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NOTE

Effectiveness of Secondary Transnasal Surgery in GH-Secreting Pituitary Macroadenomas

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Abstract. Transsphenoidal surgery is the first therapeutic option in acromegaly, but the management of persistent or recurrent cases of the disease after surgery has been controversial. This study presented the results of secondary transnasal surgery for residual or recurring growth hormone (GH)-secreting macroadenoma with reference to intraoperative GH measurement. It focused on 22 patients who underwent secondary transsphenoidal surgery for 18 residual and 4 recurring GH-secreting pituitary macroadenomas from 1990 to 1999. To assess complete tumor removal, plasma GH concentration was measured intraoperatively. Before secondary surgery, plasma GH levels without medical treatment ranged from 2.0 to 239.0 μg/l (mean 31.5 +/– 50.4). Magnetic resonance imaging demonstrated 16 transnasally resectable tumors and 6 nonresectable grossly invasive tumors. Intraoperative plasma GH concentrations declined sufficiently in 9 of 16 with transnasally resectable tumors, but in the remaining 7 cases the tumors were further explored and normalization of GH levels was ultimately obtained in 4 out of these cases. It was impossible to completely remove the tumors in all the 6 patients with transnasally nonresectable tumors. Thirteen of 22 patients achieved endocrinological remission by rigorous criteria. In transnasally resectable tumors, the endocrinological remission rate was 81.3% (13 of 16 patients) with no recurrence during the follow-up period of at least 4 years. Secondary transnasal surgery for residual or recurring GH-secreting pituitary macroadenomas is a safe and effective treatment, if done along with intraoperative GH measurement. Endocrinological remission can be obtained with high probability in patients who suffer from macroadenomas with suprasellar extension, with the exception of transnasally nonresectable grossly invasive tumors.

Key words: Pituitary adenoma, Acromegaly, Recurrence, Secondary surgery, Growth hormone

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TRANSSPHENOIDAL surgery is the established method of treating acromegaly. However, there is at present no consensus as to the best therapeutic strategy for unsuccessfully operated or recurring patients. Although several authors have reported that a low success rate for reoperation [1–6], we obtained favorable surgical outcome in cases with residual or recurring growth hormone (GH)-secreting adenoma including microadenoma-like tumors [7]. Tumor size, extension, and invasiveness of the adenoma are important predictive factors of the outcome even in secondary surgery [1, 4, 7, 8]. In microadenomas selective tumor removal is relatively easily achieved, but the success rate declines in patients with macroadenomas [1, 2, 6–13]. However, in the light of new medical therapies, the indication for surgery has to be reconsidered. The present study thus focused on recent results of secondary surgery in GH-secreting macroadenoma applying intraoperative GH measurement.

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Patients and Methods

We analyzed the data from 22 patients who underwent secondary transsphenoidal surgery for residual or

recurring GH-secreting pituitary macroadenoma by one surgeon (D.K.L) at Hamburg University Hospital between January 1990 and April 1999. As summarized in Table 1, there were 13 female and 9 male patients, ranging from 26 to 64 years (mean 43.0 +/– 11.8 standard deviation (SD)) of age.

Pre- and postoperative endocrinological investigations were performed by referring endocrinologists and included measurements of plasma GH level and insulin-like growth factor (IGF-I) and oral glucose tolerance test. Other endocrinological findings were assessed on the basis of baseline hormonal levels. Endocrine stimulation tests were used when appropriate. Gonadotropin secretion deficiency in men was diagnosed with reference to serum testosterone level, as well as LH and FSH levels. In pre-menopausal women, serum estrogen was also measured.

Radiological investigations were obtained in all patients before and after surgery. On the basis of magnetic resonance imaging (MRI) scans, tumor size and extension were classified according to Luedecke's classification system [14] with the maximum diameter of tumor used as a basis: T1, up to 9 mm; T2, 10 to 20 mm; T3, 21 to 30 mm; T4, 31 mm more. Enclosed or invasive and transnasally resectable or non-resectable were described as well. The criterion for an invasive transnasally resectable adenoma was a tumor that does not significantly extend beyond a line tangent to the lateral aspects of the intra- and supracavernous internal carotid artery. Nonresectable macroadenomas were defined as tumors with apparent total encasement of the carotid artery or other adjacent arteries. The invasiveness of tumors was also confirmed during surgery.

Table 1. Clinical characteristics of 26 persistent or recurrent acromegaly patients

Characteristics	No. of Patients
total	22
F/M ratio	13 : 9 (1.4 : 1)
age (yrs) at time of op.	26–64
mean	43
Duration from primary to secondary surgery (mo)	16–217
mean	88
recurrence	4
persistent	18
Adjuvant therapy after primary surgery	
conventional radiation	2
SMS	8
SMS/DA	9
DA	4
Tumor	
size (mm)	11–46
mean	20.2
T2	14
T3	6
T4	2
transnasally resectable	16
transnasally non-resectable	6

SMS = somatostatin analogue octreotide; DA = dopamine agonist
Assessed according to Luedecke's classification (based on the maximum diameter of tumor): T2 = 10 to 20 mm; T3 = 21 to 30 mm; T4 = 31mm more

Intraoperative GH measurement

To assess the radicality of tumor removal, GH was measured intraoperatively. A modified immunoradiometric (Pharmacia, Uppsala, Sweden) or since 1996, chemilumininescence assay for GH levels (Nicholas Institute Diagnostics, San Juan Capistrano, CA) has been used with reduced incubation time (10 min) and increased temperature (37°C). This method enables a skilled technician to perform the assay within 30 min. Appropriate dilution was determined based on the preoperative GH levels. Intraoperative GH measurements were assayed at 0, 20, 40 and 60 min after initial tumor removal, as previously described [15–17]. A plasma GH level of 4.5 μg/l or less at 60 min after tumor removal was defined as a sufficient decline. In cases with preoperative plasma GH levels of 40 μg/l or more, the half-life of tumor GH at 20 min was taken into consideration. When GH levels declined insufficiently after tumor removal, further surgery was considered during continued anesthesia.

Follow-up endocrinological data were obtained 1 day and 1 week postoperatively and later from referring endocrinologists or physicians. Criteria for endocrinological remission in this series were normalization of plasma basal IGF-1 levels, a postoperative basal GH level below 2.5 μg/l, and suppression to less than 1 μg/l by oral glucose load.

Results

Preoperative data

Between January 1990 and April 1999, secondary transnasal surgery was performed in 36 patients with

GH-secreting pituitary adenomas. This comprised 10.6% of 339 patients who underwent surgery for acromegaly. Ten of 36 cases had microadenoma-like tumors. Twenty-two patients had previously undergone transsphenoidal surgery (surgery at our institutions, n = 2; surgery elsewhere, n = 20). The remaining 4 patients whose primary surgery was transcranial were excluded from this study.

Clinical data of 22 GH-secreting pituitary macroadenomas are summarized in Table 1. All patients underwent transnasal surgery, 4 of whom had recurring and 18 of whom had residual adenomas. These four recurring cases occurred from 27 to 137 months (mean 83.0 mo), and no consecutive transsphenoidal surgery was scheduled from them. Mean duration from primary to secondary surgery was 88.0 months (range, 16–217 months). Two of these patients received conventional radiotherapy. Medical treatment was performed in 21 cases after primary surgery, using somatostatin analogue octreotide (n = 8), dopamine agonists (n = 4), or both (n = 9). No patient achieved complete endocrinological remission with these adjuvant treatments. Before secondary surgery, plasma GH levels without medical treatment ranged from 2.0 to 239.0 μg/l (mean 31.5 +/– 50.4 μg/l). Basal IGF-1 levels were elevated in all patients. Tumors measured between 11 and 46 mm in diameter (mean 20.2 +/– 8.5), including 4 enclosed and 18 invasive adenomas. T2, T3, and T4 tumors were identified in 14, 6, and 2 patients, respectively, including 16 resectable and 6 nonresectable ones.

Surgical treatment

Direct transnasal approach to the sellar region through one nostril was applied in all patients, the operative technique of which has been described in detail elsewhere [7, 16, 18]. Tumor was removed piecemeal with blunt curettes using a micro-pressure-irrigation-suction system with different tips under mirror control, especially within extrasellar parts. Microdoppler was used to identify the actual position of the carotid artery. In questionable areas, tiny samples of tumor-suspicious tissue were investigated using a smear technique during surgery or frozen section in cases with firm tissue [19].

Intraoperative GH measurement

In addition to refinements in surgical techniques, intraoperative GH measurement as introduced by us was performed in all cases. Plasma GH concentrations declined sufficiently during surgery in 9 of 16 patients (56.3%) with transnasally resectable tumors (Fig. 1). However, in the remaining 7 cases, the tumors were explored further because of insufficient decline. In 5 of these patients, tumor remnants were located and removed. Normalization of GH was obtained in 3 cases (Fig. 2). In 2 cases, suspicious areas were merely coagulated because we could not detect clear nodules of additional tumor; GH levels subsequently declined and one of these 2 cases later achieved normalization of GH. It was impossible to remove the tumors completely in the 6 patients with transnasally nonresectable adenomas. In one of the 6 patients, further tumor removal was performed to reduce residual tumor mass and GH levels as much as possible (Fig. 3). The role of surgery in these nonresectable cases was to remove all accessible adenoma and to make preparation for stereotactic radiosurgery by circumscribing the residual pituitary tissue (Fig. 4).

Postoperative data

The results of secondary surgery in this series are shown in Tables 2 and 3. One patient of 16, who obtained the normalization of GH levels intraoperatively, did not achieve endocrinological remission by strict criteria. Thirteen (59.1%) of 22 patients achieved

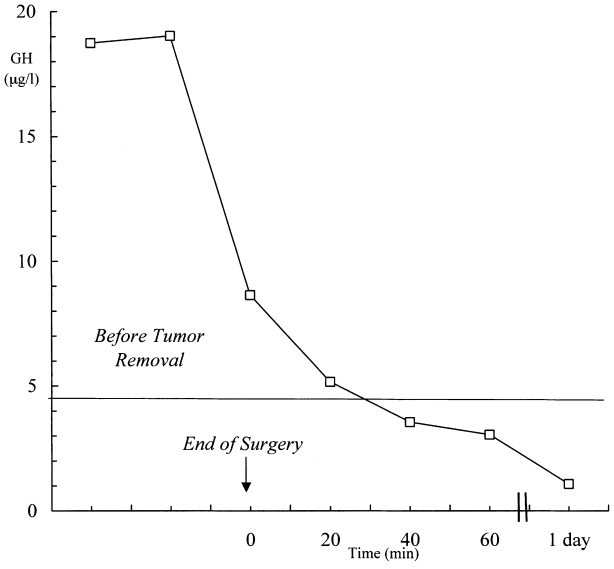

Fig. 1. Graph showing the intra- and postoperative GH measurement (mean) in cases with adequate GH decrease.

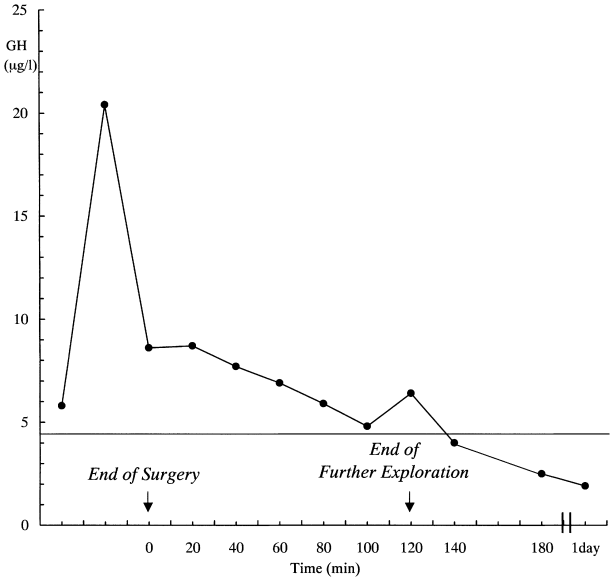

Fig. 2. Graph showing the intra- and postoperative GH measurement in a case with inadequate GH decrease (Case 16). Tumor remnant was found and completely removed with further exploration. Normalization of plasma GH concentration was then achieved.

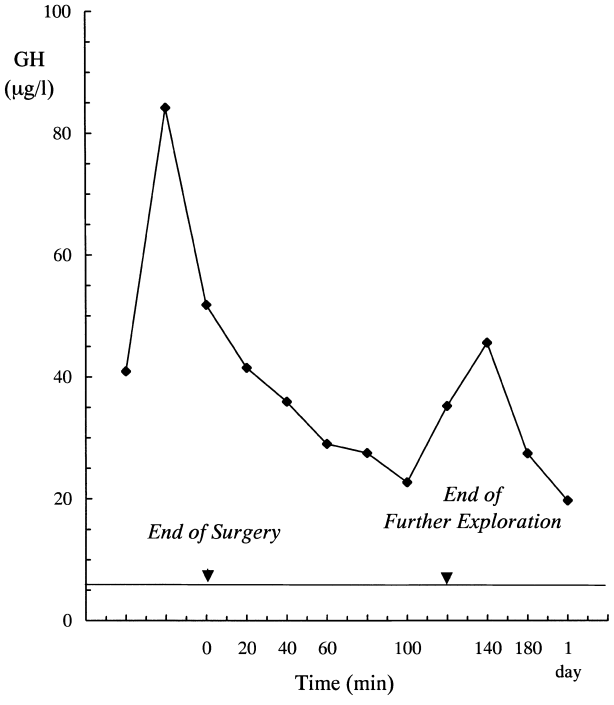

Fig. 3. Graph showing the intra- and postoperative GH measurement in a case with transnasally nonresectable grossly invasive pituitary adenoma (Case 21). Decline of plasma GH concentration was considered not to be sufficient even for nonresectable adenoma, therefore further tumor removal was undertaken.

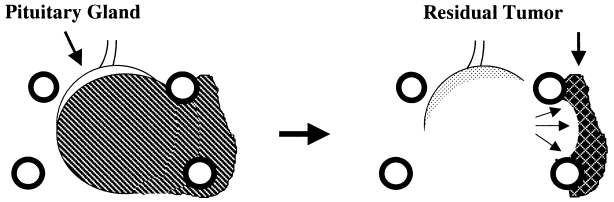

Fig. 4. Schematic drawing showing our basic principle of surgical strategies for transnasally nonresectable grossly invasive pituitary adenoma: radical removal, except for nonresectable part. After removing the intra and/or suprasellar tumor by surgery, nonresectable regions such as the cavernous sinus is considered to be a favorable target for radiosurgery.

endocrinological remission. In transnasally resectable tumors, the endocrinological remission rate was 81.3% (13 of 16 patients).

There were no cases of either major surgical complication or mortality. In 7 of 8 patients with normal pituitary function preoperatively, pituitary function was preserved after secondary surgery. No persistent diabetes insipidus was observed. No patient of 15 in remission had any recurrence during the follow-up period of more than 4 years.

After secondary surgery 3 patients underwent the Gamma Knife treatment. Medical treatment was performed in 8 cases, using the somatostatin analogue octreotide (n = 7), dopamine agonist (n = 1), or both (n = 1).

Discussion

A number of surgical series for the treatment of acromegaly have been reported [1, 2, 5–13, 20]. The frequency of recurrence after successful surgery has varied widely [1–3, 5, 6, 9], and it is difficult to distinguish between true recurrence and persistence [1, 8, 10]. Previous studies mostly include long periods of research, hence we focused on the last decade only. According to strict criteria for remission, true recurrences are rare and in most cases there is incomplete tumor removal rather than recurrence of new tumor [11]. In fact, only 4 of 22 patients had true recurrences indicating reoperation. In this study, we used the recent rigorous criteria (basal GH < 2.5 ng/ml, GH nadir after OGTT < 1 μg/l, age-sex-normalized IGF-1) for the interpretation of surgical results [21, 22].

Transsphenoidal selective adenomectomy is the es-

Table 2. Results of surgical treatment and serum GH concentrations

Case No.	Age (yrs)	Sex	GH (μg/l)					IGF-1 (ng/ml)	Adjuvant Dx	Remission by Surgery alone
			preop	intraop (high)	intraop (low)	postop	follow-up	follow-up		
Resectable adenoma (n = 18)										
1	57	F	12	10.5	3.9	2.2	1.4	189		+
2	48	M	22.5	118	18.3	2.8	1.5	253		+
3	35	M	1.9*	3	0.6	0.2	<0.05	181		+
4	40	F	3.8	21.9	9.3	1.5	0.7	214		+
5	52	M	6.1	22.8	5.6	1.3	0.4	166		+
6	59	F	8	27	8.7	4.9	<2.5	168		+
7	34	F	25*	27	12.9	17.6	<4.5	normal	SMS, gamma	–
8	64	M	5.9	10.6	5.2	2.2	1.9	131		+
9	48	F	24.8	30.6	14.7	10.3	10.1	elevated	SMS, gamma	–
10	59	F	8.6*	9.1	1.8	0.5	0.3	55.6		+
11	34	M	>5	73.4	5.8	3.8	5.8	elevated		–
12	57	M	18.7	30.1	1.3	0.9	0.4	95		+
13	26	F	3*	23.6	4.4	5.8	1	275		+
14	26	F	>5	22	4.4	0.8	0.7	161		+
15	44	F	7.1	22.6	2.9	0.9	0.8	normal		+
16	49	F	12	20.4	2.5	1.9	<0.5	203		+
Non-resectable adenoma (n = 8)										
17	40	M	7.4	34.4	10.5	36.9	8.6	elevated	SMS	–
18	31	F	97	154	73	36.4	11.2	elevated	SMS	–
19	32	M	236	281	123	67.4	8.6	elevated	SMS	–
20	36	M	19.4*	84.2	27.2	19.7	5	elevated	DA	–
21	47	F	9.3	55	33.3	11	8.2	214	DA, SMS	–
22	27	F	19.3	22.4	14.4	10.5	7.5	elevated	SMS, gamma	–

preop = preoperative data; intraop (high) = the highest GH concentration during surgery; intraop (low) = the lowest GH concentration during surgery; follow-up = the recent data; * = with medication; IGF-I = insulin-like growth factor
Adjuvant Dx = Adjuvant therapy after secondary surgery; SMS = somatostatin analogue octreotide; DA = dopamine agonist; rad = conventional radiotherapy; gamma = Gamma Knife treatment

Table 3. Results of secondary transsphenoidal surgery with intraoperative GH measurement

Tumor classification	Intraoperative GH measurement	Further Exploration	Remission
Resectable adenoma (n = 16)	sufficient decline (9)	0	9
	insufficient decline (7)	7	4
Non-resectable adenoma (n = 6)	sufficient decline (0)	0	0
	insufficient decline (6)	1	0

tablished primary treatment, but adjuvant therapy including radiotherapy and/or medical treatment should be considered, unless surgical cure is achieved [5–7, 20, 23–31]. Concerning medical treatment, suppressive therapy of GH secretion with somatostatin analogue or with the less effective dopamine agonist is often incomplete [6, 20, 23–25, 29, 30]. In previous reports, chronic octreotide treatment reduced plasma GH concentrations in the majority of patients, but lowering of GH to 2.5 μg/l or lower occurred only in 50% or less. Normalization in plasma IGF-1 occurred in 20–61% of patients. Moreover, the degree of reduction was usually less than 50% [23–25, 29, 30].

Conventional radiotherapy has been usually recommended after incomplete removal of the GH-secreting adenoma [5, 28, 30], but it takes several years to suppress the GH concentration within normal range. Roelfsema *et al*. [5] reported that 23 of the 31 irradiated patients were considered in remission of disease after a mean follow-up of 2.7 years, although the time course of radiation effectivity is much longer in most series [6, 27, 28, 30]. In addition, hypopituitarism

develops in a large proportion of patients as one of the side effects of radiotherapy [5, 27, 28, 30].

In our series, 20 patients underwent medical treatment after prior surgery including 2 with radiotherapy, but no patients achieved endocrinological remission. In such cases, we performed the surgical treatment when neuroradiological data showed the presence of a residual tumor. In fact, our remission rate in microadenomas was 100%, as previously reported [7]. Although several authors reported that the complication rate for secondary surgery was high [1, 2, 4, 5, 8], there were no major and only rarely minor morbidity in our series.

The objective of the present study was to evaluate the safety and long-term efficacy of secondary surgery for macroadenoma performed along with intraoperative GH measurement. GH measurement allows us to intraoperatively evaluate the completeness of tumor removal and thus improve the surgical outcome by further exploration in the same operative session, if necessary [13, 15, 17]. During the secondary surgery we sometimes had difficulty detecting the tumor or confirming radical tumor removal because of scarring of the intrasellar region from the previous therapy, and in such cases, intraoperative GH measurement was especially helpful. In 7 of 18 transnasally resectable cases, the tumor cavity was further explored because of insufficient GH decline. Residual adenomas were located at the cavernous sinus or infiltrated the tumor capsule in 5 of these 7 cases. However, in the remaining 2 cases, the tumors were not detected. Taking these results of further exploration into account, the remission rate for transnasally resectable adenomas improved from 56.3% to 81.3%.

Moreover, the sufficient decline of intraoperative GH levels can predict remission during long-term follow up. In our series, among 13 patients who obtained the normalization of GH levels intraoperatively, only one patient did not achieve endocrinological remission during the follow-up period. van den Berg *et al*. [32] also demonstrated that the positive predictive value was 100% in terms of long-term cure by applying 25 min as the upper normal limit for the GH plasma half-life.

In nonresectable tumors, a multimodality therapy in combination with secondary surgery and adjuvant therapy has to be considered. First, we remove tumor mass as much as possible by using refined microsurgical techniques, monitoring the reduction in GH levels by intraoperative GH measurement. Regarding tumors in surgically critical and/or nonresectable regions such as the lateral aspects of the carotid artery in the cavernous sinus, we tried to clarify the situation for subsequent stereotactic radiosurgery so that the remaining pituitary may be kept out of the radiation field [33]. We were thus able to show that secondary surgery may be helpful even in cases with gross invasion, since even an extrasellar invasive tumor, except for the part behind the carotid siphon, can be radically removed at this stage.

Conclusions

This study confirmed that intraoperative GH monitoring is a useful tool to improve the surgical results in secondary operation for acromegaly. In the majority of resectable adenomas, operations could be safely managed with reference to the results of intraoperative GH measurement. In about 20% of this group, the direct control allowed further tumor removal with low incidence of complication. In nonresectable adenomas intraoperative GH measurement was less essential, and the indication for surgery in such cases was to remove all accessible adenoma mass and to clarify the situation for subsequent stereotactic radiosurgery.

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