TRANSSPHENOIDAL SURGERY (TSS) is the first-line treatment for growth hormone (GH)-producing pituitary adenomas in most patients with acromegaly. Thanks to the recent refinements in instruments and techniques, surgical outcomes are improving, and approximately 70% of patients have a chance of achieving endocrinologic remission in experienced hands regardless of whether a microscope or endoscope is used [1-4]. The remission consensus criteria for acromegaly also have been showing continuous evolution. The current strict consensus criteria are defined as follows: a nadir serum GH level of <0.4 ng/ml after an oral glucose load, and subsequent normal sex- and age-adjusted IGF-1 levels. When the biochemical remission is clearly achieved postoperatively, the long-term recurrences are usually uncommon [5-7]. On some occasion, however, the discordance between the GH nadir and IGF-1 level, changes of these parameters associated with time, and the long-term recurrences have been reported [6-15]. In this study, we evaluated the discrepancies between the short-term (<1 year) and long-term (>4 year) outcomes and discussed the pitfalls in the early biochemical evaluation of transsphenoidal surgery in patients with acromegaly.

Methods

We retrospectively reviewed 150 consecutive patients with acromegaly who underwent primary TSS for removal of a GH-producing adenoma during 2011 and 2012 [2], which included 28.7% (150/522) of all adenomas removed by TSS during this period at Toranomon hospital. Biochemical remission was achieved in 127 of 150 patients (84.7%) in the short-term evaluation.

Among 150 patients, 21 patients were lost of follow and one patient died of uncertain cause during the follow-up. Thus 128 patients were included for the present
Oral glucose tolerant test (GTT) was performed before surgery, at one to two weeks, and then occasionally after surgery. The mean preoperative serum GH level was 30.1 ng/ml (range 1.3-541.4 ng/ml, median 13.5 ng/ml), IGF-1 level was 688 ng/ml (range 275-1,340 ng/ml, median 634 ng/ml), and IGF-1 SD score was 7.2 (range 2.8 to 12.8, median 7.0). Endocrinological outcomes were assessed according to the current consensus criteria for acromegaly.

Statistical analyses were performed using the non-parametric chi-square and the Mann-Whitney U tests.

**Results**

Among 106 patients who satisfied the remission criteria at early evaluation, 105 patients (98.1%) remained remission in the long-term follow (Fig. 1).

![Flow diagram summarizing early and long-term postoperative biochemical outcomes of 128 patients with acromegaly](image)

*Fig. 1* Flow diagram summarizing early and long-term postoperative biochemical outcomes of 128 patients with acromegaly

128 cases

Early evaluation

106 cases

nGH<0.4, ⋄IGF1

Remission

7 cases

nGH>0.4, ⋄IGF1

Non-remission

15 cases

nGH>0.4, ⋄IGF1

Long-term evaluation

1 case

nGH>0.4, ⋄IGF1

AdTx

105 (88 + 37*) cases

Remission

6* cases

(⋄IGF1) AdTx

10 (5 + 5*) cases

⋄IGF1 AdTx

1 case

nGH>0.4, ⋄IGF1

Obs.

2 cases

nGH<0.4, ⋄IGF1

Remission

3 cases

nGH NE, ⋄IGF1

Obs.

Endocrinological examinations including random GH and IGF-1 levels were performed in all patients before surgery, at one week, a few months, and at least once every year after surgery. GH levels were measured with a fluorescent enzyme immunoassay (ST AIA-PACK HGH, Tosoh Co., Tokyo, Japan). Serum IGF-1 levels were measured with an immunoradiometric method (IGF1 IRMA Daiichi, TFB Co., Tokyo, Japan).
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5 patients developed delayed normalization of IGF-1 level between 13 to 27 months after surgery without any treatment (Fig. 1, Table 1). The 5 patients were all women. None of them had been treated with preoperative SSA and had shown residual tumor in the postoperative MRI. Their early GH nadir levels were higher than 1.0 ng/ml and between 0.4 and 1.0 ng/ml in 3 and 2 patients, respectively. In the latter 2 patients, the long-term GH nadir levels became lower than 0.4 ng/ml, satisfying the remission criteria 13 and 26 months after surgery. Thus overall long-term remission was achieved in 107 patients (83.6%). Preoperative treatment with SSA did not correlated with the short- and long-term outcomes.

In the long-term follow, 21 patients were judged not cured by surgery. Tumor was invading CS in 17 patients and a residual tumor was observed in postoperative MRI in 7 patients. Beside 4 patients who are under close observation because of persistent normal IGF-1 levels and no residual tumor on MRI, 17 patients achieved remission with additional treatments. These included the followings: SSA in 5 patients, cabergoline in 5 patients, CK in 2 patients, combination of SSA and CK in 4 patients, and combination of SSA and cabergoline in one patient.

There were 7 patients who showed normal IGF-1 and high GH nadir levels at early evaluation. 6 of them had been treated with SSA preoperatively (Fig. 1). Since 2 patients had a residual tumor in the cavernous sinus (CS) on postoperative MRI, cyberknife radiotherapy (CK) was performed within a year after surgery resulting in a long-term remission. Other 4 patients developed re-elevation of IGF-1 level 12 to 36 months after surgery, and required additional treatments to control acromegaly. These 4 patients had a tumor with CS invasion and, in one patient, a residual tumor was noted in the lateral compartment of CS. In 48 patients with pretreatment with SSA, the dose and duration did not show correlation with the re-elevation of IGF-1. Another patient without preoperative SSA treatment remained normal IGF-1 level on the long-term follow. Her recent GH nadir was 0.66 ng/ml without treatment.

On the other hand, among 15 patients who failed to satisfy the remission criteria in early evaluation with high GH nadir and IGF-1 levels, 5 patients developed delayed normalization of IGF-1 level between 13 to 27 months after surgery without any treatment (Fig. 1, Table 1). The 5 patients were all woman. None of them had been treated with preoperative SSA and had shown residual tumor in the postoperative MRI. Their early GH nadir levels were higher than 1.0 ng/ml and between 0.4 and 1.0 ng/ml in 3 and 2 patients, respectively. In the latter 2 patients, the long-term GH nadir levels became lower than 0.4 ng/ml, satisfying the remission criteria 13 and 26 months after surgery. Thus overall long-term remission was achieved in 107 patients (83.6%). Preoperative treatment with SSA did not correlated with the short- and long-term outcomes.

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**Fig. 2** Illustrative case of a 25 year-old man with acromegaly

GH-producing adenoma (densely-granulated subtype) was totally resected via transphenoidal surgery. Despite biochemical remission on early evaluation, IGF-1 re-elevated 14 months after surgery. (Coronal and sagittal gadolinium-enhanced MRI images before and after surgery)
On rare occasions, normalization of IGF-1 levels may be further delayed until 12 months or more after surgery [17]. In the present series, 5 patients (33.3%) with high GH nadir and IGF-1 levels at early evaluation, showed delayed normalization of IGF-1 level between 13 to 27 months after surgery without any treatment. 2 of them satisfied the remission criteria 13 and 26 months postoperatively. Shin [17] reported in their series of 46 patients with high IGF-1 and normal GH nadir levels and without residual tumor on postoperative MRI, the delayed IGF-1 normalization, that means remission, was achieved in 24% of patients more than 12 months after surgery. Surprisingly, 7% of them achieved remission between 48 to 60 months after surgery. None of our patients had conditions that may affect IGF-1 levels, including hepatic and renal failure, thyroid dysfunction, malnutrition, malignancies, pregnancy, poorly controlled diabetes mellitus, et al. [12,18].

The discordance between the GH nadir and IGF-1 levels may be further delayed until 12 months or more after surgery [17]. In the present series, 5 patients (33.3%) with high GH nadir and IGF-1 levels at early evaluation, showed delayed normalization of IGF-1 level between 13 to 27 months after surgery without any treatment. 2 of them satisfied the remission criteria 13 and 26 months postoperatively. Shin [17] reported in their series of 46 patients with high IGF-1 and normal GH nadir levels and without residual tumor on postoperative MRI, the delayed IGF-1 normalization, that means remission, was achieved in 24% of patients more than 12 months after surgery. Surprisingly, 7% of them achieved remission between 48 to 60 months after surgery. None of our patients had conditions that may affect IGF-1 levels, including hepatic and renal failure, thyroid dysfunction, malnutrition, malignancies, pregnancy, poorly controlled diabetes mellitus, et al. [12,18].

The discordance between the GH nadir and IGF-1 levels include 2 patterns: normal GH suppression with elevated IGF-1 level and abnormal GH suppression with normal IGF-1 level. In the present series, none of our patients belonged to the former pattern after surgery. Among 7 patients with the latter pattern, 6 patients had been preoperatively treated with SSA. In 4 patients, IGF-1 levels re-elevated more than one year after surgery, and required additional treatment to control acromegaly. Two other patients underwent CK for a residual tumor. Biochemical remission may not always indicate a total removal of the tumor when GH secretory activity of the residual tumor is low.

### Discussion

The primary goal of treatment for acromegaly is to normalize both GH and IGF-1 levels. The remission consensus criteria for acromegaly have been showing continuous evolution. The current criteria are clear and concise. According to the criteria, overall remission rates ranging from 60 to 85% are reported in the large surgical series [1-4]. In general, cavernous sinus invasion of the tumor and serum GH levels are the most significant preoperative predictors of remission [1-4]. When the biochemical remission is clearly documented after surgery, recurrences are uncommon compared with those in Cushing disease and prolactinomas [6,16]. It has been generally regarded that the long-term results can be reliably predicted by the remission criteria early after surgery [6,7].

However, there is a problem concerning the evaluation immediately after surgery. The results of two tests are not always congruent. Postoperative discordance between the GH nadir and IGF-1 levels may be seen in up to 30% of patients, particularly within 3 months after surgery [6-15]. It has been reported that IGF-1 levels may show fluctuation during the immediate postoperative period toward stabilization at around 3 months postoperatively [6,9,11]. The GH nadir may also change over time, albeit slightly, in some patients. The decline in IGF-1 is more delayed compared with GH, likely due to differential half-life of IGF-binding proteins [11]. Consequently, the positive and negative values of the criteria for remission may increase from few weeks to 3 months postoperatively [6].

<table>
<thead>
<tr>
<th>Age/Gender</th>
<th>Preoperative</th>
<th>Tumor size (mm)</th>
<th>Knosp grade</th>
<th>PreTx-SSA</th>
<th>Resect.</th>
<th>Hist.</th>
<th>Early evaluation</th>
<th>Long-term evaluation</th>
<th>Months*</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>GH (SDs)</td>
<td>IGF1 (SDs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>nGH (rGH)</td>
<td>IGF1 (SDs)</td>
<td>nGH (rGH)</td>
</tr>
<tr>
<td>1. 52F</td>
<td>14.4 (9.2)</td>
<td>861 (9.2)</td>
<td>21.6</td>
<td>3 (-)</td>
<td>Total</td>
<td>SG</td>
<td>0.6 319 (3.9)</td>
<td>0.3 156 (1.4)</td>
<td>26</td>
</tr>
<tr>
<td>2. 56F</td>
<td>16.9 (9.5)</td>
<td>939 (9.5)</td>
<td>18.5</td>
<td>0 (-)</td>
<td>Total</td>
<td>DG</td>
<td>0.5 269 (3.1)</td>
<td>0.04 172 (1.2)</td>
<td>13</td>
</tr>
<tr>
<td>3. 54F</td>
<td>25.3 (8.9)</td>
<td>828 (8.9)</td>
<td>15.7</td>
<td>1 (-)</td>
<td>Total</td>
<td>DG</td>
<td>&gt;1.0 318 (3.9)</td>
<td>(1.0) 165 (1.0)</td>
<td>21</td>
</tr>
<tr>
<td>4. 63F</td>
<td>21.1 (6.6)</td>
<td>549 (6.6)</td>
<td>17.3</td>
<td>3 (-)</td>
<td>Total</td>
<td>SG</td>
<td>&gt;1.0 278 (3.5)</td>
<td>(2.3) 172 (1.6)</td>
<td>25</td>
</tr>
<tr>
<td>5. 67F</td>
<td>3.9 (4.8)</td>
<td>359 (4.8)</td>
<td>20.0</td>
<td>3 (-)</td>
<td>Total</td>
<td>DG</td>
<td>&gt;1.0 280 (3.8)</td>
<td>(1.29) 156 (1.4)</td>
<td>13</td>
</tr>
</tbody>
</table>

GH and IGF1 levels in ng/ml; SDs, SD score; PreTx-SSA, pretreatment with somatostatin analog; Resect., degree of resection on postoperative MRI; Hist., histological subtype; nGH, nadir GH after glucose load; rGH, random GH; Months*, postoperative month of IGF1 normalization; F, female; SG, sparsely-granulated subtype; DG, densely-granulated subtype.

Table 1 Summary of 5 patients who showed delayed normalization of IGF-1 level after surgery
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[19], but normal GF-1 early after surgery in these 2 patients was presumably due to the prolonged effect of preoperative SSA treatment.

The Endocrine society clinical practice guideline suggested against the routine use of preoperative SSA therapy to improve biochemical control after surgery [18]. Although controversial, some authors reported improved surgical cure rates with the pretreatment for macroadenomas [20,21]. Preoperative use of long-acting SSA induces clinically relevant tumor shrinkage in more than half of patients with acromegaly and may reduce surgical risk from comorbidities [18,20,22]. We have been introducing the preoperative SSA treatment for acromegalic patients with large tumor and/or comorbidities. In pharmacokinetic profile study of a long-acting octreotide 30mg in healthy subjects, plateau concentrations were maintained until day 70 and then gradually declined to below the limit of quantification by day 112 [23]. The profile was dose proportional [24]. The concentration of a SSA required to control GH can vary significantly between patients according to various factors including the degree of somatostatin receptor expression and receptor sensitivity. Although it is unlikely that preoperative SSA treatment had directly affected GH and IGF-1 levels for more than one year after surgery, careful interpretation is indispensable for postoperative evaluation of IGF-1 and GH nadir levels in patients with SSA pretreatment.

On the other hand, GH nadir after an oral glucose load may also fluctuate after surgery, but the lengths of fluctuation differs among the reports. Feelders [11] reported that already 1 week after surgery, GTT using 0.5 ng/ml as the GH nadir cutoff value is reproducible over time and has a high predictive value for remission. In contrast, Kristof [16] reported that the incidence of false early pathological GTT results is surprising high (16.4%) and the GTT appears to be more reliable at 3 months postoperatively. Espinosa-de-Los-Monteros [9] reported that both IGF-1 and GH nadir levels might change for a year after surgery and that the GH suppression by glucose tended to worsen rather than improve over time. In the present series, there were 2 patients who achieved delayed normalizations of both IGF-1 and GH nadir levels more than one year after surgery. Conditions other than acromegaly that may cause abnormal GH suppression including chronic renal insufficiency, liver failure, hyperthyroidism, diabetes mellitus, malnutrition, et al. [2,12] was not observed in these patients. On the other hand, gender-specific nadir GH criteria may be needed because these levels may be higher in some women than men [12,25]. Every 5 patients who showed delayed normalization of IGF-1 level despite high GH nadir at early evaluation were woman. In the 2 patients examined, their GH nadir levels became lower than 0.4 ng/ml at the long-term follow. This may also indicate that the long-term fluctuation of GH nadir and IGF-1 levels after surgery may be more frequent in women than men.

In our previous study, we found out that insulin resistance immediately after surgery was predictive of and correlated with the GH nadir at the first postoperative year evaluation [26]. Although the relationship between insulin resistance and the GH nadir is unclear, we suggested that defective central somatostatin tone as a possible cause of impaired GH suppression [27].

Conclusions

In many patients with acromegaly, the long-term surgical outcomes can be reliably predicted by early evaluation. For some patients, however, influence of preoperative SSA treatment, delayed normalization of IGF-1, and poor GH suppression due to low insulin resistance can be the pitfalls that lead to a false decision in early evaluation. In a few patients, particularly in women, a definite decision of remission using the current criteria may require more than a year after surgery.

References