Acromegaly : treatment and follow-up : the Leiden studies

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Direct postoperative and follow-up results of transsphenoidal surgery in 19 acromegalic patients pretreated with octreotide compared to those in untreated matched controls

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ABSTRACT

In this study 19 patients were preoperatively treated with octreotide for 1–17 months (mean, 5 months), with doses from 150–1500 µg daily, and those patients were matched to 19 untreated patients with comparable tumor classification and preoperative serum GH concentrations. Octreotide was started at 300 µg daily by sc injections or continuous sc infusion using a pump in increasing doses, depending on the responses of the serum GH and insulin-like growth factor I (IGF-I) concentrations. During pretreatment, seven patients achieved a serum GH concentration below 5 mU/L, whereas six patients normalized their serum IGF-I.

Postoperatively, a serum GH concentration below 5 mU/L was achieved in 15 pretreated and 14 untreated patients, a normal serum IGF-I level (<2 SD) was achieved in 10 pretreated and 15 untreated patients, and normal serum GH suppression during GTT was reached in 12 treated and 14 control patients. No differences were found in complication rate or incidence of hypopituitarism caused by surgery.

Adjuvant therapy was required in 7 treated and 5 untreated patients. At follow-up examination, 5.7 and 4 yr postoperatively, 10 pretreated and 12 control patients could be considered cured by surgery only, according to our criteria for remission (serum GH, <5 mU/L; normal GH suppression and normal serum IGF-I). In summary, we found no difference in direct postoperative and follow-up results of transsphenoidal surgery between pretreated patients and untreated patients. This finding is in discordance with other studies, which have claimed a beneficial effect of octreotide pretreatment.

INTRODUCTION

TRANSSPHENOIDAL SURGERY USING MICROSURGICAL TECHNIQUES is accepted as the treatment of choice for GH-secreting pituitary adenomas; surgical cure rates in the literature range from 30–75% depending on the criteria used. Those results are more favorable for microadenomas (±70%) than for invasive macroadenomas (45%). Tumor size has been found to be a preoperative prognostic factor (1). Another preoperative factor that has been claimed to predict outcome after surgery is the preoperative GH level (2). The importance of reducing GH levels to normal was emphasized by Bates et al., who found a higher mortality rate in a group with elevated GH levels compared with that in a group with GH levels below 5 mU/L (3).

Octreotide, a long acting somatostatin analog, is effective in suppressing GH and insulin-like growth factor I (IGF-I) concentrations in most acromegalic patients. Its use is established as an alternative of postoperative radiation therapy or in combination with radiation therapy while awaiting the long term effect of irradiation (4).

Several advantages of preoperative treatment with octreotide have been reported to date. It relieved symptoms (5) and signs, for example blood pressure and glucose intolerance preoperatively (6), thereby facilitating anesthesia management. Stevenaert et al. (5) in a non-controlled study claimed that octreotide treatment was effective in softening adenomatous tissue, facilitating surgical removal. Most studies showed a variable amount and incidence of shrinkage of the tumor mass during preoperative octreotide treatment (5 – 11), whereas the study of Spinas et al. did not (12). Stevenaert et al. reported improved postoperative results in patients with enclosed adenoma (5). Barkan et al. found improved surgical results for their patients with invasive macroadenomas (8), as did others (9, 10). Colao et al. reported improved surgical outcome for pretreated patients regardless of tumor size (6).

As most reported studies were rather small and were made in retrospect, we devised a prospective study in which not only direct postoperative results but also long term results were evaluated. The criteria we applied for cure are in line with generally accepted rules, i.e. random GH below 5 mU/L, glucose-suppressed GH values based on validated normal values in healthy controls, and normal serum IGF-I concentrations. We also aimed to investigate whether there were differences in the incidence of (surgical) complications, hypopituitarism, or duration of neurosurgical hospital stay.

SUBJECT AND METHODS

Patients

Between 1988 and 1996, 57 acromegalic patients were referred to the Leiden University Medical Center for evaluation and treatment. Presurgical treatment with octreotide was of-

fered to all patients, and after full explanation of the aim of the study and the possible effects and side-effects of octreotide treatment, 19 patients agreed to pretreatment.

These patients (10 males and 9 females) were compared to 19 nontreated patients selected from the above-mentioned group of 57 patients. Those patients were matched individually to the pretreated group primarily by tumor class and grade and secondarily by preoperative GH concentration. The mode of administration of octreotide, either by 3 daily sc injections or by continuous sc infusion, depended on the fully informed patient's preference.

Octreotide treatment was started at a daily dose of 300 µg, and treatment was evaluated by measuring GH levels. The dose was increased or decreased as necessary depending on the GH concentration; individual doses ranged from 150–1500 µg daily, the mean daily dose was 529 ± 83 µg. GH and IGF-I concentrations were obtained at 1, 3, and 4 months after the start of treatment. Nine patients were treated by a continuous infusion pump, 9 other patients received sc injections 3 times daily, and 1 patient received both administration routes during the preoperative period. Treatment was discontinued the day before surgery, the mean duration of pretreatment was 5.2 ± 0.8 months (range, 1–17 months). The mean age of the pretreated patient group was 39.3 ± 9 yr (range, 19–52 yr). One of the patients had undergone transsphenoidal surgery 3 yr previously in Turkey. None of the other patients had been previously treated with irradiation or surgery. Nineteen patients (11 males and 8 females) were matched to the octreotide-treated patients by tumor classification and preoperative mean GH level. Their mean age was 47.7 ± 15.6 yr (range, 25–77 yr).

All patients underwent an endocrine assessment preoperatively, including a serum GH profile (blood samples taken at 0800, 1130, 1630, and 2300 h), a 75-g oral glucose loading test (blood samples taken at 0, 30, 60, 90, and 120 min), and a 200-µg iv TRH test (blood samples taken at 0, 20, and 60 min), and pretreated patients underwent a 50-µg iv octreotide test, with samples taken every 30 min during 3 h. During the octreotide test, the lowest GH level was taken as the minimal value. The minimal value during this test was also expressed as a percentage of the starting GH value.

Other pituitary functions were evaluated by specific pituitary stimulation tests (LHRH, TRH, and CRH tests) and by measurement of serum testosterone, estradiol, cortisol, T_4, and IGF-I. Postoperative hormonal evaluation was performed 7–10 days after surgery by repeating the glucose tolerance (GTT) and TRH tests and measuring the IGF-I concentration and other pituitary reserve functions. At yearly follow-up visits, the GTT and measurements of mean GH and IGF-I concentrations were repeated, and evaluation of other pituitary functions was also performed. In this study the most recent hormonal investigations were used as follow-up results. Group characteristics are shown in Table 1.

All patients underwent magnetic resonance imaging scanning of the sellar region. Adenomas were classified as microadenoma (<1 cm), macroadenoma (>1 cm), or invasive adenoma (into the sellafloor, parasellar extension, or growth into the cavernous sinus).

Table 1. Preoperative data of 19 pretreated and 19 untreated patients

	Pretreated patients	Untreated patients	P value
Tumour classification			
Microadenoma	5	5	
Macroadenoma	8	8	
Invasive adenoma	6	6	
Preoperative GH-level (mU/L)	80.6 ± 19.3	69.3 ± 21.6	0.62
Preoperative IGF-I (nmol/L)	64.6 ± 4.6	47.6 ± 3.1	< 0.001
Age (yr)	39.3 ± 9.0	47.6 ± 3.6	0.052

Transsphenoidal surgery was performed by the same neurosurgeon (H.v.D.). Postoperatively, patients stayed on the neurosurgical ward for 6–9 days. Thereafter, they were transferred to the endocrinological ward, where the postoperative tests were performed.

The protocol was performed in accordance with the guidelines of the Declaration of Helsinki for human experimental studies. Informed consent was obtained from all patients.

Assays

Before 1992, serum GH was measured by RIA (Biolab/Serono, Coinsins, Switzerland) calibrated against WHO International Reference Preparation 66/217 (1 ng/ml = 2 mU/L); after 1992, it was measured with a time-resolved immunofluorometric GH assay specific for 22-kDa GH protein (Wallac, Inc., Turku, Finland) with a standard human biosynthetic GH calibrated against WHO International Reference Preparation 80–505 (1 ng/ml = 2.6 mU/L). A mean serum GH concentration of less than 5 mU/L was considered normal. GH suppression during GTT was defined as the minimal GH level during the test. Normal values for GH suppression, obtained from a group of healthy controls were less than 2.5 mU/L (RIA) and less than 1 mU/L (immunofluorometric assay).

Serum IGF-I was measured by RIA (INCSTAR Corp., Stillwater, MN); the limit of detection was 1.5 nmol/L. IGF-I levels were expressed as the SD score, depending on age-related normal values. An IGF-I SD score less than +2 SD was considered normal. Other hormones (T_4, cortisol, estradiol, testosterone, LH, FSH, PRL, TSH, and ACTH) were measured with time-resolved immunofluorometric assays. (Wallac, Inc.) or commercially available RIAs.

Statistics

Calculations were performed using SPSS Windows version 6.0 (SPSS, Inc., Chicago, IL), using Student's t (paired), χ^2, and ANOVA tests. Data were reported as the mean ± SEM (range), unless otherwise mentioned. $P < 0.05$ was considered significant.

RESULTS

The mean preoperative serum GH level in the pretreated group was 80.6 ± 19.3 (range, 8.4–355) mU/L compared to 69.3 ± 21.6 (range, 6.6–435) mU/L in the untreated group (P = 0.62; Table 1 and Fig. 1). In the pretreated group, five patients had microadenoma, eight patients noninvasive macroadenoma (2^0, n = 2; 2^A, n = 4; 2^B, n = 2), and six patients an invasive macroadenoma (3^A, n = 1; 4^E, n = 3; 2^E, n = 2). The untreated group had the following tumor classification: five patients microadenoma, eight patients had noninvasive macroadenoma (2^0, n = 3; 2^A, n = 4; 2^B, n = 1), and six patients had invasive adenomas (2^E, n = 2; 3^0, n = 1; 3^A, n = 1; 3^E, n = 1; 4^{DE}, n = 1). The mean preoperative serum IGF-I levels were 64.6 ± 4.6 nmol/L in the treated patients and 47.6 ± 3.1 nmol/L in the untreated patients (P < 0.001; see Fig. 2). Expressed as SD scores, these were 8.4 ± 0.9 and 5.5 ± 0.6 (P < 0.001), respectively (Fig. 3).

An octreotide test was performed in 17 treated patients. During this test, serum GH levels decreased from a mean basal level of 103 ± 32.9 (range, 8.5–480) mU/L to a mean suppressed serum GH level of 26.3 ± 12.6 (range, 1.2–200) mU/L. This was a mean decrease to 20 ± 3.5% (range, 5.4–52%) of the basal serum GH concentration at the beginning of the test. Eight of 17 patients (47%) reached a normal suppressed GH concentration (<5 mU/L) during this test. As expected, there was a strong correlation between the basal serum GH concentration and the minimal GH concentration during the octreotide test (r = 0.86; P < 0.001).

During octreotide treatment the serum GH concentration decreased in all patients except 1. The minimal serum GH concentration reached during octreotide treatment (at 1, 3, or 4 months of treatment) was 21.0 ± 6.8 mU/L (range, 1.8–106 mU/L) compared to 80.6 ± 19.3 mU/L before the start of treatment (P = 0.003) This was a decrease to 30.6 ± 6.8% (range, 2.2–121%) of the pretreatment value. Ten patients did have serum GH levels below 10 mU/L; 7 patients had values below 5 mU/L. The mean serum IGF-I concentration decreased from 63.7 ± 4.9 to 42.3 ± 6.6 nmol/L (range, 5.7–116; P = 0.001). Six patients (32%) reached a normal IGF-I SD score, of whom 3 patients also had a normal GH level. In the untreated group the serum GH concentration did not change significantly during the preoperative period, i.e. 83.3 ± 28.5 and 71.3 ± 18 mU/L in 15 of 19 control patients with GH concentrations measured at 2 time points preoperatively (P = 0.332). The mean duration from the first visit to the Leiden University Medical Center to operation was 4.3 ± 0.8 months.

Postoperative mean serum GH concentrations were 7.11 ± 2.23 mU/L in the treated patients and 5.99 ± 2.09 mU/L in the untreated group (P = 0.72; Table 2 and Fig. 1). The mean glucose-suppressed GH concentration was 3.16 ± 1.08 mU/L in pretreated patients and 3.16 ± 1.46 mU/L in control patients (P = 0.99). The mean serum IGF-I concentrations were 31 ± 2.4 and 24.3 ± 2.0 nmol/L, respectively (P = 0.037; Fig. 2), and mean IGF-I SD scores were 2.0 ± 0.4 and 1.0 ± 0.37, respectively (P = 0.07; Fig. 3).

In terms of normalization, direct postoperative results were as follows. Serum GH concentrations were less than 5 mU/L in 15 treated and 14 untreated patients (P = 0.7). A normal

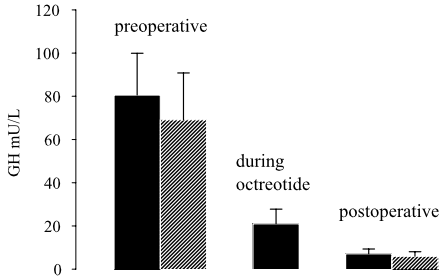

Figure 1. Mean GH concentrations (±SEM) at preoperative evaluation (pretreated and untreated patients), during octreotide treatment (pretreated patients), and directly postoperatively (pretreated and untreated patients). *Black bars*, Octreotide-treated patients; *hatched bars*, untreated patients.

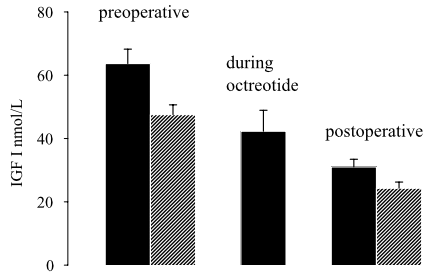

Figure 2. Mean IGF-I concentrations (±SEM) at preoperative evaluation (pretreated and untreated patients), during octreotide (pretreated patients), and directly postoperatively (pretreated and untreated patients). *Black bars*, Octreotide-treated patients; *hatched bars*, untreated patients.

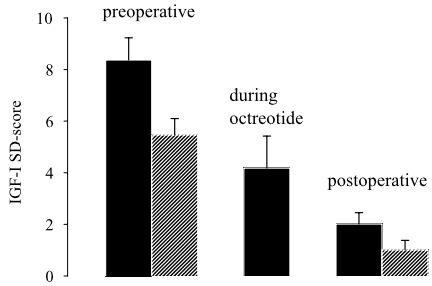

Figure 3. Mean IGF-I SD score (±SEM) at preoperative evaluation (pretreated and untreated patients), during octreotide treatment (pretreated patients), and directly postoperatively (pretreated and untreated patients). *Black bars*, Octreotide-treated patients; *hatched bars*, untreated patients.

suppression of serum GH during GTT was achieved in 12 treated patients and 14 untreated patients (P = 0.5). The IGF-I SD score normalized in 10 treated and 15 untreated patients (P = 0.08).

During follow-up, seven pretreated and five untreated patients required adjuvant therapy. Radiotherapy was given to six pretreated patients and three untreated controls; postoperative octreotide therapy was given to one pretreated patient and two untreated patients. In

Table 2. Direct postoperative results

	Pretreated patients	Untreated patients	P value
Random GH< 5 mU/L (%)	15/19(79%)	14/19(74%)	0.7
Normal GH-suppression (%)	12/19(63%)	14/19(74%)	0.5
Normal IGF-I SD-score (%)	10/19(53%)	15/19(79%)	0.08
Mean GH (mU/L)	7.11 ± 2.23	5.99 ± 2.09	0.72
Mean suppressed GH (mU/L)[1]	3.16 ± 1.08	3.16 ± 1.46	0.99
Mean IGF-I (nmol/L)	31.00 ± 2.44	24.28 ± 1.96	0.037

[1] Normal values of suppressed GH during GTT are below 2.5 mU/L before 1993 (RIA-assay) and below 1 mU/L thereafter (IFMA-assay).

addition, two pretreated patients and one untreated patient received octreotide therapy in combination with radiotherapy.

After a follow-up period of 5.7 ± 0.5 yr (treated group) and 4.0 ± 0.6 yr (untreated group), 13 of 17 pretreated patients had normal suppression during GTT compared to 13 of 17 untreated patients (P = 1.0; see Table 3). A GTT was not performed in 2 pretreated patients or 2 control patients because of obvious active disease or postoperative octreotide therapy in 2 pretreated and 1 untreated patients and because of diabetes mellitus in 1 untreated patient. The serum GH concentration was less than 5 mU/L in 15 pretreated patients and 16 control patients (P = 0.7). The mean serum GH concentration was 2.75 ± 0.85 mU/L in the pretreated group and 3.31 ± 0.83 mU/L in the untreated group (P = 0.65). The IGF-I SD score normalized in 17 pretreated and 18 untreated patients (P = 0.5). When irradiated and medically treated patients were excluded from this analysis, a normal GH suppression during GTT was achieved in 10 of 12 treated patients and 12 of 13 evaluable untreated patients (1 omitted because of overt diabetes mellitus; P = 0.82). A serum GH concentration below 5 mU/L was present in 9 of 12 pretreated and 13 of 14 control patients (P = 0.2). IGF-I SD scores normalized in 12 of 12 pretreated patients and 13 of 14 control patients (P = 0.3). As expected, surgical cure rates were higher in microadenomas (90%) and noninvasive macroadenomas (75%) than in invasive macroadenomas (17%) group (P = 0.01; data summarized in Table 4).

The mean duration of stay on the neurosurgical ward postoperatively was not significantly different between pretreated and untreated patients, i.e. 8.2 (median 8) and 7.1 (median 7) days, respectively (P = 0.06). Hormone substitution for (pan)hypopituitarism caused by surgery was necessary for two patients in each group.

Complications of surgery were reoperation for persistent cerebrospinal fluid rhinorrhea (one pretreated patient), meningitis (one pretreated patient), and temporary cerebrospinal fluid rhinorrhea (one pretreated patient).

Table 3. Follow-up results of 19 pretreated and 19 untreated patients

	Pretreated patients	Untreated patients	P value
Postoperative radiotherapy	6	3	
Postoperative medical therapy	1	2	
Follow-up period (yr)	5.7 ± 0.5	4.0 ± 0.6	
Random GH < 5 mU/L (%)	15/19(79%)	16/19 (84%)	0.7
Normal GH-suppresion (%) [1]	13/17(76%)[2]	13/17(76%)[2]	1.0
Normal IGF-I SD-score (%)	17/19(89%)	18/19 (95%)	0.6

[1] Normal values of suppressed GH during GTT are below 2.5 mU/L before 1993 (RIA-assay) and below 1 mU/L thereafter (IFMA-assay).
[2] Follow-up GTT not performed in 2 pretreated and 2 untreated patients

Table 4. Postoperative and follow-up results for micoadenomas, non-invasive macroadenomas and invasive adenomas; follow-up results include adjuvant treated patients.

	Microadenoma		Macroadenoma		Invasive	
	Pretreated	Untreated	Pretreated	Untreated	Pretreated	Untreated
Postoperative						
GH<5 mU/L	4/5	5/5	7/8	5/8	3/6	4/6
Normal GH suppression (GTT) [1]	4/5	5/5	7/8	6/8	2/6	4/6
Follow-up						
Adjuvant therapy						
RT	1		1	1	4	1
MT					1	2
GH<5mU/L	3/5	5/5	8/8	8/8	4/6	3/6
Normal GH suppression (GTT) [1]	4/5	5/5	6/8	6/7 (1missing)	2/5 (1 missing)	2/5 (1 missing)

MT, postoperative octreotide therapy; RT, radiotherapy.
[1] Normal values of suppressed GH during GTT are < 2.5 mU/L before 1993 (RIA-assay) and < 1 mU/L thereafter (IFMA-assay).

DISCUSSION

In our group of 19 pretreated acromegalic patients, octreotide suppressed the mean GH concentration to 30% of the pretreatment value. However, a "safe" GH concentration, i.e. below 5 mU/L according to Bates et al. (3), was only reached in 7 patients (37%). In 1 patient, octreotide failed to suppress the GH concentration even at a maximum daily dose of 1500 µg. The small percentage of patients reaching a GH concentration below 5 mU/L was also reported by others (5, 12). Stevenaert et al. (5) reported normalization of GH (<4 mU/L) in 3 of 14 short term treated patients and 25 of 50 patients treated longer than 3 months, and Spinas et al. (12) reported that 2 of 5 patients reached a GH concentration below 10 mU/L. Like other studies, IGF-I in our pretreated patients decreased significantly during octreotide therapy, reaching normalized values in 32% (6, 10). This percentage was somewhat lower than that reported by others. Plockinger et al. (10) reported normalization of serum IGF-I concentration in 50%, and Colao et al. (6) reported normalization in 55% of their pretreated

patients. We did not measure clinical parameters during octreotide therapy, as was done by others (5, 6, 12). Amelioration of signs and symptoms was claimed to facilitate anesthesia (5). Colao et al. (6) reported a decreased blood pressure and an improved glucose profile during octreotide treatment, thereby possibly reducing surgical risk and resulting in a shorter stay in the hospital. In our patients we found a low complication rate, with no clinical difference between groups. In addition, the length of stay on the neurosurgical ward was not significantly different between treated and untreated patients.

Because of logistic restrictions we could not repeat the magnetic resonance imaging scan of the sellar fossa preoperatively to evaluate the effect of octreotide treatment on tumor size. This effect was carefully investigated by others (5, 6, 8, 10). Plockinger et al. (10) found a tumor size reduction of 20–54% in 5 of 10 pretreated patients regardless of plasma GH response or receptor status of the adenomas. Barkan et al. (8) reported tumor reduction of 20–54% in all of their patients (n = 10), whereas Stevenaert et al. (5) reported a size reduction of more than 25% in 14 of 48 patients treated for more than 3 months. Colao et al. (6) reported tumor reduction of more than 30% in 5 of 22 pretreated patients. Generally, the first sign of tumor shrinkage was already seen at 1 week of octreotide therapy (8, 10), whereas maximal tumor shrinkage was reached in 3 months according to Stevenaert et al. (5) and Barkan et al. (8). The duration of treatment in our patients should be sufficient to attain tumor shrinkage.

Direct postoperative results in the present study were not significantly different between pretreated and untreated patients. A serum GH concentration below 5 mU/L was reached in 79% of pretreated patients and 74% of untreated patients, normalization of GH suppression was achieved in 63% and 74%, respectively, and normalization of serum IGF-I concentration occurred in 53% and 79% respectively. These criteria are stricter than those used by others, except for the studies by Stevenaert et al. (5) and Plockinger et al. (10). Direct postoperative results in this study were significantly better for microadenomas than for invasive adenomas, which is in accordance with the results of a large series of transsphenoidally operated acromegalic patients, recently summarized by Lissett et al. (13). When the different tumor classes were compared, we could not demonstrate a significant difference between treated and untreated cases for microadenomas, macroadenomas, and invasive adenomas. However, the number of patients in the different tumor groups was small. Looking at a group of 10 patients with invasive macroadenomas, Lucas et al. (9) found a remission rate of 60% using remission criteria of suppressed GH below 4 mU/L and normalization of IGF-I concentration, which was better than that in untreated cases from their own experience (28%) or from the literature. Barkan et al. (8) found a remission rate of 80% in the treated group of 10 patients with invasive macroadenomas compared to 31% in a comparable untreated group, using the criterion of random GH concentration below 10 mU/L. Plockinger et al. (10), studying 10 patients with macroadenomas, found a remission rate of 60% in the pretreated group, using glucose-suppressed GH levels below 2 mU/L as a remission criterion. Colao et al. (6) found a significantly better postoperative result regardless of tumor size in 22 pretreated patients

(54%) compared to 37 untreated patients (30%) using the liberal criterion of GH concentration below 10 mU/L and normalization of IGF-I. Stevenaert et al. (5) reported a significantly higher remission rate in pretreated patients with enclosed adenomas of 94% compared to 74% in the untreated group using strict criteria, i.e. GH concentration below 4 mU/L, suppressed GH below 2 mU/L, and normalization of IGF-I. The difference in results is difficult to explain. Although most researchers found better results in pretreated patients with (invasive) macroadenoma, the large series of Stevenaert only found better results in microadenoma patients, whereas we could not demonstrate a difference at all.

Admittedly, the selection of patients differs among these studies, with regard to previous therapy, medical treatment (octreotide dose and duration), criteria for remission, etc. On the other hand, GH suppression, tumor shrinkage, and clinical improvement do occur early in the treatment with octreotide, so this effect might be comparable in the different studies. Another influence on the results of octreotide pretreatment is probably related to the á priori chance of reaching remission by surgery alone, leaving variable additional value for octreotide. Surgical results do vary between series (13, 14). In our follow-up data at 5.7 and 4 yr, respectively, both groups had the same remission rate, without a significant difference in requirement for adjuvant treatment or pituitary substitution therapy. No other follow-up study was reported, except for Colao et al. (6); their remission rate at 1 yr was identical to their direct postoperative results (25 of 37 untreated patients vs. 12 of 22 pretreated patients).

In summary, we could not demonstrate a difference in outcome between pretreated and untreated patients, either directly postoperatively or at follow-up examination.

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