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CLINICAL ARTICLE

Endoscopic endonasal versus transcranial surgery for primary resection of craniopharyngiomas based on a new QST classification system: a comparative series of 315 patients

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OBJECTIVE An assessment of the transcranial approach (TCA) and the endoscopic endonasal approach (EEA) for craniopharyngiomas (CPs) according to tumor types has not been reported. The aim of this study was to evaluate both surgical approaches for different types of CPs.

METHODS A retrospective review of primary resected CPs was performed. A QST classification system based on tumor origin was used to classify tumors into 3 types as follows: infrasellar/subdiaphragmatic CPs (Q-CPs), subarachnoidal CPs (S-CPs), and pars tuberalis CPs (T-CPs). Within each tumor type, patients were further arranged into two groups: those treated via the TCA and those treated via the EEA. Patient and tumor characteristics, surgical outcomes, and postoperative complications were obtained. All variables were statistically analyzed between surgical groups for each tumor type.

RESULTS A total of 315 patients were included in this series, of whom 87 were identified with Q-CPs (49 treated via TCA and 38 via EEA); 56 with S-CPs (36 treated via TCA and 20 via EEA); and 172 with T-CPs (105 treated via TCA and 67 via EEA). Patient and tumor characteristics were equivalent between both surgical groups in each tumor type. The overall gross-total resection rate (90.5% TCA vs 91.2% EEA, $p = 0.85$) and recurrence rate (8.9% TCA vs 6.4% EEA, $p = 0.35$) were similar between surgical groups. The EEA group had a greater chance of visual improvement (61.6% vs 35.8%, $p = 0.01$) and a decreased risk of visual deterioration (1.6% vs 11.0%, $p < 0.001$). Of the patients with T-CPs, postoperative hypothalamic status was better in the TCA group than in the EEA group ($p = 0.016$). Postoperative CSF leaks and nasal complication rates occurred more frequently in the EEA group (12.0% vs 0.5%, and 9.6% vs 0.5%; both $p < 0.001$). For Q-CPs, EEA was associated with an increased gross-total resection rate (97.4% vs 85.7%, $p = 0.017$), decreased recurrence rate (2.6% vs 12.2%, $p = 0.001$), and lower new hypopituitarism rate (28.9% vs 57.1%, $p = 0.008$). The recurrence-free survival in patients with Q-CPs was also significantly different between surgical groups (log-rank test, $p = 0.037$). The EEA required longer surgical time for T-CPs ($p = 0.01$).

CONCLUSIONS CPs could be effectively treated by radical surgery with favorable results. Both TCA and EEA have their advantages and limitations when used to manage different types of tumors. Individualized surgical strategies based on tumor growth patterns are mandatory to achieve optimal outcomes.

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KEYWORDS classification; complications; craniopharyngioma; craniotomy; endonasal; endoscopic; outcomes; pituitary surgery

ABBREVIATIONS CP = craniopharyngioma; DI = diabetes insipidus; EEA = endoscopic endonasal approach; EOR = extent of resection; GTR = gross-total resection; NTR = near-total resection; Q-CP = infrasellar/subdiaphragmatic CP; RFS = recurrence-free survival; S-CP = subarachnoidal CP; STR = subtotal resection; TCA = transcranial approach; T-CP = pars tuberalis CP.

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Craniopharyngiomas (CPs) are thought to originate from ectodermal remnants of Rathke's pouch.[1] They account for 2%–5% of primary intracranial tumors.[2] Although histologically benign, CPs pose a great challenge to the neurosurgeon due to their close relationship with the hypothalamus, pituitary, and vital vessels. Surgery remains the mainstay of treatment and radical resection maximizes the potential for oncological cure,[3–6] although some authors have suggested subtotal resection (STR) followed by adjuvant radiotherapy to avoid placing the critical structures at risk.[7–10] Advances in surgical techniques have allowed for safe tumor removal, with the gross-total resection (GTR) rates ranging from 68.9% to 89.6%.[11–14]

The traditional transcranial approach (TCA) offers direct access to the suprasellar/parasellar compartments and is particularly effective for tumors extending laterally beyond the bifurcation of internal carotid arteries.[15] The TCA requires brain retraction, and the optic apparatus as well as vital vessels often requires manipulation for tumor exposure.[6,16–18] Direct visualization of these tumors may be difficult due to their deep location behind the optic chiasm and upward extension toward the third ventricle.[19] Over the last decade, the refinement of the endoscopic endonasal approach (EEA) has provided an alternative route for tumor removal. The EEA avoids brain retraction, provides direct visualization of the retrochiasmatic compartment, and is especially suitable for prefixed chiasmatic tumors with upward extension.[20–22]

According to the literature,[15,19,23] few series comparing TCA and EEA for CPs have been reported, and the sample sizes are relatively small, reducing the statistical power for outcome analysis. Moreover, tumor type is a considerable factor affecting the surgical strategy, suggesting that studies based on tumor types are necessary for more accurate assessment of approaches. However, to our knowledge none of current studies compared surgical approaches in different types of CP. Therefore, we used our new QST classification system in this study to evaluate the outcomes of different types of primary CPs treated by TCA or EEA, and thereby provide more convincing evidence regarding the optimal approach for an individual patient.

Methods

Study Design, Setting, and Participants

All patients with CPs that were histologically identified and surgically treated at our institution between 2006 and 2016 were retrospectively reviewed. Patients with recurrent tumors and/or who had radiotherapy were excluded to avoid confounding bias. Patients with incomplete records or loss to follow-up were also excluded to reduce the bias.

A new QST classification based on tumor origin and preoperative radiological evaluation was used to specify the tumor type of enrolled patients.[24,25] All tumors were classified into 3 types as follows: 1) Q-CPs arise from the subdiaphragmatic infrasellar space with an enlarged pituitary fossa, and the gland is scarcely recognizable; 2) S-CPs arise from the middle or inferior segment of the stalk and tend to extend among cisterns, and the entire stalk can be recognized on MRI; and 3) T-CPs arise in the top of the pars tuberalis, mainly extend upward, and occupy the space of the third ventricle. The lower segment of the stalk in this third type of CP can usually be identified on MRI (Fig. 1). Two senior neurosurgeons classified the tumors by reviewing preoperative MRI in a blinded fashion. If they failed to reach consensus, a third neurosurgeon was assigned to make the final decision. Finally, patients with each tumor type were arranged into two groups: those treated via the TCA and those treated via the EEA. The study was approved by the institutional review board. Given its retrospective nature, no informed consent was required. The manuscript conforms to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.

Variables and Data Sources

All variables were collected from a prospectively maintained database. Each patient's age, sex, history, presenting symptoms, hormonal status, vision examination, operative time, and imaging data were reviewed. Tumor volumes were measured on preoperative MRI by using the following equation: tumor volume = $(A \times B \times C)/2$, where A, B, and C represent the maximal diameters of tumor in three orthogonal planes. Tumor consistency (solid, cystic, or mixed) was identified by MRI. Extent of resection (EOR) was determined by immediate MRI review within 48 hours after surgery by an independent neuroradiologist. Accordingly, GTR was defined as 100% macroscopic tumor resection, near-total resection (NTR) was defined as ≥ 95% but < 100% resection, STR was defined as ≥ 80% but < 95% resection, and partial resection was defined as < 80% resection.

Postoperative surgical outcomes were reviewed in each patient, including pathological reports, visual status, endocrine assessment, hypothalamic status, complications, follow-up period, and recurrences. Follow-up MRI sessions were scheduled at 3 and 9 months postoperatively and then annually thereafter. Postoperative hypopituitarism refers to newly developed hypopituitarism. If a patient had a preexisting hormone deficit, worsened endocrine status (e.g., hormone deficit in more axes) was also regarded as new hypopituitarism. Pituitary function was monitored by hormone level assessment at 1, 3, and 6 months after surgery, and then every 6 months thereafter. Postoperative hypothalamic disturbance, including weight gain, hyperphagia, memory deficits, thermoregulatory abnormalities, emotionally labile behavior, and sleep-wake cycle disruption, was also evaluated and recorded at least 3 months after surgery. The patients' hypothalamic status was evaluated using a 4-tiered grading scale (hypothalamic status score) as follows: grade 1, normal hypothalamic function; grade 2, overweight ($24 < \text{BMI} \leq 28$) and lack of behavior indicative of hypothalamic dysfunction; grade 3, obesity (BMI > 28) or weight gain without hyperphagia or an associated change in affective behavior or memory; and grade 4, obesity (BMI > 28) and hyperphagia with cognitive dysfunction, rage behavior, and impaired thirst or disturbances of thermoregulation concomitant with sleep-wake disruption or extreme emaciation.[25]

Statistical Analysis

A Student t-test or ANOVA was used to compare con-

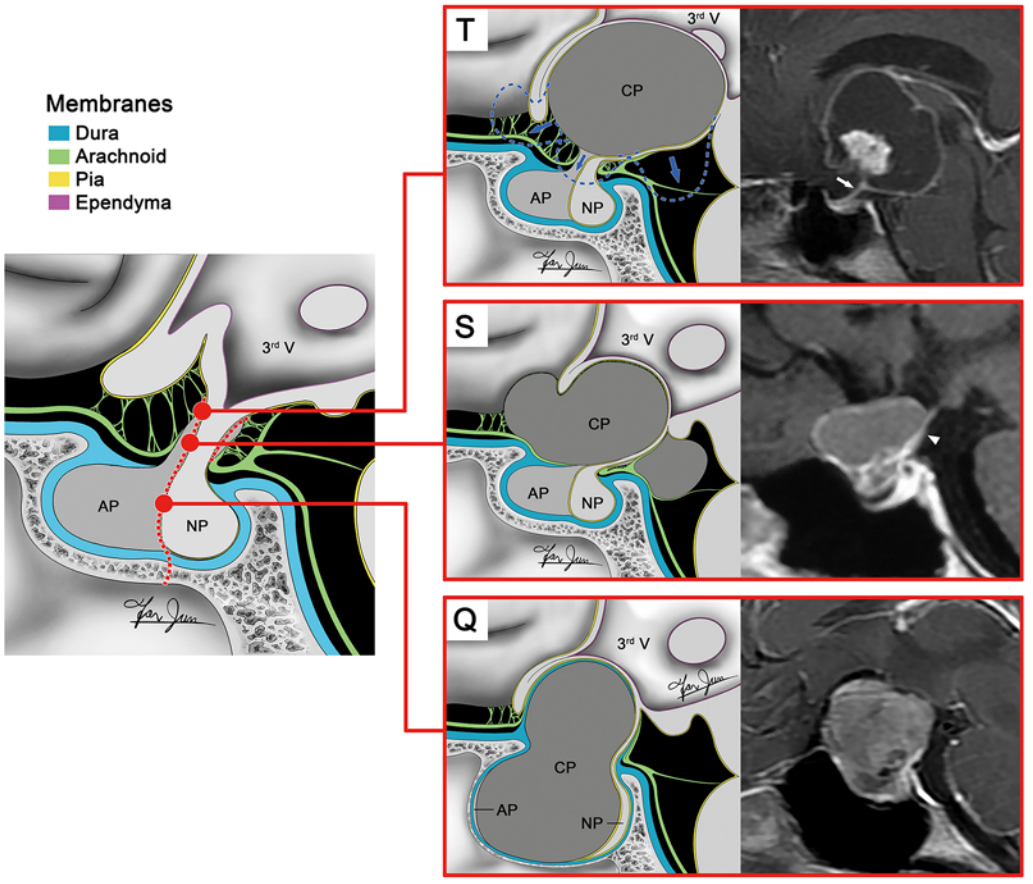

FIG. 1. Schematics demonstrating the QST classification of CPs (**left and center columns**). CPs are thought to originate from ectodermal remnants of Rathke's pouch (*red dashed line*). The QST classification system is established based on tumor origin (*red dots*) and surrounding membranous (dura, diaphragma, arachnoid, and pia) and neurovascular structures. **T, S, and Q:** Illustrations (center column) and corresponding postcontrast T1-weighted MRI examples (**right column**) showing 3 types of tumors according to QST classification: T-CPs (panel T), S-CPs (panel S), and Q-CPs (panel Q). As shown in panel T, T-CPs arise from residual Rathke's pouch precursor cells in the top of the pars tuberalis, mainly extend upward, and present a close relationship to the third ventricular floor/hypothalamus. The lower segment of the pituitary stalk (right column, *white arrow*) can often be identified on MRI. In some cases, tumors may extend into subarachnoid cisterns (center column, *blue arrows and dashed line*). As shown in panel S, S-CPs arise from the middle or inferior segment of the stalk and tend to extend among the subarachnoid cisterns. The entire stalk (*white arrowhead*) can usually be recognized on MRI. As shown in panel Q, Q-CPs arise from the subdiaphragmatic intrasellar space and tightly adhere to surrounding residual gland. Typically, MRI shows an enlarged pituitary fossa and the gland is scarcely recognizable. The suprasellar portion of these tumors, however, is separated from surrounding critical structures by several membranous layers (diaphragma, basal arachnoid membrane, and bundles of trabecular arachnoid). AP = adenohypophysis; NP = neurohypophysis; 3rd V = third ventricle. Copyright Jun Fan. Published with permission. Figure is available in color online only.

tinuous variables. Independent categorical variables were compared by use of the chi-square test or Fisher's exact test. The Mann-Whitney U-test was used to compare nonparametric variables between groups. The recurrence-free survival (RFS) curves were generated using the Kaplan-Meier method, and differences of recurrence rates in each group were evaluated using the log-rank test. All statistical analyses were performed using IBM SPSS version 21.0 (IBM Corp.). The data were expressed as the mean ± SD. A p value ≤ 0.05 was considered to be statistically significant.

Results

A total of 547 patients with CPs were identified at our institution between 2006 and 2016. Of these, 213 patients with recurrent tumors and/or radiotherapy and 19 patients with incomplete data or loss to follow-up were excluded from the analysis. Ultimately, 315 patients were included in this study. Enrolled cases were classified into subtypes according to QST classification and then arranged into two surgical groups separately: 87 patients were identified with Q-CPs (49 treated via TCA and 38 via EEA); 56 with S-CPs (36 treated via TCA and 20 via EEA); and 172 with T-CPs (105 treated via TCA and 67 via EEA) (Fig. 2). Complete concordance on tumor type between two reviewers working in a blinded fashion was noted in 96.8% of enrolled cases.

Patient and Tumor Characteristics

No significant demographic differences in age, sex, or

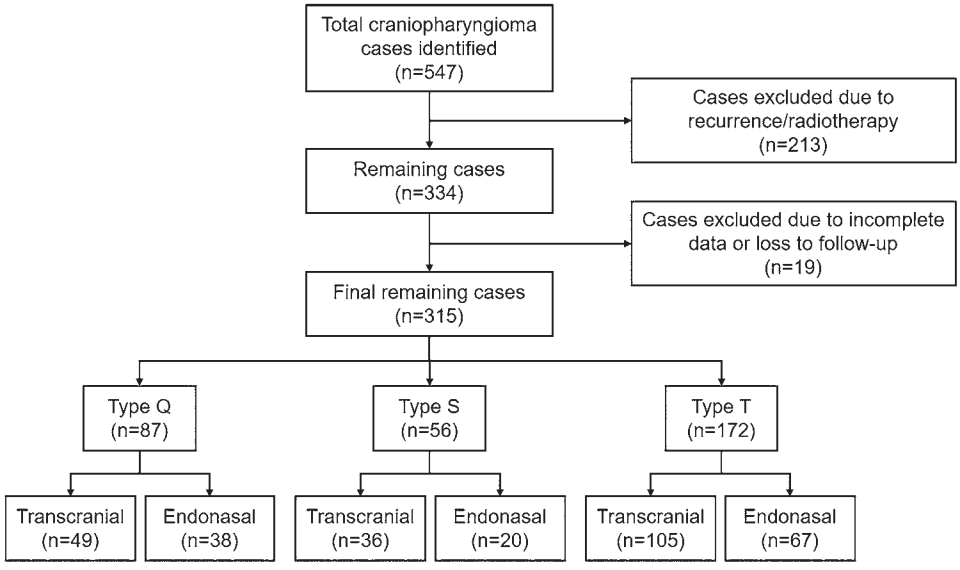

FIG. 2. Flow diagram demonstrating case identification and exclusion to achieve final surgical group numbers.

presenting symptoms were identified between TCA and EEA groups in any of the tumor types. Q-CPs occurred predominantly in children, whereas S-CPs and T-CPs were more frequently observed in adults. Visual disturbance represented the most frequent presenting symptom in both groups, and headache was the second most common preoperative complaint, followed by hypopituitarism and then diabetes insipidus (DI) (Table 1). The tumor volumes and the consistency of any tumor type were not significantly different between surgical groups. According to pathological reports, adamantinomatous CPs were the predominant type in both TCA and EEA groups; no significant group differences were detected (Table 1).

Surgical Outcomes

All surgical procedures were performed by three senior surgeons who specialized in both endonasal and transcranial skull base surgery. Of the TCA cases, 57.4% were treated via a bifrontal basal interhemispheric approach, 27.9% via a pterional approach, and 14.7% via combined or other approaches. Within the EEA cases, all patients underwent a transsphenoidal/transtuberculum approach. In 85.6% of cases, closure used a multilayer reconstruction technique with a pedicled nasoseptal flap. A free graft including fascia lata or middle turbinate flap was used for closure in the remaining cases. An analysis of surgical trends over time shows a dramatic shift in surgical methods between 2006 and 2016. The cases treated via the endonasal approach increased stably, whereas the number of craniotomies decreased, due to increasing experience in endonasal surgery and innovation of instrumentation (Fig. 3).

The GTR rate of all tumor types was not significantly different between the TCA and EEA groups (90.5% vs 91.2%, $p = 0.85$). Specifically, however, the GTR rate of Q-CPs was higher in the EEA group (97.4% vs 85.7%, $p = 0.017$). For S-CPs and T-CPs, the rates were similar between the two surgical groups. Due to our radical surgical strategy, no patient underwent partial resection. The overall mean operative time was also equivalent between groups, whereas EEA for T-CPs was associated with a longer operative time ($p = 0.01$) (Table 2).

The improved visual outcome of the entire cohort occurred more commonly in the EEA group regardless of tumor types (61.6% vs 35.8%, $p = 0.01$). Similarly, transcranial surgery had a greater risk of damage to visual function in all tumor types (11.1% vs 1.6%, $p < 0.001$) (Table 2).

The overall postoperative hypothalamic status was not significantly different between the two surgical approaches ($p = 0.63$). However, the patients with T-CPs treated by craniotomy had a better postoperative hypothalamic status than those treated by endonasal surgery, with 38.1% and 59.7% of patients scoring grade 3 or 4, respectively, for hypothalamic status ($p = 0.016$) (Table 2). For patients with Q-CPs or S-CPs, no significant differences in postoperative hypothalamic status were detected between surgical groups.

The mean follow-ups in patients with each tumor type were similar between the TCA and EEA groups. Recurrence was noted in 25 patients during the follow-up, and the mean time to recurrence was 26 months (range 12–113 months) after surgery. Of the 25 recurrent cases, 17 underwent a repeated surgery, 5 received adjuvant radiotherapy at other institutions, and 3 refused treatment. The overall recurrence rate regardless of tumor type was not significantly different between the two surgical cohorts. However, for Q-CPs the EEA had a lower recurrence rate than the TCA (2.6% vs 12.2%, $p = 0.001$). For S-CPs and T-CPs, no significant difference of the recurrence rates was detected between the two surgical groups (Table 2). Additionally, Kaplan-Meier curves were constructed for the RFS for both surgical groups in patients with each tumor type. For patients with Q-CPs, there was a significant difference in RFS between TCA and EEA groups (log-rank test, $p = 0.037$). No significant difference in the RFS curves of patients with S-CPs or T-CPs was noted between surgical groups based on the log-rank test (Fig. 4).

TABLE 1. Clinical and tumor characteristics in 315 patients with 3 types of CPs

Variable	Type Q			Type S			Type T			All Types		
	TCA, n = 49	EEA, n = 38	p Value	TCA, n = 36	EEA, n = 20	p Value	TCA, n = 105	EEA, n = 67	p Value	TCA, n = 190	EEA, n = 125	p Value
Age in yrs												
Mean	24.6 ± 19.7	26.5 ± 18.1	0.67	47.1 ± 13.2	46.9 ± 13.8	>0.99	42.3 ± 16.5	42.8 ± 15.3	>0.99	40.9 ± 16.2	42.5 ± 15.8	0.87
Range	4–63	4–67		8–72	10–68		2–68	2–71		2–72	2–71	
Children, ≤16 yrs	37 (75.5%)	29 (76.3%)	0.83	7 (19.4%)	4 (20.0%)	>0.99	36 (34.3%)	23 (34.3%)	>0.99	80 (42.1%)	56 (44.8%)	0.74
Adults, >16 yrs	12 (24.5%)	9 (23.7%)	0.92	29 (80.6%)	16 (80.0%)	>0.99	69 (65.7%)	44 (65.7%)	>0.99	110 (57.9%)	69 (55.2%)	0.65
Female sex	18 (36.7%)	15 (39.5%)	0.73	17 (47.2%)	9 (45.0%)	0.88	43 (41.0%)	29 (43.3%)	0.82	78 (41.1%)	53 (42.4%)	0.79
Follow-up in mos												
Mean	86.3 ± 32.6	88.7 ± 29.6	0.47	88.5 ± 31.1	86.7 ± 29.8	>0.99	92.6 ± 29.9	83.8 ± 31.5	0.21	90.1 ± 32.2	84.6 ± 30.2	0.53
Range	28–142	32–136		33–135	27–128		32–144	30–126		28–144	27–128	
Presenting symptom												
Headache	22 (44.9%)	16 (42.1%)	0.75	12 (33.3%)	6 (30.0%)	0.69	66 (62.9%)	40 (59.7%)	0.45	100 (52.6%)	62 (49.6%)	0.57
Visual disturbance	42 (85.7%)	33 (86.8%)	0.83	29 (80.6%)	17 (85.0%)	0.37	53 (50.5%)	34 (50.7%)	>0.99	124 (65.3%)	84 (67.2%)	0.92
Hypopituitarism	28 (57.1%)	24 (63.2%)	0.47	5 (13.9%)	2 (10.0%)	0.35	30 (28.6%)	18 (26.9%)	0.79	63 (33.2%)	44 (35.2%)	0.68
DI	16 (32.7%)	13 (34.2%)	0.75	4 (11.1%)	1 (5.0%)	0.32	11 (10.5%)	8 (11.9%)	0.83	31 (16.3%)	22 (17.6%)	0.61
Tumor vol in cm^3	31.5 ± 10.3	26.9 ± 8.1	0.45	41.7 ± 20.3	33.5 ± 13.6	0.27	33.9 ± 14.2	29.8 ± 9.3	0.39	33.3 ± 12.8	26.6 ± 9.1	0.35
Tumor consistency												
Cystic	9 (18.4%)	8 (21.0%)	0.37	9 (25.0%)	4 (20.0%)	0.51	24 (22.8%)	16 (23.9%)	0.75	42 (22.1%)	28 (22.4%)	>0.99
Solid	3 (6.1%)	3 (7.9%)	0.67	4 (11.1%)	3 (15.0%)	0.29	13 (12.4%)	8 (11.9%)	0.9	20 (10.5%)	14 (11.2%)	0.87
Mixed	37 (75.5%)	27 (71.1%)	0.37	23 (63.9%)	13 (65.0%)	0.83	68 (64.8%)	43 (64.2%)	>0.99	128 (67.4%)	83 (66.4%)	0.93
Pathological type												
Adamantinomatous	35 (71.4%)	29 (76.3%)	0.41	27 (75.0%)	15 (75.0%)	>0.99	78 (74.3%)	54 (80.6%)	0.61	140 (73.7%)	98 (78.4%)	0.89
Papillary	14 (28.6%)	9 (23.7%)	0.48	9 (25.0%)	5 (25.0%)	>0.99	27 (25.7%)	13 (19.4%)	0.28	50 (26.3%)	27 (21.6%)	0.57

Unless otherwise indicated, values are expressed as the number (%) or the mean ± SD.

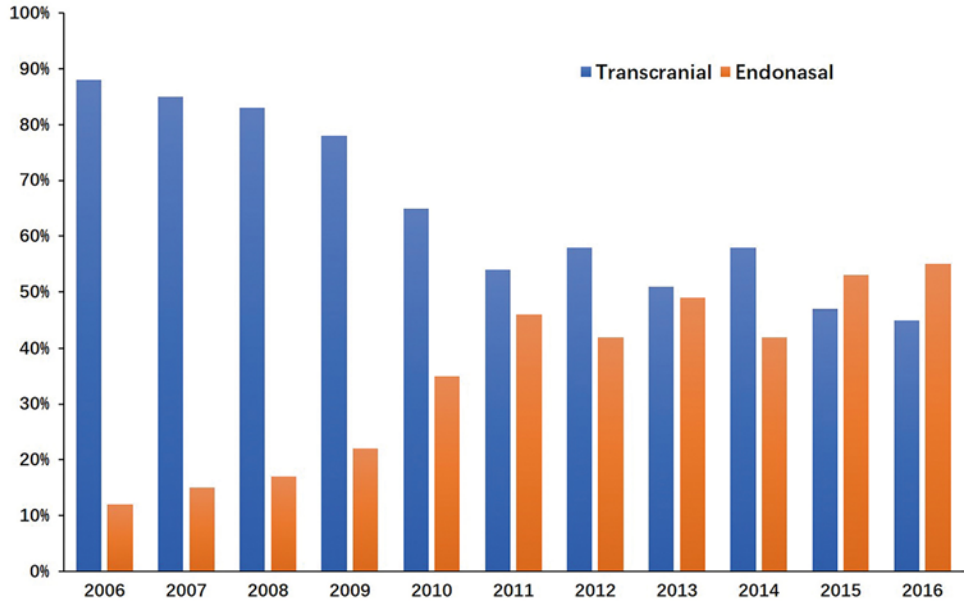

FIG. 3. Bar graph showing percentage of cases treated by craniotomy versus endonasal surgery between 2006 and 2016. Figure is available in color online only.

Complications

Permanent DI represented the most frequent complication, without significant differences in any of the tumor types between TCA and EEA groups. However, the rate of new hypopituitarism (including partial and panhypopituitarism) in Q-CPs resected via the TCA was higher than that in Q-CPs resected via the EEA (57.1% vs 28.9%, $p = 0.008$). CSF leaks were more common in the EEA group in all 3 tumor types (Q-CPs: 10.5% vs 2.0%, $p = 0.02$; S-CPs: 10.0% vs 0%, $p < 0.001$; T-CPs: 13.4% vs 0%, $p < 0.001$). Most of these patients recovered after receiving conservative treatment—only 2 underwent surgical repair. A higher incidence of nasal complications, including crusting, anosmia, or persistent drainage, was observed in the EEA group (9.6% vs 0.5%, $p < 0.001$). The mortality rate was 2.6% in the TCA group and 2.4% in the EEA group ($p = 0.72$). Major contributors associated with mortality included severe hypothalamic dysfunction, progressive cerebral infarction, multidrug-resistant meningitis and/or pneumonia, pulmonary embolism, and cardiovascular accident. Other complications were similar between the two surgical groups in all tumor types (Table 3).

Discussion

Patient and Tumor Characteristics

For all tumor types, the patient and tumor characteristics were equivalent between the endonasal and transcranial groups. All recurrent cases and cases in which patients were treated with radiotherapy were excluded from our series to eliminate interference factors caused by increased surgical difficulty, confusion about tumor type, or existing neurological deficits associated with previous surgery and/or radiotherapy. Additionally, either the tumor volume or the sample size in our cohort is larger than in previously reported comparative studies,[15,19,23] increasing the power to detect the differences in variables.

Extent of Resection

The EOR for CPs remains controversial, although numerous studies have demonstrated an association between GTR and reduced recurrences or improved long-term outcomes.[3–6,16,26–28] In our experience, radiotherapy could not effectively prevent the recurrence of residual tumor, and it significantly increased the difficulty of repeated surgery because of severe adhesion, caused by radiation, between the tumor and surrounding vital structures. Therefore, we believe that GTR is the only possible method that might achieve oncological cure for CPs at present, and for that reason we follow a radical surgical strategy. This is the main reason for higher GTR rates in our series compared with other publications.[11–14,19,29–33] However, for giant tumors involving vital structures, especially for those with massive calcifications and major vascular encasement, attempted radical resection presents a great challenge to surgeons, which may result in serious consequences, including artery injury, visual deterioration, and severe hypothalamic disturbance. This was supported by the fact that such challenging cases were related to lower GTR rates but much higher complication and mortality rates in this series (data not shown).

The GTR rates of all tumor types were similar between surgical groups in this series, but we found a higher rate in Q-CPs treated via the EEA. Q-CPs arise from the intrasellar space, and blind spots exist when approaching the intrasellar tumor via a transcranial route, especially for cases with a significantly enlarged pituitary fossa, which may result in incomplete resection. In contrast, the endonasal approach allows the dissection of intrasellar tu-

TABLE 2. Surgical outcomes in 315 patients with 3 types of CPs

Variable	Type Q			Type S			Type T			All Types		
	TCA, n = 49	EEA, n = 38	p Value	TCA, n = 36	EEA, n = 20	p Value	TCA, n = 105	EEA, n = 67	p Value	TCA, n = 190	EEA, n = 125	p Value
EOR												
GTR	42 (85.7%)	37 (97.4%)	0.017*	34 (94.4%)	18 (90.0%)	0.64	96 (91.4%)	59 (88.1%)	0.45	172 (90.5%)	114 (91.2%)	0.85
NTR	6 (12.3%)	1 (2.6%)	0.005*	2 (5.6%)	1 (5.0%)	0.2	7 (6.7%)	7 (10.4%)	0.43	15 (7.9%)	9 (7.2%)	0.95
STR	1 (2.0%)	0 (0%)	0.45	0 (0%)	1 (5.0%)	0.32	2 (1.9%)	1 (1.5%)	0.93	3 (1.6%)	2 (1.6%)	>0.99
Op time in mins	326 ± 125	333 ± 92	0.86	319 ± 121	329 ± 98	0.42	310 ± 117	392 ± 131	0.01*	320 ± 128	349 ± 108	0.25
Visual outcomes												
Improved	27 (55.1%)	31 (81.6%)	0.005*	14 (38.9%)	14 (70.0%)	0.003*	27 (25.7%)	32 (47.8%)	0.02*	68 (35.8%)	77 (61.6%)	0.01*
Unchanged	17 (34.7%)	7 (18.4%)	0.15	17 (47.2%)	5 (25.0%)	0.2	67 (63.8%)	34 (50.7%)	0.35	101 (53.2%)	46 (36.8%)	0.22
Worsened	5 (10.2%)	0 (0%)	<0.001*	5 (13.9%)	1 (5.0%)	0.01*	11 (10.5%)	1 (1.5%)	<0.001*	21 (11.0%)	2 (1.6%)	<0.001*
Hypothalamic status			0.44†			0.41†			0.016*†			0.63†
Grade 1	28 (57.2%)	24 (63.2%)		16 (44.4%)	11 (55.0%)		15 (14.3%)	6 (9.0%)		59 (31.0%)	41 (32.8%)	
Grade 2	15 (30.6%)	12 (31.5%)		14 (38.9%)	7 (35.0%)		50 (47.6%)	21 (31.3%)		79 (41.6%)	40 (32.0%)	
Grade 3	5 (10.2%)	2 (5.3%)		4 (11.1%)	1 (5.0%)		25 (23.8%)	27 (40.3%)		34 (17.9%)	30 (24.0%)	
Grade 4	1 (2.0%)	0		2 (5.6%)	1 (5.0%)		15 (14.3%)	13 (19.4%)		18 (9.5%)	14 (11.2%)	
Follow-up in mos												
Mean	86 ± 33	89 ± 30	0.47	89 ± 31	87 ± 30	>0.99	93 ± 30	84 ± 32	0.21	90 ± 32	85 ± 30	0.53
Range	28–142	32–136		33–135	27–128		32–144	30–126		28–144	27–128	
Recurrence	6 (12.2%)	1 (2.6%)	0.001*	3 (8.3%)	1 (5.0%)	0.27	8 (7.6%)	6 (9.0%)	0.58	17 (8.9%)	8 (6.4%)	0.35

Unless otherwise indicated, values are expressed as the number (%) or the mean ± SD.
* Statistically significant at $p \leq 0.05$.
† Mann-Whitney U-test.

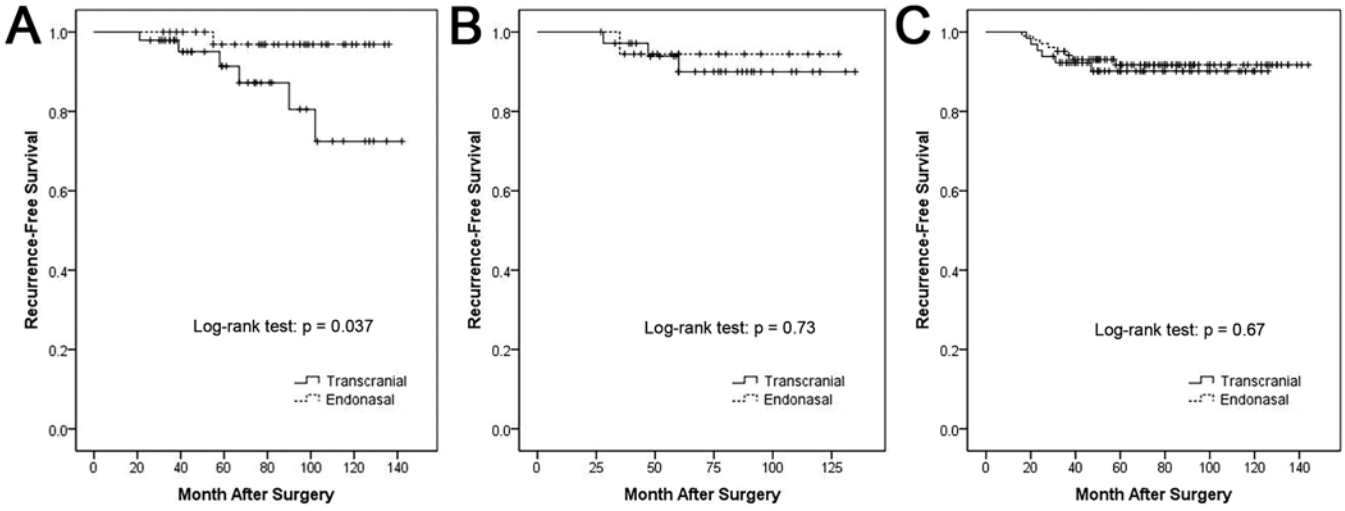

FIG. 4. Kaplan-Meier curves comparing RFS for patients undergoing craniotomy versus endonasal surgery for CPs with each tumor type. **A:** Kaplan-Meier curve for Q-CPs. **B:** Kaplan-Meier curve for S-CPs. **C:** Kaplan-Meier curve for T-CPs.

mor under direct visualization, increasing the chance of complete resection. This is the main reason that the EEA achieved a higher GTR rate for Q-CPs. However, the GTR rate for S-CPs or T-CPs was similar between the two surgical groups, suggesting that the EOR for these 2 types of tumor was not associated with surgical approaches.

Endocrine Outcomes

The overall rates of postoperative permanent DI and new hypopituitarism in our series were comparable with those of other studies.[6,12,14,16,19,23,27,29,30,33–36] DI occurred equivalently in all 3 tumor types between surgical groups, and the overall hypopituitarism rates were also without differences. However, the hypopituitarism rate of Q-CPs treated by transcranial surgery was higher than that in Q-CPs treated by endonasal surgery. The difference could be associated with the dissection of the intrasellar tumor under direct visualization provided by the endonasal approach, which helps to clearly identify and preserve the residual pituitary gland.

Visual Outcomes

Similar to the findings in other publications,[15,19,37] endonasal surgery in this series achieved higher rates of visual improvement in all 3 tumor types. Komotar et al.[35] also demonstrated a significant difference of improved vision between nthe EEA and TCA groups in their meta-analysis (56.2% vs 33.1%, $p < 0.003$). On the other hand, transcranial surgery was associated with increased risk of visual deterioration in all 3 tumor types, and the rates were comparable to those reported in other studies.[12,15,16] Shi et al.[14] even reported an overall rate as high as 24.4% in their microsurgical series of 1054 patients. Our results further add to the growing evidence that the EEA has the advantage over the TCA by increasing the chance of visual improvement but reducing visual deterioration, possibly because of early decompression and less retraction of the optic apparatus through retrochiasmatic manipulation. However, it should be noted that more-complex giant tumors were approached via the transcranial route in this series, increasing the proportion of injury to optic apparatus.

Other Outcomes

Of the patients with T-CPs, the TCA group had a better postoperative hypothalamic status than the EEA group, possibly due to less preservation of the third ventricular floor/hypothalamus when using the endonasal approach. The endonasal route may provide direct visualization of the ventricular floor, theoretically increasing the chance of preservation during tumor dissection. However, limited freedom of manipulation associated with the narrow endonasal corridor makes it difficult to perform delicate dissection between the tumor and hypothalamus, especially when managing severe thinning of ventricular floor compressed by the tumor. Nevertheless, further study is required to quantitatively evaluate the extent of preservation for the third ventricular floor and to investigate whether and/or how it will affect postoperative hypothalamic function.

The complication rates in this series were consistent with other studies. Most of the complications did not differ in any of the tumor types between surgical groups. However, the postoperative CSF leaks and nasal complications occurred more commonly in the EEA group due to the inherent nature of the approach, in which nasal cavity and skull base must be deconstructed to access the tumor. It should be mentioned that the CSF leak rate related to endonasal surgery has declined to 5.0% in the last 60 cases, due to the increasing experience with skull base reconstruction. No difference in the overall operative time was detected between surgical groups, which is consistent with another series by Moussazadeh et al.[15] However, the EEA was associated with longer operative time when used for T-CPs. A possible explanation could be that more time was spent dissecting the adhesion between the tumor and hypothalamus due to narrow space and limited freedom of manipulation by endonasal surgery.

TABLE 3. Complications in 315 patients with 3 types of CPs

Variable	Type Q			Type S			Type T			All Types		
	TCA, n = 49	EEA, n = 38	p Value	TCA, n = 36	EEA, n = 20	p Value	TCA, n = 105	EEA, n = 67	p Value	TCA, n = 190	EEA, n = 125	p Value
New hypopituitarism	28 (57.1%)	11 (28.9%)	0.008*	10 (27.8%)	5 (25.0%)	0.85	41 (39.0%)	31 (46.3%)	0.27	79 (41.6%)	47 (37.6%)	0.39
Partial hypopituitarism	13 (26.5%)	5 (13.2%)	0.13	9 (25.0%)	4 (20.0%)	0.93	31 (29.5%)	22 (32.9%)	0.65	53 (27.9%)	31 (24.8%)	0.54
Panhypopituitarism	15 (30.6%)	6 (15.8%)	0.11	1 (2.8%)	1 (5.0%)	>0.99	10 (9.5%)	9 (13.4%)	0.43	26 (13.7%)	16 (12.8%)	0.82
Permanent DI	28 (57.1%)	18 (47.4%)	0.33	16 (44.4%)	9 (45.0%)	0.65	56 (53.3%)	36 (53.7%)	>0.99	100 (52.6%)	63 (50.4%)	0.55
CSF leak	1 (2.0%)	4 (10.5%)	0.02*	0 (0%)	2 (10.0%)	<0.001*	0 (0%)	9 (13.4%)	<0.001*	1 (0.5%)	15 (12.0%)	<0.001*
Meningitis	2 (4.1%)	2 (5.3%)	0.67	2 (5.6%)	1 (5.0%)	0.88	6 (5.7%)	6 (9.0%)	0.35	9 (4.7%)	9 (7.2%)	0.45
Hydrocephalus	2 (4.1%)	2 (5.3%)	0.57	2 (5.6%)	2 (10.0%)	0.36	10 (9.5%)	8 (11.9%)	0.72	14 (7.4%)	12 (9.6%)	0.65
Seizure	1 (2.0%)	0	0.75	1 (2.8%)	0	0.58	3 (2.9%)	0	0.38	5 (2.6%)	0 (0%)	0.45
Stroke/hemorrhage	2 (4.1%)	1 (2.6%)	0.45	2 (5.6%)	1 (5.0%)	0.92	7 (6.7%)	2 (3.0%)	0.37	11 (5.8%)	4 (3.2%)	0.59
Nasal complications	0 (0%)	3 (7.9%)	<0.001*	0 (0%)	2 (10.0%)	<0.001*	1 (1.0%)	7 (10.4%)	<0.001*	1 (0.5%)	12 (9.6%)	<0.001*
Death	1 (2.0%)	0 (0%)	0.32	1 (2.8%)	1 (5.0%)	0.23	3 (2.9%)	2 (3.0%)	0.85	5 (2.6%)	3 (2.4%)	0.72

* Statistically significant at $p \leq 0.05$.

Recurrence

Numerous studies have reported high recurrence rates ranging from 20% to 59.5% after surgery for CPs.[3–5,9,11,26,29–31,38] The lower rates in our series (8.9% for TCA and 6.4% for EEA) may be attributed to the high GTR rates. Of the overall cohort, the recurrence rates did not differ between surgical groups. Komotar et al.[35] also reported no difference in recurrence rates between endonasal and transcranial surgery in their meta-analysis. However, we observed a higher recurrence rate in Q-CPs associated with craniotomy, and a significant difference in RFS was also noted between the two surgical approaches. A possible reason is that the endonasal route may allow intrasellar tumor dissection under direct visualization and thereby minimize the risk of residual tumor. In addition, we noted less recurrence after GTR than after NTR and STR (3.8% for GTR vs 48.3% for NTR and STR, $p < 0.001$; data not shown), suggesting a negative correlation between EOR and recurrence.

QST Classification

Previous CP classification systems were based on tumor relationships with the diaphragma sellae, pituitary stalk, or third ventricular floor, or on tumor location and vertical extension.[31,39–43] These systems are useful to a certain extent for understanding tumor growth. However, they are established based on a radiological presentation that only represents the final tumor stage at the time of diagnosis and cannot reflect its exact origin and real relationships to surrounding structures, especially for those lesions exhibiting similar imaging appearances. Our QST classification system is established by preoperative radiological evaluation, intraoperative morphological observation, and histological investigation based on nearly 1000 consecutive surgical cases. The system lays emphasis on the tumor origin and its relationship with surrounding membranous (dura, diaphragma, arachnoid, and pia) and neurovascular structures.[24,25,44,45] This classification may help to improve our understanding of the morphological features and growth patterns of CPs, as well as their exact relationships with the hypothalamic-pituitary axis.

Surgical Considerations Based on QST Classification

Q-CPs

Q-CPs arise from the subdiaphragmatic intrasellar space and adhere tightly to residual pituitary gland (Fig. 1 panel Q). Their suprasellar portions, however, are separated from critical structures by the membranous barrier and can be easily dissected (Fig. 1 panel Q, Fig. 5). The EEA may provide direct visualization and initial dissection of an intrasellar tumor's origin, increasing the chance to achieve complete tumor resection while preserving the residual gland. In contrast, the TCA has a blind spot when managing intrasellar space, especially when the sella turcica is remarkably enlarged, which may result in incomplete tumor resection or unnecessary removal of normal gland. This can be validated by higher GTR rates but lower hypopituitarism rates in patients with Q-CPs following endonasal surgery. In addition, a patient with Q-CP (not included in this series) experienced repeated recurrence

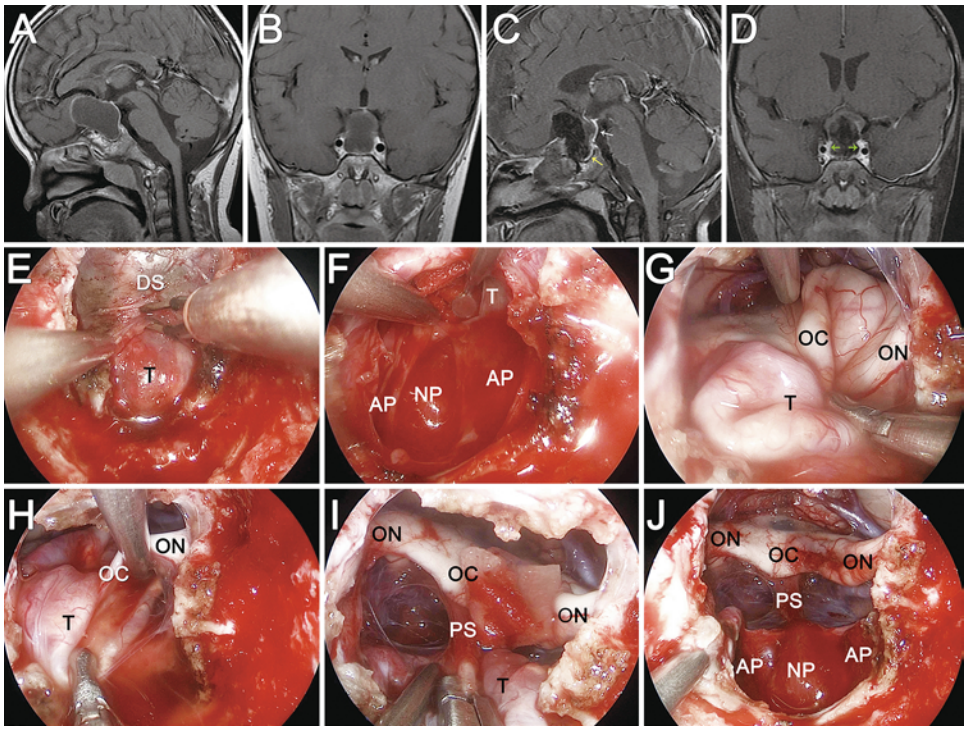

FIG. 5. An illustrative case with Q-CP removed by endonasal surgery. **A and B:** Preoperative MRI. **C and D:** Immediate postoperative MRI showing that the tumor was totally removed and that the pituitary stalk (*white arrow*), residual adenohypophysis (*green arrows*), and neurohypophysis (*yellow arrow*) were preserved. **E–J:** Intraoperative endoscopic photographs showing step-by-step removal of the tumor. In panel E, the upper portion of the tumor with overlying diaphragma sellae is shown after dural incision. In panel F, the interface between the intrasellar tumor origin and the residual pituitary gland was clearly identified and carefully dissected under direct visualization. In panels G and H, although suprasellar tumor compression caused severe stretching of the optic chiasm, a clear membranous interface still existed between the tumor and chiasm, and the dissection was quite easy. In panel I, the pituitary stalk was identified after circumferential dissection of the tumor. In panel J, both the residual adenohypophysis and neurohypophysis were well preserved after tumor removal. AP = adenohypophysis; DS = diaphragma sellae; NP = neurohypophysis; OC = optic chiasm; ON = optic nerve; PS = pituitary stalk; T = tumor. Figure is available in color online only.

despite undergoing four transcranial procedures and multiple sessions of radiotherapy. Interestingly, no recurrence was observed during the 10-year follow-up after an endonasal surgery, further suggesting the advantage of EEA when managing intrasellar tumor origin. Taken together, these findings support the assertion that the EEA seems more suitable for most Q-CPs, except for those with extremely bilateral suprasellar extension.

S-CPs

S-CPs arise from the middle or inferior segment of the pituitary stalk and usually extend among subarachnoid cisterns (Fig. 1 panel S). Regular tumors are typically located in a single cistern, and their originating site can be easily accessed using both EEA and TCA. The GTR, recurrence, and postoperative hypopituitarism rates also did not differ between the two surgical approaches. Given better visual outcomes, the EEA could be preferred when approaching these regular S-CPs. However, for large tumors involving multiple cisterns, especially for those with significantly lateral extension or with severe vessel encasement, it is quite difficult to safely remove the entire tumor by the endonasal route. In this case, the TCA could be a better choice.

T-CPs

T-CPs originate from residual Rathke's pouch precursor cells in the top of the pars tuberalis and are the most challenging CPs due to their close relationship with the hypothalamus, which is severely compressed by the tumor and becomes extremely delicate (Fig. 1 panel T). At this point, totally removing tumors whenever possible while maximizing preservation of the hypothalamus should be the primary goal of surgery. The EEA reduced the risk of visual deterioration by retrochiasmatic manipulation, but it resulted in worse postoperative hypothalamic status due to less preservation of the third ventricular floor. Therefore, T-CPs with moderate ventricular extension could be indicated for endonasal surgery; for tumors with extreme ventricular extension, transcranial microsurgery should be recommended for the purpose of gaining better hypothalamic outcomes.

Study Limitations

First, the craniotomy procedure has been in use for a long period, whereas endonasal surgery has been used for only 2 decades, and surgeons were undoubtedly more skilled in later endonasal cases. The imbalance of surgi-

cal experience may affect outcome analysis and result in selection bias. The problem is expected to be resolved in the future when endonasal techniques reach a stable level comparable to transcranial microsurgery.

Second, selection bias is inherent in any retrospective surgical study because inclusion cannot be strictly randomized. For example, tumor volume may not reflect surgical difficulty, and surgeons usually choose an approach based on individual experience and preference. These factors may affect surgical strategies and lead to different outcomes. In a comparative study of TCA and EEA for CPs reported by Jeswani et al.,[19] complete concordance regarding surgical approach among three blinded reviewers was noted in only 11% of cases, and they concluded that approach selection appeared mostly to reflect surgeon preference rather than specific tumor characteristics. Nevertheless, an ideal prospective randomized controlled trial to eliminate the bias seems unlikely to be performed due to differential expertise bias and ethical concerns.

Finally, although our mean follow-up duration was comparable to that in other studies, the amount of time may be insufficient to evaluate the true recurrence rate. Studies with longer follow-up times are required to resolve this problem.

Conclusions

CPs could be effectively treated by radical surgery without increasing the morbidity or mortality rate. QST classification may improve our understanding of the tumor growth patterns and is helpful for preoperative surgical planning. Both TCA and EEA have their advantages and limitations when managing different types of tumors. Individualized surgical strategies based on tumor growth patterns are mandatory to achieve optimal outcomes.

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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: Fan, Bao, Nie, Wang, Qiu. Acquisition of data: Liu, Bao, Nie, Wang, Qiu. Analysis and interpretation of data: Liu. Drafting the article: Fan. Critically revising the article: Fan. Reviewed submitted version of manuscript: Qi. Approved the final version of the manuscript on behalf of all authors: Qi. Statistical analysis: J Peng. Administrative/technical/material support: Pan, Y Peng. Study supervision: Qi.

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