Presurgical treatment with somatostatin analogs in patients with acromegaly: effects on the remission and complication rates

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Object. The question of whether preoperative therapy with somatostatin analogs can improve surgical outcome in acromegaly has not been definitively answered. In this paper, the authors report the effects of preoperative treatment with somatostatin analogs in a large sample of patients with acromegaly.

Methods. Between 1990 and 2003, 399 consecutive patients with acromegaly underwent surgery at the Istituto Scientifico San Raffaele. Thirty-three patients who had previously undergone surgery or radiation treatment, 48 patients treated with somatostatin analogs for fewer than 3 months, and patients who had stopped therapy for too long a time before surgery were excluded from the study. One hundred forty-three patients who had received somatostatin analogs prior to surgery (Group 1) were randomly matched to 143 patients who had never been treated with somatostatin analogs (Group 2). Matching criteria were tumor size and invasiveness into the cavernous sinus. Before surgery, Group 1 patients showed reduction of growth hormone levels to less than 50% of baseline in 64% of cases, but insulin-like growth factor–I was normalized in only 19.5%. Surgical remission occurred in 81 Group 1 patients (56.6%) and in 91 Group 2 patients (63.6%; p = 0.28). No significant difference in the remission rate was observed when cases were analyzed according to tumor size or invasiveness. Logistic regression analysis confirmed that pretreatment with somatostatin analogs was not associated with surgical outcome. Surgical morbidity was mild and similar in Group 1 and Group 2 patients (7 and 5.6%, respectively; p = 0.81). Surgical remission and complication rates in patients with acromegaly who received treatment with somatostatin analogs prior to surgery were not significantly different from those of matched patients who did not receive these agents.

Conclusions. At present, the routine use of presurgical therapy with somatostatin analogs for patients with acromegaly cannot be recommended.

Key Words • pituitary surgery • pituitary neoplasm • growth hormone • somatostatin analogs • acromegaly

Acromegaly is usually caused by a GH-secreting pituitary adenoma and is associated with elevated levels of GH and its peripheral mediator, IGF-I. If untreated, acromegaly is associated with severe morbidity and an almost doubled risk of death. However, restoration of normal GH secretion by different treatment modalities improves the adverse prognosis and increases the life expectancy of patients with acromegaly.

There is wide consensus that transsphenoidal surgery is the first treatment choice for patients with acromegaly, except in select patients for whom there is an unacceptable anesthesia-related risk. In the hands of an experienced neurosurgeon, the rate of surgical remission is approximately 60%. On the other hand, the advent of highly effective somatostatin analogs, such as octreotide and lanreotide, has caused medical therapy to assume a more prominent role in the treatment strategy for acromegaly. Somatostatin analogs not only inhibit GH secretion, but also reduce tumor size in patients who did not receive these agents prior to surgery, even though the degree of tumor shrinkage is marginal in most cases. It is likely that the positive effect on tumor size is driven by direct antiproliferative activity of somatostatin analogs on adenomatous GH-secreting cells.

The question of whether preoperative therapy with somatostatin analogs can improve surgical outcome in acromegaly has not been definitively answered. The beneficial effects of preoperative medical treatment with octreotide have been proven in one study, suggested but not proven in some, and not proven at all in others. Moreover, methodological drawbacks, especially those related to small
sample size, weaken the conclusions of most studies.²⁴ No information is available regarding the effects of preoperative treatment with the long-acting formulations of somatostatin, that is, octreotide LAR and lanreotide, as all previous studies have used octreotide sc only.

The aim of this retrospective, case–match study was to report the effects of preoperative treatment with different somatostatin analogs on the results of surgery in a large series of patients with acromegaly who underwent surgery at a single center.

**Clinical Material and Methods**

*Patient Selection*

Between 1990 and 2003, 399 consecutive patients with acromegaly were referred to the Department of Neurosurgery of the Istituto Scientifico San Raffaele in Milan, Italy, for surgical removal of pituitary adenoma (Fig. 1). Diagnosis of active acromegaly was based on the clinical picture, demonstration of GH and IGF-I hypersecretion, and a pituitary tumor visualized using MR imaging. After the exclusion of patients who had previously undergone pituitary surgery (31 patients) or radiotherapy (two patients), 366 remained available for inclusion in the study. Among these patients, we identified 191 who had received therapy with somatostatin analogs before surgery (Group 1; Fig. 1). In most cases, the referring endocrinologist decided whether to initiate therapy with somatostatin analogs. There were patients in this group who were then excluded from the study for the following reasons: 1) The duration of somatostatin analog therapy was less than 3 months (16 patients); 2) The patient had stopped taking somatostatin analogs for more than 10 days before surgery in the case of octreotide sc, more than 2 months in the case of lanreotide 30 mg, or more than 3 months in the case of octreotide LAR or lanreotide 60 mg (32 patients).

A total of 175 patients, who had not undergone treatment with any somatostatin analog before surgery, underwent surgery in our department during the study period (Group 2; Fig. 1). Group 1 patients were then individually matched to Group 2 patients. To this end, Group 2 patients were pooled according to the matching criteria and then selected randomly. Matching criteria were tumor size (defined as micro- or macroadenoma) and invasion of the cavernous sinus (yes or no), as judged using MR imaging. Classification of tumor characteristics for Group 1 patients was based on the MR imaging studies performed at the time of diagnosis, before the start of somatostatin therapy. Tumors were considered invasive into the cavernous sinus when they corresponded to Grade 3 or 4 of the classification of Knosp and coworkers.²⁹ Tumor volume was calculated using the following formula: volume = 0.5 × anteroposterior × vertical × horizontal dimensions. Given the irregular shape of some tumors, volume measurement should be considered only a rough estimate of real tumor volume.

Tumor shrinkage was defined as a reduction of at least 2 mm in the greatest diameter on a posttreatment MR image,²² which was available for review in 78 patients. Occurrence of operative and perioperative morbidity as well as evaluation of pituitary function were prospectively recorded for each patient.

**Transsphenoidal Surgery and Histological Analysis**

Transsphenoidal surgery was performed in all patients by two surgeons (P.M. and M.G.). The operative technique has been described in detail elsewhere.²⁷ Surgically removed specimens were immediately fixed in 10% buffered formalin and subsequently embedded in paraffin. Standard H & E–stained sections were used for diagnosis. Tumors were further characterized for their secretory activity by immunocytochemical analysis with the aid of commercially available antisera, as previously described.²⁵

**Assays and Remission Criteria**

Serum GH, IGF-I, and PRL concentrations at diagnosis, during somatostatin analog therapy, and 4 to 6 months after surgery were measured by the referring endocrinologist at a large number of laboratories that use different assay kits. For patients in whom acromegaly was diagnosed and who underwent follow up in our hospital, serum GH levels before 1994 were measured using a commercially available radioimmunoassay; levels from 1994 to the present were measured with an immunofluorimetric assay (Tosoh, Tokyo, Japan) specific for the 22K GH moiety. Serum PRL levels were determined using commercially available immunoenzymatic assay (Immuno1; Bayer Corp., Divisione Diagnostici, Milan, Italy). Serum IGF-I levels were measured by a specific commercially available radioimmunoassay (Bioclone, Marrickville, Australia) after acid extraction. Criteria for postsurgical cure were those suggested in a consensus conference,²⁷ with the exception that, when GH levels were measured by an assay not specific for the 22K moiety of GH, the cutoff for a normal GH level during an oral glucose tolerance test was set at 2 μg/L.

To avoid misclassification of surgical outcome as a result of prolonged inhibition of GH secretion induced by somatostatin analogs, we classified Group 1 patients on the basis of

![Fig. 1. Flowchart of the study design. “Pretreated” denotes patients who received somatostatin analogs before surgery (Group 1); “untreated” denotes patients who had not been treated with somatostatin analogs before surgery (Group 2). Group 1 patients were required to have stopped somatostatin analogs for at least 3 months and to have stopped the drug no later than 10 days in the case of octreotide sc, 2 months in the case of lanreotide 30 mg, or 3 months in the case of octreotide LAR and lanreotide 60 mg.](attachment:image.png)
Presurgical therapy with somatostatin analogs

hormonal evaluation performed at least 4 months after surgery.

Statistical Analysis

Continuous data were examined for homogeneity of variance. Because the distributions of GH and PRL levels before surgery were markedly skewed, we performed logarithmic transformation of the data. However, GH and PRL levels are presented in the usual decimal format in the text and figures. Continuous data are expressed as means ± SEMs, except for GH and PRL levels, which are presented as median values and interquartile ranges. A t-test for unpaired data was used to compare continuous variables among groups. Chi-square tabulation with Yates correction was used to compare binomial proportions. Multiple logistic regression analysis was used to determine which variables independently predicted surgical remission of acromegaly. A probability value less than 0.05 was considered to indicate statistical significance, and all reported probability values are two-tailed. All calculations were performed using the statistical package StatView 5.0 (SAS Institute, Cary, NC).

Results

Characteristics of Group 1 and Group 2 Patients

One hundred forty-three consecutive patients with acromegaly (73 female, 70 male) had been treated with somatostatin analogs before surgery. Sixty (41.9%) had received octreotide sc, 46 (32.2%) had received octreotide LAR, and the remaining 37 (25.9%) had received lanreotide. The estimated mean total dose of drug received by the patients before surgery was 181 ± 33 mg octreotide sc, 573 ± 136 mg octreotide LAR, and 1012 ± 216 mg lanreotide. The mean duration of drug therapy before surgery was 16 ± 2, 17 ± 3, and 13 ± 2 months for octreotide sc, octreotide LAR, and lanreotide, respectively (p = 0.50). The mean period of drug withdrawal before surgery was 3.5 ± 0.4 days for octreotide sc, 32.3 ± 3.0 days for octreotide LAR, and 27.5 ± 3.6 days for lanreotide. Treatment with somatostatin analogs reduced the basal GH level by more than 50% of the pretreatment value in 56.8, 72.7, and 60.6% of patients who received octreotide sc, octreotide LAR, and lanreotide, respectively (p = 0.29). However, normalization of IGF-I during medical treatment was achieved in only 18.4, 19.6, and 20.6% of patients treated with octreotide sc, octreotide LAR, and lanreotide, respectively (p = 0.96). Magnetic resonance imaging studies obtained during treatment with somatostatin analogs showed a reduction of tumor diameter greater than 2 mm compared with MR images obtained prior to treatment with these agents in 31.4, 37.9, and 23.1% of patients treated with octreotide sc, octreotide LAR, and lanreotide, respectively (p = 0.63). Patients in Group 1 did not significantly differ in any of the aforementioned characteristics from the other 48 patients who were treated with somatostatin analogs but excluded from the study (data not shown).

One hundred forty-three Group 2 (82 female and 61 male) patients were randomly matched to those in Group 1 according to tumor size (microadenoma or macroadenoma) and invasiveness into the cavernous sinus (yes or no). Clinical and demographic characteristics of all patients are summarized in Table 1. As expected on the basis of the study design, the number of patients with macroadenoma as well as invasion into the cavernous sinus was equal in the two groups. Moreover, other characteristics that had not been used for matching, such as mean age at surgery, sex distribution, history of dopaminergic therapy, median basal GH and PRL levels at diagnosis, invasion of sphenoid sinus, and presence of diabetes mellitus and hypertension at diagnosis did not significantly differ between the two groups (Table 1). The only exception was the mean tumor volume at diagnosis, which was significantly lower in Group 1 patients compared with Group 2 patients.

One surgeon (Surgeon 1) performed 208 surgical procedures (72.7%; 106 in Group 1 and 102 in Group 2), and the other (Surgeon 2) performed the remaining 78 procedures (27.3%; 37 in Group 1 and 41 in Group 2).

Surgical Remission

Surgical remission of acromegaly, defined according to the criteria outlined in Clinical Material and Methods, was achieved in 172 of the 286 patients included in the study (60.1%; Table 2). No significant difference in surgical results was observed according to the surgeon who performed the surgical procedure (remission rate of Surgeons 1 and 2, 62.5 and 53.8%, respectively; p = 0.23). Normalization of GH secretion occurred in 81 patients in Group 1 (56.6%) and in 91 Group 2 patients (63.6%, p = 0.28). Surgical remission was achieved in 37 (61.7%) of 60, 24 (52.2%) of 46, and 20 (54%) of 37 patients in Group 1 who were treated with octreotide sc, octreotide LAR, and lanreotide.

TABLE 1

Clinical and hormonal characteristics of 286 patients with acromegaly according to preoperative treatment with somatostatin analogs*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean age ± SEM (yrs)</td>
<td>45.0 ± 1.1</td>
<td>43.9 ± 1.2</td>
<td>0.52</td>
</tr>
<tr>
<td>no. of patients (%)</td>
<td>70 (48.9)</td>
<td>82 (57.3)</td>
<td>0.19</td>
</tr>
<tr>
<td>female</td>
<td>23 (16.1)</td>
<td>25 (17.5)</td>
<td>0.87</td>
</tr>
<tr>
<td>previous dopaminergic therapy</td>
<td>125 (87.4)</td>
<td>125 (87.4)</td>
<td>NA</td>
</tr>
<tr>
<td>macroadenomas†</td>
<td>32 (22.4)</td>
<td>32 (22.4)</td>
<td>NA</td>
</tr>
<tr>
<td>cavernous sinus invasion‡</td>
<td>19 (13.3)</td>
<td>26 (18.2)</td>
<td>0.33</td>
</tr>
<tr>
<td>sphenoid sinus invasion</td>
<td>23 (16.1)</td>
<td>26 (18.2)</td>
<td>0.75</td>
</tr>
<tr>
<td>diabetes mellitus at diagnosis</td>
<td>45 (31.5)</td>
<td>46 (32.2)</td>
<td>0.92</td>
</tr>
<tr>
<td>hypertension at diagnosis</td>
<td>19.6 (10.3–39.3)</td>
<td>13.0 (6.4–35.0)</td>
<td>0.13</td>
</tr>
<tr>
<td>median GH concentration at diagnosis in µg/L (IQR)</td>
<td>10.5 (6.2–28.9)</td>
<td>12.9 (5.6–27.0)</td>
<td>0.74</td>
</tr>
<tr>
<td>mean PRL concentration at diagnosis in µg/L (IQR)</td>
<td>3.4 ± 0.5</td>
<td>6.2 ± 1.3</td>
<td>0.04</td>
</tr>
</tbody>
</table>

* IQR = interquartile range; NA = not applicable.
† This characteristic was used to match Group 1 (those who had received somatostatin analogs prior to surgery) and Group 2 (those who had not received somatostatin analogs prior to surgery) patients. There were 143 patients in each group.
‡ Tumor volume was not available in four Group 1 patients and in 15 Group 2 patients.
respectively (p = 0.58; Fig. 2). On the basis of tumor size, surgical remission was obtained in 30 (83.3%) of 36 patients with microadenoma and in 142 (56.8%) of 250 patients with macroadenoma (p < 0.001). The percentage of patients with microadenoma who achieved surgical remission was similar in patients in both groups (77.8% in Group 1 and 88.9% in Group 2, p = 0.65; Fig. 3). In patients with macroadenoma, the surgical remission rate also did not differ between the two groups (56.6 and 60.0% in Group 1 and Group 2 patients, respectively, p = 0.37; Fig. 3). On the basis of tumor invasion into the cavernous sinus, surgical remission was obtained in 163 (73.4%) of 222 patients with noninvasive tumors and in nine (14.1%) of 64 patients with invasive tumors (p < 0.001). The percentage of patients with noninvasive tumors who achieved surgical remission was similar in Groups 1 and 2 (68.5 and 78.4%, respectively, p = 0.13; Fig. 3). Similar results were obtained in patients with invasive tumors (remission rate, 15.6 and 12.5% in Group 1 and 2 patients, respectively, p = 0.72; Fig. 3). The surgical remission rate in the 26 Group 1 patients who demonstrated a reduction of tumor size during therapy (50%) was similar to that of the other 52 Group 1 patients who did not show tumor reduction (53.8%, p = 0.94). The other patient characteristics are summarized according to surgical outcome in Table 2. Univariate analysis revealed that younger age at surgery, higher GH levels at diagnosis, macroadenoma, invasiveness into the cavernous sinus, and larger maximum tumor diameter were all associated with a poor surgical outcome.

Because of the likely interrelationships among several of these variables, we next performed a logistic regression analysis with surgical outcome as the dependent variable. In the multivariate analysis, an unfavorable surgical outcome was significantly associated with the log of GH level at diagnosis (odds ratio 4.38 per log unit increase, 95% CI 1.96–9.7; p < 0.001), tumor invasion into the cavernous sinus (odds ratio 11.68, 95% CI 4.67–29.2; p < 0.001), and maximum tumor diameter (odds ratio 1.052 per unit increase, 95% CI 1.003–1.104; p = 0.04), whereas age, the classification into micro- or macroadenoma, and the surgeon performing the procedure had no independent prognostic value. Even in the multivariate model, pretreatment with somatostatin analogs was not associated with surgical outcome (unfavorable outcome odds ratio 1.85, 95% CI 0.97–3.52, p = 0.062). Finally, we performed another logistic regression analysis, in which we also included the Group 1 patients who had been excluded after the matching procedure, but again, we obtained similar results (data not shown).

Complications of Surgery

No operative or perioperative deaths occurred. Surgical morbidity was recorded in 18 patients (6.3%) and was similar in Group 1 and 2 patients (7 and 5.6%, respectively; p = 0.81). Most complications were mild and caused no permanent disability. The most frequent complication was hypotension (defined as a serum sodium concentration < 130 mmol/L), which occurred in five patients (three in Group 1 and two in Group 2) and was responsive to simple water restriction alone in four of the five patients. Difficult intubation, requiring postponing surgery for 1 day and a subsequent 1-day stay in the intensive care unit, was encountered in two patients (one in each group); two other patients (one in each group) experienced hypoxemia during anesthesia without clinical consequences. Two Group 1 patients, both with a history of peptic ulcer disease, experienced hematemesis not requiring blood transfusion on the 1st postoperative day. Other complications, occurring in one patient each, were uterine hemorrhage requiring blood transfusion, biliary colic, left sixth cranial nerve palsy of 2 months’ duration.

### Table 2

**Clinical and hormonal characteristics of 286 patients with acromegaly according to surgical outcome**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cured (172 patients)</th>
<th>Not Cured (114 patients)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (in yrs)</td>
<td>45.9 ± 1.0</td>
<td>42.2 ± 1.3</td>
<td>0.02</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>90 (52.3)</td>
<td>62 (54.4)</td>
<td>0.83</td>
</tr>
<tr>
<td>Previous dopaminergic therapy</td>
<td>28 (16.3)</td>
<td>20 (17.5)</td>
<td>0.91</td>
</tr>
<tr>
<td>Macroadenomas*</td>
<td>142 (83.5)</td>
<td>108 (94.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cavernous sinus invasion</td>
<td>9 (5.2)</td>
<td>56 (49.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sphenoid sinus invasion</td>
<td>22 (12.8)</td>
<td>23 (20.2)</td>
<td>0.13</td>
</tr>
<tr>
<td>Tumor size (mm)</td>
<td>16.7 ± 0.5</td>
<td>24.6 ± 1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GH concentration at diagnosis (µg/L)</td>
<td>12.2 (6.2–26.3)</td>
<td>26.4 (12.8–50.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PRL concentration at diagnosis (µg/L)</td>
<td>10.0 (5.6–20.4)</td>
<td>15.7 (7.0–33.9)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

* This characteristic was used to match Group 1 and Group 2 patients.

No operative or perioperative deaths occurred. Surgical morbidity was recorded in 18 patients (6.3%) and was similar in Group 1 and 2 patients (7 and 5.6%, respectively; p = 0.81). Most complications were mild and caused no permanent disability. The most frequent complication was hypotension (defined as a serum sodium concentration < 130 mmol/L), which occurred in five patients (three in Group 1 and two in Group 2) and was responsive to simple water restriction alone in four of the five patients. Difficult intubation, requiring postponing surgery for 1 day and a subsequent 1-day stay in the intensive care unit, was encountered in two patients (one in each group); two other patients (one in each group) experienced hypoxemia during anesthesia without clinical consequences. Two Group 1 patients, both with a history of peptic ulcer disease, experienced hematemesis not requiring blood transfusion on the 1st postoperative day. Other complications, occurring in one patient each, were uterine hemorrhage requiring blood transfusion, biliary colic, left sixth cranial nerve palsy of 2 months’ duration.
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![Graph showing surgical remission rates](image)

Fig. 3. Graphs showing the surgical remission rates in 143 Group 1 and 143 Group 2 patients with acromegaly, stratified by tumor size (microadenoma and macroadenoma; upper) and tumor invasiveness into cavernous sinus (noninvasive and invasive tumors; lower). Differences in the surgical remission rate were not significant in any subgroup. Dotted white bar represents Group 1; dotted black bar represents Group 2.

ration (all in Group 1), nasal bleeding requiring another nasal tamponade 10 days after surgery, thrombosis of a superficial leg vein, loss of taste and smell sensation, and inguinal infection with Candida albicans (all in Group 2).

Postoperative diabetes insipidus, lasting at least 2 months, developed in 10 patients (3.5%). Its occurrence was similar in Group 1 and 2 patients (2.8 and 4.2%, respectively; p = 0.74).

Postoperative worsening of pituitary function was quite uncommon: hypogonadism occurred in one (Group 1) of the 156 patients at risk, hypothyroidism in two (both Group 2) of the 246 patients at risk, and hypoadrenalism in two (both Group 2) of the 276 patients at risk.

Discussion

Previous Results of Presurgical Treatment

As chronic therapy with somatostatin analogs may soften and induce tumor shrinkage in patients with acromegaly, previous studies have shown that both effects would make surgical removal of the tumor easier and would also translate into better surgical results. Moreover, reduced or even normalized GH and IGF-I levels achieved using medical therapy might improve the presurgical anesthesiological condition of patients with acromegaly, thus reducing the risk of perioperative complications.

Indeed, the first preliminary reports suggested a better outcome in invasive macroadenoma pretreated with somatostatin analogs. However, these studies were small anecdotal series in which the results were compared with those of historical controls. With only one exception, authors of subsequent larger series (Table 3) did not detect a significant difference in the surgical outcome between patients who had undergone treatment with somatostatin analogs prior to surgery and those who had not. Stevenaert and Beckers described a significant improvement in surgical outcome in a subgroup of patients with enclosed macroadenoma. However, when the main analysis of a study has favorable results, post hoc examination of subgroups is subject to considerable bias and may be useful only as a hypothesis-generating tool rather than a means of drawing definite conclusions. Abe and Ludecke found a nonsignificant trend toward an improved outcome in a subgroup of patients with an invasive, but potentially resectable, macroadenoma. One prospective study and another study in which the authors matched patients who had not undergone somatostatin treatment prior to surgery to those who had did not demonstrate any improvement in the rate of surgical remission of medically pretreated patients. The principal drawback of both studies is, however, the small sample size (24 and 38 patients), which leaves open the possibility of a Type II error, that is, failure to detect a significant difference because of an insufficient sample size.

Effects of Presurgical Treatment on the Remission Rate of Acromegaly

In our study, the largest ever reported, we found no beneficial effect of treatment with somatostatin analogs prior to surgery on the surgical remission rate (56.6% in Group 1 patients and 63.6% in Group 2 patients), thus confirming most of the previous reports (Table 3). Even subgroup analysis according to tumor size and invasiveness failed to demonstrate a better outcome in Group 1 patients and did not confirm earlier suggestions from other authors. The strength of our study lies in the large number of patients included in the analysis. The sample size has an 80% power to detect a 16% improvement of the surgical remission rate in patients pretreated with somatostatin analogs. Our study, as well as many others on this issue, was retrospective and not randomized. To circumvent some caveats of retrospective studies, we chose an experimental design similar to that used by Biermasz and coworkers. The matching procedure used to eliminate the excess of patients with microadenoma or invasive tumor who did not receive somatostatin analogs prior to surgery was performed using a table of random numbers to minimize any potential bias. Both characteristics chosen to match the two groups of patients, that is, tumor size and invasiveness into the cavernous sinus, are known to be important determinants of surgical outcome in cases of acromegaly. The two groups of patients were similar with regard to most of the other clinical and demographi-
softening of the pituitary tumor and easier discrimination of disease characteristics (Table 1). The only imbalance was a greater tumor volume in Group 2 patients compared with Group 1 patients. This difference is probably due to a preference to refer patients with a very large macroadenoma for immediate surgery rather than after 3 to 4 months of medical treatment. Regardless, the imbalance between the two groups should have favored those treated with somatostatin analogs prior to surgery (Group 1).

At variance with all previous reports on this topic, we included not only patients treated with octreotide sc, but also those treated with the long-acting somatostatin analogs octreotide LAR and lanreotide. The characteristics of the patients, the GH and IGF-I response to therapy, and the surgical remission rate were similar in all Group 1 patients. Therefore, failure of somatostatin analogs to improve surgical outcome does not depend on the different formulations of drug used.

Because of logistic restraints before surgery, we could not perform repeated MR imaging studies in all Group 1 patients. A reduction greater than 2 mm in any tumor diameter occurred in 33.3% (26 of 78) of the patients available for this analysis, with no difference among the different analogs used. Because near-maximal tumor shrinkage is usually reached within 3 months from the beginning of therapy, and because we excluded from the study all patients who had received somatostatin analogs for less than 3 months, the lack of any beneficial effect on the surgical remission rate seems not to be ascribed to a too-short period of presurgical therapy. Moreover, we did not detect any significant difference in the surgical remission rate between patients in whom tumor shrinkage was or was not demonstrated during somatostatin therapy.

Softening of the pituitary tumor and easier discrimination between the tumor and the normal gland have been reported more frequently in patients pretreated with somatostatin analogs. We did not check both variables because of the unblinded nature of our study. Moreover, the lack of any improvement in surgical remission rate, as demonstrated in the present and previous studies, makes changes of tumor color and consistency irrelevant issues.

**Effects of Presurgical Treatment on the Safety of Surgery**

Although transsphenoidal surgery is a low-risk procedure when performed by an experienced neurosurgeon, it is well known that patients with acromegaly may face an increased anesthesia-related risk of perioperative morbidity and difficult intubation, mainly because of cardiovascular, respiratory, and metabolic dysfunction as well as soft-tissue swelling. Therapy with somatostatin analogs consistently improves the cardiovascular status of patients with acromegaly and reduces laryngeal and pharyngeal soft-tissue hypertrophy and swelling. Colao and coworkers reported a significantly shorter period of postoperative hospitalization in patients with acromegaly who underwent treatment with octreotide before surgery compared with those who did not (8.6 ± 0.7 days) and suggested that it resulted from a lower frequency of cardiac arrhythmia, respiratory impairment, and respiratory infections in the treated group. These data have not been confirmed in other studies. We also did not detect any difference in either the occurrence or severity of perioperative complications (7% in Group 1 patients and 5.6% in Group 2 patients). It is noteworthy that most complications were mild and did not cause permanent disability in any patient. We did not monitor our patients for cardiac arrhythmias after surgery, except when clinically indicated, and therefore we cannot comment on the reduced rate of electrocardiographic abnormalities in patients treated with octreotide sc before surgery. However, the lack of important cardiovascular complications in our cohort of 286 patients suggests that most of the reported electrocardiographic abnormalities have a negligible role in determining the risk of clinically relevant perioperative complications in acromegaly. It is unlikely that a selection bias to treat sicker patients with somatostatin analogs before surgery was responsible for this finding.
Pretreatment therapy with somatostatin analogs occurred, as two important comorbidity characteristics, diabetes mellitus and hypertension, had similar frequency in the two groups of patients at diagnosis.

Postoperative worsening of pituitary function and diabetes insipidus occurred rarely and were not affected by presurgical treatment with somatostatin analogs.

As only clinically relevant complications of anesthesia were recorded, we cannot exclude the possibility that presurgical treatment with somatostatin analogs might improve the anesthetic grade of the patient or ease difficulty of intubation. Only a prospective study specifically designed to this aim can answer that question.

Conclusions

Our study failed to demonstrate any significant improvement in the surgical remission or complication rates in patients with acromegaly who had been treated with somatostatin analogs before surgery. The main limitation of our study is, of course, its retrospective nature. Even though we tried to minimize any potential source of bias by carefully matching the two groups of patients according to the most important prognostic factors, unrecognized differences in the two study populations might still be responsible for the apparent lack of benefit of somatostatin therapy. Another potential and, in our study, unavoidable source of bias was the nonrandomized choice to treat or not to treat patients before surgery, which was usually decided by the referring endocrinologist. We agree with Ben-Shlomo and Melmed that only a controlled, randomized, and blinded study may give the ultimate answer to this question. On the other hand, considering the rarity of the disease, it is unlikely that a trial of sufficient size at a single center will be implemented on this issue. At present, on the basis of results and the costs in a single center will be implemented on

References


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