CLINICAL STUDY

Effects of preoperative octreotide treatment on different subtypes of 90 GH-secreting pituitary adenomas and outcome in one surgical centre

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Abstract

Objective: To investigate the possible impact of pretreatment with octreotide on different subtypes of GH-secreting pituitary adenomas and on the outcome of transnasal surgery.

Methods: We reviewed a consecutive series of 90 acromegalic patients treated with octreotide alone before transnasal surgery. On the basis of magnetic resonance imaging, the tumours were classified into four groups: group A, microadenoma ($n = 7$); group B, transnasally resectable macroadenoma ($n = 21$); group C, invasive, potentially transnasally resectable macroadenoma ($n = 43$); group D, non-resectable grossly invasive macroadenoma ($n = 19$). All patients were treated for at least 3 months before surgery, with a mean daily dose of $221 \pm 31 \mu\text{g}$ octreotide. The mean follow-up was 51.7 ± 1.4 months. The comparative group included 57 acromegalic patients who were not receiving octreotide treatment.

Results: After pretreatment with octreotide, tumour shrinkage was clearly observed in 28 of the 90 patients (31%). At surgery, the tumours after octreotide treatment were more often white or grey in colour (91% compared with 75%) and were observed to be slightly more often fluid or soft in texture (86% compared with 79%) than those in the comparative series. Endocrinological remission was achieved in all patients in group A, 95.2% in group B, and 81.4% in group C. In only 10 of the 14 patients with tumour shrinkage in group C, endocrinological remission was also achieved (71.4%). In the comparative series, endocrinological remission was achieved in 92.9% of group A, 87.5% of group B, and 73.9% of group C.

Conclusions: Octreotide treatment slightly improved the already relatively high rate of endocrinological remission in invasive, potentially transnasally resectable macroadenomas. The rate of tumour shrinkage was found to decrease with extrasellar size. With the exception of tumour growth in approximately 7% of invasive adenomas and pituitary apoplexy in one patient, there was no disadvantage associated with the octreotide pretreatment.

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Introduction

It is well accepted that octreotide induces clinical improvement in most acromegalic patients by inhibition of the secretion of growth hormone (GH) and, consequently, that of insulin-like growth factor (IGF)-I (1–9). Octreotide has also been shown to reduce pituitary tumour size to a variable extent (2–15). In view of these results, octreotide has proven to be an alternative therapy in patients unsuitable for surgery, and an additional treatment after incomplete removal of tumour. Few studies have focused on the influence of octreotide pretreatment on surgical outcome. Several studies have suggested that pretreatment with octreotide improved the results of transsphenoidal surgery in

acromegaly (7, 8, 11, 16–18). Conversely, other authors have observed no significant difference in surgical results between octreotide-pretreated patients with invasive adenomas and those who did not receive octreotide before surgery (7, 8, 12, 19, 20). However, with two exceptions (7, 8), these reported series have included too few patients to permit definitive conclusions to be drawn for subtypes of different tumours. The purpose of the present study was to determine the impact of pretreatment with octreotide on the operative findings and results of transnasal surgery in a sufficiently large number of acromegalic patients to permit analysis of subtypes of pituitary adenomas. Therefore, we retrospectively analysed data recorded from 90 patients treated with octreotide before primary

transnasal surgery; 57 patients operated on over the same period but without specific pretreatment served as comparative group.

Patients and methods

Patients

Between January 1992 and December 1995, 147 patients with active acromegaly underwent surgery via a primarily transnasal route at either Hamburg University or the Marienkrankenhaus in Hamburg. Among them, a consecutive series of 90 acromegalic patients (61%) treated with octreotide alone before surgery was reviewed in the present study. Only one patient developed pituitary apoplexy with low GH concentrations and was excluded from this surgical series. The patients included 45 females and 45 males, ranging in age from 7 to 82 years (mean $\pm$ S.E., 46.1 ± 1.4 years). Only one male patient was younger than 20 years. The comparative group consisted of 57 acromegalic patients who did not receive preoperative octreotide treatment who underwent primary transnasal surgery during the same period. These patients included 30 males and 27 females, ranging in age from 23 to 76 years (47.6 ± 1.7 years). The option of octreotide pretreatment was discussed for all patients and was strongly recommended in cases of grossly invasive adenomas; in non-pretreated patients this group was small, and included only four, compared with 19 patients in the treated group. The preoperative diagnosis of acromegaly was confirmed by endocrinological examination.

Statistical analysis

The data are presented as the mean $\pm$ standard error (S.E.). Student's *t*-test and chi-square analysis were used

for comparison of the groups of treated and untreated patients. A *P* value <0.05 was considered significant.

Tumour classification

T1-weighted coronal and sagittal magnetic resonance imaging (MRI) with and without contrast medium was performed before and after octreotide therapy. Using MRI, tumour size and extension before octreotide treatment were evaluated by the surgeon (D L) (21), and cavernous sinus invasion was classified according to the classification system of Knosp *et al.* (22). These results were re-evaluated by the other author (T A). On the basis of these results, the tumours were classified into four groups (Fig. 1): group A, microadenoma; maximum tumour diameter less than 10 mm; group B, transnasally resectable macroadenoma; group C, invasive, potentially transnasally resectable macroadenoma; group D, non-resectable macroadenomas such as grossly invasive tumours with apparent encasement of the carotid artery. A transnasally resectable macroadenoma was defined as a tumour with suprasellar extension or slight cavernous sinus invasion, or both. An invasive, potentially transnasally resectable adenoma was defined as a tumour extension not extending to the lateral aspects of the intra- and supracavernous internal carotid arteries (23); this represents a slight modification of the Knosp classification (22), including growth beyond the lateral tangent of the carotid artery, but without complete encasement.

Microadenomas (group A) were seen in seven of the 90 octreotide-treated patients (7.8%). Macroadenomas were found in 83 patients (92.2%), of whom 21 (23.3%) were classified as group B, 43 (47.8%) as group C, and 19 patients (21.1%) as group D. In the comparative group of 57 patients, 14 (24.6%) were classified as group A, 16 (28.1%) as group B, 23 (40.3%) as group C, and four (7.0%) as group D.

Figure 1 A modification of the Knosp classification (22). Tumour classification on coronal MRI. Group A: microadenoma (less than 10 mm in diameter). Group B: transnasally resectable macroadenoma; tumour extension to the suprasellar area or one that does not pass a line between the cross-sectional centres of the carotid arteries (internal carotid line). Group C: invasive, potentially transnasally resectable macroadenoma; tumour extension does not extend past a line tangent to the lateral aspects of the intra- and supracavernous internal carotid artery, but allows transgression of the line if potentially resectable (oblique lines). Group D: non-resectable macroadenoma; tumour extension lateral to the lateral tangent of the intra- and supracavernous internal carotid artery with a grossly invasive tumour, apparent encasement of the carotid artery, or both. T, tumour.

Table 1 Plasma GH and IGF-I values before and during octreotide treatment in 90 acromegalic patients, and in a comparative series ($n = 57$). Values are mean $\pm$ s.e. (range).

	Octreotide treatment		Comparative series ($\mu\text{g/l}$)
	Before ($\mu\text{g/l}$)	During ($\mu\text{g/l}$)	
Group A ($n = 7$)			($n = 14$)
GH	10.9 $\pm$ 1.5 (5.8–15.8)	1.1 $\pm$ 0.2 (0.7–1.7)	13.8 $\pm$ 2.5 (5.5–39.1)
IGF-I	814 $\pm$ 99 (579–1224)	395 $\pm$ 57 (208–582)	970 $\pm$ 84 (497–1500)
Group B ($n = 21$)			($n = 16$)
GH	22.3 $\pm$ 3.9 (5.2–66.5)	6.8 $\pm$ 2.3 (0.3–40.3)	22.5 $\pm$ 5.1 (6.9–64.8)
IGF-I	847 $\pm$ 67 (433–1370)	469 $\pm$ 56 (74–1022)	998 $\pm$ 78 (488–1600)
Group C ($n = 43$)			($n = 23$)
GH	41.0 $\pm$ 5.3 (5.7–150)	8.6 $\pm$ 2.0 (0.2–80)	28.1 $\pm$ 3.4 (5.2–58.3)
IGF-I	965 $\pm$ 54 (465–1865)	588 $\pm$ 43 (190–1470)	1043 $\pm$ 136 (406–3745)
Group D ($n = 19$)			($n = 4$)
GH	67.2 $\pm$ 13.2 (14.1–235)	13.2 $\pm$ 3.1 (0.1–58.5)	36.3 $\pm$ 17.1 (14.2–86.3)
IGF-I	1101 $\pm$ 85 (570–2180)	696 $\pm$ 77 (221–1452)	934 $\pm$ 183 (474–1350)

Group A: microadenoma.

Group B: transnasally resectable macroadenoma.

Group C: invasive, potentially transnasally resectable macroadenoma.

Group D: non-resectable macroadenoma.

Hormonal measurements

Several measurements of plasma GH and IGF-I concentrations were taken before and during octreotide treatment. Plasma GH measurements were performed by immunoradiometric assay (Pharmacia, Uppsala, Sweden). Plasma GH (normal range for adults $<2.5 \mu\text{g/l}$) and IGF-I concentrations before octreotide treatment were examined in relation to tumour classification (Table 1). Age-corrected normal ranges for plasma IGF-I concentrations were 50–356 $\mu\text{g/l}$ for 7–8 years, 85–369 $\mu\text{g/l}$ for 20–29 years, 67–318 $\mu\text{g/l}$ for 30–39 years, 41–272 $\mu\text{g/l}$ for 40–49 years, 59–215 $\mu\text{g/l}$ for 50–59 years, 42–250 $\mu\text{g/l}$ for 60–69 years and 75–218 $\mu\text{g/l}$ for age more than 70 years, respectively. Preoperative plasma GH and IGF-I concentrations of the comparative series were also examined (Table 1).

Treatment with octreotide

All patients were treated for at least 3 months before the operation with subcutaneous injections of the somatostatin analogue, octreotide (Sandostatin; Sandoz Pharmaceuticals (now Novartis), Basle, Switzerland) at a daily dose of at least 100 μg . Seventy-one patients (78.9%) were treated with a daily dose of at least 300 μg octreotide. The dose was increased in a number of patients whose plasma GH and IGF-I concentrations were insufficiently suppressed. One day before the operation, octreotide administration was stopped, to avoid interference with intraoperative GH measurements (23–25). The mean duration and daily dose of octreotide treatment were 9.0 ± 1.4 months (range 3–14 months) and $221 \pm 31 \mu\text{g}$ (range 100–300 μg) in group A, 6.6 ± 0.9 months (range 3–21 months) and $426 \pm 85 \mu\text{g}$ (range, 100–1500 μg) in group B, 7.3 ± 0.5 months (range 3–17 months) and $465 \pm 55 \mu\text{g}$

(range 150–1500 μg) in group C, and 9.2 ± 1.0 months (range 4–18 months) and $543 \pm 82 \mu\text{g}$ (range 100–1500 μg) in group D.

Effects of octreotide treatment

The results of octreotide therapy were evaluated with respect to plasma GH and IGF-I levels. Suppression of plasma GH and IGF-I was defined as a decline of at least 50%. MRI was performed at the start of octreotide treatment and less than 1 month before operation. Tumour shrinkage was defined as at least 2 mm reduction in greatest diameter on MRI (2). The results were evaluated by the referring neuroradiologists and the authors.

Transnasal microsurgery

Direct transnasal microsurgery was performed in all patients by one author (DKL). The operative technique has been described in detail elsewhere (26, 27). During surgery, the surgeon documented the colour (white or grey, and yellow) and consistency (fluid or soft, and hard) of the tumours. A tumour with several textures was described by the dominant colour and consistency. Intraoperative GH concentrations were quantified by immunoradiometric assay as described previously (23–25). In patients who exhibited an inadequate decline in GH after initial tumour removal, subsequent surgery was considered during continued anaesthesia. Surgical results were examined in relation to tumour classification. Histological study of the surgically removed material consisted of routine staining using haematoxylin and eosin. Five of the 90 adenomatous tissues were identified by intraoperative smear only and were too small for subclassification.

Criterion of remission and follow-up examination

The mean follow-up times after surgery in the octreotide and comparative groups were 51.7 ± 1.4 months (range 28–75 months) and 49.3 ± 2.9 months (range 39–74 months) respectively. The endocrinological criterion of remission in this series was post-operative plasma GH concentration less than $2.5 \mu\text{g/l}$ when clear-cut normalization of plasma IGF-I concentrations could also be proved by follow-up within the first year after operation. Borderline cases in remission were decided on the basis of suppression of plasma GH concentrations to less than $1 \mu\text{g/l}$ in response to oral glucose administration. The follow-up examination was performed by different endocrinologists, who classified the results independently of the authors and without discrepancies.

Results

Hormonal response

Plasma GH and IGF-I values during octreotide treatment are shown in Table 1. Normalization of GH or IGF-I concentrations or both was observed in 43 (47.8%), 33 (36.7%), and 27 (30.0%) of the 90 patients respectively. In all groups, mean GH and IGF-I concentrations decreased with octreotide treatment. A more than 50% suppression of plasma GH/IGF-I was observed in 100%/85.7% of group A, in 85.7%/42.9% of group B, in 81.4%/30.2% of group C, and in 89.5%/26.3% of group D respectively. Mean GH and IGF-I concentrations under octreotide treatment were normal only in microadenomas and correlated with the degree of the tumour extension.

Tumour shrinkage

MRI indicated tumour shrinkage in 28 of the 90 patients (31%) after octreotide treatment (Table 2). The range, rate and quantitative degree of tumour shrinkage are also presented in Table 2. Fourteen of the 43 tumours in group C were reclassified as group B (Figs 2 and 3).

In contrast, tumour size increased in six of the 90 patients (6.7%) during octreotide treatment – four patients in group C and two in group D. The mean quantitative increase in tumour size was 6.8 ± 2.2 mm (range 3–17 mm). These patients were treated for 4–6 months before the operation with octreotide at a daily dose of 300–600 μg . In these patients, plasma GH and IGF-I concentrations did not decrease with octreotide treatment.

Surgical findings

Surgical findings are shown in Table 3, in relation to tumour classification. Acromegalic adenomas after octreotide treatment were more often white or grey in colour (91.1% compared with 75.4%) and more often fluid or soft in texture (85.6% compared with 78.9%) than those not subjected to octreotide treatment. In the 14 patients in group C whose tumours were reclassified as group B after octreotide treatment, the tumour was fluid or soft in consistency ($n = 14$) and white or grey in colour ($n = 13$).

Surgical outcome

Surgical outcomes in relation to tumour classification are summarized in Table 4. In 62 of the 90 patients (68.9%) with preoperative octreotide treatment, endocrinological remission was achieved. In these 62 patients, postoperative mean plasma GH and IGF-I concentrations were $1.0 \pm 0.1 \mu\text{g/l}$ (range

Table 2 Tumour shrinkage (>2 mm) after octreotide pretreatment, in relation to tumour classification.

	Tumour classification			
	Group A ($n = 7$)	Group B ($n = 21$)	Group C ($n = 43$)	Group D ($n = 19$)
Shrinkage present (number (% of group))	1 (14.3)	11 (52.4)	14* (32.6)	2 (10.5)
Shrinkage				
Range (mm)	9→7	10–18→8–16	11–32→9–28	32–33→26–28
Mean (mm)	9→7	$14.3 \pm 0.9 \rightarrow 11.3 \pm 0.9$	$20.4 \pm 1.7 \rightarrow 15.9 \pm 1.5$	$32.5 \rightarrow 27$
Rate (%)†	22.2	11.1–29.4	12–35	12.5–21.2
Mean (%)	22.2	21.3 ± 1.8	22.9 ± 2.3	16.4 ± 4.4
Quantitative degree (mm)	2	2.0–4.0	2.0–10.0	4.0–7.0
Mean (mm)	2	2.7 ± 0.2	4.5 ± 0.6	5.5

Group A: microadenoma.

Group B: transnasally resectable macroadenoma.

Group C: invasive, potentially transnasally resectable macroadenoma.

Group D: non-resectable macroadenoma.

*Fourteen tumours in group C were reclassified as group B after octreotide pretreatment.

†Percentage reduction in maximum tumour diameter.

Figure 2 Coronal enhanced T1-weighted MRI (a) before and (b) 3 months after octreotide treatment. Tumour transformation from an invasive, potentially transnasally resectable macroadenoma (a) to a faintly invasive, transnasally-resectable macroadenoma after octreotide treatment (b). Endocrinological remission was achieved after transnasal surgery.

0.2–2.4 µg/l) and 241 ± 12 µg/l (range 106–403 µg/l) respectively. In 44 of the 57 patients (77.2%) who did not receive octreotide treatment (comparative series), endocrinological remission was

achieved. In these 44 patients, postoperative mean plasma GH and IGF-I concentrations were 0.9 ± 0.1 µg/l (range 0.1–2.2 µg/l) and 261 ± 12 µg/l (range 112–416 µg/l) respectively. For comparison of results in pretreated and untreated patients, it is necessary to exclude the group with non-resectable tumours (group D), who were clearly in greater numbers in the pretreated group. Thus combining groups A, B and C, the remission rate for the pretreated group was 62 of 71 patients (87.3%), compared with 44 of 53 patients (83.0%) for the comparative group. Although the differences did not achieve statistical significance, surgical outcomes had a tendency to improve in groups B and C who received octreotide treatment (remission rate; 85.9%), compared with the comparative, untreated, series (79.4%). The improve-

Table 3 Surgical findings. Values are number.

	Tumour colour		Tumour consistency	
	White or Gray	Yellow	Fluid or Soft	Hard
Patient groups with preoperative octreotide treatment				
(n = 90)				
Group A	7	0	6	1
(n = 7)				
Group B	17	4	16	5
(n = 21)				
Group C	40	3	39	4
(n = 43)				
Group D	18	1	16	3
(n = 19)				
Total	82 (91.1%)		77 (85.6%)	
Patient groups without octreotide treatment comparative series (n = 57)				
Group A	13	1	13	1
(n = 14)				
Group B	13	3	13	3
(n = 16)				
Group C	15	8	17	6
(n = 23)				
Group D	2	2	2	2
(n = 4)				
Total	43 (75.4%)		45 (78.9%)	

Group A: microadenoma.

Group B: transnasally respectable macroadenoma.

Group C: invasive, potentially transnasally respectable macroadenoma.

Group D: non-resectable macroadenoma.

Table 4 Endocrinological remission rate in relation to tumour classification.

	Tumour classification			
	Group A	Group B	Group C	Group D
Octreotide pretreatment	100%	95.20%	81.40%	0%
(n = 90)	(7/7)	(20/21)	(35/43)	(0/19)
Comparative series	92.90%	87.50%	73.90%	0%
(n = 57)	(13/14)	(14/16)	(17/23)	(0/4)
P value†	>0.05	>0.05	>0.05	>0.05

Group A: microadenoma.

Group B: transnasally respectable macroadenoma.

Group C: invasive, potentially transnasally respectable macroadenoma.

Group D: non-resectable macroadenoma.

†For difference between octreotide and comparative groups.

Figure 3 Coronal enhanced T1-weighted MRI (a) before and (b) 9 months after octreotide treatment. The tumour shrank after octreotide treatment, and its invasiveness classification changed to faintly invasive (b). Endocrinological remission was achieved after transnasal surgery.

ment of outcome was about 7% in group C (remission rate 81.4%). In only 10 of the 14 patients in whom tumours were reclassified from group C into group B after octreotide treatment (71.4%), endocrinological remission was fully achieved. In group D, with or without octreotide pretreatment, no clinical remission could be achieved.

Surgical complications

In this series, there was no mortality in patients either with or without octreotide pretreatment. In the patients who did receive octreotide pretreatment, surgical morbidity included two patients with postoperative nasal bleeding, three with temporary diabetes insipidus of more than 1 week, one with temporary cerebrospinal fluid (CSF) leak, and one with transient abducens nerve palsy.

In the comparative groups, traumatic carotid cavernous fistula occurred in one patient. This was treated with balloon occlusion and bypass surgery. CSF leak

with reoperation occurred in one patient. Other surgical morbidity included two patients with post-operative nasal bleeding, and four with temporary diabetes insipidus.

Pathological findings

The diagnosis of a GH-secreting pituitary adenoma was histologically confirmed in all patients. In 85 of the 90 pretreated patients, immunohistological examinations were available. Immunohistological studies revealed a positive reaction for GH alone in 52 patients (61.2%) and for GH and prolactin (PRL) in 16 patients (18.8%). Plurihormonal tumour was found in 17 patients (20%). In the comparative series, immunohistological examinations were available in all patients ($n = 57$). Immunohistological studies revealed a positive reaction for GH alone in 27 patients (47.4%) and for GH and PRL in 11 patients (19.3%). Plurihormonal tumour was found in 19 patients (33.3%).

Discussion

Recent achievements in the field of medical therapy for acromegaly have supplemented the classical treatment, which consisted of surgery and radiotherapy, with pre-surgical treatment with octreotide. The efficacy of octreotide treatment in decreasing the plasma GH and IGF-I concentrations is well recognized (2, 4, 5, 9, 14, 15). In the present study, plasma GH and IGF-I concentrations decreased after octreotide pretreatment, in most patients. Normalization of both GH and IGF-I concentrations was observed in 27 of the 90 patients (30%) and was more frequent in microadenomas (57.1%) and enclosed macroadenomas (47.6%) than in invasive adenomas.

Octreotide treatment before surgery is used increasingly. It relieves the symptoms of acromegaly and improves the patient's general condition for surgery (2–5, 9, 14, 15). Octreotide may also shrink or soften pituitary adenomas, and facilitate their removal (7, 8, 11, 16, 17). Octreotide has been shown to reduce pituitary adenoma size (2–9, 11–15, 18). It remains unclear in which tumour type the shrinkage may be of importance in facilitating tumour removal. In our series of patients, tumour shrinkage was observed in about one-third of patients, especially in the case of macroadenomas: 14 of the 43 invasive, questionable but potentially transnasally resectable macroadenomas (group C) were reclassified as transnasally resectable macroadenomas (group B) after treatment (32.6%). However, non-resectable adenomas (group D) did not change to potentially transnasally resectable tumours. Although a >50% reduction in tumour size (5, 6, 10, 13, 14) and the complete disappearance of tumour (10, 13, 28) after octreotide treatment have occasionally been reported in other studies, they were not observed in the present series. One patient developed pituitary apoplexy under octreotide treatment, and achieved endocrinological remission without further treatment, but had severe pituitary insufficiency. This patient was excluded from this series.

To date, a limited number of authors have reported surgical findings in patients who received octreotide treatment before surgery (7, 8, 12, 16, 17, 20, 29). We observed a soft consistency of adenomatous tissue in 85.6% of the 90 patients who received octreotide treatment and in 78.9% of the 57 comparative patients. This tendency to a change in consistency may be especially advantageous for the removal of tumour extending beyond the confines of the sella or invading the cavernous sinus. An additional benefit of octreotide treatment may be the change in tumour colour to more white or grey, which was first described by Landolt *et al.* (29). This was a more frequent appearance in the pretreated patients than in the comparative patients and may facilitate the discrimination of tumour tissues from anterior lobe tissues. Nevertheless, softness and whitish colour are also the

predominant findings in untreated adenomas, and therefore no major effect on outcome can be expected by this influence of octreotide. It was not observed that presurgical treatment with octreotide increased the presence of significant fibrosis or firmness of the adenomas.

As reported by others, surgical outcome in acromegaly correlated with tumour consistency, location, size, and the degree of invasiveness into adjacent structures. Therefore, in group A (microadenoma) and group B (transnasally resectable macroadenoma) patients, endocrinological remission can be achieved in most cases. At the other extreme of non-resectable (grossly invasive) macroadenomas (group D), presurgical octreotide treatment, by definition, could not improve the rate of GH normalization. It reduced tumour size only in 11% of the group, and rarely returned the plasma GH or IGF-I concentrations to the normal range, and tumour consistency was mostly soft. As shown by others (7, 8, 15), surgical results in grossly invasive adenomas could not be influenced by octreotide pretreatment using normalization of plasma GH concentrations as the endpoint. Therefore, if this subtype of tumour is under-represented in the untreated group, overall results are not comparable. This is obviously the reason why, in this study, the overall remission rate (68.9%) was actually slightly lower than that in the comparative series (77.2%). These limitations in the comparison of octreotide-treated patients with non-treated patients in this non-randomized study have to be taken into consideration. Because clinical improvements were to be expected in most patients before surgery, we left the decision concerning pretreatment to the patients, but strongly recommended it in the case of large grossly invasive adenomas.

The major objective of this evaluation was to characterize the reaction to octreotide in different subtypes of adenomas. Obviously, group A could not be further improved, as the remission rate was already near 100%, and group D rarely showed shrinkage and never changed to a potentially resectable grade. As previously shown by Stevenaert *et al.* (7, 8), enclosed macroadenomas (group B) comprised the group exhibiting an improvement of outcome after pretreatment with octreotide. In our hands, the normalization rate in group B was 95.2%, compared with 87.5% in untreated patients, and thus approached the range achieved for microadenomas. Nevertheless, the difference was not statistically significant. We introduced an additional tumour group, group C, including macroadenomas characterized by invasiveness with extra-sellar extension but without encasement of the carotid artery and without other parts of the tumour being clearly out of reach of transsphenoidal access, thus remaining potentially resectable. Only about one-third of this group showed tumour shrinkage under octreotide treatment. In 10 (71.4%) of the 14 patients in

whom tumours could be reclassified from group C to group B, endocrinological remission was achieved. Thus preoperative octreotide treatment may have improved the remission rate of a subset of group C by shrinkage of the tumour to a better resectable stage (group B), as shown in Figs 2 and 3. With use of micromirrors and micropressure irrigation suction system, the adenomas could be finally removed (26). The slight improvement of the remission rate from 73.9% in the comparative group to 81.4% is not statistically significant, and may be attributed to a combination of effects on the tumours that cannot be discriminated by our study. Shrinkage did not change the classification of non-resectable to resectable and the results were slightly worse in the shrunken adenomas of group C. Conversely, it must be mentioned that, in approximately 7% of invasive adenomas (groups C and D), an increase of tumour size was observed in spite of octreotide treatment.

Until recently, octreotide had to be administered subcutaneously in frequent daily doses. Long-acting octreotide is now available (30–32), although it was not included in our series. The potential for further improvement in the remission rates after administration of long-acting octreotide remains unresolved. Further studies are necessary; the difficulties in recruiting a large number of patients from a single institution would tend to favour a multicentre trial.

Conclusions

Unfortunately, for the medical and combined medical-surgical treatment of acromegaly, we found octreotide to be less effective with increasing tumour size. Nevertheless, for combinations of a slightly more often softer texture and more often white colour, in addition to a subgroup tumour shrinkage, there was a tendency to greater remission rates in potentially transnasally resectable macroadenomas, even in those with invasive potential. However, no transformation of a non-resectable (grossly invasive) adenoma into a transnasally resectable adenoma was observed. An increase in adenoma size in approximately 7% of these patients, in spite of octreotide treatment, has to be taken into consideration. As would be expected, relatively high remission rates in resectable macroadenomas compared with those reported in the current literature (33) are unlikely to be further improved to statistically significant extents by means of additional methods such as pretreatment with octreotide. Nevertheless, the tendency of an improved outcome seems to justify a trial with medication before surgery in potentially resectable macroadenomas. In this surgical report, we excluded evaluation of the clinically beneficial effects of octreotide, which may improve the general preoperative condition of the patients.

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