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Short-term Preoperative Octreotide Treatment of GH-secreting Pituitary Adenoma: Predictors of Tumor Shrinkage

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Abstract. We reviewed the cases of 32 patients with growth hormone (GH)-secreting macroadenoma who underwent short-term octreotide treatment before transsphenoidal surgery to determine which types of adenoma the preoperative treatment were sensitive and whether predictors of tumor shrinkage could be identified. The effects of preoperative octreotide treatment, endocrinologic effect and effect on tumor volume in 32 patients were evaluated retrospectively in relation to tumor features on magnetic resonance images and responses to endocrinologic challenge tests. At a daily dose of 300 μg for 2–3 weeks, octreotide reduced serum GH and insulin-like growth factor-1 (IGF-1) levels to 31.9 % and 51.6% of pretreatment values, respectively, and led to a mean tumor volume of 68% of pretreatment volume in 52% of the patients. The endocrinologic effect and the effect on tumor volume were larger in Knosp grades 0–2 than in Knosp grades 3–4. Tumor shrinkage occurred significantly more often among patients that had a good response to both octreotide and bromocriptine challenge tests. For surgical removal of the tumor, the effect of reducing tumor to 68% of pretreatment volume will be beneficial for the macroadenomas of Knosp grades 1–2. Preoperative short-term octreotide treatment is effective for GH-secreting macroadeomas of Knosp grades 1–2 and a good response to both octreotide and bromocriptine challenge tests is a predictor of subsequent tumor shrinkage. These results will lead to more effective selection of patients for preoperative octreotide treatment.

Key words: Acromegaly, Octreotide, Bromocriptine, Tumor shrinkage

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ACROMEGALY is an insidious disorder caused by GH-secreting pituitary adenoma and resulting in high circulating serum GH and insulin-like growth factor-1 (IGF-1) levels [1]. It is widely accepted that GH-secreting adenoma requires multimodal treatment, for example, surgery, radiation (radiosurgery), and medical treatment with somatostatin analogues (*e.g.* octreotide) and dopamine agonists. Even with the development of medical treatment and radiosurgery, transsphenoidal surgery is still widely accepted as the first choice treatment [2].

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According to new remission criteria for acromegaly (Cortina consensus) [3], 80–90% of patients with GH-secreting microadenoma and 40–65% of those with macroadenomas are controlled by transsphenoidal surgery alone at the experienced centers [2, 4–7]. Tumor size and degree of invasion into the cavernous sinus are critical factors for the outcome of transsphenoidal surgery [8]. Improving the surgical remission rate of GH-secreting macroadenomas is an important objective for pituitary neurosurgeons.

Octreotide decreases serum GH and IGF-1 levels and reduces the size of the GH-secreting adenoma in some patients, and it has been widely used postoperatively in patients without surgical remission. Octreotide has also been applied preoperatively in the hope of favorable effects on the surgical outcome. Several reports have shown the benefits of preoperative oct-

reotide treatment in tumor shrinkage, tumor softening, and improvement of the patient's general condition by reducing the serum GH level, which also reduces perioperative morbidity [9–17]. However, whether this treatment improves surgical results in cases of the GH-secreting macroadenoma remains controversial [18, 19]. Recent studies have shown that preoperative octreotide treatment is beneficial in some but not all types of macroadenoma [13, 15]. Although reducing the size of GH-secreting adenoma by octreotide is thought to improve surgical results, the effect of octreotide treatment on tumor volume is unpredictable and is not correlated with its endocrinologic effects [9, 10, 18, 20].

Here, we review our experience with 32 acromegalic patients with GH-secreting macroadenoma who underwent short-term preoperative octreotide treatment (2–3 weeks). We aimed to determine for which types of GH-secreting adenoma, preoperative octreotide treatment is effective, and whether there are predictive factors for tumor shrinkage. This is the first substantial report regarding preoperative octreotide treatment for acromegaly in Asia.

Materials and Methods

Patients

During the period from December 1993 to May 2004, 71 acromegalic patients underwent 82 surgeries (78 transsphenoidal surgeries and 4 craniotomies) at Osaka University Hospital, and 44 of them underwent preoperative treatment with octreotide (Sandostatin). Preoperative octreotide treatment was recommended particularly for patients with GH-secreting macroadenoma, but not for those with microadenoma.

To evaluate the efficacy of short-term octreotide treatment, the following 12 patients were excluded; seven who had undergone long-term octreotide treatment (two who were treated for over a year at other hospitals, and five with a large adenoma that extended into the middle or posterior fossa who were treated for over 5 weeks), four with GH/PRL-secreting adenoma who were also treated with dopamine agonists, and one treated 20 years previously with conventional radiotherapy. Therefore, 32 patients, 18 men and 14 women were included in this study. Mean patient age was 45.6 years, with a range of 22 to 68 years. Thirty cases were newly diagnosed, and two were recurrent. Appropriate written informed consent was obtained from each patient and family prior to therapeutic procedure.

Endocrinologic evaluation

All patients underwent careful endocrinologic examination in the pre- and postoperative periods. Examinations included measurements of the serum GH and IGF-1 levels, TRH test, LH-RH test, insulin stimulation test, and a 75 g-oral glucose tolerance test (OGTT). In addition, octreotide challenge tests, with blood samples taken before and 30 min and 1, 2, 4, 6, and 12 hours after subcutaneous injection of 100 μg octreotide were performed in 30 of the 32 patients. Bromocriptine challenge tests, with blood samples taken before and 1, 2, 4, 8, 12, and 24 hours after oral administration of 2.5 mg bromocriptine (Parodel), were also performed in 29 patients. Serum GH levels and IGF-1 levels were measured by a commercial kit (GH-immunoradiometric assay (IRMA), IGF-1-IRMA, Dai-ichi Radioisotope Laboratory, Tokyo, Japan) [21].

The data are shown as mean ± S.E.M. (range). Reductions in serum GH or IGF-1 levels and tumor volume are shown as percentages of post-/pretreatment values.

Tumor classification based on magnetic resonance images

All patients underwent magnetic resonance (MR) imaging at 1.5 Tesla, which provided 3 mm-thick T1-weighted slices before and after intravenous gadolinium administration. Pituitary macroadenoma was revealed in all patients, irrespective of its size. Referring to the lateral extension in coronal sections, adenomas were classified into five groups according to the Knosp grade: grade 0, normal findings within the cavernous sinus space; grade 1, tumor extending and passing the medial aspect of the intra- and supracavernous internal carotid artery (ICA) but not going beyond the intercarotid line; grade 2, tumor extending beyond the intercrossed line and slightly past the tangent on the lateral aspects of the intra- and supracavernous ICA; grade 3, tumor extending past the lateral tangent of the intra- and supra-cavernous ICA; grade 4, total encasement of the intracavernous carotid artery [22]. Suprasellar extension was observed in nine patients and compression of the optic chiasm was observed in seven.

Preoperative treatment with octreotide

Patients received subcutaneous injections of octreotide at a dose of 100 μg three times daily, the standard dose covered by general health insurance in Japan, until the day before the operation, for 2 weeks in 26 patients and 3 weeks in 6 patients. All patients underwent abdominal echography before or during treatment to screen for gallstones.

Endocrinologic effects of short-term octreotide treatment were evaluated by comparing serum GH and IGF-1 levels on the day of or day before surgery with pretreatment values.

MR images were obtained within 3 days before surgery for 27 patients. The effect of octreotide treatment on tumor volume was estimated by comparing the MR images with those obtained during the pretreatment period. Because each tumor was shaped irregularly with or without invasion into surrounding structures (sphenoid sinus or cavernous sinus), tumor size was estimated by measurement of the maximum width, length, and height on the MR images. Tumor shrinkage was defined as a greater than 2 mm reduction in the maximum diameter [15]. Tumor volume was calculated according to the formula $V = \text{height} \times \text{length} \times \text{width} \times \pi/6$ [10, 14, 23].

To evaluate the effect of octreotide on tumor consistency, intraoperative findings on tumor texture was classified as hard, soft, and fluid-like according to the surgical records.

Postoperative remission criteria and follow up

For postoperative evaluation, we used the remission criteria of nadir GH levels on OGTT less than 1.0 ng/ml, and normal age and sex-related IGF-1 levels [3, 24, 25]. All patients underwent 75 g OGTT in the postoperative period (2–3 weeks after surgery). Serum IGF-1 level sampled at least 3 months after surgery was evaluated. Normal ranges for IGF-1 were as follows (ng/ml): 20–29 years, male 85–369, female, 119–389; 30–39 years, male 67–318, female 73–311; 40–49 years, male 41–272, female 46–282; 50–59 years: male 59–215, female 37–266; 60–69 years, male 42–250, female 37–150; 70– years: male 75–218, female 38–207 (–1.96 S.D.– + 1.96 S.D., Dai-ichi Radioisotope Laboratory, Tokyo, Japan)

Results

Effects of short-term octreotide treatment on GH and IGF-1 levels

The pretreatment serum GH level was 82.8 ± 22.2 ng/ml (range 9–436 ng/ml) and that of IGF-1 was 1055 ± 53.4 ng/ml (385–1480 ng/ml). In all patients, the serum GH level was not decreased below 1 ng/ml during the 75 g OGTT. Endocrinologic effects of short-term octreotide treatment are shown in Table 1. Serum GH levels were reduced to 22.2 ± 4.4 ng/ml (0.5–88.8 ng/ml, $P<0.01$, paired t-test), corresponding to a mean reduction to 31.9 ± 6.9% (1.9–118.9%) of the pretreatment value. Serum IGF-1 levels were reduced to 553 ± 42.0 ng/ml (147–866 ng/ml, $P<0.001$, paired t-test), corresponding to 51.6 ± 3.2% (22.4–77.8%) of the pretreatment value. Serum GH levels were reduced below 2.5 ng/ml in 6 of 32 patients (18.8%), and IGF-1 was decreased to the normal range in 4 patients (12.5%).

Effects of octreotide treatment on tumor volume and Knosp classification

Mean tumor diameter before octreotide treatment was 20.6 ± 0.9 mm. Tumor shrinkage was observed in 14 of 27 patients (51.9%) who underwent preoperative MR imaging. In patients in whom tumor shrinkage was observed, the mean diameter reduction was 2.8 ± 0.4 mm, corresponding to a volume reduction to 68 ± 2% of the initial volume. Subsequent to tumor shrinkage, the tumors in 4 patients were reclassified to other Knosp grades; 2 patients from grade 1 to grade 0 (Fig. 1) and 2 from grade 2 to grade 1. Compression of optic chiasm disappeared in 2 of the 7 patients. Of 10

Table 1. Effect of short-term preoperative octreotide treatment

Serum GH level (pre-Oct; ng/ml)	82.8 ± 16.4
Serum GH level (post-Oct; ng/ml)	22.2 ± 4.4
Ratio of serum GH levels (post/pre-Oct; %)	31.9 ± 5.4
Serum IGF-1 level (pre-Oct; ng/ml)	1055 ± 53.4
Serum IGF-1 levels (post Oct; ng/ml)	553 ± 42.0
Ratio of serum IGF levels (post/pre-Oct; %)	51.6 ± 3.2%
Occurrence of tumor shrinkage	52% (14/27 patients)
Volume reduction (post/pre,%) (in patients with tumor shrinkage)	68 ± 2%

Oct: octreotide treatment, mean ± S.E.M are shown.

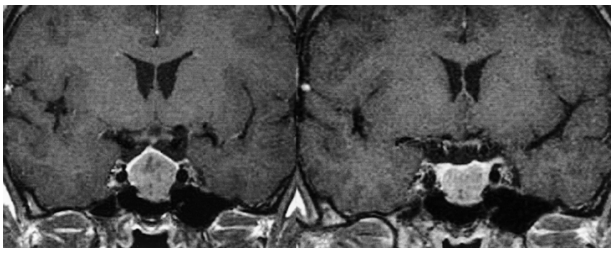

Fig. 1 Representative coronal T1-weighted MR image with gadolinium enhancement (*left*: pre-, *right*: post-octreotide treatment) shows tumor shrinkage in a 44-year-old male acromegalic patient. With volume reduction in width as well as in height, the tumor was reclassified from Knosp grade 1 to grade 0.

patients with prominent reduction in the serum GH level (to less than 10% of the pretreatment value) after octreotide treatment, 8 showed tumor shrinkage. However, in total, there was no significant difference in octreotide-induced reduction in the GH level between the group with tumor shrinkage and the group without shrinkage (P = 0.13, Mann-Whitney U-test).

Based on MR images before octreotide treatment, patients were classified into five groups according to the Knosp classification: grade 0 (n = 5), grade 1 (n = 9), grade 2 (n = 6), grade 3 (n = 7), grade 4 (n = 5). The effect of octreotide treatment and surgical results differed between these groups (Table 2). When these groups were combined into two larger groups (grade 0–2 and grade 3–4), reduction of serum GH levels by octreotide treatment was significant in the grade 0–2 group compared to the grade 3–4 group (mean reduction to 27.0% versus 52.9%, P<0.05; Mann-Whitney U-test). Tumor shrinkage was also observed more frequently in grade 0-2 groups (62.5%) than in grade 3–4 groups (36.4%).

Postoperative endocrinologic remission was observed in 16 (50%) of 32 patients. With respect to initial Knosp grade, surgical remission was observed in 100% of the patients with a grade 0 tumor, 78% of the patients with grade 1 tumor, 50% of the patients with a grade 2 tumor, 14% of the patients with a grade 3 tumor, and 0% in the patients with a grade 4 tumor (Table 2).

Octreotide and bromocriptine challenge tests

Before octreotide treatment, 30 patients underwent an octreotide challenge test. Subcutaneous injection of 100 μg octreotide reduced the mean serum GH level from 78.1 ± 19.4 ng/ml (10.4–567 ng/ml) to 10.4 ± 4.7 ng/ml (0.8–140.7 ng/ml), corresponding to a mean reduction to 16.1 ± 3.4% (1.9–92.7%) of the baseline value. There was a rough correlation in reduction of the serum GH level between results of the octreotide challenge test and short-term preoperative octreotide treatment ($r = 0.42$, $r^2 = 0.17$, $P<0.05$). A poor response in the octreotide challenge test indicated poor response to preoperative octreotide treatment.

With respect to Knosp classification, a significant difference in GH reduction in response to the octreotide challenge test was observed between the grade 0–2 group and grade 3–4 group. Mean reductions in serum GH levels were to 10.6% and to 29.6% of baseline values, respectively (P<0.05, Mann-Whitney U-test). Twenty-five patients underwent both the octreotide challenge test and post-octreotide MR imaging. The reduction of GH level in response to octreotide challenge test was to 9.6 ± 2.6% of the baseline value in patients with tumor shrinkage, significantly lower than the reduction to 26.8 ± 7.0% of the baseline value in patients without tumor shrinkage (P<0.01, Mann-Whitney U-test). However, when a good response to the octreotide challenge test was defined as reduction

Table 2. Octreotide effect and surgical results relative to Knosp classification

Knosp grade	n	Post/pre-Oct (%)				Surgical remission	
		GH	IGF-1	Mean tumor diameter (mm)	Shrinkage occurrence	n	Rate
Grade 0	5	28.1	62.3	15.5	33% (1/3)	5	100%
Grade 1	9	22.2	52.9	15.8	72% (5/7)	7	78%
Grade 2	6	23.9	75.5	19.2	67% (4/6)	3	50%
Grade 3	7	49.6	45.4	22.0	29% (2/7)	1	14%
Grade 4	5	50.2	46.9	26.0	50% (2/4)	0	0%
Total	32	31.9	51.6	20.6	52% (14/27)	16	50%

Oct: octreotide treatment

in the serum GH level to less than 10% of the pretreatment value or 2.5 ng/ml, there was no correlation between good response and the occurrence of tumor shrinkage (P = 0.07, χ^2 test with Fisher's exact probability method) (Table 3).

Bromocriptine suppressed serum GH level from 72.7 ± 16.2 ng/ml (9.1–466.2 ng/ml) to 25.6 ± 10.1 ng/ml (0.6–304.5 ng/ml), corresponding to the reduction to 34.4 ± 6.3%. The difference between the mean reduction of the serum GH levels of 28.8 ± 4.8% in the grade 0–2 group and of 45.8 ± 15.0% in the grade 3–4 group was not significant (P = 0.64, Mann-Whitney's U test). Twenty-five patients underwent both the bromocriptine challenge test and postoctreotide MR imaging. Reduction in the serum GH level in response to bromocriptine challenge test was 29.9 ± 6.9% in patients with tumor shrinkage, and to 46.7 ± 13.1% of baseline values in patients without tumor shrinkage (no significant difference, P = 0.31, Mann-Whitney U-test). When a good response to the bromocriptine challenge test was defined as a reduction to less than 20% of the pretreatment value or 5 ng/ml, there was no correlation between a good response to the bromocriptine challenge test and occurrence of tumor shrinkage (P = 0.29, χ^2 test with Fisher's exact probability method) (Table 3).

Both octreotide and bromocriptine challenge tests and postoctreotide MR imaging were performed for 24 patients. Although a good response to either challenge test alone did not correlate with the occurrence of tumor shrinkage, there was a significant correlation between a good response to both tests and occurrence of tumor shrinkage (Table 3) ($p<0.01$, χ^2 test with Fisher's exact probability method).

Table 3. Octreotide/bromocriptine challenge test results in relation to the effect of short-term octreotide treatment

	Effect of octreotide on tumor volume		
	Shrinkage	No shrinkage	
Octreotide challenge test (n = 25)			
Good response	10	4	
Other	3	8	NS
Bromocriptine challenge test (n = 25)			
Good response	7	3	
Other	6	9	NS
Octreotide and bromocriptine tests (n = 24)			
Good response in both	7	0	
Other	6	11	P<0.01

χ^2 test with Fisher's exact probability method
NS: not significant

Adverse effects of preoperative octreotide treatment

Tinnitus and transient abdominal symptoms, including abdominal pain, diarrhea, and nausea were observed in more than half of the patients following preoperative octreotide treatment and resolved within 3–5 days. There were no major complications during the 2–3 weeks of octreotide treatment.

Surgical finding on tumor texture

According to surgical records, tumor texture was classified as hard in five patients, soft in 21, and fluid-like in six. Four tumors which had partly hard portions were classified as hard. After octreotide treatment, no tumor showed fibrous change. All of the six patients with fluid-like tumors were the good responders in both octreotide and bromocriptine tests.

Discussion

Compared to the currently available long-acting form of octreotide (octreotide-LAR) [26], octreotide which requires daily injection is more suitable for short-term treatment. Our results indicated that short-term preoperative octreotide treatment had a beneficial effect in acromegalic patients who showed good GH responses to both octreotide and bromocriptine challenge tests and those with adenoma of Knosp grade 1 or 2.

The effect of short-term preoperative octreotide treatment in our study (Table 1) was consistent with that of previous studies that used the same dose and treatment period [13, 20]. Other studies have shown a more profound reduction in serum GH and IGF-1 levels with higher doses and longer treatment periods [10, 13, 15, 18, 26, 28]. Dose and treatment period should be modified when the objective of preoperative treatment is to lower the serum GH level and to improve the patient's general condition [29]. However, we have rarely seen patients with severe cardiac or respiratory problems in response to general anesthesia or transsphenoidal surgery. Although there were no major cardiac or respiratory complications in our series of patients, we cannot conclude that preoperative octreotide treatment decreased the surgical morbidity.

From a surgical aspect, the most anticipated effect of preoperative octreotide treatment is reduction of tumor volume and tumor softening. Tumor shrinkage was observed in 52% of our patients with a mean reduction to 68% of the initial volume. Similar to the results of Lucas-Morante *et al.*, tumor shrinkage occurred within 2 weeks of a daily dose of 300 μg octreotide [20], thus a treatment period of 2–3 weeks appears to be sufficient for patients who are responsive to octreotide.

The effect of reducing the tumor to 68% of pretreatment volume would be negligible for large adenomas of Knosp grade 3 or 4 with a high likelihood of invasion into the cavernous sinus. Even in a good responder, it is unlikely that octreotide treatment could transform an invasive adenoma into an enclosed adenoma [13, 15]. For adenomas classified as Knosp grade 0, a high remission rate can be obtained by surgery alone, and there appears to be no additional benefit. However, for Knosp grade 1 and 2 adenomas, reduction of the tumor volume would be beneficial and aid in total surgical removal. As indicated in other reports [13, 15], preoperative octreotide treatment is beneficial for improving the surgical remission rate in cases of enclosed adenomas with no apparent or suspected invasion, *i.e.*, Knosp grade 1 and 2 adenomas. Our results also indicate that the endocrinologic effect of octreotide treatment is more profound in Knosp grade 0–2 tumors than in Knosp grade 3–4 tumors.

Previous studies have indicated that octreotide treatment induces various degrees of tumor shrinkage in 23–60% of patients using different criteria for tumor shrinkage as well as different doses and treatment periods [9–17]. However, octreotide-induced tumor shrinkage is unpredictable, and does not correlate with the endocrinologic effect [9, 10, 18, 20]. It should be mentioned that very poor endocrinologic response appears to be a negative indicator of tumor shrinkage. Somatostatin receptor subtypes 2 and 5 are the predominant receptors found on the surface of pituitary somatotropes [31]. GH-secreting adenomas may express these receptors at an increased density; however, the expression is also highly variable, even within the same tumor, leading to resistance of some tumors to octreotide treatment [31–34]. Somatostatin receptor scintigraphy was unable to predict the effect of octreotide on tumor shrinkage or on hormone response, indicating that factors other than the expression levels of somatostatin receptors are involved in the clinical response to octreotide [34, 35].

Interestingly, our results showed that good responders to both octreotide and bromocriptine challenge tests showed a significantly higher incidence of tumor shrinkage in response to preoperative octreotide treatment (Table 2). This indicates that dopamine D2 receptor is associated with the effect of somatostatin on tumor volume. Some reports have shown that good octreotide responders are more likely to respond to bromocriptine treatment [36, 37], but a relation with tumor shrinkage has not been documented. Rocheville *et al.* reported that the dopamine D2 receptor and somatostatin receptor interact physically through hetero-oligomerization to create a novel receptor with enhanced functional activity [38]. In animal models, interaction between the somatostatinergic and dopaminergic systems have been observed in the basal ganglia and cerebral cortex [39–41]. We suspected that in GH-secreting adenomas, the presence of D2 receptors enhances the effect of octreotide through the interaction, leading to tumor shrinkage and tumor softening. All of the six patients with fluid-like tumors were the good responders in both octreotide and bromocriptine tests in this study. This finding seems to be noteworthy and similar to a previous report [15], although the tumor texture is generally soft in GH-secreting adenomas.

A somatostatin/dopamine chimeric ligand has been developed as a novel tool for treatment of acromegaly [42]. This chimeric ligand may constitute a potent drug for volume reduction of GH-secreting adenomas. It has also been reported that cotreatment with somatostatin and dopamine agonists reduces the serum GH level in patients with acromegaly more effectively than either agonist alone [42, 43], but there has been no evidence regarding reduction tumor volume.

The greatest benefit of surgery for GH-secreting adenomas is the possibility of cure. For large macroadenoma as Knosp grade 3 and 4, the objective of surgery is not to cure but to control the serum GH levels with the combination of other modalities [44]. Long-term octreotide-LAR treatment has shown profound endocrinologic effect and tumor volume reduction and may be useful in the preoperative treatment of large macroadenomas [26]. Of course, short-term octreotide treatment may have less advantage over long-term octreotide-LAR treatment. However, from our results, preoperative octreotide treatment even for short term may achieve better surgical results in Knosp grade 1–2 tumor and good responders in octreotide and bromocriptine challenge tests.

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