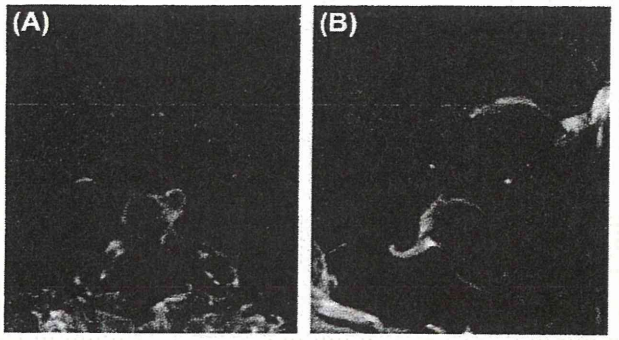

Fig. 1. Magnetic resonance imaging (MRI; A and B) shows a cystic mass in the parasellar region with extension mainly to the left side, causing a mass effect on the surrounding structures without hydrocephalus.

procedures.[1] Most of these are intracerebral hemorrhage, or chronic or acute subdural hematoma. In an analysis of 259 cases of patients who underwent conventional TSS, Kalfas and Little.[1] found only two cases with post-operative haemorrhagic complications that occurred in the intrasellar region. There has been, however, no report of multiple epidural hematomas far from the operated site.[2] The pathogenesis of these complications is not well understood at present. We consider that two issues should be discussed: the mechanism of bleeding and the location of haematoma formation. Even though it is plausible that post-operative haematoma could occur if the patient suffers from hypertension or coagulopathy, our patient did not have any pathophysiological conditions during the perioperative period. However, rapid draining of a substantial volume of CSF during surgery might have played an important role in the development of extradural haematoma at a remote site. The dural opening was much larger than normal in the present case because of excessive tumour extension to the posterior fossa, and we believe that this enhanced the amount of CSF drainage during eTSS. Sagittal MRI after eTSS showed displacement of the brain in a caudal direction, and the withered surface of the dura was observed during the two surgeries for extradural haematoma evacuation. These findings coincided with severe intracranial hypotension as reported earlier,[3] which might result in intracranial venous hypertension leading to expansion of the dural sinuses as a result of an increased gradient between intravascular and CSF pressures in the extradural space. A further decrease in intracranial pressure due to continuous CSF loss could cause increased transluminal venous pressure with subsequent rupture of the dural sinuses. It is possible that adhesion between the dura and cranium is less tight in younger patients, such as this 28-year-old patient, than in the elderly. Subsequent rupture of the dural sinuses into the extradural space could lead to stripping of the dura, and the increase in extradural space might result in remote site extradural hematomas. The source of bleeding, other than the

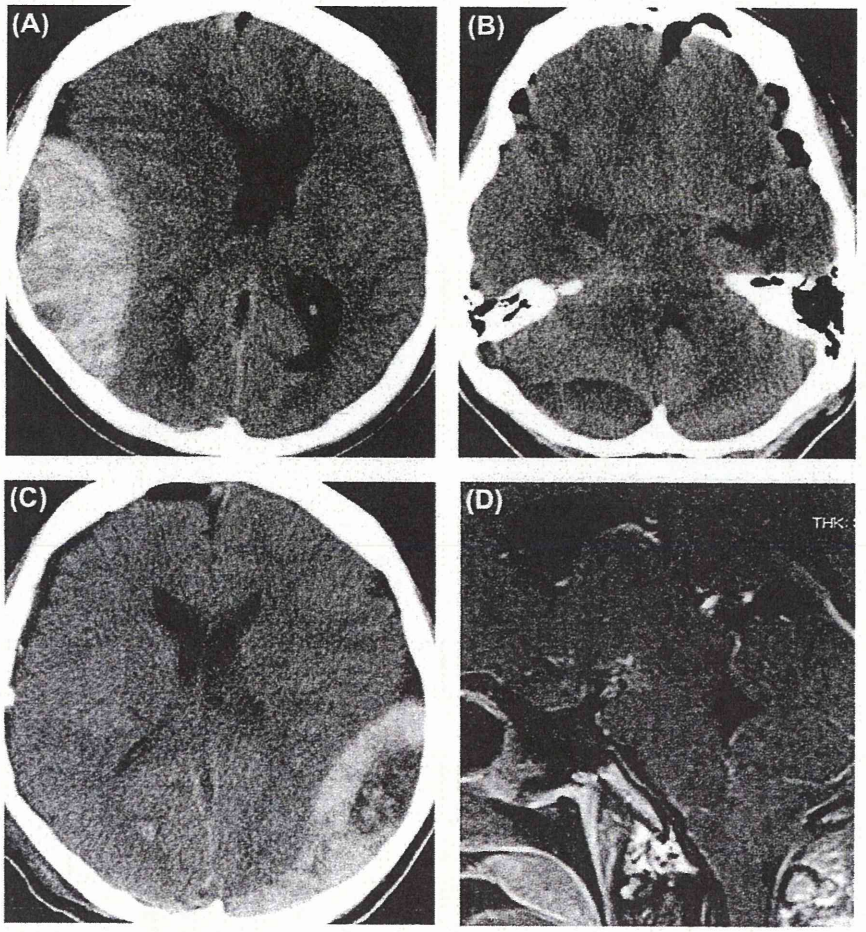

Fig. 2. Initial post-operative CT scan shows an extradural haematoma in the right parieto-occipital (A) and right posterior fossa region (B). CT at the time of the second episode (C) shows left parietal extradural haematoma. Sagittal T1-weighted magnetic resonance imaging (D) shows caudal brain displacement with downward herniation of the third ventricle to the dorsum sellae.

surface of the transverse and sigmoid sinus junction, could not be identified during surgery for haematoma evacuation. Therefore, the pathogenesis of extradural hematoma in our patient remained unclear. Most likely, rapid and much CSF loss during eTSS and leakage through a dural patch after surgery caused significant intracranial hypotension, resulting in continuous development of extradural hematoma.

Although it is extremely rare, remote extradural haematoma should be included as one of the serious complications of eTSS for large craniopharyngioma. Avoiding rapid and excessive CSF loss may be an important consideration to prevent post-surgical hemorrhagic complications related to intracranial hypotension.

Declaration of interest: The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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Aggressive transsphenoidal resection of tumors invading the cavernous sinus in patients with acromegaly: predictive factors, strategies, and outcomes

Clinical article

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Object. Cavernous sinus (CS) invasion is the most important preoperative predictor of remission in the surgical treatment of growth hormone–producing pituitary adenomas. The purpose of this study was to evaluate the effectiveness of an aggressive technique for removal of tumors invading the CS in patients with acromegaly.

Methods. The authors retrospectively reviewed the cases of 150 consecutive patients with acromegaly who underwent primary transsphenoidal surgery in 2010 and 2011. The authors reviewed preoperative Knosp grade, intraoperative findings, histology of the medial wall of the CS, and surgical outcome according to the current consensus criteria for acromegaly.

Results. Cavernous sinus invasion was identified in 55 patients (36.7%): definite CS involvement by the tumor was observed under direct vision in 41 patients (74.5%), while invasion was histologically verified in 39 patients (70.9%). Invasion increased in frequency with the higher Knosp grade but was observed in 14.4% (13 of 90) of Grade 0 and 1 tumors. Overall, the remission rate fulfilling stringent criteria was 84.7% (127 of 150). Although CS invasion was significantly associated with an unfavorable outcome ($p < 0.0001$), remission was achieved in 69.1% (38 of 55) of patients with invasion. No major complications occurred in this series.

Conclusions. Cavernous sinus invasion is the most significant, independent predictor of unfavorable outcome. Confirmation of invasion requires direct observation within the CS regardless of the microscope or endoscope used. Particularly in cases in which only the medial wall is involved, histological verification is always necessary to detect the occult invasion. Direct removal of the invading tumor, by sharp excision of the medial wall of the CS, is effective and safe and increases the chance of remission.

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Key Words • acromegaly • cavernous sinus invasion • occult invasion • pituitary adenoma • transsphenoidal surgery • oncology

Transsphenoidal surgery (TSS) is the first-line treatment for growth hormone (GH)–producing pituitary adenomas in patients with acromegaly. With recent refinements in surgical instruments and techniques, surgical results are improving, and in approximately 70% of patients there is a chance of achieving biochemical remission after a single TSS performed by an experienced surgeon. Regardless of whether a microscope or endoscope is used, serum GH levels and cavernous sinus (CS) invasion of the tumor are the most significant preoperative predictors of remission.[7,8,13,15,17] Cavernous sinus invasion restricts safe and complete adenoma removal during TSS. However, identification of invasion is difficult on preoperative MRI and even during surgery in some cases.[2,4,5,10,12,14,18] The definition of CS invasion is therefore uncertain, resulting in a relatively wide range of reported frequencies. The grading system proposed by Knosp et al.[10] for evaluating parasellar (lateral) extension of the tumor has been widely used to evaluate CS invasion on preoperative MRI. The grading system has also been reported to correlate with surgical outcomes in GH-producing adenomas. We have been performing an aggressive resection of GH-producing adenomas for more than 20 years.[17] Recently, adenomas invading the CS have been directly removed by wide excision of the medial wall of the CS.[15] In this study, we evaluated the relationships among preoperative Knosp grade, intraoperative findings, histological findings, and surgical outcomes.

Abbreviations used in this paper: CS = cavernous sinus; GH = growth hormone; IGF-I = insulin-like growth factor–I; SD = standard deviation; TSS = transsphenoidal surgery.

This article contains some figures that are displayed in color online but in black-and-white in the print edition.

Methods

Patients

We retrospectively reviewed data obtained in 150 consecutive patients with acromegaly who underwent primary TSS for removal of a GH-producing adenoma in 2011 and 2012, which included 28.7% (150 of 522) of all adenomas removed by TSS during this period at Toranomon Hospital. The patients included 77 men and 73 women whose mean age was 47 years (range 7–76 years, median 46 years). Fifty-six patients (37.3%) received preoperative octreotide treatment. The mean follow-up period was 22 months (range 11–34 months, median 22 months). After receiving informed consent from patients, in accordance with the requirement of the Clinical Research Ethics Committee of Toranomon Hospital, tumor samples were collected and evaluated.

Magnetic Resonance Imaging and Endocrine Investigations

Preoperative contrast-enhanced MRI (1.5 or 3.0 T) was performed in all patients, and the coronal imaging features were evaluated using the Knosp grading system.[10] The lesions consisted of 17 microadenomas and 133 macroadenomas. The mean maximum tumor diameter was 17.8 mm (range 6.0–55.6 mm, median 15.5 mm). Endocrinological examinations were performed in all patients before surgery, at 1 week after surgery, and at several months after surgery. The mean preoperative serum GH level was 29.0 ng/ml (range 1.3–541.4 ng/ml, median 12.7 ng/ml), the insulin-like growth factor–I (IGF-I) level was 679 ng/ml (range 241–1480 ng/ml, median 631 ng/ml), and the IGF-I standard deviation (SD) score was 7.2 (range 2.8–14.4, median 7.0). Endocrinological outcomes were assessed according to the current consensus criteria for acromegaly: a nadir serum GH level of < 0.4 ng/ml after an oral glucose load, and subsequent normal sex- and age-adjusted IGF-I levels.

Definition and Classification of CS Invasion

We simply classified as CS invasion cases in which the CS was partially or totally involved by the tumor, as seen under direct vision during surgery. When only the medial wall of the CS seemed to be infiltrated by tumor, however, it was difficult to judge by observation alone. In this situation, we always sharply excised the medial wall and submitted a specimen for histological examination (Fig. 1).

Cavernous sinus invasion was classified into 1 of 2 types: partial invasion or diffuse invasion. The medial wall and partial medial and/or dorsal CS compartments are invaded by the tumor in the former type, whereas the tumor extends into the ventral and lateral CS compartments in the latter type. The tract of CS invasion through the medial wall was roughly classified into 1 of 3 corridors: medial, lateral, or both.[1–3] The corridor medial to the intracavernous carotid artery is formed by the C-shaped segment of the carotid artery. The corridor lateral to the intracavernous carotid artery is demarcated by the carotid artery posteriorly, the vidian nerve inferiorly, and the medial pterygoid process anteriorly.

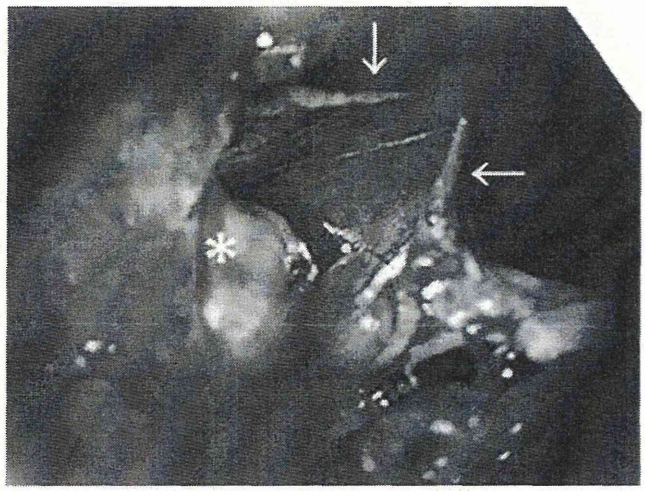

FIG. 1. Illustrative case of a 72-year-old man with a nonfunctioning adenoma. The medial wall of the right cavernous sinus *(arrows)*, which showed histological evidence of adenoma invasion, was sharply incised and dissected. *Asterisk* indicates the intracavernous carotid artery.

Surgical Approach According to CS Invasion

Transsphenoidal surgery was performed via an endonasal transseptal route. The approach was chosen according to the type of CS invasion. In cases of partial CS invasion, the medial approach was used. The sellar bone was removed according to the tumor extension, but bone covering the anterior surface of the CS was removed as needed to directly expose the medial CS wall. The sellar component of the tumor was typically removed using a microsurgical dissection technique, and the tumor was dissected from the medial wall of the CS, while carefully checking for infiltration into the wall, especially in cases in which preoperative MRI showed contact between the tumor and the medial wall. The medial wall was opened sharply, dissected, and excised along with any tumor infiltrating the wall and any portion partially protruding into the CS. If the tumor invaded the dorsal CS space beneath the genu of the carotid artery, an angled endoscope (30° and 70°) was used to visualize the tumor. During these procedures, there was usually profuse bleeding from the CS, which was easily controlled using Gelfoam (Pfizer). In achieving these fine surgical maneuvers, as well as effective control of massive venous hemorrhage, we found that microscopic techniques were superior to endoscopic techniques.

For tumors extending into the ventral and lateral CS compartments (that is, a diffuse invasion type, mainly corresponding to Knosp Grade 4 tumors), the lateral approach was used mainly by endoscopic surgery. A partial middle turbinectomy and/or a posterior ethmoidectomy was performed when the lateral CS required a wide exposure. The dural incision was widely extended to the lateral CS tailored to the tumor. Removal of tumor invading the medial, ventral, and lateral compartments resulted in exposure of the carotid artery, which could be partly mobilized. In these patients, venous bleeding from the surrounding CS was not as profuse as in patients with partial invasion and could easily be controlled using

gelatin foam. A surgical navigation system (StealthStation, Medtronic), eye movement–monitoring device, and mini-Doppler ultrasound were used to achieve safe and maximum removal of tumors with CS invasion.[15]

Histological Examinations

All excised adenomas underwent routine histological and immunohistochemical examination. In some cases, the medial wall of the CS and the adjacent dura were also submitted for the examination. The avidin-biotin-peroxidase complex technique was used for immunohistochemistry. The primary antisera used were polyclonal antisera to GH (1:2000; Dako, A0570) and Ki 67, and clone MIB-1 (1:75; Dako, M7240).

Statistical Analysis

Statistical analyses were performed using the nonparametric chi-square test and the Mann-Whitney U-test. A multiple logistic regression model yielding odds ratios and 95% confidence intervals was used to identify predictors of remission using SPSS software (SPSS version 21).

Results

Tumor invasion into the CS was observed during surgery in 55 cases (36.7%). In 3 patients, the tumor had invaded both sides of the CS. Definite CS invasion was observed under direct vision in 41 cases (74.5%) (Fig. 2), including 4 Knosp Grade 4 tumors. Invasion of adenoma within the CS was histologically confirmed in 27 cases. In addition, histological examination showed invasion of the medial wall in 16 (88.9%) of 18 samples (Fig. 3). Since histological evidence of both CS and CS medial wall invasion was found in 4 cases, CS invasion was histologically verified in 39 cases (70.9%). Furthermore, invasion of the adjacent dura was histologically observed in 27 of 34 samples. Cavernous sinus invasion was significantly more common in patients with larger tumors ($p = 0.0175$) and higher preoperative serum GH levels ($p = 0.0321$) but was not correlated with age, sex, serum IGF-I level, or IGF-I SD score. Cavernous sinus invasion was more frequent in tumors with an advanced Knosp grade (Table 1), being observed in 100% (4 of 4) of Knosp Grade 4 tumors and 86.4% (19 of 22) of Grade 3 tumors. However, partial CS invasion was observed in 6.5% (2 of 31) of Knosp Grade 0 tumors and 18.6% (11 of 51) of Grade 1 tumors, respectively (Figs. 2 and 3). Tumor invaded the CS mainly through the medial corridor in 38 cases, through the lateral corridor in 11 cases, and through both in 9 cases. The 9 tumors affecting both corridors were Knosp Grade 2, 3, or 4, and the 11 tumors affecting only the lateral corridor were Knosp Grade 0, 1, or 2.

Among the 56 patients (37.3%) who underwent preoperative octreotide treatment, a significant decrease in tumor size (> 20%) was observed in 27 cases (48.2%). However, the Knosp grade did not change in any of these patients.

Biochemical remission was achieved in 127 (84.7%) of 150 patients. The remission rate was significantly lower in patients with GH-producing adenomas that invaded the CS than in patients without CS invasion (38 [69.1%] of 55 patients vs 89 [93.7%] of 95, $p < 0.0001$; Table 2). The remission rate was negatively correlated with the Knosp grade (Table 3), with a remission rate of approximately 90% in patients with Knosp Grade 0 to 2 tumors, 68.2% (15 of 22) in patients with Grade 3 tumors, and no remission in patients with Grade 4 tumors. Remission was also less frequent in patients with larger tumors ($p = 0.0001$) and higher preoperative GH levels ($p = 0.0032$). Remission was achieved in all 17 microadenomas and in 110 (82.7%) of 133 macroadenomas (not statistically significant). The surgical outcome was not correlated with age, sex, preoperative IGF-I level, or the IGF-I SD score. In a multiple logistic regression, the odds ratio for CS invasion to non-CS

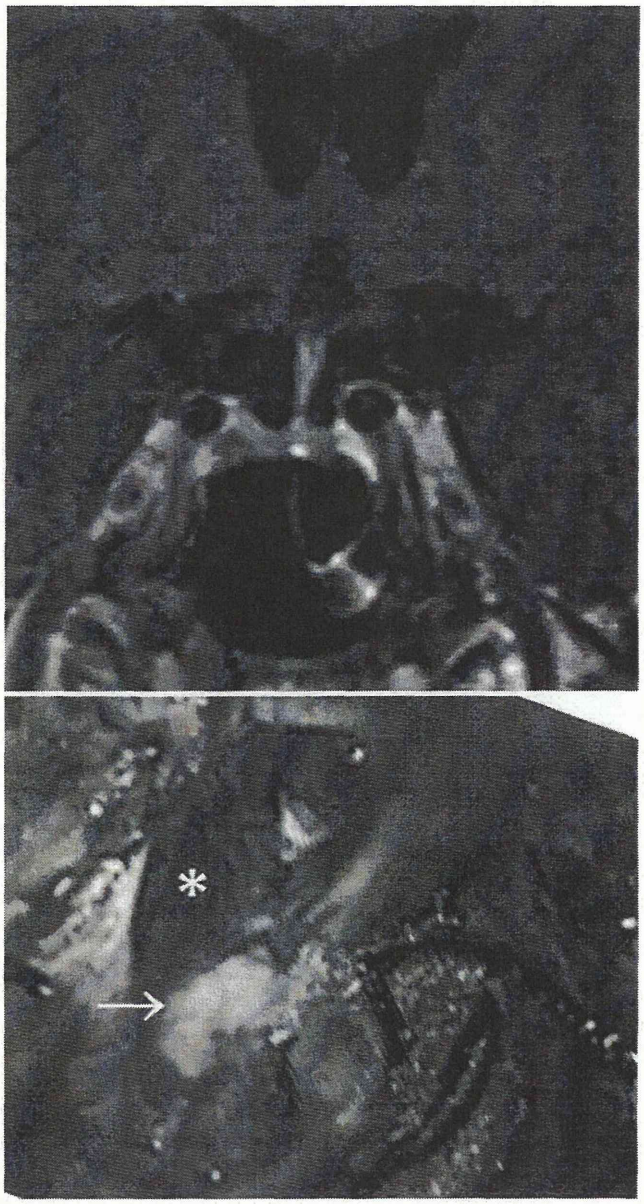

Fig. 2. Upper: A Knosp Grade 0 microadenoma in a 63-year-old man who presented with acromegaly. **Lower:** Intraoperative image showing adenoma *(arrow)* directly invading the right cavernous sinus *(asterisk)*.

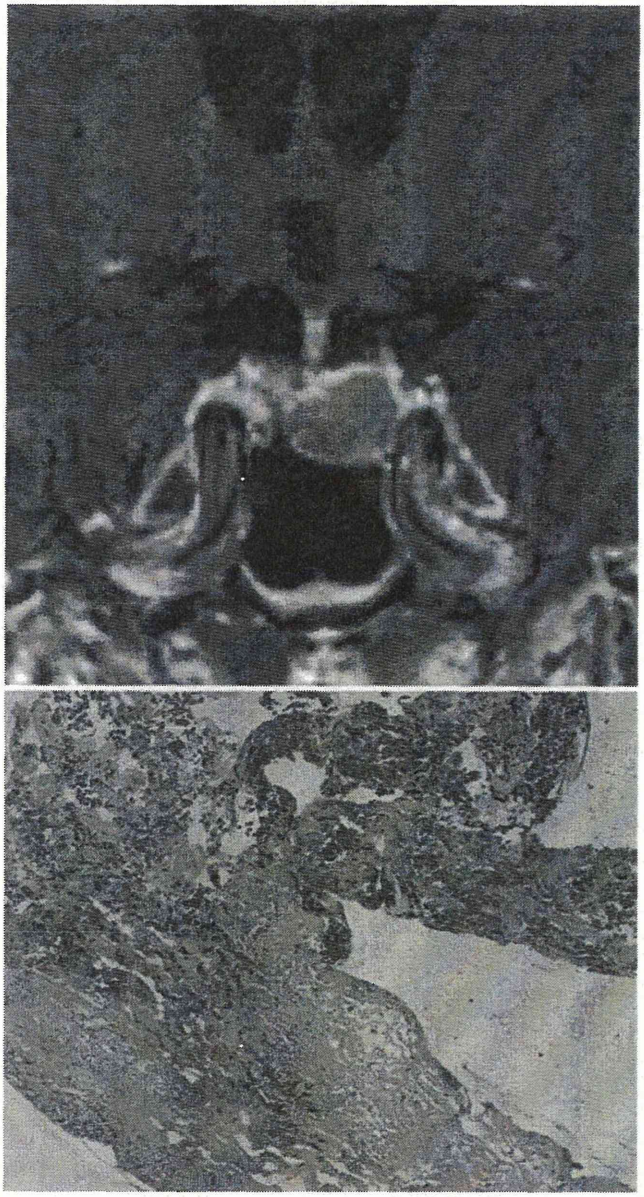

FIG. 3. **Upper:** A Knosp Grade 1 macroadenoma in a 67-year-old man who presented with acromegaly. **Lower:** Photomicrograph of the medial wall of the cavernous sinus showing invasion of adenoma. H & E, original magnification ×220.

TABLE 1: Correlations between Knosp grade and intraoperative CS invasion

Knosp Grade	CS Invasion		% w/ CS Invasion
	Yes	No	
0	2	29	6.5
1	11	48	18.6
2	19	15	55.9
3	19	3	86.4
4	4	0	100
total no. of cases	55	95	35.5

TABLE 2: Correlations between intraoperative CS invasion and surgical outcome

Factor	No. of Case (%)	
	Criteria-0.4*	Criteria-1.0†
total no. of cases	127 (84.7) of 150	131 (87.3) of 150
CS invasion		
absent	89 (93.7) of 95	90 (94.7) of 95
present	38 (69.1) of 55	41 (74.5) of 55
p value	<0.0001	0.0003

* Criteria-0.4: nadir GH < 0.4 ng/ml after an oral glucose load, and normal IGF-I level.

† Criteria-1.0: nadir GH < 1.0 ng/ml after an oral glucose load, and normal IGF-I level.

invasion was 7.125 (95% CI 2.344–21.659, p = 0.001) after adjustment for GH level and tumor diameter (Table 4).

Using the previous remission criteria (nadir GH < 1.0 ng/ml after an oral glucose load), the overall remission rate was 87.3% (131 of 150), with remission achieved in 74.5% (41 of 55) of patients with CS invasion and 94.7% (90 of 95) of patients without CS invasion (Table 2). Using the previous criteria as opposed to the current criteria, 4 additional patients would be classified as having achieved remission, including 1 patient with a Grade 4 tumor.

The mean MIB-1 index of the tumor was 1.1% ± 1.2% (range 0.1%–7.5%, median 1.0%), with no significant difference between adenomas with and without CS invasion (1.3% ± 1.4% vs 1.0% ± 1.0%). The MIB-1 index was not correlated with the preoperative GH level, IGF-I level, IGF-I SD score, or tumor size.

No major complications occurred in this series. The total volume of intraoperative blood loss (including CSF) was significantly larger in patients with CS invasion than in patients without invasion (436 ± 323 ml vs 220 ± 179 ml, p < 0.0001). No patients required blood transfusion. One patient who underwent complete removal of a Grade 3 tumor that invaded the CS developed transient abducent nerve paralysis, which fully resolved after 3 months. No other complication related to the intra-CS procedure developed after surgery.

Surgical remission was not achieved in 23 patients (15.3%). During the mean follow-up of 22 months, 8 of these patients underwent periodic endocrine assessments without further treatment because their IGF-I levels remained normal, and 14 achieved remission by treatment with long-acting octreotide (n = 4), cabergoline (n = 4), pasireotide (n = 1), pegvisomant (n = 1), or combined stereotactic radiotherapy and pharmacological treatment (n = 4). The remaining patient has not achieved remission and is undergoing a change from cabergoline to long-acting octreotide.

Discussion

The lateral surface of the pituitary gland is not constant and has variable features that may include tongue-like lateral protrusion of the pituitary and medial indentation by the intracavernous carotid artery.[4,14,18] The thin

TABLE 3: Correlations between Knosp grade and surgical outcome*

Knosp Grade	No. of Cases (%)	
	Criteria-0.4	Criteria-1.0
0	30 (96.8) of 31	30 (96.8) of 31
1	52 (88.1) of 59	53 (89.8) of 59
2	30 (88.2) of 34	31 (91.2) of 34
3	15 (68.2) of 22	16 (72.7) of 22
4	0 (0) of 4	1 (25.0) of 4
total no. of cases	127 (84.7) of 150	131 (87.3) of 150

* See Table 2 for definitions of criteria.

medial wall of the CS and the variability in the shape, size, and distribution of the venous plexus make it difficult to identify adenoma invasion of the CS on MRI. Despite efforts to predict CS invasion on MRI, confirmation of invasion still requires surgical examination.[4,5,10,14] In addition, the rate of CS invasion may vary between intraoperative visual inspection and histological examination,[8] which may explain the different frequencies of CS invasion reported among studies. Furthermore, Dickerman and Oldfield[5] have claimed the clinical importance of occult dural invasion—that is, invasion of the dura or CS that is not evident on imaging studies and is not obvious to the surgeon—as the basis of recurrence or persistent tumor and endocrinopathy in their series on Cushing's disease. Since it was difficult to assess invasion by observation when only the medial wall was involved, we always sharply excised the medial wall to verify "occult invasion" histologically. This may be the reason why the frequency of CS invasion in the present study was higher than previously estimated. Cavernous sinus invasion was even found in 14.4% of Knosp Grade 0 or 1 tumors, which were previously considered to be rarely associated with invasion.[10] Moreover, our current strict assessment in each case clearly indicated that CS invasion cannot always be predicted by preoperative MRI findings alone.[5]

The authors of several clinicopathological studies used biological markers such as MIB-1 and p53 to assess tumor invasiveness. However, the usefulness of the MIB-1 index for differentiating between adenomas with CS invasion and those without CS invasion appears controversial. We found no correlation between the MIB-1 index and CS invasion in either the present study or our previous studies of nonfunctioning adenomas,[11,16] but we did find that CS invasion was more frequent in cases involving larger tumors. Anatomical and biochemical weakness of the medial wall has been reported to contribute to CS invasion.[12,18] Because the superior part of the medial wall is weaker than the thicker inferior part close to the carotid artery, adenomas tend to extend into the CS through the medial corridor and exhibit a mediodorsal growth pattern.[2,3,9] Adenomas that extend into the CS through the lateral corridor and that show a ventrolateral growth pattern are less common. This pattern was confirmed in the present study. Both corridors were affected in 9 cases in which the tumors were Knosp Grade 2–4, whereas in the 11 tumors extending only through the lateral corridor the lesions were all Knosp Grade 0–2. The latter group contributed to the discrepancy between the Knosp grade and CS invasion.

The medial approach is adequate for partial invasion–type tumors that have minor and limited invasion of the medial or dorsal compartment of the CS.[2,3,6,9] At our institute, the medial wall of the CS is sharply excised if CS invasion is suspected. This approach avoids missing tumor invasion, thereby improving endocrinological outcomes. We also believe that CS invasion can be reliably confirmed only by excision of the medial wall. Venous bleeding from the CS is usually more severe when invasion is partial rather than diffuse. The lateral approach is required for the diffuse invasion type including Knosp Grade 4 tumors.[2,3,6,9] This approach is considered to be more invasive than the medial approach and carries a higher risk of cranial nerve injuries. We prefer to use endoscopic TSS for the lateral approach because the lateral CS is more easily accessible using an endoscope via a middle turbinectomy and/or posterior ethmoidectomy.

Management of massive venous hemorrhage from the CS is one of the most important issues in CS surgery. Control of bleeding and good visualization of the surgical field are necessary for effective and safe removal of an invasive tumor. In our view, microscopic techniques are superior to endoscopic techniques when meticulous maneuvers, including excision of the medial wall while controlling massive venous hemorrhage, are required. Other important issues include identification of the carotid artery and monitoring of the cranial nerves. In addition to proper use of the endoscope and microscope, mini-Doppler ultrasound, surgical navigation system, and an eye movement–monitoring device are considered indispensable for successful and safe removal of adenomas with CS invasion.[9,15]

In the present series of 150 consecutive patients with acromegaly, the overall remission rate was 84.7%. Although CS invasion was associated with a significantly lower rate of remission, remission was achieved in nearly 70% of patients with CS invasion. These rates are higher than those reported in other surgical series in which the current consensus criteria were applied.[7,8,13] By multivariate analysis, we also demonstrated that CS invasion is the

TABLE 4: Logistic regression analyses identifying predictors of remission

Factor (category)	Univariate Analysis p Value	Multivariate Analysis	
		Hazard Ratio (95% CI)	p Value
CS invasion (yes vs no)	<0.001	7.125 (2.344–21.659)	0.001
tumor diameter (≥16 vs <16 mm)	<0.001	4.718 (1.406–15.825)	0.012
basal GH level (≥7.5 vs <7.5 ng/ml)	0.02	0.162 (0.20–1.347)	0.092

most significant, independent factor affecting surgical results, not only in primary surgery but also in secondary surgery.[15] This indicates that improvements in surgical removal of tumor invading the CS would greatly contribute to increase the overall surgical remission rate in acromegaly. We believe that our aggressive approach to removing tumors invading the CS did contribute to our current high remission rate.

In addition to refinements in surgical instruments and techniques, advances in pharmacological treatments and stereotactic radiotherapy techniques are contributing to improvements in outcomes of patients with GH-producing adenomas. Cavernous sinus invasion has been considered to be a major limitation of successful surgical removal of GH-producing adenomas. At present, the likelihood that Knosp Grade 4 tumors can be completely removed is low. However, many GH-producing adenomas with mild to moderate CS invasion can be safely and completely resected. Because we incise the medial wall in every case when invasion was suspected, there were a few cases that we finally judged to have no invasion after further observation and histological assessments. Unless invasion can be accurately determined by imaging studies or by observation of the anatomy outside the CS, however, we believe that incision of the medial wall is necessary whenever invasion is suspected.

Conclusions

Cavernous sinus invasion was the most important, independent factor heralding an unfavorable surgical outcome. The Knosp grading system is useful for prediction of CS invasion, but confirmation requires direct observation within the CS and histological verification in some cases. The technique described in this paper for removal of GH-producing adenomas with CS invasion is highly effective, is associated with a low morbidity rate, and increases the chance of remission.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Nishioka. Acquisition of data: Nishioka, Horiguchi. Analysis and interpretation of data: Nishioka, Fukuhara. Drafting the article: Nishioka. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Nishioka. Study supervision: Yamada.

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for GH-secreting tumors, tumors that are extremely slow growing (signs of acromegaly are present on average for 9 years before diagnosis in patients with acromegaly), is of limited use for predicting the incidence of long-term remission in these patients.

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Disclosure

The author reports no conflict of interest.

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Response

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We are very grateful to Dr. Edward H. Oldfield for his thoughtful and insightful comments regarding our recent study of the surgical approach to tumors with cavernous sinus invasion (CSI) in acromegaly. Indeed, it is still controversial whether adenomas with CSI are biologically more active or aggressive than those without CSI,[1] but CSI is the most important and independent unfavorable factor affecting surgical outcome.[5] Therefore, we believe that improving the surgical results associated with tumors with CSI will increase the overall surgical cure rates of all types of pituitary adenoma. To accomplish this, we must first definitively determine whether the tumor is invading the cavernous sinus (CS). However, except for Knosp Grade 4 tumors, this may not always be possible on the basis of preoperative MRI alone.[4] It is also extremely difficult to correctly identify invasion of the CS intraoperatively if the extended lateral part of the tumor is removed blindly with the use of suction and a ring curette, during either microscopic or endoscopic surgery.

We completely agree with Dr. Oldfield that ascertaining the relationship between the lateral edge of the anterior lobe of the pituitary or the tumor itself and the medial wall of the CS is essential to determine whether the medial wall of the CS is invaded or whether the tumor is additionally passing completely through the medial wall and filling the CS interstices. We believe that this can be accomplished only by meticulous dissection under direct vision of the lateral edge of the anterior lobe of the tumor, although an angled endoscope is often required to judge the relationship if the tumor extends laterally underneath the genu of the ICA. When tumor invasion is partial (involving the medial wall with or without protrusion into the CS), we dissect and finally excise the CS medial wall sharply with the invaded tumor, using Gelfoam to control severe venous bleeding from the CS and using special care to avoid injury to the ICA. To perform these meticulous maneuvers, we continue to believe that microscopic dissection is superior to endoscopic surgery.

Dr. Oldfield indicated that when invasive tumor "spills over" into the CS, surgery is unlikely to be curative because of tumor infiltration of the ICA adventitia, cranial nerves, and other regions of the dura that cannot be safely removed. This is especially likely to occur with Knosp Grade 4 tumors. Nevertheless, although total re-

moval of Knosp Grade 4 tumors is generally impossible, we advocate that they be excised as much as possible to enhance the possibility of tumor remission with postoperative adjuvant therapy (involving either medications or irradiation). This is particularly applicable for tumors associated with drug-resistant acromegaly.

For adenomas with complete CSI, wide exposure of the CS floor is the key to attaching both sides of the ICA, and the endoscopic approach is superior for this purpose. The quantity of tumor around the ICA that can be removed surgically depends on the degree of fibrosis and consistency of the tumor. In our experience, tumors with complete CSI are usually soft and easily removed by suction during primary surgery, but they are often too firm to be removed during repeat surgery for remaining or recurrent GH-cell adenomas, especially if there was a history of medication or radiation treatment. We also emphasize that intraoperative monitoring devices are indispensable tools to improve the safety of aggressive surgical approaches to tumors invading the CS. These devices include surgical navigation systems to facilitate orientation, micro-Doppler devices to confirm the location of the ICA, and eye ocular movement devices to help prevent postoperative eye movement impairment.[3]

Dr. Oldfield stated that the follow-up period of less than 22 months in one-half of our patients and our maximum follow-up of 34 months are of limited use for predicting the incidence of long-term remission in patients with GH-secreting tumors. We acknowledge that long-term follow-up for at least 5 years would be necessary to draw more definitive conclusions. Dr. Oldfield also noted that in many instances in which the early endocrine results after pituitary surgery suggest curative surgery, the patient is indeed not cured, since many tumors later recur in patients with Cushing's disease and acromegaly who clearly meet the most stringent endocrine criteria for cure and have a negative pituitary MRI after surgery. We agree with this statement for patients with Cushing's disease but note that it is not necessarily applicable to those with acromegaly. For example, in their series of 668 patients, Nomikos et al. identified only 2 patients (0.4%) with recurrent acromegaly during a mean follow-up period of more than 10 years after the current endocrine criteria for remission were met.[2] Our surgical experience of no less than 1000 patients with acromegaly is consistent with this finding. The recurrence of acromegaly is extremely rare compared to the recurrence of other functioning adenomas, such as prolactinomas or those producing Cushing's disease, if patients fulfill the current endocrine criteria for cure at 1 year after surgery (that is, a nadir serum GH level < 0.4 ng/ml after a 75-g glucose load and normal age- and sex-adjusted IGF-I level) and have no apparent residual tumor on the postoperative MRI. However, it is important to note, as Dr. Oldfield also indicated, that some acromegalic patients with macroadenoma meet the current endocrine criteria for remission yet have residual tumor in the CS that is clearly visible on MRI. This may be attributed to low GH secretion by these tumors, which are usually sparsely granulated GH-cell adenomas.[6]

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