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Treatment strategies for giant pituitary adenomas in the era of endoscopic transsphenoidal surgery: a multicenter series

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OBJECTIVE Given the anatomical complexity and frequently invasive growth of giant pituitary adenomas (GPAs), individually tailored approaches are required. The aim of this study was to assess the treatment strategies and outcomes in a large multicenter series of GPAs in the era of endoscopic transsphenoidal surgery (ETS).

METHODS This was a retrospective case-control series of 64 patients with GPAs treated at two tertiary care centers by surgeons with experience in ETS. GPAs were defined by a maximum diameter of ≥ 4 cm and a volume of ≥ 10 cm^3 on preoperative isovoxel contrast-enhanced MRI.

RESULTS The primary operation was ETS in all cases. Overall gross-total resection rates were 64% in round GPAs, 46% in dumbbell-shaped GPAs, and 8% in multilobular GPAs ($p < 0.001$). Postoperative outcomes were further stratified into two groups based on extent of resection: group A (gross-total resection or partial resection with intracavernous remnant; 21/64, 33%) and group B (partial resection with intracranial remnant; 43/64, 67%). Growth patterns of GPAs were mostly round (11/14, 79%) in group A and multilobular (33/37, 89%) in group B. In group A, no patients required a second operation, and 2/21 (9%) were treated with adjuvant radiosurgery. In group B, early transcranial reoperation was required in 6/43 (14%) cases due to hemorrhagic transformation of remnants. For the remaining group B patients with remnants, 5/43 (12%) underwent transcranial surgery and 12/43 (28%) underwent delayed second ETS. There were no deaths in this series. Severe complications included stroke (6%), meningitis (6%), hydrocephalus requiring shunting (6%), and loss or distinct worsening of vision (3%). At follow-up (mean 3 years, range 0.5–16 years), stable disease was achieved in 91% of cases.

CONCLUSIONS ETS as a primary treatment modality to relieve mass effect in GPAs and extent of resection are dependent on GPA morphology. The pattern of residual pituitary adenoma guides further treatment strategies, including early transcranial reoperation, delayed endoscopic transsphenoidal/transcranial reoperation, and adjuvant radiosurgery.

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KEYWORDS giant pituitary adenoma; invasive; endoscopic; outcome; pituitary surgery

Giant pituitary adenomas (GPAs) constitute 5%–15% of all pituitary tumors and, due to their diameter of at least 4 cm, commonly present with symptoms of mass effect. Given that GPAs have a tendency to extend into multiple anatomical compartments, frequently encase neurovascular structures, and exhibit high rates of invasiveness, treatment remains particularly challenging.[1,2] Besides medical therapy for prolactin-secreting tumors, a combination of transcranial and transsphenoidal microsurgical approaches, simultaneously or consecutively, has been advocated for surgical removal of the multiple adenoma compartments and regions of extension associated with the majority of GPAs.[1,3] Due to their considerable size and their involvement of and adherence to neurovascular structures, however, surgery for GPAs is still associated with considerable perioperative morbidity and mortality.[4]

ABBREVIATIONS ACoA = anterior communicating artery; DI = diabetes insipidus; EOR = extent of resection; ETS = endoscopic transsphenoidal surgery; GKS = Gamma Knife surgery; GPA = giant pituitary adenoma; GTR = gross-total resection; ICA = internal carotid artery; ICU = intensive care unit; PR = partial resection; STR = subtotal resection; TCS = transcranial surgery; TMZ = temozolomide.

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Despite this, the growth patterns of GPAs result in a low rate of gross-total resection (GTR), and this prompts the need for additional treatments.[5–8]

The advent of endoscopic transsphenoidal surgery (ETS) has improved intraoperative visualization and accessibility, resulting in an increased overall rate of GTR in transsphenoidal surgery for pituitary adenomas.[6,9] Recent studies have demonstrated that the endoscopic transsphenoidal approach, with the possibility of extended approaches, offers improved resection rates of GPAs. However, the value of the ETS in the treatment strategy of GPAs, rate of resection, and complications remains to be defined.[10]

The aim of this study was to describe the treatment strategy and outcome of a large consecutive multicenter series of GPAs in the era of ETS, with particular attention to predictors of a requirement for additional intervention and overall tumor control rates.

Methods

A retrospective analysis of patients undergoing neurosurgical treatment for GPAs in two tertiary centers by surgeons experienced in ETS was performed. GPAs were defined by a maximum diameter of ≥ 4 cm and a volume of ≥ 10 cm^3 on preoperative isovoxel contrast-enhanced MRI.[11] Tumors fulfilling only one of these criteria were excluded.

Only patients in the time frame of the ETS technique were included (from 2011 to 2019 at Keck School of Medicine, University of California; and from 2004 to 2019 at Medical University of Vienna). This study was approved by the two institutional review boards.

Patients and Tumor Characteristics

Demographic patient data were retrieved from hospital archives and MRI scans were obtained from hospital PACS. The radiological growth pattern on MRI was classified as round, dumbbell-shaped, or multilobular according to Koutourousiou et al.[12] (Fig. 1). Parasellar adenoma extension was classified according to the Knosp grading system.[13] Volumetric assessment was performed using radiological image analysis software (Synapse3D, Fujifilm; Stealth Station S7, Medtronic).

For endocrine assessment, preoperative levels of serum prolactin, insulin-like growth factor–I, growth hormone (oral glucose tolerance testing), cortisol, adrenocorticotrophic hormone, thyroid-stimulating hormone, follicle-stimulating hormone, and luteinizing hormone were measured to evaluate pituitary insufficiency and to identify functioning adenoma.

Treatment Strategy

In both centers we used a transnasal endoscopic approach as the primary surgery for all GPAs. Extended ETS was chosen in cases of extensive parasellar and/or suprasellar growth according to the surgeon's discretion. If an intracranial adenoma remnant was suspected during the ETS and/or the patient exhibited postoperative neurological deterioration, patients were transferred to the intensive care unit (ICU) after CT scan to rule out hemorrhagic ad-

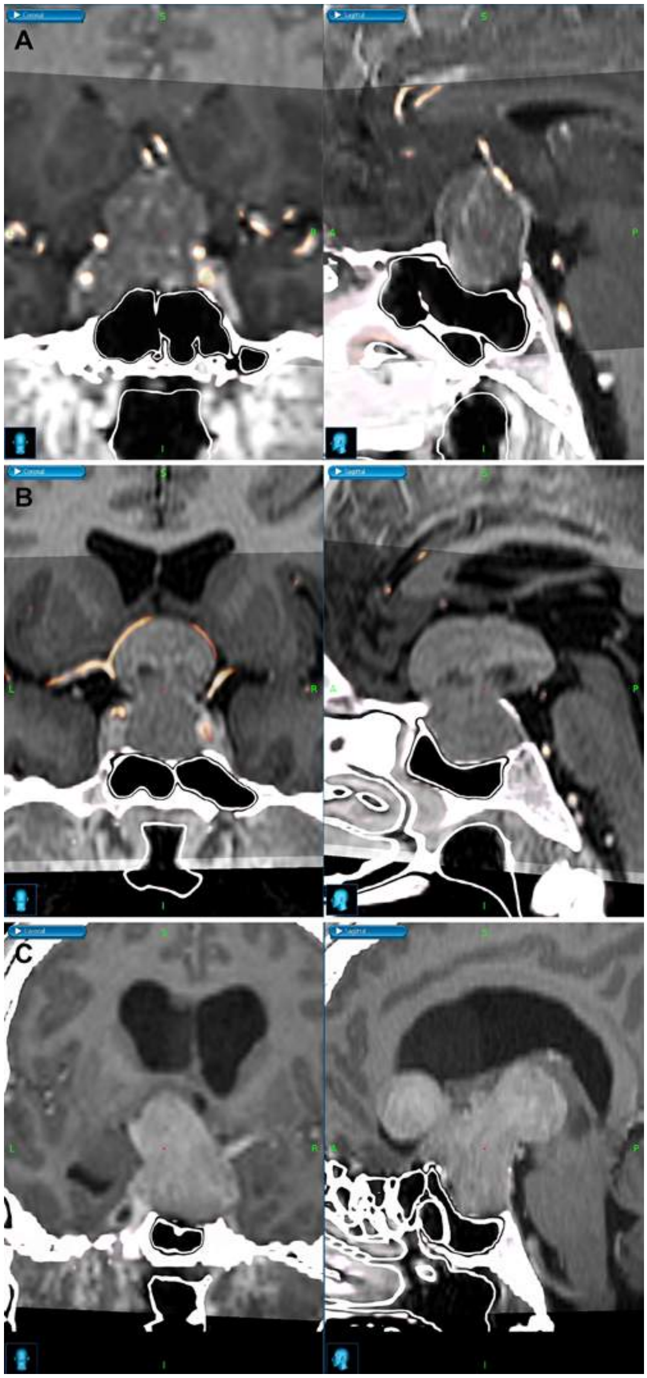

FIG. 1. MRI sequences showing growth patterns of GPAs. **A:** Round GPA (coronal [*left panel*], sagittal [*right panel*]) demonstrating an extensive suprasellar extension without signs of parasellar invasiveness. **B:** Dumbbell-shaped GPA (coronal [*left panel*], sagittal [*right panel*]) with displacement of the anterior cerebral artery and far extension behind the dorsum sellae. **C:** Multilobular GPA (coronal [*left panel*], sagittal [*right panel*]) with extension into multiple compartments and ventricular system. Figure is available in color online only.

enoma remnant transformation. In the case of a remnant with increasing mass effect and/or neurological deterioration, early transcranial reoperation was performed.

GTR with no visible tumor on MRI, subtotal resection (STR; > 80%), or partial resection (PR; ≤ 80%), as well as extent of resection (EOR), was assessed on postoperative MRI. According to the EOR and location of remnant (intracavernous vs intracranial), the results of ETS were stratified into group A (GTR or PR with only an intracavernous remnant) and group B (PR that includes an intracranial remnant besides a possible intrasellar or intracavernous tumor remnant).

Furthermore, surgical reports were scanned for tumor consistency (soft, fibrous, cystic) and intraoperative invasiveness based on direct endoscopic visualization. Fibrous tumor components were defined as unsuctionable and difficult to resect with curettes, with a septated tumor matrix.[14]

During the complete follow-up period, the number and mode of treatments (ETS, transcranial surgery [TCS], medication, radiation) were compiled. The results of the surgical strategy were stratified to the radiological classification of tumor growth pattern. At the last follow-up control, endocrine (insufficiency/replacement therapy, ongoing medical treatment of hypersecretion) and radiological (stable disease/progression) outcomes were assessed.

Complication Assessment

Complications were counted as events that occurred within 30 days of surgery and were subdivided into surgical and endocrine complications. Surgical complications included death, internal carotid artery (ICA) injury, stroke (including a permanent vegetative state), meningitis, loss of vision, permanent cranial nerve palsy, postoperative CSF leak, hydrocephalus necessitating a ventriculoperitoneal shunt, and epistaxis. Endocrine complications included a postoperative hypopituitarism, transient and permanent diabetes insipidus (DI), and hyponatremia.

Statistical Analysis

The data are presented as the mean (range) for continuous variables and as frequencies for categorical variables. To analyze a difference among groups of various tumor formations (round, dumbbell, multilobular), a chi-square test with Pearson's correlation coefficient has been performed. A p value < 0.05 was considered significant. For statistical analyses, SPSS version 25.0 software (IBM Corp.) was used.

TABLE 1. Demographic and tumor characteristics in 64 patients with GPAs

Variable	Value (range)	%
Patient characteristics		
No. of patients	64	
1st op	51	80
Reop	13	20
Age in yrs	50.6 (22–84)	
≤65	53	83
>65	11	17
Sex; F:M	1:0.94	
Follow-up in yrs	2.8 (0.5–16)	
Tumor characteristics		
Functional classification		
Functioning	7	11
Nonfunctioning	57	89
WHO 2017 classification		
Somatotroph	3	5
Lactotroph	2	3
Mammosomatotroph	2	3
Thyrotroph	2	3
Corticotroph	3	5
Gonadotroph	16	25
Null cell	32	50
Plurihormonal	4	6
Apoplexy	11	17
Size in mm; maximum diameter	46.6 (40–74)	
Vol in cm^3	32.8 (10–121)	
Consistency		
Cystic	4	6
Soft	42	66
Fibrous	18	28
Invasiveness on direct endoscopic visualization	56	88
Mean Ki-67; %	2.6 (0.6–8.4)	
Knosp high grade; 3A, 3B, 4	47	73
Suprasellar extension	62	97
Ventricular system	13	20
Infrasellar extension	38	59
Nasal cavity	9	14

Values are expressed as the mean (range) or as the number and percent.

Results

Patient and Tumor Characteristics

The study cohort consisted of 64 patients. The mean age was 51 years (range 22–84 years), 33 patients (52%) were female, and 31 patients (48%) were male (Table 1).

The most common presenting complaint was visual impairment in 55 patients (86%). On objective visual examination, a bitemporal visual field cut was found in 32 patients (50%), and visual acuity loss was observed in 14 patients (22%). Severe headache was reported in 36/64 (56%) cases as a presenting symptom. Preoperative hypopituitarism in ≥ 1 axis was found in 26 cases (41%; panhypopituitarism was noted in 10/26, 38%), which improved in 5/26 (19%) cases postoperatively (Table 2).

On MRI, the mean maximal tumor diameter was 47 mm (range 40–74 mm) and the mean tumor volume was 33 cm^3 (range 10–121 cm^3). The growth patterns were round (14 cases, 22%), dumbbell-shaped (13 cases, 20%), and multilobular (37 cases, 58%). GPAs extended into the suprasellar space in 62 cases (97%), into the infrasellar space in 38 cases (59%), and showed a Knosp high-grade parasellar extension (grades 3A, 3B, and 4) in 47 cases (73%).

TABLE 2. Presenting symptoms in 64 patients with GPAs

Symptom	No.	%
Ophthalmological symptoms		
Visual impairment	55	86
Visual acuity loss	14	22
Bitemporal visual field cut	32	50
Diplopia	7	11
Headache	36	56
Endocrinological symptoms		
Panhypopituitarism	10	16
Acromegaly	4	6
Cushing disease	1	2
Hyperprolactinemia (>250 ng/mL)	2	3

Nonfunctioning pituitary adenomas comprised 89% of GPAs. Functioning adenomas were as follows: 6% were somatotroph or mammosomatotroph adenoma (acromegaly), 3% were lactotroph adenoma (hyperprolactinemia) due to apoplectic acute visual impairment, and 2% were corticotroph adenoma (Cushing's disease). If clinically justifiable, medical pretreatment of functioning adenomas was performed.

Treatment Strategy

The primary surgical approach was the endoscopic transsphenoidal procedure in all 64 GPAs (extended ETS in 34%). The result of ETS was GTR in 18 cases (28%), STR in 34 cases (53%), and PR in 12 cases (19%). Intraoperative tumor consistency was soft (42 cases, 66%), fibrous (18 cases, 28%), and cystic (4 cases, 6%). The overall EOR was 84% (range 45%–100%). The EOR for round GPAs was 96.5% (range 76%–100%), for dumbbell-shaped tumors it was 90.9% (range 74%–100%), and it was 77.5% (range 45%–100%) for multilobular GPAs.

According to the EOR and location of remnant, group A (GTR or PR with intracavernous remnant) comprised 21/64 (33%) cases and group B (PR with intracranial remnant) 43/64 (67%) cases. Growth patterns were mostly round (11/14, 79%) in group A and multilobular in group B (33/37, 89%).

No patient in group A required a second operation; however, 2/21 (9%) were treated with stereotactic radiosurgery to treat an intracavernous adenoma remnant. In group B alone, early transcranial reoperation was required due to hemorrhagic transformation of remaining intracranial adenoma tissue that was causing mass effect and/or neurological deterioration in 6/43 (14%) cases. In addition, 3/43 (7%) group B cases required a second ETS for a descending adenoma remnant, 5/43 (12%) underwent TCS, and 9/43 (21%) underwent extended ETS (mean 2 surgeries in group B, range 1–5). No significant difference of EOR was detected between further TCS or extended ETS (Fig. 2, Table 3).

Clinical Outcome and Complications

Of the 55 patients with visual impairment at the time of diagnosis, vision improved postoperatively in 41 patients (64%), remained stable in 19 patients (30%), and worsened in 4 patients (6%) (Table 4, Fig. 3).

A permanent CSF shunt was required in 4/5 patients with preoperative hydrocephalus. In the remaining patient, transient CSF diversion via external ventricular drain was sufficient. All of these patients harbored a GPA with ventricular extension.

After a mean follow-up of 3 years (range 0.5–16 years), MRI demonstrated no residual disease in 18 cases (28%). Of the 46 cases (72%) with STR or PR, a stable tumor remnant was found in 42/46 (91%) cases. In patients with residual tumor, radiation therapy was applied in 16/46 (35%) cases. No significant time of progression-free survival was found between patients undergoing radiation and patients with no radiation. Tumor progression developed in 4/46 (9%) cases over a mean period of 12 months, despite multimodality treatment.

There were no deaths in this series. Morbidity at follow-up included the following: stroke (4 cases [6%], all from TCS reoperation; in 2 cases after an acute infarction of suprasellar tumor remnant following an ETS); a postoperative vegetative state resulting from bilateral posterior cerebral artery infarct after transcranial removal of hemorrhagic transformed residual adenoma in 1 patient (2%); meningitis (4 cases [6%], all following ETS); new postoperative hydrocephalus requiring CSF diversion (1 case [2%], after TCS) after a reoperation; and loss of vision or distinct acute worsening (2 cases [3%], 1 from ETS vs 1 from TCS in the case of a reoperation). Furthermore, postoperative CSF leaks occurred in 9 cases (14%, all from ETS), 6/9 cases in reoperations. Permanent DI occurred in 4 cases (3 after ETS vs 1 after TCS), and new postoperative anterior pituitary insufficiency was found in 11 cases (17%; 8 from ETS vs 3 from TCS; in 6/11 after a reoperation) (Table 4).

Overall GTR within the cohort was 28%: no significant difference of the rate of GTR was found between round and dumbbell-shaped GPAs (64% vs 46%, $p = 0.81$). However, with a GTR of 64% of round and 46% of dumbbell-shaped tumors, the rate of GTR was significantly higher than in multilobular GPAs (8%; $p < 0.001$ for both round and dumbbell-shaped vs multilobular tumors).

Additional Therapy

Further postoperative treatments included radiation therapy in 16 patients (25%); in 10 cases this consisted of external radiation (linear accelerator [LINAC]), and in 6 cases Gamma Knife surgery (GKS) was used. The mean time from first surgery to radiation therapy was 68 months (range 11–120 months). GKS was performed early in only 1 patient, after 11 months. In 2 of these patients, tumor progression occurred despite radiation therapy.

Postoperative medical therapy was initiated in 4 patients. The 2 lactotroph adenomas were treated with cabergoline, and 2 patients were treated with octreotide (1 with somatotroph, 1 with mammosomatotroph adenoma). Two patients were treated with temozolomide (TMZ) after repeated surgery and external-beam radiation; one patient presented with a lactotroph adenoma resistant to dopamine agonist therapy, and the other patient presented with

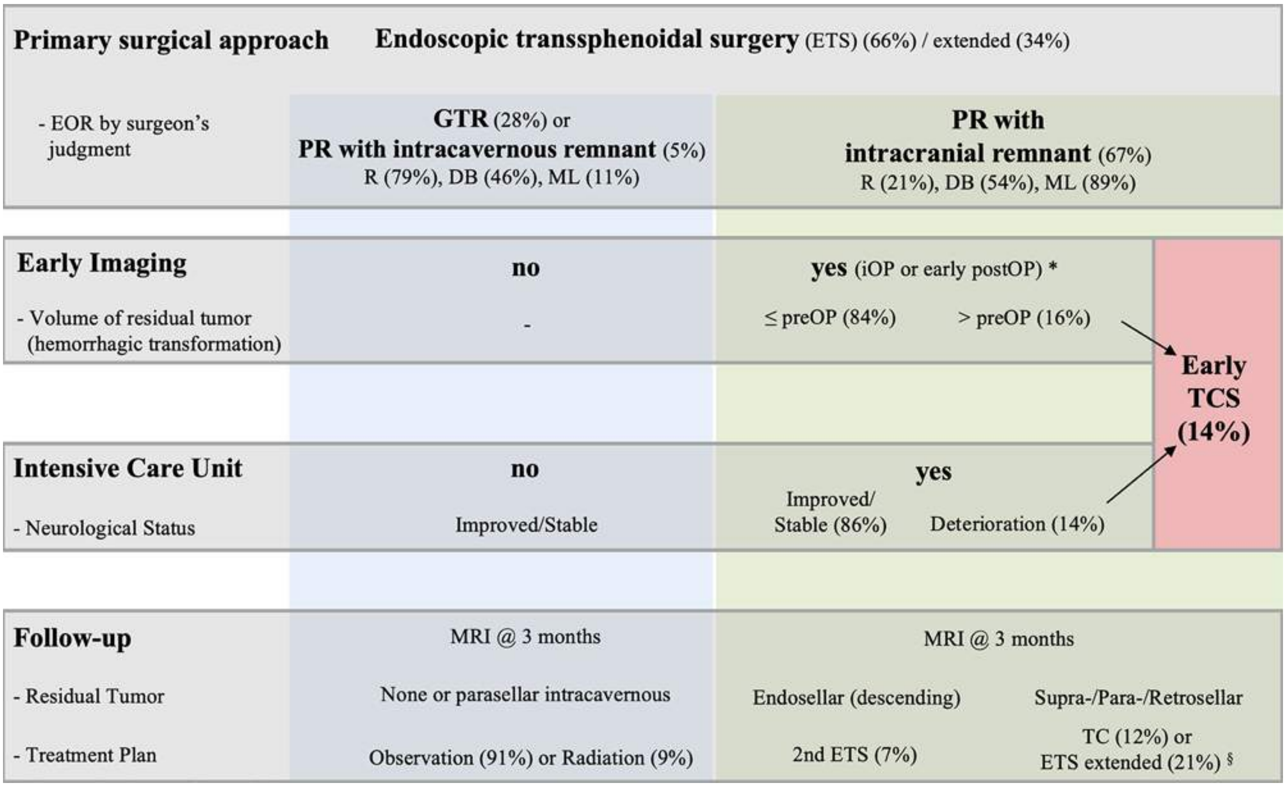

FIG. 2. Flowchart showing surgical treatment schema. *Early postoperative imaging not done in 14 cases. §More than 2 operations in 8 cases (range 3–5), all multilobular GPAs. DB = dumbbell formation; iOP = intraoperative; ML = multilobular formation; R = round formation; TC = transcranial surgery. Figure is available in color online only.

TABLE 3. Outcome in 64 patients with GPAs

	Tumor Morphology			
Outcome	Overall, n = 64	Round, n = 14	Dumbbell, n = 13	Multilobular, n = 37
EOR for primary ETS				
GTR	18 (28%)	9 (64%)	6 (46%)	3 (8%)
STR; >80%	34 (53%)	5 (36%)	6 (46%)	23 (62%)
PR; ≤80%	12 (19%)	NA	1 (8%)	11 (30%)
No. of surgeries	1.7 (1–5)	1.1 (1–2)	1.2 (1–2)	2 (1–5)
Postsurgical treatment				
Medical therapy	4 (6%)	1 (7%)	NA	3 (8%)
Radiosurgery	16 (25%)	1 (7%)	1 (8%)	14 (38%)
Stable disease	42/46 (91%)	5/5 (100%)	7/7 (100%)	30/34 (88%)
Progression	4/46 (9%)	NA	NA	4/34 (12%)
Complications*				
Minor	28 (44%)	3 (21%)	6 (46%)	19 (51%)
Major	10 (16%)	NA	2 (15%)	8 (22%)

NA = not applicable.
Values are expressed as the mean (range) or as the number (percent).
* Minor complications (≥ 1 complication/patient): postoperative CSF leak, hydrocephalus, epistaxis, new anterior pituitary insufficiency, diabetes insipidus, hyponatremia. Major complications (≥ 1 complication/patient): ICA injury, stroke, meningitis, loss or distinct worsening of vision, cranial nerve palsy.

TABLE 4. Complications in 64 patients with GPAs

Complication	No.	%	% in Group A	% in Group B
ICA injury	0	0	0	0
Stroke	3	5	0	100
Vegetative state	1	2	0	100
Meningitis	4	6	25	75
Loss or distinct worsening of vision	2	3	50	50
Cranial nerve palsy (permanent)	2	3	0	100
III, IV, VI	1	2	0	100
III	1	2	0	100
Postop CSF leak	9	14	22	78
Hydrocephalus requiring shunting	4	6	0	100
Epistaxis	2	3	50	50
New anterior pituitary insufficiency (permanent)	11	17	36	64
DI				
Transient	10	16	50	50
Permanent	4	6	0	100
Hyponatremia	5	8	40	60

Nelson adenoma. In the latter, tumor progression despite TMZ treatment was observed and the patient finally died of the disease[15] (Fig. 2).

Discussion

GPAs pose a significant challenge not only to the neurosurgical but also to the whole interdisciplinary treatment team. In particular, in multilobular GPAs that demonstrate growth/invasion into multiple anatomical compartments and encase neurovascular structures, surgeons have a significantly lower chance of achieving GTR than in round or dumbbell-shaped GPAs. Furthermore, due to extensive frontal and suprasellar growth, tumor remnants in patients with PR and in these compartments (group B) can develop hemorrhagic transformation, which can require an early transcranial approach to achieve the goals of decompression of the optochiasmal system and hypothalamus.

Treatment Strategies

Besides medical therapy for prolactin-secreting tumors, surgery is the mainstay of treatment for GPAs to reduce mass effect and achieve long-term tumor control. A combination of transcranial and transsphenoidal microsurgical approaches, simultaneously or consecutively, has been advocated for surgical removal of the multiple adenoma compartments.[1,3]

Primary TCS

After the groundbreaking work of Hardy and Wigser,[16] the transsphenoidal route for resection of pituitary adenomas has surpassed the transcranial route since the 1970s, based on the fact that especially infradiaphragmal adeno-

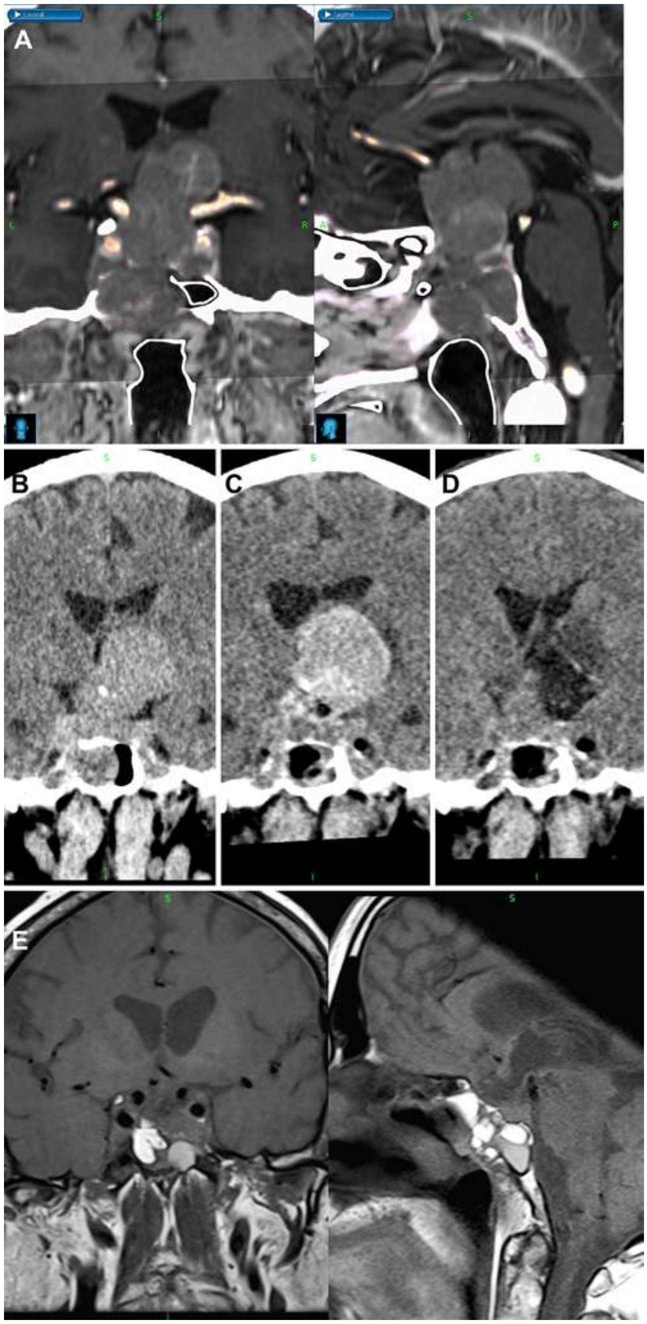

FIG. 3. MRI and CT sequences obtained in a patient with postoperative deterioration and early TCS. **A:** Recurrent multilobular GPA (coronal [*left panel*], sagittal [*right panel*] sequences) with displacement of the third ventricle. **B:** Preoperative CT scan (coronal). **C:** CT scan obtained immediately after ETS showing a hemorrhagic transformation and increased volume of suprasellar tumor remnant. **D:** Postoperative imaging obtained after early TCS before transferring the patient to the ICU. **E:** MRI control sequences obtained 2 years postoperatively demonstrating a tumor remnant within the left cavernous sinus (MRI was done without contrast enhancement due to a newly developed renal insufficiency that was not associated with the treatment of the GPA). Figure is available in color online only.

ma components are more sufficiently visualized and accessible from the inferior direction, allowing selective adenomectomy in functioning pituitary adenomas. However, adenoma components that have an extreme paramedian or frontal location or that encase the arteries of the circle of Willis (except the ICA: 9/64, 14%) are more accessible by a transcranial approach. In theory, these extensions could be removed first by a transcranial approach followed by ETS. However, the transcranial approach is rarely used nowadays as a primary surgery for GPAs due to a high morbidity rate that is associated with possible risk of injury of arteries and perforators.[2,17] We do not dogmatically advise an ETS as a primary approach; however, we are confident that primary ETS can safely reduce intracranial tumor volume and intratumoral pressure, which facilitates time-delayed transcranial tumor remnant removal after ETS, as well as second-stage radiation therapy. Furthermore, hemostasis is facilitated during transsphenoidal surgery, due to devascularization of tumor feeding vessels.

Primary ETS

The ETS has become the mainstay of pituitary adenoma surgery due to the higher degree of visibility and thus the ability to explore deeper into the sellar fossa by using angled endoscopes while approaching the outer limits of larger tumors.[3,6,8,10,18–20]

The overall rate of GTR after primary ETS in this multicenter series was only 28%, compared to a reported GTR rate in the literature of 20.4%–46.5%.[10,20,21] This may be attributed to the high rate of cavernous sinus invasion (73% compared to 9.3%–53.9% in the literature[6,8,22]) and the high number of multilobular GPAs (58% compared to 42%–61% in the literature[12,23]), in which accessibility of the intracavernous and intracranial components is limited even with extended ETS.

Because treatment strategies for intracavernous and intracranial adenoma remnants differ considerably, we stratified our series in two groups: groups A and B. In group A, no intracranial tumor remnant is perceived during ETS. Purely intracavernous tumor remnants are usually followed with MR surveillance and treated with radiosurgery/radiotherapy as soon as they start enlarging or if hormone secretion occurs. In group B, intracranial adenoma remnants after ETS are fraught with the danger of infarction because detaching the blood supply or impairment of the venous drainage[24] induces hypoxia, and rupture of immature tumor vessels may lead to hemorrhagic transformation.[25] To anticipate increasing mass effect from such an event, early imaging after ETS and TCS is required to prevent neurological deterioration. In our series, these events led to an immediate reoperation in 14% of cases. Therefore, patients with intracranial adenoma remnants that are stable on initial imaging should be closely monitored in the ICU as part of the treatment strategy, and this is why no deaths occurred in our series.

In cases of a stable suprasellar remnant not causing neurological deterioration, a second surgery can be delayed until a potential descent of these tumor components occurs, which may be treated via a second ETS. Hence, the probability of an intracranial adenoma remnant after ETS will determine the treatment strategy of GPAs. We observed such intracranial remnants in all but 3 multilobular GPAs, in half of the dumbbell-shaped GPAs, and in none of the round GPAs.

The main criteria for further treatment—surgical, radiation, or observation—were existing or emerging neurological deficit. Concepts included partial removal to relieve opticochiasmatic structures and to create a space between the remaining tumor tissue for further radiation therapy.

The multilobular growth pattern is defined by adenoma components separated from the sellar tumor by anatomical structures that prevent complete removal with ETS: the subfrontal component by anterior communicating artery (ACoA) complex; the third ventricle between ACoA and basilar artery; retrosellar by basilar artery; temporal through the lateral cavernous sinus wall; the parapeduncular component through the oculomotor triangle; and infrasellar through the sellar floor, limited by the confines of the sphenoid sinus.

In the case of dumbbell-shaped GPAs, the nonthinned diaphragma sellae cause a tight diaphragmal opening that prevents GTR if only a direct approach is used.[2] In the later cases in our series, the extended approach was more often applied to this GPA growth pattern. In the case of a round growth pattern, firm attachment of the pseudocapsule or diaphragmal layer to vascular structures of the ACoA complex may prevent complete descent of the suprasellar adenoma component.

Although GTR is rarely achieved in multilobular GPAs, primary ETS is a safe procedure that can be used to reduce considerable amounts of tumor tissue to improve visual outcome and facilitate later TCS.

Combined ETS and TCS

Primary combined ETS and TCS may be performed either simultaneously (with 2 surgical teams) or sequentially (first ETS, then image scan, and finally TCS). However, only small case series have focused on a simultaneous ETS and TCS approach.[26–28] Their results showed that this approach has a high morbidity rate with no advantage of a higher grade of tumor removal, and that it should be limited to a subset of patients with a realistic chance of GTR. In our opinion, the simultaneous approach compromises positioning and maneuverability for both teams.

In contrast, the sequential approach—either immediate or time-delayed—has the advantages of optimal patient positioning and maneuverability for both surgeries. Furthermore, a delayed second ETS for a descending suprasellar component may lead to an easier detachment from neurovascular structures.

Complications and Their Avoidance

Perforator Injury

In this multicenter series, major complications included 1 case (2%) of a vegetative state and 3 cases (5%) of stroke due to an injury of perforating vessels during TCS. Tight adherence of the perforators to the pseudocapsule or diaphragmal layer of the tumor is not uncommon and can prevent access to adenoma tissue during TCS. Dissection of these perforators off the capsule poses the risk of infarction of deep brain structures. In our series, immediate TCS after ETS did not result in a higher rate of stroke than for

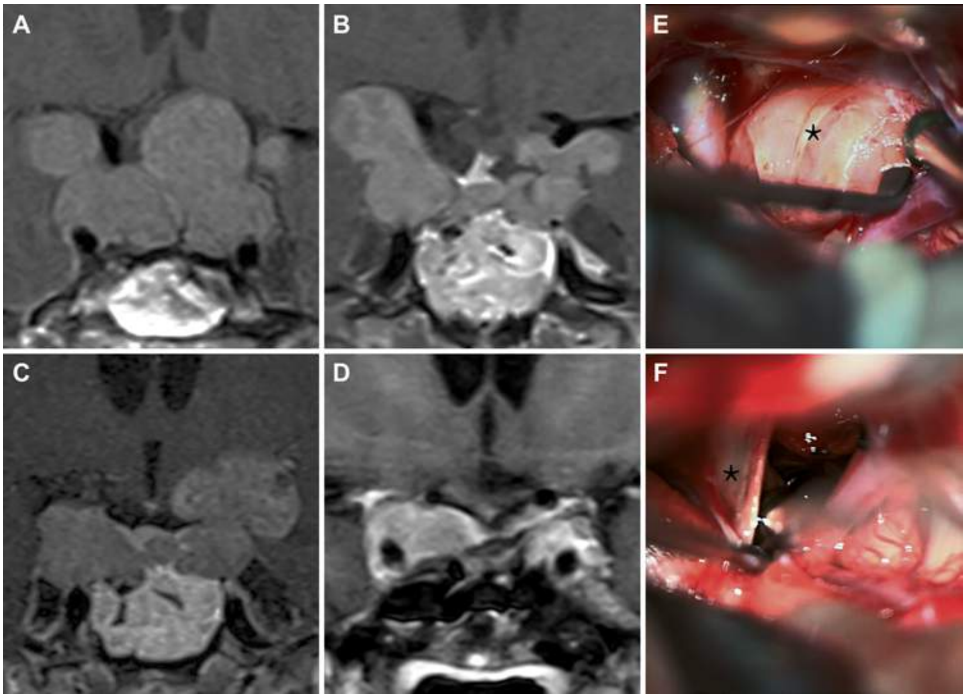

FIG. 4. Postoperative third cranial nerve palsy after TCS. **A:** Imaging obtained in 2013—multilobular GPA (coronal) before ETS of the endosellar/suprasellar part. **B:** Imaging obtained in 2018—preoperative MR scan (coronal) acquired before right subfrontal surgery of oculomotor triangle component. The patient experienced postoperative third cranial nerve palsy at 6 months. **C:** Imaging obtained in 2019—preoperative MR scan (coronal) acquired before left subfrontal surgery of oculomotor triangle component. **D:** Imaging obtained in 2020—postoperative imaging acquired after proton beam radiation. At last follow-up the patient had a normal pituitary function, and vision remained unchanged. **E:** Intraoperative imaging obtained in 2018—right subfrontal surgery demonstrating a displaced third cranial nerve. **F:** Intraoperative imaging obtained in 2018 showing the third cranial nerve after resection of the supracavernous tumor component. *Asterisks* designate the third cranial nerve on the right side. Figure is available in color online only.

delayed TCS. Meticulous surgical preparation of perforating vessels or even STR of adjacent adenoma tissue followed by radiation therapy is therefore recommended to avoid such a devastating complication.

Visual Outcome

The most common presenting symptom was visual impairment (86% of cases). In the literature, ETS of pituitary adenomas is well known to rapidly improve symptoms of chiasmal compression. Given that pressure on the optochiasmal system is also exerted by GPAs mainly from below, debulking from the inferior direction is the major indication for primary ETS.

In our series of GPAs treated with ETS only, visual improvement occurred in 64% of cases. However, in our early cases of ETS for GPA, we observed visual decline in 1 patient with a 5-cm dumbbell-shaped adenoma and severe visual compromise preoperatively.

In our series of serial combined ETS and TCS, visual improvement occurred in 61% of cases. In 1 patient, visual deterioration (from 0.7 to 0.2) was encountered ipsilateral after delayed TCS, possibly due to manipulation of the suprasellar adenoma component that was tightly adherent to optochiasmal structures. Sharp dissection of the tumor capsule to prevent excessive manipulation, maintaining meticulous respect for the vascular supply, may avoid harm to the optochiasmal system during TCS. Overall, 64% of our patients experienced visual improvement and another 30% had stable visual acuity and visual field.

Cranial Nerve Deficit

Permanent cranial nerve deficit from TCS after primary ETS was encountered in 2 cases: one patient suffered from a complete ophthalmoplegia (grade 4 parasellar and parapeduncular extension), and the other patient experienced a third nerve palsy (parapeduncular extension only). In both cases, the tumor extended through the oculomotor triangle into the parapeduncular space.[29]

In GPAs in which the intracavernous ICA is encased (Knosp grade 4), GTR is extremely unlikely, and attempts to remove tumor from the lateral cavernous sinus compartment put cranial nerves at high risk.[14] Hence, radiotherapy of parasellar remnants should be considered instead.

In cases of tumor components extending through the oculomotor triangle into the parapeduncular space, the oculomotor nerve is at risk because its variable course should be anticipated; in addition to the common medial position, it may also be pushed up and forward and may adhere to the tumor surface before turning medially. In such cases with extensive parapeduncular growth (2/64, 3%), a second-stage TCS has been performed (Fig. 4).

CSF Leaks

The overall rate of CSF leaks in this multicenter series of GPAs was 14%, and was therefore comparable to the reported rates of 6%–29%.[6,30,31] This rate has decreased in recent years due to the consequent use of a vascularized pediculated nasoseptal flap in extended ETS.[32,33]

Endocrine Deficits

The normal pituitary gland is often not visible on preoperative MRI due to a distinct displacement by the GPA tumor mass. Although an extension of tumor components into the third ventricle was found in 20% of cases, a hypothalamic disturbance of note was not encountered preoperatively.

We found preoperative hypopituitarism (≥ 1 axis) in 41% of cases, with panhypopituitarism in 16% of cases. In those cases of hypopituitarism, a partial improvement of normal pituitary gland function was found in 19%. However, new and permanent hypopituitarism after multimodality treatment was present in 17% of cases at last follow-up control. To improve the rate of normal pituitary gland function, exact localization of pituitary gland tissue is crucial to preserve it. Therefore, improvements of preoperative MRI, such as volumetric interpolated breath-hold examination (VIBE) sequences, are necessary.[34]

With a rate of 16% of cases, transient DI was not uncommon in our series. Permanent DI occurred in 6% of cases and was therefore equal to the rate reported by Koutourousiou et al.[12,35,36] These endocrine complications are likely to be explained by the increased gland and stalk traction of the giant tumors and the necessary retraction during resection.[35,37]

Adjuvant Treatments

Tumor invasiveness is frequently encountered in GPAs (73%), and inaccessible tumor remnants that show a distinct growth rate require adjuvant treatments.[38] In cases of GPAs that are recurrent despite multiple surgeries, we recommend a tailored approach depending on the available treatment modalities.

In our multicenter series, we applied radiotherapy in 16 patients (25%); at one center primarily radiotherapy was used, and at the other center GKS was used for cavernous sinus adenoma remnants. The rate of postoperative radiotherapy was similar to that in the literature (20%–28%).[12,39]

Off-label chemotherapy with TMZ was administered in 2 patients as compassionate use; one tumor was a dopamine agonist–resistant lactotroph adenoma, and the other was a Nelson tumor. Both were progressive GPAs after multimodality treatment; the first showed a partial response, and the second was unresponsive to TMZ.

Several authors have tried to create predictors for the EOR expected in a given patient with GPA. The prediction was based on factors such as tumor volume and shape[6,8] as well as tumor extension.[2,8,31] For example, as proposed by the Transsphenoidal Extent of Resection Study (TRANSSPHER) group in a grading system for nonfunctioning macroadenomas[40] that is based on factors of individual tumor anatomy and extension, a patient's probability of GTR of a GPA could also possibly be predicted, and this would be a valuable tool in surgical planning and in anticipating additional postoperative therapy. These suggestions are supported by our finding of mainly multilobular adenomas in group B that were treated by multiple surgical approaches.

Limitations

Despite a careful analysis of the available data, we recognize that the current study has limitations due to its retrospective character. To overcome this issue, we compared the results for radiological and outcome parameters in two tertiary centers with surgeons experienced in ETS, to optimize the generalizability and external validity of our findings.

Conclusions

Given the anatomical complexity of GPAs, individually tailored approaches are required. Here we summarize the surgical strategies in two centers with surgeons who are experienced in ETS for these challenging adenomas. GPA morphology (round, dumbbell, multilobular) often guides EOR and subsequent treatment interventions. To relieve mass effect from optochiasmal structures, primary treatment via ETS proved safe and effective in the majority of cases. For those adenoma components that were unreachable via ETS initially, our strategy was to watch and wait for tumor tissue descending into the sellar compartment and to perform a delayed second ETS. Due to the risk of postoperative hemorrhagic transformation of adenoma remnants, we performed early imaging and reoperation if mass effect occurred. In the cases of nondescending or inaccessible lateral adenoma components, further surgery via transcranial approach was required. Additional treatment modalities such as radiotherapy were required for long-term control of unresectable adenoma remnants.

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Disclosures

Dr. Wolfsberger is currently an educational consultant for Medtronic Surgical Technologies.

Author Contributions

Conception and design: Zada, Micko. Acquisition of data: Micko, Agam, Brunswick, Strickland, Rutkowski. Analysis and interpretation of data: Micko, Brunswick. Drafting the article: Micko. Critically revising the article: Zada, Micko, Knosp, Wolfsberger. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Zada. Statistical analysis: Micko. Administrative/technical/material support: Carmichael, Shiroishi. Study supervision: Zada, Wolfsberger.

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