Original Article

The role of multimodal navigation in endoscopic endonasal surgery for giant pituitary adenomas

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Background: Giant pituitary adenoma (GPA) (diameter >40 mm) remains challenging to treat, and the radical resection rate is low. The intraoperative multimodal navigation is sometimes used in endoscopic endonasal surgery (EES). However, the effect of this technique on GPA surgical outcomes is not clear. This study aims to explore the surgical and clinical outcomes of the navigation used in EES for GPA.

Methods: A retrospective review of 60 consecutive patients with GPA who underwent EES was performed. The total resection rate, residual volume, clinical outcomes, and complications were compared. Factors associated with tumor gross total resection (GTR) were analyzed by multinomial logistic regression analysis.

Results: There were 31 patients in the standard group in which intraoperative multimodal navigation was not used, with a mean maximum tumor diameter of 5.21±1.24 cm; meanwhile, there were 29 patients in the navigation group, in which navigation was used, with a mean maximum tumor diameter of 5.32±1.18 cm. GTR was achieved in 10 patients (32.26%) in the standard group, which was significantly lower than that in the navigation group (18/29=62.07%). The residual volume was 7.93±10.78 cm^3 in the standard group which was significantly greater than that in the navigation group (2.44±1.26 cm^3, P=0.046). There was no significant difference between the two groups in terms of cerebrospinal fluid (CSF) leak, new pituitary deficit, and postoperative diabetes insipidus (DI). The higher Knosp grade of tumor, lobulated configuration and lack of intraoperative multimodal navigation use were relative risk factors associated with the GTR.

Conclusions: The intraoperative multimode navigation appeared to be safe and effective when used in EES for GPA with higher GTR and lower residual tumor volume.

Keywords: Giant pituitary adenoma (GPA); endoscopic endonasal surgery (EES); navigation

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Introduction

Giant pituitary adenomas (GPAs), which are defined as tumors with a maximum diameter larger than 40 mm, account for 5–14% of adenomas that are treated surgically (1,2). Surgery for patients with a GPA is challenging due to the enormous tumor size, irregular extension, and invasiveness. Gross total resection (GTR) is achieved in less than 50% of GPAs, with a reported 10% to 20% complication rate (1,3,4). Surgery remains the main treatment option for GPA, excluding most prolactinomas. Recently, with advances in endoscopic surgical techniques, a purely endoscopic endonasal surgery (EES) has gained acceptance for the surgical treatment of GPA (5-7). Additionally, in comparisons with microsurgical approaches, EES has shown equivalent or superior outcomes with respect to length of stay, rate of resection, postoperative diabetes insipidus (DI), incidence of cerebrospinal fluid (CSF) leaks, and visual outcomes (4,8-12). The most advantageous features of adapting EES are the panoramic views enabled through the angled endoscopes which generally allow visualization of lesion boundaries, neurovascular structures, and its suprasellar extension (13-15). However, for large and giant adenomas, there is a risk of vascular injury or cranial nerve damage from resecting tumor grossly invading the cavernous sinus (8,10,16,17). Additionally, inadequate tumor resection occasionally causes subdural and subarachnoid hemorrhage and peritumoral swelling because of hemorrhage from the residual tumor and results in deteriorated visual and neurologic outcomes (6,18,19). The primary goal of GPA is complete resection of the tumor with maximal preservation of the normal pituitary gland.

Advance in EES for treatment of pituitary tumors has involved the implementation of intraoperative navigation systems and micro-Doppler, which enable enhanced visualization of adjacent vascular, neural, and ventricular structures (20). Image-based pre-operative vascular and neural element segmentation is highly informative preoperatively and could help young and inexperienced neurosurgeons to avoid vascular and neural injury during trans-sphenoidal surgeries, as well as provide reassurance to more experienced surgeons (20). The effectiveness of multimodal navigation has been proven and is occasionally used in EES; however, whether the implementation of intraoperative multimodal navigation in EES for GPA would improve the removal rates and clinical outcomes has not been substantially addressed.

The purpose of this study was to review the clinical outcomes of a series of 60 consecutive patients with GPA who had undergone EES and to investigate the efficacy and complications with respect to the application of intraoperative multimodal navigation.

Methods

Patient population and study design

After obtaining approval from the review board of the Tangdu Hospital Institutional (No. TDLL-2011034), we retrospectively reviewed a database of more than 300 consecutive cases of endoscopic endonasal pituitary adenoma recorded between January 2012 and December 2015. All surgeries were primarily performed by the lead neurosurgeon (Dong Jia) during this time period. All clinical data, including medical records, radiologic evaluations, laboratory data, and pathologic examinations, were retrospectively reviewed until March 2019. Inclusion criteria were patients with pathology confirmed pituitary adenoma with a maximum tumor diameter >4 cm in at least 1 dimension and an estimated tumor volume >10 cm^3. Patients who did not complete the follow-up nor had no postoperative MRI were excluded from the study. Based on whether intraoperative multimodal navigation was applied, 60 GPA patients were categorized into two groups: the standard group and the navigation group. Given the study design of a retrospective chart review, patient consent was not required.

Surgical techniques

All procedures were performed using a purely endoscopic endonasal approach, which was performed with a 2-surgeon, 3-hand technique via a single nostril. The endoscope was manually managed by an assistant. Under general anesthesia, the patient was placed supine with the head in a neutral position, and the trunk elevated around 30°. For the cases in the navigation group, the patient's head was registered in the intra-op neuronavigation system (Stealth Station; Medtronic, TN, USA). After surgical exposure, each segmented neural or vascular element was validated by manual placement of the navigation probe directly on that object or as closely as possible to the target. A vascularized nasoseptal flap based on the sphenopalatine artery was prepared for reconstruction in almost all cases, as described previously (21). The middle turbinate was preserved routinely. The anterior portion of the vomer bone, rostrum of the sphenoid bone, and the bony septum inside the sphenoid sinus were removed by high-speed drilling. The extent of the bony removal of sellar floor depended on the shape of the lesion. In cases with notable suprasellar extension, an extended transsphenoidal approach was used so that the bone over the planum and/or tuberculum would be removed. The navigation system was used to determine boundaries between the lesion and normal and eloquent structures before the bony removal in the navigation group. Meanwhile, in the standard group, the scope of bony removal depended on preoperative imaging and the surgeon's experiences. In cases with significant cavernous sinus invasion, the sellar floor overlying the carotid protuberance was removed. In the navigation group, a micro-Doppler was used to detect the audible pulses of the bilateral internal carotid artery (ICA) to identify the trajectory of the carotid artery prior to dural opening, particularly for exposure of the cavernous sinus. After the dural opening, the resection of the tumor was performed in an extracapsular fashion whenever feasible. Lesionectomy was performed using microscissors, ring curettes, suctions, and an ultrasonic aspirator if necessary. The navigation system was used to confirm the extent of lesion resection and minimize residual tumors before reconstruction. Skull base reconstruction was performed in a multilayer fashion using artificial dura mater, SURGICEL (Ethicon Inc.), tissue glue, gelfoam, and the vascularized nasoseptal flap.

Data collection

All pre- and postoperative radiologic evaluations, endocrinology studies, postoperative outcomes, complications, and clinical records were compared for analysis. Visual acuity and Humphrey visual field tests were performed by an independent neuro-ophthalmologist for all patients preoperatively and approximately 12 weeks postoperatively. The records of visual deficits, laterality of deficits, and duration of deficits before surgery were analyzed.

Laboratory examinations were performed preoperatively and approximately 3 months postoperatively in all patients and included tests for triiodothyronine (T3), thyroxine (T4), free T4, thyrotropin-stimulating hormone, adrenocorticotropic hormone, cortisol, serum growth hormone, insulin-like growth factor 1, prolactin, follicle-stimulating hormone, luteinizing hormone, and either testosterone in males or estrogen in females. Postoperatively, all patients were routinely monitored for serum sodium, urine output, and particular attention was paid to DI and electrolyte imbalance.

All patients underwent preoperative magnetic resonance imaging (MRI) and computed tomography scan for evaluation of the size, location, and extension of the pituitary mass lesion. The parameters including the maximum tumor diameters, lobulated tumor configuration, and the intracranial extension index (defined as the approximate ratio of intracranial to total tumor volume measured by sagittal and coronal images) were assessed on preoperative MRI. All patients underwent postoperative MRI within 72 hours or at approximately 12 weeks postoperatively. The extent of tumor resection was evaluated based on the first postoperative MRI and categorized into 3 statuses, which were GTR, near-total resection (NTR) (>90%), or subtotal resection (STR) (<90%), according to the completeness of resection. When GTR was not achieved, the volume of residual tumor was calculated using the following formula: (A×B×C)/2, where A, B, and C are the maximum tumor diameters in each of the 3 dimensions.

Complications included CSF leak, visual disturbance, hematoma, new pituitary deficit, DI, and other clinical deterioration during the first 30 days postoperatively that needed further management.

Statistical analysis

Preoperative patient characteristics, clinical outcomes, and extent of resection, and complications of the two groups were statistically compared. The data were analyzed using version 17.0 of SPSS (SPSS, Chicago, IL, USA) software. Variables were classified as continuous or categorical. Independent Student's *t*-tests were used for continuous variables between the two groups. Fisher's exact test or Pearson's χ^2 test was used for comparison of categorical variables among groups. Factors associated with tumor GTR were analyzed by multinomial logistic regression analysis. A two-tailed P value <0.05 was considered statistically significant.

Results

Patient demographics and clinical presentation

A total of 60 consecutive patients who received EES for GPA were included in the study, which accounted for 19.87% of 302 cases of pituitary adenomas who received surgery during the study period. Patients were classed into two groups: the standard group (n=31) and the navigation group (n=29). There was no significant difference between the two groups in terms of patient sex, age, mean maximum tumor diameter, tumor volume, visual dysfunction, tumor pathology, Knosp grade, and the use of extended EES (*Table 1*). However, there were 10 cases of recurrent tumors after previous endoscopic or microscopic transsphenoidal surgery in the navigation group which was significantly more than those in the standard group (P=0.02). The mean age at the time of EES was 51.38±13.33 years (mean ± SD) in the standard group and 50.69±15.40 years in the navigation group, both with a male predominance (67.74%

Table 1 Preoperative patient characteristics

Characteristics	Standard (n=31)	Navigation (n=29)	P
Sex			0.919
Male	21	20	
Female	10	9	
Age (years)			0.852
Mean	51.38	50.69	
Range	17–75	21–74	
SD	13.33	15.40	
Mean maximum tumor diameter (cm)	5.21±1.24	5.32±1.18	0.733
Tumor volume (cm^3)	50.19±47.69	53.60±49.47	0.572
Decreased visual acuity			0.553
Yes	18	19	
No	13	10	
Visual field deficits			1.000
Yes	27	26	
No	4	3	
Pathology			0.847
Nonfunctioning	28	25	
GH secreting	2	2	
PRL secreting	1	2	
Knosp grade			0.745
0	3	3	
1	4	2	
2	6	7	
3	13	9	
4	5	8	
Recurrent tumor	3	10	0.020
Extended EES	10	15	0.126

EES, endoscopic endonasal surgery.

and 68.96%, respectively). GPAs were confirmed by both preoperative MRI and postoperative histopathologic diagnosis, for tumor size and pathology, respectively. The mean maximum tumor diameter in the preoperative MRI was 5.21±1.24 cm in the standard group and 5.32±1.18 cm in the navigation group, while the preoperative mean tumor volume was 50.19±47.69 and 53.60±49.47 cm^3, respectively. The most common presenting symptom was visual field deficits (87.09% in the standard group and 89.65% in the navigation group) and decreased visual acuity (58.06% and 65.51%, respectively). The most common pathology of tumor was nonfunctional adenomas (28 in the standard group and 25 in the navigation group). The functional GPAs included 4 growth hormone-secreting tumors and 3 medically resistant prolactinomas. Based on the Knosp classification, there were 3, 4, 6, 13, and 5 patients of Knosp grade 0, 1, 2, 3, and 4 in the standard group, and 3, 2, 7, 9, and 8 in the navigation group, respectively (*Table 1*).

The extent of resection and clinical outcomes

The overall mean follow-up time was 42.53±10.29 months. There was a significant difference between the two groups in the extent of resection (P=0.039). GTR was achieved in 10 patients (32.26%) in the standard group, which was significantly lower than that in the navigation group (18/29=62.07%) (*Figure 1*). NTR was achieved in 15 patients (48.39%) in the standard group and 10 patients (34.48%) in the navigation group (*Figure 2*), while STR was achieved in 6 patients (19.35%) and in 1 patient (3.45%), respectively (*Table 2*). For the residual tumors, the mean residual volume was compared between the two groups. The residual volume was 7.93±10.78 cm^3 in the standard group which was significantly more than that in the navigation group (2.44±1.26 cm^3, P=0.046).

All patients completed postoperative visual acuity and visual field tests. Although the rates of visual acuity and visual field improvement were much higher in the navigation group, there was no significant difference between the two groups (*Table 2*). For the visual acuity, 18 patients in the standard group and 19 patients in the navigation group decreased preoperatively, and of these, 7 (7/18=38.89%) patients and 9 (9/19=47.37%) patients had visual acuity improvement, while 23 patients and 20 patients had no changes, respectively. Only 1 patient in the standard group with decreased preoperative visual acuity and visual field deficit developed visual deterioration after surgery. For the visual field, 27 patients in the standard group and 26 patients in the navigation group had preoperative visual field deficits, and of these, 20 (20/27=74.07%) patients and 24 (24/26=92.31%) patients had visual field improvement, while 10 patients and 5 patients had no changes, respectively (*Table 2*).

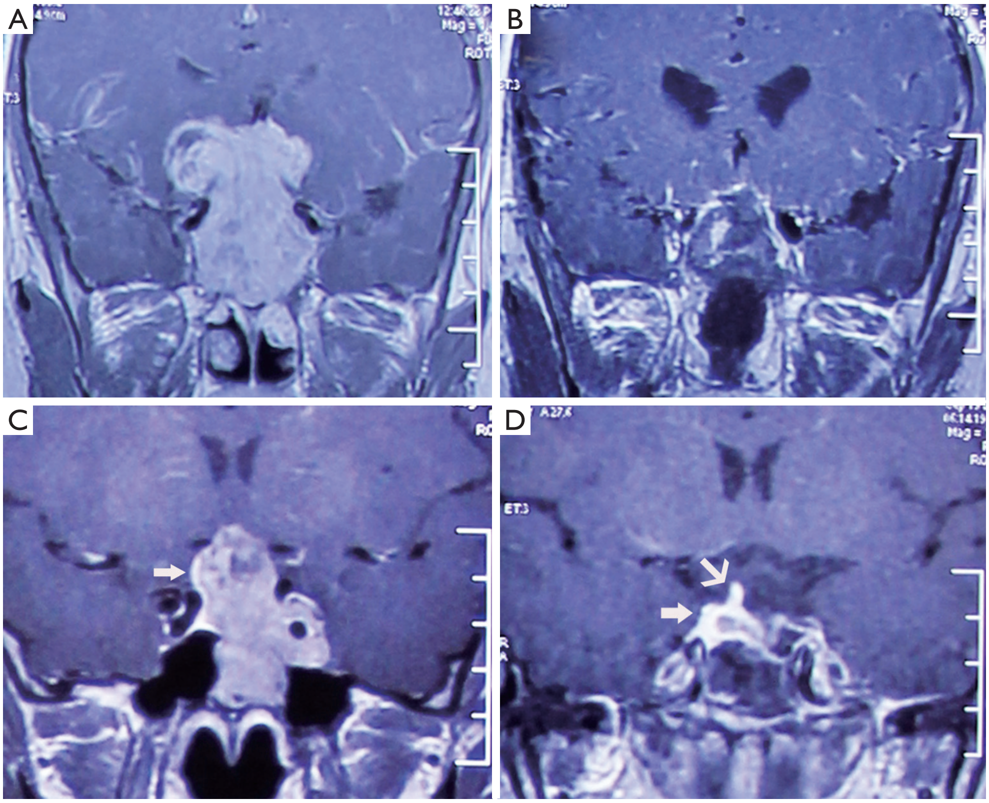

Figure 1 Examples of gross total resection (GTR) in our series. (A and B) Case 1. (A) Preoperative contrast-enhanced coronal T1-weighted magnetic resonance imaging (MRI) showing a giant pituitary adenoma (GPA) with invasion of the sphenoid sinus and extension into the third ventricle; (B) postoperative MRI showing GTR after endoscopic endonasal surgery (EES). (C and D) Case 2; (C) preoperative contrast-enhanced coronal MRI demonstrating a GPA with invasion of the left cavernous sinus and extension into the third ventricle. The arrow indicates the compressed pituitary gland in the right margin of the lesion; (D) postoperative MRI showing GTR with retention of the pituitary stalk and gland (arrows).

Complications

CSF leak was the most common complication of EES, especially during operation. There were 14 patients (45.1%) in the standard group and 19 patients (65.5%) in the navigation group in whom intraoperative CSF leak occurred. However, there was only 1 patient who developed a postoperative CSF leak in the standard group and no patients in the navigation group who had postoperative CSF leak. There was no significant difference between the two groups regarding CSF leak (*Table 3*). The intraoperative CSF leak was managed immediately in a multilayer fashion after tumor resection. All but 1 intraoperative CSF leak patient in the standard group was successfully repaired, and there was no postoperative CSF rhinorrhea or related meningitis. The patient had a postoperative CSF leak, which was successfully treated with 7 days' lumbar drainage.

There were 5 patients (16.1%) in the standard group and 3 patients (10.3%) in the navigation group who developed a new pituitary deficit in 1 or more pituitary axes without significant difference between the two groups (*Table 3*). There were no patients with panhypopituitarism. Generally, the changes to the endocrine functions that were altered postoperatively were transient.

There was no significant difference between the two groups in postoperative DI, both transit (P=0.732) and permanent (P=1.00). There were 6 patients (19.3%) who had DI postoperatively; a permanent condition did occur in 2 patients in the standard group and required medication. In contrast, DI occurred in 4 patients (13.8%) in the navigation group, but was permanent in only 1 patient.

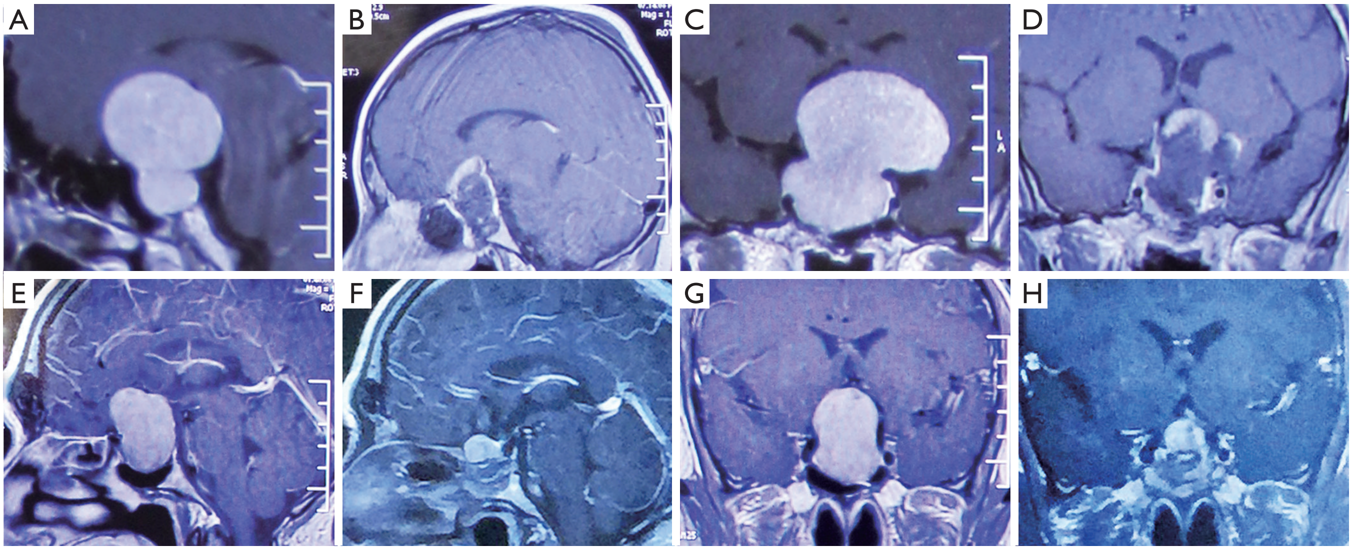

Figure 2 Examples of near-total resection (NTR) in our series. (A-D) Case 1. Preoperative contrast-enhanced sagittal (A) and coronal (C) T1-weighted magnetic resonance imaging (MRI) showing a giant pituitary adenoma (GPA) invasion of the sphenoid sinus, anterior skull base, and clivus and extension into the third ventricle, the anterior cranial fossa, and the middle cranial fossa. (B and D) Postoperative MRI showing NTR after expanded endoscopic endonasal surgery (EES) and a very small residual tumor in the superior pole. The lateral extension part was resected completely. (E-H) Case 2. Preoperative contrast-enhanced sagittal (E) and coronal (G) T1-weighted MRI demonstrating a GPA with invasion of the sphenoid sinus, anterior skull base, and extension into the third ventricle and the anterior cranial fossa. (F and H) Postoperative MRI showing NTR after standard EES and a very small residual tumor descended into the sphenoid plane from the superior pole.

Table 2 Clinical outcomes and extent of resection

Characteristics	Standard	Navigation	P
Extent of resection, number (%)			0.039
GTR	10 (32.26%)	18 (62.07%)	
NTR (>90%)	15 (48.39%)	10 (34.48%)	
STR	6 (19.35%)	1 (3.45%)	
Residual volume (cm^3)	7.93±10.78 (n=19)	2.44±1.26 (n=11)	0.046
Visual acuity			0.563
Improved	7	9	
Stable	23	20	
Woresen	1	0	
Visual fields			0.185
Improved	20	24	
Stable	10	5	
Woresen	1	0	

Table 3 Complications

Characteristics	Standard	Navigation	P
CSF leak			
Intraoperative	14 (45.1%)	19 (65.5%)	0.113
Postoperative	1 (3.2%)	0	1.00
New pituitary deficit	5 (16.1%)	3 (10.3%)	0.708
Diabetes insipidus			
Transient	6 (19.3%)	4 (13.8%)	0.732
Permanent	2 (6.5%)	1 (3.4%)	1.00

Factors associated with tumor GTR

To explore the risk factors associated with tumor GTR, 60 patients were classified into two subgroups according to the extent of resection: subgroup A including 28 patients (46.67%) achieved GTR, and subgroup B, including 32 patients (53.33%) had residual tumor. The extent of resection in the two groups did not significantly differ in terms of patient age, sex, intracranial extension index, and

Table 4 Comparison of patient age, sex, tumor characteristics, and surgical approaches between tumor total resection (group A) and residual tumor (group B)

Variables	Group A (n=28)	Group B (n=32)	P
Age (years)	17–75 (53.11)	21–74 (49.25)	0.300
Sex, male:female	18:10	23:9	0.586
Tumor diameter (cm)	4.0–6.8 (4.8)	4.1–9.6 (5.6)	0.011
Tumor volume (cm^3)	18.4–124.8 (40.5)	20.6–265.4 (65.1)	0.039
Knosp grade			0.000
0, 1, 2	20	5	
3, 4	8	27	
Lobulated configuration			0.000
Yes	7	25	
No	21	7	
Intracranial extension index (%)	0–86 (49.2)	5–94 (55.9)	0.302
Extended EES			0.116
Yes	15	10	
No	13	22	
Navigation			0.037
Yes	18	11	
No	10	21	

EES, endoscopic endonasal surgery.

the use of extended EES (*Table 4*). For patients in subgroup B, occurrence of residual tumors was significantly associated with a larger maximum tumor diameter (mean 5.6 cm; P=0.011) and tumor volume (mean 65.1 cm^3; P=0.039), higher Knosp grade (27/32 with grade 3 or grade 4; P=0.000), lobulated tumor configuration (25/32; P=0.000) and lack of intraoperative navigation (21/32; P=0.037) (*Table 4*). In a multinomial logistic regression, the relative risk for Knosp grade 3 and grade 4 to Knosp grade 0–2 was 52.431 [95% confidence interval (CI): 3.13 to 878.391, P=0.006], from lobulated tumor configuration to no lobulated tumor configuration it was 10.829 (95% CI: 1.153 to 101.735, P=0.037), and from multimode navigation to without navigation it was 0.026 (95% CI: 0.001 to 0.604, P=0.023) (*Table 5*).

Discussion

In the present series, 60 consecutive patients who received EES for GPA by the same senior surgeon were retrospectively reviewed. Based on whether intraoperative multimodal navigation was applied, patients were divided into two groups. Preoperative patient characteristics, clinical outcomes, the extent of resection, residual tumor volume, and complications were statistically compared between the two groups. By using intraoperative multimodal navigation, a much higher GTR, and lower residual tumor volume was achieved, while the clinical outcomes and complications were similar. A multinomial logistic regression model was used to explore the risk factors associated with tumor

Table 5 Multinomial logistic regression analysis of tumor gross total resection

Variables	RR	95% (CI)	P
Age (>53 years)	0.502	0.054–4.694	0.546
Gender	8.993	0.544–148.619	0.125
Tumor diameter (>5.0 cm)	0.342	0–334.565	0.76
Tumor volume (>37 cm^3)	17.068	0.033–8,726.546	0.373
Knosp grade (3 and 4)	52.431	3.13–878.391	0.006
Lobulated configuration	10.829	1.153–101.735	0.037
Intracranial extension index (>53%)	1.889	0.166–21.449	0.608
Extended EES	0.156	0.009–2.805	0.207
Navigation	0.026	0.001–0.604	0.023

RR, relative risk; CL, confidence interval; EES, endoscopic endonasal surgery.

GTR. Higher Knosp grade of tumor, lobulated tumor configuration, and lack of intraoperative multimodal navigation were relative risk factors associated with GTR. Therefore, intraoperative multimodal navigation appeared to benefit surgical management of GPA by EES. This study is one of the few reports that show the efficacy and the safety of using intraoperative multimodal navigation in EES for GPA. A relatively high GTR for these challenging tumors was achieved in the present series.

GPAs are mostly histological benign, slow-growing, and nonfunctional. Surgical resection remains the main treatment option for GPA. Due to the wide panoramic, up-close visualization of the endoscope, EES has been the primary approach for sellar and parasellar lesions (22,23). Some adenomas that had been considered previously not manageable by EES, such as suprasellar-extended large adenomas with an hourglass constriction, can be endoscopically treated with success and by extended approaches (3,23). The superiority of EES over open transcranial surgery in achieving the GTR of adenomas, with lower perioperative mortality and rate of recurrence, has been reported (4). Nevertheless, surgery in patients with GPA is challenging, and the GTR is still low. On the one hand, it is not uncommon that incomplete resection of GPA may cause postoperative critical apoplexy in which bleeding occurs within the confines of the residual tumors. On the other hand, the recurrence rate of the GPA after its radical resection is low (5). Consequently, the surgical goal of GPA should be a safe and maximum tumor resection depending on the tumor characteristics and the patient.

In general, GPA with a smooth configuration and without massive intracranial extension and cavernous sinus invasion can be resected effectively and safely by EES. However, there are several factors that limit the radical resection of GPA. In evaluating endoscopic surgery for "big" adenomas, Cappabianca *et al.* (24) noted that "size does not matter"; instead, attention should mostly be paid to the pattern of intracranial growth. Goel proposed a classification system of giant pituitary tumors that assists in indicating the nature of anatomic extensions of the tumor, ease of surgical resection, and possibilities of complete resection, in addition to assessing the need for adjuvant treatment and predicting long-term outcomes (5). According to the classification system, grade I tumors, those that do not invade into the cavernous sinus, can be resected radically and completely, while the resection of tumors within the cavernous sinus in grade II and grade III tumors is less straightforward. Grade IV tumors are those that transgress the diaphragma sella boundary and extend into the subarachnoid spaces of the brain, which are relatively rare, but a challenging clinical problem; only some of these tumors can be resected radically. Similarly, according to Koutourousiou *et al.* (3), the true limitations of EES are tumors with a mulitlobular configuration and extensions beyond the lateral wall of the CS. Consequently, the radical resection rate of GPA is still low. Our findings were in reasonable agreement with these previous studies in that CS invasion, and lobulated tumor configuration were the predictors of limited the radical resection. Furthermore, we found that the lack of intraoperative multimodal navigation during EES was another independent risk factor for radical resection.

In the present series, GTR was achieved in 28 patients (46.67%), overall, and the GTR reached 62.07% when the multimode navigation system was introduced. In the literature, Elshazly *et al.* (25) retrospectively reported a 55-case series with GPA, in which GTR was achieved in 24 patients (44%). In their study, neuromonitoring, consisting of motor and somatosensory evoked potentials, was generally used in giant adenomas with vascular involvement. Moreover, Nakao and Itakura (14) presented a total of 43 consecutive patients with pituitary adenomas with a suprasellar extension of >20 mm who underwent tumor resection with a purely endoscopic endonasal approach; GTR was achieved in 20 out of 43 patients (46.51%). They used a navigation system to confirm anatomical landmarks and tumor location. Our overall GTR in the present series was comparable with previously reported series where the GTR ranged from 21.1% to 46.5% (13,14,25,26); however, in our study, the GTR significantly improved when intraoperative navigation was used.

There is little doubt that the marked cavernous sinus invasion is a definitive factor that limits total tumor resection (27). A surgical navigation system, mini-Doppler, and an eye movement monitoring device may help to achieve safe and maximum removal of these tumors (28). It was important to use intraoperative Doppler probe and image guidance to identify the ICA trajectory and reduce the risk of ICA injury (17). Navigation was highly informative in terms of the lateral extent of bone removal at the sellar floor and the limits of lateral explorations, especially in cases of CS involvement, and could be extremely helpful for the protection of the ICA during tumor resection (20). Consistent with previous study, in our present study, the implementation of multimode navigation improved the GTR, reduced the residual tumor volume, and did not increase complication incidence. Although the application of intraoperative multimodal navigation was not random, it seemed to be more frequently used in Knosp grade 4 and recurrent GPA in which GTR was more difficult to achieve; however, the reliability of the conclusion was unaffected.

The effectiveness and utility of the navigation system have been proven, particularly in determining the boundaries between lesions and normal and eloquent structures (17,28). It has a similarly important utility in EES and also aids in the prevention of iatrogenic neurovascular injuries during operation. More modern navigation techniques have been introduced; for example, Micko *et al.* (29) reported an advanced image guidance protocol that extracted information from multiple modalities and formed them into a single image that included fine sinunasal structures and arteries which could intraoperatively visualize the fine sinunasal sinus structures and small arteries with a high degree of detail. This may help to reduce the rate of complications in endoscopic trans-sphenoidal surgery. However, to the best of our knowledge, there has been a lack of credible evidence suggesting that implementing navigation in EES for GPA can improve surgical outcomes. It is undeniable that navigation cannot precisely displace borders of lesions and normal structures in some cases because the superior and lateral boundaries of GPA are usually surrounded by soft tissues that can drop and displace during tumor evacuation. Although it is not widely available, intraoperative MRI seems to be the best modality for evaluation of residual tumors (30). There are at least two reasons why the application of intraoperative multimodal navigation may facilitate improving the GTR and reduce residual tumor volume in EES for GPA. One is that the operation seems more "aggressive" when applied and takes advantage of the intraoperative navigation system and Doppler probe. Although there was no significant difference in the use of extended EES between the two groups in our study, it seemed to be more frequently used in extended EES in the navigation group. Furthermore, the bone overlying the sellar and parasellar region was more frequently removed in the navigation group than in the standard group, especially in the cases of CS involvement and extension into the anterior cranial fossa. The other reason is that the navigation system is used to evaluate the extent of resection whenever necessary which can minimize "unexpected" residual tumors and improve the rate of GTR.

The relatively small number of cases for each group and its retrospective design were the major limitations of the current study. Furthermore, a selection bias could have been present because the use of intraoperative multimode navigation was not random. Multimode navigation seemed to be more frequently used in Knosp grade 4 and recurrent tumors. It is worth noting the possible biases that there were more recurrent tumors in the navigation group than those in the standard group. Multimode navigation might be extremely useful in recurrent cases, as GTR of these tumors seems to be more challenging. Indeed, the use of navigation yielded more GTRs and lowered residual tumor volume which further confirms the value of applying navigation during EES for GPA. Further studies of a larger sample size and longer follow-up are necessary to validate the effectiveness and superiority of intraoperative multimode navigation in EES for GPA.

Conclusions

In the current series of GPA, the use of intraoperative multimode navigation in EES yielded more GTRs and lower residual tumor volume. Therefore, intraoperative multimode navigation appears to be safe and effective in EES for GPA. In particular, it is recommended that intraoperative multimode navigation be used for the more "aggressive" and recurrent GPA.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work (if applied, including full data access, the integrity of the data, and the accuracy of the data analysis) in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the institutional ethics committee of Tangdu Hospital (No. TDLL-2011034). Given the study design of a retrospective chart review, patient consent was not required.

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