



Endocrine and Metabolic Outcomes After Transcranial and Endoscopic Endonasal Approaches for Primary Resection of Craniopharyngiomas

Xiaoqing Li^{1,3}, Wei Wu¹, Qing Miao¹, Min He¹, Shuo Zhang¹, Zhaoyun Zhang¹, Bin Lu¹, Yehong Yang¹, Xuefei Shou², Yiming Li¹, Yongfei Wang², Hongying Ye¹

■ **OBJECTIVE:** Craniopharyngiomas have traditionally been resected through the transcranial approaches (TCA). The endoscopic endonasal approach (EEA) has recently been developed as an alternative for surgeons, but controversy remains regarding which approach has better outcomes. We compared the endocrine and metabolic outcomes of TCA and EEA in patients who underwent primary resection of craniopharyngiomas.

■ **METHODS:** A retrospective analysis was conducted of patients with craniopharyngioma who were treated by the department of endocrinology and metabolism at our institution between 2011 and 2015.

■ **RESULTS:** Of 43 patients assessed, 26 underwent TCA and 17 underwent EEA. After surgery, 29.4% (5/17) of patients in the EEA group had normal anterior pituitary function, whereas none in the TCA group had complete anterior pituitary function. Higher prevalences of corticotrophic deficiency (92.3% vs. 52.9%, $P = 0.009$), thyrotrophic deficiency (96.2% vs. 52.9%, $P = 0.003$), and hypogonadotropic hypogonadism (100% vs. 70.6%, $P = 0.014$) were found in the TCA group. The TCA group showed a trend toward having more patients with at least 3 anterior pituitary deficits (88.5% vs. 58.8%, $P = 0.060$). The mean body mass index at last follow-up tended to be lower in the EEA group ($24.13 \pm 3.16 \text{ kg/m}^2$ vs. $26.79 \pm 4.5 \text{ kg/m}^2$, $P = 0.079$), and the preoperative body mass index was comparable between groups. Similar prevalences

of overweight/obesity, hypertension, hyperglycemia, and metabolic syndrome were detected in the 2 groups. Moreover, no significant differences were observed in the rates of cerebrospinal fluid leakage and intracranial infection between the 2 groups.

■ **CONCLUSIONS:** EEA may provide the same gross total resection rate for craniopharyngioma as TCA while providing better protection of anterior pituitary function.

INTRODUCTION

Craniopharyngiomas are rare embryologic tumors arising from the remnants of squamous epithelium along the craniopharyngeal duct. They are typically located in the sellar/parasellar region, close to several critical neural and vascular structures such as the optic apparatus, the pituitary gland, and the hypothalamus.¹ Despite high survival rates, craniopharyngiomas are frequently associated with poor outcomes. It is reported that 54% to 100% of patients with craniopharyngioma had at least 3 anterior pituitary deficiencies after treatment and 25% to 86% had central diabetes insipidus.¹⁻⁴ Both hypopituitarism and diabetes insipidus contribute to the excess mortality in craniopharyngioma.² Moreover, patients with hypothalamic damage often experience substantial weight gain, resulting in remarkably increased metabolic morbidities and cardiovascular mortalities.^{3,4}

Surgical removal is the predominant treatment of craniopharyngioma. Complete resection was reported with significantly lower

Key words

- Craniopharyngioma
- Endocrine outcomes
- Endoscopic endonasal approach
- Metabolic outcomes
- Transcranial approach

Abbreviations and Acronyms

- BMI:** Body mass index
- CSF:** Cerebrospinal fluid
- EEA:** Endoscopic endonasal approach
- EOR:** Extent of resection
- HDL-c:** High-density lipoprotein cholesterol
- MRI:** Magnetic resonance imaging
- MS:** Metabolic syndrome

TCA: Transcranial approach
TG: Triglyceride

From the Departments of ¹Endocrinology and Metabolism, and ²Neurosurgery, Huashan Hospital, Fudan University, Shanghai, China

To whom correspondence should be addressed: Hongying Ye, M.D.; Yongfei Wang, M.D. [E-mail: yehongying@huashan.org.cn; eamns@hotmail.com]

Xiaoqing Li and Wei Wu contributed equally to this article.

³Present address: Department of Endocrinology and Metabolism, the First People's Hospital of Shangqiu, Shangqiu, Henan Province 476000, China

Citation: *World Neurosurg.* (2019) 121:e8-e14.
<https://doi.org/10.1016/j.wneu.2018.08.092>

Journal homepage: www.journals.elsevier.com/world-neurosurgery

Available online: www.sciencedirect.com

1878-8750/\$ - see front matter © 2018 Elsevier Inc. All rights reserved.

relapse rates, but usually at the cost of critical neuroendocrine function.⁵ Instead, some investigators advocated more conservative surgical approaches followed by radiotherapy to obtain comparable local control and fewer complications.⁶⁻⁸ Traditionally, these tumors have been surgically removed via transcranial approaches (TCA), including anterolateral approaches (frontolateral, pterional, orbitopterional, orbitozygomatic, and supraorbital eyebrow), midline approaches (frontobasal interhemispheric and transbasal subfrontal), and lateral approaches (combined subtemporal and petrosal).⁹ These approaches share increased risks for visual deterioration, stroke, and other neurologic complications resulting from brain retraction and manipulation of neurovascular structures.¹⁰⁻¹⁵

Over the past decade, the endoscopic endonasal approach (EEA) has been developed as an alternative for surgeons. This approach provides a direct access to tumors via a subchiasmatic corridor without brain retraction and manipulation of neurovascular structures, and it offers a wide operative field. Postoperative cerebrospinal fluid (CSF) leak is the major problem associated with this approach. However, the incidence of CSF leak has been dramatically reduced because of the introduction of endoscopic skull base reconstruction with the vascularized nasoseptal flap.^{14,16,17}

Although there are numerous reports of individual experiences with the TCA and EEA, there are only 4 single-institution series analyses and 1 meta-analysis comparing surgical outcomes.^{15,18-21} These studies comparing surgical outcomes were focused on resection rate and visual and neurologic outcomes, but endocrine deficiencies were roughly categorized as panhypopituitarism and diabetes insipidus. No individual pituitary axis function or metabolic outcomes were reported. Besides, stimulation tests were not performed in most of these studies. Furthermore, most of these studies included patients after both primary and repeated resections. It remains unclear whether the choice of TCA or EEA for the primary resection offers any advantage in endocrine and metabolic outcomes. In the present study we compared the endocrine and metabolic outcomes after initial resection of craniopharyngioma via TCA and EEA at our institution.

MATERIALS AND METHODS

Study Population

We searched the electronic medical case system of Huashan Hospital for patients with pathologic diagnosis of craniopharyngioma made between January 2011 and December 2015. Patients who received repeated surgery or radiotherapy were excluded to avoid confounding factor. Patients less than 18 years old were also excluded. In order to reduce the selection bias, preoperative magnetic resonance images (MRI) were reviewed by an independent neurosurgeon who masters both approaches, and patients were included only if the neurosurgeon confirmed that the tumor was amenable to both EEA and TCA. All the surgeries were performed at our institution. The senior author (YF Wang) performed all the EEA surgeries, while 4 different surgeons, including the senior author (YF Wang), performed all the TCA cases. All 4 surgeons have more than 10 years of experience in craniopharyngioma resection. Gross total resection with special attention on preserving hypothalamic-pituitary function and optic nerve was the primary goal for all patients. This study was approved by the

institutional review board of Huashan Hospital, Fudan University. All patients were informed of the purpose of this study and signed a written consent form.

Data Collection

Medical records of all recruited patients were reviewed. Demographic information including age and gender, presenting symptoms, radiologic findings, extent of resection (EOR), follow-up period, endocrine outcomes, body mass index (BMI), metabolic outcomes and complications of surgery were analyzed. Patients were separated into the TCA and EEA groups according to their surgical approach and comparisons were made between the 2 groups.

Neuroradiologic characteristics were identified from preoperative MRI in all cases. Tumor topography was classified into 5 categories using the classification scheme of Barrios as reported by Prieto et al.^{22,23} and Pascual et al.²⁴ Tumor consistencies were divided into predominantly cystic, predominantly solid, and mixed. Maximum tumor diameters were also recorded. Presence of calcification was determined by surgical records or preoperative computed tomographic scans if available. EOR was estimated based on postoperative MRI.

All patients underwent standardized endocrine evaluation in our department before and after surgery. Patients with a morning cortisol level <3 $\mu\text{g/dL}$ was deemed to have central adrenal insufficiency, and a morning cortisol level >15 $\mu\text{g/dL}$ was regarded as normal.²⁵ Patients whose morning cortisol levels between 3 and 15 $\mu\text{g/dL}$ underwent adrenocorticotropic hormone stimulation test or insulin tolerance test, and a peak cortisol value <18 $\mu\text{g/dL}$ was defined as central adrenal insufficiency. Central hypothyroidism was diagnosed by serum free thyroxine level below the reference range with insufficiently elevated thyroid-stimulating hormone. In men, central hypogonadism was diagnosed if testosterone was low in conjunction with normal or low luteinizing hormone and follicle-stimulating hormone. In premenopausal women, central hypogonadism was diagnosed if low or normal gonadotropins coincided with estradiol levels <100 pmol/L, oligomenorrhea, amenorrhea, or infertility. In postmenopausal women, central hypogonadism was diagnosed by low serum luteinizing hormone and/or follicle-stimulating hormone. Clinical presentation, urine specific gravity, urine and serum osmolality, serum sodium level and need for desmopressin treatment were comprehensively evaluated for the diagnosis of central diabetes insipidus. Some but not all patients underwent water deprivation testing.

Metabolic syndrome (MS) was diagnosed if patients met 3 or more of the following criteria: 1) overweight (BMI ≥ 24 kg/m^2) or obesity (BMI ≥ 28 kg/m^2) according to the Working Group on Obesity in China²⁶; 2) elevated blood pressure (systolic blood pressure ≥ 130 mm Hg and/or diastolic blood pressure ≥ 85 mm Hg); 3) hyperglycemia (fasting plasma glucose ≥ 5.6 mmol/L or use of antidiabetic drugs); 4) elevated triglyceride (TG) (fasting TG ≥ 1.7 mmol/L); 5) reduced high-density lipoprotein cholesterol (HDL-c) (fasting HDL-c <1.0 mmol/L in men or <1.3 mmol/L in women).²⁷ In addition, dyslipidemia was identified as having raised fasting TG with or without lowered fasting HDL-c.²⁷

Statistical Analyses

Statistical analyses were performed using SPSS (The IBM Corporation, Armonk, New York, USA), and figures were created by

Table 1. Demographics and Presenting Symptoms of Patients

| | TCA (n = 26) | EEA (n = 17) | P Value |
|---|-------------------|-------------------|---------|
| Age, years: mean \pm SD | | | |
| Age at presentation | 40.31 \pm 15.52 | 43.59 \pm 14.98 | 0.496 |
| Age at last follow-up | 44.08 \pm 14.63 | 44.35 \pm 14.08 | 0.951 |
| Sex | | | 0.494 |
| Male | 15 | 8 | |
| Female | 11 | 9 | |
| Follow-up, months: median (range) | 9 (3.0–22.9) | 5.5 (3.0–7.0) | 0.052 |
| Presenting symptoms | | | |
| Visual disturbance | 20 (76.9%) | 15 (88.2%) | 0.595 |
| Headache | 11 (42.3%) | 4 (23.5%) | 0.207 |
| Menstrual disorder/impaired sexual function | 11 (42.3%) | 5 (29.4%) | 0.392 |
| Polyuria/polydipsia | 8 (30.8%) | 5 (29.4%) | 0.925 |
| Fatigue | 7 (26.9%) | 6 (35.3%) | 0.559 |

TCA, transcranial approach; EEA, endoscopic endonasal approach.

GraphPad Prism (The GraphPad Software, Inc, La Jolla, California, USA). Continuous variables were described with means \pm standard deviations, medians, and interquartile ranges as appropriate. Categorical variables were described as frequencies and percentages. Comparisons of continuous variables between the 2 groups were performed using the Student t test or the Mann-Whitney U test. χ^2 tests or Fisher exact tests were used to compare categorical variables. Additionally, paired t test was used for preoperative and postoperative BMI of each group. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 62 adult patients underwent primary resection of craniopharyngioma at our institution during the study period. Nineteen patients with significant lateral extension of the tumors were excluded because they were not amenable to either EEA or TCA. The remaining 43 patients were included in this retrospective analysis, among which 26 patients underwent resection by TCA and 17 by EEA. Representative preoperative and postoperative MRI of both approaches are shown in [Supplementary Figure 1](#). In the TCA group, the surgical approaches included subfrontal (11.5%), supraorbital keyhole (11.5%), pterional (69.2%), and longitudinal fissure approach (7.7%). The diagnoses of craniopharyngioma were all histologically confirmed. Pathologic subtypes were available in a majority of patients. The ratios of adamantinomatous variant versus papillary variant in the TCA and EEA groups were 11:11 and 6:8, respectively; no significant differences were found between the groups ($P = 0.676$).

Demographic characteristics and presenting symptoms are shown in [Table 1](#). The mean age at presentation was comparable between the TCA and EEA groups (40.31 \pm 15.52 vs. 43.59 \pm 14.98

years, $P = 0.496$). No differences were found in the proportion of women (42.3% vs. 52.9% in the TCA and EEA groups, respectively, $P = 0.494$) between the 2 groups. The TCA group showed a tendency of having longer follow-up (median, 9.0; range, 3.0–22.9 months vs. median, 5.5; range, 3.0–7.0 months; $P = 0.052$). Visual disturbance was the most prevalent presenting symptom in both groups. Other common presenting symptoms included headache, menstrual disorder or impaired sexual function, polyuria and polydipsia, fatigue, weight gain, and cognitive impairment. There were no significant differences in presenting symptoms between groups.

As shown in [Table 2](#), the distribution of craniopharyngioma topography was similar between the 2 groups ($P = 1.000$). More than half of these tumors were mixed and calcified. The mean maximum tumor diameter was 29.51 \pm 9.49 mm in the TCA group and 25.18 \pm 8.25 mm in the EEA group. No significant differences were found in the above radiologic characteristics between the 2 groups. Gross total resection was achieved in 17 (65.4%) patients in the TCA group and in 11 (64.7%) patients in the EEA group. The EOR was comparable between the groups ($P = 0.964$).

Endocrine Outcomes

Prevalence of preoperative endocrine deficiencies was similar between the 2 groups ([Table 3](#)). After surgery, endocrine deficiencies

Table 2. Radiologic Characteristics at Presentation and Extent of Resection

| | TCA (n = 26) | EEA (n = 17) | P Value |
|--|------------------|------------------|---------|
| Tumor topography | 26 | 17 | 1.000 |
| Sellar-suprasellar | 4 | 3 | |
| Suprasellar-pseudointraventricular | 7 | 5 | |
| Secondary intraventricular | 5 | 3 | |
| Infundibulo-tuberal or not strictly intraventricular | 9 | 6 | |
| Strictly intraventricular | 1 | 0 | |
| Consistency | 25 | 17 | 0.075 |
| Predominantly cystic | 1 | 5 | |
| Mixed | 16 | 9 | |
| Predominantly solid | 8 | 3 | |
| Calcification | 24 | 15 | 1.000 |
| Yes | 16 | 10 | |
| No | 8 | 5 | |
| Maximum tumor diameter (mm), mean \pm SD | 29.51 \pm 9.49 | 25.18 \pm 8.25 | 0.146 |
| Extent of resection | 26 | 17 | 0.964 |
| Gross total | 17 | 11 | |
| Subtotal | 9 | 6 | |

TCA, transcranial approach; EEA, endoscopic endonasal approach; SD, standard deviation.

were more frequent in the TCA group than in the EEA group (Table 4). The TCA group had a significantly higher prevalence of corticotrophic deficiency (92.3% vs. 52.9%, $P = 0.009$), thyrotrophic deficiency (96.2% vs. 52.9%, $P = 0.003$), and hypogonadotropic hypogonadism (100% vs. 70.6%, $P = 0.014$). No significant differences were found in central diabetes insipidus (61.5% in TCA vs. 64.7% in EEA, $P = 0.834$). There was a trend toward more patients with at least 3 anterior pituitary deficits in the TCA group (88.5% vs. 58.8%, $P = 0.060$). Moreover, 29.4% (5/17) of patients in the EEA group had normal anterior pituitary function at the last follow-up, whereas none in the TCA group were observed with complete anterior pituitary function.

Metabolic Outcomes

The mean preoperative BMI was comparable in the 2 groups (23.87 ± 4.12 kg/m² in the TCA group vs. 23.14 ± 3.93 kg/m² in the EEA group, $P = 0.572$). After surgery, a remarkable increase in BMI was seen in each group (Figure 1), whereas at the latest follow-up, the mean BMI showed a trend toward being lower in the EEA group than in the TCA group (24.13 ± 3.16 vs. 26.43 ± 4.62 kg/m², $P = 0.079$). Similarly, the proportion of overweight or obesity did not differ significantly between groups (Table 5).

The TCA group had lower HDL-c than did the EEA group (0.87 ± 0.25 vs. 1.08 ± 0.32 mmol/L, $P = 0.023$). There was also a trend of elevated TG in the TCA group (3.10 ± 2.16 vs. 2.19 ± 0.94 mmol/L, $P = 0.075$). Total cholesterol, low-density lipoprotein cholesterol, fasting plasma glucose, and glycosylated hemoglobin A1c were similar between the 2 groups (Table 5). Moreover, the prevalence of elevated blood pressure, dyslipidemia, and hyperglycemia was comparable between the 2 groups (Table 5). Seventeen patients (65.4%) of the TCA group and 7 patients (41.2%) of the EEA group met the criteria of MS ($P = 0.118$). No difference was found in the number of features of MS between the 2 groups.

Complications

Three patients in the EEA group experienced CSF leakage after surgery (17.6% in EEA group vs. 0.0% in TCA group, $P = 0.108$), all underwent additional repair before discharge. One patient in each group experienced intracranial infection (5.9% in EEA group vs. 3.8% in TCA group, $P = 1.000$).

Table 3. Preoperative Endocrine Deficiencies*

| | TCA (n = 26) | EEA (n = 17) | P Value |
|-----------------------|---------------|--------------|---------|
| Adrenal insufficiency | 5/23 (21.7%) | 4/17 (23.5%) | 0.799 |
| Hypothyroidism | 13/24 (54.2%) | 5/17 (29.4%) | 0.116 |
| Hypogonadism | 18/24 (75.0%) | 9/16 (56.3%) | 0.215 |
| Diabetes insipidus | 8/26 (30.8%) | 5/17 (29.4%) | 0.925 |

TCA, transcranial approach; EEA, endoscopic endonasal approach.

*Numerator = number of patients with confirmed endocrine deficiencies; denominator = number of patients with available data.

Table 4. Endocrine Deficiencies at Last Follow-Up

| | TCA (n = 26) | EEA (n = 17) | P Value |
|--|--------------|--------------|---------|
| Normal anterior pituitary function | 0 (0.0%) | 5 (29.4%) | 0.014* |
| Adrenal insufficiency | 24 (92.3%) | 9 (52.9%) | 0.009* |
| Hypothyroidism | 25 (96.2%) | 9 (52.9%) | 0.003* |
| Hypogonadism | 26 (100.0%) | 12 (70.6%) | 0.014* |
| At least 3 anterior pituitary deficits | 23 (88.5%) | 10 (58.8%) | 0.060 |
| Diabetes insipidus | 16 (61.5%) | 11 (64.7%) | 0.834 |

TCA, transcranial approach; EEA, endoscopic endonasal approach.
*P value <0.05.

DISCUSSION

The optimal surgical approach for craniopharyngiomas remains controversial. Surgeons have traditionally opted to use TCAs for resection of suprasellar tumors with or without lateral extension (schematic diagrams and videos of these approaches can be found in the website <https://www.neurosurgicalatlas.com>). The common concerns for these approaches are the neurologic complications caused by brain retraction and optic nerve manipulation.^{18,28} Over the past decade, EEA has evolved into an alternative approach for the treatment of suprasellar craniopharyngiomas. It offers ventral access to the suprasellar compartment, avoiding retraction of the brain and cranial nerves, and providing better visualization of the pituitary gland.²⁹ A growing amount of evidence shows significantly improved visual outcomes and decreased neurologic injuries in patients receiving the EEA as compared with the TCA, despite more CSF leakage in the EEA.¹⁸⁻²¹ However, it is unclear whether the EEA has better endocrine and metabolic outcomes.

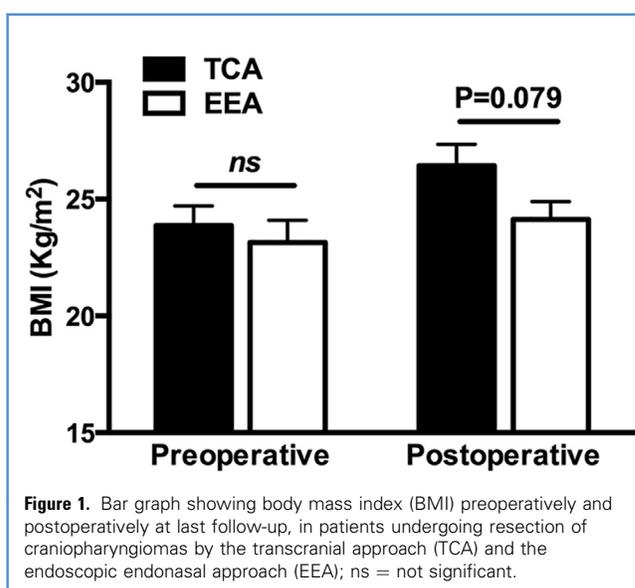


Figure 1. Bar graph showing body mass index (BMI) preoperatively and postoperatively at last follow-up, in patients undergoing resection of craniopharyngiomas by the transcranial approach (TCA) and the endoscopic endonasal approach (EEA); ns = not significant.

Table 5. Metabolic Data at Last Follow-Up

| | TCA (n = 26) | EEA (n = 17) | P Value |
|--|--------------|--------------|---------|
| TG (mmol/L) | 3.10 ± 2.16 | 2.19 ± 0.94 | 0.075 |
| CHO (mmol/L) | 5.52 ± 1.50 | 5.06 ± 1.17 | 0.292 |
| LDL-c (mmol/L) | 3.14 ± 1.28 | 2.98 ± 0.94 | 0.676 |
| HDL-c (mmol/L) | 0.87 ± 0.25 | 1.08 ± 0.32 | 0.023 |
| FPG (mmol/L) | 5.68 ± 1.54 | 5.25 ± 0.73 | 0.318 |
| HbA1c (%) | 6.15 ± 1.42 | 5.76 ± 0.81 | 0.326 |
| Overweight/obesity | 18 (69.2%) | 8 (47.1%) | 0.146 |
| Elevated blood pressure | 9 (34.6%) | 7 (41.2%) | 0.663 |
| Dyslipidemia | 22 (84.6%) | 12 (70.6%) | 0.470 |
| Hyperglycemia | 12 (46.2%) | 4 (23.5%) | 0.133 |
| MS | 17 (65.4%) | 7 (41.2%) | 0.118 |
| Number of features of MS, median (range) | 3 (2–4) | 2 (1–3) | 0.164 |

TCA, transcranial approach; EEA, endoscopic endonasal approach; TG, triglyceride; CHO, total cholesterol; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin A1c; MS, metabolic syndrome.

In this study, most patients underwent standardized endocrine and metabolic evaluation after the initial surgery to remove the craniopharyngioma. The TCA and EEA approaches had comparable gross total resection rates, whereas postoperative endocrine deficiencies were significantly decreased in the EEA group. Indicators of MS, including blood glucose, blood pressure, BMI, and lipid profile were not different between the 2 groups, except that a higher level of HDL-c was observed in the EEA group. These findings indicated that anterior pituitary function preservation should be considered an advantage of EEA when the tumor is amenable to both approaches.

The demographic profile and presenting symptoms were similar between the EEA and TCA groups. Furthermore, no differences were found in tumor topography, consistency, size, and preoperative endocrine deficiencies between the 2 groups. This homogeneity suggests that the differences in surgical outcomes derive from surgical approaches rather than the differences in the selected patients or tumors.

The EOR was similar between the TCA and EEA groups as well, with gross total rates of 65.4% and 64.7%, respectively. These rates were comparable to those reported by previous studies.^{8,30,31} Interestingly, the meta-analysis by Komotar et al.,¹⁸ which included 88 studies and 3470 patients, found a significantly higher rate of gross total resection in the EEA cohort than in the TCA cohort. One possible explanation is that those workers primarily included studies with a single surgical approach rather than studies comparing the 2 approaches. In addition, the gross total resection rates of primary surgery were not separated from those of reoperation in the meta-analysis. Supporting this explanation are 2 prior reports finding no differences in EOR between the 2 approaches after the initial surgery for craniopharyngioma.^{19,21}

Moreover, preoperative characteristics such as mean age, presenting symptoms, and intraventricular extension were different between the 2 cohorts in the meta-analysis, which might have played a role in the surgical outcomes. Because all reports, the present study included, are retrospective, further investigation is needed to definitively establish the differences in EOR between these 2 approaches.

An important observation from this study was that the postoperative rates of adrenal insufficiency, hypothyroidism, and hypogonadism were significantly lower in the EEA group than in the TCA group. Furthermore, there were more patients with normal anterior pituitary function in the EEA group. These findings indicate that the EEA group had better endocrine outcomes after primary resection. This is reminiscent of earlier findings of substantially fewer new endocrine deficits after transsphenoidal surgery than after transcranial surgery.^{12,32} It is possible that early debulking of the tumor through the ventral approach and better visualization of the hypothalamus and tumor surface provided by the EEA aids with preservation of hypothalamic-pituitary function.^{18,33} However, it is difficult to directly compare these results with previous studies comparing endocrine outcomes of the EEA and TCA, in as much as individual pituitary axis function was not reported in their studies.^{19–21}

With regard to at least 3 anterior pituitary deficits, there was a trend toward a lower rate in the EEA group although statistical significance was not reached. This might be due to limited power of the small study population. It is noteworthy that several previous findings showed that panhypopituitarism rate appeared to be comparable between these 2 approaches.^{18,19,21} However, most of those studies included patients who underwent repeated surgeries or radiotherapy; whether the EEA itself was responsible for better endocrine outcomes still needs to be explored. In addition, we found no differences in the rate of diabetes insipidus between the 2 approaches. Although the meta-analysis displayed a significantly reduced rate of diabetes insipidus in the EEA group, 2 studies comparing surgical outcomes in a single institution reported similar rates of diabetes insipidus between the 2 approaches.^{19,21}

Hypothalamic obesity is linked to excess cardiovascular mortality. In this study, we found a trend toward lower BMI at last follow-up in the EEA group, although no differences were found in the proportion of overweight or obese patients. As reported, rapid weight gain occurred frequently after treatment for craniopharyngioma, usually within the first 12 months.^{34–36} Consequently, the prevalence of obesity can reach 40% to 75% after treatment.^{3,37–40} Given the relatively short follow-up periods in our series, and better preservation of hypothalamic-pituitary function in the EEA group indicated by improved endocrine outcomes, it is reasonable to suppose that EEA could decrease the occurrence of hypothalamic obesity. This will be an important direction of further investigations.

We found a much higher prevalence of MS, especially dyslipidemia and hyperglycemia, in both groups after primary resection than in the general population in China.^{41,42} This is consistent with previous findings that MS and type 2 diabetes mellitus were more frequent in patients with craniopharyngioma.^{2,37,40,43} It is also reported that both childhood and adult craniopharyngioma patients had increased rates of dyslipidemia.^{4,37,40} We detected no differences in the prevalence of these metabolic features between

the 2 groups, except that the EEA group had significantly elevated HDL-c, which is negatively associated with coronary heart disease.⁴⁴ Whether the different surgical approaches affect cardiovascular mortalities and morbidities deserves further investigation.

There are several limitations to this study. First, we recruited patients retrospectively. The choice of surgical approach was determined by the surgeons and was not based on randomization. However, it is reasonable to believe that the tumors included in this study were amenable to both approaches, in as much as the image characteristics were comparable between the 2 groups. Second, 4 different surgeons performed all the TCA cases. To explore whether surgeons' experience and skills would influence the outcomes, we classified the TCA group into 4 subgroups according to the surgeons and found no significant differences in gross total resection rate, postoperative endocrine deficiencies, and metabolic outcomes among the 4 groups (data not shown). Third, only patients with available follow-up data were analyzed. It is possible that those with endocrine deficiencies or other discomforts were more likely to be admitted to hospital, which might have caused overestimation of all complications. Fourth, prevalence of growth hormone deficiency

and preoperative MS was not evaluated in our series. However, we found similar preoperative rates of adrenal insufficiency, hypothyroidism, and hypogonadism, along with comparable BMI, between the 2 groups. Finally, the limited follow-up duration might affect the validities of our findings on postoperative BMI. In addition, we could not draw any conclusion on the differences in recurrence rates between the 2 approaches because of the short follow-up period. Further studies are needed to conclusively address this issue.

CONCLUSION

Our results demonstrate that hypopituitarism and metabolic disorders are common complications of patients after initial resection of craniopharyngioma. Although it remains to be tested, our findings highlight better preservation of anterior pituitary function by the EEA. Our data add to the increasing evidence that EEA is a safe and effective alternative for craniopharyngiomas.

ACKNOWLEDGMENTS

The authors thank Dr. Xiaoming Zhu for statistical consultation and Dr. Ryan P. Ceddia for language editing.

REFERENCES

- Karavitaki N, Cudlip S, Adams CB, Wass JA. Craniopharyngiomas. *Endocr Rev*. 2006;27:371-397.
- Olsson DS, Andersson E, Bryngelsson IL, Nilsson AG, Johannsson G. Excess mortality and morbidity in patients with craniopharyngioma, especially in patients with childhood onset: a population-based study in Sweden. *J Clin Endocrinol Metab*. 2015;100:467-474.
- Pereira AM, Schmid EM, Schutte PJ, Voormolen JH, Biermasz NR, van Thiel SW, et al. High prevalence of long-term cardiovascular, neurological and psychosocial morbidity after treatment for craniopharyngioma. *Clin Endocrinol*. 2004;62:197-204.
- Crowley RK, Hamnvik OP, O'Sullivan EP, Behan LA, Smith D, Agha A, et al. Morbidity and mortality in patients with craniopharyngioma after surgery. *Clin Endocrinol*. 2010;73:516-521.
- Muller HL, Gebhardt U, Pohl F, Flentje M, Emser A, Warmuth-Metz M, et al. Relapse pattern after complete resection and early progression after incomplete resection of childhood craniopharyngioma. *Klin Padiatr*. 2006;218:315-320.
- Muller HL. Childhood craniopharyngioma: treatment strategies and outcomes. *Expert Rev Neurother*. 2014;14:187-197.
- Iannalfi A, Fragkandrea I, Brock J, Saran F. Radiotherapy in craniopharyngomas. *Clin Oncol (R Coll Radiol)*. 2013;25:654-667.
- Yang I, Sughrue ME, Rutkowski MJ, Kaur R, Ivan ME, Aranda D, et al. Craniopharyngioma: a comparison of tumor control with various treatment strategies. *Neurosurg Focus*. 2010;28:E5.
- Liu JK, Sevak IA, Carmel PW, Eloy JA. Microscopic versus endoscopic approaches for craniopharyngiomas: Choosing the optimal surgical corridor for maximizing extent of resection and complication avoidance using a personalized, tailored approach. *Neurosurg Focus*. 2016;41:E5.
- Yasargil MG, Curcic M, Kis M, Siegenthaler G, Teddy PJ, Roth P. Total removal of craniopharyngiomas: approaches and long-term results in 144 patients. *J Neurosurg*. 1990;73:3-11.
- Duff J, Meyer FB, Ilstrup DM, Laws ER Jr, Schleck CD, Scheithauer BW. Long-term outcomes for surgically resected craniopharyngiomas. *Neurosurgery*. 2000;46:291-302 [discussion 302-305].
- Fahlbusch R, Honegger J, Paulus W, Huk W, Buchfelder M. Surgical treatment of craniopharyngiomas: experience with 168 patients. *J Neurosurg*. 1999;90:237-250.
- Maira G, Anile C, Rossi GF, Colosimo C. Surgical treatment of craniopharyngiomas: an evaluation of the transsphenoidal and pterional approaches. *Neurosurgery*. 1995;36:715-724.
- Fernandez-Miranda JC, Gardner PA, Snyderman CH, Devaney KO, Strojan P, Suarez C, et al. Craniopharyngioma: a pathologic, clinical, and surgical review. *Head Neck*. 2012;34:1036-1044.
- Chakrabarti I, Amar AP, Couldwell W, Weiss MH. Long-term neurological, visual, and endocrine outcomes following transnasal resection of craniopharyngioma. *J Neurosurg*. 2005;102:650-657.
- Campbell PG, McGettigan B, Luginbuhl A, Yadla S, Rosen M, Evans JJ. Endocrinological and ophthalmological consequences of an initial endonasal endoscopic approach for resection of craniopharyngiomas. *Neurosurg Focus*. 2010;28:E8.
- Solari D, Morace R, Cavallo LM, Amoroso F, Cennamo G, Del Basso DECM, et al. The endoscopic endonasal approach for the management of craniopharyngiomas. *J Neurosurg Sci*. 2016;60:454-462.
- Komotar RJ, Starke RM, Raper DM, Anand VK, Schwartz TH. Endoscopic endonasal compared with microscopic transsphenoidal and open transcranial resection of craniopharyngiomas. *World Neurosurg*. 2012;77:329-341.
- Jeswani S, Nuno M, Wu A, Bonert V, Carmichael JD, Black KL, et al. Comparative analysis of outcomes following craniotomy and expanded endoscopic endonasal transsphenoidal resection of craniopharyngioma and related tumors: a single-institution study. *J Neurosurg*. 2016;124:627-638.
- Moussazadeh N, Prabhu V, Bander ED, Cusic RC, Tsiouris AJ, Anand VK, et al. Endoscopic endonasal versus open transcranial resection of craniopharyngiomas: a case-matched single-institution analysis. *Neurosurg Focus*. 2016;41:E7.
- Wannemuehler TJ, Rubel KE, Hendricks BK, Ting JY, Payner TD, Shah MV, et al. Outcomes in transcranial microsurgery versus extended endoscopic endonasal approach for primary resection of adult craniopharyngiomas. *Neurosurg Focus*. 2016;41:E6.
- Prieto R, Pascual JM, Barrios L. Topographic diagnosis of craniopharyngiomas: the accuracy of MRI findings observed on conventional T1 and T2 images. *AJNR Am J Neuroradiol*. 2017;38:2073-2080.
- Prieto R, Pascual JM, Barrios L. Optic chiasm distortions caused by craniopharyngiomas. Clinical-MRI correlation and influence on visual outcome. *World Neurosurg*. 2014;83:500-529.
- Pascual JM, Prieto R, Carrasco R, Barrios L. Displacement of mammillary bodies by craniopharyngiomas involving the third ventricle: surgical-MRI correlation and use in topographical diagnosis. *J Neurosurg*. 2013;119:381-405.
- Fleseriu M, Hashim IA, Karavitaki N, Melmed S, Murad MH, Salvatori R, et al. Hormonal replacement in hypopituitarism in adults: an Endocrine

- Society clinical practice guideline. *J Clin Endocrinol Metab.* 2016;101:3888-3921.
26. Zhou BF. Predictive values of body mass index and waist circumference for risk factors of certain related diseases in Chinese adults: study on optimal cut-off points of body mass index and waist circumference in Chinese adults. *Biomed Environ Sci.* 2002;15:83-96.
 27. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International diabetes Federation Task Force on Epidemiology and Prevention; National heart, Lung, and blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation.* 2009;120:1640-1645.
 28. Liu JK, Cole CD, Kestle JR, Brockmeyer DL, Walker ML. Cranial base strategies for resection of craniopharyngioma in children. *Neurosurg Focus.* 2005;18:E9.
 29. Conger AR, Lucas J, Zada G, Schwartz TH, Cohen-Gadol AA. Endoscopic extended trans-sphenoidal resection of craniopharyngiomas: Nuances of neurosurgical technique. *Neurosurg Focus.* 2014;37:E10.
 30. Van Effenterre R, Boch AL. Craniopharyngioma in adults and children: a study of 122 surgical cases. *J Neurosurg.* 2002;97:3-11.
 31. Cavallo LM, Frank G, Cappabianca P, Solari D, Mazzatenta D, Villa A, et al. The endoscopic endonasal approach for the management of craniopharyngiomas: a series of 103 patients. *J Neurosurg.* 2014;121:100-113.
 32. Mortini P, Losa M, Pozzobon G, Barzaghi R, Riva M, Acerno S, et al. Neurosurgical treatment of craniopharyngioma in adults and children: early and long-term results in a large case series. *J Neurosurg.* 2011;114:1350-1359.
 33. Cavallo LM, Solari D, Esposito F, Villa A, Minniti G, Cappabianca P. The role of the endoscopic endonasal route in the management of craniopharyngiomas. *World Neurosurg.* 2014;82:S32-S40.
 34. Ahmet A, Blaser S, Stephens D, Guger S, Rutkas JT, Hamilton J. Weight gain in craniopharyngioma: a model for hypothalamic obesity. *J Pediatr Endocrinol Metabol.* 2006;19:121-127.
 35. Van Gompel JJ, Nippoldt TB, Higgins DM, Meyer FB. Magnetic resonance imaging-graded hypothalamic compression in surgically treated adult craniopharyngiomas determining post-operative obesity. *Neurosurg Focus.* 2010;28:E3.
 36. Park SW, Jung HW, Lee YA, Shin CH, Yang SW, Cheon JE, et al. Tumor origin and growth pattern at diagnosis and surgical hypothalamic damage predict obesity in pediatric craniopharyngioma. *J Neurooncol.* 2013;113:417-424.
 37. Gautier A, Godbout A, Grosheny C, Tejedor I, Coudert M, Courtillot C, et al. Markers of recurrence and long-term morbidity in craniopharyngioma: a systematic analysis of 171 patients. *J Clin Endocrinol Metab.* 2012;97:1258-1267.
 38. Srinivasan S, Ogle GD, Garnett SP, Briody JN, Lee JW, Cowell CT. Features of the metabolic syndrome after childhood craniopharyngioma. *J Clin Endocrinol Metab.* 2004;89:81-86.
 39. Stripp DC, Maity A, Janss AJ, Belasco JB, Tochner ZA, Goldwein JW, et al. Surgery with or without radiation therapy in the management of craniopharyngiomas in children and young adults. *Int J Radiat Oncol Biol Phys.* 2004;58:714-720.
 40. Sahakitrungruang T, Klomchan T, Supornsilchai V, Wacharasindhu S. Obesity, metabolic syndrome, and insulin dynamics in children after craniopharyngioma surgery. *Eur J Pediatr.* 2011;170:763-769.
 41. Song QB, Zhao Y, Liu YQ, Zhang J, Xin SJ, Dong GH. Sex difference in the prevalence of metabolic syndrome and cardiovascular-related risk factors in urban adults from 33 communities of China: the CHPSNE study. *Diab Vasc Dis Res.* 2015;12:189-198.
 42. Ming J, Xu S, Yang C, Gao B, Wan Y, Xing Y, et al. Metabolic syndrome and chronic kidney disease in general Chinese adults: results from the 2007-08 China National Diabetes and Metabolic Disorders Study. *Clin Chim Acta.* 2014;430:115-120.
 43. Simoneau-Roy J, O'Gorman C, Pencharz P, Adeli K, Daneman D, Hamilton J. Insulin sensitivity and secretion in children and adolescents with hypothalamic obesity following treatment for craniopharyngioma. *Clin Endocrinol.* 2010;72:364-370.
 44. Gotto AM Jr, Brinton EA. Assessing low levels of high-density lipoprotein cholesterol as a risk factor in coronary heart disease: a working group report and update. *J Am Coll Cardiol.* 2004;43:717-724.

Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received 29 March 2018; accepted 13 August 2018

*Citation: World Neurosurg. (2019) 121:e8-e14.
https://doi.org/10.1016/j.wneu.2018.08.092*

Journal homepage: www.journals.elsevier.com/world-neurosurgery

Available online: www.sciencedirect.com

1878-8750/\$ - see front matter © 2018 Elsevier Inc. All rights reserved.