Surgical Results and Predictors of Initial and Delayed Remission for Growth Hormone-Secreting Pituitary Adenomas Using the 2010 Consensus Criteria in 162 Patients from a Single Center

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■ BACKGROUND: **The factors associated with initial and delayed remission after growth hormone (GH)-secreting pituitary adenoma excision have not been completely elucidated.**

■ METHODS: **We recruited 185 consecutive patients who had undergone resection of GH-secreting pituitary adenomas from January 2013 to December 2014 and assessed their tumor characteristics and surgical outcomes. The criteria for initial or delayed remission (using the 2010 consensus criteria) were normalized insulin-like growth factor 1 (IGF-1) levels, GH levels <0.4 μg/L with an oral glucose tolerance test, and/or random GH levels <1.0 μg/L at or after the postoperative 3-month (PO3M) follow-up, without adjuvant therapy.**

■ RESULTS: **Remission was achieved in 92 of 162 patients (56.8%) after surgery alone and was associated with a lower Knosp grade of 0–2 and lower postoperative day 1 GH level on multivariate regression analysis. A baseline IGF-1 index (IGF-1 level/upper limit of normal) of <2.835 predicted for initial remission at the PO3M follow-up (positive predictive value, 95.3%; negative predictive value, 36.6%; *P* < 0.001). The PO3M IGF-1 index was significantly lower in the delayed remission group than in the nonremission group. Furthermore, the former had had fewer invasive tumors (1.23 ± 0.21 vs. 1.77 ± 0.37 [9.52% vs. 76.47%]; *P* < 0.001). A PO3M IGF-1 index of <1.485 predicted for delayed remission during subsequent follow-up (positive predictive value, 84.6%; negative predictive value, 92.3%; *P* < 0.001).**

■ CONCLUSIONS: **A lower Knosp grade of 0–2 and lower postoperative day 1 GH level were independent predictors of surgical remission. The baseline IGF-1 and PO3M IGF-1 indexes might predict for initial and delayed remission, respectively.**

INTRODUCTION

Growth hormone (GH)-secreting pituitary adenoma (PA) is an insidious disease with an estimated annual incidence of 30–50 cases/1 million population.[1] It has an associated 1.72-fold increase in mortality risk, mainly because of cardiovascular, respiratory, and metabolic complications.[2]

Transsphenoidal surgery is the first-line treatment of GH-secreting PAs.[3] The 2010 consensus criteria defined remission as the restoration of insulin-like growth factor 1 (IGF-1) levels to normal, a reduction of GH levels to <0.4 μg/L during an oral

Key words
- Acromegaly
- Delayed remission
- Initial remission
- Pituitary adenoma

Abbreviations and Acronyms
AUC: Area under the curve
CI: Confidence interval
CSF: Cerebrospinal fluid
CV: Coefficient of variation
GH: Growth hormone
IGF-1: Insulin-like growth factor 1
MRI: Magnetic resonance imaging
NPV: Negative predictive value
OR: Odds ratio
PA: Pituitary adenoma
PO3M: Postoperative 3-month
POD1: Postoperative day 1
PPV: Positive predictive value
ROC: Receiver operating characteristic

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glucose tolerance test, and/or random GH levels to <1.0 μg/L.[4] Most patients will achieve an initial remission within 3 months; however, some have shown delayed remission without adjuvant therapy.[5] IGF-1 levels can require several months or longer to revert to normal levels after surgery,[6] and the rate of discordance between the GH and IGF-1 levels after surgery has been >30%.[7] These factors could complicate the interpretation of surgical outcomes and interfere with decision-making regarding postoperative adjuvant therapy. Previous studies have revealed that preoperative serum GH levels, tumor volumes, the presence of cavernous sinus invasion, and surgeon experience are the most significant factors influencing remission.[8,9] However, the factors that influence initial versus delayed remission and the discordance between the GH and IGF-1 levels have not been completely elucidated. Hence, the aims of the present study were to evaluate the efficacy of neurological surgery as a treatment of GH-secreting PAs and identify the predictors for both initial and delayed remission.

METHODS

Patients

We performed a retrospective study of prospectively recorded outcomes of PA excision surgery performed from January 2013 to December 2014 at the largest tertiary referral center in East China. The study included 185 consecutive patients with GH-secreting PAs (80 men and 105 women); their mean age was 44 ± 12 years. The inclusion criteria were failure to suppress GH levels <1 μg/L in response to a 75-g oral glucose load, serum IGF-1 levels greater than the age- and sex-matched reference range, and a pathological diagnosis of a GH-secreting adenoma. Patients without follow-up data for ≥3 months after surgery were excluded from further analysis of the surgical outcomes. The patients' medical records and imaging studies were reviewed after the Huashan institutional review board approved the present study.

Endocrine Assessment

The levels of GH, IGF-1, and all adenohypophyseal hormones were measured in the pre- and postoperative endocrinologic evaluation. GH was measured using the 2-site chemiluminescent immunometric assay AutoDELFIA hGH (PerkinElmer Life and Analytical Sciences, Wallac Oy, Finland), which had an intra-assay coefficient of variation (CV) of 5.3%–6.5%, an interassay CV of 5.7%–6.2%, and a sensitivity of ≤0.01 μg/L (≤0.026 mU/L). IGF-1 was measured using the highly purified recombinant IGF-1 (World Health Organization first international standard according to the Consensus Criteria 2010) using an Immulite 2000 solid-phase, enzyme-labeled chemiluminescent immunometric assay (Siemens Healthcare Diagnostic Products Limited, Surrey, UK). The expected values stratified by age were as follows: 1–6 years, 49–327 μg/L; 7–11 years, 57–551 μg/L; 12–13 years, 143–850 μg/L; 14–16 years, 220–996 μg/L; 17–18 years, 163–731 μg/L; 19–20 years, 127–483 μg/L; 21–35 years, 115–358 μg/L; 36–50 years, 94–284 μg/L; and >50 years, 55–238 μg/L. The intra-assay CV was 2.3%–3.5%, the interassay CV was 7.0%–7.1%, and the sensitivity was 20 μg/L. The IGF-1 index was calculated as IGF-1/upper limit of normal.[10]

Radiological Assessment

Magnetic resonance imaging (MRI) with and without contrast was performed preoperatively, every 3–6 months during the first postoperative year, and annually thereafter. PAs with diameters <10 mm and ≥10 mm were defined as microadenomas and macroadenomas, respectively. Suprasellar extension and sphenoid sinus invasion by the tumors were categorized according to the Hardy-Wilson classification. Invasive adenoma was defined as grade ≥III or stage C–E.[11] Cavernous sinus invasion was evaluated using the Knosp classification. Knosp grade 3–4 was considered cavernous sinus invasion.[12] The tumor volume was estimated using the equation developed by Di Chiro and Nelson[13] (volume = 0.5 × length × height × width).

Surgical Approaches and Techniques

The vast majority of the surgical procedures (n = 183) were performed via the transsphenoidal route, including 142 using a microscopic approach and 41 using an endoscopic approach. In 2 patients with invasive, asymmetrical suprasellar, retrosellar, and/or supraclinoidal parasellar extension, transcranial surgery via a pterional approach was used. The microscopic technique used was based on the standard microscopic transseptal approach popularized by Hardy and Vezina.[14] After submucosal detachment, a nasal speculum was used to visualize the floor of the sphenoid sinus and sella, after which the dura was opened and tumor removed using suction and curettes. The endoscopic approach used has been described previously.[15] In brief, the sellar floor between the carotid protuberances was removed under microvascular Doppler ultrasound guidance, and a wide dural opening was then created from the medial cavernous sinus walls and from the intercavernous sinus to the clivus. The 4-hand bi-nostril bimanual technique was used to excise the tumor. The transcranial pterional approach used has been described previously.[16] After a frontal temporal craniotomy, the sphenoid ridge was resected downward to the superior orbital fissure. The arachnoid membrane covering the Sylvian fissure and optic-carotid cistern was dissected. Tumor removal was performed between the optic nerves, chiasm, and carotid arteries; preserving these important structures and the pituitary stalk was prioritized.

Statistical Analysis

Data are presented as the mean ± standard deviations (or median and interquartile range) for continuous variables normally or not normally distributed and as frequencies for categorical variables. Normality was tested using the Kolmogorov-Smirnov test. The mean values were compared using the unpaired t test when the data distribution was normal and the Wilcoxon rank sum (Mann-Whitney U) test when the variables were not normally distributed. For categorical variables, the differences were analyzed using the χ^2 or Fisher exact test, as appropriate. Odds ratios (OR) and 95% confidence intervals (CIs) were calculated using univariate logistic regression. Clinical covariates that predicted the remission with a univariate P value <0.15 were subjected to multivariable logistic regression analysis.[17] After construction of receiver operating characteristic (ROC) curves, Youden indexes were calculated to determine the optimal cutoffs that can predict surgical remission (sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV]). Statistical analysis was performed using the SPSS, version 24.0, statistical software (IBM Corp., Armonk, New York, USA). A 2-tailed P value <0.05 was considered to indicate statistical significance.

RESULTS

Patient and Tumor Characteristics

The study included 177 patients with macroadenoma (97.3%) and 5 with microadenoma (2.7%); no preoperative MRI data were available for the remaining 3 patients. The characteristics of the study population are summarized in Table 1. All the patients showed symptoms of acromegaly. In addition, 7 patients complained of visual defects, 1 of diplopia, 9 of menstrual disorders, and 1 of infertility. The median duration of disease was 4 years (interquartile range, 2–6). Using the Hardy-Wilson classification, 98 tumors were invasive (53.8%) and 84 were noninvasive (46.2%; Table 2). Additionally, 109 tumors were Knosp grade 0–2 (59.9%) and 73 were Knosp grade 3–4 (40.1%). Immunohistochemical examination revealed GH-secreting adenomas in all patients. The invasive adenomas were significantly larger (4.38 cm^3 vs. 1.14 cm^3; P < 0.001), had a longer maximum diameter (2.50 cm vs. 1.55 cm; P < 0.001), and had produced greater baseline GH levels (31.69 μg/L vs. 14.73 μg/L; P < 0.001) compared with the noninvasive adenomas. The average follow-up period from surgery to the most recent follow-up laboratory test was 24 months (range, 3–48).

Surgical Results and Predictors for Remission

Of the 185 patients, 162 (87.6%) had undergone follow-up examinations for ≥3 months after surgery; remission was achieved in 92 patients (56.8%) after surgery alone. The remission rate for those with microadenomas and macroadenomas was 100% (4 of 4) and 56.1% (88 of 157), respectively (P = 0.136). The remission rate for those with invasive and noninvasive adenomas was 28.9% (24 of 83) and 87.2% (68 of 78), respectively (P < 0.001). The remission rate for those with invasive adenomas with and without cavernous sinuous invasion was 14.3% (9 of 63) and 75% (15 of 20), respectively (P < 0.001). The remission rate after primary and repeat surgery was 57.8% and 46.7%, respectively (P = 0.406). Finally, the remission rate for patients who had undergone microscopic versus endoscopic surgery was 60.0% and 48.6%, respectively (P = 0.172). Details of the remission rates for the Hardy-Wilson classified tumors are presented in Table 2.

We divided patients into those with remission (n = 92) and those without remission (n = 70; Table 3). The patients in the remission group compared with the nonremission group were older (P = 0.001), had smaller tumor volumes and shorter maximum diameters (P < 0.001), had lower baseline GH levels (P < 0.001), and had fewer invasive tumors and fewer with cavernous sinus invasion (P < 0.001 for both). No differences were found in disease duration, sex distribution, incidence of intraoperative cerebrospinal fluid (CSF) leak, baseline IGF-1 index, or Ki-67 index between the 2 groups (P > 0.05). Further analysis of the noninvasive adenomas showed no differences in tumor volume, maximum diameter, and patient age between the remission (n = 68) and nonremission (n = 10) groups (P > 0.05; Supplementary Table 1). After univariate analysis (Table 4), patient age, tumor volume, maximum diameter, noninvasiveness, Knosp grade 0–2 (i.e., no cavernous sinus invasion), Ki-67 index, baseline GH level, and postoperative day 1 (POD1) GH level were included in the multivariate analysis. The independent predictors

Table 1. Baseline Characteristics

Variable	Value
Sex	
Male	80
Female	105
Age (years)	44 ± 12
Duration (years)	4 (2–6)
Ki-67 index (%)	2.0 (1.0–2.0)
Maximum tumor diameter (cm)	1.90 (1.50–2.73)
Tumor volume (cm^3)	2.07 (0.91–5.38)
Tumor invasion (%, *n*)	53.8 (98/182)
Cavernous sinus invasion (%, *n*)	40.1 (73/182)
GH (μg/L)	21.25 (8.61–43.15)
IGF-1 index	2.95 ± 0.84

Data presented as mean ± standard deviation or median (interquartile range) for continuous variables normally or not normally distributed and as % (n/N) for categorical variables. Normality was tested using the Kolmogorov-Smirnov test.
GH, growth hormone; IGF-1, insulin-like growth factor 1.

Table 2. Hardy-Wilson Classification of Our Cohort

Hardy-Wilson Classification	Patients (*n*)	Patients with Follow-Up Data (*n*)	Patients in Remission (*n*)	Remission Rate (%)
10	3	3	3	100
20	37	36	34	94
2A	36	31	25	81
2B	8	8	6	75
2C	2	2	2	100
2D	2	2	1	50
2E	49	46	7	15
30	16	11	7	64
3A	3	3	3	100
3B	1	1	1	100
3C	1	1	1	100
3E	20	16	2	13
4E	3	0	0	0
5E	1	1	0	0
NA	3	1	0	0

NA, not available.

Table 3. Comparison of Baseline Variables Between Remission and Nonremission Groups

Variable	Remission Group (n = 92)	Nonremission Group (n = 70)	P Value
Age (years)	46 ± 12	40 ± 11	0.001*
Male sex (%, n)	38.0 (35/92)	44.3 (31/70)	0.423
Duration (years)	4.0 (2.0–7.3)	4.0 (2.0–5.0)	0.617
Ki-67 index (%)	1.0 (1.0–2.0)	2.0 (1.0–2.0)	0.059
Maximum tumor diameter (cm)	1.70 (1.30–2.40)	2.30 (1.75–3.10)	<0.001*
Tumor volume (cm^3)	1.26 (0.60–4.00)	3.74 (1.63–6.98)	<0.001*
Baseline GH (μg/L)	14.27 (5.82–27.64)	37.35 (15.01–55.38)	<0.001*
Baseline IGF-1 index	2.89 ± 0.77	3.01 ± 0.89	0.391
Invasive adenoma	26.1 (24/92)	85.5 (59/69)	<0.001*
Cavernous sinus invasion	9.8 (9/92)	78.3 (54/69)	<0.001*
Intraoperative CSF leak	79.3 (73/92)	70.6 (48/68)	0.202

Data presented mean ± standard deviation, as median (interquartile range), or % (n/N).
GH, growth hormone; IGF-1, insulin-like growth factor 1.
*Statistically significant.

of remission were a Knosp grade of 0–2 (OR, 19.492; 95% CI, 2.954–128.633; P = 0.002) and a lower POD1 GH level (OR, 0.594; 95% CI, 0.451–0.782; P < 0.001; Table 5). ROC curve analysis was performed to estimate the predictive value of POD1 GH level for remission (Figure 1). The area under the curve (AUC) was 0.879 (P < 0.001), which indicated a reliable diagnostic value. The cutoff POD1 GH level that would distinguish between the remission and nonremission groups was 1.442 μg/L, with a PPV of 83.0%, an NPV of 79.4%, sensitivity of 84.8%, and specificity of 77.1% (95% CI, 0.824%–0.934%).

Table 4. Univariate Analysis Results for Predictors of Biochemical Remission

Variable	OR (95% CI)	P Value
Age (years)	1.045 (1.016–1.075)	0.002
Maximum tumor diameter	0.499 (0.345–0.722)	<0.001
Tumor volume	0.887 (0.818–0.961)	0.003
Noninvasiveness	16.717 (7.392–37.803)	0.001
Knosp grade 0–2	33.200 (13.571–81.221)	<0.001
Ki-67 index	0.530 (0.281–1.000)	0.050
POD1 GH	0.560 (0.448–0.700)	<0.001
Baseline GH	0.990 (0.985–0.995)	<0.001

OR, odds ratio; CI, confidence interval; POD1, postoperative day 1; GH, growth hormone.

Table 5. Multivariate Analysis Results for Predictors of Biochemical Remission

Variable	OR (95% CI)	P Value
Knosp grade 0–2	19.492 (2.954–128.633)	0.002
POD1 GH	0.594 (0.451–0.782)	<0.001

OR, odds ratio; CI, confidence interval; POD1, postoperative day 1; GH, growth hormone.

The remission rate for patients undergoing curative intent surgery (i.e., those without cavernous sinus invasion) was 84.7% (83 of 98). The baseline GH (P < 0.001) and IGF-1 index (P = 0.032) were significantly lower in the remission group (n = 83) than in the nonremission group (n = 15; Supplementary Table 2). Univariate and multivariate analyses (Supplementary Tables 3 and 4) revealed that the only perioperative independent predictor of remission for patients who had undergone curative intent surgery was the POD1 GH level (OR, 0.478; 95% CI, 0.314–0.725; P = 0.001). Noncavernous sinus invasion was not associated with remission after surgery.

Initial and Delayed Remission

At the postoperative 3-month (PO3M) follow-up visit, initial remission had been achieved in 71 patients, discordance in the GH

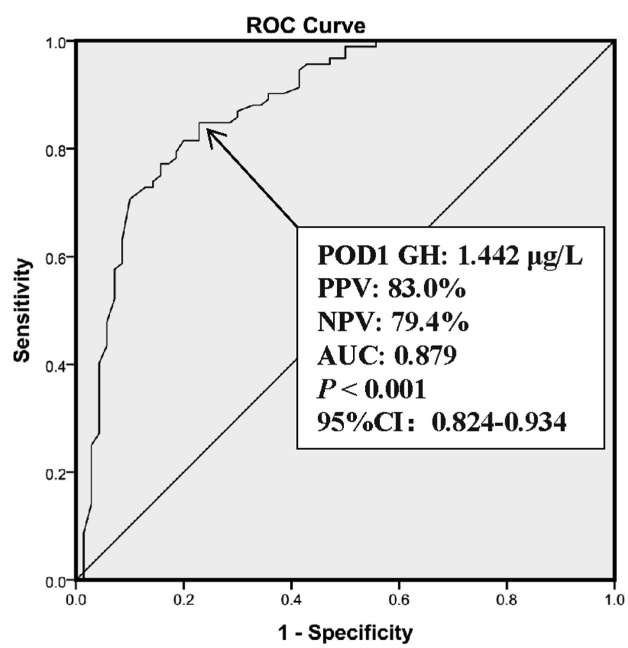

Figure 1. Receiver operating characteristic (ROC) curve analysis of postoperative day 1 (POD1) growth hormone (GH) level for predicting biochemical remission after surgery. The *central line* indicates neutrality, and the *arrow* shows that the cutoff value of POD1 GH is 1.442 μg/L, with a positive predictive value (PPV) of 83.0% and negative predictive value (NPV) of 79.4% (area under the curve [AUC], 0.879; P < 0.001). CI, confidence interval.

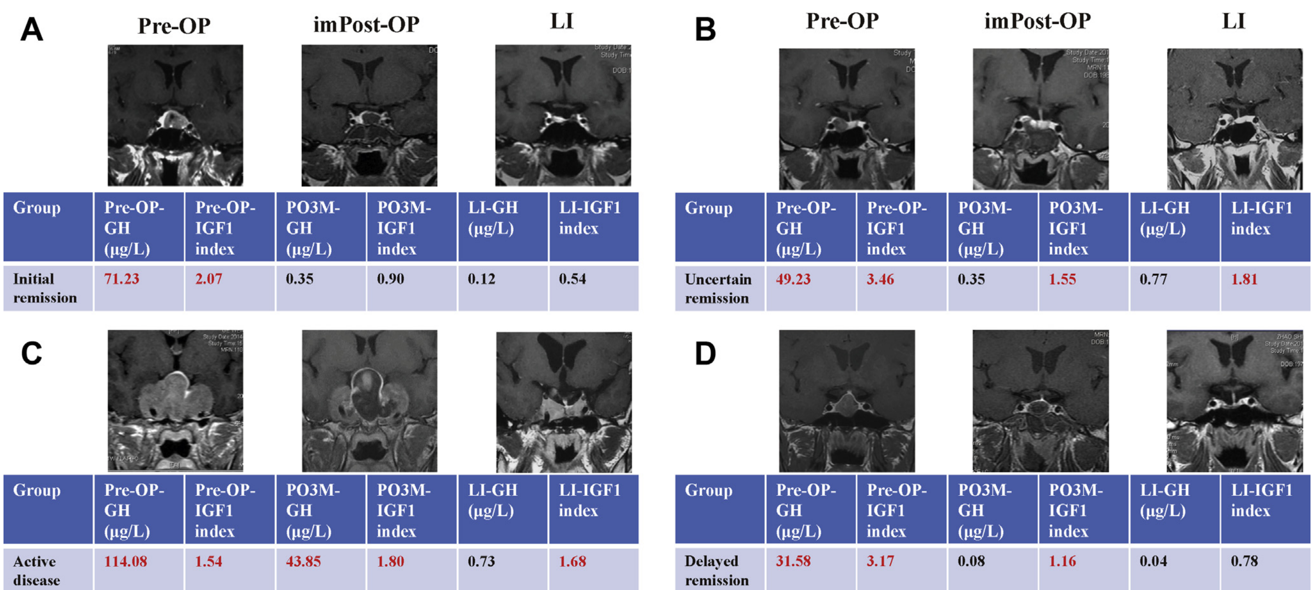

Figure 2. Illustrative cases with preoperative (Pre-OP), immediate postoperative (imPost-OP), and last investigation (LI) magnetic resonance images (coronal plane) for the (**A**) initial remission group, (**B**) uncertain remission group, (**C**) active disease group, and (**D**) delayed remission group. Pre-OP, postoperative 3-month (PO3M), and LI growth hormone (GH) and insulin-like growth factor 1 (IGF-1) indexes are also shown. Patient C underwent conventional fractionated radiotherapy 3 months after transsphenoidal surgery and received somatostatin analogs after radiotherapy for 6 months. Elevated GH and IGF-1 indexes are shown in *red text.*

and IGF-1 levels (uncertain remission) was observed in 38 patients, and active disease was present in 53 patients (Figure 2A–C). All 38 patients with an uncertain remission status were in GH remission with elevated IGF-1 levels. Of the 38 patients, 21 achieved a delayed remission without adjuvant therapy (Figure 2D), 6 had developed active disease during the follow-up period, and 11 remained in uncertain remission status at their most recent evaluation.

Patients in remission after surgery alone were divided into initial remission ($n = 71$) and delayed remission ($n = 21$) groups. The baseline and POD1 IGF-1 indexes were significantly lower in the initial remission group than in the delayed remission group (2.73 ± 0.68 vs. 3.50 ± 0.81 and 1.62 ± 0.74 vs. 2.33 ± 0.68, respectively; $P < 0.001$; Table 6). Based on the univariate analysis results (Supplementary Table 5), the following parameters were included in the multivariate analysis: noninvasiveness ($P = 0.065$), baseline IGF-1 index ($P = 0.001$), and POD1 IGF-1 index ($P = 0.002$). Only the baseline IGF-1 index was a predictor of initial remission on multivariate analysis (OR, 0.339; 95% CI, 0.128–0.895; $P = 0.029$; Supplementary Table 6). ROC curve analysis revealed that the optimal baseline IGF-1 index cutoff value that distinguished between initial and delayed remission was 2.835, with a PPV of 95.3%, an NPV of 36.6%, sensitivity of 61.2%, and specificity of 88.2% (AUC, 0.780; 95% CI, 0.651–0.908; $P < 0.001$; Figure 3A).

Patients in uncertain remission (Supplementary Table 7) who had normal GH levels but elevated IGF-1 levels at the PO3M evaluation were divided into delayed remission ($n = 21$) and nonremission ($n = 17$) groups (Table 7). The PO3M IGF-1 index was significantly lower in the delayed remission group than in the nonremission group (1.23 ± 0.21 vs. 1.77 ± 0.37; $P < 0.001$). Fewer invasive tumors and fewer tumors with extensive cavernous sinus invasion were present in the delayed remission group compared with the nonremission group (9.5% vs. 76.5% and 4.8% vs. 70.6%, respectively; $P < 0.001$ for both). ROC curve analysis showed that

Table 6. Comparison of Perioperative Variables Between Initial Remission and Delayed Remission Groups

Variable	Initial Remission Group ($n = 71$)	Delayed Remission Group ($n = 21$)	P Value
Age (years)	46 ± 12	48 ± 11	0.382
Maximum tumor diameter (cm)	1.70 (1.30–2.40)	1.60 (1.30–2.35)	0.892
Tumor volume (cm^3)	1.27 (0.61–4.40)	1.25 (0.53–3.18)	0.885
Baseline IGF-1 index	2.73 ± 0.68	3.50 ± 0.81	<0.001*
Baseline GH (μg/L)	11.43 (5.62–24.42)	22.75 (11.70–33.46)	0.058
Invasiveness	31.0 (22/71)	9.5 (2/21)	0.092
Cavernous sinus invasion	11.3 (8/71)	4.8 (1/21)	0.643
POD1 GH (μg/L)	0.69 (0.38–1.15)	0.73 (0.44–1.21)	0.473
POD1 IGF-1 index	1.62 ± 0.74	2.33 ± 0.68	<0.001*

Data presented as median (interquartile range), mean ± standard deviation, or % (n/N).
GH, growth hormone; IGF-1, insulin-like growth factor 1.
*Statistically significant.

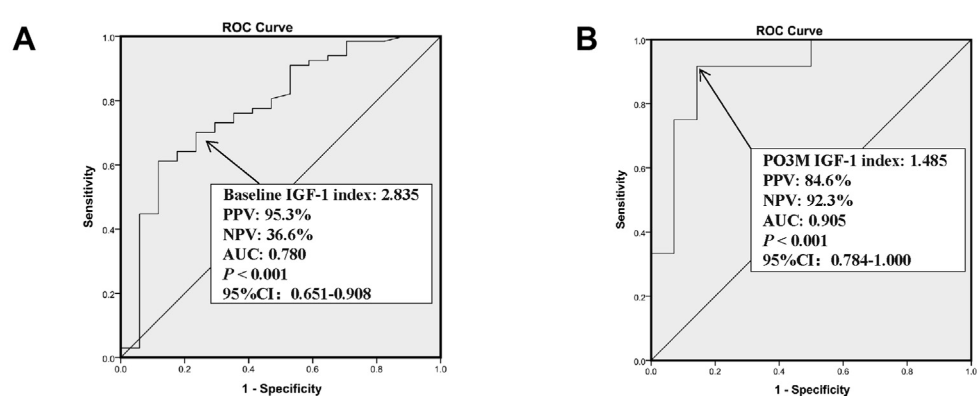

Figure 3. (**A**) Receiver operating characteristic curve analysis of the baseline insulin-like growth factor 1 (IGF-1) index for predicting initial remission after surgery. The *central line* indicates neutrality, with the *arrow* indicating that the cutoff value for the baseline IGF-1 index is 2.835, with a positive predictive value (PPV) of 95.3% and a negative predictive value (NPV) of 36.6% (area under the curve [AUC], 0.780; $P < 0.001$). (**B**) Receiver operating characteristic curve analysis of the postoperative 3-month (PO3M) IGF-1 index for predicting delayed remission in the uncertain group. The *central line* indicates neutrality, and the *arrow* indicates that the optimal cutoff value for the PO3M IGF-1 index is 1.485, with a PPV of 84.6% and a NPV of 92.3% (AUC, 0.905; $P = 0.010$).

the optimal PO3M IGF-1 index cutoff value that predicted delayed remission was 1.485, with a PPV of 84.6%, an NPV of 92.3%, sensitivity of 91.7%, specificity of 85.7% (AUC, 0.905; 95% CI, 0.784–1.000; $P < 0.001$; Figure 3B).

Complications

None of the patients died during the study period, although 45 patients (24.3%) had intraoperative CSF leakage. One patient (0.5%) experienced intraoperative carotid injury but recovered well after stent implantation. One patient (0.5%) experienced epistaxis and another (0.5%) developed a transient postoperative third nerve palsy that recovered spontaneously 1 month after surgery. No patient reported deterioration in visual acuity or worsening in their visual field deficit. No incidents of postoperative CSF leakage, meningitis, intracerebral/intrasellar hemorrhage, or permanent diabetes insipidus occurred. Surgery-induced hypoadrenalism, hypothyroidism, and male hypogonadism developed in 3.2%, 0.8%, and 12.5% of the patients, respectively.

Table 7. Comparison of Variables Between Delayed Remission and Nonremission Groups of Patients in Uncertain Remission Status at Postoperative 3-Month Follow-Up Evaluation

Variable	Delayed Remission Group (n = 21)	Nonremission Group (n = 17)	*P* Value
Age (years)	48 ± 11	42 ± 10	0.081
Male sex (%)	52.4 (11/21)	47.1 (8/17)	0.744
Maximum tumor diameter (cm)	1.60 (1.30–2.35)	1.80 (1.45–2.35)	0.453
Tumor volume (cm^3)	1.25 (0.53–3.18)	1.95 (1.03–3.35)	0.419
Ki-67 index (%)	1.00 (1.00–2.00)	2.00 (1.00–2.00)	0.486
Invasive adenoma	9.5 (2/21)	76.5 (13/17)	<0.001*
Cavernous sinus invasion	4.8 (1/21)	70.6 (12/17)	<0.001*
PO3M IGF-1 index	1.23 ± 0.21	1.77 ± 0.37	<0.001*
PO3M GH (μg/L)	0.17 (0.04–0.54)	0.33 (0.17∼ 0.47)	0.160

Data presented as median (interquartile range), mean ± standard deviation, or % (n/N).
PO3M, postoperative 3-month; GH, growth hormone; IGF-1, insulin-like growth factor 1.
*Statistically significant.

DISCUSSION

We found that neurological surgery resulted in biochemical remission in 56.8% of acromegalic patients without adjuvant therapy; 43.8% of the patients had achieved initial remission 3 months after surgery, and 13.0% had achieved delayed remission (mostly within 24 months). Discordance of GH and IGF-1 levels (uncertain remission) was observed in 23.5% of the patients at the PO3M follow-up. Of these patients, 55.3% achieved delayed remission during the subsequent follow-up period, 28.9% remained in uncertain remission status, and 15.8% had progressed to active disease. The perioperative independent factors predictive of remission were a lower Knosp grade of 0–2 and a lower POD1 GH level. A POD1 GH level value <1.442 μg/L predicted overall remission after surgery alone. In contrast, a baseline IGF-1 index value less than the cutoff value of 2.835 predicted for initial remission at 3 months postoperatively. In the uncertain remission group, a PO3M IGF-1 index value <1.485 predicted for delayed remission during the subsequent follow-up period.

A recent meta-analysis indicated that the pooled overall remission rate (based on the 2010 criteria) was 54.8%,[18] which was very close to that found in our study. However, the remission rates varied greatly among different series (25.3%–84.7%;Supplementary Table 8),[5,9,19-29] depending on patient selection and the proportions of macroadenomas and invasive tumors. In our cohort, 97.3% of the patients had macroadenomas using the Hardy-Wilson classification, including 53.8% with invasive adenomas. The rate of cavernous sinus invasion detected by preoperative MRI was ~40% according to the Knosp classification. The remission rate after surgery alone was 87.2% and 28.9% for noninvasive and invasive adenomas, respectively, in our cohort. Among those with invasive adenomas, the remission rate was 75.0% and 14.3% for those with noncavernous and cavernous sinuous invasion, respectively (Table 2). For PAs with cavernous invasion, our surgical strategy was relatively conservative compared with that of Nishioka et al.,[9] who had performed a similar study. Subtotal resection followed by treating the remnant with gamma-knife radiosurgery or somatostatin analog therapy was our first choice, because we speculated that aggressive surgical debulking potentially risks iatrogenic injury to important neurovascular structures.[30] Therefore, the overall surgical remission rate in our cohort was closely related to the cavernous sinuous invasion rate (~40%) and our surgical strategy. Our complication rate was relatively low.

Several studies have investigated the perioperative factors that can predict PA surgery outcomes. The most common parameters included age,[28,31] sex,[32] tumor size,[26,33] invasiveness,[9,24] baseline GH level,[9,34] baseline IGF-1 level,[7,31] previous surgery,[26,35] and POD1 GH levels.[36] Others have investigated the effect of surgeon experience,[37] tumor granularity,[36,38] nuclear expression of p21,[36] the Ki-67 index,[31,36] empty sella,[39] cystic change,[40] visual disturbance,[25] and extrapseudocapsular resection.[19] Some of these findings have contradicted others, likely owing to different sample sizes, ethnic compositions, remission criteria, follow-up periods, and surgical skills. In our cohort, a lower Knosp grade of 0–2 and a lower POD1 GH level were independent predictors of remission. Furthermore, ROC curve analysis revealed that a POD1 GH level <1.442 μg/L was associated with achieving a postoperative remission likelihood of 83.0%, and a POD1 GH level >1.442 μg/L was associated with a 79.4% possibility of not achieving remission.

The role of ultra-early postoperative GH levels in predicting long-term remission is controversial. Starke et al.[25] reported that a POD1 GH cutoff of 1.15 μg/L had a PPV of 92% and an NPV of 54% for predicting remission. Jane et al.[35] reported that a POD1–POD2 GH cutoff of 2.5 μg/L had a PPV of 100% and an NPV of 87%. Sarkar et al.[38] reported that the sensitivity and specificity of a POD1 cutoff of 3.66 μg/L was 93.1% and 79.2%, respectively. However, in the study by Hazer et al.,[21] the sensitivity and specificity was 65.2% and 77.3%, respectively, for a POD1 GH cutoff of 2.33 μg/L, with an AUC of 0.772, indicating a relatively low prediction efficiency. Babu et al.[36] concluded that the POD1 GH level could not be used as an independent reliable measure of remission, because the specificity was 83% but the sensitivity was only 47% for a POD1 GH cutoff of 1 μg/L in their study. The variations in PPV, NPV, sensitivity, and specificity across numerous studies were influenced by the different cutoff values of ultra-early postoperative GH levels. One explanation for the relatively low sensitivity (or NPV) in some studies is that residual tumor cells can initially secrete GH but ultimately undergo autonecrosis in the ensuing weeks, resulting in remission.[41] Although we believe that the ultra-early postoperative GH level is an effective tool for predicting the surgical outcome of GH-secreting PAs, it should be applied with caution, especially when using the NPV.

The currently used criteria for remission after acromegaly management, including the Cortina and 2010 consensus criteria, require suppression of GH and normalization of IGF-1 levels. Considering the long half-life of IGF-1, surgical outcomes should not be evaluated until the PO3M evaluation. Remission achieved at that follow-up point is known as initial remission, and remission achieved later is considered delayed remission.[36,42] Furthermore, several discrepancies were found between the GH and IGF-1 levels, which complicated the interpretation of surgical outcomes and the choice of adjuvant therapy. The most commonly encountered discrepancy was normal GH levels with persistently elevated IGF-1 levels. Explanations for this divergence include the long half-life of IGF-1, different half-lives of IGF-binding proteins, heterogeneity between the different immunoassays, enhanced liver sensitivity to GH that promotes a further increase in IGF-1, GH–IGF-1 feedback inhibition, hepatic and renal failure, thyroid dysfunction, malnutrition, malignancies, pregnancy, and poorly controlled diabetes mellitus.[7] Because the predictors of initial and delayed remission have not been completely identified,[18] they are worth investigating (especially in patients with uncertain remission).

Our results have shown that the baseline IGF-1 index was lower in the initial remission group than in the delayed remission group (Table 6). These data were similar to those of Kinoshita et al.[43] to some extent. Moreover, to the best of our knowledge, we were the first to determine that the baseline IGF-1 level (IGF-1 index) was an independent predictor of initial remission on multivariate regression analysis and that a baseline IGF-1 index <2.835 was associated with a 95.3% chance of achieving initial remission at the PO3M follow-up examination.

Among the patients with uncertain remission, the PO3M IGF-1 index was significantly lower in the delayed remission group than in the nonremission group. ROC curve analysis showed that when the PO3M IGF-1 index was <1.485, the chance of achieving delayed remission was 84.6%, and a PO3M IGF-1 index >1.485 produced a 92.3% possibility of not achieving remission during the subsequent follow-up period. The combination of baseline and PO3M IGF-1 index cutoff values would be helpful for predicting initial and delayed remission both perioperatively and at the PO3M follow-up evaluation. For invasive adenomas with uncertain remission at PO3M, the probability of achieving delayed remission was poor (13.3% vs. 82.6% for noninvasive adenomas; $P < 0.001$). Thus, invasive adenomas should be treated more aggressively if initial remission was not achieved. As such, our findings can be applied to identify patients predicted to have initial remission, delayed remission, and persistent active disease after neurological surgery, especially among those with an uncertain remission status. This could help with decision-making regarding adjuvant therapy after surgery.

The strengths of our study included the experience of our surgeons, because all surgeries in our cohort were performed by 2 senior pituitary specialists who had each performed >200 pituitary surgeries annually.[44] Although the size of our cohort was not the largest to date, the 185 consecutive patients included in our study were investigated within a very short period of 2 years, which reduced confounding factors such as different surgeons, surgical procedures, assays, and other such variables.

The potential limitations of our study included its retrospective nature and the loss of 23 patients to follow-up. The median follow-up period of 24 months might not be long enough to assess recurrence or mortality extensively.

CONCLUSIONS

Our results have demonstrated that a lower Knosp grade of 0–2 and a lower POD1 GH level were independent predictors of surgical remission in patients with GH-secreting PAs. The baseline and PO3M IGF-1 indexes can predict initial and delayed remission, respectively. Invasive adenomas should be treated more aggressively if initial remission was not achieved.

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SUPPLEMENTARY DATA

Supplementary Table 1. Comparison of Variables Between Remission and Nonremission Patients with Noninvasive Adenoma

Variable	Remission Group ($n = 68$)	Nonremission Group ($n = 10$)	*P* Value
Age (years)	46 ± 11	41 ± 11	0.191
Male sex	41.2 (28/68)	40 (4/10)	1.000
Duration (years)	4.00 (2.00–6.00)	4.50 (2.75–5.00)	0.709
Maximum tumor diameter (cm)	1.50 (1.20–2.00)	1.70 (1.55–2.15)	0.152
Tumor volume (cm^3)	0.89 (0.57–2.24)	1.48 (1.05–2.86)	0.069
Baseline GH (μg/L)	12.32 (5.27–24.13)	31.53 (14.19–46.52)	0.025*
Ki-67 index (%)	1.00 (1.00–2.00)	2.00 (1.00–2.00)	0.133
Baseline IGF-1 index	2.95 ± 0.81	3.12 ± 0.99	0.555
Intraoperative CSF leak	85.3 (58/68)	90 (9/10)	1.000

Data presented as mean ± standard deviation; median (interquartile range); or % (n/N).
GH, growth hormone; IGF-1, insulin-like growth factor 1; CSF, cerebrospinal fluid.
*Statistically significant.

Supplementary Table 2. Comparison of Baseline Variables Between Remission and Nonremission Patients Undergoing Curative Intent Surgery (i.e., Those without Cavernous Sinus Invasion)

Variable	Remission Group ($n = 83$)	Nonremission Group ($n = 15$)	*P* Value
Age (years)	47 ± 12	44 ± 11	0.469
Male sex (%, n)	37.3 (31/83)	40 (6/15)	0.845
Duration (years)	4.00 (2.00–7.25)	5.00 (4.00–6.00)	0.340
Maximum tumor diameter (cm)	1.50 (1.30–2.00)	1.70 (1.60–2.00)	0.204
Tumor volume (cm^3)	1.04 (0.58–2.47)	1.90 (1.06–3.04)	0.086
Invasive adenoma	18.1 (15/83)	33.3 (5/15)	0.177
Baseline GH (μg/L)	13.12 (5.68–24.42)	40.27 (16.69–52.54)	0.001*
Ki-67 index (%)	1.00 (1.00–2.00)	2.00 (1.00–2.00)	0.204
Baseline IGF-1 index	2.91 ± 0.77	3.41 ± 1.01	0.032*
Intraoperative CSF leak (%)	83.1 (69/83)	86.7 (13/15)	1.000

Data presented as mean ± standard deviation; median (interquartile range); or % (n/N).
GH, growth hormone; IGF-1, insulin-like growth factor 1; CSF, cerebrospinal fluid.
*Statistically significant.

Supplementary Table 3. Univariate Analysis Results for Predictors of Remission in Patients Undergoing Curative Intent Surgery (i.e., Those without Cavernous Sinus Invasion)

Variable	OR (95% CI)	*P* Value
Baseline GH	0.989 (0.981–0.997)	0.008
Baseline IGF-1 index	0.491 (0.251–0.962)	0.038
POD1 GH	0.523 (0.376–0.726)	<0.001
POD1 IGF-1 index	0.590 (0.315–1.104)	0.099
Noninvasiveness	2.267 (0.676–7.604)	0.185

OR, odds ratio; CI, confidence interval; GH, growth hormone; IGF-1, insulin-like growth factor 1; POD1, postoperative day 1.

Supplementary Table 4. Multivariate Analysis Results for Predictors of Remission in Patients Undergoing Curative Intent Surgery (i.e., Those without Cavernous Sinus Invasion)

POD1 GH	Value
Odds ratio	0.478
95% Confidence interval	0.314–0.725
P value	0.001

POD1, postoperative day 1; GH, growth hormone.

Supplementary Table 5. Univariate Analysis Results for Predictors of Initial Remission

Variable	OR (95% CI)	*P* Value
Noninvasiveness	0.234 (0.050–1.095)	0.065
Knosp grade 0–2	0.394 (0.046–3.343)	0.393
Baseline IGF-1 index	0.231 (0.099–0.542)	0.001
POD1 IGF-1 index	0.289 (0.134–0.625)	0.002

OR, odds ratio; CI, confidence interval; POD1, postoperative day 1; IGF-1, insulin-like growth factor 1.

Supplementary Table 6. Multivariate Analysis Results for Predictors of Initial Remission

Baseline IGF-1 Index	Value
Odds ratio	0.339
95% Confidence interval	0.128–0.895
P value	0.029

Supplementary Table 7. Patient and Hormonal Data From Uncertain Remission Group at Postoperative 3-Month Follow-Up Evaluation

Variable	Value
Sex	
Male	19
Female	19
Age (years)	45 ± 11
Maximum tumor diameter (cm)	1.80 (1.40–2.33)
Tumor volume (cm^3)	1.36 (0.66–3.17)
Tumor invasion	39.5 (15/38)
Cavernous sinus invasion	34.2 (13/38)
Baseline GH (μg/L)	21.84 (11.22–34.27)
Baseline IGF-1 index	3.30 ± 0.91
GH (μg/L)	
POD1	1.06 (0.57–1.72)
PO6W	0.23 (0.10–0.40)
PO3M	0.25 (0.12–0.49)
PO6M	0.23 (0.08–0.63)
PO12M	0.08 (0.05–0.26)
PO24M	0.15 (0.07–0.41)
IGF-1 index	
POD1	2.21 ± 0.68
PO6W	1.55 ± 0.37
PO3M	1.52 ± 0.41
PO6M	1.10 ± 0.35
PO12M	1.31 ± 0.43
PO24M	1.23 ± 0.45

Data presented as mean ± standard deviation or median (interquartile range) for continuous variables normally or not normally distributed and as % (n/N) for categorical variables; normality was tested using the Kolmogorov-Smirnov test.

GH, growth hormone; IGF-1, insulin-like growth factor 1; POD1, postoperative day 1; PO6W, postoperative 6-week (follow-up evaluation); PO3M, postoperative 3-month (follow-up evaluation); PO6M, postoperative 6-month (follow-up evaluation); PO12M, postoperative 12-month (follow-up evaluation); PO24M, postoperative 24-month (follow-up evaluation).

Supplementary Table 8. Review of Reported Remission Rates According to the 2010 Criteria After Surgery

Investigator	Patients (*n*)	Microadenoma	Macroadenoma	Invasive Adenoma	Overall
Hofstetter et al.,[29] 2010	24	NA	NA	NA	37.5 (9/24)
Albarel et al.,[5] 2013	115	65 (13/20)	31.6 (30/95)	28.1 (18/64)	37.4 (43/115)*; 49.5 (49/99)†
Starke et al.,[25] 2013	113	87 (20/23)	65.5 (59/90)	35.5 (11/31)	69.9 (79/113)
Hazer et al.,[21] 2013	214	62.7 (32/51)	62.6 (102/163)	40.7 (22/54)	62.6 (134/214)
Sun et al.,[26] 2014	59	81.8 (9/11)	45.8 (22/48)	10 (2/20)	52.5 (31/59)
Nishioka et al.,[9] 2014	150	100 (17/17)	82.7 (110/133)	57.7 (15/26)	84.7 (127/150)
Yildirim et al.,[28] 2014	56	80 (4/5)	64.7 (33/51)	16.7 (3/18)	66.1 (37/56)
Sarkar et al.,[24] 2014	113	56 (9/16)	27.8 (27/97)	10.2 (5/49)	31.9 (36/113)
Fathalla et al.,[20] 2015	65	NA	NA	39.4 (13/33)	41.5 (27/65)
Netuka et al.,[23] 2016	105	75 (12/16)	58.4 (52/89)	NA	61 (64/105)
Ku et al.,[22] 2016	187	91.7 (44/48)	66.2 (92/139)	NA	72.7 (136/187)
Yano et al.,[27] 2017	47	62.5 (5/8)	53.8 (21/39)	42.3 (11/26)	55.3 (26/47)
Anik et al.,[19] 2017	401	81.3 (87/107)	63.2 (186/294)	40.7 (35/86)	68.1 (273/401)

Data presented as % (n/N).
NA, not assessed/not reported.
*Outcome at the 3-month follow-up evaluation.
†Outcome data at the long-term follow-up evaluation were available only for a subgroup of patients.