

Clinical Article

Parasellar Extension Grades and Surgical Extent in Endoscopic Endonasal Transsphenoidal Surgery for Pituitary Adenomas : A Single Surgeon's Consecutive Series with the Aspects of Reliability and Clinical Validity

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Objective : The inter-rater reliability of the modified Knosp's classification was measured before the analysis. The clinical validity of the parasellar extension grading system was evaluated by investigating the extents of resection and complication rates among the grades in the endoscopic endonasal transsphenoidal surgery (EETS) for pituitary adenomas.

Methods : From November 2008 to August 2015, of the 286 patients who underwent EETS by the senior author, 208 were pituitary adenoma cases (146 non-functioning pituitary adenomas, 10 adrenocorticotrophic hormone-secreting adenomas, 31 growth hormone-secreting adenomas, 17 prolactin-secreting adenomas, and 4 thyroid-stimulating hormone-secreting adenomas; 23 microadenomas, 174 macroadenomas, and 11 giant adenomas). Two neurosurgeons and a neuroradiologist independently measured the degree of parasellar extension on the preoperative sellar MRI according to the modified Knosp's classification. Inter-rater reliability was statistically assessed by measuring the intraclass correlation coefficient. The extents of resection were evaluated by comparison of the pre- and post-operative MR images; the neurovascular complications were assessed by reviewing the patients' medical records. The extent of resection was measured in each parasellar extension grade; thereafter, their statistical differences were calculated.

Results : The intraclass correlation coefficient value of reliability across the three raters amounted to 0.862. The gross total removal (GTR) rates achieved in each grade were 70.0, 69.8, 62.9, 21.4, 37.5, and 4.3% in Grades 0, 1, 2, 3A, 3B, and 4, respectively. A significant difference in the extent of resection was observed only between Grades 2 and 3A. In addition, significantly higher complication rates were observed in the groups above Grade 3A.

Conclusion : Although the modified Knosp's classification system appears to be complex, its inter-rater reliability proves to be excellent. Regarding the clinical validity of the parasellar extension grading system, Grades 3A, 3B, and 4 have a negative predictive value for the GTR rate, with higher complication rates.

Key Words : Cavernous sinus · Complications · Endoscopy · Pituitary neoplasms · Reliability · Transsphenoidal surgery.

INTRODUCTION

Pituitary tumors are second frequently diagnosed primary CNS tumors in both Korea and the United States^{15,23}. The conventional classifications are based on the size and functional status of tumors. Furthermore, several other classifications of suprasellar extension and parasellar extension of pituitary adenomas have been proposed^{12,18}. Parasellar extension is measured

based on the preoperative MR image and reflects the cavernous sinus (CS) invasion status of the pituitary adenoma¹⁸.

Regarding the extent of resection for pituitary adenomas by endoscopic endonasal transsphenoidal surgery (EETS), good predictive factors include preoperative tumor size, volume, parasellar extension grade, and the skill of the operating surgeon^{5,16,26}. Among these factors, the highest predictive value has been reported for parasellar extension grades^{5,16}.

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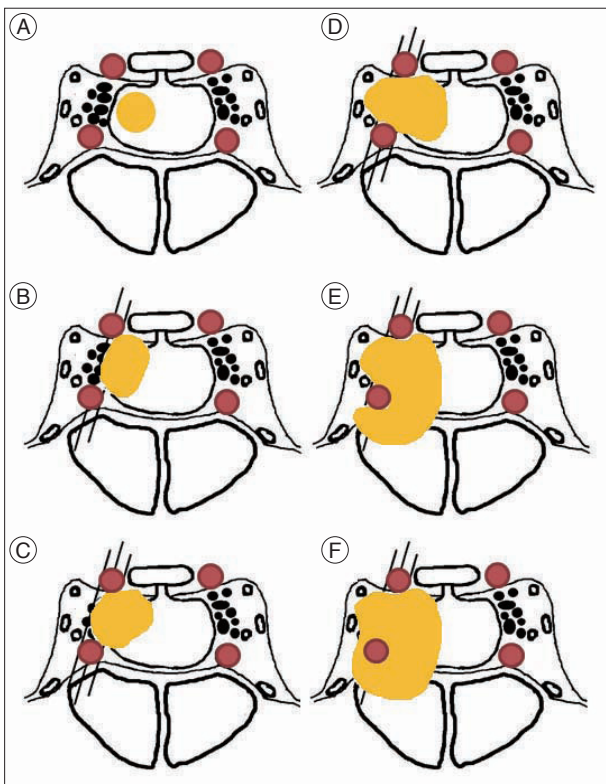


Fig. 1. According to the article of Micko et al.²¹⁾, SHL redraws illustration of the modified Knosp's classification. A : Grade 0 : the adenoma does not encroach on the CS space. Thus, the tangent of the medial aspects of the intracavernous and supracavernous ICAs is not passed. B : Grade 1 : the medial tangent is passed, but the extension does not go beyond a line drawn between the cross-sectional centers of the intracavernous and supracavernous ICAs (the intercarotid line). C : Grade 2 : the tumor extends beyond the intercarotid line, but does not pass the tangent on the lateral aspects of the intracavernous and supracavernous ICAs. D : Grade 3A : the tumor extends lateral to the lateral tangent of the intracavernous and supracavernous ICAs into the superior CS compartment. E : Grade 3B : the tumor extends lateral to the lateral tangent of the intracavernous and supracavernous ICAs into the inferior CS compartment. F : Grade 4 : there is total encasement of the intracavernous carotid artery. CS : cavernous sinus, ICA : internal carotid artery.

In their revision of the Knosp's parasellar extension grading system (Fig. 1), Micko et al.²¹⁾ divided Grade 3 of the previous classification into Grades 3A and 3B based on the involvement of the CS compartment. Grade 3A adenomas extend into the superior CS compartment, while Grade 3B adenomas extend into the inferior CS compartment. Micko et al. demonstrated that, with higher parasellar extension grades, the rates of the CS invasion increase and the possibility of gross total removal (GTR) and endocrinologic remission decrease. The additional division of Grade 3 results in significantly different outcomes of pituitary adenomas in Grades 3A and 3B.

However, when applying the Knosp's parasellar extension grading system, the lateral extent of the tumor extension showed ambiguous findings in several cases. In addition to the comparison of the gadolinium-enhanced T1 coronal images, routine comparison of T2 coronal images is mandatory (Fig. 2). Due to a more complex criterion, further subdivision of the grades can

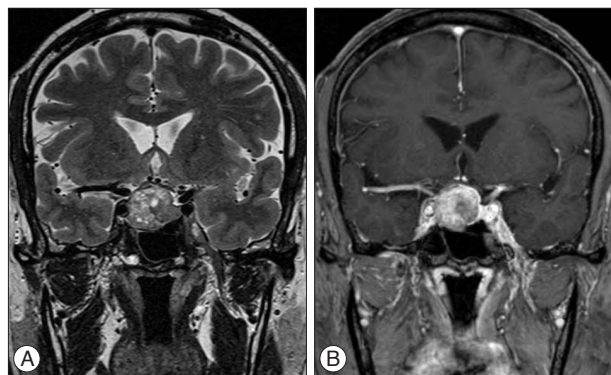


Fig. 2. An illustrative case emphasizing routine inspection of the T2 weighted image, as well as the gadolinium-enhanced T1 image on a preoperative magnetic resonance image scan. A : T2 weighted image. Cavernous ICA does not seem to be encased by the pituitary mass. In grading, two raters confirmed these cases as Grades 1 and 2, respectively. B : T1 weighted image with gadolinium enhancement. Right cavernous ICA seems to be encased by the pituitary mass. One rater confirmed this case as Grade 4. ICA : internal carotid artery.

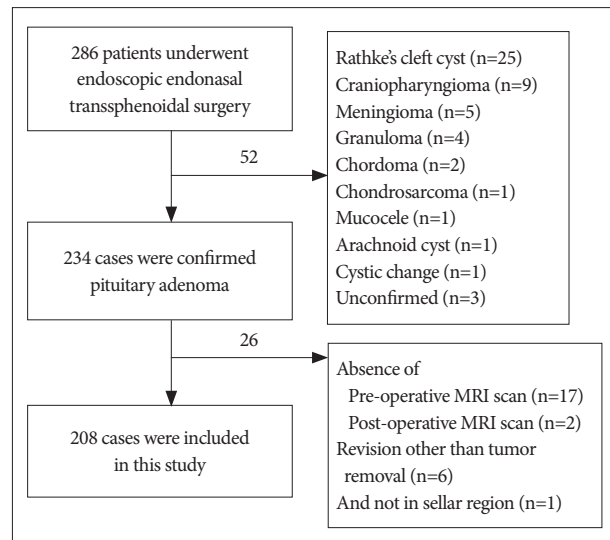


Fig. 3. Inclusion and exclusion flow chart. 208 cases are included in this study.

intensify this ambiguousness. Therefore, the inter-rater reliability of the grading system was assessed to show the agreement across different raters. The clinical validity was evaluated by analyzing the extent of resection and complications rates of each grade.

MATERIALS AND METHODS

Patient characteristics

From November 2008 to August 2015, 286 EETs were performed with the binostril approach by the senior author (YKH) in Seoul St. Mary's Hospital, the Catholic University of Korea. Of those, only pathologically confirmed pituitary adenoma cases were included in this study, regardless of the size and hormonal function of adenomas; the total number of cases amount-

ed to 234. The cases without proper pre- and post-operative image for analysis, revision surgeries not for tumor removal, and pathologies other than those in the sellar area were excluded from the dataset (Fig. 3). The summary of the demographic

Table 1. Patient and tumor characteristics (n=208)

Demographics	Value
Sex, M : F	1 : 1.20
Age (mean±SD)	50.7±14.4 (19–84)
Localization	
Parasellar grading*	
Grade 0	10
Grade 1	63
Grade 2	62
Grade 3A	42
Grade 3B	8
Grade 4	23
Size	
Microadenoma	23
Macroadenoma	174
Giant [†]	11
Hormonal subtype	
Inactive	146
Active	62
ACTH	10
GH	31
PRL	17
TSH	4
Visual symptom	
Yes [‡]	104
No	104

*Modified Knosp's classification, graded by SHL, [†]Includes ptosis and diplopia, [‡]Giant adenoma defined as the one-sized >4 cm. ACTH : adrenocorticotropic Hormone, GH : growth Hormone, PRL : prolactin, TSH : thyroid-stimulating hormone

data is provided in Table 1.

Data acquisition

This study was approved by the Institutional Review Board of Seoul St. Mary's Hospital. Baseline characteristics of the patients and tumors were acquired in the retrospective manner by reviewing the medical records; then, the characteristics were categorized according to their parasellar extension grades in the preoperative MR images. By including single surgeon's data, we sought to minimize the bias from different surgical skills of endoscopic operators.

The grading was performed by two neurosurgeons and one neuroradiologist using the coronal section of preoperative T2 and gadolinium-enhanced T1 images by the modified Knosp's grading system²¹. The grading results of the raters were blinded to each other during the procedure. The extent of resection rate was evaluated by the neuroradiologist's comparison of the pre- and postoperative MR images and review of the operation records. GTR was rated in cases when there was no remaining tumor in the postoperative MR image. Subtotal tumor removal (STR), partial tumor removal (PR), and biopsy were rated when >90%, 50–90%, and <50% of the tumor volume was removed in the postoperative MR image.

Furthermore, we collected additional data about neurovascular and endocrinologic complications and evaluated the relationship between the parasellar extension and surgical complication rates. These complications included visual and endocrine dysfunctions, vascular complication, cerebrospinal fluid (CSF) leakage, and meningitis (Table 2). A condition was considered as 'serious' in cases when the patient 1) had to receive prolonged hospitalization with or without further invasive procedures or medication; 2) had remaining neurologic deficit even after a long-term follow-up done at least six months after discharge; or 3) had endocrinologic dysfunction that required supplementary

Table 2. Surgical complications in each parasellar extension grade

Complications	Grade 0 (%)	Grade 1 (%)	Grade 2 (%)	Grade 3A (%)	Grade 3B (%)	Grade 4 (%)	n (%)
Visual dysfunction	-	-	4 (6.5)	-	-	2 (8.7)	6 (2.9)
Visual field or Visual acuity	-	-	3 (4.8)	-	-	1 (4.4)	4 (1.9)
Diplopia	-	-	1 (1.6)	-	-	1 (4.4)	2 (1.0)
Hormonal dysfunction*	-	-	10 (16.1)	8 (19.0)	1 (12.5)	4 (17.5)	23 (11.1)
Diabetes insipidus	1 (10.0)	1 (1.6)	3 (4.8)	4 (9.5)	2 (25.0)	-	11 (5.3)
Transient DI	1 (10.0)	-	1 (1.6)	-	2 (25.0)	-	4 (1.9)
Permanent DI	-	1 (1.6)	2 (3.2)	4 (9.5)	-	-	7 (3.4)
Vascular complications	-	1 (1.6)	-	2 (4.8)	-	1 (4.4)	17 (8.2)
Intrasellar hematoma	-	1 (1.6)	-	2 (4.8)	-	1 (4.4)	4 (1.9)
Injury of carotid artery	-	-	-	1 (2.4)	-	-	1 (0.5)
SAH	-	-	-	-	-	-	0 (0.0)
Meningitis	-	1 (1.6)	2 (3.2)	3 (7.1)	-	1 (4.4)	7 (3.4)
Postoperative CSF leak [‡]	-	1 (1.6)	2 (3.2)	4 (9.5)	-	1 (4.4)	8 (2.4)
Death	-	-	-	-	-	-	0 (0.0)

*Not including DI. When the patient had an endocrinologic dysfunction requiring supplementary medication, [‡]Two cases needed second surgery for sellar floor reconstruction, while 3 cases were recovered spontaneously. DI : diabetes insipidus, SAH : subarachnoid hemorrhage, CSF : cerebrospinal fluid

medication.

Surgical technique

The surgical technique was identical to the method described in a recent publication of the author group²⁴. All operations were performed via the binostrials-four hands technique. In this technique, the main surgeon uses two hands to use surgical instruments, while an assistant neurosurgeon uses two hands to hold the endoscope. A rhinology surgeon performed surgery in the nasal and sphenoid stage, neurosurgeon performed surgery in the sellar stage; sellar repair was performed by both surgeons.

The patient's head was placed on a horseshoe-shaped headrest and an electromagnetic frameless navigation system (Medtronic®, Louisville, KY, USA) was used. On taking proper measures to the superior, middle, and inferior turbinates on both sides for visualization, the natural orifice of the sphenoid sinus was identified. Bilateral modified “rescue” flaps introduced by Kim et al.¹⁷ were used. We attempted to harvest the posterior septal bone in an en-bloc fashion to further use in the sellar floor reconstruction. The sellar floor was revealed after the procedure and a modified “rescue” flap was made along the removed septal bone.

The sellar floor was drilled out until the blue-colored dura, supposedly CS, was observed. After coagulation of the dura, it was opened using a de DIVITIIS-CAPPABIANCA Scalpel (Karl Storz®, Mittelstrasse, Tuttlingen, Germany). The initial dural incision was made horizontally on the lower part of the dura with perpendicular excisions superiorly most of the times (for further detail, see Dusick et al.)⁹. Doppler sonography, DVM-4300 Doppler Volume Flowmeter (Hadecco®, Kawasaki, Japan), was used to identify the exact location of the cavernous internal carotid artery (ICA) and care was taken not to injure. In cases with suspected CS invasion, the bony opening and the dural opening needed to be sufficiently lateral, without making injuries to the cavernous ICA.

After the dural opening, the tumor was removed using the binostrials-four hands technique performed by two neurosurgeons using various endoscopic instruments (Karl Storz®, Mittelstrasse, Tuttlingen, Germany). Whenever possible, en-bloc tumor removal was performed. When the tumor was removed in the piecemeal fashion, the mass was removed from the inferior to the superior direction in order to prevent blocking of the view by bulging of the diaphragm sellae. Finally, the mass suspected for the CS invasion was removed to avoid hindering the operative view from sinus bleeding after tumor removal.

If the CSF leakage occurred after tumor removal, the sellar floor was reconstructed using the previously reported modified CSF leakage repair technique¹⁷.

Data analysis

Inter-rater reliability was statistically assessed by measuring intraclass correlation coefficient (ICC) from a two-way ANOVA. The reliability was ranked as excellent, good, moderate, and poor

for ICC>0.75, 0.60–0.75, 0.40–0.59, and <0.40, respectively¹¹.

The GTR rates were measured in each parasellar extension grade and their statistical differences were calculated. Pearson's χ^2 test (Fisher's exact test) was performed; *p*-values <0.05 were considered to be statistically significant. Bonferroni correction was applied 5 times to calculate significant differences between adjacent grades (G0/G1, G1/G2, G2/G3A, G3A/G3B, and G3B/G4). In post-hoc test, *p*<0.01 (0.05/5) was considered to be statistically significant.

The relationships among ‘serious’ complication rates regarding parasellar extension and extents of resection were also analyzed using a logistic regression test.

All statistical analyses were performed using the SPSS 18.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

Comparing the grading performed by three different raters (SHL, JSP, and SL), the reliability value of ICC amounted to 0.863, suggesting an excellent agreement across the raters. The inter-rater reliability values between two raters were also calculated using the Kohen's kappa method; the obtained value amounted to 0.759 between SHL and JSP, 0.831 between SHL and SL, and 0.826 between JSP and SL; therefore, all values suggested excellent agreement (Table 3).

The distribution between the grades was 4.8, 30.3, 29.8, 20.2, 3.8, and 11.1% for Grades 0, 1, 2, 3A, 3B, and 4, respectively. The GTR rates achieved in each grade were 70.0, 69.8, 62.9,

Table 3. Comparing intraclass correlation coefficient among the raters

Raters	ICC	95% limits of agreement
SHL-JSP-SL	0.863	0.827–0.892
SHL-JSP	0.759	0.683–0.816
SHL-SL	0.831	0.777–0.871
JSP-SL	0.826	0.772–0.868

ICC : intraclass correlation coefficient

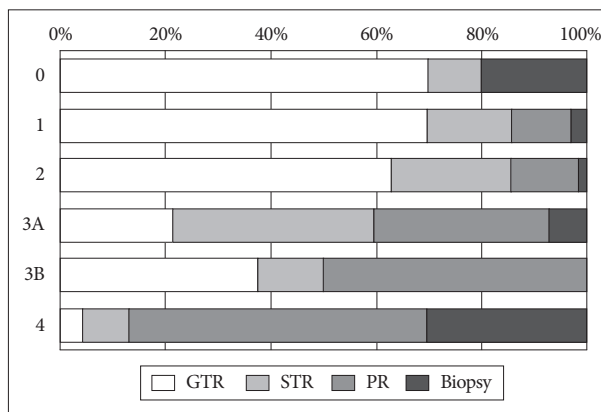


Fig. 4. Schematic chart representing the distribution of the extent of resection in each grade. Gross total removal rate shows an inverse proportional relationship with the grade increase. GTR : gross total removal, STR : subtotal tumor removal, PR : partial removal.

Table 4. The rates of gross total removal and specific numeric data

Grade	Biopsy	PR	STR	GTR (%)*	Total No. (%) [†]
G0	2	0	1	7 (70.0)	10 (4.8)
G1	2	7	10	44 (69.8)	63 (30.3)
G2	1	8	14	39 (62.9)	62 (29.8)
G3A	3	14	16	9 (21.4)	42 (20.2)
G3B	0	4	1	3 (37.5)	8 (3.8)
G4	7	13	2	1 (4.3)	23 (11.1)

*Percentage of GTR among each grade, [†]Percentage of each grade among the total case number. PR : partial removal, STR : subtotal tumor removal, GTR : gross total removal

21.4, 37.5, and 4.3% for Grades 0, 1, 2, 3A, 3B, and 4, respectively. The extent of resection according to the parasellar extension grade is shown in Fig. 4. The specific numeric data are presented in Table 4. This table shows inverse proportional relationships between parasellar extension grades and the rates of GTR.

In post-hoc test between adjacent grades regarding the GTR rates, Grade 2 adenomas had a significantly higher GTR rate as compared to Grade 3A adenomas ($p < 0.001$). No statistically significant differences of GTR rate were observed across other grades; p -values were 0.992, 0.412, 0.329 and 0.016 for G0/1, G1/2, G3A/3B, and G3B/4, respectively. In this post-hoc test, $p < 0.01$ was considered to be statistically significant.

Regarding 'serious' complications rates, significantly higher rates of complications were revealed in the groups above Grade 3A [odds ratio (OR)=2.862, $p=0.007$, 95% confidence interval 1.325–6.185]. No significant differences of complication rates among the extents of resection subgroups were observed (OR=1.146, $p=0.730$, 95% confidence interval 0.529–2.483).

DISCUSSION

To predict the CS invasion, we used the parasellar extension grading system suggested by Micko et al.²¹⁾. The newly proposed grading system is valuable in that it further categorizes the extent of the CS invasion. The preoperative grading was applied to help make surgical plans, whether or not to remove the tumor with CS invasion. However, when applied in clinical settings, the distinction between each grade remains relatively unclear in many cases. Several aspects, including technical, tumor, and interpreter factors, underpin the reasons for this discrepancy. Technical factors include the available type of preoperative image, the quality of the image, and the slice gained for coronal imaging. The tumor factors refer to the shape of the tumor, thickening of the tumor capsule, the tortuosity of cavernous ICA, and the type of the previous treatment received. The interpreter factors include the interpreter's experience and interpretation of the exact tumor extent.

Due to the complexity of the aforementioned grading system, the parasellar extension grade between different raters has, in some cases, remained inconsistent. In order to statistically evaluate the reliability of this grading system, we assessed the inter-

rater reliability across different raters, which, to the best of our knowledge, has never been done in previous literature. In evaluating reliability, test-retest reliability and inter-rater reliability are both commonly used^{2,6,25)}. The reason underpinning our decision to evaluate only the inter-rater reliability is that, in clinical settings, such as measuring the parasellar extension grades, retesting is not necessary in most cases. Since the parasellar extension by Knosp's classification is based on preoperative images, the image findings are unlikely to change over time. Rather, they are used only for communication before surgery to predict the extent of resection. For that reason, many previous studies checked only inter-rater reliability for assessing reliability of a diagnostic tool^{3,20)}.

In the present study, inter-rater reliability was assessed by calculating ICC by two-way ANOVA. The reliability value amounted to 0.863, suggesting an excellent agreement across the raters. This finding highlights that the modified Knosp's classification, however complex it might appear, can be reliably used as a new standard of evaluating parasellar extension, replacing thus the previous version of the classification system. Therefore, we would like to encourage the usage of this classification by other institutes and further comparisons the new findings with those reported in the present study.

Next, we attempted to verify the clinical validity of the grading system by assessing the extents of resection and complication rates among parasellar extension grades. Regarding the GTR rate among the grades, a statistically significant difference was observed only between Grades 2 and 3A. While the grading system by Micko et al. showed lower GTR rates as the grade ascends, with a significant difference between Grade 3A and 3B, our results showed more decreased GTR rates on Grade 3A patients than Grade 3B patients. However, this finding was statistically insignificant, probably due to the diminished case number on each subgroup. Although our study population was relatively large, after dividing the studied cases into 6 parasellar extension grades, the proportion of each grade got smaller. If the study had been conducted on a larger scale, with a sufficient proportion of cases in each grade, more significant differences might have been observed between other subgroups as well.

However, the present study showed a significant difference between Grades 2 and 3A in the GTR rate. Additionally, we performed 2 more post-hoc tests between Grades 0 and 2, Grades 3A and 4 ($p=0.665$ and 0.068 , respectively) to further analyze the statistically significant differences in non-adjacent grades. These findings suggest that, in cases with parasellar extension of the grades higher than 3A, the likeliness of GTR will significantly decrease. The CS invasion has already been reported to have a negative predictive value on the tumor removal rate, although most previous studies do not set distinct criteria for the parasellar extension grade affecting the tumor removal rate^{1,8,10)}. Hereby, we would like to propose the negative predictive value of Grades 3A, 3B, and 4 regarding the tumor removal rate.

According to the initial Knosp's classification, only Grades 3

and 4 premise that there is a genuine CS invasion¹⁸. Although Micko et al.²¹ reported some portion of the CS invasions with grades lower than Grade 3, our findings suggest that parasellar extension grades above Grade 3A have a clinically relevant CS invasion.

We also analyzed the complication rates among parasellar extension grades. In our results, the cases with Grades 3A, 3B, and 4 showed significantly higher complication rates as compared to other cases. Considering that, in higher grades, an attempted GTR can lead to further neurologic sequelae to the cranial nerves III, IV, and VI, we also analyzed the relationship between complication rates and extents of resection. No significant differences among extent of resection subgroups were observed. Therefore, we can safely assume that parasellar extension Grades 3A, 3B, and 4 are related to higher complication rates, regardless of the extents of resection.

In the present study, no microscopic or endoscopic verification of parasellar extension grading was performed. Owing to this procedure, the study could have obtained a more detailed description of the CS invasion among each of the studied parasellar extension grades. Due to the retrospective nature of the present study, this limitation could not have been overcome. Further prospective studies should be warranted to amend for this limitation.

Besides the presence of the CS invasion, the surgical goal and skills are also important to predict the extent of resection¹⁶. The surgical goals for functioning and non-functioning pituitary adenomas are slightly different in our institution. In cases of functioning pituitary adenoma, the surgical goal would be endocrinologic remission without considerable operative morbidity. When endocrinologic remission was not achieved, medical treatment, such as bromocriptine, cabergoline in prolactinoma, or somatostatin in the GH-producing pituitary adenoma, was applied to the patient^{4,27}. On the other hand, in the cases of non-functioning pituitary adenomas, the surgical goal was symptom relief by decompression with a maximally safe resection without complications¹³. Due to this difference between the surgical goals in functioning and non-functioning pituitary adenoma surgery, the GTR rate should have been evaluated in the subgroup analysis. Considering the purpose of the present study and due to the sufficient number of the analyzed cases, we assumed that this negligence of analysis would not affect the results. The difference of the GTR rates between the two groups is one of the factors intended for inclusion in our future research.

In addition, the skills of the operating surgeon, novice or expert, are also important. The study population of our research was operated by an endoscopic surgeon in our institute with over several hundred cases of experience. Moreover, the complication rates in the present study can be considered to be equivalent to other international series¹⁹. The operations were performed in the fully endoscopic manner, which is now widely acknowledged as the most popular method for transsphenoidal surgery^{7,14,22}.

CONCLUSION

The modified Knosp's grading system shows a high inter-rater reliability with an excellent agreement across the raters. Pre-operative parasellar extension grading is valuable in predicting the extents of resection and surgical complication rates in EETS for pituitary adenomas. Parasellar extension Grades 3A, 3B, and 4 have a negative predictive value for the GTR rate, with higher complication rates.

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