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Endoscopic approach for giant pituitary adenoma: clinical outcomes of 205 patients and comparison of two proposed classification systems for preoperative prediction of extent of resection

Savas Ceylan, MD,[1] Harun Emre Sen, MD,[1] Bedrettin Ozsoy, MD,[1] Ecem Cemre Ceylan, MD,[1] Anil Ergen, MD,[1] Alev Selek, MD,[2] Yonca Anik, MD,[3] Sibel Balci, PhD,[4] Burak Cabuk, MD,[1] and Ihsan Anik, MD[1]

Departments of [1]Neurosurgery and Pituitary Research Center, [2]Endocrinology, [3]Radiology, and [4]Biostatistics and Medical Informatics, Kocaeli University School of Medicine, Kocaeli, Turkey

OBJECTIVE Giant pituitary adenoma is considered a challenging pathology for surgery owing to its complications and low resection rate. In this study, the authors present their experience of using the endoscopic endonasal approach to treat patients with giant pituitary adenoma, and they aimed to develop a classification system for prediction of extent of resection.

METHODS The institutional medical records of patients diagnosed with giant pituitary adenoma who underwent endoscopic endonasal transsphenoidal surgery between August 1997 and December 2019 were retrospectively reviewed. Surgical and clinical outcomes were evaluated in detail. The effects of tumor characteristics on extent of resection were analyzed. The findings were used to develop two classification systems that could preoperatively predict extent of resection. Morphological score was based on tumor characteristics, and landmark-based classification was defined according to surgical zones based on neurovascular landmarks. The effects of change in surgical strategy, which aimed to maximize tumor resection and capsule dissection, on rates of resection and complications were evaluated before and after 2017.

RESULTS This study included 205 patients, with a mean patient age of 46.95 years and mean preoperative tumor diameter of 46.56 mm. Gross-total resection (GTR) was achieved in 35.12% of patients, near-total resection (NTR) in 39.51%, and subtotal resection (STR) in 25.36%. Extent of resection differed significantly between the grades and zones of the classification systems ($p < 0.001$ for both). Among patients with grade 3 tumor, 75.75% of patients achieved STR, 21.21% achieved NTR, and 3.03% achieved GTR. Among patients with zone 3 tumor, 65.75% achieved STR, 32.87% achieved NTR, and 1.36% achieved GTR. Both grade 3 and zone 3 indicated limited extent of resection. The mean (range) follow-up duration was 50.16 (9–247) months. Postoperative recovery of at least one hormone axis was seen in 15.24% of patients with pituitary deficiency, and development of new hormonal deficiency was observed in 22.43% of patients. Complications included permanent diabetes insipidus (7.80%), cerebrospinal fluid leakage (3.90%), postoperative apoplexy (3.90%), meningitis (3.41%), and epistaxis (3.41%). The surgical mortality rate was 1.46%. Among 85 patients treated before 2017, 27.05% of patients achieved GTR, 37.64% achieved NTR, and 35.29% achieved STR; among 120 patients treated after 2017, 40.83% achieved GTR, 40.83% achieved NTR, and 18.33% achieved STR. Seven patients in the pre-2017 cohort had postoperative apoplexy versus only 1 patient in the post-2017 cohort. There were no statistically significant differences between the two periods in terms of the incidence rates of other complications.

CONCLUSIONS Capsule dissection and GTR are valuable for preventing serious complications and reducing recurrence of giant adenoma. Treatment of giant pituitary adenoma may be better managed with the help of a classification system that provides information about extent of resection that can be achieved with an endoscopic approach.

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KEYWORDS giant pituitary adenomas; endoscopic transnasal approach; prediction of the extent of resection; pituitary surgery; classification

ABBREVIATIONS ACTH = adrenocorticotropic hormone; DI = diabetes insipidus; GH = growth hormone; GTR = gross-total resection; NTR = near-total resection; PRL = prolactin; STR = subtotal resection; TSH = thyroid-stimulating hormone; VF = visual field.

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Pituitary adenoma constitutes approximately 10%–15% of all intracranial tumors,[1] whereas giant adenoma comprises 5%–16% of all pituitary adenomas.[2–5] Common symptoms associated with giant adenoma include visual disturbance, headache, cranial nerve palsy, endocrine dysfunction, and hormone hypersecretion–related syndromes.[6] The primary treatment of choice—resection—is often complicated by large tumor size, irregular extensions, and frequent involvement of critical neurovascular structures, resulting in high risk of complications and low rates of gross-total resection (GTR). The popularity of endoscopic endonasal transsphenoidal surgery for pituitary adenoma resection has greatly increased owing to the improved visualization granted by this technique and its less invasive nature. Several studies have reported on the efficacy of endoscopic endonasal transsphenoidal surgery for giant pituitary adenoma in the last decade.[2,4,5,7–14] However, the high incidence rates of complications and recurrence highlight the need for a classification system that allows preoperative prediction of extent of resection, and research in this area is currently underway at several centers.[15,16]

The current study presents the surgical and endocrinological outcomes of 205 patients diagnosed with giant pituitary adenoma. We aimed to evaluate the effects of our improved surgical strategy on resection and complication rates. In our series, we applied two classification systems and preoperative MRI to 1) score tumor characteristics on the basis of their contribution to surgical difficulty and 2) identify surgical zones on the basis of their relationships to neurovascular landmarks. We assessed the suitability of each system for preoperative prediction of extent of resection of giant pituitary adenoma.

Methods

We retrospectively analyzed data on 2561 patients with pituitary adenoma who were treated between August 1997 and December 2019 at the Pituitary Research Center and Department of Neurosurgery, Kocaeli University Faculty of Medicine, Kocaeli, Turkey. All clinical data, including findings on preoperative and postoperative MRI, results of visual function tests, laboratory results, and findings included in medical records and pathology reports, were reviewed. In total, 218 patients met the radiological criteria for giant adenoma and were treated at our clinic within the study period. Of these, 8 patients did not comply with both the 3- and 6-month follow-up appointments after discharge, 3 had unavailable preoperative and/or postoperative MRI scans, and 2 were diagnosed with a pathology other than pituitary adenoma; these patients were excluded. Therefore, 205 patients with pituitary adenoma exceeding 4 cm in diameter in at least one direction, as noted on preoperative MRI, were included. Patients who had undergone previous surgery or radiosurgery and had presented with relapsed tumor greater than 4 cm were also included. The minimum follow-up period required for inclusion was 9 months. Adequate follow-up was defined as MRI examination, endocrinological evaluation, and visual function tests performed at 3 and 6 months postoperatively, followed by clinical and radiological evaluations performed every 12 months.

Clinical Evaluation

An expert endocrinologist performed the hormonal assessments, including preoperative and postoperative basal and functional pituitary hormone assays, in all patients. Preoperative, postoperative, and follow-up visual field (VF) and acuity tests were performed by an independent ophthalmologist. Visual acuity was assessed with Snellen optotypes, and the Humphrey VF analyzer (HFA II 750, Carl Zeiss Meditec) was used to record VF defects. A good outcome was declared if the patient's visual test results improved or remained unchanged over the follow-up period. All tumor specimens underwent histopathological and immunohistochemical analysis to confirm the diagnosis of pituitary adenoma and to evaluate multiple pituitary hormone stains and Ki-67 rates.

Postoperative remission of functional adenoma was defined as no additional medical treatment at ≥ 3 months after surgery. Remission was defined according to the following criteria: normal insulin-like growth factor 1 level for age and sex; postoperative random growth hormone (GH) level < 1 ng/ml (before 2010) or < 0.4 ng/ml (after 2010) after an oral glucose tolerance test for patients with acromegaly; normalization of thyroid-stimulating hormone (TSH) and circulating thyroid hormone levels for patients with thyrotropinoma; normalization of prolactin (PRL) level for patients with prolactinoma; restoration of diurnal cortisol rhythm; and suppression of cortisol level to < 1.8 μg/dl after low-dose dexamethasone suppression test for patients with Cushing disease.

Radiological Evaluation

Preoperative, postoperative, and follow-up MR images were evaluated by an independent radiologist. Preoperative MRI was used to assess and to categorize tumors according to size (4–5 cm, 5–6 cm, and > 6 cm), shape (dumbbell shaped, multilobular, or round), and extension. Cavernous sinus invasion, according to the Knosp classification, and invasion involving the lateral compartment were identified.[17,18] The height of the tumor in the suprasellar area, and the ratio of suprasellar volume to infrasellar volume, were also determined. The first postoperative MRI examination was performed within 24 hours after surgery, followed by additional MRI examinations at 3, 6, and 12 months of follow-up. Extent of resection was assessed with the MRI examination performed in the first 24 hours postoperatively. GTR was defined as no evidence of residual tumor on postoperative MRI, whereas near-total resection (NTR) was defined as ≥ 90% reduction in tumor volume. Tumor volume reduction < 90% was defined as subtotal resection (STR).

Scoring Systems

Preoperative MRI was used to classify tumors using the following two classification systems.

Morphological Score

This classification system aimed to grade tumors by scoring morphological tumor characteristics that may affect extent of resection, similar to previously presented systems.[15,16] Seven characteristic features were used as cri-

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teria: suprasellar height > 2 cm; multilobular or dumbbell-shaped morphology; invasion of the lateral compartment to the cavernous sinus (2 points if bilateral); ratio > 1.5 of the maximum horizontal dimension (x) of the tumor in the suprasellar area to the supraclinoid intercarotid distance (y) on coronal MRI (i.e., x/y > 1.5); and extensions into the anterior cranial fossa, posterior fossa, and inferior wall of the lateral ventricle (Fig. 1). Each characteristic was assigned 1 point, and tumors were given an overall score ranging between 0 and 8 points. Tumors were then graded (grade 1 for ≤ 2 points, grade 2 for 3 or 4 points, grade 3 for ≥ 5 points), and patient groups were evaluated according to their resection rates.

Landmark-Based Classification

This classification system aimed to evaluate the relationship between visual anatomical landmarks and tumor extension. The suprasellar part of zone 1 was defined as an elliptical area with boundaries determined on coronal and sagittal MR images. The lateral borders were represented by parallel lines drawn from the cavernous segment of the carotid artery at the level where the horizontal segments were farthest from each other, and the upper border was 20 mm superior to the supraclinoid segment of the carotid artery on coronal MRI. On the sagittal plane, the boundaries were represented by lines drawn from the anterior bend of the cavernous carotid segment, from the posterior border of the clivus, and from 20 mm superior to the supraclinoid carotid segment. The boundaries of the infrasellar part of zone 1 were defined by the intact sphenoid sinus walls. There was no cavernous sinus invasion by tumor in zone 1. Zone 2 was defined according to the 10-mm border around the circumference of zone 1 (Fig. 2). Zone 3 was defined as the region outside the border of zone 2.

Statistical Analysis

All statistical analysis was performed using SPSS for Windows version 20.0 (IBM Corp.). The association between two categorical variables was examined with the chi-square test. Multinomial logistic regression analysis was performed to identify factors associated with resection rate. All statistical analysis was performed with a 5% level of significance, and a 2-sided p value < 0.05 was considered statistically significant.

Surgical Approach

In our series, most surgical procedures were performed using the standard transsellar approach. When deemed necessary, the extended transsellar approach was preferred for tumors with advanced frontal extension, and the transpterygoidal parasellar approach was preferred for tumors with invasion to the lateral compartment of the cavernous sinus and temporal lobe extension. These techniques have been previously described in detail.[17,19–21] Exposure of the dura mater may extend through the tuberculum sellae, clival recess, and carotid protuberances owing to the configuration of the tumor. At first, the infrasellar and sellar components of the tumor were excised to the dorsum sellae posteriorly and the medial walls of the cavernous sinus laterally. In patients with cavernous sinus invasion, we reached the cavernous sinus compartments by opening the medial or anterior wall of the cavernous sinus, as described for the transpterygoidal approach (Video 1).

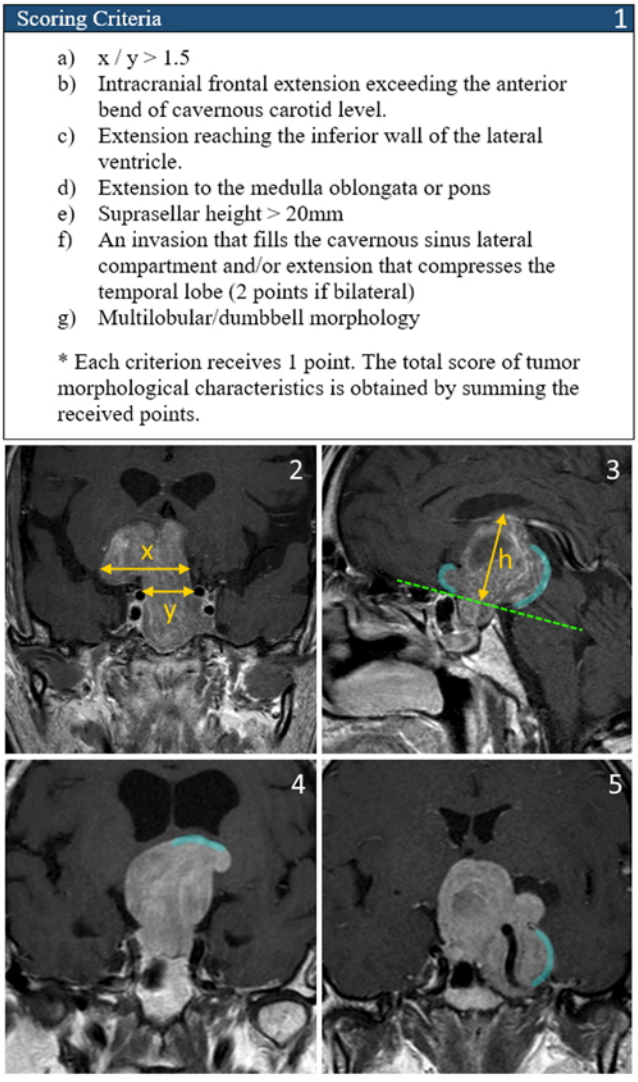


FIG. 1. Morphological scoring criteria and MR images demonstrating morphological tumor characteristics. **1:** Morphological scoring criteria. **2:** The tumor's maximum horizontal dimension in the suprasellar direction (*x*) and the distance between the supraclinoid carotid arteries (*y*) at the level of the diaphragma sellae are shown. **3:** Suprasellar height (*h*), as well as frontal and posterior extensions (*dotted line*) of the tumor in the sagittal plane, is shown. **4:** A tumor extending and compressing the inferior wall of the lateral ventricle. **5:** A tumor filling the lateral compartment of the cavernous sinus and compressing the temporal lobe.

VIDEO 1. Access to the left lateral compartment and excision of a tumor with bilateral cavernous sinus invasion. Copyright Prof. Dr. Savas Ceylan. Published with permission. Click here to view.

Excision of the suprasellar component of the tumor was carried out in a posterosuperior-to-anterior direction, and the anterosuperior portion of the tumor was removed last. This technique results in internal decompression and near-total excision of the adenoma, leaving a thin capsule. Thereafter, the most suitable areas for capsule dissection are the medial walls of the cavernous sinus and dorsum

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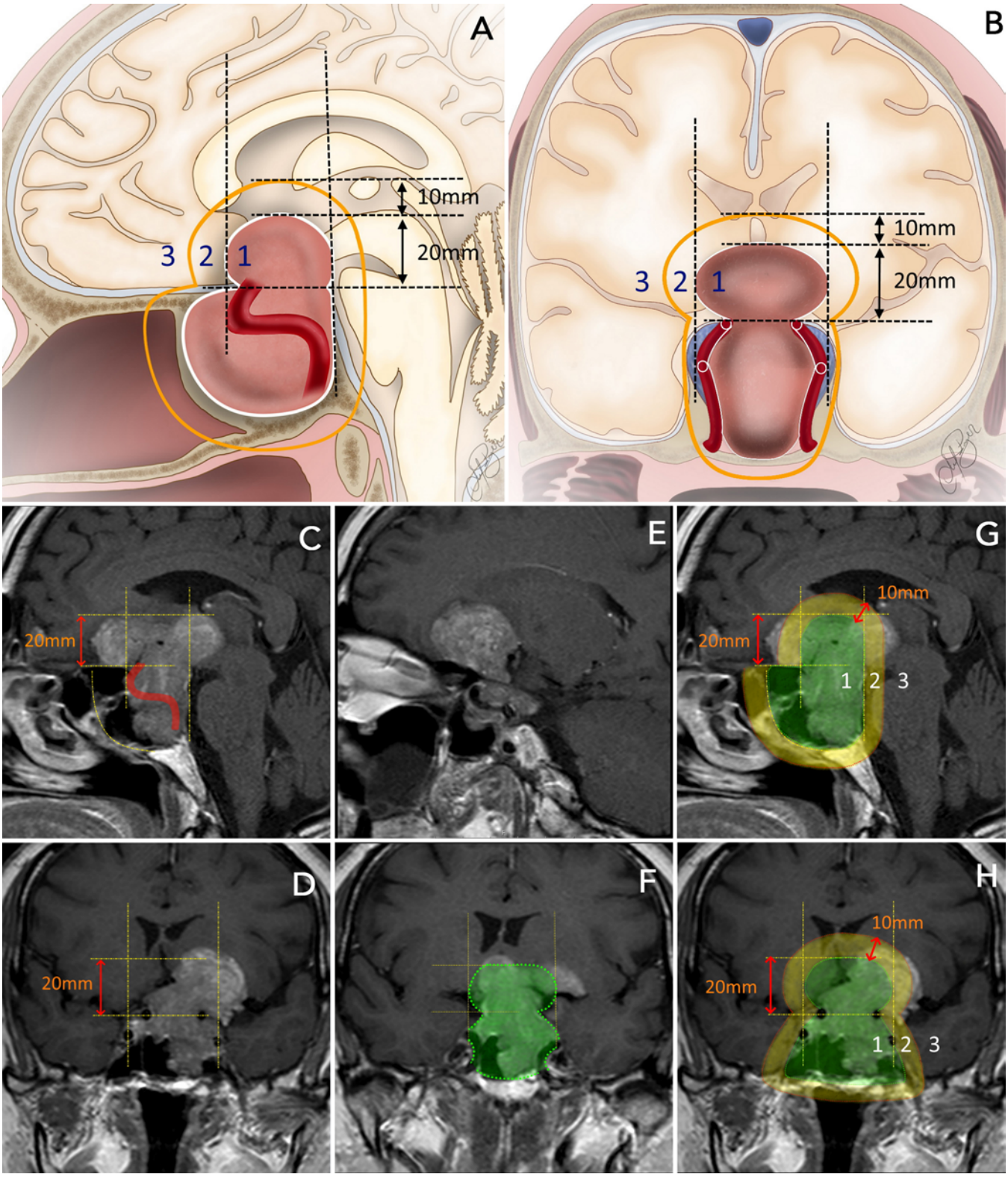


FIG. 2. Schematic drawings and MR images demonstrating the surgical zones described by the landmark-based classification system. Sagittal (**A**) and coronal (**B**) schematic drawings demonstrate the surgical zones and their relationships with neurovascular structures. The borders of zone 1 are shown on sagittal (**C**) and coronal (**D**) MR images. A sagittal MR image (**E**) shows the course of the cavernous carotid segment. A coronal MR image (**F**) shows the relationship between the inferolateral borders of zone 1 and the paraclival carotid segments in a patient with giant adenoma. The borders of zone 1 (*green*) and zone 2 (*yellow*) are shown on sagittal (**G**) and coronal (**H**) MR images. Panels A and B: Copyright Prof. Dr. Savas Ceylan. Published with permission.

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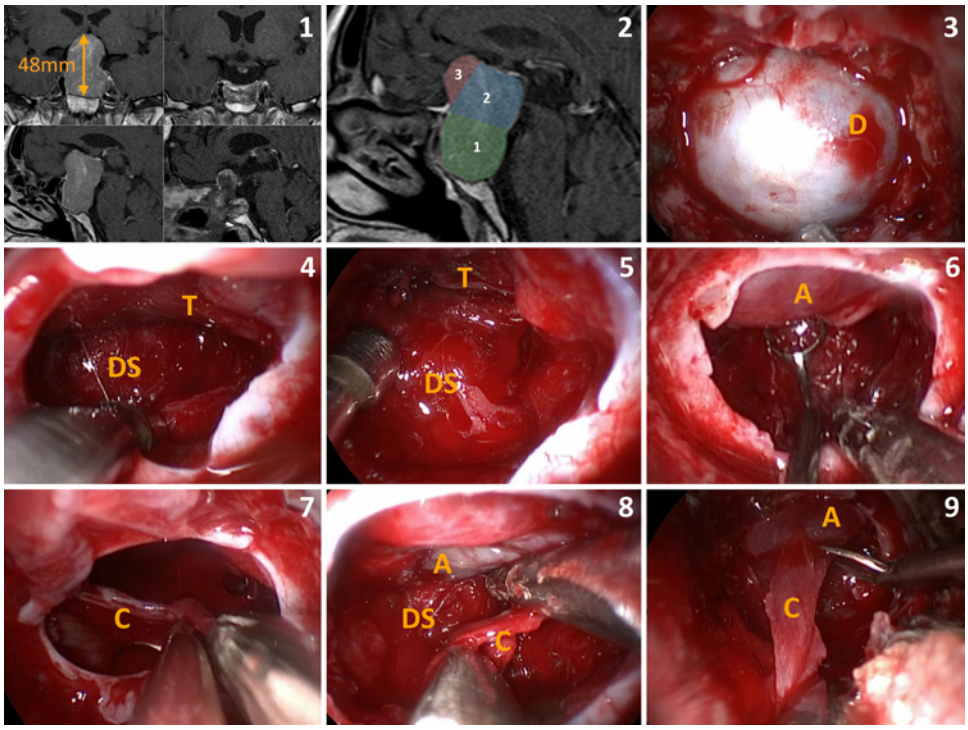


FIG. 3. MR and intraoperative images demonstrating the surgical stages (Video 2). **1:** Preoperative and postoperative MR images of a giant adenoma. **2:** Tumor excision stages are shown as numbers. **3:** Exposure of the dura mater (*D*). **4:** Excision of the infrasellar part of the tumor (*T*) to the dorsum sellae (*DS*). **5:** Excision of the suprasellar part of the tumor. **6:** Excision of the anterior parts of the suprasellar tumor and visualization of the arachnoid membrane (*A*). **7:** Dissection of the tumor capsule (*C*) adjacent to the right medial wall of the cavernous sinus. **8:** Capsule dissection of the suprasellar tumor from the dorsum sellae and arachnoid membrane. **9:** Excision of the capsule by cutting areas adhering to the arachnoid membrane. Copyright Prof. Dr. Savas Ceylan. Published with permission.

sellae. Normal tissue and capsule differentiation can be best done in these areas, and capsule dissection can be initiated without causing CSF leakage. Capsule dissection was carried out in a posterosuperior-to-anterior direction. A minimal amount of capsule can be left adhering to the arachnoid structure if dissection poses a risk of CSF leakage (Fig. 3, Video 2).

VIDEO 2. Resection and capsule dissection of a giant adenoma. Copyright Prof. Dr. Savas Ceylan. Published with permission. Click here to view.

The described technique aimed to ensure that the arachnoid membrane adjacent to the suprasellar cistern did not obstruct surgical access to the posterior part of the tumor owing to inferior herniation.

The preferred technique for skull base reconstruction varies according to the situation (e.g., intraoperative CSF leakage, herniation of the arachnoid membrane, width of the surgical area). In our series, synthetic dural graft, fascia lata graft, adipose tissue, nasoseptal flap, and fibrin sealants were used in different combinations for reconstruction. Instead of employing a standard strategy, the surgeons had the liberty to select the reconstruction technique of their choice.

Surgical Strategy

In the early years of our surgical experience, our treatment plan for giant adenoma comprised endoscopic transsphenoidal surgical decompression of the optic chiasm and internal debulking of the tumor. With increasing experience, our clinic has become a tertiary center for the treatment of challenging sellar masses, and the number of giant adenoma cases has increased in recent years. This has allowed us to adopt a more aggressive surgical strategy aimed at improving tumor resection and capsular dissection rates over the last 3 years. In this study, we aimed to assess the effects of alteration in surgical strategy and increased level of experience on resection and complication rates by evaluating patients treated before and after 2017.

Results

Demographic Data and Clinical Presentation

The current study (n = 205) included 143 males (69.75%) and 62 females (30.24%), and the mean (range) age was 46.95 (16–80) years. The most common presenting symptom was loss of vision (145 patients [70.73%]), followed by headache (77 [37.56%]), pituitary dysfunction (165 [80.48%]), pituitary hypersecretion (52 [25.36%]), deterioration of mental status (5 [2.43%]), and cranial nerve palsy (5 [2.43%]). No patients in the study group presented to our clinic with symptoms of pituitary apoplexy. However, regions that may have been compatible with intratumoral hemorrhage were observed on the preoperative MRI scans

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of 8 patients. This study included 35 (17.07%) patients with recurrent tumor, 12 of whom were treated by our team and 23 at other medical centers. The mean (range) follow-up duration was 50.16 (9–247) months. During follow-up, 13 patients with residual or recurrent masses who were considered unsuitable for surgery received Gamma Knife treatment.

Preoperative Radiological Findings and Tumor Characteristics

The mean (range) maximum tumor diameter was 46.56 (40–87) mm. Evaluation of cavernous sinus invasion showed that 87 patients had Knosp grade 1–2 invasion and 118 had Knosp grade 3a, 3b, and 4 invasion. Moreover, the tumor completely filled the lateral compartment of the cavernous sinus in 79 patients. Tumor characteristics, as noted on preoperative MRI, are presented in Table 1.

Surgical Management and Extent of Resection

The standard transsellar approach was performed on 168 patients, whereas the extended approach was used to treat 37 patients and the transpterygoidal technique was used to treat 12 cases. Medical treatment was the primary option for management of PRL-secreting adenoma; however, surgery was performed on 25 patients with giant prolactinoma. The surgical indications were acute deteriorated vision in 9 patients, drug resistance/intolerance in 9, symptoms of hypothalamic or frontal cortical compression in 5, and cranial nerve dysfunction in 2. Intraoperative tumor consistency was classified as completely soft or with firm or fibrotic components. Tumors with firm or fibrotic components were encountered in 36 patients. Evaluation of extent of resection showed that GTR was achieved in 72 patients, NTR in 81 patients, and STR in 52 patients.

Results of the analysis of effects of various tumor characteristics on extent of resection are shown in Tables 1 and 2. Tumor characteristics that negatively affected resection included suprasellar part of the tumor exceeding 2 cm in height ($p < 0.001$); invasion of the lateral compartment of the cavernous sinus ($p < 0.001$); extensions of the tumor to the anterior cranial fossa ($p < 0.001$), inferior wall of the lateral ventricle ($p < 0.001$), and posterior cranial fossa ($p < 0.001$); multilobulated/dumbbell-shaped configuration ($p < 0.001$); and x/y ratio exceeding 1.5 ($p < 0.001$).

Staged endoscopic surgery was performed on 11 patients. The aim was endoscopic resection of the entire tumor in the first operation. The planned resection could not be performed owing to firm tumor consistency in 2 patients, prolonged surgery duration (exceeding 7 hours) in 1 patient, and intraoperative cardiac problems in 1 patient. In 7 patients, 24-hour postoperative MRI showed an unexpected residual tumor that could be excised with an endoscopic approach. An early second staged endoscopic surgery was recommended to these patients. In line with their preferences, 8 patients underwent a second staged endoscopic surgery within the first week and 3 patients within a month. Among these cases, GTR was achieved in 5 patients, NTR in 4, and STR in 2. Endoscopic and transcranial combined surgery was performed on 12 patients. As planned, simultaneous endoscopic and transcranial surgery was performed on 5 patients. For 7 patients, reoperation with a transcranial approach was recommended on the basis of the evaluation of residual tumor with 24-hour postoperative MRI. In line with the preferences of these patients, craniotomy was performed within the first week in 5 patients and within 2 months in 2 patients. Among these patients, GTR was achieved in 7 patients, NTR in 3, and STR in 2.

Twelve of the 35 patients with recurrent tumor had their first surgery performed at our center. When first diagnosed, 3 of these patients had a tumor between 3 and 4 cm that was invading the cavernous sinus and 9 had giant adenoma. All these first operations resulted in STR. The main (range) interval between the two surgical procedures was 46.44 (14–114) months. Among all 35 patients with recurrent tumor, GTR was achieved in 8 patients, NTR in 15, and STR in 12.

The resection rates for the periods before and after 2017, calculated according to date that our surgical strategy was changed, were evaluated. Before 2017, 85 patients were treated and GTR was achieved in 23 (27.05%) patients, NTR in 32 (37.64%), and STR in 30 (35.29%). After 2017, 120 patients were treated and GTR was achieved in 49 (40.83%) patients, NTR in 49 (40.83%), and STR in 22 (18.33%) (Table 3).

Clinical Outcomes

VF and visual acuity tests were performed on all patients with giant adenoma, regardless of whether they presented with visual symptoms. Preoperative loss of vision was reported by 145 patients, but vision impairment was detected in 167 patients. During follow-up, partial improvement was observed in 84 (50.29%) patients and complete recovery in 25 (14.97%). There was no change in vision loss in 54 (32.33%) patients, but further deterioration of symptoms was noted in 4 (2.39%) patients. No improvement in eye movements during follow-up was observed in the 5 patients with preoperative cranial nerve palsy.

Preoperative pituitary hormone deficiency of any type was seen in 164 (80.00%) patients, including 33 (16.09%) with panhypopituitarism. Gonadotropin (n = 116), TSH (54), and adrenocorticotropic hormone (ACTH) (43) deficiencies were also seen frequently. Postoperative recovery from any hormonal deficiency was attained in 15.24% (n = 25) of patients with pituitary deficiency; the most common of these were gonadotropin (n = 10), TSH (6), and ACTH (5) deficiencies. However, new hormonal deficiency also developed postoperatively in 46 (22.43%) patients; among these patients, ACTH (n = 20), TSH (16), and gonadotropin (16) deficiencies, either isolated or combined, were the most frequent. After surgery, 24 patients had permanent diabetes insipidus (DI), including 16 (7.80%) patients with new-onset DI and 7 patients with transient DI. Fifty-two (25.36%) patients had functional adenoma, and the overall surgical remission rate was 17.30% (40.00% for patients with GH-secreting adenoma, 66.66% for patients with TSH-secreting adenoma, and 33.33% for patients with GH- and PRL-secreting adenoma; in addition, 0 patients with other functional adenomas had remission). Immunohistochemical evaluation of adenoma tissues showed that 116 patients had Ki-67 staining < 3%, 74 had staining between 3% and 10%, and 15 had Ki-67 staining > 10%.

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TABLE 1. Analysis of patient and tumor characteristics with resection rates

Characteristic	Pts	GTR	NTR	STR	p Value
Age, yrs					
<40	60	26 (43.33)	22 (36.66)	12 (20.00)	
40–60	105	39 (37.14)	39 (37.14)	27 (25.71)	0.101
>60	40	7 (17.50)	20 (50.00)	13 (32.50)	
Sex					
Female	62	19 (30.64)	22 (35.48)	21 (33.87)	0.180
Male	143	53 (37.06)	59 (41.25)	31 (21.67)	
Max tumor dimension, cm					
4–5	151	65 (43.04)	55 (36.42)	31 (20.52)	
5–6	38	6 (15.78)	20 (52.63)	12 (31.57)	**<0.001**
>6	16	1 (6.25)	6 (37.50)	9 (56.25)	
Suprasellar height, cm					
<2	129	63 (48.83)	43 (33.33)	23 (17.82)	
2–3	64	9 (14.06)	34 (53.12)	21 (32.81)	**<0.001**
>3	12	0 (0)	4 (33.33)	8 (66.66)	
Suprasellar/infrasellar vol ratio					
>1	55	10 (18.18)	23 (41.81)	22 (40.00)	**0.002**
≤1	150	62 (41.33)	58 (38.66)	30 (20.00)	
Hormone secretion					
Nonfunctional	153	58 (37.90)	58 (37.90)	37 (24.18)	0.378
Hormone secreting	52	14 (26.92)	23 (44.23)	15 (28.84)	
Previous surgery					
Primary	170	64 (37.64)	66 (38.82)	40 (23.52)	0.209
Recurrent/residual tumor	35	8 (22.85)	15 (42.85)	12 (34.28)	
Extension other than to the chiasmatic cistern					
Anterior cranial fossa	63	6 (9.52)	32 (50.79)	25 (39.68)	**<0.001**
Temporal lobe	67	7 (10.44)	25 (37.31)	35 (52.23)	**<0.001**
Posterior fossa	36	3 (8.33)	10 (27.77)	23 (63.88)	**<0.001**
Inferior wall of lateral ventricle	29	3 (10.34)	8 (27.58)	18 (62.06)	**<0.001**
x/y ratio*					
>1.5	62	4 (6.45)	24 (38.70)	34 (54.83)	**<0.001**
≤1.5	143	68 (47.55)	57 (39.86)	18 (12.58)	
Shape					
Round	59	43 (72.88)	16 (27.11)	0 (0)	
Dumbbell shaped	25	9 (36.00)	13 (52.00)	3 (12.00)	**<0.001**
Multilobular	121	20(16.52)	52 (42.97)	49 (40.49)	
Intraop tumor consistency					
Soft	169	66 (39.05)	65 (38.46)	38 (22.48)	**0.023**
w/ firm or fibrotic components	36	6 (16.66)	16 (44.44)	14 (38.88)	
Cavernous sinus invasion, Knosp grade					
1–2	87	49 (56.32)	32 (36.78)	6 (6.89)	**<0.001**
3–4	118	23 (19.49)	49 (41.52)	46 (38.98)	
Complete invasion of lateral compartment	79	9 (11.39)	32 (40.50)	38 (48.10)	**<0.001**

Values are shown as number or number (percent) unless indicated otherwise. Boldface type indicates statistical significance ($p < 0.05$).

* This was the first criterion of the morphological scoring system.

Nine patients had ACTH-positive nonfunctional adenoma, which was defined as silent corticotroph adenoma.

Complications

Intraoperative CSF was seen or noted in 60 (29.26%) patients, and proper sellae floor reconstruction was performed. Within the first month, postoperative CSF leak was observed in 8 patients; 6 cases had been intraoperatively noted, and 2 were not detected intraoperatively and therefore transsphenoidal reconstruction was performed. Seven patients exhibited epistaxis complications in the early postoperative period. Temporary postopera-

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TABLE 2. Multivariate analysis of effect of tumor characteristics on resection

Variable	OR (95% CI)*	p Value
GTR		
Intercept		**<0.001**
Extension of tumor		
Anterior cranial fossa		
Yes	Reference	
No	9.680 (2.746–34.119)	**<0.001**
Inferior wall of lateral ventricle		
Yes	Reference	
No	6.533 (1.059–40.306)	**0.043**
Posterior fossa		
Yes	Reference	
No	4.974 (0.890–27.792)	0.068
Lateral compartment invasion		
Yes	Reference	
No	28.556 (8.488–96.067)	**<0.001**
Consistency		
Soft	4.610 (1.161–18.307)	**0.030**
Firm or fibrotic	Reference	
Previous surgery		
Primary	1.293 (0.315–5.312)	0.721
Recurrent	Reference	
x/y ratio†		
≤1.5	8.905 (2.184–36.302)	**0.002**
>1.5	Reference	
NTR		
Intercept		**<0.001**
Extension of the tumor		
Anterior cranial fossa		
Yes	Reference	
No	1.389 (0.571–3.378)	0.469
Inferior wall of lateral ventricle		
Yes	Reference	
No	4.511 (1.393–14.612)	**0.012**
Posterior fossa		
Yes	Reference	
No	3.111 (1.104–8.772)	**0.032**
Lateral compartment invasion		
Yes	Reference	
No	5.829 (2.208–15.386)	**<0.001**
Consistency		
Soft	2.336 (0.816–6.684)	0.114
Firm or fibrotic	Reference	
Previous surgery		
Primary	0.862 (0.292–2.548)	0.789
Recurrent	Reference	
x/y ratio†		
≤1.5	2.222 (0.889–5.552)	0.087
>1.5	Reference	

Boldface type indicates statistical significance ($p < 0.05$).

* STR was the reference category.

† This was the first criterion of the morphological scoring system.

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TABLE 3. Complications and clinical and surgical outcomes

Characteristic	Pts (n = 205)	Landmark-Based Classification			Morphological Score			Pre-2017 (n = 85)	Post-2017 (n = 120)
		Zone 1 (n = 55)	Zone 2 (n = 77)	Zone 3 (n = 73)	Grade 1 (n = 117)	Grade 2 (n = 55)	Grade 3 (n = 33)		
Complication									
CSF leak	8 (3.90)	1 (1.81)	5 (6.49)	2 (2.73)	4 (3.41)	3 (5.45)	1 (3.03)	3 (3.52)	5 (4.16)
Meningitis	7 (3.41)	1 (1.81)	3 (3.89)	3 (4.10)	2 (1.70)	3 (5.45)	2 (6.06)	3 (3.52)	4 (3.33)
Epistaxis	7 (3.41)	2 (3.63)	3 (3.89)	2 (2.73)	3 (2.56)	3 (5.45)	1 (3.03)	3 (3.52)	4 (3.33)
New-onset pituitary deficit	46 (22.43)	16 (29.09)	17 (22.07)	13 (17.80)	30 (25.64)	9 (16.36)	7 (21.21)	20 (23.52)	26 (21.66)
Permanent DI	16 (7.80)	4 (7.27)	5 (6.49)	7 (9.58)	9 (7.69)	6 (10.90)	1 (3.03)	9 (10.58)	7 (5.83)
Postoperative apoplexy	8 (3.90)	0	0	8 (10.95)	0	1 (1.81)	7 (21.21)	7 (8.23)	1 (0.83)
Death	3 (1.46)	0	0	3 (4.10)	0	1 (1.81)	2 (6.06)	3 (3.52)	0
Recurrence	12 (5.85)	0	2 (2.59)	10 (13.69)	0	4 (7.27)	8 (24.24)	12 (14.11)	0
Clinical outcomes									
Recovered pituitary deficiency	25/164 (15.24)	11/46 (23.91)	8/58 (13.79)	6/60 (10.00)	18/97 (18.55)	6/39 (15.38)	1/28 (3.57)	9/71 (12.67)	16/93 (17.20)
Improvement in vision loss	109/167 (65.26)	22/26 (84.61)	48/70 (68.57)	39/71 (54.92)	68/81 (83.95)	35/53 (66.03)	6/33 (18.18)	40/73 (54.79)	69/94 (73.40)
Follow-up, mos	50.16							83.86	26.28
Resection rates									
GTR	72 (35.12)	46 (83.63)	25 (32.46)	1 (1.36)	66 (56.41)	5 (9.09)	1 (3.03)	23 (27.05)	49 (40.83)
NTR	81 (39.51)	9 (16.36)	48 (62.33)	24 (32.87)	43 (36.75)	31 (56.36)	7 (21.21)	32 (37.64)	49 (40.83)
STR	52 (25.36)	0	4 (5.19)	48 (65.75)	8 (6.83)	19 (34.54)	25 (75.75)	30 (35.29)	22 (18.33)

Values are shown as number (percent) or mean.

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tive hemiplegia was observed in 1 patient who underwent the combined approach, and the part of the tumor extending into the ventricle was excised with a transcallosal and transcortical approach. No new-onset cranial nerve palsy was observed in our series. Apoplexy complications were observed in 8 patients within the first 24 hours postoperatively, and endoscopic hematoma excision and hemostasis were performed immediately; an additional 3 patients underwent transcranial surgery. Meningitis complications were seen in 7 patients, and appropriate antibiotic therapy was administered. One of these patients underwent transcranial surgery for apoplexy and developed *Pseudomonas* meningitis; this patient did not respond to medical treatment and died. Two patients who underwent reoperations owing to apoplexy developed serum sodium imbalance during intensive care follow-up; these patients did not respond well to medical treatment and died. The total mortality rate of this study was 1.46% (3 patients). In the group of 72 patients who achieved GTR, 19 (26.39%) had new-onset pituitary deficiency, 6 (8.33%) had permanent DI, and 5 (6.94%) had CSF leak complications. No instances of recurrence, postoperative apoplexy, or death were noted in this group. Complications data are presented in Table 3.

Outcomes of Proposed Classification Systems

Among 117 patients with grade 1 tumor (≤ 2 points) according to the morphological scoring system, 6.83% achieved STR, 36.75% achieved NTR, and 56.41% achieved GTR. The rates of STR, NTR, and GTR were 34.54%, 56.36%, and 9.09%, respectively, among the 55 patients with grade 2 tumor (3–4 points); these rates were 75.75%, 21.21%, and 3.03%, respectively, among the 33 patients with grade 3 tumor (≥ 5 points). The rate of NTR was 16.36% and the rate of GTR was 83.63% among the 55 patients with zone 1 tumor according to the landmark-based classification system; there were 0 patients who achieved only STR. The rates of STR, NTR, and GTR were 5.19%, 62.33%, and 32.46% among the 77 patients with zone 2 tumor; these rates were 65.75%, 32.87%, and 1.36% among the 55 patients with zone 3 tumor. The resection rates according to both classification systems are shown in Table 3, and MRI scans of the zones and resections are presented in Fig. 4.

The clinical outcomes and complications data were correlated with the grades and zones provided by the classification systems (Table 3). The following findings were statistically significant. According to the landmark-based classification system, the incidence rates of recurrence ($p = 0.002$) and apoplexy complication ($p = 0.007$) were higher in patients with zone 3 tumors. In addition, a higher rate of postoperative improvement in vision ($p = 0.017$) was observed in patients with zone 1 tumor and vision loss. Similarly, there were higher incidence rates of recurrence ($p < 0.001$) and apoplexy complications ($p < 0.001$) in patients with grade 3 tumors according to the morphological scoring system, and patients with grade 1 tumor and vision loss had a higher rate of postoperative improvement in vision ($p < 0.001$).

Discussion

We present the results of our study on patients with giant adenoma, including the effects of increased experience, tumor characteristics, and surgical capsule dissection on resection and complication rates. Additionally, the suitability of each classification system for preoperative prediction of extent of resection was assessed.

Pituitary adenoma is a benign, slow-growing tumor that can become large over a long period without causing typical symptoms such as loss of vision and headache.[22] In patients with large adenoma, tumor removal is challenging owing to the proximity of extensions to critical neurovascular structures and invasion of the cavernous sinus.[23,24] Therefore, the primary surgical goals for giant adenoma include maximum tumor removal in a safe manner, intracapsular debulking, and decompression of the chiasma.[5,13,14,23] Historically, transcranial and microscopic transnasal approaches have been widely used for this purpose, and the advantages and disadvantages of both techniques have been discussed extensively.[25–27] The endoscopic transsphenoidal technique can be used for almost all surgical indications in the sellar region and is superior to other approaches because it provides a panoramic view of the surgical area, regardless of the width and depth of the entrance.[5,7] Moreover, the high resection and low complication rates of this approach have made it the preferred surgical technique for giant adenoma.[9–14]

Previous studies have reported that cavernous sinus invasion is one of the most important limiting factors of total resection of adenoma,[5,8,13,19] with some authors suggesting a transcranial approach or stereotactic radiosurgery depending on the configuration and degree of cavernous invasion.[3,28] Cavernous sinus compartments, first described by Harris and Rhoton in 1976, have become increasingly important in recent years.[17,29,30] In our experience, patients with involvement of the lateral compartment to the cavernous sinus and superolateral extension from the cavernous sinus comprise a challenging group in endoscopic surgery.[17] The morphological structure of the foramen of the diaphragma sellae facilitates suprasellar extension of adenoma because it is displaced laterally, leaving only the arachnoid membrane layer between the tumor capsule and critical neurovascular structures.[31] In patients with adenoma, peritumoral compressed cells and layers of reticulin may form the capsule that maintains surgical integrity.[32] Unlike those of smaller adenomas, the capsule of giant adenoma tends to exhibit general thickening, possibly due to existing compression. Dissection of the capsule, adjacent to the arachnoid structure in the suprasellar direction and the cavernous sinus walls inferiorly, was not our primary surgical goal before 2017.

Experience plays an important role in increasing surgical success of endoscopic transnasal surgery, and articles that highlight the importance of experience have been published.[33,34] With increasing experience, over the last 3 years we have adopted a more aggressive surgical strategy aimed at higher resection and capsular dissection rates. Since 2017, almost the entire capsule has been removed from patients who achieved GTR and NTR. In patients with cavernous sinus invasion who achieved STR, a partial capsule was left behind in areas where dissection could not be performed. We determined that surgical procedures performed after 2017 could achieve adequate

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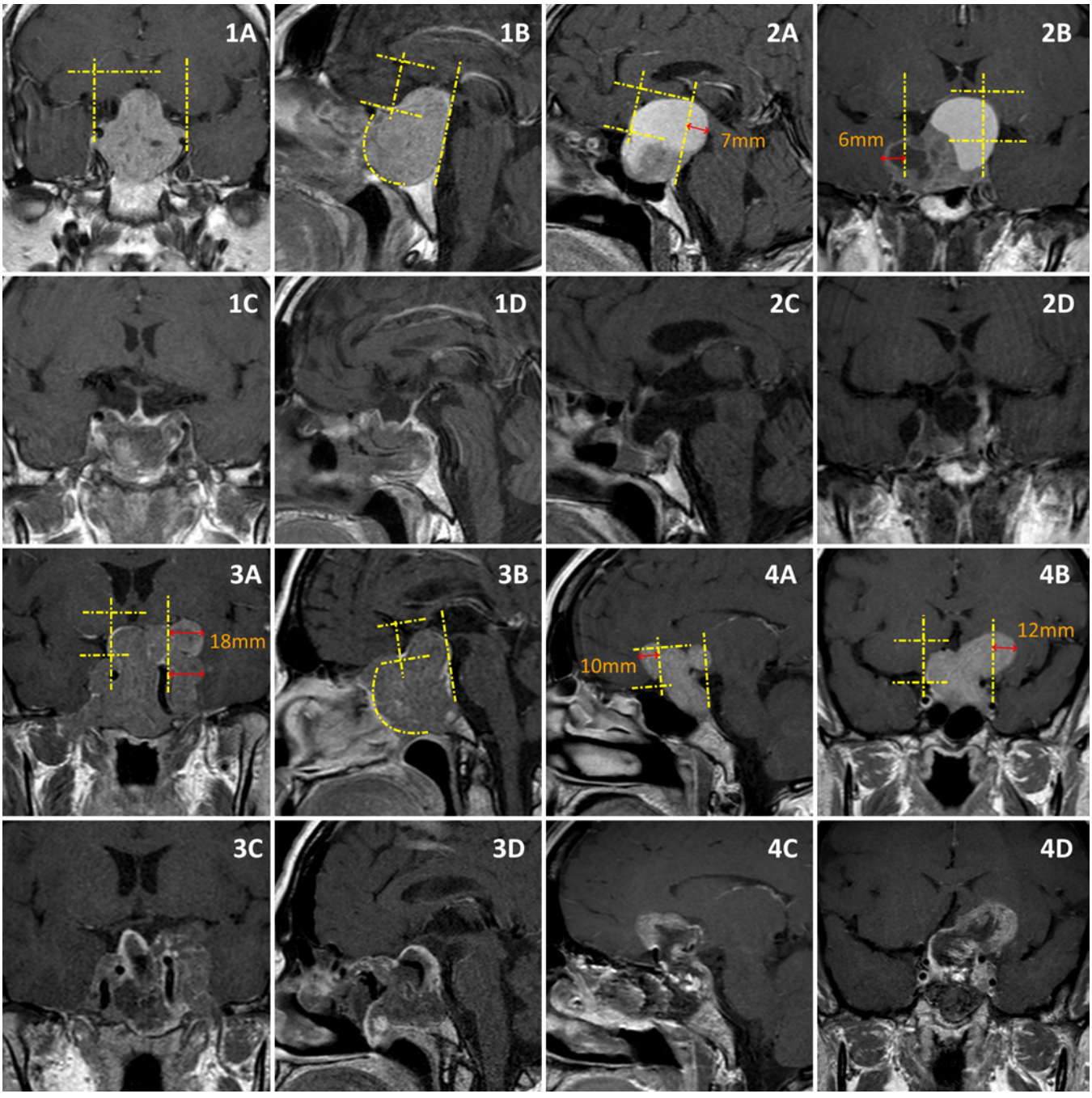


FIG. 4. MR images of giant adenomas and the zones according to the landmark-based classification system. In the first example, the tumor was defined as zone 1 and GTR was performed. Preoperative coronal (**1A**) and sagittal (**1B**) contrast-enhanced T1-weighted MR images show the zone boundaries (*dotted lines*); postoperative coronal (**1C**) and sagittal (**1D**) MR images are also shown. In the second example, a tumor with cavernous sinus invasion and cystic components, which we defined as zone 2, is presented. Sagittal (**2A**) and coronal (**2B**) MR images show the zone boundaries of the tumor. Postoperative sagittal (**2C**) and coronal (**2D**) MR images show GTR. In the third example, a tumor with bilateral lateral compartment invasion, which we defined as zone 3, is presented; NTR of this tumor was achieved (Video 1). Preoperative coronal (**3A**) and sagittal (**3B**) MR images, as well as postoperative coronal (**3C**) and sagittal (**3D**) MR images, are shown. In the fourth example, a tumor that was slightly larger than 4 cm but with extensions that made surgery challenging, which we also defined as zone 3, is presented; STR was achieved. The zones on sagittal (**4A**) and coronal (**4B**) MR images, as well as postoperative sagittal (**4C**) and coronal (**4D**) MR images, are shown.

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capsule dissection. Among 120 patients treated after 2017, 26 (21.66%) had new-onset pituitary deficiency, 7 (5.83%) had permanent DI, 5 (4.16%) had CSF leak, and 1 (0.83%) had postoperative apoplexy complications. No instances of recurrence or death were observed in this group. Complications data from before and after 2017 were compared and evaluated. There were no significant differences in the incidence rates of CSF leakage, permanent DI, and new-onset pituitary deficiency between before 2017 and after 2017 when the goal was capsule dissection, but notable decreases in the incidence rates of apoplexy and recurrence were observed. However, the difference in the mean follow-up durations between these two periods is a limitation that prevents a proper comparison regarding recurrence.

Historically, the definitions by Yasargil, as well as the classification by Hardy and Vezina, have been widely used to evaluate pituitary adenoma.[35,36] In addition, the TRANSSPHER grade system by Mooney et al. and the Zurich score by Serra et al. are remarkable classification systems that were recently published.[15,16] However, there is a need for a classification system for giant adenomas that can predict extent of resection and indicate when the endoscopic approach alone may be insufficient. This study adopted and compared two different classification systems: morphological score and landmark-based classification. Current classifications are based on scores for some morphological characteristics and their contributions to surgical difficulty. Our morphological scoring system is a comprehensive tumor-scoring system established on the basis of criteria specified in current classifications and the results of our series. It is not an original system, but instead an improved version of existing classification systems. In contrast, the landmark-based classification system is based on the relationships between tumor extension and anatomical landmarks. Large size, multilobular configuration, and cavernous sinus invasion are some factors that adversely affect extent of resection of giant adenoma.[7,13,14] In addition, by evaluating the effects of tumor characteristics on extent of resection (Tables 1 and 2), we determined the criteria to be used in the morphological scoring system (Fig. 1). Additionally, similar to the study by Serra et al.,[16] the ratio of the largest horizontal tumor dimension in the suprasellar region to the distance between the supraclinoid carotid segments (which correspond to the level of the diaphragma sellae) was measured and included as a scoring criterion. Thus, the difference in size between the tumor's suprasellar part and the endoscopic entrance area to the suprasellar tumor was evaluated as a factor that affects resection. Accessing and excising tumors with excessive extension into the anterior cranial fossa with the standard sellar technique is quite challenging, and therefore frontal extension characteristics were included in both classification systems. While growing, a giant adenoma pushes neurovascular structures and moves them away from their anatomical positions. However, the distal ring of the carotid sulcus, where the supraclinoid arteries are close to each other, exhibits high resistance and ensures that the arteries maintain their anatomical positions in the presence of giant adenoma;[37] this often results in the formation of tumor lobulations in this area. The intracranial part of the tumor is accessed via this level and was included in our landmark-based classification system to allow differentiation of the infrasellar and suprasellar parts of the tumor. The horizontal segments of the cavernous carotid artery generally correspond to the level of the sellar floor, and the enlarged sellar floor of giant adenoma facilitates access to the suprasellar area. Therefore, parallel lines drawn from the horizontal segments of the cavernous carotid artery, where they are the farthest from each other on coronal MRI, were included as anatomical landmarks in the landmark-based classification system; these lines allowed accurate identification of the lateral contours of the relatively easily accessible suprasellar part of the tumor. Although tumor extending into the sphenoidal sinus can be easily accessed via endoscopic surgery, any tumor beyond the sinus walls, and particularly that with posterolateral extension to the lateral parts of the paraclival carotid artery, is often challenging to resect. The anterior and inferior boundaries of the sphenoid sinus were represented by the sinus walls in zone 1, and the posterolateral boundary was represented by the paraclival carotid artery.

Our motive for developing the morphological scoring system was to compare landmark-based classification with a score based on giant adenoma–specific characteristics. In our study, the two classification systems showed similar results with respect to prediction of extent of resection. However, landmark-based classification was preferable because it provided better evaluation of tumors with advanced extension in one direction and low score on the morphological scoring system. Existing classification systems predict resection on the basis of cavernous sinus invasion, suprasellar size, and tumor characteristics;[15,16,36] however, these systems do not assess tumors with advanced infrasellar extension and invasion of the clivus and sphenoidal sinus walls. The advantages of the landmark-based classification system include its ability to predict resection of tumor with infrasellar extension, and surgeons can easily use this system to visually identify the relationships between anatomical landmarks and tumor zone.

Although the aim of the first endoscopic surgery is total resection, the planned tumor resection may not be achieved in some patients because of various reasons, or there may be unexpected residual tumor on postoperative MRI. An early second staged endoscopic surgery is recommended to patients if the residual tumor is in a position amenable to resection with an endoscopic approach. In the present series, a staged endoscopic approach was performed on 11 patients (Fig. 5). A transcranial approach may be considered if the endoscopic approach fails to achieve adequate resection of tumor with advanced extensions or if preoperative evaluation suggests that this approach may be insufficient.[26,38] In such cases at our clinic, a combined approach consisting of the best possible endoscopic tumor resection followed by craniotomy to resect residual tumor was performed. With increasing experience, surgeons can widen the limits of endoscopic surgery to avoid using a combined approach and to minimize the amount of remnant tumor that may require transcranial intervention. In the current series, the combined approach was preferred for 12 patients (Fig. 5), and 4 of these patients were treated after 2017. All these patients had zone 3 and grade 3 tumors according to our classification systems. Surgeons

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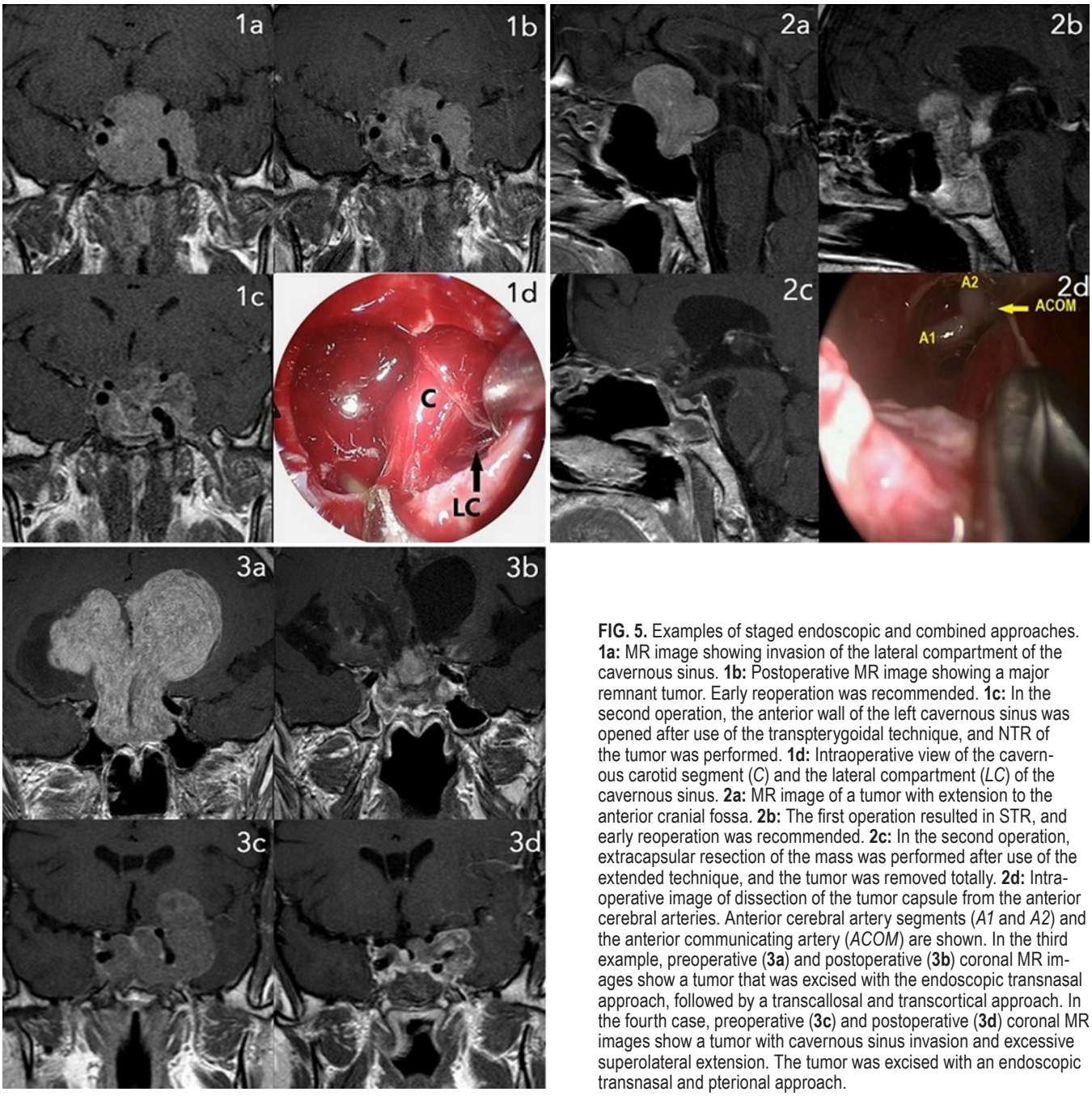


FIG. 5. Examples of staged endoscopic and combined approaches. **1a:** MR image showing invasion of the lateral compartment of the cavernous sinus. **1b:** Postoperative MR image showing a major remnant tumor. Early reoperation was recommended. **1c:** In the second operation, the anterior wall of the left cavernous sinus was opened after use of the transpterygoidal technique, and NTR of the tumor was performed. **1d:** Intraoperative view of the cavernous carotid segment (*C*) and the lateral compartment (*LC*) of the cavernous sinus. **2a:** MR image of a tumor with extension to the anterior cranial fossa. **2b:** The first operation resulted in STR, and early reoperation was recommended. **2c:** In the second operation, extracapsular resection of the mass was performed after use of the extended technique, and the tumor was removed totally. **2d:** Intraoperative image of dissection of the tumor capsule from the anterior cerebral arteries. Anterior cerebral artery segments (*A1* and *A2*) and the anterior communicating artery (*ACOM*) are shown. In the third example, preoperative (**3a**) and postoperative (**3b**) coronal MR images show a tumor that was excised with the endoscopic transnasal approach, followed by a transcallosal and transcortical approach. In the fourth case, preoperative (**3c**) and postoperative (**3d**) coronal MR images show a tumor with cavernous sinus invasion and excessive superolateral extension. The tumor was excised with an endoscopic transnasal and pterional approach.

should keep in mind that zone 3 and grade 3 tumors have a high risk of residual tumor after endoscopic surgery. Furthermore, craniotomy may be considered before the endoscopic approach for some patients with giant adenoma and excessive intracranial extensions.

Theoretically, the infraclinoidal branches of the internal carotid artery, including the meningohypophyseal and inferolateral trunks, are the main vascular feeders of giant pituitary adenoma.[39] Recurrence and apoplexy complications could be minimized with successful hemostasis of tumor-feeding areas, even if residual mass remains. Conversely, some authors have reported high incidence rates of apoplexy and cerebral infarction in patients with remnant tumor, and they suggested use of a transnasal and transcranial combined approach.[40] Intratumoral hemorrhage is the most serious complication and has been reported in 2.1%–3.7% of patients with giant adenoma.[2,26] After taking into account the complication and recurrence rates, we considered decompression with inferior debulking alone as too risky for the treatment of giant adenoma, and we preferred to ensure that no large residual tumor remained. In our series, NTR and GTR could not be achieved in any of the 8 patients with apoplexy complications.

Clinical outcomes and complications data were cor-

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related with our classifications, and the results were quite similar for the equivalent zones and grades. There were no significant differences between the zone and grade groups in terms of the incidences rates of new-onset pituitary deficiency, permanent DI, CSF leak, and postoperative recovery from hormone deficiency. However, the rates of apoplexy complications and recurrence were significantly higher in patients with zone 3 and grade 3 tumors. The effect of alteration in surgical strategy in 2017 on the decreased rate of apoplexy complications should also be considered.

Dopamine agonists should be the first-line treatment of giant prolactinoma, whereas surgery merely serves as a remedy for drug resistance and compression symptoms such as severe optic nerve compression. Surgical remission was not expected for patients who did not achieve GTR. As stated in the literature, most patients with giant prolactinoma do not achieve postoperative hormonal remission and require continuous medical treatment.[41]

Surgery-related mortality rates after endoscopic transsphenoidal resection of giant pituitary adenoma were reportedly 4.6% by Hofstetter et al., 4% by Gondim et al., 7.1% by Constantin et al., 0% by Elshazly et al., and 3.8% by Fallah et al.[5,11,13,14,28] The mortality rate in the current series was 1.46%, and the primary cause of death of all 3 patients was hematoma of the residual mass. Vascular injuries are rare but have been described as significantly related to morbidity and mortality.[42,43] No carotid artery injuries were observed in the current study. Recent studies have shown that radiosurgery effectively prevents progression of pituitary adenoma and contributes to hormonal remission of functional adenoma; the results of stereotactic radiosurgery, in particular, are considered reference values regarding progression and remission.[44,45] In the current series, 13 patients with residual or recurrent mass who were not considered suitable for surgery received Gamma Knife treatment.

Conclusions

Capsule dissection and GTR of pituitary adenoma, especially giant adenoma, play crucial roles in the prevention of serious complications and reduction of recurrence. Experience also considerably affects surgical outcomes by expanding the limits of endoscopic transnasal surgery. Moreover, preoperative tumor evaluation with a classification system may help identify when the endoscopic approach may prove insufficient, thus allowing for accurate treatment and preparation for serious complications that may occur. Regarding classification systems, the most important factor to consider is reliability, followed by ease of use and practicability.

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Disclosures

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

Conception and design: S Ceylan, Sen. Acquisition of data: S Ceylan, Sen. Analysis and interpretation of data: S Ceylan, Sen, Selek. Drafting the article: S Ceylan, Sen. Critically revising the article: S Ceylan. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: S Ceylan. Statistical analysis: Sen, Balci. Administrative/technical/material support: S Ceylan, Sen, Ergen. Study supervision: S Ceylan.

Supplemental Information

Videos

Video 1. https://vimeo.com/531306119.
Video 2. https://vimeo.com/531303162.

Correspondence

Savas Ceylan: Kocaeli University, Kocaeli, Turkey. ssceylan@yahoo.com.

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