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Endoscopic endonasal versus open transcranial resection of craniopharyngiomas: a case-matched single-institution analysis

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OBJECTIVE The authors compared clinical and radiological outcomes after resection of midline craniopharyngiomas via an endoscopic endonasal approach (EEA) versus an open transcranial approach (TCA) at a single institution in a series in which the tumors were selected to be equally amenable to gross-total resection (GTR) with either approach.

METHODS A single-institution retrospective review of previously untreated adult midline craniopharyngiomas was performed. Lesions were evaluated by 4 neurosurgeons blinded to the actual approach used to identify cases that were equally amenable to GTR using either an EEA or TCA. Radiological and clinical outcome data were assessed.

RESULTS Twenty-six cases amenable to either approach were identified, 21 EEA and 5 TCA. Cases involving tumors that were resected via a TCA had a trend toward larger diameter ($p = 0.10$) but were otherwise equivalent in preoperative clinical and radiological characteristics. GTR was achieved in a greater proportion of cases removed with an EEA than a TCA (90% vs 40%, respectively; $p = 0.009$). Endoscopic resection was associated with superior visual restoration (63% vs 0%; $p < 0.05$), a decreased incidence of recurrence ($p < 0.001$), lower increase in FLAIR signal postoperatively ($–0.16 \pm 4.6$ cm^3 vs 14.4 ± 14.0 cm^3; $p < 0.001$), and fewer complications (20% vs 80% of patients; $p < 0.001$). Significantly more TCA patients suffered postoperative cognitive loss (80% vs 0; $p < 0.0001$).

CONCLUSIONS An EEA is a safe and effective approach to suprasellar craniopharyngiomas amenable to GTR. For this select group of cases, the EEA may provide higher rates of GTR and visual improvement with fewer complications compared with a TCA.

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KEY WORDS craniopharyngioma; endonasal; endoscope; skull base; suprasellar; oncology

Craniopharyngiomas are epithelial tumors that arise from the remnants of Rathke's pouch in the suprasellar compartment along the path of the craniopharyngeal duct.[16] With an incidence of 0.2/100,000 and a frequently benign histology, these tumors are a challenging neurosurgical disease with a 3-year relative survival of 88%.[38] Invasive components make resection technically challenging and associated with potential morbidity. These tumors also frequently recur after resection or adjuvant therapy, and frequently result in neurological deficits, with common presenting symptoms including hypopituitarism, cognitive dysfunction, and visual impairment.[3,15] Furthermore, malignant transformation has been described. While a minority display papillary-squamous histology, which is associated with the pathognomonic *BRAF* V600E mutation and which has been reported to respond to targeted anti-BRAF and anti-MEK1/2 inhibition, most cases are of adamantinomatous histology, which does not have a known therapeutically amenable driver.[1,2,21,39]

The treatment of craniopharyngioma is primarily centered on excision, with gross-total resection (GTR) the gold standard treatment, although recent evidence supports comparable control rates with subtotal resection and adjuvant radiotherapy.[35] However, cyst enlargement after radiotherapy may cause symptomatic progression requiring treatment. Given the often large size of these tumors and their relationship to vital anterior skull base neurovascular structures, including the pituitary gland, infun-

ABBREVIATIONS EEA = endoscopic endonasal approach; EOR = extent of resection; GTR = gross-total resection; TCA = transcranial approach.

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dibulum, hypothalamus, optic apparatus, and the anterior cerebral artery–anterior communicating artery complex, resection is often technically challenging.

While craniopharyngiomas have traditionally been resected via open transcranial approaches (TCAs) including the pterional, supraorbital, and, for retrochiasmatic lesions, subfrontal and interhemispheric corridors, the endoscopic endonasal approach (EEA) has been recently developed as an alternative that eliminates the need for brain retraction and minimizes the manipulation of neurovascular structures by providing a more direct trajectory to the tumor, but it is limited in its lateral reach.[23,24] Early experience with the EEA has yielded positive results in terms of extent of resection (EOR), visual outcomes, and rates of diabetes insipidus and hypopituitarism, but in some series this approach has also been reported to be associated with greater rates of CSF leakage.[2,4,19] However, comparisons between the EEA and TCA have been problematic since tumors selected for TCA may have lateral extension and not be amenable to EEA. These tumors may be more difficult to remove, and thus tumors selected for EEA may have better results based on case selection bias. For this reason, we designed a study in which all cases included were amenable to complete resection via either the EEA or TCA based on blinded review of the preoperative MRI scans.

Methods

The pathology records of all neurosurgical procedures performed in patients aged 18 years and older at a single institution (Weill Cornell Medical College) between January 2000 and June 2015 were examined and all cases of craniopharyngioma were identified. A digital slideshow presentation of a single axial, sagittal, and coronal image of the preoperative MRI scans was shown to 4 surgeons who specialize in endonasal and transcranial skull base surgery, including the senior author (T.H.S.) of this article (see *Acknowledgments*). These reviewers, including the senior author who performed all the EEA cases, were blinded as to which approach was used in each case (TCA or EEA). Cases were selected for inclusion in this study if all 4 authors agreed that cases were amenable to GTR using either a TCA or EEA.

Anatomical criteria for this designation generally include tumors with significant suprasellar extension whose lateral extent does not pass the carotid bifurcation. Extension to the roof of the third ventricle or purely intraventricular tumors were included as were those with extension into the prepontine cistern. Reoperations and pediatric cases were excluded. Institutional review board approval from the local committee was obtained for this project.

Patient demographics, surgical outcomes, and clinical data including pathological, ophthalmological, and endocrinological assessments were collected and analyzed as of last clinical follow-up. Ophthalmological assessment consisted of neurosurgical evaluation as well as neuroophthalmological evaluation and formal visual field testing when possible. Endocrinological assessment consisted of neuroendocrine evaluation and pre- and postoperative studies of cortisol, adrenocorticotropic hormone, thyroid function, growth hormone, insulin-like growth factor–I, and prolactin. Complications were recorded for each surgery based on postoperative and follow-up visit reports, including cognitive loss, seizure, stroke, CSF leak, hemorrhage, meningitis, pulmonary embolism, and deep venous thrombosis.

Both EEA and TCA were performed by neurosurgeons considered experts in the field in each approach. Surgical TCAs and EEAs to pathologies in the suprasellar compartment were performed as previously described, either via an extended transplanum approach for the EEA or a pterional approach for the TCA.[4,22,28,30,37]

Radiological Analysis

Data from all patients included in this study were retrospectively analyzed by a certificate of added qualification (CAQ)–certified neuroradiologist (A.J.T.). Preoperative images were reviewed in GE PACS (General Electric) to evaluate tumor location, dimensions, proportions of cystic versus solid disease, volume of surrounding tumoral edema, and presence or absence of calcifications. Postoperative images were reviewed in GE PACS to evaluate extent of resection and edema volume. Quantitative analysis was performed using AW software (version 2.0 Ext 11.0, General Electric).

Preoperative enhancing tumor volume was assessed on the basis of MRI (24 of 26 patients) or CT scanning (2 of 26 patients). The preferred MRI sequence used for enhancement analysis was 3D spoiled gradient–recalled (SPGR) echo, T1-weighted (6.0/1.9 msec [TR/TE]), Gd-enhanced MR images with 1.0- or 1.5-mm section thickness (axial acquisition in 22 of 24 patients, coronal acquisition in 1 of 24 patients), obtained from either a 1.5-T or 3.0-T MR unit (SignaHDx, General Electric); in 1 patient a coronally acquired Gd-enhanced T1-weighted VIBE (volumetric interpolated breath-hold examination) sequence with 1.6-mm section thickness was obtained. Prior to 2/6/2013, the intravenous contrast agent used was Magnevist 0.2 ml/kg (Bayer HealthCare Pharmaceuticals Inc.). Thereafter, Gadavist 0.1 ml/kg was used (Bayer HealthCare Pharmaceuticals). The remaining 2 patients had preoperative CT images obtained using a 4- or 16-detector CT scanner (Lightspeed Qx/i and Lightspeed 16, General Electric), with 1.25-mm thickness. Tumor volume was measured using the "Quick Paint" tool in the aforementioned GE AW server software. Tumor volume was measured in total and then again including only the solid enhancing component; the volume of the cystic component was calculated by subtracting solid volume from total volume. Preoperative parenchymal edema volume was calculated using the "Auto Select" tool in the AW server software.

Surrounding tumoral edema was evaluated on 5-mm axial T2-weighted FLAIR images (9000/141 msec [TR/TE]) (available for all 24 patients who underwent MRI). Presence or absence of calcification was determined using the preoperative MRI study or a separate preoperative CT scan if available. CT scans were given priority for determining calcification, but if no CT scan was available, the MR susceptibility-weighted images or gradient-recalled echo images were evaluated. Some patients' records did not include initial CT, susceptibility-weighted, or gradient-

TABLE 1. Clinical characteristics

Characteristic	Endoscopic	Transcranial	p Value
No. of patients	21	5	
Age in yrs (mean ± SD)	50.9 ± 13.4	50.0 ± 25.2	0.92
Female sex (%)	16 (76.2)	3 (66.7)	0.48
Follow-up in mos (mean ± SD)	30.1 ± 28.9	56.8 ± 54.1	0.13
Pathology (no.)			
Adamantinomatous	7	3	0.29
Papillary	3	0	0.39
Not specified	11	2	
Presenting symptom (no.)			
Visual deficit	10	3	0.64
Endocrinopathy	2	0	0.49
Visual deficit + endocrinopathy	5	1	0.86
Headache/incidental	4	1	0.96

recalled echo images (10 of 26 patients), precluding assessment of calcification.

Extent of resection was determined via postoperative enhancement on postcontrast T1-weighted MR images (in 23 of 26 patients) or CT scans (in 3 of 26 patients, not overlapping with those patients without preoperative MR images) by using the "Quick Paint" tool for residual tumor. Where available, postoperative edema was quantified on the T2-weighted FLAIR images by using the "Auto Select" tool (same 23 of 26 cases with postcontrast T1-weighted images available).

Statistical Analysis

Outcome parameters were compared using the 2-tailed Student t-test or chi-square analysis; $p < 0.05$ was considered significant.

Results

Clinical Characteristics

Twenty-six cases met inclusion criteria, of a total 106 cases of pathologically confirmed craniopharyngioma performed in 79 unique patients during the studied time period. Of these, 21 craniopharyngiomas were resected via the EEA and 5 by the TCA. Demographic characteristics of the 2 groups (age, sex, follow-up time, pathology, and presenting symptoms) were not statistically different (Table 1). Mean age at presentation was 50.9 ± 13.4 years (EEA group) and 50.0 ± 25.2 years (TCA group) ($p = 0.92$), and the prevalence of females was also equivalent (76% vs 67%, respectively; $p = 0.48$). The mean duration of follow-up was 30.1 months for EEA patients and 56.8 months for TCA patients ($p = 0.13$). The most common presenting symptom was visual loss, with or without endocrinopathy, in both groups (71% and 80% in EEA and TCA groups, respectively).

Tumor Characteristics and Surgical Outcomes

Twenty-one EEA and 5 TCA patients had images available for volumetric analysis (Table 2). There was a trend toward larger mean preoperative volume of enhancement in the TCA group than the EEA group (13.9 ± 7.8 cm^3 vs 8.5 ± 5.9 cm^3, respectively; $p = 0.10$). Radiological characteristics were otherwise equivalent, including volume of surrounding FLAIR, proportion of nonenhancing (cystic) disease, presence of mineralization, and anatomical delineation. Forty percent of tumors in either group extended beyond the suprasellar cistern over the dorsum sella or prepontine cistern.

The mean EOR was not significantly different between the groups (99.7 ± 1.3 for EEA vs 98.6 ± 2.1 for TCA cases, $p = 0.15$; Table 3). However, GTR was achieved in 90% of EEA cases and 40% of the open cohort ($p = 0.009$; Figs. 1 and 2). A significantly lower increase in FLAIR signal postoperatively was also seen in EEA cases than in TCA cases (–0.16 ± 4.5 cm^3 vs 14.4 ± 14.0 cm^3, respectively; $p = 0.0005$). Despite a larger proportion of post-TCA resection lesions receiving adjuvant radiotherapy (60% vs 10%), these tumors recurred at a higher rate (60% vs 0%; $p < 0.0001$). Operative time was equivalent between the groups, while length of hospital stay trended toward being shorter in patients who underwent EEA ($p = 0.11$).

Neurological Outcomes

More patients experienced visual improvement in the EEA group than in the TCA group (63% vs 0%, $p = 0.025$; Table 4). One patient with normal preoperative vision experienced postoperative visual decline, but no difference

TABLE 2. Summary of preoperative radiological characteristics

Characteristic	EEA	TCA	p Value
Vol of enhancement (cm^3)	8.5 ± 5.9 (n = 21)	13.9 ± 7.8 (n = 5)	0.10
Vol of FLAIR signal (cm^3)*	3.6 ± 4.0 (n = 18)	1.0 ± 1.7 (n = 5)	0.17
Cystic proportion	0.64 ± 0.28 (n = 21)	0.64 ± 0.35 (n = 5)	1.0
Microcalcification (no. of cases)*	10/15	1/3	0.31
Anatomical bounds			
Suprasellar cistern (no. of cases)	12	3	
+ sellar	4	1	
+ prepontine	4	0	
+ sellar + prepontine	1	0	
+ sellar + prepontine + subraorbital	0	1	

* Note: cases for which radiographic determinations are less than total cohort reflect availability of relevant imaging.

TABLE 3. Summary of surgical outcomes

Variable	EEA	TCA	p Value
EOR (%)	99.7 ± 1.3 (n = 21)	98.6 ± 2.1 (n = 5)	0.15
GTR	19/21 (90%)	2/5 (40%)	0.009
NTR	2/21 (10%)	3/5 (60%)	
Change in FLAIR vol (cm^3)	−0.16 ± 4.6	14.4 ± 14.0	0.0005
Adjuvant radiation	2/21	3/5	0.002
Recurrence	0/21	3/5	<0.0001
Re-resection	0/21	2/5 (21–82 mos postop)	
Op time (mins)	407 ± 53	398 ± 151	0.83
LOS (days)	9.3 ± 6.6	15.0 ± 7.9	0.11

LOS = length of stay; NTR = near-total resection (≥ 90%).

was found between the 2 groups in terms of worsening vision (2 of 20 patients in the EEA group vs 0 of 5 in the TCA group; p = 0.48).

No statistical differences were seen between EEA and TCA groups in terms of endocrinological outcome. Endocrinopathy included panhypopituitary syndrome in 11 of 15 symptomatic EEA patients and 2 of 4 TCA patients, and diabetes insipidus and isolated prolactinemia accounted for the remainder of cases.

There were significantly more complication events in the TCA group compared with the EEA group (4 [80%] of 5 in the TCA group vs 4 [20%] of 20 patients in the EEA group, p = 0.009; Table 5). Significantly more TCA patients suffered postoperative cognitive loss (80% vs 0; p < 0.0001) and aseptic meningitis (20% vs 0; p < 0.05), while other complications including stroke, hemorrhage, and infectious and thromboembolic events did not differ between groups. There were no seizures or deaths related to either procedure.

Discussion

The mainstay of craniopharyngioma management has been excisional cytoreduction, with an initial attempt at GTR if possible, followed by adjuvant irradiation in the case of subtotal resection or recurrence. Tumors often surround critical neurovascular structures including the optic apparatus and hypothalamic-pituitary axis, leading to a high risk for invasion, subtotal resection, iatrogenic injury, and a recurrence rate in the range of 20%–50%.[18,33] Traditional TCAs, including those involving the pterional transsylvian, subfrontal, and interhemispheric corridors, offer direct access to the suprasellar/parasellar compartments and are particularly effective for removal of tumors that extend laterally into the middle fossa beyond the supraclinoid ICA. These approaches are also associated with morbidity, however, owing to the relatively long corridor requiring lobar retraction, late visualization of the infundibulum and optic chiasm, brain retraction leading to encephalomalacia, and the frequent need for reoperation in the setting of progressive disease.

Over the last 10 years, extended EEAs have been successfully employed in an increasing array of anterior cranial base compartments, with endoscopy frequently offered in the treatment of lesions arising from the tuberculum sella/planum sphenoidale, olfactory groove/cribriform plate, petroclival ridge, and in Meckel's cave and beyond.[7,25] Early technical limitations resulting in a historical association with CSF leaks have largely been eliminated at many centers employing strategies including vascularized nasoseptal flaps, intrathecal dye injection, and multilayer closure techniques.[26] Transtuberculum-transplanum corridors to the suprasellar cistern and third ventricle are among the most recent extensions of the EEA, with technique centered on careful negotiation of the optic nerves, chiasm, pituitary gland, and infundibulum, as well as on successful closure of high-flow CSF leaks.

Controversy remains as to the optimal surgical treatment of craniopharyngioma, with the literature limited by selection bias. While one large population-based study demonstrated an association between subtotal resection and prolonged survival, reduced recurrence rates are generally associated with achievement of GTR in the reported literature.[11,31–33,38]

In the present series, we sought to directly compare outcomes of patients with lesions ultimately resected via either a pterional or EEA route at a center experienced in both skull base approaches. To reduce the selection bias inherently limiting retrospective review, cases fitting strict anatomical criteria were presented to 4 blinded neurosurgeons who had to exhibit equipoise, from the perspectives of accessibility, ability to achieve GTR, and knowledge of predicted morbidity, prior to case inclusion into the study. One limitation of the study is that there was a trend

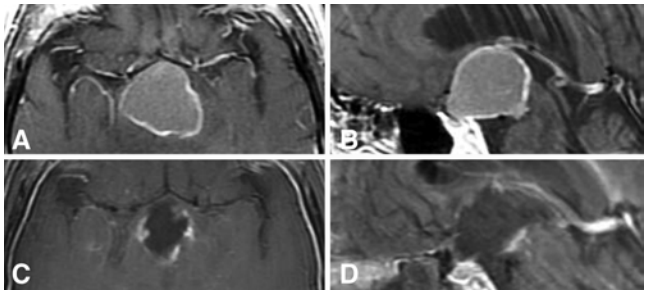

FIG. 1. Representative GTR achieved via an EEA. Gadolinium-enhanced T1-weighted preoperative (*upper*) and postoperative (*lower*) MR images demonstrate complete tumor removal on axial sequences (**A and C**) and sagittal reconstructions (**B and D**).

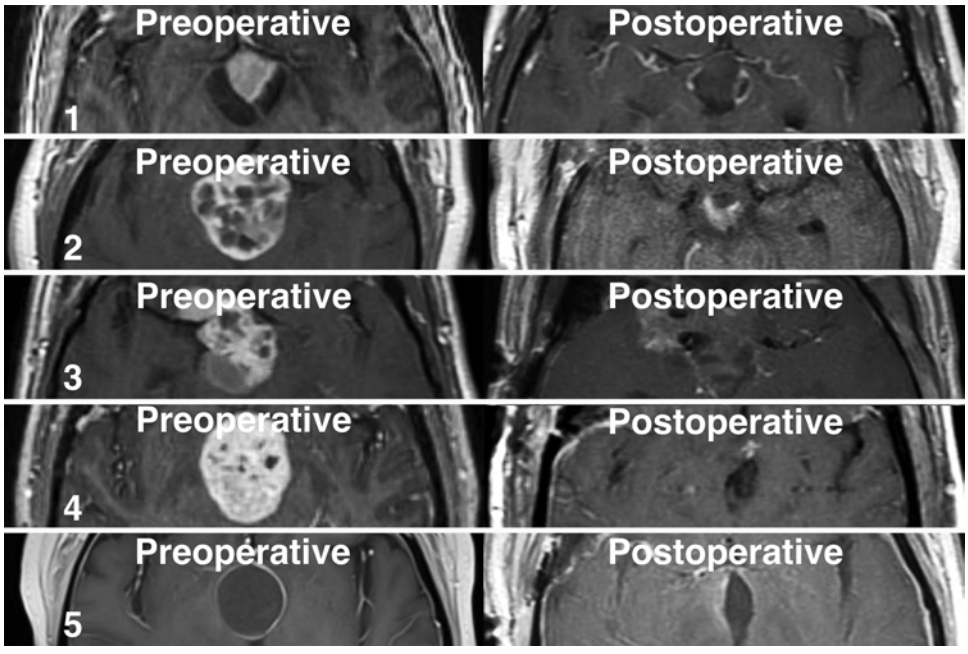

FIG. 2. Preoperative and postoperative Gd-enhanced T1-weighted MR images of near-total resections. Patients 1 and 2 underwent an EEA, while Patients 3–5 underwent a TCA.

toward larger tumors being removed through a TCA, although this did not reach statistical significance ($p = 0.10$). Moreover, since a different surgeon did the TCA than did the EEA, cases were not chosen for one or the other approach based on tumor characteristics but rather the randomness of referrals. Another limitation is that there were more cases in the EEA group. However, only statistically significant results were highlighted, indicating that groups were adequately powered. One final limitation is that we did not examine nasal complications such as crusting, anosmia, or persistent drainage. However, a prior study on nasal quality of life showed stability and even a trend toward improved nasal quality of life after EEA surgery for craniopharyngiomas.[27]

Our data clearly demonstrate a higher rate of GTR, a higher rate of visual improvement, and an increased safety profile for EEA compared with TCA in the subgroup of patients amenable to GTR by EEA. It is important to understand that the results of this study do not suggest that all craniopharyngiomas should be removed through an EEA and not a TCA but, rather, that for those tumors amenable to GTR through EEA, outcomes may be better when using the EEA. Moreover, differences were not found with respect to hormone preservation or rates of diabetes insipidus, which were equivalent for both approaches. Hence, these outcome measures should not be promoted as advantages of the EEA.

While our series demonstrates a clear advantage of an EEA in a small selected cohort of matched cases predicted to be amenable to either approach, it is important to contextualize these data among other series that show more favorable absolute resection and morbidity outcomes with the TCA. Several series demonstrate GTR rates above 50%, with many approaching 90% while preserving neurological safety.[6,9,11–14,29,32,34,36] In a meta-analysis of pediatric craniopharyngiomas, Elliott et al. demonstrated a transcranial GTR rate of 61% in 2955 children, with a 9% rate of neurological morbidity and a 48% rate of improvement in those with baseline visual deficits.[10] It is also important to note that while our transcranial GTR rate was significantly lower than that shown in other published series, we still achieved > 98% resection in either group. Our emphasis is on reporting even minute residual disease with the knowledge that GTR is an important modifier of this disease, when achieved safely.

The results of this study are comparable to those presented in unmatched comparative series with larger numbers of patients, albeit with a lower rate of CSF leak due to the development of secure methods of closing the skull base like the gasket seal and our use of intrathecal fluorescein.[26] In Elliott et al.'s meta-analysis of pediatric cra-

TABLE 4. Summary of neurological outcomes

Outcome	EEA	TCA	p Value
Vision			
Improved	10/16 w/ deficit	0/4 w/ deficit	0.025
Stable	8/20*	5/5	0.015
Worsened	2/20	0/5	0.48
Endocrinopathy			
Improved	1/7	0/1	1.0
Stable	4/20	1/5	1.0
Worsened	15/20†	4/5‡	0.82

* Denominator reflects 1 EEA patient lost to follow-up. One of 2 patients with worsened vision postoperatively had a preoperative visual deficit.
† Eleven patients with panhypopituitarism, 3 with diabetes insipidus, and 1 with hyperprolactinemia.
‡ Two patients with panhypopituitarism and 2 with diabetes insipidus.

TABLE 5. Surgical complications

Complication	No. of Patients (%)		p Value
	EEA (n = 20)	TCA (n = 5)	
Cognitive deficit	0	4 (80)	<0.0001
Stroke	2 (10)	0	0.48
CSF leak	1 (5)	0	0.63
Hemorrhage	1 (5)	1 (20)	0.29
Meningitis (aseptic)	0	1 (20)	0.04
DVT	1 (5)	0	0.63
PE	1 (5)	0	0.63

DVT = deep venous thrombosis; PE = pulmonary embolism.

niopharyngiomas, TCA was performed on larger tumors but resulted in lower rates of GTR and higher neurological and endocrinological morbidity compared with EEA.[10] A similar series including 3470 adult and pediatric craniopharyngiomas demonstrated an increased rate of GTR (67% with EEA vs 48% with TCA; $p < 0.003$), improved visual outcome (56% with EEA vs 33% with TCA), but an increased rate of CSF leak (18% with EEA vs 3% with TCA; $p < 0.003$).[19]

Others have additionally shown the utility of EEA for the recurrent disease or staged residual resection.[5,8,17] Together, these data support the use of EEA for the upfront treatment of amenable craniopharyngiomas via a purely endoscopic approach. Though some institutions now advocate the use of endoscopy for the treatment of every craniopharyngioma, we still believe in the reservation of transcranial staging for tumors with significant middle fossa, ambient, or third ventricular roof disease.[20] Considerations or relative contraindications also include a poorly pneumatized sphenoid sinus, sinus pathology precluding endoscopy or inability to raise a vascularized flap, and a narrow intercarotid distance.[4] While a prospective trial is unlikely, further long-term data will elucidate any oncological outcome differences in this challenging disease.

Conclusions

An EEA is potentially preferable to a TCA for tumors amenable to GTR through an EEA. Our study reports higher rates of GTR and visual improvement with fewer complications and less retraction injury to the brain when using an EEA.

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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: Schwartz, Moussazadeh, Prabhu, Anand. Acquisition of data: Prabhu, Bander, Cusic, Tsiouris. Analysis and interpretation of data: Schwartz, Moussazadeh, Bander, Cusic, Tsiouris. Drafting the article: Moussazadeh. Critically revising the article: Schwartz, Moussazadeh, Bander, Cusic. Reviewed submitted version of manuscript: all authors. Statistical analysis: Moussazadeh. Study supervision: Schwartz, Anand.

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