-treatment group, octreotide was initiated at a dose of 50 µg sc. tid for the first week and 100 µg sc. tid for the second week. From the third week on, the patients received octreotide LAR 20 mg im. every 28th day for six months. They underwent transsphenoidal surgery within 28 days of the last injection. If surgery was delayed, an extra octreotide LAR injection was given before surgery. Hence, all patients in the pre-treatment group underwent surgery with therapeutic levels of the study medication. All patients were operated by standard microneurosurgical technique via the transsphenoidal route. During surgery, the consistency of the adenoma was graded as soft, mixed or firm, and the neurosurgeon evaluated the operative result as radical vs. subtotal resection. Peri- and postoperative surgical complications and duration of postoperative hospital stay were registered. If indicated, octreotide could be administered after the three months postoperative evaluation.

Aims of the study:

The aim of the study was to investigate whether six months treatment with the somatostatin analogue octreotide prior to transsphenoidal surgery in newly diagnosed acromegalic patients would improve the outcome, using cure rate at evaluation three

months postoperatively as the primary endpoint. Secondary endpoints included postoperative hospital stay duration and complication rates.

Definition of cure: Cure was evaluated three months postoperatively primarily by fasting IGF-1 \leq age adjusted ULN (20,21). In addition, a GH nadir \leq 1.0 mcg/L during an OGTT was used.

Statistics: All statistical procedures, except estimation of confidence intervals (CI), were performed with SPSS version 13.0. CI's were estimated by binominal exact estimations using Stata Corp., version 9.0 (College station, Texas, USA). Data are presented as absolute numbers or means and standard deviations (SD). Two-sided Fischer`s exact test for categorical variables and two-sided t-tests for independent samples for continuous variables were used. No adjustments for multiple testing were performed. P-values $<$ 0.05 were considered significant.

Results:

Baseline data:

Eighty-three patients with previously undiagnosed acromegaly were identified during the inclusion period of five years and two months. With 4.5 million inhabitants in Norway this equals an incidence of acromegaly in Norway of 3.6 cases/million/year.

At baseline there were significantly more males than females ($p = 0.042$) and lower IGF-1 levels ($p = 0.004$) in the pre-treatment group. However, when evaluating IGF-1 as percentage of age-adjusted ULN this difference lost its significance ($p=0.056$). Patient age, working status, GH nadir during an OGTT, tumor volume and ratio between micro- and macroadenomas did not differ between groups (table 1). All the included patients were Caucasians. One male patient with a microadenoma did not

undergo surgery because the tumor regressed during pre-treatment. He was excluded from analyses of surgical cure rates. None of the patients withdrew from the study or were lost to follow-up during the study period.

MRI scans:

By central blinded evaluation of baseline MRI scans, there were 11 microadenomas (\leq 10 mm in the largest diameter) and 51 macroadenomas. In six patients, at least one of the MRI scans was not available for central evaluation. For these patients the classification of adenoma size and estimation of tumor volume was based on local evaluation of the tumor during the study.

At inclusion there were six adenomas in the direct surgery group with signs of cavernous sinus invasion. In the pre-treatment group there were four adenomas with signs of cavernous sinus invasion both before octreotide treatment and the same number after pre-treatment but prior to surgery.

Primary outcome:

IGF-1 Criteria:

Cure, defined solely by IGF-1 \leq ULN three months postoperatively, was established in 14 out of 31 (45%) pretreated patients versus 7 out of 30 (23%) direct surgery patients ($p = 0.11$) (table 2). Subdividing tumors according to initial size, 1 out of 5 pretreated patients versus 3 out of 5 direct surgery patients with microadenomas were cured ($p = 0.52$). In patients with macroadenomas, 13 out of 26 (50%) pretreated patients versus 4 out of 25 (16%) direct surgery patients were cured ($p = 0.017$).

Cure was also estimated for age-adjusted cut-off levels of IGF-1 ranging from 80% to 120% of the ULN (table 3). In macroadenomas, pre-treatment significantly

increased cure rates evaluated by IGF-1 at cut-off levels ranging from 95% to 120% of ULN ($p = 0.009-0.034$).

None of the six patients with signs of cavernous sinus invasion in the direct surgery group were cured. One of four patients with signs of cavernous sinus invasion after pre-treatment with octreotide was cured.

The overall cure rates according to IGF-1 levels ranged from 0 to 62 % in the participating study centers with the smaller ones performing as well as the larger one (table 2).

Combined criteria:

When adding a GH-nadir during OGTT ≤ 1.0 mcg/L to the cure criteria, three patients, all with macroadenomas, lost their status of being cured (GH-nadirs of 1.8, 2.9 and 3.5 mcg/L). Thus, the overall cure rate in the total study population was reduced to 35% (pre-treated) and 23% (direct surgery), respectively ($p = 0.40$). In macroadenomas 38% (10 out of 26 pre-treated) versus 16% (4 out of 25 direct surgery) of patients were cured when adding GH-nadir during OGTT to the cure criteria ($p = 0.12$).

Tumor volume:

In the pretreated patients both initial tumor volume (1.98 ± 1.61 ml vs. 1.49 ± 1.13 ml; $p = 0.33$) and tumor volume change during pre-treatment (-38 ± 30 % vs. -31 ± 29 %; $p = 0.56$) were equally distributed among cured and non-cured patients, accordingly. Also, when performing separate analyses with the macroadenomas, initial tumor volume and percent change during pre-treatment were equal (data not shown).

Three months postoperatively tumor volume was 0.51 ± 0.73 ml in pretreated patients and 0.80 ± 1.45 ml in direct surgery patients ($p = 0.34$).

Secondary outcomes:

Tumor consistency: In pretreated patients the tumor was classified as firm in eight and mixed in one patient. In direct surgery patients no firm and five mixed tumors were identified. The rest of the tumors were soft ($p = 0.002$). Data on two pretreated and one direct surgery patient were missing.

Surgical complications: Immediate surgical complications were reported in four patients (2 transient liquorrhea, 1 hematoma, 1 transient diabetes insipidus) in the pretreated group vs. 2 patients (1 transient liquorrhea, 1 sinusitis) with direct surgery ($p = 0.67$). During the postoperative period prior to the three months postoperative evaluation further complications were seen. Persistent surgical complications were seen in three patients (1 anterior pituitary insufficiency, 1 diabetes insipidus, 1 minor bitemporal visual field deficit, 1 nose complication) in the pretreated group vs. 4 patients (1 anterior pituitary insufficiency, 1 diabetes insipidus, 1 olfactory nerve dysfunction, 1 eye muscle palsy; most probable secondary to progressive cavernous sinus growth) in the group with direct surgery ($p = 0.71$).

Altogether, surgical complication was seen in 2 out of the 21 (10%) cured patients and in 9 out of 40 (23%) non cured patients ($p = 0.30$). In patients without surgical complications 8 out of 39 (21%) adenomas were classified as mixed or solid vs. 4 out of 14 (29%) mixed or solid adenomas in patients with surgical complications ($p = 0.54$). Data were missing in 8 patients.

The postoperative hospital stay was similar between groups, being 3.7 ± 1.8 days in pretreated patients versus 3.6 ± 1.6 days in direct surgery patients ($p = 0.54$).

Surgical resection evaluation: In all the 21 patients cured by the IGF-1 criteria cure was anticipated by the neurosurgeon. However, surgical cure were also anticipated in 27 of

the 37 non-cured patients. Non-cure were anticipated in 3 out of 29 pretreated patients versus 7 out of 29 direct surgery patients ($p = 0.16$). Data were missing on 3 patients.

Discussion

The present prospective, randomized study indicates that pre-treatment of newly diagnosed acromegalic patients with octreotide prior to transsphenoidal surgery leads to an increased surgical cure rate in patients with macroadenomas, whereas no benefit, or even a possible adverse effect, was seen in patients with microadenomas. Our findings are in accordance with some (12,14,15) but not all previous reports (13,16,17).

In acromegaly levels of IGF-1 as well as mean daytime GH levels and GH-nadir during an OGTT can be used as criteria for cure (21). However, IGF-1 measurements correlate better than GH levels with clinical disease activity (22). And in patients with very mild disease IGF-1 is elevated while GH secretory parameters are virtually normal (23).

In the present study, only stored fasting serum was available for centralised analyses. Hence, central quality control was only possible for IGF-1 measurements and not for dynamic GH measurements (24). Therefore, and in accordance with the protocol, we primarily used IGF-1 as criteria for cure. This decision was also supported by the fact that in the general population both GH and IGF-1 levels decline with increasing age, while age adjusted reference values are available for the latter only (25).

The biochemical criteria for cure based on different commercial assays for GH and IGF-1 is presently a matter of debate (24,26). We set the primary endpoint ULN according to the age adjusted 95 percentile found by regression in our own laboratory. This might have induced a systematic error with respect to the ULN used. However, interassay variability was thereby reduced to a minimum, thereby optimising the evaluation of cure at a given level. The overall very low cure rate, however, might be

influenced by this method, but should not affect the difference between the two treatment arms. Moreover, additional analysis of cure rates according to ULN ranging from 95% to 120% of the values used in the present study all showed significant benefit in the group of pre-treated patients with macroadenomas. This way of presenting IGF-1 data is untraditional. Nevertheless, given the present discussion on the IGF-1 measurements and reference ranges, we believe this presentation is valuable in underlining that our results are relatively independent of the values for ULN used.

In the present study evaluation of cure was performed three months postoperatively which is in accordance with present clinical routine in Norway. This means that the patients were evaluated at least 12 weeks, but some as long as 16 weeks after the last injection with octreotide. Pharmacokinetic studies indicate that by that time levels of octreotide are well below therapeutic levels (27,28,29). Furthermore, withdrawal and dose extension studies indicate that in the great majority of patients octreotide effects has disappeared 12 weeks after the last injection (30,31,32). All though this does not quite fit with the present guidelines demanding at least four months delay in evaluation when using a long-acting SSA (33), this essentially rules out the possibility that the observed effect three months postoperatively, is only representing a “hangover” effect of pre-operative octreotide treatment.

Overall the cure rates observed in the POTA study were 23% in newly diagnosed acromegalic patients treated directly with transsphenoidal surgery and 45% in patients pretreated for six month with octreotide LAR and still being on treatment during the surgical procedure. In patients with macroadenomas, the cure rate tripled from 16% in direct surgery patients to 50% in octreotide pretreated patients. This effect was evenly distributed between the largest and the smaller study centers (data not shown). This is an impressive increase which is only possible when cure rates in control patients are low. And low overall cure rate in direct surgery patients (29.7%) was also

observed in one previous study indicating benefit of SSA pre-treatment before surgery (14). Thus, one intriguing question is whether the effect of pre-treatment with octreotide depends on the low cure rate seen in direct surgery patients in the present study. It should be emphasized that the low cure rate also reflects the strict criteria for cure used. Moreover, in a pragmatic multi-centre study like this one, overall cure rates are expected to be lower than results from a center of excellence. Low overall cure rate has recently been presented in the AcroBel study that also used strict criteria for cure (34).

It is interesting to observe the absolute numbers for patients with microadenomas. The results might indicate an adverse effect of pre-treatment. However, there were too few patients with microadenomas in the study to draw firm conclusions ($p = 0.52$). Nevertheless, this is an important clinical question, which should be explored in future studies.

Contrary to previously published observations indicating that treatment with a SSA tends to increase the softness of the adenomas this prospective randomized study showed a significant increase in the firmness of the adenomas. Hence, it is not likely that our findings depend on the open design and the possible awareness by the neurosurgeons of previous data indicating increased softness of the adenomas by SSA treatment (12).

If octreotide treatment increases the firmness of the adenoma, this might affect the surgical outcome negatively. However, we found no indication of an adverse effect of firm tumor consistency on surgical cure in micro- or macroadenomas (data not shown). One possible explanation is that SSA induced changes in tumor consistency might assist in the discrimination between the adenoma and surrounding tissue, including normal pituitary tissue, and thus, facilitate surgical cure. On the other hand a change in tumor consistency might be more pronounced with more prolonged treatment with SSAs. If so, this might evolve as a relative contraindication for long-term primary

octreotide treatment of acromegalic patients that later might be considered for pituitary surgery. Therefore, future studies should also aim to evaluate the optimum duration of preoperative SSA treatment.

In contrast with one previous report (14), pre-treatment with octreotide did not affect the duration of hospital stay. However, the standard care of pituitary surgery patients has changed markedly over the last decade which might have influenced the results. Further, we did not find any difference in surgical complication rates between the study groups.

Preliminary results from our study, based on local classification of tumor size and IGF-1 measurements, were presented at the European Congress of Endocrinology in Gothenburg in September 2005. No difference between study groups was reported. The discrepancies between these preliminary results and the final results are due to reclassification of initial tumor size and cure by centralized MRI and IGF-1 evaluations. These changes were mainly related to one study center. This emphasises the importance of central quality evaluation of data and measurements in multi-centre studies. This is illustrated by the discrepancy between locally and centrally measured IGF-1 levels which supports our decision to rely primarily on a centrally measured variable (Figure 1).

In conclusion, the POTA study indicates that pre-treatment with octreotide before transsphenoidal surgery improve surgical cure rates in patients with GH-secreting pituitary macroadenomas. The effect on microadenomas is inconclusive due to small numbers. Pre-treatment does not affect surgical complications or duration of hospital stay. These finding have to be confirmed by future well designed studies.

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Table 1. Baseline data according to treatment group

	Pretreatment* (n=32)	Direct surgery* (n=30)	P-value §
Age (years)	49.9 ± 13.8	45.1 ± 12.3	0.79
Gender (male/female) (no.)	20/12	11/19	0.042 [#]
Working status (working/sick leave) (no.)	20/12	16/14	0.47 [#]
GH nadir during OGTT (mcg/L)	19.3 ± 19.9	16.7 ± 13.2	0.55
IGF-1 (nmol/L)	92.1 ± 32.0	132.0 ± 60.3	0.004 ^{&}
IGF-1 (% of ULN)	326 ± 116	415 ± 222	0.056
Tumor classification (micro/macro) (no.)	6/26	5/25	0.83 [#]
Tumor volume (cm ³)	1.66 ± 1.38	1.96 ± 2.60	0.57

* Values given as means ± SDs if otherwise not stated

§ P-values given as independent samples t-tests used if otherwise not stated

[#] P-values given as two-sided Pearson Chi-Square tests

[&] This was also significantly different (p < 0.05) for both men and women

ULN = Upper Limit of Normal

Table 2. Cure according to IGF-1 \leq ULN and GH nadir \leq 2.0 mIU/L during OGTT three months postoperative.

	Treatment	According to IGF-1					According to IGF-1 and GH-nadir				
		N=	Cured	Not cured	P-value *	Cure (95% CI)	N=	Cured	Not cured	P-value *	Cure (95% CI)
All	Pretreatment	31	14	17		45% (27-64)	31	11	20		35% (19-55)
	Direct surgery	30	7	23	0.11	23% (10-42)	30	7	23	0.40	23% (10-42)
Microadenomas	Pretreatment	5	1	4		20% (1-72)	5	1	4		20% (1-72)
	Direct surgery	5	3	2	0.52	60% (5-95)	5	3	2	0.52	60% (5-95)
Macroadenomas	Pretreatment	26	13	13		50% (30-70)	26	10	16		38% (20-59)
	Direct surgery	25	4	21	0.017	16% (5-36)	25	4	21	0.12	16% (5-36)
All											
Center 1	Pretreatment	15	5	10		33% (12-62)	15	5	10		33% (12-62)
	Direct surgery	14	1	13	0.17	8% (2-34)	14	1	13	0.17	8% (2-34)
Center 2-5	Pretreatment	16	9	7		56% (30-80)	16	6	10		38% (15-65)
	Direct surgery	16	6	10	0.48	38% (15-65)	16	6	10	1.00	38% (15-65)

* P-value given as two-sided Fischer`s exact test for difference between treatment groups

ULN = Upper Limit of Normal

Table 3. Cure according to IGF-1 \leq ULN three months postoperative.

IGF-1 as percent of ULN	Treatment group	All			Microadenomas			Macroadenomas		
		Cured	Not cured	P-value	Cured	Not cured	P-value	Cured	Not cured	P-value
80 %	Pretreatment	8	23		0	5		8	18	
	Direct surgery	5	25	0.53	3	2	0.17	2	23	0.075
85 %	Pretreatment	9	22		0	5		9	17	
	Direct surgery	7	23	0.77	3	2	0.17	4	21	0.20
90 %	Pretreatment	11	20		1	4		10	16	
	Direct surgery	7	23	0.40	3	2	0.52	4	21	0.12
95 %	Pretreatment	13	18		1	4		12	14	
	Direct surgery	7	23	0.17	3	2	0.52	4	21	0.034
100 %	Pretreatment	14	17		1	4		13	13	
	Direct surgery	7	23	0.11	3	2	0.52	4	21	0.017
105 %	Pretreatment	15	16		1	4		14	12	
	Direct surgery	8	22	0.11	3	2	0.52	5	20	0.020
110 %	Pretreatment	15	16		1	4		14	12	
	Direct surgery	8	22	0.11	3	2	0.52	5	20	0.020
115 %	Pretreatment	16	15		1	4		15	11	
	Direct surgery	8	22	0.067	3	2	0.52	5	20	0.009
120%	Pretreatment	17	14		1	4		16	10	
	Direct surgery	10	20	0.12	3	2	0.52	7	18	0.025

* P-value given as two-sided Fischer`s exact test for difference between treatment groups
 ULN = Upper Limit of Normal

Figure 1. Bland-Altman plot of locally and centrally measured IGF-1 levels three months postoperatively

