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Advances in craniopharyngioma: From physiology to clinical management

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Published in
Frontiers in Neurology
Frontiers in Oncology

ISSN 1664-8714
ISBN 978-2-83251-757-4
DOI 10.3389/978-2-83251-757-4

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Advances in craniopharyngioma: From physiology to clinical management

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Citation

Gui, S., Laws, E. R., Cappabianca, P., eds. (2023). *Advances in craniopharyngioma: From physiology to clinical management*. Lausanne: Frontiers Media SA.

doi: 10.3389/978-2-83251-757-4

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frontiers | Frontiers in Neurology

TYPE Editorial
PUBLISHED 10 February 2023
DOI 10.3389/fneur.2023.1118806

OPEN ACCESS

EDITED AND REVIEWED BY
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SPECIALTY SECTION
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Neurology

RECEIVED 08 December 2022
ACCEPTED 04 January 2023
PUBLISHED 10 February 2023

CITATION
Gui S (2023) Editorial: Advances in craniopharyngioma: From physiology to clinical management. *Front. Neurol.* 14:1118806. doi: 10.3389/fneur.2023.1118806

Editorial: Advances in craniopharyngioma: From physiology to clinical management

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KEYWORDS

craniopharyngioma, advances, physiology, clinical management, future

Editorial on the Research Topic
Advances in craniopharyngioma: From physiology to clinical management

Craniopharyngioma (CP) is any epithelial tumor that originates from remnants of the craniopharyngeal duct epithelium. There are 0.5–2.5 new cases per million people per year worldwide. CP accounts for 1.2–4.6% of all intracranial tumors and 5–11% of brain tumors in children (1, 2). The clinical manifestations include pituitary/hypothalamic deficiencies, visual impairment, and increased intracranial pressure. These symptoms are caused by the tumor mass impacting the optic nerves/chiasm and hypothalamic–pituitary axis. In the early twentieth century, surgery for CP was extremely challenging and risky owing to the close anatomical proximity to the optic chiasm and hypothalamic–pituitary axis. Quality of life (QOL) and neuropsychological function are frequently impaired following surgery, such as visual deterioration, neuroendocrine deficiencies and hypothalamic injury (3). Current treatment strategies are debated, ranging from radical surgical strategies such as gross-total resection (GTR) and the extended transsphenoidal endoscopic endonasal approach (EEA) to limited surgical approaches focused on the preservation of hypothalamic and visual integrity and QOL after treatment (4). Therefore, research on how to protect neurological structures and functions of the optic nerve, pituitary stalk and hypothalamus during the surgical resection of CP is crucial. This Research Topic focused on the protection of important structures during surgical resection of CP, the mechanism of the development of CP and its related neurocognitive deficits. The aim of this Research Topic was to integrate the high-quality and up-to-date advances in the above fields. Therefore, we enrolled 20 articles (including 16 original research, 3 reviews and 1 opinion) covering the following themes:

1. Intraventricular craniopharyngiomas (IVCs): In the last few decades, experience gained from using the EEA has made this technique the gold standard for treating most IVCs. This group of articles studied special features in clinical presentation, imaging, management, and surgical outcome of IVCs (Deopujari et al.). Their deep-seated location and limited surgical field of-view makes minimally invasive EEA most suitable for their excision, especially the expanded Transsphenoidal Trans-Lamina Terminalis Approach (TLTA) (Cao et al.). Notably, the concept of "maximum safe resection," which prioritizes the preservation of hypothalamic functions and psychological autonomy over the completeness of resection should guide surgical actions when dealing with such a complex lesion (Pascual et al.).

2. Pediatric craniopharyngiomas: Extended endoscopic endonasal resection of CP may be used as a safe and effective approach for children. Due to the poor pneumatization of the sphenoid sinus and Narrow surgical space in children, surgical techniques of exposing the sellar region, removing the tumor, and reconstructing the skull base, as well as post-operative management of patients were proposed (Wu D. et al.). Remarkably, Boekhoff et al. also analyzed the incidence of cerebral infarction (CI) in a cohort of 244 German childhood-onset CP patients recruited between 2007 and 2019 with a high degree of completeness in the prospective, randomized trial KRANIOPHARYNGEOM 2007.
3. Hypothalamic involvement/invasion: Hypothalamic damage may severely impair the QOL of patients and has an impact on long-term mortality. The most dramatic complication is the development of a hypothalamic syndrome (HS), which is typically associated with neuroendocrine disorders and includes neurocognitive changes, morbid hypothalamic obesity and related systemic complications, a variety of sleep disorders (Romigi et al.), and metabolic syndrome (Scarano et al.). Neurocognitive and physiopathological assessment and intervention before and after surgery are important in patients with larger tumors, invading the third ventricle, and tumors with hypothalamic invasion (Zhao R. et al.). The management of patients suffering from HS should be multidisciplinary, and future avenues for development of new drugs may hopefully lead to positive effects.
4. Visual protection: Specific to visual function protection, visual-evoked potentials (VEP) have proven to be an effective modality for reflecting the integrity of visual pathway from retina to the pulvinar cortex. Furthermore, optical coherence tomography (OCT) can serve as a non-invasive *in vivo* method to quantitatively and objectively measure thinner circumpapillary retinal nerve fiber layer (cpRNFL) and macular ganglion cell complex (mGCC), which have been applied to surgeries with the risk of visual pathway damage and serve as a predictor of visual recovery after surgery. Two studies found that OCT and VEP were valuable for predicting post-operative visual function in patients undergoing CP resection *via* extended EEA and intraoperative VEP monitoring is an effective method for preventing visual deterioration (Qiao et al.; Tao et al.).
5. Endocrinological function protection/pituitary stalk preservation: One article reviewed the latest research progress on the pathogenesis, presentation, significance, and treatment of endocrine disorders in patients with CP (Zhou et al.). And Tao Hong retrospectively studied a total of 183 patients with CP and demonstrated that intact hypothalamic structure is critical in maintaining pituitary function, suggesting that the pituitary stalk infiltrated by CP could be sacrificed to achieve radical resection, without substantially rendering significantly worse endocrinological efficiency 1 year after surgery (Wu J. et al.). Whereas, Chen et al. found that preserving the pituitary stalk does not appear to increase the risk of non-GTR and tumor recurrence/progression and might help reduce the risk of surgically induced hypothyroidism and diabetes insipidus. Thus, the latter authors recommend preserving the pituitary stalk in peripheral type suprasellar CP with normal pituitary function, especially in cases without hypothyroidism or diabetes insipidus, and stalk sacrifice can be considered in central type tumors with severe pre-operative endocrinopathy.
6. Surgical approach/strategy comparison: A retrospective review compared surgical outcomes and complications between transcranial surgery (TCS) and endoscopic endonasal surgery (EES) of CP (Nie et al.). The conclusion supported the view that EES is a safe and effective minimally invasive surgery compared to TCS. Compared to TCS, EES has fewer surgical complications and a lower recurrence rate (5).
7. Basic research: One study performed unsupervised cluster analysis on the 725 immune-related genes and arrays of 39 patients with adamantinomatous craniopharyngioma (ACP) patients in GSE60815 and GSE94349 databases. Two novel immune subtypes were identified, namely immune resistance (IR) subtype and immunogenic (IG) subtype. The expression levels of immune checkpoint molecules (PD1, PDL1, PDL2, TIM3, CTLA4, Galectin9, LAG3, and CD86) were significantly upregulated in the IG subtype (Yuan et al.). Guo introduced an integrated algorithm for identifying lncRNAs and TFs regulating the ACP-related pathway, which may serve as a valuable resource for understanding the mechanisms underlying ACP-related lncRNAs and TFs (Xu, Guo et al.).
8. New classification/technology: A WDR89-based nomogram mode was constructed to predict the immune classification of ACP with excellent performance (Yuan et al.). This predictive model provided a reliable classification assessment tool for clinicians and aids treatment decision-making in the clinic. The technical route of intelligent diagnosis is based on the application of traditional machine learning and deep learning models in the clinical diagnosis of CP from the aspects of differential classification, prediction of tissue invasion and gene mutation, prognosis prediction, and so on (Qin et al.). One study aimed to establish and validate a nomogram based on preoperative imaging features and blood indices to differentiate between cystic-solid pituitary adenomas and CP (Zhao Z. et al.).
9. Future trends: Exploring novel methods of automatized analysis of data for gaining knowledge in any medical field is an encouraging task, particularly in such an extremely challenging tumor as CP. Two articles researched the clinical features and long-term recurrence of CP, investigated the research trends and evaluated research hotspots using bibliometric analysis and nomograms of a retrospective, multiple-center, cohort study, separately (Li et al.; Xu, Wei et al.). This research provides a comprehensive analysis of the scientific progress of CP in the past decades, and insight into the development of the CP research field, highlights research trends over time, and helps identify valuable future directions, whose conclusions could serve as the practical tool for individual strategies based on the patient's baseline characteristics to achieve a better prognosis.

In conclusion, professional expertise and advanced technology in diagnostics and treatment have a relevant impact on outcome and prognosis after CP. Multicenter-based networks for reference assessments should be considered to assure high standards of treatment quality (6). Future efforts to improve prognosis, outcome and QOL in patients with CP should be focused on improving our understanding of the molecular pathogenesis of CP, with the perspective of developing targeted therapies effective against

progression and hypothalamic involvement as well as surgical and radio-oncological treatment strategies, aiming at hypothalamus-sparing approaches to prevent sequelae, and treatments and interventions for hypothalamic obesity and neuropsychological sequelae after CP resection. Furthermore, policy efforts should be made to establish and confirm criteria for the quality of multidisciplinary treatment of CP as well as to improve the infrastructure of surgical instrumentation to provide equitable care across the world (7).

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers in Oncology

ORIGINAL RESEARCH
published: 09 July 2021
doi: 10.3389/fonc.2021.709321

Development of a Nomogram Based on Preoperative Bi-Parametric MRI and Blood Indices for the Differentiation Between Cystic-Solid Pituitary Adenoma and Craniopharyngioma

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Background: Given the similarities in clinical manifestations of cystic-solid pituitary adenomas (CS-PAs) and craniopharyngiomas (CPs), this study aims to establish and validate a nomogram based on preoperative imaging features and blood indices to differentiate between CS-PAs and CPs.

Methods: A departmental database was searched to identify patients who had undergone tumor resection between January 2012 and December 2020, and those diagnosed with CS-PAs or CPs by histopathology were included. Preoperative magnetic resonance imaging (MRI) features as well as blood indices were retrieved and analyzed. Radiological features were extracted from the tumor on contrast-enhanced T1 (CE-T1) weighted and T2 weighted sequences. The two independent samples *t*-test and principal component analysis (PCA) were used for feature selection, data dimension reduction, and radiomics signature building. Next, the radiomics signature was put in five classification models for exploring the best classifier with superior identification performance. Multivariate logistic regression analysis was then used to establish a radiomic-clinical model containing radiomics and hematological features, and the model was presented as a nomogram. The performance of the radiomics-clinical model was assessed by calibration curve, clinical effectiveness as well as internal validation.

Results: A total of 272 patients were included in this study: 201 with CS-PAs and 71 with CPs. These patients were randomized into training set (n=182) and test set (n=90). The radiomics signature, which consisted of 18 features after dimensionality reduction, showed superior discrimination performance in 5 different classification models. The area under the curve (AUC) values of the training set and the test set obtained by the radiomics signature

OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: *13 May 2021*
Accepted: *18 June 2021*
Published: *09 July 2021*

Citation:
Zhao Z, Xiao DD, Nie CS, Zhang H, Jiang XB, Jecha AR, Yan PF and Zhao HY (2021) Development of a Nomogram Based on Preoperative Bi-Parametric MRI and Blood Indices for the Differentiation Between Cystic-Solid Pituitary Adenoma and Craniopharyngioma. Front. Oncol. 11:709321. doi: 10.3389/fonc.2021.709321

are 0.92 and 0.88 in the logistic regression model, 0.90 and 0.85 in the Ridge classifier, 0.88 and 0.82 in the stochastic gradient descent (SGD) classifier, 0.78 and 0.85 in the linear support vector classification (Linear SVC), 0.93 and 0.86 in the multilayers perceptron (MLP) classifier, respectively. The predictive factors of the nomogram included radiomic signature, age, WBC count, and FIB. The nomogram showed good discrimination performance (with an AUC of 0.93 in the training set and 0.90 in the test set) and good calibration. Moreover, decision curve analysis (DCA) demonstrated satisfactory clinical effectiveness of the proposed radiomic-clinical nomogram.

Conclusions: A personalized nomogram containing radiomics signature and blood indices was proposed in this study. This nomogram is simple yet effective in differentiating between CS-PAs and CPs and thus can be used in routine clinical practice.

Keywords: pituitary adenoma, craniopharyngioma, radiomics, machine learning, predictive model, nomogram

INTRODUCTION

Pituitary adenomas (PAs) and craniopharyngiomas (CPs) are the two most common neoplasms in the sellar/parasellar region (1). PAs are benign tumors arising from the adenohypophysial cells; with an incidence of 80–90 patients per 100,000 population, they account for 15-20% of all central nervous system (CNS) tumors (2, 3). Cystic-solid pituitary adenomas (CS-PAs) refer to those PAs with such features as cystic change, necrosis, and hemorrhage. CPs are also benign neoplasms that are thought to be derived from the remnants of Rathke's pouch or primitive craniopharyngeal duct (4, 5). CPs are relatively rare compared with PAs, with an incidence reported to be approximately 0.13-7.1 patients per 100,000 population; they account for 2-5% of all CNS tumors in adults and 5.6-13% in children (6–8). Although with different origins and pathogenesis, CS-PAs and CPs share many commonalities in their clinical manifestations, including intracranial hypertension, endocrine dysfunction, and visual disturbance. Besides, treatment considerations and prognosis are also different for the two entities. Therefore, accurate preoperative differentiation between them carries great clinical importance.

Up till now, preoperative identification of CS-PAs and CPs is primarily based on the combined information from different imaging modalities. Computed tomography (CT) is useful in demonstrating calcification, a feature that can often be observed in CPs, but this feature can also be present in some cases with CS-PAs (9, 10), thus diminishing its differentiating effectiveness. Magnetic resonance imaging (MRI), with the advantages of good tissue contrast, no bone artifacts, and multi-faceted imaging, is currently the most established imaging modality for the diagnosis of sellar/parasellar tumors (11). Several studies have investigated possible MRI features that can help differentiate between these two tumor types, such as tumor location, tumor shape, T1 image signal intensity, and cystic changes. Their results preliminarily showed the effectiveness of certain imaging features. However, a major limitation of these features lies in their subjective and qualitative nature. The actual performance of these parameters is highly subjected to the experience and expert knowledge of the neurosurgeons/neuroradiologists, which limits their clinical application. In contrast, objective and quantitative methods are preferable in these scenarios.

Radiomics is an emerging method for such tasks (12). Radiomics can extract a large number of image features in a high-throughput manner from medical images, which can quantitatively and objectively reflect tumor texture and heterogeneity (13–15). These features are usually impossible to be directly detected by the naked eye. In previous studies, radiomics has been applied to the differential diagnosis as well as prognosis prediction in various brain tumors, such as meningiomas (16–18), gliomas (19–21), and metastases (22), and lymphomas (23). However, its utility in sellar/parasellar tumors is still unclear. Besides, some preoperative blood indices, especially inflammatory markers, also deserve investigation. These indices appear to be of diagnostic and prognostic value in several neoplastic diseases including intracranial tumors (24, 25). These two categories of parameters share the advantage of being able to be retrieved directly from routine preoperative examination and thus suitable for future clinical application.

In the present study, we aimed to determine whether routine preoperative data could be used to differentiate between CS-PAs and CPs. We developed a multivariate prediction model based on a combination of preoperative bi-parametric MRI and blood indices, and internally validated its diagnostic performance. In addition, we presented the model as a nomogram for ease of clinical use.

PATIENTS AND METHODS

Study Population

This study was conducted in accordance with the Declaration of Helsinki and approved by the institutional review board of Wuhan Union Hospital, the patients' informed consent was waived due to the retrospective nature of the study. We collected cases from January 2012 to December 2020 that were pathologically confirmed as CS-PAs or CPs in the database.

All patients were assessed by the inclusion and exclusion criteria. The inclusion criteria were as follows: (1) pathologically diagnosed with CS-PAs or CPs; (2) preoperative MRI included CE-T1 weighted and T2 weighted sequences (3) the number of lesion-bearing image slices was not less than three; (4) blood examinations included blood routine test and liver function test, which should be performed within two weeks before surgery; (5) there were no apparent signs of infection. The exclusion criteria were as follows: (1) with incomplete MRI data [for example, some patients may undergo MRI scans in other hospitals, or MRI data were incomplete/inaccessible on the Picture Archiving and Communication System (PACS)]; (2) with a history of brain trauma, brain tumors, surgery, hematological diseases, or ongoing infectious diseases; (3) have received chemotherapy, radiotherapy, or hormone therapy for any reasons before surgery. Finally, 272 patients were included in this study, of which 201 were with CS-PAs and 71 were with CPs. This selection process is presented in **Figure 1**.

Data Acquisition and Processing

The preoperative MRI images were collected from the PACS of the Radiology Department in our hospital. These images were performed using a 1.5T (Siemens Avanto, Erlangen, Germany) or 3.0T (Siemens Trio, Erlangen, Germany) magnetic resonance clinical scanner with standard head and neck coils, and the scans were performed in coronal, sagittal, and transverse positions.

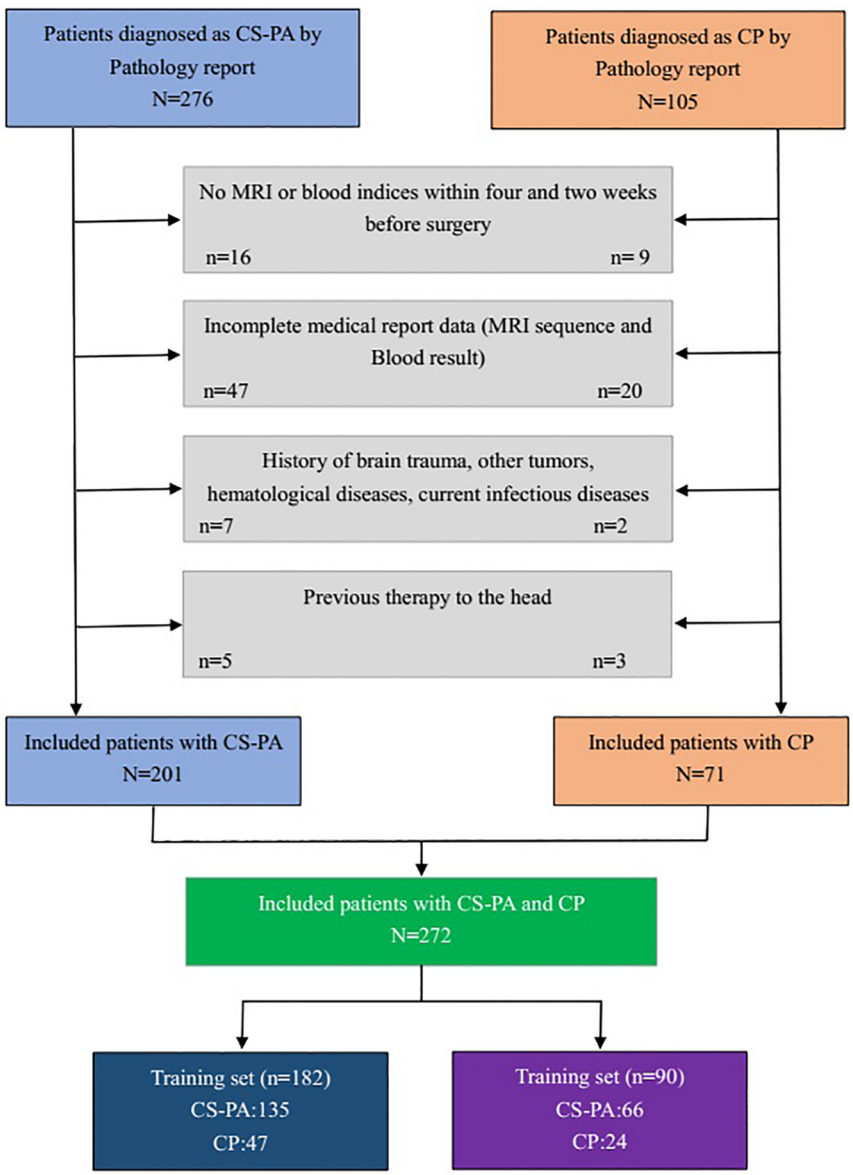

FIGURE 1 | The flowchart of patient selection.

The sequence parameters on the CE-T1 weighted images were as follows: The repetition time (TR)/echo time (TE)= 660/10 ms, data matrix = 256 × 256, slice thickness = 3 mm, flip angle = 90°. The sequence parameters on the T2 weighted images were as follows: TR/TE= 3000/65 ms, data matrix = 256 × 384, slice thickness = 5 mm, flip angle = 90°. The contrast-enhanced scanning was conducted within 200 s after injection of gadopentetate dimeglumine (0.1 mmol/kg). In our study, CE-T1 and T2-weighted images were used for analysis.

Region of interest (ROI), drawn manually by one researcher (Z Zhao, with 3 years of experience in PA research), was performed layer by layer on CE-T1 and T2 weighted images for all patients by using ITK-SNAP software (University of Pennsylvania, www.itksnap.org). Then, the complete 3D images of the tumor were extracted after segmentation. Lots of irrelevant information will be introduced when painting a very small tumor area. Therefore, the sections with too small tumor areas (<10 pixels) are eliminated in the process of tumor segmentation. Since the tumor region is usually not as strongly enhanced as the surrounding tissues after gadolinium-based contrast administration, CE-T1 weighted images can distinguish PAs and CPs from surrounding tissues, thereby facilitating segmentation of ROI on the images (26). In addition, CE-T1 weighted images were also referred when the tumor boundaries on T2 weighted images were uncertain.

In order to assess the stability of the identification features, 50 patients were randomly selected from the entire samples. Another experienced neurosurgeon (DD Xiao, with 6 years of experience in sellar tumor research) also described ROI on CE-T1 and T2 weighted images. Then the same feature extraction process was performed on the ROI drawn by the two researchers, and the inter-observer correlation coefficient (ICC) was calculated to evaluate the consistency of all quantitative features extracted from CE-T1 and T2 weighted images. Moreover, disagreements regarding tumor boundaries were recorded and resolved by a senior neurosurgeon (PF Yan, with 10 years of clinical experience in neurosurgery).

Extraction of Radiomic Features

The feature extraction was conducted by using the open-source python package named pyradiomics (version 3.0.0, https://github com/AIM-Harvard/pyradiomics) (27). The images were pre-processed before feature extraction, including normalization, discretization and resampling to a 3x3x3mm isotropic voxel size. These steps are considered to improve the reliability and robustness of radiomic analysis and are recommended by the software package developer as part of the workflow (28, 29). There are three types of features calculated in total. First-order statistic features (N=18) describe the histogram of voxel intensity values contained within the ROI through the widely used metrics, such as mean, standard deviation, and variance. Geometric features (N=14) describe the 3D shape and size of the ROI and were calculated only on the 3D mask of the ROI (i.e., independent from the gray level intensity distribution in the ROI). Textural features describing patterns or spatial distribution of voxel intensities were calculated from gray level co-occurrence matrix (GLCM, N=21), gray level size zone matrix (GLSZM, N=16), gray level run length matrix (GLRLM, N=16), neighboring gray tone difference matrix (NGTDM, N=5), gray level dependence matrix (GLDM, N= 14) texture matrices. In addition to the original image, 10 derived images were generated using LoG or Wavelet filters. Hence, a total of 1015 features were extracted for each patient: 14 shape features, 198 first-order features, and 803 textural features. In addition, the volume of the entire tumor was calculated by using PyRadiomics, too. The algorithm can be found in **Supplementary Section 1**.

Blood Indices

The blood indices within two weeks before surgery was obtained and included from the electronic medical record system. If multiple results are available, the latest results before surgery will be used. From these results, the absolute counts of white blood cells (WBC), red blood cells (RBC), hemoglobin, platelets, neutrophils, lymphocytes, monocytes, albumin and fibrinogen (FIB) were collected. Furthermore, the following blood indices were calculated through the above indices: NLR (the neutrophil-to-lymphocyte ratio), dNLR [derived NLR, neutrophil/(leukocyte- neutrophil)], PLR (the platelet-to-lymphocyte ratio), MLR (the monocyte-to-lymphocyte ratio), LMR(the lymphocyte-to- monocyte ratio), NPR (the neutrophil-to-platelet ratio), NPI [prognostic nutritional index, albumin+(5*lymphocyte)], SII (platelet*NLR). This calculation method has been reported in many studies (25, 30, 31).

Feature Selection Method

Firstly, the features of the CE-T1, T2 and CE-T1&T2 were normalized with z-scores in order to obtain a standard normal distribution of image intensities. Z-scores normalization is also called standard deviation standardization. The mean value of the processed data is 0 and the standard deviation is 1, the conversion formula is as follows:

$$X^* = \frac{X - \overline{X}}{\sigma}$$

Where X^* is the transformed eigenvalue of the variable X, $\overline{X}$ is the mean value of the original data, σ is the standard deviation of the original data.

High-dimensional data may contain highly redundant and irrelevant information, which may lead to overfitting and greatly reduce the performance of the machine learning algorithm (32). Therefore, feature dimensionality reduction is necessary. In this study, the two steps were performed to achieve the best dimensionality reduction effect and effectively avoid overfitting. The meaningful features were selected based on the univariate statistical test (*t*-test) between the CS-PAs group and the CPs group in all patients. Then, the principal component analysis (PCA) with varimax-rotation was applied for dimensionality reduction, and in an effort to retain more variance and reduce redundancy of the variables. Furthermore, the logistic regression was conducted in all samples to compare the diagnostic performance with the feature sets of CE-T1, T2 and CE-T1&T2, respectively.

Construction of Classification Models

Based on the above model comparison, the feature set with diagnostic performance was selected for classification model construction. Since the patient numbers of CS-PAs and CPs are quite different, the patients were divided into a training set and test set with 2:1 according to stratification cross-validation. The random up-sampling technique is used to up-sample the training set so that the positive and negative sample sizes of the training set are the same (The positive and negative samples refer to CS-PAs and CPs in this study, respectively.). The *t*-test was employed to filter the meaningless features, next the PCA was applied for data dimensionality reduction and the variance was set to 0.9. In order to avoid overfitting in the training set, the recursive feature elimination method of five-fold cross-validation was conducted to select the optimal feature set size.

Besides, for the purpose of exploring better machine-learning classification models, we applied five machine learning algorithms: logistic regression, Ridge classifier, stochastic gradient descent (SGD) classifier, linear support vector classification (Linear SVC) and multilayers perceptron (MLP) classifier. The area under the curve (AUC), accuracy, sensitivity (i.e. true positive rate) and specificity (i.e. true negative rate) were used to evaluate the predictive performance and stability of the classifiers. Then the trained model was assessed in an independent test set. The classifier with AUC>0.9 in the training set and the highest AUC value in the test set are considered to be the final radiomics model. Feature classification methods are all implemented using SCRICIT-LEARN machine-learning library.

Development of an Individualized Nomogram

The Least absolute shrinkage and selection operator (LASSO) was performed for filtering the variables on the following clinical candidate predictors: age, gender, tumor volume, blood indices and their derivation results. A recursive feature elimination method of five-fold cross-validation was applied to select the best λ (a parameter in LASSO to be determined).

Giving that providing a more personalized prediction model, combined the remaining clinical parameters and the radiomics signature, a nomogram based on multiple logistic regression was established in the training set and validated in the test set. The overall workflow of radiomics processing and nomogram construction is shown in **Figure 2**.

The calibration curves were plotted for the training and test sets, and the Hosmer-Lemeshow test was conducted to assess the agreement between the predicted risks and observed outcomes. Furthermore, the decision curve analysis (DCA) was conducted to determine the clinical usefulness of the nomogram by quantifying the net benefits at different threshold probabilities.

Statistical Analysis

The statistical analysis and figure plots were performed using R software (version 4.0.1; http://www.R-project.org) and Python software (version 3.7, http://www.python.org). The continuous variables are reported as mean ± standard deviation (SD) or median and inter quartile range (IQR), whereas categorical variables are presented as the absolute and relative frequencies. Statistical testing utilized non-parametric tests with Mann-

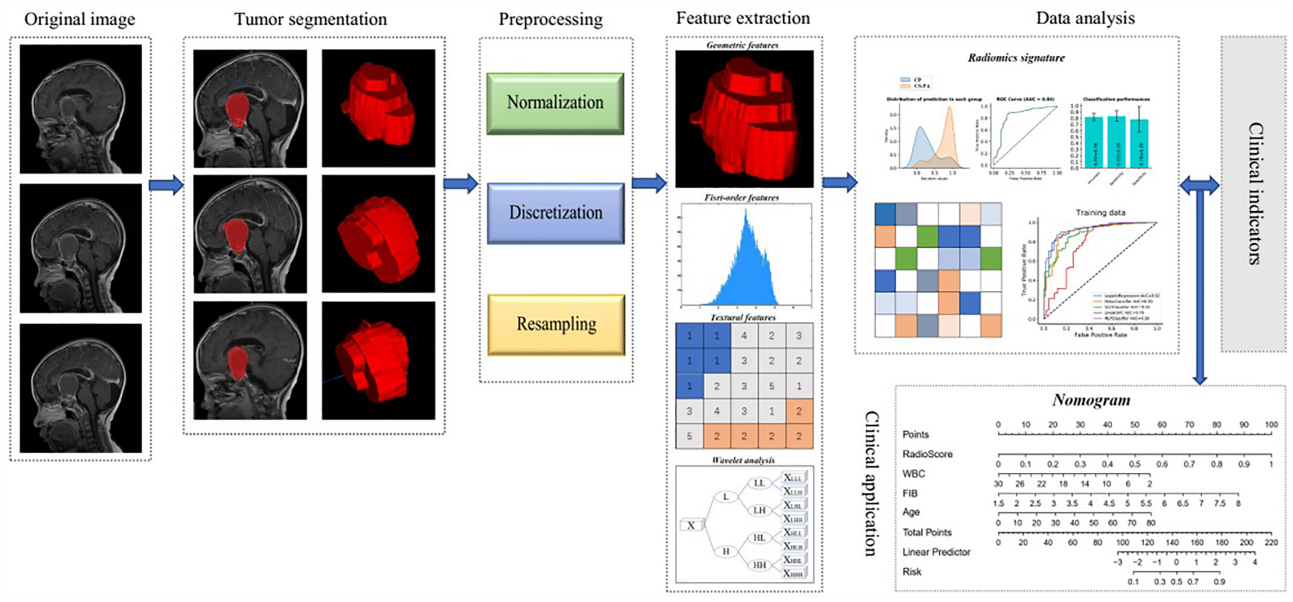

FIGURE 2 | The overall workflow of radiomics processing and nomogram construction.

Whitney U test and Kruskal-Wallis test for continuous variables, and the chi-square test or Fisher exact test for categorical variables. All statistical tests were two-tailed and conducted with a statistical significance level set at $p<0.05$.

RESULTS

Patient Characteristics

Among of 272 patients included in this study (age, 50.11 ± 11.85 years), 201 (73.9%) were diagnosed as CS-PAs and 71 (26.1%) as CPs based on gold standard-postoperative pathological results. The patients characteristics in the groups of CS-PAs and CPs are listed in **Table 1**. Demographic results show that the patients of the CS-PAs group and the CPs group have significant statistical significance in age ($p<0.001$) and tumor volume ($p=0.028$), but there was no significant difference in gender ($p=0.417$). Among the blood indices, WBC count ($p<0.001$), neutrophil ($p<0.001$), monocyte ($p=0.023$) and FIB ($p<0.001$) are statistically different between the CS-PAs group and CPs group, and the other indicators are not statistically significant (all $p>0.05$). Moreover, satisfactory inter-observer reproducibility was achieved for both CE-T1 and T2 imaging features, with the calculated ICC range of 0.753–0.932 for CE-T1 features and 0.732–0.895 for T2 features. Therefore, it can be basically considered that the ROIs drawn by two neurosurgeons are highly consistent.

Feature Selection Method

Firstly, we applied the *t*-test between the CS-PAs group and the CPs group in all patients as a prefilter for meaning features. Therefore, 730, 455, and 1185 features are retained in the CE-T1, T2, CE-T1&T2, respectively, after the *t*-test. Next, the remaining features of three feature sets were reduced by PCA and then three new matrices are formed by data information with variance greater than 0.9. It is found that the new matrix of CE-T1&T2 performed better diagnostic performance than CE-T1 or T2 by using the logistic regression model to evaluate the entire sample (**Supplementary Figure S1**). From this result, we can speculate that multi-modal MRI features are superior to single-modal MRI features in terms of differential diagnosis of tumors, which agrees with those reported by Li et al. (33).

Construction of Classification Models

The patients were divided into the training set and test set with 2:1 according to stratification cross-validation, including 182 patients in the training set and 90 patients in the test set.

The feature set of CE-T1&T2 is used to construct the classification model due to predominant diagnostic performance. The *t*-test and PCA were applied for feature filtering and reduction, and features with variance greater than 0.9 were retained. Finally, an optimal feature set with 18 features is obtained through the recursive feature elimination method of five-fold cross-validation (**Supplementary Figure S2**). Based on the above representative features, they are put into 5 classifier models for training, and an independent test set is used for model verification. In the training set, the AUC value and accuracy of logistic regression are 0.92 and 0.85, Ridge classifier is 0.90 and 0.85, SGD classifier are 0.88 and 0.79, Linear SVC are 0.78 and 0.80, and MLP classifier are 0.93 and 0.87, respectively. The results in the test set are also excellent, the AUC value and accuracy of logistic regression are 0.88 and 0.83, Ridge classifier are 0.85 and 0.79, SGD classifier are 0.82 and 0.81, Linear SVC is 0.85 and 0.76, and MLP classifier is 0.86 and 0.80, respectively. These data and the 95% confidence interval (CI) of AUC are listed in **Table 2**. The receiver operating characteristic curve (ROC) of the training and test sets for five classification models are showed in **Figure 3**. The logistic regression model has represented the most reliable diagnostic performance in discrimination between CS-PAs and CPs whether in the training set or the test set.

Development of an Individualized Nomogram

The radiomics signature, the absolute counts of WBC and FIB, and age were identified as independent factors for differentiating CS-PAs

TABLE 1 | Baseline characteristics of patients with CS-PAs and CPs.

	CS-PAs	CPs	P value
N	201	71	
Age (mean ± SD)	48.3 ± 13.5	37.3 ± 19.9	<0.001
Gender (%)			0.417
Male	40	102	
Female	31	99	
Tumor volume (median [IQR])	9323.26 [4949.48, 15792.47]	10828.50 [7044.23, 21169.28]	0.028
Laboratory test (median [IQR])			
RBC	4.15 [3.83, 4.46]	4.08 [3.75, 4.53]	0.996
Hemoglobin	126 [115, 134]	123 [114, 132]	0.474
Platelet	210 [172, 252]	223 [166, 276]	0.290
WBC	6.51 [5.16, 8.97]	9.39 [5.57, 15.10]	<0.001
Neutrophil	3.69 [2.66, 6.72]	6.51 [2.75, 13.42]	<0.001
Lymphocyte	1.73 [1.07, 2.25]	1.52 [0.70, 2.05]	0.250
Monocyte	0.40 [0.29, 0.52]	0.43 [0.32, 0.65]	0.023
Albumin	41.0 [37.4, 44.3]	41.1 [36.6, 44.4]	0.550
FIB	3.17 [2.78, 3.89]	3.02 [2.58, 3.37]	<0.001

SD, Standard deviation; IQR, Inter quartile range; RBC, red blood cell; WBC, white blood cell; FIB, Fibrinogen.

TABLE 2 | Diagnostic performance of classifiers in the training and test groups.

	Training set			Test set		
	AUC Score	95%CI	Accuracy	AUC Score	95%CI	Accuracy
Logistic regression	0.92	0.89-0.95	0.85	0.88	0.81-0.94	0.83
Ridge classifier	0.90	0.86-0.94	0.85	0.85	0.78-0.93	0.79
SGD classifier	0.88	0.85-0.92	0.79	0.82	0.77-0.89	0.81
Linear SVC	0.78	0.72-0.83	0.80	0.85	0.76-0.93	0.76
MLP classifier	0.93	0.89-0.96	0.87	0.86	0.78-0.91	0.80

SGD Classifier, stochastic gradient descent classifier; Linear SVC, linear support vector classification; MLP Classifier, multilayers perceptron classifier; AUC, area under the curve; CI, Confidence interval.

and CPs. The model that incorporated these independent predictors was developed and presented as a nomogram (**Figure 4**).

Performance Assessment of the Nomogram

The radiomic-clinical nomogram, involved the radiomics signature, age, WBC count, and FIB, yielded an AUC of 0.93 (95% CI, 0.89–0.96) in the training set and 0.90 (95% CI, 0.85-0.95) in the test set. The radiomic-clinical nomogram was significantly superior to the radiomics model whether in the training set or the test set (p=0.031 and p=0.038 respectively; DeLong test).

The calibration curve of the radiomic-clinical nomogram demonstrated good calibration in the training set and the test set (**Figures 5A, B**). The Hosmer–Lemeshow test showed a nonsignificant statistic difference in the training and test set (p=0.367 and p=0.113, respectively), suggesting no departure from the perfect fit.

The DCA for the clinical model, radiomics model, and radiomic-clinical nomogram are presented in **Figure 6**. The DCA showed that if the threshold probability is higher than 20%, then using a radiomic-clinical nomogram to diagnose CS-PAs and CPs differentially has a greater advantage than using a radiomics model and simple clinical model in terms of clinical application.

DISCUSSION

On account of the similarity of clinical symptoms, imaging features and lesion location between CS-PAs and CPs, it is challenging to accurately differentiate between the two tumors before surgery. Existing studies have suggested that PAs and CPs are different in imaging characteristics, and the cystic change is the main criterion for distinguishing them. However, both CS-PAs and CPs will have different degrees of cystic changes, thus this criterion is of little significance in the differential diagnosis of CS-PAs and CPs. Furthermore, the treatment strategies for these two tumors are different in clinical practice. The surgical treatment is recommended for CPs once found due to the aggressive behavior, while CS-PAs can be treated by the wait-and-see approach if there are no clinical symptoms. What's more, the surgical methods of the two tumors are not the same even if they are treated surgically. Most patients of the surgical method for CS-PAs is transnasal sphenoidal microsurgery, while CPs is basically craniotomy. Therefore, it is necessary to accurately differentiate and diagnose the two types of tumors before surgery.

Certainly, some neurosurgeons and radiologists have made sustained efforts to solve the above problems. Zhang et al. (34) constructed a model for identifying between CS-PAs and CPs based on 5 different imaging manifestations and 3 types of

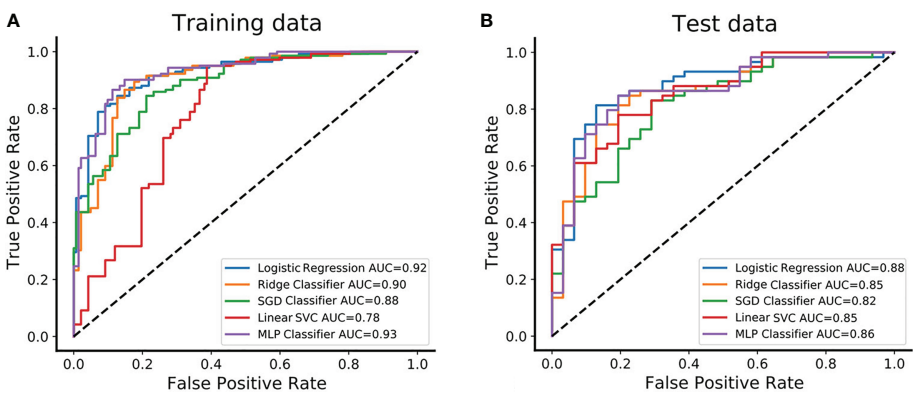

FIGURE 3 | The predictive performance of distinguishing between CS-PAs and CPs in different classifiers. **(A)** The receiver operating characteristic curve (ROC) and the area under the curve (AUC) of the five different classifiers are showed in the training set, respectively. **(B)** The ROC and AUC of the five different classifiers are showed in the test set, respectively. SGD Classifier, stochastic gradient descent classifier; Linear SVC, linear support vector classification; MLP Classifier, multilayers perceptron classifier.

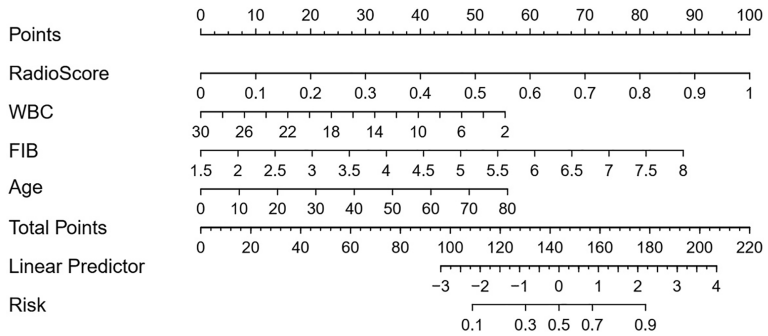

FIGURE 4 | Developed radiomic-clinical nomogram. The nomogram, incorporated radiomics signature, age, WBC count and FIB, was developed in the training set. The risk represents the predictive probability of CS-PAs.

radiomic texture features. In the same year, their team used 5 machine learning algorithms to establish different differential diagnosis models for the two tumors based on 17 different features. The best AUC value of the training group was 0.804 and the test group was 0.845, which achieved good diagnostic results (13). Therefore, the non-invasive radiomic features based on the freely available images can be used as a more convenient biomarker for identifying these two tumors. Unfortunately, these two retrospective studies did not construct a nomogram that can be applied clinically. We have developed and verified a diagnostic nomogram based on radiomic features and blood indices, which contains four items: radiomics signature, age, WBC count and FIB. It helps to personalize diagnosis of CS-PAs and CPs before surgery by combining radiomic features and clinical risk factors into an easy-to-use nomogram.

Data processing, closely related to the performance of the model, is an indispensable process in machine learning (32). Standardization of images and data can not only uniformly transform data of different magnitudes into the same magnitude to make the data comparable, but also can improve the convergence speed and reduce the amount of calculation. Z-score, as the most commonly used data standardization method, was applied in this study. It is especially suitable when the maximum and minimum values in the data are unknown. Furthermore, the high-dimensional features of small data may lead to overfitting, and unbalanced categories of tumors may lead to misleading results (32, 35). In our study, the *t*-test was used to screen out features that are not statistically different from CS-PAs and CPs (these features have no discriminative significance), and then PCA was conducted to select sensitive component features, which could make our model more reliable and robust. The principle of PCA is to delete the redundant features (closely related variables) for all the features originally proposed, and create few new features that are pairwise uncorrelated as possible. Interestingly, these new variables keep the

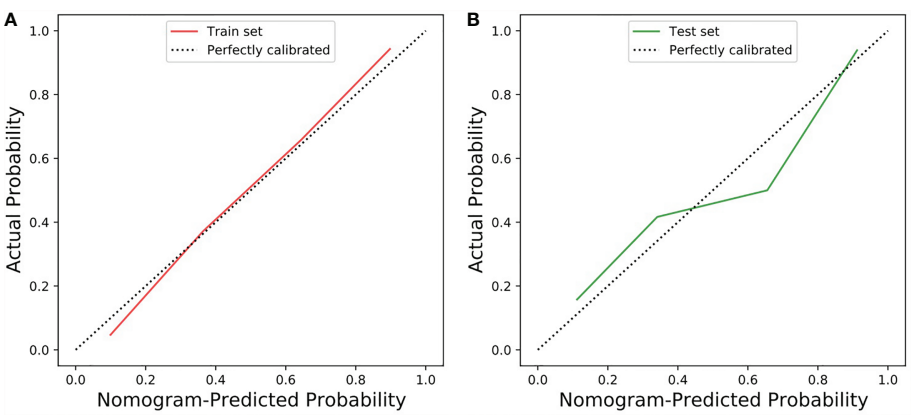

FIGURE 5 | Calibration curve of the radiomic-clinical nomogram in the training and test sets. **(A)** Calibration curve of the radiomic-clinical nomogram in the training set. **(B)** Calibration curve of the radiomic-clinical nomogram in the test set. The calibration curve showed the calibration of the models in terms of the consistency between the predictive performance of CS-PAs and the actual results observed for calibration. The Y-axis represents the actual performance, and the X-axis represents the performance predicted by the nomogram. The oblique dashed line represents the perfect prediction by an ideal model. The red and green solid lines represent the performance of the nomogram in the training set and the test set, respectively. In addition, a fit closer to the diagonal dashed line indicates a better prediction. (The Hosmer–Lemeshow test showed p=0.367 and p=0.113 in the training and test set, respectively).

original information as much as possible in reflecting the information of the tumors (36, 37).

In this study, we tried to compare the classification models based on CE-T1 weighted images, T2 weighted images, and CE-T1&T2 weighted images in the identification of CS-PAs and CPs. The results demonstrated that CE-T1&T2 weighted images are better than the single CE-T1 weighted and T2 weighted images. This finding is consistent with many previous reports that the value of multi-modals imaging information is higher than that of single-modal imaging information in both diagnosis and prognosis models. The study was performed by Zhang et al. to predict the brain invasion of meningiomas. They considered that, compared with the T1-CE sequence model or T2 sequence model, the combination of the T1-CE and T2 sequences model increased the discrimination ability by 4.77% and 6.34%, respectively (38). In addition, in terms of the comparison of the single-sequence model, in the study of Zeynalova et al. (39), the result showed that T2-weighted images is better in predicting the consistency of pituitary macroadenoma. Peng et al. (35) also obtained consistent results, which showed that the T2-weighted images are better than the CE-T1 weighted images and T1 weighted images for the classification of pituitary tumor subtypes. In the preliminary model exploration of our study, T2-weighted images contains more discrimination information than CE-T1 weighted images. On the contrary, Niu et al. (40) did not think so, in the model of predicting the invasion of cavernous sinus by pituitary tumors, they concluded that the AUC value of the T1-CE radiomics model (0.796) was higher than that of the T2 radiomics model (0.720). Therefore, the feature of CE-T1 model was chosen as the final radiomics signature according to the Bayesian information criterion. The reason for this discrepancy may not be clear, as for the potential mechanism needs to be further studied.

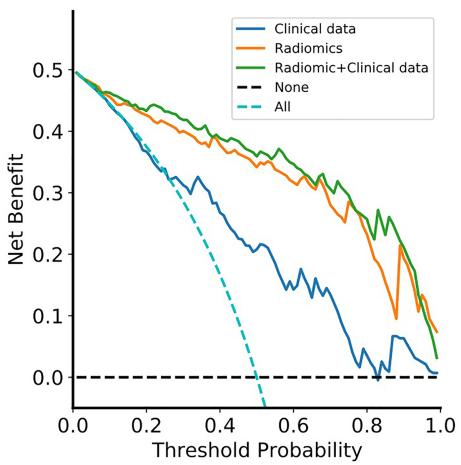

FIGURE 6 | Decision curve analysis for the radiomic-clinical nomogram, radiomics model and clinical model. The decision curve showed that if the threshold probability was higher than 20%, then using the radiomic-clinical nomogram to differentially diagnose CS-PAs and CPs has a greater advantage than using a radiomics model and simple clinical model in terms of clinical application. Clinical data, clinical model; Radiomics, radiomics model; Radiomic+Clinical data, radiomic-clinical nomogram.

Note that three independent clinical predictors are used for the differential diagnosis of CS-PAs and CPs, including age, WBC count and FIB. Age as an independent predictor is well understood by us. CS-PAs usually occur in young adults, while CPs occur mostly in children and adults. The age of the patients with CPs has a bimodal distribution, with the peak onset being 5-14 years old and 50-74 years old, respectively (41). White blood cells are widely existed in various tumors, especially malignant tumors, which are closely related to the important biological characteristics of tumors such as proliferation, migration, immune escape and prognosis (42–44). To the knowledge of us, malignant tumors are prone to recurrence or regrowth even after complete resection. The biological characteristics of CPs are precisely similar to this situation. Chen et al. (25) showed that in the detection results of peripheral blood inflammatory markers, the WBC and lymphocyte counts of the CPs group were higher than those of pituitary tumors, and the difference was statistically significant ($p<0.05$), which means that the progress of CPs may be related to inflammation. Furthermore, the existing reports have proved that the value of FIB in the differential diagnosis and prognosis of tumors. The theory, firstly proposed in 1865, was that the tumor is conducive to the activation of coagulation function, and then hypercoagulable state or chronic disseminated intravascular coagulation for tumor patients (45). Therefore, the radiomics model plus three readily available clinical variables make the prediction performance of the nomogram more superior.

Certainly, some limitations of this study warrant mention. Firstly, it is a retrospective study, thus some uncertain confounding factors may exist. Secondly, the patients with available preoperative MRI, blood indices and postoperative pathological results were only included for analysis, and there were relatively few samples of patients with CPs in the study population. Thirdly, all patients were from a single-center, no external validation was performed. Although we randomly divided the patients into the independent training set and test set. If a multi-center data set with different parameters is used, the performance of the model may be different. Fourthly, there are more and more multi-omics researches, thus radiomics can be combined with other omics such as genomics, so as to more accurately identify tumors and guide postoperative comprehensive treatment.

In conclusion, the study found that the logistic regression based on dual-parameters has better diagnostic performance than the other four classifiers. In addition, a new nomogram based on radiomics signature and clinical indicators was proposed, which provided a non-invasive and convenient method to individually distinguish between CS-PAs and CPs in clinical practice.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Union Hospital, Tongji Medical College, Huazhong

University of Science and Technology. Written informed consent for participation was not provided by the participants' legal guardians/next of kin because: The informed consent of patients was waived on account that was a retrospective study.

AUTHOR CONTRIBUTIONS

Conception and design: HYZ and PFY. Collection and assembly of the data: ZZ, DDX, CSN, XBJ, and HYZ. Language editing and grammar correction: ARJ. Development of the methodology: ZZ, DDX, and PFY. Data analysis and interpretation: All authors. Manuscript writing: All authors. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.709321/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

ORIGINAL RESEARCH
published: 12 July 2021
doi: 10.3389/fonc.2021.691288

Development and Validation of Predicting Nomograms for Craniopharyngioma: A Retrospective, Multiple-Center, Cohort Study

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Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: 06 April 2021
Accepted: 28 June 2021
Published: 12 July 2021

Citation:
Xu D, Wei Q, Li Z, Hu Y, Hu P, Zhao S, Song D, Lei S, Zhang M, Gao Q, Zhang L, Lin F, Zuo Y, Liu X, Feng M, Ma C and Guo F (2021) Development and Validation of Predicting Nomograms for Craniopharyngioma: A Retrospective, Multiple-Center, Cohort Study. Front. Oncol. 11:691288. doi: 10.3389/fonc.2021.691288

Craniopharyngiomas (CPs) are benign tumors arising from the sellar region. However, little is known about their clinical features and long-term recurrence due to low morbidity and the lack of large cohort studies. Thus, we aimed to develop nomograms to accurately predict the extent of resection and tumor recurrence using clinical parameters. A total of 545 patients diagnosed with CP between 2009 and 2019 were examined: 381 in the development cohort and 164 in the validation cohort. Least absolute shrinkage and selection operator (LASSO) and Cox regression analyses were performed to establish two nomograms. Receiver operating characteristic (ROC) curves, calibration curves, decision curve analysis (DCA) and Kaplan-Meier (KM) curves were used to evaluate their predictive performance and discriminative power, respectively, in the two cohorts. In addition, the EORTC QLQ-BN20 questionnaire was used to assess neuropsychological status in the follow-up. In the development cohort, the area under the curve (AUC) and C-index were 0.760 and 0.758, respectively, for predicting the extent of resection and 0.78 and 0.75, respectively, for predicting 3-year progression-free survival (PFS) and 5-year PFS. Additionally, the model had a predictive accuracy of 0.785. Both nomograms showed acceptable discrimination in the two cohorts. Moreover, DCA demonstrated excellent clinical benefits from the two nomograms. Finally, participants were classified into two distinct risk groups according to the risk score, and an online calculator was created for convenient clinical use. During long term follow-up, hypothyroidism (77.61%) and hypocortisolism (76.70%) were the most common endocrine dysfunction after surgery and significant deficits were observed concerning visual disorder, motor dysfunction and seizures in the recurrent groups. In particular, better quality of life was associated with gross total resection (GTR), postoperative radiation, anterior interhemispheric (AI) approach and transsphenoidal approach. To our knowledge, these are the first

nomograms based on a very large cohort of patients with CP that show potential benefits for guiding treatment decisions and long-term surveillance. The current study demonstrated the online calculator serve as the practical tool for individual strategies based on the patient's baseline characteristics to achieve a better prognosis.

Keywords: craniopharyngioma, nomogram, risk stratification, progression-free survival, long-term surveillance, online calculator, neuropsychological status

INTRODUCTION

Craniopharyngiomas (CPs) are benign suprasellar tumors accounting for 2-4% of intracranial tumors (1, 2). Although histologically classified as WHO I tumors, total resection and postoperative management are huge challenges associated with CPs because they are adjacent to vital brain structures, such as the optic chiasm and hypothalamus. Radical resection is considered the first-line treatment because it yields the best overall survival (OS) and progression-free survival (PFS). However, complete resection could lead to increased mortality or poor functional results because of severe endocrine disorders (3). The rate of long-term recurrence could reach an astonishing 58% with or without radiotherapy in the subtotal resection group of some studies (4), so subsequent treatment often becomes an unavoidable problem for such patients. Secondary resection, salvage radiotherapy or intratumoral chemotherapy (5, 6) can be carried out in relapsed patients, though its therapeutic effect is not satisfactory.

In the long-term follow-up, clinical doctors generally pay more attention to the endocrine status of patients than to the neuropsychological status. Only a few studies have focused on these issues. Giese et al. described a cohort of 71 patients with impaired learning performance and short-term memory loss in those with tumor volumes larger than 9 cm^3 or in those with tumors located in the third ventricle (7). In another center, impaired quality of life and decreased OS were observed in patients with hypothalamus involvement over a minimum 10-year follow-up (8). Nevertheless, there is still a lack of detailed preoperative and postoperative neurological and neurological evaluations in a large cohort.

In recent years, an increasing number of studies have focused on baseline clinical characteristics, such as image features and laboratory tests to predict prognosis and long-term disease recurrence (9, 10). Nomograms, as more friendly and visual tools, have been increasingly used in clinical practice. For instance, the Memorial Sloan Kettering Cancer Center (MSKCC) launched different predictive models to guide clinical treatment more accurately. Although nomograms are extensively used in clinical work, due to the low morbidity associated with CPs, predictive models for CP have not yet been established.

Therefore, this study aimed to develop a novel prognostic model for CP combining preoperative and postoperative features based on two large cohorts. The long-term neuropsychological status of patients was also assessed with the QLQ-BN20 questionnaire. To our knowledge, this is the first study to establish a clinical prediction model and the largest retrospective study of neuropsychological function in CP.

MATERIALS AND METHODS

Patient Selection

This retrospective study was approved by the Ethics Committee of Zhengzhou University. All patients gave written informed consent for the surgery and use of data for research purposes prior to the surgery. The protocol was reviewed by the university review board. A total of 545 consecutive patients were diagnosed with CPs and treated at the Department of Neurosurgery, the First Affiliated Hospital of Zhengzhou University, Henan Provincial People's Hospital and the Third Affiliated Hospital of Zhengzhou University between September 2009 and September 2019. The exclusion criteria were as follows: (1) multiple intracranial tumors with CPs; (2) a history of preoperative adjuvant therapy or surgery in another hospital; (3) death unrelated to disease progression within 1 month after the operation (**Supplemental Table 1**); (4) patients without complete information or refusal to join the study; and (5) malignant CPs. Thus, based on these criteria, 381 patients were included in the development cohort, and 164 patients (7:3) were selected in the validation cohort (**Figure 1**).

Clinical Parameter Acquisition and Follow-Up Data

All the clinical parameters of patients were recorded and obtained from the hospital electronic medical system. Patients are routinely reviewed at the first 3 months, 1 year, 2 years and 3 years after surgery. Follow-up data were acquired by telephone and in outpatient reviews. Tumor recurrence was assessed by MRI. Endocrinology indicators, including prolactin, luteinizing hormone, follicle stimulating hormone, 24 h ACTH and cortisol, growth hormone, T3, T4 and TSH, were routinely tested in the pre- and postoperative periods.

The operations were performed *via* the pterional approach (n=232), subfrontal approach (n=174), anterior interhemispheric (AI) approach (n=72), transsphenoidal approach (n=47) and transcallosal-interfornix (TI) approach (n=20). The grade of tumor resection was classified as gross total resection (GTR) and subtotal resection (STR). GTR was only assumed when there were no tumor or cystic remnants. CT or MRI reexamination was performed within 1 day of the operation to determine the residual status. Radiotherapy was

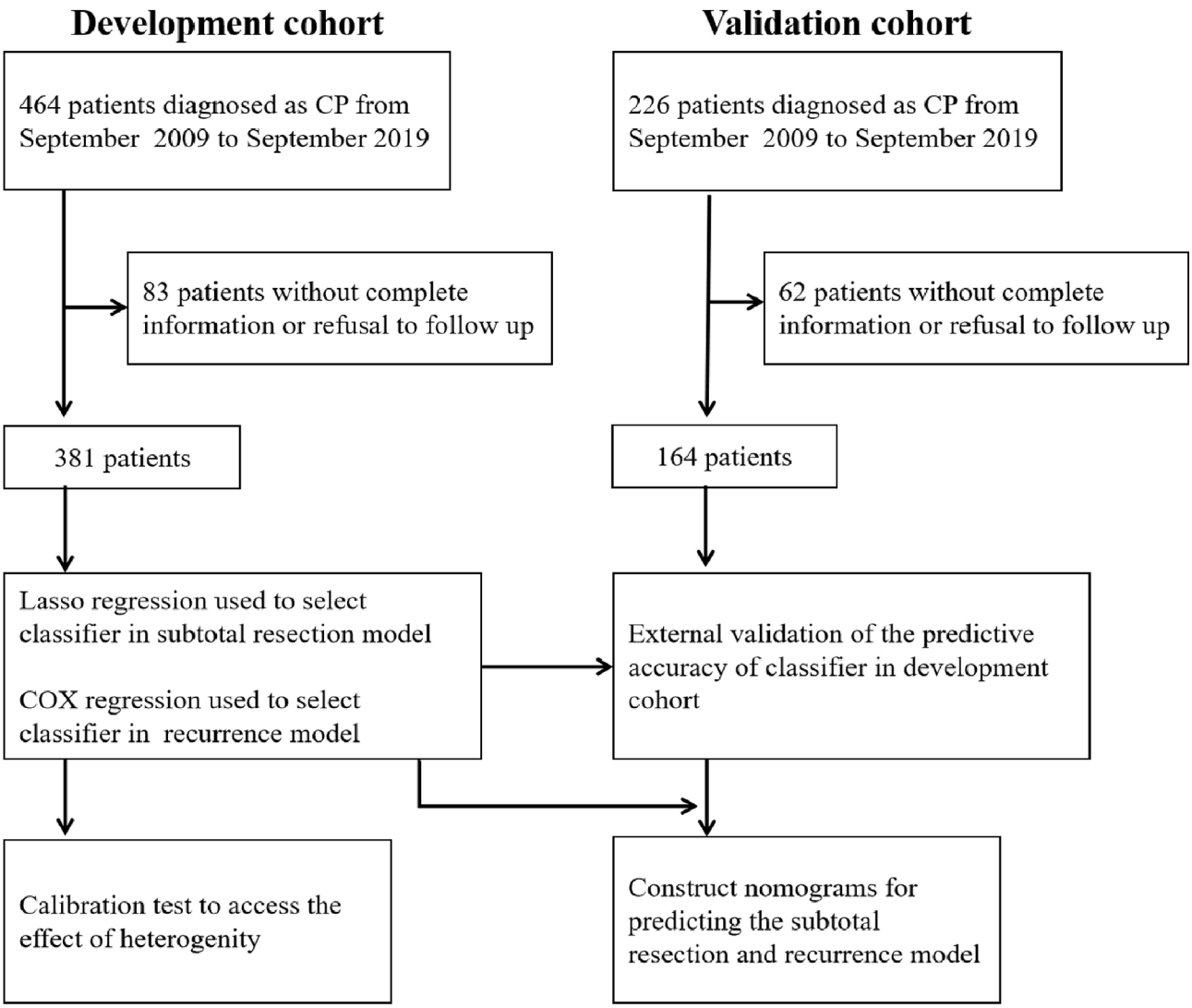

FIGURE 1 | Study cohort.

defined as sequential adjuvant radiotherapy after surgery, excluding salvage therapy when tumor recurrence occurred.

Image Assessments

All patients routinely underwent MRI or CT upon admission. Moreover, tumor location, hypothalamus and optic nerve involvement, hydrocephalus, calcification and tumor character (Cystic, solid or mix) were obtained from the Picture Archiving and Communication Systems (PACS). The maximum diameter of the tumor was defined as tumor size.

Quality of Life Questionnaire

The EORTC QLQ-BN20 questionnaire was used to assess health status as previously described (11, 12). Briefly, the QLQ-BN20 consists of four multi-item scales and seven single items, with a high score reflecting severe neuropsychological deficits. The questionnaire was given by telephone and in the outpatient review. Finally, follow-up data were obtained from a total of 317 patients, including 217 patients in the training cohort and 100 patients in the validation cohort.

Statistical Analysis

All analyses were performed using SPSS version 25 (IBM, Armonk, NY, USA), GraphPad Prism 8.0 and R version 4.0.0 (Package: limma, pheatmap, estimate, ggpubr, e1071, preprocessCore, survival, glmnet, survminer, survivalROC, rms, timeROC). Continuous variables are expressed as the mean ± standard deviation and interquartile range (IQR), while categorical variables are reported as the frequency and percentage. The Shapiro-Wilk test was used to assess the data distribution. Data in normal distribution between two groups were evaluated with the two-tailed Student's t-test. The Mann-

Whitney U and Kruskal Wallis test was used for those that did not conform to a normal distribution. The chi-squared test, Student's t-test and Kruskal Wallis test with *post hoc* Bonferroni correction were used for data comparison. Then, Kaplan-Meier (KM) survival analyses were used to assess PFS. A log-rank test was used to test the equality of the KM curves.

Depending on the outcome, we first used LASSO or Cox logistics regression analysis to select significant predictors. Then, 5 factors were used to construct two nomograms. Moreover, receiver operating characteristic (ROC) curves, Harrell's concordance index (C-index), calibration curves and decision curve analysis (DCA) were used to evaluate the predictive performance of the nomograms in both the development and validation cohorts. We further categorized patients into high- and low-risk groups based on their median risk score. Survival analysis was performed to test differences between the two groups. Finally, a risk factor-stratified calculator for long-term recurrence was generated and is available in the additional information online (**Supplementary File**).

RESULTS

Patient Characteristics

A total of 545 patients were included in this group of studies: 381 in the training cohort and 164 in the validation cohort. The baseline demographics and clinical characteristics of the patients are listed in **Table 1**. The most frequent symptoms were headaches and visual deficits, which occurred in 256 patients (47.0%) and 258 patients (47.3%), respectively. The mean duration of symptoms to the time of diagnosis was 11.10 ± 18.71 months. The tumor size ranged from 5 mm to 123 mm, with a median diameter of 32 mm, and we changed this factor from a continuous variable to a categorized variable and divided tumor size into 10-mm intervals. A total of 399 (73.2%) patients had varying degrees of hydrocephalus at the preoperative examination. The most common endocrinological deficit before surgery was hypogonadism (273, 50.09%) followed by hypocortisolism (231, 42.39%) and hypothyroidism (230, 42.20%), whereas the percentage of hypogonadism was decreased after surgery (210,38.53%). What's more, endocrinological dysfunction of corticotropic (418, 76.70%) and thyrotrophic axes (423, 77.61%) were significantly increased in postoperative outcomes (**Table 2**).

The total resection ratio reached 53.5% in the development cohort and 59.1% in the validation cohort. The GTR rates of the different approaches are shown in **Figure 2**; however, there were no significant differences. The mean follow-up time was 40.35 months, and a total of 125 patients experienced tumor recurrence during this period. The cumulative recurrence rates at 1 year, 2 years, 3 years, 5 years and 10 years were 10.8%, 16.0%, 19.3%, 21.3%, and 22.8%, respectively. Finally, 452 adamantinomatous craniopharyngiomas (ACPs, 82.9%) and 93 papillary craniopharyngiomas (PCPs, 17.1%) were enrolled in our study. 292/452 (64.6%) ACPs were accompanied by calcification features, whereas only 12/93 (13.0%) PCPs exhibited calcification features. There was no significant difference in long-term recurrence between these two pathological types (**Figure 3**). In this group, radiotherapy included stereotactic radiotherapy, and 34 patients underwent this treatment after subtotal resection. No malignant transformations were observed in the radiotherapy cohort (34 cases) with a mean follow-up of 43.5 months. There were no differences in long-term recurrence between the GTR and subtotal resection + radiotherapy groups, but radiotherapy significantly improved the PFS rate of patients who underwent subtotal resection (**Figure 3**). No significant differences in overall survival were observed in the extent of resection and pathological type. In addition, initial hydrocephalus had no impact on the extent of resection and PFS.

Quality of Life

A total of 317 patients were followed up: 217 in the development cohort and 100 in the validation cohort. The mean total score was 26.30 ± 7.11 in the training cohort and 26.38 ± 9.59 in the validation cohort, and a detailed description is shown in **Table 3**. The total BN20 score was not significantly different according to radiotherapy, relapse groups or pathological type, however difference were observed concerning different items ($p<0.05$). Significant differences in visual disorder (5.00 ± 2.34 *vs* 4.36 ± 1.94, $p<0.05$), motor dysfunction (4.34 ± 2.25 *vs* 3.74 ± 1.42, $p<0.05$) and seizures (1.38 ± 0.86 *vs* 1.10 ± 0.48, $p<0.01$) were observed between the recurrence cohort and the other cohorts. Patients who received radiotherapy had higher scores related to future uncertainty (6.46 ± 3.04 *vs* 5.13 ± 1.94, $p<0.01$) and hair loss (1.27 ± 0.60 *vs* 1.10 ± 0.44, $p<0.05$) than patients who did not receive radiotherapy. In addition, scores related to future uncertainty in ACP was higher than that in PCP(5.39 ± 2.23 *vs* 4.66 ± 1.20, $p<0.05$). We further explored the impact of different approaches on terminal BN20 scores. The patients in subfrontal approach and pterional approach had higher scores related to future uncertainty versus AI approach (5.49 ± 2.56 *vs* 4.38 ± 0.90, 5.36 ± 1.95 *vs* 4.38 ± 0.90, $p<0.01$); The BN20 scores related to weak of legs with the pterional approach, subfrontal approach, AI approach, and transsphenoidal approach versus the TI approach were 1.35 ± 0.80, 1.36 ± 0.76, 1.21 ± 0.59, and 1.23 ± 0.63 *vs* 2.63 ± 1.19, respectively ($p<0.01$, **Figure 4**). Moreover, the TI approach demonstrated higher scores than the AI approach concerning future uncertainty and motor dysfunction (4.38 ± 0.90 *vs* 6.50 ± 1.93 and 3.43 ± 1.19 *vs* 6.00 ± 3.07, $p<0.01$, **Figure 4**). Detailed description and P value were shown in supplemental material.

Nomogram Construction and External Validation

Based on the LASSO and Cox regression models, two nomograms that integrated significant predictors were generated, as demonstrated in **Figures 5** and **6**. The nomograms used to predict the extent of resection compromised tumor size, duration of symptoms, hypothalamus involvement, calcification and characteristics. As shown in **Figure 5**, the AUCs of individual tumor size, duration of symptoms,

TABLE 1 | Baseline characteristics of patients in the development and validation cohort.

	Development training cohort (n = 381)	Validation training cohort (n = 164)	Total
Sex			
Male	208 (54.6)	89 (54.3)	297 (54.5)
Female	173 (45.4)	75 (45.7)	248 (45.5)
Age, years			
Median	37	39	38
IQR	15-52	12.75-61.25	16-52
Range	1-71	2-77	1-77
Tumor Size, mm			
Median	32	32	32
IQR	25-42	25-40	25-41
Range	5-123	15-115	5-123
Duration of symptoms, months			
0-6	238 (62.5)	105 (64.0)	343 (62.9)
6-12	47 (12.3)	17 (10.4)	63 (11.7)
12-24	46 (12.1)	22 (13.4)	68 (12.5)
>24	50 (13.1)	20 (12.2)	70 (12.8)
Preoperative endocrine			
Normal	74 (19.4)	36 (22.0)	110 (20.2)
Abnormal	307 (80.6)	128 (78.0)	435 (79.8)
Hypothalamus involvement			
Yes	256 (67.2)	107 (65.2)	363 (66.6)
No	125 (32.8)	57 (34.8)	182 (33.4)
Optic nerve involvement			
Yes	340 (89.2)	152 (92.7)	492 (90.3)
No	41 (10.8)	12 (7.3)	53 (9.7)
Location			
Intrasellar	14 (3.7)	8 (4.9)	22 (4.0)
Suprasellar	174 (45.7)	60 (36.6)	234 (42.9)
Intrasellar-suprasellar	193 (50.7)	96 (58.5)	289 (53.1)
Calcification			
Yes	207 (54.3)	97 (59.1)	304 (55.8)
No	174 (45.7)	67 (40.9)	241 (44.2)
Hydrocephalus			
Yes	272 (71.4)	127 (77.4)	399 (73.2)
No	109 (28.6)	37 (22.6)	146 (26.8)
Features			
Solid-cystic	295 (77.4)	133 (81.1)	428 (78.5)
Cystic	59 (15.5)	16 (9.8)	75 (13.8)
Solid	27 (7.1)	15 (9.1)	42 (7.7)
Pathology subtype			
ACP	312 (81.9)	140 (85.4)	452 (82.9)
PCP	69 (18.1)	24 (14.6)	93 (17.1)
Surgical approach			
Pterional approach	163 (42.8)	69 (42.1)	232 (42.6)
Subfrontal approach	124 (32.5)	50 (30.5)	174 (31.9)
AI approach	52 (13.6)	20 (12.2)	72 (13.2)
Transsphenoidal approach	29 (7.6)	18 (11.0)	47 (8.6)
TI approach	13 (3.5)	7 (4.2)	20 (3.7)
Surgical resection			
Total resection	204 (53.5)	97 (59.1)	301 (55.2)
Subtotal resection	177 (46.5)	67 (40.9)	244 (44.8)
Radiotherapy			
Yes	20 (5.2)	14 (8.5)	34 (6.2)
No	361 (94.8)	150 (91.5)	511 (93.8)
Recurrence			
Yes	101 (26.5)	23 (14.0)	124 (22.8)
No	280 (73.5)	141 (86.0)	421 (77.2)
PFS, months			
Median	33	32	33
IQR	16-59	12.25-61.75	25.50-60.50
Range	1-115	3-107	1-115

IQR, interquartile range; AI, anterior interhemispheric; TI, transcallosum-interfornix; ACP, Adamantinomatous craniopharyngioma; PCP, Papillary craniopharyngioma.

TABLE 2 | Summary of endocrinological in pre and postoperative period.

Endocrinological results before and after surgery					
axis	**pre**	**%**	**post**	**%**	**p**
Hypothyroidism	230	42.20%	423	77.61%	p<0.01
Hypocortisolism	231	42.39%	418	76.70%	p<0.01
Hypogonadism	273	50.09%	210	38.53%	p<0.01
GH deficiency	39	7.16%	36	6.61%	p=0.72
Normal	110	20.18%	34	6.24%	p<0.01

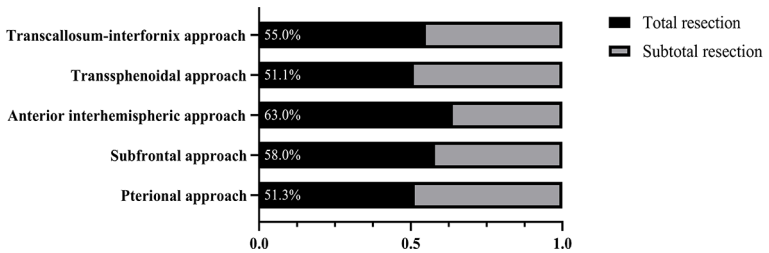

FIGURE 2 | The gross total resection rates of different surgical approaches in CPs.

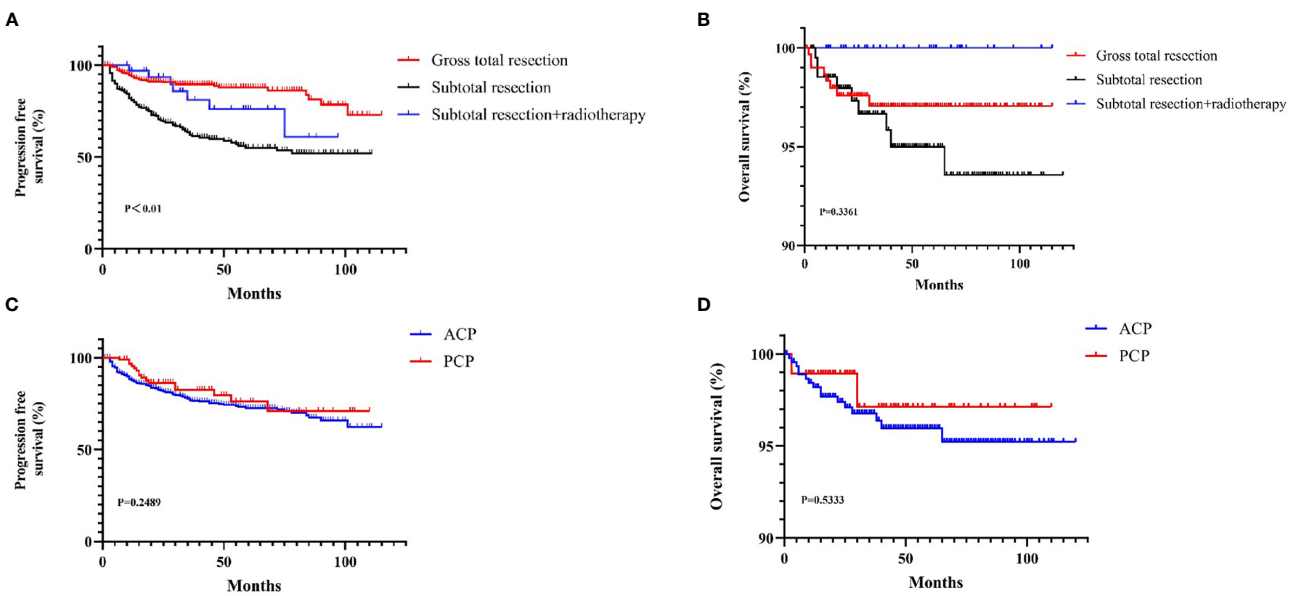

FIGURE 3 | The KM curves for Survival curves for the patients with or without adjuvant treatment **(A, B)** and pathological type **(C, D)**.

hypothalamus involvement, calcification and characteristics were 0.587, 0.502, 0.489, 0.244 and 0.422, respectively, but the combination nomogram reached an AUC of 0.760 (95% CI: 0.73-0.78), with a C-index of 0.758 (95% CI: 0.721-0.793). To further verify the efficacy of the nomogram, we investigated the model with the validation cohort. The AUC of the external cohort was 0.704 (95% CI: 0.68-0.74), with an AUC that was obviously lower than that of other individual predictors. The calibration curve yielded agreeable results. DCA showed more favorable clinical applications with the nomograms than with individual predictors, demonstrating the feasibility of the nomograms for making valuable judgments on prognosis.

To better predict long-term recurrence during follow-up, nomograms involving age, tumor size, hypothalamus involvement,

TABLE 3 | BN20 scores of patients in the development and validation cohort.

	Development training cohort (n = 217)	Validation training cohort (n = 100)	Total
Future uncertainty	5.08 ± 1.61	5.29 ± 2.28	5.15 ± 1.85
Visual disorder	4.55 ± 1.92	4.47 ± 2.08	4.53 ± 1.97
Motor dysfunction	3.84 ± 1.44	3.83 ± 1.83	3.84 ± 1.57
Communication deficit	3.67 ± 1.64	3.89 ± 2.16	3.74 ± 1.82
Headaches	1.18 ± 0.54	1.10 ± 0.41	1.15 ± 0.50
Seizures	1.45 ± 0.88	1.38 ± 0.79	1.43 ± 0.85
Drowsiness	1.25 ± 0.63	1.22 ± 0.58	1.24 ± 0.61
Hair loss	1.11 ± 0.43	1.12 ± 0.48	1.11 ± 0.44
Itchy skin	1.25 ± 0.62	1.21 ± 0.59	1.24 ± 0.61
Weakness of legs	1.47 ± 0.86	1.39 ± 0.75	1.44 ± 0.83
Bladder control	1.45 ± 0.74	1.48 ± 0.89	1.46 ± 0.79
Total scores	26.30 ± 7.11	26.38 ± 9.59	26.33 ± 7.96

calcification and subtotal resection were generated. The AUCs of the 3- and 5-year PFS nomograms were 0.78 (95% CI: 0.72-0.83) and 0.75 (95% CI: 0.69-0.80, C-index: 0.785, 95% CI: 0.757-0.809), respectively; the AUCs in the validation cohort reached 0.72 (95% CI: 0.69-0.76) and 0.69 (95% CI: 0.65-0.72, C-index: 0.735, 95% CI: 0.703-0.75), respectively. The calibration curve was favorable. Moreover, DCA was performed in both cohorts (**Figure 6**).

Performance of the Nomogram in Stratifying Patient Risk

To better distinguish the patients, we further stratified individuals into high- and low-risk groups based on their median risk score. The hazard ratios (HRs) and 95% confidence intervals (CIs) of the high-risk groups in the training and validation cohorts were 1.67 (95% CI: 1.04-2.58,

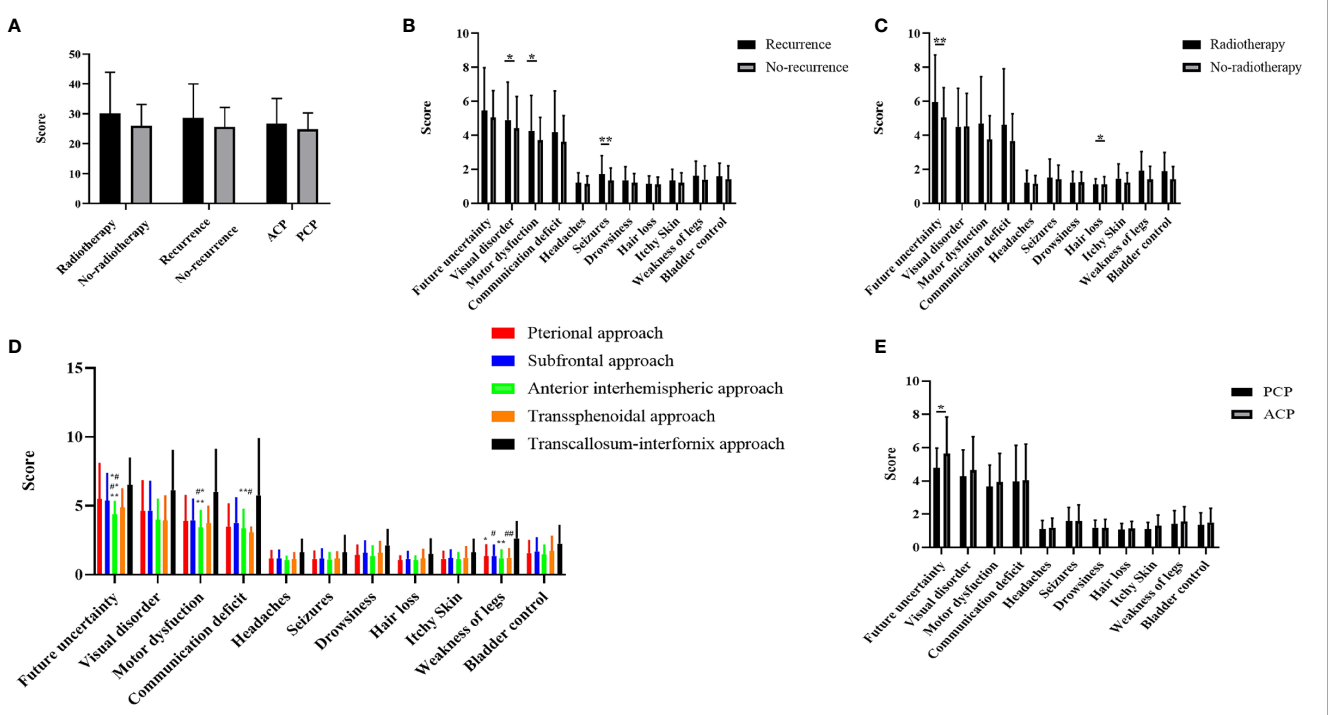

FIGURE 4 | **(A)** Comparison of three groups of variables on the total BN20 score (Mann-Whitney U test, *p < 0.05, **p < 0.01). **(B)** Comparison of craniopharyngioma patient life quality between recurrence and non-recurrence groups (Mann-Whitney U test, *p < 0.05, **p < 0.01). **(C)** Comparison of craniopharyngioma patient life quality between radiotherapy and non-radiotherapy groups (Mann-Whitney U test, *p < 0.05, **p < 0.01). **(D)** Comparison of craniopharyngioma patient life quality between five different approaches (Kruskal Wallis test with *post hoc* Bonferroni correction, p < 0.01, *represent pterional approach *vs*. TI approach, **represent AI approach *vs*. TI approach, $^{\#}$represent subfrontal approach *vs*. TI approach, $^{\#\#}$represent transsphenoidal approach vs. TI approach, $^{*\#}$represent pterional approach *vs* AI approach, $^{\#*}$represent subfrontal approach vs AI approach, $^{**\#}$represent subfrontal approach *vs* transsphenoidal approach). **(E)** Comparison of craniopharyngioma patient life quality between PCP and ACP groups (Mann-Whitney U test, *p < 0.05).

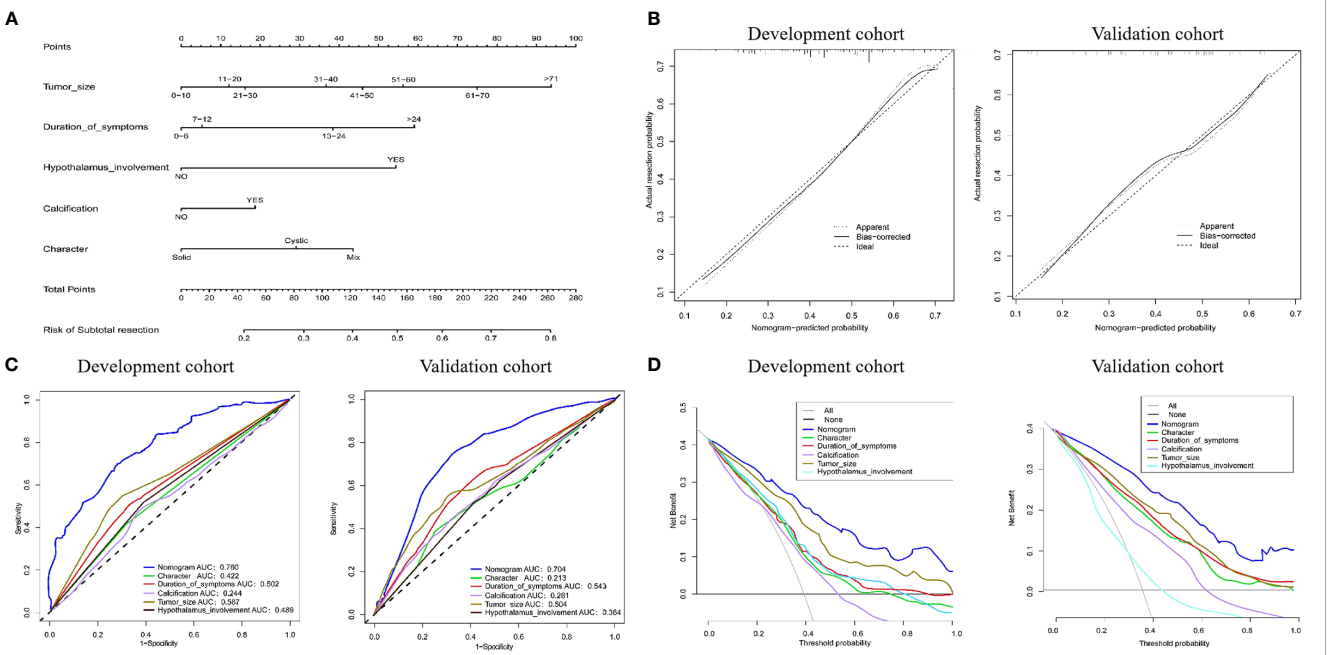

FIGURE 5 | **(A)** Nomogram for predicting the extent of resection. For each variable, a verticle line was drawn to the upward point line and the total score of 6 variables could be obtained to calculate the risk of subtotal resection. **(B)** Calibration curves for development and validation cohort. **(C)** The ROC curves of the nomogram, tumor size, duration of symptoms, hypothalamus involvement, calcification, character and combined nomogram in the development and validation cohort. **(D)** The decision curve analysis of the nomogram. The Y-axis represents the net benefit. The larger net benefit means a patient can obtain the more benefit of the model.

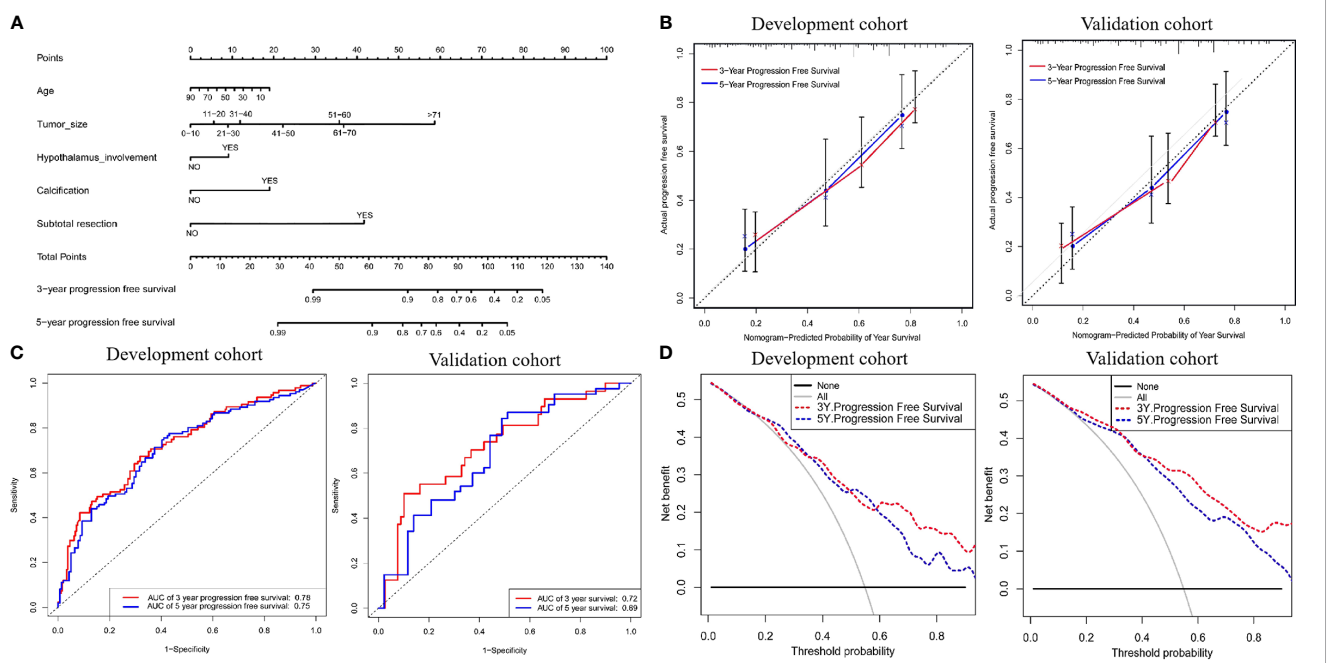

FIGURE 6 | **(A)** Nomogram for predicting the probability of 3- and 5-year progression free survival. For each variable, a verticle line was drawn to the upward point line and the total score of 6 variables could be obtained to calculate the probability of progression free survival. **(B)** Calibration curves for development and validation cohort. **(C)** The ROC curves of the nomogram, age, tumor size, hypothalamus involvement, calcification, character and combined nomogram in the development and validation cohort. **(D)** The decision curve analysis of the nomogram. The Y-axis represents the net benefit. The larger net benefit means a patient can obtain the more benefit of the model.

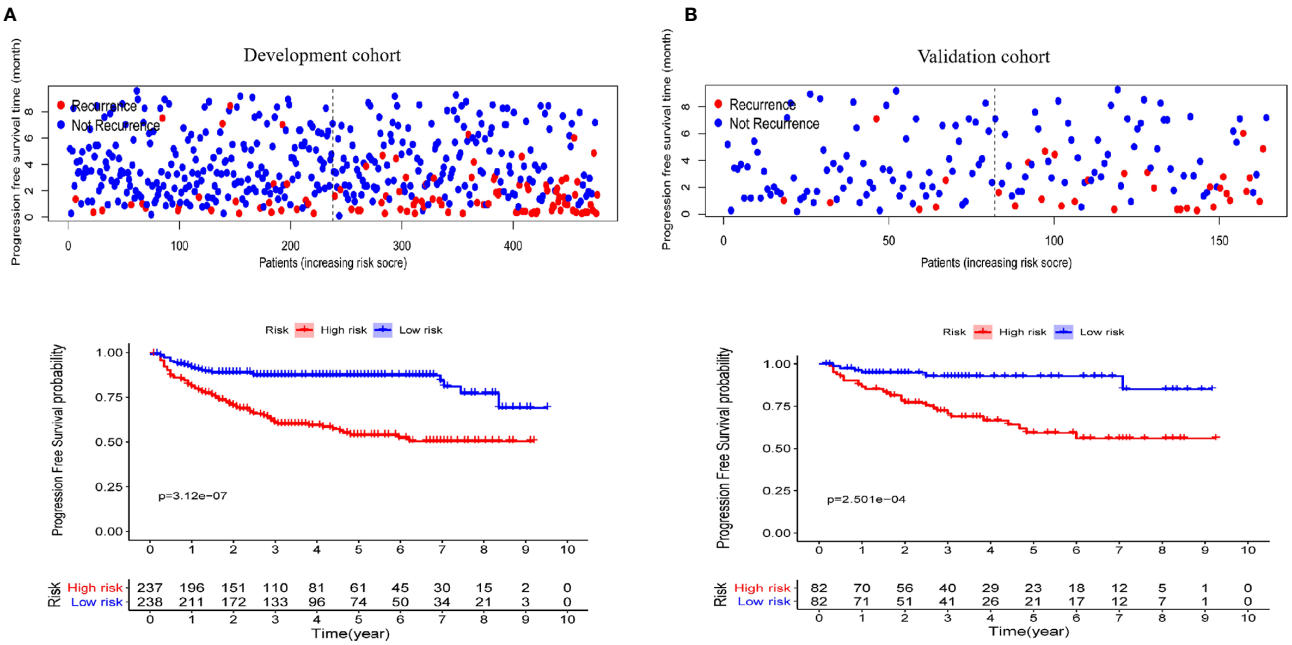

FIGURE 7 | The KM curves for high-risk group (red) and low-risk group (blue) in the development **(A)** and validation cohort **(B)**.

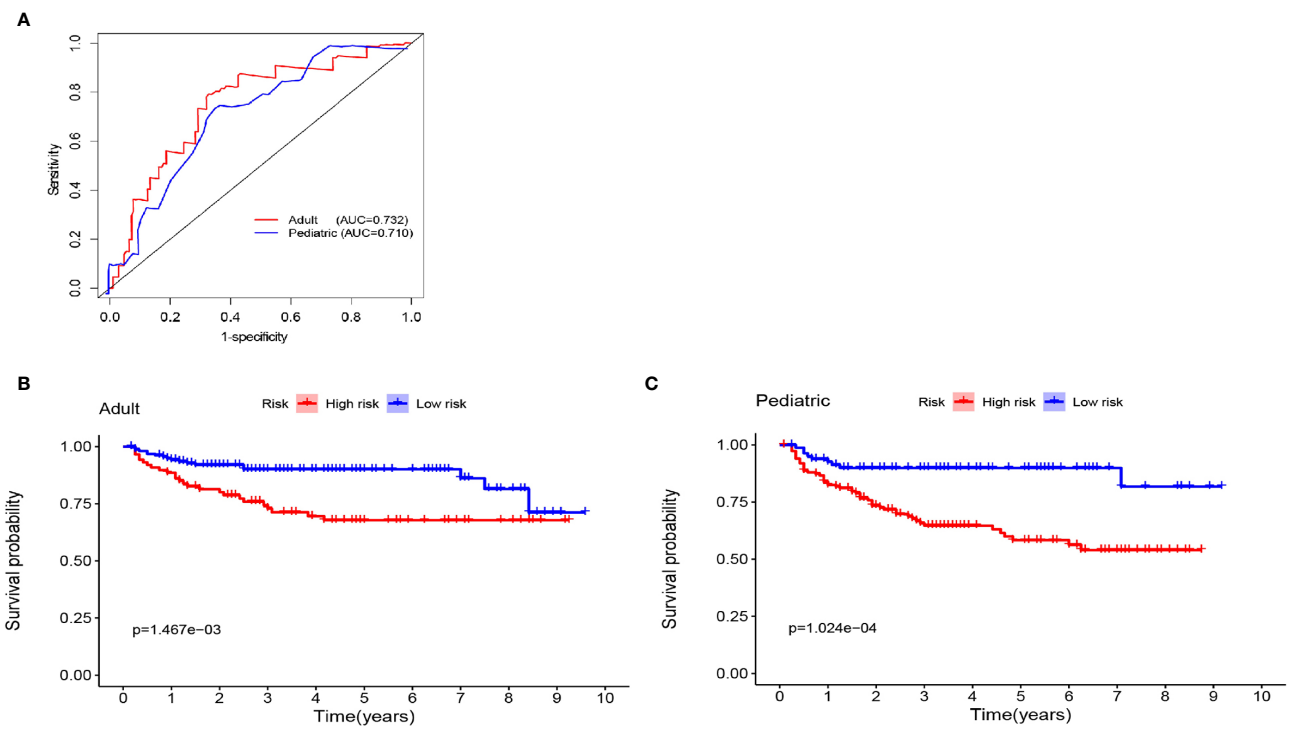

FIGURE 8 | **(A)** Nomogram for predicting the extent of resection in adult and pediatric cohort. The KM curves for high-risk group (red) and low-risk group (blue) in the adult **(B)** and pediatric cohort **(C)**.

p<0.01) and 1.41 (95% CI:1.18-2.14, p<0.01), respectively (compared to the low-risk groups, **Figure 7**). Moreover, as shown in **Figure 7**, PFS in the first three years decreased significantly faster than that over the following years. In addition, the AUCs of the adult and pediatric nomograms were 0.732 (95% CI: 0.711-0.753) and 0.710 (95% CI: 0.693-0.727), respectively. We further verified the reliability of predicting long-term recurrence in the adult and pediatric groups using KM curve analysis. The hazard ratios (HRs) 95% and confidence intervals (CIs) of the high-risk groups in the adult and pediatric cohorts were 1.59 (**Figure 8**, 95% CI: 1.32-1.86, p<0.01) and 1.41 (95% CI:1.42-1.84, p<0.01). An online calculator is available at https://dingkangxu.github.io/Predicting_tool_for_craniopharyngioma/.

DISCUSSION

Although mounting studies and abundant clinical experience could guide neurosurgeons to perform skilled resection of CPs, an accurate assessment of the characteristics of each patient during the perioperative period remains necessary for individualized treatment. In this study, we developed a new clinical decision-making system to predict the resection and long-term recurrence risks of CP based on a large cohort and validated it on a cohort from another hospital. This system might allow clinicians to make more informed therapeutic decisions regarding adjuvant treatment. In addition, there were some striking features obtained from the present series of patients: 1. the risk of long-term recurrence in the high-risk group was significantly higher than that in the low-risk group; 2. the risk of recurrence among all patients was 19% within the first three years of surgery and then entered a plateau; 3. there was no difference in the BN20 score according to sex or pathological subtype; however, the radiotherapy and recurrence groups demonstrated higher scores than the other groups; 4. there was no significant difference in PFS between the GTR and STR+ radiotherapy groups, but radiotherapy prolonged PFS in the STR group; 5. the transcallosal fornix approach was associated with poor neuropsychological function, whereas the transsphenoidal approach exhibited better performance; and 6. hypothalamus involvement was a strong indicator in predicting both the grade of resection and long-term recurrence. To our knowledge, this is the first time predicting tools have been reported in CPs. The risk classification of patients and imaging reexamination plan based on these nomograms for postoperative follow-up and long-term surveillance will greatly benefit the clinical work.

In general, GTR should be pursued for the treatment of CP because it provides a chance for clinical cure, whereas radical treatment might cause catastrophic hypothalamic damage, especially in children. Different surgical approaches applied in the management of CP depend on tumor location, the growth pattern and the surgeon's experience (13) since there was no difference in the grade of resection between surgical approaches in our cohort. Based on our experience, strict indications should be required for the transnasal approach (14) (e.g., tumors purely in the sellar region). The ideal approach should maximize total tumor resection and maintain high-quality survival after surgery. Currently, an increasing number of approaches are being used in the resection of CPs (15), but a large study is needed to verify the results. It was reported Liu et al. proposed a novel QST classification for understanding the growth pattern of tumors and could be used to guide surgical procedures (16). Considering the current medical environment in China and the risks brought by radical resection, in particular, the expectations of patients may be influenced by the local culture. We believe that it is necessary to objectively predict the degree of resection based on clinical features before surgery. Of note, predictive tools cannot replace intraoperative judgments about the possible degree of resection. Thus, the predictive model can become an important and timely communication tool between doctors and patients and allow patients to better understand the risks of surgery from the doctor's perspective.

In the past, several independent risk factors related to tumor recurrence, such as age, extent of resection, hypothalamus involvement, and postoperative radiotherapy, have been reported (1, 2), but what does the proportion of these factors play in tumor recurrence? Therefore, identification of the risk of recurrence in patients with CP is crucial for personalized treatment planning. Here, we established a model that can accurately predict long-term tumor recurrence. De Vile C J et al. described an age less than 5 years as a significant predictive factor for recurrence, which might be due to the difficulty associated with giving adjacent radiotherapy to children and its side effects on cognitive function (17). To date, the prognostic value of pathological subtype remains controversial, with some viewpoints suggesting that PCP has a better prognosis than ACP (18). In our study. ACP and PCP were not different according to the KM survival curves (**Figure 3**). At present, some surgeons believe that total resection can achieve the best therapeutic effect and that subtotal resection + radiotherapy does not improve prognosis and might even result in the side effects observed with radiotherapy (19–23); however, radiotherapy can significantly prolong the PFS period following incomplete resection, similar positive effect of radiotherapy were observed in previous literatures (19). Patients were stratified by risk scores into high- and low-risk groups based on the median risk scores to scientifically guide long-term follow-up in the clinic and more efficiently monitor tumor recurrence and reduce time and economic cost. The first three years after the operation was the peak period of tumor recurrence, after which it entered a plateau period, and only a few patients relapsed at this time. Based on the prediction tool and the plateau, we strongly recommend that patients at high risk undergo MRI at least every 6 months for 3 years after surgery. There are some points that need to be considered when applying the model. For the study of baseline data, we tried to avoid bias that may have been caused by subjective factors, such as operative time and amount of bleeding. Although this may reduce the coverage of the model, it would be more suitable for clinical practice. Finally, calcification in the CT scan was not always in accordance with intraoperative manipulation, suggesting that a

thin-layer CT scan should be performed as much as possible to determine the authentic situation and to improve the efficiency of the two nomograms.

With the development of neurosurgery technology, total resection of CP can obtain long-term OS. The latest viewpoints have gradually transformed CP from a curative tumor to a chronic disease (24), so its neuropsychological outcome it has been noted in recent years. A large proportion of patients cannot return to work because of the endocrine disorders and mental deficits remaining after surgery (7). Considering the *post hoc* LSD test may show false positive results whereas the Bonferroni correction is conservative (0.5 *vs* 0.05) in the evaluation of neuropsychological function, $p<0.01$ was used as the threshold for the pairwise comparison. We have attached the original P value to **Supplementary Material**. In our cohort, radiotherapy was associated with higher risks concerning hair loss, consistent with our understanding (25). Regarding the surgical approach, the BN20 scores were better with the AI approach than with the TI approach. On the one hand, the latter could be explained by its closer location to the third ventricle, larger size, and requirement for an incision in the corpus callosum. On the other hand, the AI approach could reduce the stretching of brain tissue. Moreover, the transsphenoidal approach showed better quality of life in terms of long-term neurological function after surgery. When using the transsphenoidal approach, the surgeon needs to be aware of the catastrophic consequences of vascular disturbances during the operation. Unfortunately, this study focused only on function at the last postoperative follow-up. A detailed functional assessment both pre- and postoperatively is necessary in the future.

However, there are a few limitations to this research. Although two nomograms were developed and validated in three large centers, our study was retrospective, with inevitable limitations. Furthermore, some data, such as BMI and morbid obesity were lacking during the follow-up. Thus, our results need to be further validated in a prospective cohort and in other populations.

CONCLUSION

In conclusion, we developed novel nomograms to better predict the extent of resection before surgery and the risk of long-term recurrence; thus, these nomograms might allow neurosurgeons and patients to benefit from clinical care and decision making. Finally, we developed an online calculator to stratify patients into different risk groups to increase the utility of follow-up surveillance and management strategies. As the first nomogram with external validation based on a large series, we believe that these two predictive tools will provide guidance in individual treatment and clinical applications.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

DX and FG: conception and design, analysis, data collection, and manuscript writing. QW, PH, YH, YZ, and MF: data collection, analysis, and manuscript reviewing. QW, ZL, SZ, DS, SL, MZ, QG, LZ, and FL: data collection and analysis. FG, XL, and CM: manuscript reviewing. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by grants from the National Natural Science Foundation of China (U1204807), the Science and Technology Department of Henan Province (192102310113), the Medical Science and Technique Foundation of Henan Province (SB201901007), and the Educational Department of Henan Province (19B320017).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.691288/full#supplementary-material

Supplementary Table 1 | Excluded patients in postoperative period.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

ORIGINAL RESEARCH
published: 14 July 2021
doi: 10.3389/fonc.2021.698150

Cerebral Infarction in Childhood-Onset Craniopharyngioma Patients: Results of KRANIOPHARYNGEOM 2007

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OPEN ACCESS

Edited by:
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Capital Medical University, China

Reviewed by:
Salvatore Massimiliano Cardali,
University of Messina, Italy
Yazhuo Zhang,
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Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: 20 April 2021
Accepted: 28 June 2021
Published: 14 July 2021

Citation:
Boekhoff S, Bison B, Genzel D, Eveslage M, Otte A, Friedrich C, Flitsch J and Müller HL (2021) Cerebral Infarction in Childhood-Onset Craniopharyngioma Patients: Results of KRANIOPHARYNGEOM 2007. Front. Oncol. 11:698150. doi: 10.3389/fonc.2021.698150

Background: Cerebral infarction (CI) is a known vascular complication following treatment of suprasellar tumors. Risk factors for CI, incidence rate, and long-term prognosis are unknown for patients with childhood-onset craniopharyngioma (CP).

Methods: MRI of 244 CP patients, recruited between 2007 and 2019 in KRANIOPHARYNGEOM 2007, were reviewed for CI. Risk factors for CI and outcome after CI were analyzed.

Results: Twenty-eight of 244 patients (11%) presented with CI based on reference assessment of MRI. One CI occurred before initial surgery and one case of CI occurred after release of intracystic pressure by a cyst catheter. 26 of 28 CI were detected after surgical tumor resection at a median postoperative interval of one day (range: 0.5-53 days). Vascular lesions during surgical procedures were documented in 7 cases with CI. No relevant differences with regard to surgical approaches were found. In all 12 irradiated patients, CI occurred before irradiation. Multivariable analyses showed that hydrocephalus and gross-total resection at the time of primary diagnosis/surgery both were risk factors for CI. After CI, quality of life (PEDQOL) and functional capacity (FMH) were impaired.

Conclusions: CI occurs in 11% of surgically-treated CP cases. Degree of resection and increased intracranial pressure are risk factors, which should be considered in the planning of surgical procedures for prevention of CI.

Keywords: craniopharyngioma, cerebral infarction, surgery, irradiation, quality of life

INTRODUCTION

Childhood-onset, adamantinomatous craniopharyngiomas (CP) are rare embryonal malformational tumors, originating in the sellar and parasellar region with WHO grade I malignancy. Long-term prognosis and quality of life (QOL) are frequently impaired due to sequelae caused by the anatomical location of CP close to the pituitary gland, the hypothalamus,

and the optic chiasm (1–5). In CP patients with hypothalamic involvement both survival rates and QOL are reduced (6–8). When compared with the general population, CP patients were observed to present with a 3–19 fold higher cardiovascular mortality rate (9–11). An even higher risk was reported for women with CP (12). A 14% rate of cerebrovascular events has been reported by Regine et al. (13), all in patients with CP who received irradiation doses >61 Gy.

The purpose of our study was to determine the incidence of cerebral infarction (CI) in a cohort of 244 German childhood-onset CP patients recruited between 2007 and 2019 with a high degree of completeness in the prospective, randomized trial KRANIOPHARYNGEOM 2007 (German Childhood Craniopharyngioma Registry) (14, 15). Furthermore, we analyzed outcome and risk factors for CI, based on evaluation of clinical and neuroradiological presentation and treatment modalities in these CI patients when compared to CP patients without CI, recruited in the trial KRANIOPHARYNGEOM 2007 during the same time period.

PATIENT COHORTS AND METHODS

Two hundred and eighty-two patients (143 females/139 males) diagnosed with adamantinomatous CP (median age at CP diagnosis: 9.2 years, ranging from 1.3 to 17.9 years) were recruited between 2007 and 2019 in the trial KRANIOPHARYNGEOM 2007 (Clinical Trial No. NCT01272622) (16) and prospectively observed after a median follow-up interval of 4 years, ranging from 0.01 to 13.1 years). Adamantinomatous CP as the histological diagnosis was confirmed by pathological reference assessment in all cases. In KRANIOPHARYNGEOM 2007, the timepoint of irradiation (XRT) after incomplete resection was randomisized in patients with >5 years of age at diagnosis (arm I: immediate XRT after diagnois *versus* arm II: XRT at the time of progression of the residual tumor). A further secondary endpoint and question of the trial KRANIOPHARYNGEOM 2007 was the rate of CI. The following analyses included 244 patients (125 females/119 males) with available MRI at diagnosis and during a follow-up of at least 56 days after surgery.

Neuroradiological Diagnostics

According to the KRANIOPHARYNGEOM 2007 protocol (17–19), cranial MRIs were performed at the time point of CP diagnosis and prospectively at 3-months intervals during the first year follow-up. Neuroradiologists (B.B: and D.G.) blinded for clinical information assessed presurgical hypothalamic involvement (HI), tumor volume and location of CP, degree of surgical resection, and surgical hypothalamic lesions (HL). HI of CP was categorized into defined degrees: grade 0 of HI: no detectable HI on presoperative MRIs; grade 1 HI: HI of the anterior hypothalamic area not involving mammillary bodies (MB) and hypothalamic structures dorsal of MB; and grade 2 HI: HI of both anterior and posterior hypothalamic structures, i.e. involving anterior hypothalamic area, MB and hypothalamic structures dorsal of MB (17, 18).

Based on postsurgical MRIs, postsurgical HLs were categorized according to the same criteria in 3 grades: grade 0 HL: no detectable HL on postoperative MRIs; grade 1 HL: HL of anterior hypothalamic structures not involving MB, and grade 2 HL: HL involving anterior hypothalamic areas, MB and hypothalamic structures dorsal of MB. The tumor size of CP was calculated using the formula "½ (A x B x C)" (aligned to the ellipsoid model: 4/3 π [A x B x C]), where A, B and C are the maximum dimensions in the standard planes: axial (transverse, A), coronal (craniocaudal, B) and sagittal (anteroposterior, C).

Pre- and postsurgical MRIs were reference-assessed by neuroradiologists (B.B. and D.G.) for the presence of CI. The imaging features of CI were defined as high MRI signal intensity on T2-weighted and/or proton density-weighted and/or fluid attenuation inversion recovery (FLAIR) weighted and/or restricted diffusion-weighted imaging (DWI) with high signal on the b1000 images and a low acquired diffusion coefficient (ADC) with the typical shape of an ischemic lesion (**Figure 1**). Preoperative imaging was also checked in patients with CI, for ischemic lesions to verify that CI was definitely associated to therapeutic interventions since DWI was not performed during all postoperative MRI examinations and some postoperative MRIs were too late to detect restricted diffusion. Furthermore, in CP patients with CI the vessel territory of the CI area, the maximum diameter of ischemic lesion on the first postoperative MRI and postoperative clinical complaints were analyzed.

Clinical Parameters

In all CP patients, clinical and auxiological parameters were analyzed based on the protocol of the KRANIOPHARYNGEOM 2007 trial (15). Body weight, body height (SDS) (20), and body mass index (BMI) were measured at the time of CP diagnosis and prospectively at 3-months intervals after diagnosis. BMI (w/h^2; w= weight/kilogram, h= height/meter) was calculated as standard deviation score (SDS) according to the age-related references of Rolland-Cachera et al. (21) for each subject at diagnosis of CP and at defined time points (one and 3 years after CP diagnosis, and at last follow-up visit).

Quality of Life Questionnaires

The Pediatric Quality of Life (PEDQOL) (22, 23) questionnaire was used to assess health-related QOL in patients diagnosed with CP at an age ≥5 years, at defined time points (3, 12 and 36 months after diagnosis of CP). In CP patients younger than 18 years of age at the time of study, parental assessment of CP patient QOL was obtained using the PEDQOL questionnaire. The PEDQOL instrument is defining health-related QOL within the domains: autonomy, emotional stability, body image, cognition, physical function, social functionality in family, and among friends. A high PEDQOL score is equivalent to more negative self- or parental-assessed QOL (22).

To analyze functional capacity, we used the German daily life ability scale Fertigkeitenskala Münster-Heidelberg (FMH) at the defined time points 3 months, one and 3 years after diagnosis of CP and at last visit (24). Based on 56 items, the FMH instrument measures the capacity for routine, daily life actions. FMH was normalized with 971 individuals (45% female), aged between 0

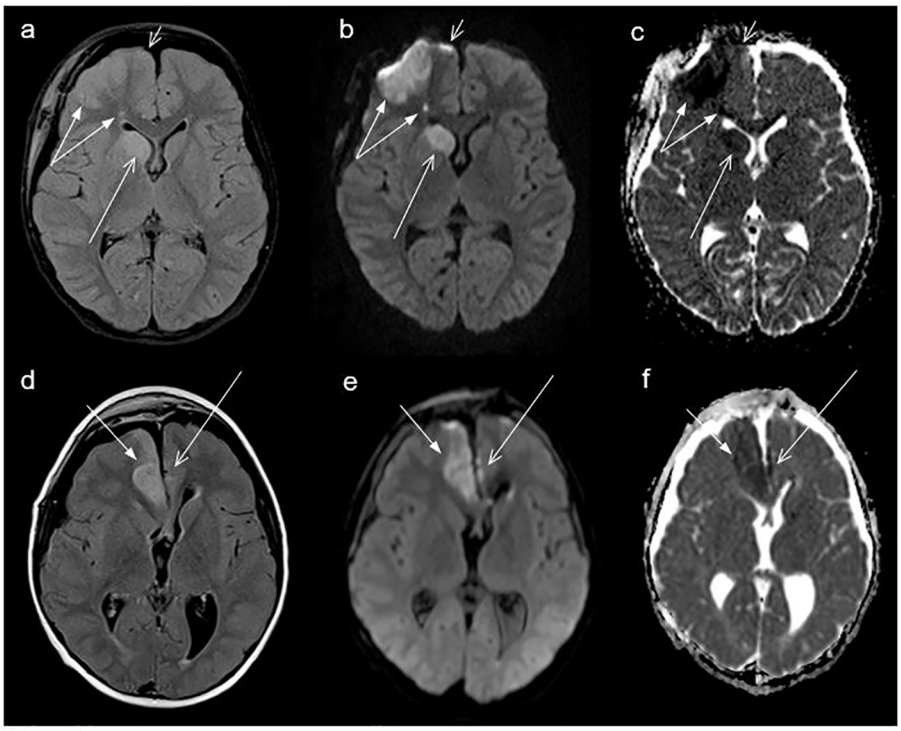

FIGURE 1 | Cranial magnetic resonance imaging (MRI) of a craniopharyngioma patient (case #25, **Table 2**) with cerebral infarction (CI) of middle cerebral artery (MCA) on the right side (double arrow, territorial CI), anterior cerebral artery ACA (Heubner) right side (long arrow), and the top of ACA right side (short arrow, paired with contusions), performed 4 days after surgery **(A–C)**; and MRI of a craniopharyngioma patient (case #19, **Table 2**) with cerebral infarction (CI) of the anterior cerebral artery (ACA) on the right side (short arrow) and on the left side (long arrow) showing a linear cortical CI, MRI performed one day after surgery **(D–F)**. **(A, D)** show fluid-attenuated inversion recovery (FLAIR) sequences, **(B, E)** show DWI b1000, and **(C, F)** show apparent diffusion coefficient (ADC) images, all axial plane.

and 102 years. FMH scores have the format of age-dependent percentiles (25). The time for answering the FMH questionnaire is in average 4.5 minutes (24).

Statistical Methods

Statistical analyses were performed using SPSS 26 (SPSS, Inc.) and SAS software, version 9.4 for Windows, SAS Institute, Cary, NC, USA. Data are displayed as median (range) or frequency (percent). For comparison of continuous variables between two independent groups, the Mann-Whitney U test was used. In order to analyse possible risk factors for CI, logistic regression was used. The final model was chosen by a stepwise selection algorithm. Results are shown as odds ratio (OR) and corresponding 95%-confidence interval (CI). All inferential statistics are intended to be exploratory (hypotheses generating), not confrimatory, and are interpreted accordingly.

RESULTS

Twenty-eight of 244 patients (11%) developed CI based on central review of MRI. Patients developing CI were comparable to patients without CI in terms of gender, age at CP diagnosis (**Figure 2**), BMI, height SDS, grade of HI and tumor location at the time of CP diagnosis. There was a trend (p=0.094) towards larger tumors in 28 patients with CI (median tumor size: 25.1 cm^3; range: 0.01–187 cm^3) when compared with patients without CI (median tumor size: 15.7 cm^3; range: 0.01–286 cm^3). A hydrocephalus was diagnosed in 22 of 28 patients with CI (79%), whereas only 76 of 216 patients without CI (35%) presented with hydrocephalus at the time of CP diagnosis (p<0.001) (**Table 1**).

One CI (case #2, **Table 2**) was detected before initial surgery. At the time of diagnosis, MRI showed a suprasellar tumor with close connection and displacement of the right internal carotid artery as well as anterior and medial cerebral arteries. A large cystic tumor compartment showed typical MRI signs of an intracystic hemorrhage leading to CI. Another CI (case #1, **Table 2**) occurred during a surgical procedure replacing an intracystic catheter, which did not drain properly due to occlusion. All other 26 cases of CI (96%) were detected after initial tumor resection at a median interval between surgery and CI diagnosis of one day, ranging from 0.5 to 53 days. In one case of CI (case #21, **Table 2**), an additional left frontal lobe bleeding was observed. 12 of 28 patients with CI were irradiated (2 photon XRT; 10 proton beam therapy). In all irradiated cases, CI was

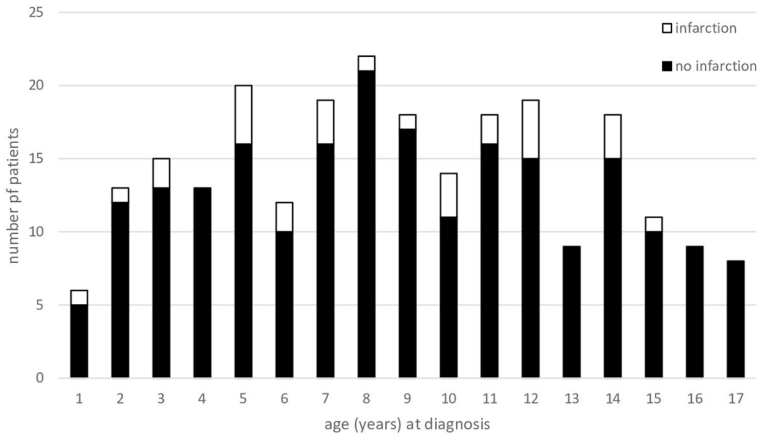

FIGURE 2 | Age of 244 patients (recruited in KRANIOPHARYNGEOM 2007 between 2007 and 2019) at the time of primary surgery/diagnosis of adamantinomatous, childhood-onset craniopharyngioma. Patients presenting with cerebral infarction (CI) are represented by open parts of columns; patients without CI are depicted as solid black parts of columns.

diagnosed before the start of irradiation (XRT) (median interval between CI diagnosis and XRT: 13 months; range: 1.8 – 34.5 months).

In further analyses, we excluded the above-mentioned two cases (case #1 and case #2, **Table 2**) and analyzed the remaining 26 CP patients with initial surgical intervention leading to CI. The realized degree of surgical resection was different between 26 CI and 216 no-CI patients. Gross-total resection (GTR) was performed more frequently in CI patients (39%) when compared with non-CI patients (23%). With regard to surgical approaches, we observed that a transsphenoidal route was chosen in 38 of 216 patients without CI (18%) and in 2 of 26 patients with CI (8%). As a potential measure of surgical experience, we analyzed also data for CP patient load of neurosurgical centers and found no associations between patient load and rate of CI (**Table 1**).

Analyzing surgical reports with regard to intraoperative complications leading to CI, in 7 of 26 patients (27%) bleeding complications resulting in CI have been reported. In 14 of 26 patients no intraoperative complications resulting in vascular lesions with consecutive bleeding were mentioned in surgical reports. The outcome of 7 patients with intraoperative bleeding was comparable with the outcome in 20 CI patients without intraoperative bleeding episodes mentioned in surgical reports with regard to QOL and functional capacity (data not shown).

Whereas the rate of presurgical HI was similar in patients with and without CI, patients with CI were characterized by a different pattern of surgical HL when compared with patients without CI. Patients without CI more frequently showed no surgical HL (28% *vs.* 0%), whereas patients with CI had a higher rate of anterior and posterior hypothalamic surgical lesions (58% *vs.* 34%) (p=0.0007) (**Table 1**). In 46% of all CI cases, CI occurred in both cerebral hemispheres mainly after bifrontal surgical approach (38%). In 54% of CI, bleeding was observed in one hemisphere – right-sided in all cases, after right-sided surgical approach in 73% (**Table 2**).

Logistic regression analysis including age at diagnosis, initial tumor volume, hydrocephalus, degree of surgical resection, and surgical HL as potential risk factors for CI, showed that hydrocephalus and GTR were relevant risk factors for CI. Both were included in a multivariable logistic regression model. The risk of CI was increased [OR = 7.7, 95%-confidence interval (2.70, 21.72)] when patients initially presented with hydrocephalus or when GTR was achieved [OR = 2.76, 95%-confidence interval (1.09, 6.86)] (**Table 3**).

QOL as measured by PEDQOL was lower for CI patients at the time points 3 months, one, and 3 years after CP diagnosis in self-assessment as well as parental assessment (**Figure 3**). Furthermore, functional capacity as measured by FMH was reduced one year after CP diagnosis (p=0.014), 3 years after CP diagnosis (p=0.024) and at last visit in patients with CI (p<0.001), when compared with CP patients without CI. When functional capacity was compared between CI and no CI patients with regard to the frequency of surgical interventions, we observed that FMH scores were reduced in CI patients with more than one surgical intervention (**Figure 4**).

DISCUSSION

Long-term outcome after CP is frequently impaired by morbidity due to hypothalamic obesity including cardiovascular (26) and neurovascular disease (27). Neurovascular complications such as CI in CP may result from injury to any of the major intracranial vessels and their branches, due to tumor location/infiltration and/or treatment-related lesions such as surgical injury, postoperative vasopasms or XRT-induced vessel damage.

Increased rates of cerebrovascular disease have been reported in a number of studies after pituitary XRT. In a series of 156 patients with sellar masses, increased CI rates were found in patients with higher administered XRT doses (28). Cerebral XRT was also reported to be associated with increased risk for Moyamoya syndrome. In patients treated with XRT for primary brain tumors, the estimated prevalence of Moyamoya syndrome

TABLE 1 | Characteristics of the study population showing data for patients with and without cerebral infarction (CI) recruited in KRANIOPHARYNGEOM 2007 between 2007 and 2019.

	Patients without CI	Patients with CI	*Case 1*	*Case 2*	*P value*
Patient number, n	216	26	1	1	
Gender, female/male, n (%)	113 (52)/103 (48)	11 (42)/15 (58)	female	male	0.423[a]
Age at diagnosis (year)	9.2 (1.3 – 17.9)	10.1 (1.7 – 15.6)	5.0	2.0	0.642[a]
Duration of history (months)	5 (0.1 – 108)	7 (0.1 – 96)	36.0	0.5	0.735[a]
Follow-up time (year)	4.9 (0.2 – 13.1)	3.7 (0.1 – 9.9)	5.8	2.0	0.080[a]
BMI at dgx [SDS (21)]	0.4 (-11.8 – 10.0)	1.5 (-3.0 – 9.1)	2.9	-1.3	0.058[a]
Height at dgx [SDS (20)]	-1.0 (-4.9 – 3.6)	-1.0 (-4.2 – 1.8)	-1.1	1.8	0.974[a]
BMI at last visit [SDS (21)]	3.0 (-2.0 – 20.8)	4.4 (-1.1 – 13.2)	4.1	0.7	0.044[a]
Height at last visit [SDS (20)]	-0.3 (-3.9 – 3.1)	0.1 (-4.1 – 2.5)	-0.1	1.7	0.216[a]
Tumor volume (3D cm³)	15.7 (0.01 – 286.3)	25.1 (0.01 – 187.6)	11.5	13.4	0.094[a]
Hydrocephalus, n (%)	76 (35.2)	21 (80.8)	x		<0.001[a]
Frequency of surgical interventions, n (%)	2 (1 – 12)	2 (1 – 7)	4	1	0.528[a]
Degree of first surgical resection, n (%)					0.091[b]
Complete resection	49 (23)	10 (39)			
Incomplete resection	167 (77)	16 (62)		x	
no resection	0	0	x		
Surgical approach at first resection, n (%)					0.578[b]
Bifrontal	17 (8)	2 (8)			
Endoscopy	4 (2)	1 (4)	x		
Posterior fossa	1 (0.5)	0			
Transsphenoidal	38 (18)	2 (8)			
Transventricular/transcallosal	8 (4)	1 (4)			
Unilateral, fronto-temporal or variations of this approach	145 (67)	20 (76)		x	
n.a.	3 (1)	0			
Transsphenoidal *vs.* "other"	38/175	2/24			0.269[b]
Surgical experience (patient load/year)					0.611[b]
≤1 patient per year/centre, n	174 (80)	20 (77)	x	x	
>1 patient per year/centre, n	42 (20)	6 (23)			
Hypothalamic involvement (HI), n (%)					0.219[b]
No HI	11 (5)	0			
Anterior HI	60 (28)	4 (15)		x	
Anterior and posterior HI	144 (67)	22 (85)	x		
n.a.	1 (1)	0			
Hypothalamic lesion (HL), n (%)					0.0007[b]
No HL	61 (28)	0		x	
Anterior HL	80 (37)	11 (42)			
Anterior and posterior HL	74 (34)	15 (58)	x		
n.a.	1 (1)	0			

BMI, body mass index; SDS, standard deviation score; pts., patients; yr., year; HI, presurgical hypothalamic involvement; HL, surgical hypothalamic lesion; n.a., data not available. [a]*all patients with CI, including case #1 and case #2,* [b]*patients with CI, except case #1 and case #2. Depicted are medians and ranges in paraenthesis or frequency and percentage in parenthesis.*

ranges from 3.5% to 9% (29–31). Ullrich et al. (29) observed that, Moyamoya was diagnosed in 12 of 345 patients (3.5%), at a median follow-up of 54 months after XRT for brain tumors.

CI or ischemic stroke after XRT of a skull base tumor, is usually a delayed event (28, 32–36) and most of the patients in a study of Astradsson et al. (37) had a stroke with onset several years after XRT. Tumors of the anterior skull base are located close to anatomical structures such as the Circle of Willis and the cavernous sinus, so that collateral XRT of these structures may occur and lead to vascular sequelae (38, 39).

We have previously reported on fusiform dilatations of the internal carotid artery (FDCA) representing a potential complication after surgery for childhood-onset CP with suprasellar extension. We could show that FDCA is a extremely rare complication associated with surgical treatment of CP patients without relevant impact on prognosis and clinical outcome after CP (27).

In the literature, associations between CI and hypothalamic lesions, release of inflammatory substances during neurosurgical resection, and direct surgical injury to the blood vessels in the basal cisterns have been reported (40, 41). During and after CP surgery, vasospasm may occur due to spillage of CP cyst fluid inducing chemical meningitis (42). Spontaneous rupture of CP cysts inducing preoperative vasospasm has been observed (42). Arterial spasms of femoral vessels have been reported in animal models four days after instillation of cyst fluid on the femoral vessel (43). Diabetes insipidus and consequent hypovolemia need close peri and postoperative monitoring as potential risk factors for CI. Diabetes insipidus results in volume deficits. Accordingly, cerebral hypoperfusion and ischemia could be worsened in cases of intravascular fluid depletion.

Wijnen et al. (44) reported on an increased risk for CI after CP (SIR: 4.9, 95%-confidence interval: 3.1, 8.0). The excess risk for CI was higher in female patients with childhood-onset CP, and in patients with hydrocephalus and CP recurrence.

TABLE 2 | Characteristics of 26 patients with childhood-onset craniopharyngioma (CP) patients (recruited in KRANIOPHARYNGEOM 2007 between 2007 and 2019) with cerebral infarction (CI) confirmed by central neuroradiological review.

No.	Sex (f/m)	Age at surgery (yr)	CP-Volume at dgx (cm^3)	HI (grade)	Degree of surgical resection	Surgical approach (1,2,3,4)	Intra.-operative vascular lesions	HL (grade)	Interval btw. surgery and CI detection (days)	Cerebral infarction (CI)	Volume of CI (cm^3)	Cerebral infarction (CI)	Volume of CI (cm^3)	Cerebral infarction (CI)	Volume of CI (cm^3)	age at XRT (yr)
1	f	5.5	11.5	2	None	4	/	2	0	AChA ri.	3.2	/	/	/	/	7.0
2*	m	2.0	13.4	1	Incompl.	1 ri.	/	0	-3 before OP	MCA ri. multifocal	2.0	/	/	/	/	/
3	m	11.8	10.7	2	Compl.	1 ri.	/	2	2	ACA le. basal	13.5	ACA ri. basal	14.4	MCA ri. frontal	72	/
4	m	15.6	1.9	2	Compl.	1 ri.	/	2	53	ACA ri. (Heubner)	3.5	MCA ri. BG multifocal	0.7	MCA ri. temporal	1.6	/
5	f	8.0	187.6	2	Incompl.	2	/	2	0	ACA multifocal ri.+le.	0.9	AChA ri.	0.3	/	/	9.8
6	m	2.4	33.5	2	Incompl.	1 ri.	/	1	2	MCA ri. frontal	0.6	/	/	/	/	2.5
7	f	12.0	19.4	2	Compl.	1 ri.	/	2	18	ACA ri. (Heubner)	0.6	/	/	/	/	
8	m	3.6	28.4	2	Compl.	2	/	1	0	ACA ri. frontobasal	11.9	ACA le. frontobasal	6.5	/	/	5.5
9	f	10.4	26.2	2	Incompl.	1 ri.	Surgical vascular lesion	2	7	AChA ri.	1.8	/	/	/	/	/
10	m	14.5	15.4	2	Incompl.	1	/	2	11	ACA ri.	1.8	/	/	/	/	/
11	m	3.5	74.8	1	Compl.	1	/	1	4	ACA ri. (Heubner)	0.5	ACA le. (Heubner)	0.8	MCA le. BG	0.4	/
12	m	9.8	28.1	2	Incompl.	1 ri.	Arterial tumor bleeding	1	0	ACA ri.	2.8	ACA + ACM le.**	/	/	/	10.7
13	f	8.5	3.4	1	Compl.	1	/	1	1	ACA ri.	3.3	ACA le.	1.0	/	/	/
14	m	14.8	6.4	1	Incompl.	1 le.	/	1	1	ACA ri. basal	6.3	ACA le. basal	1.9	/	/	/
15	f	10.5	13.8	2	Incompl.	1	/	2	2	ACA ri. (Heubner)	9.8	/	/	/	/	/
16	m	6.4	36.6	2	Incompl.	1 ri.	/	2	0	MCA ri. cortical***		ACA ri. hochfrontal	0.03	/	/	7.4
17	m	10.5	30.8	2	Incompl.	1	Surgical vascular lesion	2	1	ACA li. basal	2.5	ACA ri. basal	0.6	/	/	11.5
18	m	9.2	13.7	1	Incompl.	1 ri.	/	1	1	MCA ri., capsula int.		/	/	/	/	/
19	m	6.0	31.9	2	Compl.	1 ri.	/	2	1	ACA ri. basal	10.4	ACA le. basal	1.6	/	/	/
20	f	12.5	10.7	2	Compl.	1 ri.	Surgical vascular lesion	2	0	MCA ri.	1.1	MCA ri.	0.5	/	/	15.4
21	f	7.2	14.1	2	Compl.	1	/	2	0	ACA le. basal	0.7	ACA ri. basal		/	/	/
22	m	11.7	57.6	2	Incompl.	1 le.	Surgical vascular lesion	2	1	ACA le. (Heubner)	6.0	PCA ri.	0.3	/	/	/
23	m	12.7	0.01	2	Incompl.	4	Surgical vascular lesion	2	1	ACA ri. (Heubner)	3.1	ACA le. (Heubner)	4.6	/	/	/
24	f	12.2	32.0	2	Incompl.	3	Venous bleeding	1	1	PCA le.	0.4	ACP ri.	0.3	PCA le.	1.7	/

(Continued)

TABLE 2 | Continued

No.	Sex (f/m)	Age at surgery (yr)	CP-Volume at dgx (cm^3)	HI (grade)	Degree of surgical resection	Surgical approach (1,2,3,4)	Intra.-operative vascular lesions	HL (grade)	Interval btw. surgery and CI detection (days)	Cerebral infarction (CI)	Volume of CI (cm^3)	Cerebral infarction (CI)	Volume of CI (cm^3)	Cerebral infarction (CI)	Volume of CI (cm^3)	age at XRT (yr)
25	f	5.4	17.9	2	Incompl.	1 ri.	/	2	4	MCA ri. ****		ACA ri. (Heubner)	3.2	ACA ri.	0.2	6.5
26	f	5.9	94.2	2	Compl.	1 le.	/	1	1	ACA ri. (Heubner)	9.0	ACA ri. frontobasal #	/	ACA le. basal #	/	7.7
27	m	7.7	107.2	2	Incompl.	1 ri.	/	1	1	ACA ri. (Heubner)	3.7	/	/	/	/	7.9
28	f	14.2	24.0	2	Incompl.	3	surgical vascular lesion	1	1	ACA ri. (Heubner)	0.06	/	/	/	/	15.3

*ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; AChA, anterior choroidal arteryri., right; le., left; m, male; f, female; yr, year; ant., anterior; compl., complete; incompl., incomplete; int., interna; Surgical approach: 1=unilateral, 2=bifrontal, 3=transsphenoidal, 4=endoscopical; BG = Basal ganglia; * patient with CI detected before initial surgery; ** cortical along frontal lobe reaching the insula, precise measurement not possible, <25% ACA and MCA region; *** precise measurement not possible, < 75% of MCA region; **** cortical frontal with temporopolar extension, precise measurement not possible, 25-50% of MCA region; # (linear along the border of resection), precise measurement not possible.*

In our cohort of the German Craniopharyngioma Registry, 11% of all CP cases developed CI. In one patient, CI occurred before surgical and radiooncological treatment, indicating that the tumor disease itself represents a certain risk for CI. In 27 of 28 cases, CI occurred following surgical procedures. Intraoperative bleeding was mentioned in the records of only 25% of cases with CI, indicating that pathogenic mechanisms different from surgical vascular damage could also play a role in CI. The risk for CI was not gender or age-related in our study. We observed an association between CI and increased intracranial pressure and the degree of surgical resection. We speculate that sudden shifts in intracranial pressure and brain shifts due to hydrocephalus treatment and tumor resection results in circulatory changes. Such changes – especially when associated with hypovolemic episodes due to diabetes insipidus - are hypothesized to increase the risk for CI. Accordingly, a two-stage surgical treatment strategy could be discussed in CP patients presenting with initial hydrocephalus: 1.) decreasing and stabilizing intracranial pressure by drainage of cerebrospinal fluid (CSF); 2.) stabilizing salt and fluid homeostasis by sufficient desmopressin substitution, and 3.) definite surgical intervention for tumor resection without vascular or hypothalamic damage after a time of sufficient stabilization achieved for 1.) and 2.). However, as CI in one of our (cases #1) occurred after cyst drainage, it is important to be aware that rapid changes in intracranial pressure – as caused for instance by cyst drainage or presumably also by CSF drainage – could be a potential risk factor on its own for CI even without a concomitant resecting intervention. Further studies on prevention of CI are warranted to answer controversies on this speculation. Interestingly, XRT was not associated with increased risk for CI. However, longer follow-up is necessary to estimate long-term risks of XRT for vascular events such as CI.

In multivariable analysis, radical surgical strategies such as GTR had independent impact on the risk for CI. Patients with CI had a higher rate of GTR when compared with CP patients without CI. We recommend limited surgical strategies in order to preserve hypothalamic integrity and functionality for prevention of special risks for CI and deterioration of long-term QOLand functional capacity (2). Reduced functional capacity was also associated with high frequency of surgical interventions after CI diagnosis.

Due to retrospective analysis and small cohort size, the results of our study are limited. At this point, some of our observations and conclusions are speculative. However, given the high degree of completeness with regard to multicentre recruitment of patients with childhood-onset CP in KRANIOPHARYNGEOM 2007, our study has the advantage to provide reliable data on the rate of CI in these patients. The exact time point of each CI cannot be confirmed based on our data. Diagnosis of CI is based on centrally reviewed MRI, which has been performed postoperatively and at 3-months intervals after primary diagnosis as part of the KRANIOPHARYNGEOM 2007 study protocol. The data on intraperative surgical vascular lesions are based on the available surgical records.

We conclude that especially in CP patients with initial hydrocephalus and surgical procedures such as GTR leading to

TABLE 3 | Result of univariable logistic regression for potential risk factors of cerebral infarcts (CI) and multivariable logistic regression model for CI chosen by a stepwise selection algorithm in patients with childhood-onset craniopharyngioma recruited in KRANIOPHARYNGEOM 2007 between 2007 and 2019.

Effect	Comparison	p-value (Wald)	Odds ratio (95% confidence interval)
	Univariable logistic regression model for potential risk factors of CI		
Age at diagnosis (n = 242)	per year	0.9637	0.998 (0.908; 1.096)
Sex (n = 242)	female *vs.* male	0.3372	0.668 (0.294; 1.522)
Initial tumor volume (n = 220)	per cm^3	0.2753	1.005 (0.996; 1.013)
Grade of HI (n = 241)	2 *vs.* 1 or 0	0.0762	2.711 (0.900; 8.167)
Hydrocephalus (n = 222)	yes *vs.* no	0.0003	6.632 (2.399; 18.331)
Gross-total resection (n = 242)	yes *vs.* no	0.0819	2.130 (0.909; 4.993)
Grade of HL (n = 241)	2 *vs.* 1 or 0	0.0237	2.598 (1.136; 5.943)
	Multivariable logistic regression model for CI chosen by a stepwise selection algorithm		
Hydrocephalus	yes *vs.* no	0.0001	7.652 (2.695; 21.722)
Gross-total resection	yes *vs.* no	0.0319	2.757 (1.092; 6.958)

HI, preoperative hypothalamic involvement; HL surgical hypothalamic lesion.

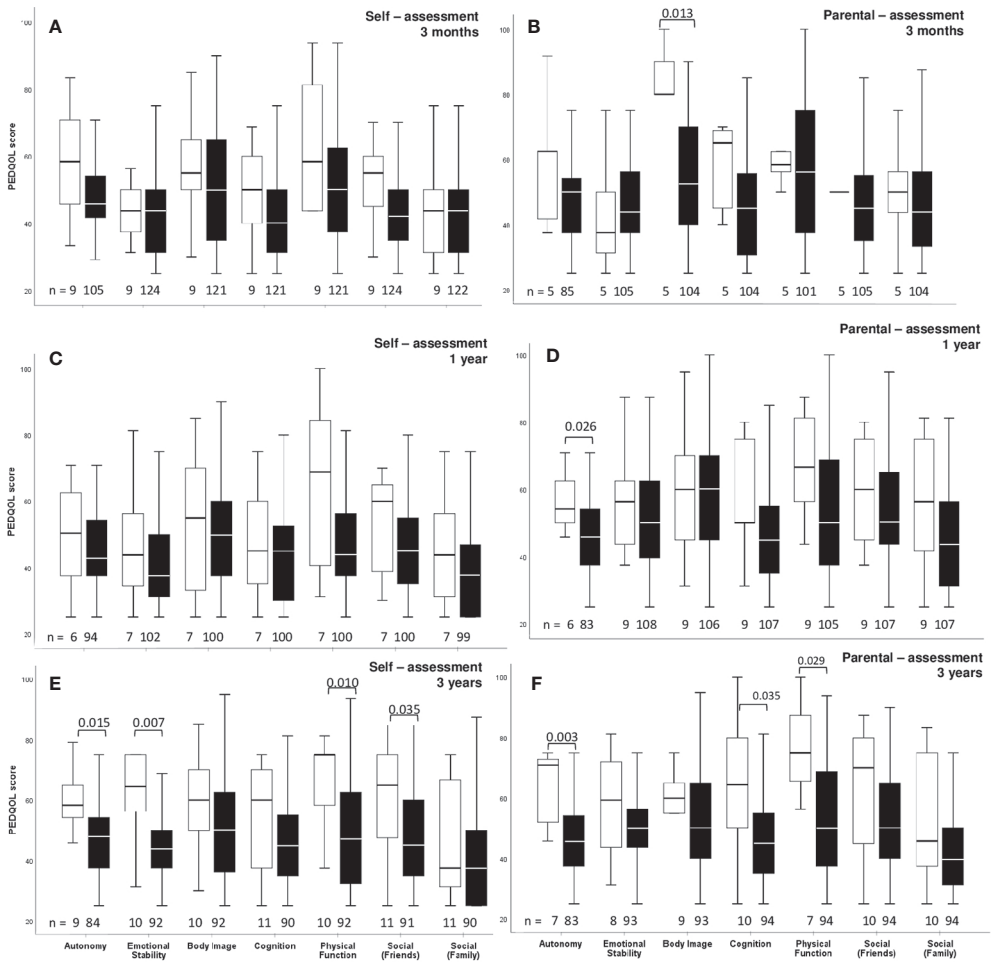

FIGURE 3 | Self-assessment **(A, C, E)** and parental assessment **(B, D, F)** of quality of life by Pediatric Quality of Life questionnaire (PEDQOL) in childhood-onset craniopharyngioma (CP) patients, recruited in KRANIOPHARYNGEOM 2007 between 2007 and 2019, with regard to cerebral infarction (CI) confirmed by central neuroradiological review. White boxes: CI, and black boxes: no CI. PEDQOL scores are shown as negative rating at the time points three months **(A, B)**, one year **(C, D)**, and three years **(E, F)** after CP diagnosis. The horizontal line in the middle of the box depicts the median. The top and bottom edges of the box respectively mark the 25th and 75th percentiles. Whiskers indicate the range of values that fall within 1.5 box-lengths.

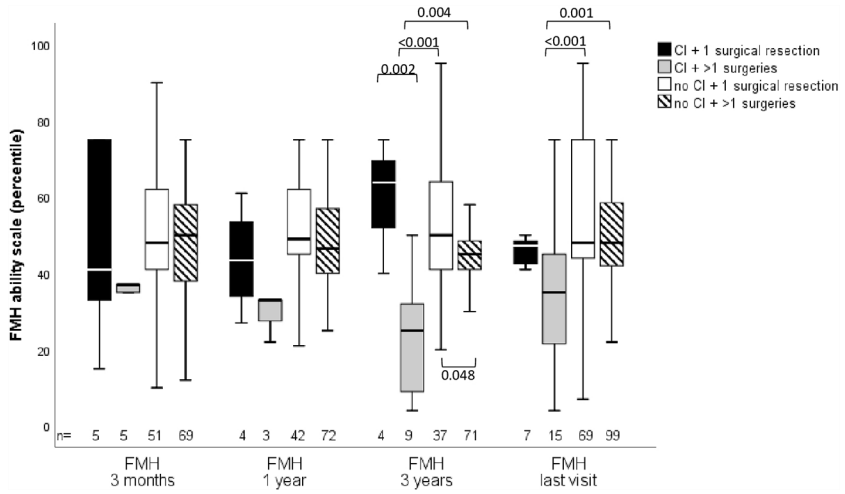

FIGURE 4 | Functional capacity as measured by capability scale Fertigkeitenskala Münster Heidelberg (FMH) in childhood-onset craniopharyngioma (CP) patients (recruited in KRANIOPHARYNGEOM 2007 between 2007 and 2019) with or without cerebral infarction (CI) and with a single or multiple surgical interventions at the time points 3 months, one year, 3 years after CP diagnosis, and at the time of last visit.

complete resection in complicated tumor locations/adhesion of vessels, the risk of CI is increased. CI leads to severe impairment of QOL and functional capacity during long-term follow-up after childhood-onset CP.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The study KRANIOPHARYNGEOM 2007 (Clinical trial registration number: NCT01272622) was approved by the local standing-committee on ethical practice of the Medizinische Fakultät, Julius-Maximilians-Universität Würzburg, Germany (140/99; 94/06, respectively). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

SB researched the data and wrote and reviewed the manuscript. BB and DG did neuroradiological assessment of all imaging. BB is the neuroradiologist, who performs reference-assessment of imaging in all patients recruited in KRANIOPHARYNGEOM 2007. They prepared the imaging data and their presentation and reviewed/edited the manuscript. ME supervised statistical analyses and reviewed/edited the manuscript. CF and AO contributed to the analytical plan, data analysis/presentation and discussion and reviewed/edited the manuscript. As a neurosurgeon, JF contributed to the analytical plan and discussion and reviewed/edited the manuscript. HM initiated and conducted the multicenter trials HIT-Endo and KRANIOPHARYNGEOM 2000/2007, contributed to the analytical plan and discussion and reviewed/edited the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This study was funded by a grant (HM, DKS2014.13; BB, DKS2018.02) of the German Childhood Cancer Foundation, Bonn, Germany.

ACKNOWLEDGMENTS

The authors want to thank all participating colleagues for recruiting patients in KRANIOPHARYNGEOM 2007, and the patients and their parents for participating in this study.

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Conflict of Interest: HM has received reimbursement of participation fees for scientific meetings and continuing medical education events from the following companies: Ferring, Lilly, Pfizer, Sandoz/Hexal, Novo Nordisk, Ipsen, and Merck Serono. He has received reimbursement of travel expenses from Ipsen and lecture honoraria from Pfizer.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

ORIGINAL RESEARCH
published: 30 September 2021
doi: 10.3389/fonc.2021.744308

Status Quo and Research Trends of Craniopharyngioma Research: A 10-Year Bibliometric Analyses (From 2011 to 2020)

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OPEN ACCESS

Edited by:
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Reviewed by:
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Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: 20 July 2021
Accepted: 14 September 2021
Published: 30 September 2021

Citation:
Li T, Yang A, Liu G, Zou S, Chen Y, Ni B, Liu Y and Fan J (2021) Status Quo and Research Trends of Craniopharyngioma Research: A 10-Year Bibliometric Analyses (From 2011 to 2020). Front. Oncol. 11:744308. doi: 10.3389/fonc.2021.744308

Background: Craniopharyngioma (CP) is a challenging intracranial tumor due to its special hypothalamus-pituitary location. Each patient with CP should be evaluated and treated separately. Exploring novel methods of automatized analysis of data for gaining knowledge on any medical field is an encouraging task, particularly in such an extremely challenging tumor as CP. We aim to summary the situations, investigate the research trends and evaluate research hotspots using bibliometric analysis for the CP research.

Methods: We extracted all the CP-related literatures from 2011 to 2020 from the Web of Science database. An Online analysis platform of literature metrology (Bibliometric), BICOMB, gCLUTO and CiteSpace softwares were used to do bibliometric analysis. As a supplement, we also analyzed the top 100 cited case reports with particular and certainly infrequent information to improve the analysis.

Results: According to our retrieval strategy, we found a total of 1262 CP-related literatures. The United States has maintained a leading position in global CP research, followed by China and Germany. Among institutions, Capital Med Univ, St Jude Childrens Res Hosp and Southern Med Univ rank in the top 3 in terms of the number of articles published. "WORLD NEUROSURGERY" is the most popular journal for CP-related research. Moreover, MULLER HL, MERCHANT TE, QI ST and others have made great achievements in the study of CP. Finally, we did biclustering analysis on keywords and identified 4 CP research hotspot clusters.

Conclusions: Our research provides a comprehensive analysis of the scientific progress of CP in the past 10 years, and insight into the development of CP research field, highlight research trends over time, and help identify valuable future directions.

Keywords: craniopharyngioma, bibliometrics, citation, hotspots, trends

INTRODUCTION

Craniopharyngioma (CP) is an epithelial tumor that origins from remnants of the craniopharyngeal duct epithelium. There are 0.5-2.5 new cases per million people per year worldwide. They account for 1.2-4.6% of all intracranial tumors and 5-11% of brain tumors in children (1–3). In children, symptoms such as central diabetes insipidus, visual impairment, headache, and growth retardation are highly indicative of CP. In adults, increased intracranial pressure (such as headache), endocrine defects (such as impaired sexual function), and hypothalamic syndrome (such as disturbances in water balance and body temperature regulation) are the main symptoms. CP includes adamantinomatous craniopharyngioma (ACP) and papillary craniopharyngioma (PCP). ACP is a more common subtype that affects people of all ages, while PCP is mostly limited to adults (4).

Different from other medical fields, CP is one of the most complex tumors could be analyzed by automatic algorithm. Although CP is a pathologically benign tumor and its histological grade is WHO I, it often affects the prognosis and outcome of patients because CP occurs in the special location of the hypothalamus-pituitary axis (1). There is no fixed treatment plan that is effective for this kind of pathology. Therefore, each patient with CP should be evaluated and treated separately.

With the continuous improvement of the quality of life and medicine, people pay more attention to CP. However, the large number of variables involved in the results of each patient and the expertise gained from surgical treatment vary greatly among authors, which brings greater complexity to the analysis of results. As early as the 1930s, Harvey Cushing, the first neurosurgeon to deal with these lesions extensively, predicted this problem (2).

It is an encouraging task to explore new methods for automated data analysis to acquire knowledge in any medical field, especially in such an extremely challenging tumor as CP. Through bibliometric methods and tools, we can make a more macro analysis on the basis of a large amount of literature data, which has become an important method to grasp the development trend of a field accurately. However, there are very few bibliometric studies on CP. Only Gnacio Jusue-Torres et al. summarized the 100 most cited articles (3). This literature lacks an analysis of the relationship among countries/regions, institutions, and authors, and prediction of CP research hotspots. And only analyzed the most cited 100 literatures, the scope is not large enough. Previous studies have shown that biclustering analysis can help to identify critical areas of research and relevant representative literatures (4). In this paper, through a comprehensive analysis of the relevant literatures and external characteristics of CP, we summarized various information of articles about CP and help identify valuable future directions.

MATERIALS AND METHODS

Data Search and Download

Based on the Science Citation Index-Expanded database, the bibliometric analysis was carried out. In the Web of Science database, we set the subject word (search title, abstract, author and keywords, etc.): craniopharyngioma; time: 2011-2020; article types: original articles and reviews. Through the above search strategy, the literatures related to CP were obtained. At the same time, in order to make our research more comprehensive, we included top 100 cited case reports during this period in the analysis, which could provide information on particular and certainly infrequent cases.

Data Collection

The data including fully recorded and quoted references was downloaded from Web of Science and imported into the Online Analysis Platform of Bibliometrics (http://bibliometric.com/) and CiteSpace (version 5.7.R3, Drexel University, USA). CiteSpace is an outstanding tool for collaborative network analysis to connect various publication features. Import the data downloaded from Web of Science database into it, and click the relevant categories to analyze the relationship among countries, institutions, authors, etc. By obtaining keywords with high citation rate, the research frontier and emerging trends in this field are predicted (5). Bibliographic Item Co-Occurrence Matrix Builder (BICOMB, version 2.01, China Medical University, China) (6) and gCLUTO (version1.0, University of Minnesota, USA) software for bibliometric analysis and corresponding clustering can be obtained. BICOMB can generate a binary matrix with source literatures as columns and keywords as rows. Import the binary matrix into gCLUTO, select the default setting, and adjust the number of clusters to get the appropriate cluster.

Bibliometric Analysis

We included publishing characteristics such as countries, institutions, journals, authors, and H-index in our analysis. At the same time, the 2020 version of Journal Citation Reports (JCR) and impact factor (IF), as important indicators to measure the scientific value of research, were also included in the analysis (7). Using the bibliometric, we analyzed the changes in the volume of articles and the cooperative relations of various countries. In CiteSpace, we connected all kinds of publication characteristics through collaborative network analysis. At the same time, we also obtained highly cited keywords to predict the research frontiers and emerging trends in this field (5, 6).

Biclustering Analysis of Research Hotspots

Biclustering can be used to show the relationship between frequent keywords, as well as the relationship between frequent keywords and the original literatures. In order to investigate the research hotspots of CP, we carried out the biclustering analysis of the publications and keywords. Through BICOMB, we constructed a binary matrix with source documents as columns and keywords as rows. Then used the software gCLUTO to analyze the matrix (4, 8). Finally, the semantic relationship between keywords and source documents was drawn through mountain and matrix visualization.

RESULTS

The Search Results of Related Literatures

The flow chart of the search is shown in **Figure 1**. According to our strategy, a total of 1262 related literatures were retrieved from 2011 to 2020.

The Contributions of Countries and Institutions to Global Publications

The volume of articles related to CP in the past 10 years is shown in **Figure 2A**. Generally speaking, there is little fluctuation in the volume of articles. Among them, the number of literature is the largest in 2020 (154) and the lowest in 2013 (99). The number of literature in the past five years has increased significantly compared with the previous five years. At least 57 countries and regions are doing research on CP. In the past 10 years, the United States has made the most significant contribution to the study of CP, followed by China, Germany, Japan etc. (**Figure 2B**). Centrality can be used to measure the importance of nodes in the network. The higher the centrality, the greater the importance of nodes. The results showed that the influence of the United States is more significant than that of any other country (centrality = 0.33), followed by England (0.22) and Germany (0.20) (**Table 1**).

The analysis of international cooperation shows that the United States cooperates frequently with other countries. Although China ranks second in the number of articles published, it cooperates less with other countries (**Figure 3A**). In terms of research institutions, the top 10 (**Table 1**) included Capital Med Univ(32), St Jude Childrens Res Hosp(30), Southern Med Univ(28), Univ Calif San Francisco(24), Harvard Med Sch (23),UCL(23), La Princesa Univ Hosp(22), Univ Florida(22), Sichuan Univ(20), Univ Colorado(20). The network density of CP research is only 0.0155 (**Figure 3B**), meaning that the research teams are relatively dispersed in several institutions and do not cooperate closely enough. Among these 10 institutions, only the centrality of Southern Med Univ(0.16) and UCL(0.22) is greater than 0.1, which indicates that the influence degree and cooperation degree of these two institutions are high in recent 10 years. However, on the whole, most institutions have a low degree of influence and lack of cooperation.

Journals Publishing Researches on CP

In this 10 years, 313 journals publish literatures in the field of CP. Of the 1262 articles on CP we studied, the top 10 journals published 460 (44.43%) (**Table 2**). In terms of the number of publications, the top 3 are WORLD NEUROSURGERY (IF=1.829), CHILDS NERVOUS SYSTEM (IF=1.298) and JOURNAL OF NEUROSURGERY (IF=3.968). In terms of the average number of citations, the top 3 are JOURNAL OF CLINICAL ENDOCRINOLOGY (IF=5.399), EUROPEAN JOURNAL OF ENDOCRINOLOGY (IF=5.308) and JOURNAL OF NEUROSURGERY (IF=3.968). According to JCR of 2020, the 3 journals belong to Q1.

The Contributions of Authors to CP Research

The top 10 authors (the number of literature published) were listed in **Table 3**. Among those, HERMANN L MUELLER, from the Department of Pediatrics and Pediatric Hematology/ Oncology, University Children's Hospital, ranked first. At the same time, he is also at the first of the list in the analysis of co-cited authors. And 2 of the top 10 high-cited papers were published by him (**Table 4**). Those show that MUELLER has made outstanding achievements in CP researches. Through CiteSpace, we analyzed the author's citation information and visualized it into a network (**Figure 4**). According to the clustering information, the top 10 authors were roughly divided into five modules. Module 1 includes QI ST, PAN J

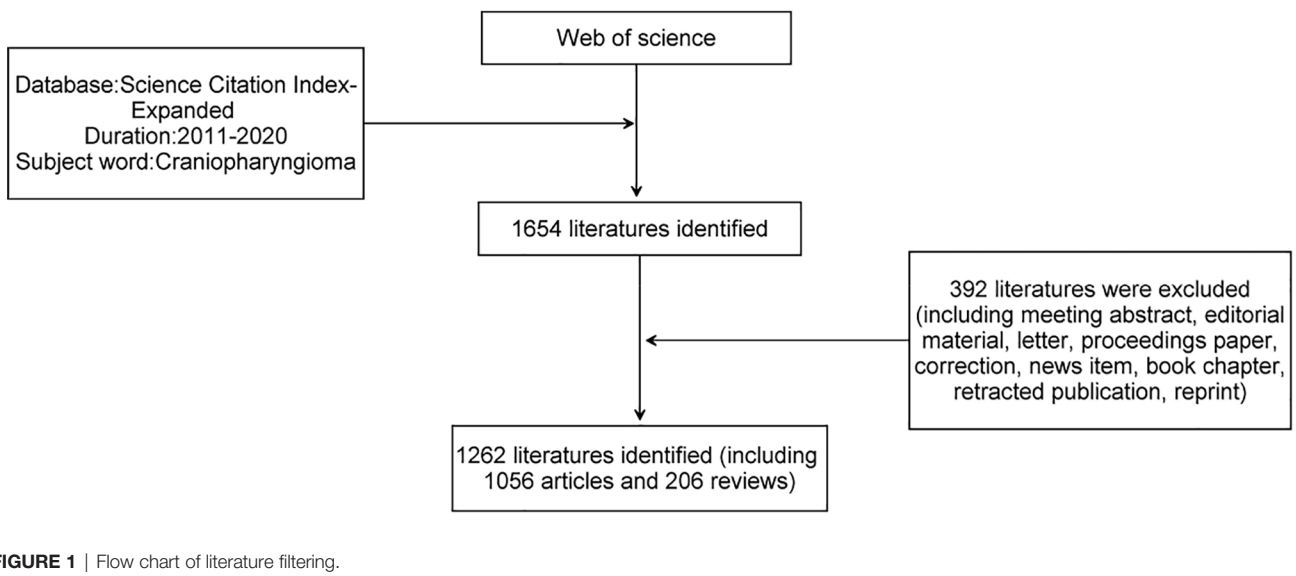

FIGURE 1 | Flow chart of literature filtering.

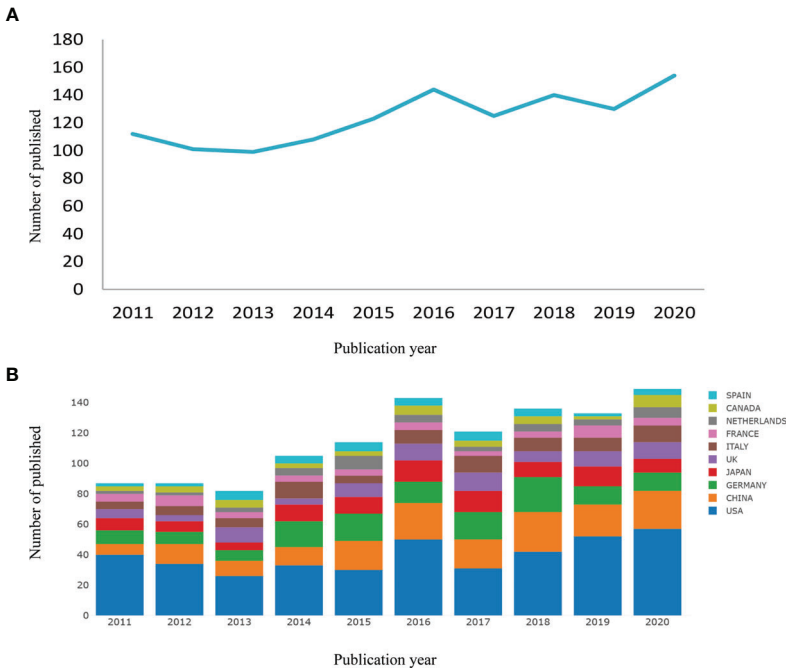

FIGURE 2 | Output of related literature. The number of annual publications **(A)** and growth trends of the top 10 countries/regions **(B)** in craniopharyngioma research from 2011 to 2020. Conducted by online analysis platform of Bibliometrics.

and XU JG. They are all from China, of which QI ST and PAN J are from the same unit, Southern Medical University, Nanfang Hospital, Department of Neurosurgery. Module 2 includes MULLER HL and MERCHANT TE. In recent 10 years, they occupy the top 2 in terms of the number of articles about CP. Simultaneously, the module they represent contains a large number of researchers and is closely related to other modules, occupying a core position in the study of CP. Module 3 contains many authors who have made outstanding contributions to CP, but only MARTINEZ-BARBERA JP is in the top 10. Module 4 includes PASCUAL JM and PRIETO R. Module 5 includes SCHWARTZ TH and ANAND VK. These two modules contain few authors and have little connection with other modules, but their contribution to CP is also outstanding.

Analysis of the Top 100 Case Reports

We searched and retrieved 364 case reports related to CP from 2011 to 2020, and ranked the 100 most cited cases (**Table S1**). Among the top 100 case reports, the highest number of citations was 99 (the first article) and the lowest number was 17 (the last 6 articles). Overall, the top 100 case reports were cited 1743 times, with a median of 11 times, with an average of 174.3 times per article. According to the average annual citations, the top article is cited 19.8 times per year (the first article). The bottom article

TABLE 1 | The top 10 countries/regions and institutions contributing to publications in craniopharyngioma research.

Rank	Countries	Article counts	Percentage	Centrality	Institutions	Article counts	Centrality	Total number of citation	Average number of citations
1	USA	405	32.09%	0.33	Capital Med Univ	32	0.07	199	6.22
2	PEOPLES R CHINA	172	13.63%	0.01	St Jude Childrens Res Hosp	30	0.06	413	13.77
3	GERMANY	141	11.17%	0.2	Southern Med Univ	28	0.16	175	6.25
4	JAPAN	103	8.16%	0.02	Univ Calif San Francisco	24	0.05	558	23.25
5	ITALY	85	6.74%	0.15	Harvard Med Sch	23	0.05	109	4.74
6	ENGLAND	78	6.18%	0.22	UCL	23	0.22	477	20.74
7	FRANCE	53	4.20%	0.05	La Princesa Univ Hosp	22	0.01	416	18.91
8	NETHERLANDS	47	3.72%	0.01	Univ Florida	22	0.03	251	11.41
9	CANADA	44	3.49%	0.01	Sichuan Univ	20	0.02	89	4.45
10	SPAIN	44	3.49%	0.05	Univ Colorado	20	0.04	162	8.1

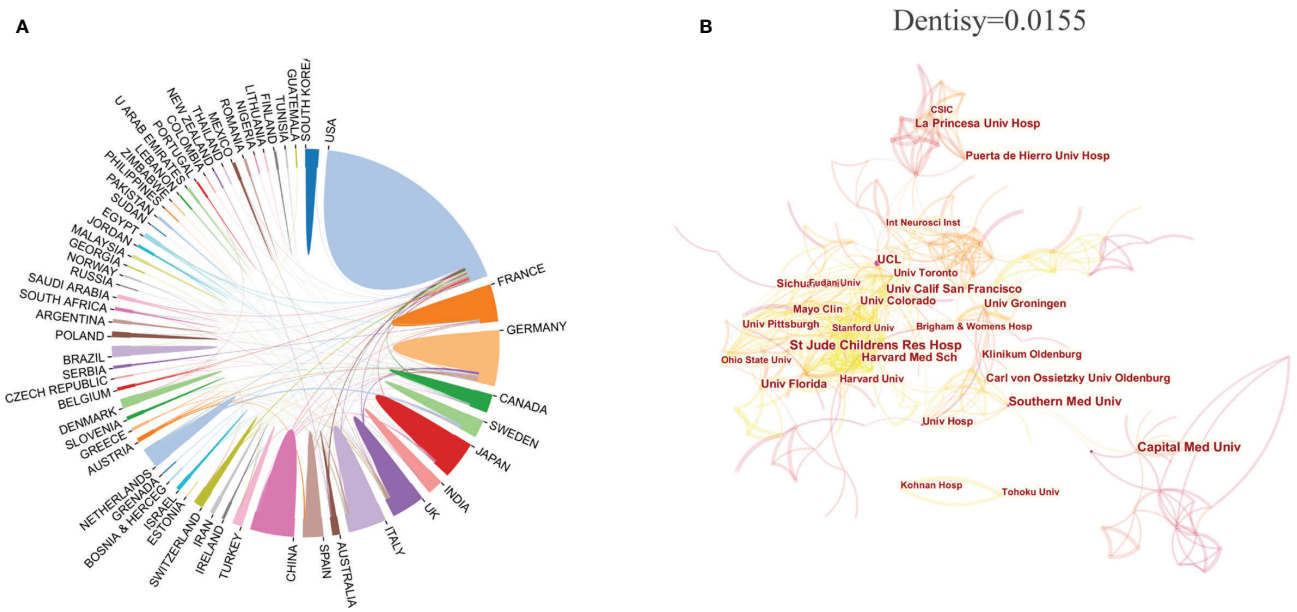

FIGURE 3 | The distribution of countries/regions and institutions. Cooperative relations among countries/regions **(A)** (The area represents the number of articles, and the connection represents the cooperative relationship. Conducted by online analysis platform of Bibliometrics) and institutions **(B)**. [Conducted by CiteSpace (version 5.7.R3, Drexel University)].

articles are cited 0.8 times a year (articles 93 and 94). The top 100 case reports could provide attractive information on particular and certainly infrequent cases, such as pathological characteristics, clinical manifestations and so on, which play important roles in a more comprehensive understanding of CP. At the same time, it also shows the difference of some surgical methods, the effect of radiotherapy and the exploration of targeted therapy.

Analysis of the CP Hotspots

We used BICOMB to extract and statistically analyze the data downloaded from the Web of science. For a more comprehensive analysis, we included keywords with a frequency greater than 10 (including 10) and generated a matrix for follow-up analysis, which accounted for 31.88% of all words. According to the 25 terms with the largest number of citations from 2011 to 2020, the time trend of hot spot transfer was analyzed (**Figure 5**). Through "gCLUTO", we used the biclustering method to sort 4 different clusters and used mountain (**Figure 6A**) and matrix visualization (**Figure 6B**) to map the relationship between source literature and keywords. The mountain visualization can more intuitively understand the content of high-dimensional dataset. In mountain visualization, peaks 0-3 represent different clusters. Peak, volume, altitude, and color are all used to depict information about the associated category. The distance between a pair of peaks on a plane indicates the relative similarity of their categories. The altitude of each peak is positively correlated with the internal similarity of the categories. The size of the peak is proportional to the number of main keywords contained in the category. Finally, the color of the peak represents the standard deviation within the category. Red

TABLE 2 | The top 10 most active journals that published articles in craniopharyngioma research (sorted by count).

Rank	Journal title	Article counts	Percentage	Total number of citations	Average number of citations	IF	JCR	H-index
1	WORLD NEUROSURGERY	102	8.08%	904	8.863	2.103	Q3	16
2	CHILDS NERVOUS SYSTEM	60	4.75%	480	8.000	1.475	Q4	11
3	JOURNAL OF NEUROSURGERY	54	4.28%	1281	23.722	5.112	Q1	21
4	PITUITARY	48	3.80%	619	12.896	4.102	Q2	14
5	JOURNAL OF NEURO ONCOLOGY	39	3.09%	594	15.231	4.13	Q2	14
6	NEUROSURGICAL FOCUS	39	3.09%	688	17.641	4.044	Q1	17
7	JOURNAL OF NEUROSURGERY PEDIATRICS	31	2.46%	257	8.290	2.372	Q2	9
8	JOURNAL OF CLINICAL ENDOCRINOLOGY METABOLISM	30	2.38%	877	29.233	5.958	Q1	15
9	ACTA NEUROCHIRURGICA	29	2.30%	257	8.862	2.212	Q3	8
10	EUROPEAN JOURNAL OF ENDOCRINOLOGY	28	2.22%	675	24.107	6.661	Q1	17

TABLE 3 | The top 10 most productive authors and co-cited authors contributed to publications in craniopharyngioma research.

Rank	Author	Article counts	Total citation	Average number of citations	H-index	Modules	Co-cited author	Citation counts
1	MULLER HL	51	1242	24.353	21	2	MULLER HL	378
2	MERCHANT TE	28	476	17.000	12	2	KARAVITAKI N	309
3	QI ST	27	203	7.519	9	1	FAHLBUSCH R	206
4	SCHWARTZ TH	27	723	26.778	13	5	YASARGIL MG	183
5	PAN J	25	187	7.480	9	1	BUNIN GR	169
6	PASCUAL JM	25	427	17.080	12	4	MERCHANT TE	161
7	PRIETO R	25	427	17.080	12	4	VAN EFFENTERRE R	155
8	ANAND VK	21	621	29.571	11	5	DEVILE CJ	155
9	MARTINEZ-BARBERA JP	21	594	28.286	14	3	PUGET S	154
10	XU JG	19	80	4.211	6	1	ELLIOTT RE	147

indicates a low deviation, while blue indicates a higher deviation. In matrix visualization, the column tags represent source literatures and row tags represent keywords. The cluster trees on the left represent frequent keywords associations and the cluster trees above represent literature associations. The matrix values are represented graphically, and their colors describe the frequency at which keywords appear in a literature. The color gradually deepens from white to red, indicating a gradual increase in significance. The above-mentioned high-frequency words were divided into 4 categories, and the representative literatures of each category were studied and summarized. Finally, we have identified 4 hotspots:

(0) Surgery and radiotherapy of CP

(I) Early diagnosis of CP

(II) Mechanisms/pathophysiology of CP

(III) Treatment of complications of CP

DISCUSSION

Through statistics and quantitative analysis, we found that the number of articles on CP published in the last 5 years from 2011 to 2020 was more than that in the previous 5 years. Although the research direction of CP was relatively extensive, there is a lack of summary and analysis of research hotspots. In this paper, we got 4 clusters through the biclustering analysis, and use the top 100 case reports to supplement the specific and uncommon information. Focusing on discussing and explaining these clusters can help identify valuable future directions.

TABLE 4 | The top 10 high-cited papers in craniopharyngioma research during 2011 to 2020.

Rank	Title	Journal	Authors	Publication year	Total citation	JCR	IF
1	Increased Wingless (Wnt) signaling in pituitary progenitor/stem cells gives rise to pituitary tumors in mice and humans	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA	Gaston-Massuet	2011	153	Q1	11.201
2	Craniopharyngioma	ENDOCRINE REVIEWS	Mueller, Hermann L.	2014	137	Q1	19.874
3	Post-operative hypothalamic lesions and obesity in childhood craniopharyngioma: results of the multinational prospective trial KRANIOPHARYNGEOM 2000 after 3-year follow-up	EUROPEAN JOURNAL OF ENDOCRINOLOGY	Mueller, Hermann L.	2011	124	Q1	6.66
4	Endoscopic Endonasal Compared with Microscopic Transsphenoidal and Open Transcranial Resection of Craniopharyngiomas	WORLD NEUROSURGERY	Komotar, Ricardo J.	2012	120	Q3	2.103
5	Neurosurgical treatment of craniopharyngioma in adults and children: early and long-term results in a large case series	JOURNAL OF NEUROSURGERY	Mortini, Pietro	2011	119	Q1	5.11
6	Endoscopic, Endonasal Resection of Craniopharyngiomas: Analysis of Outcome Including Extent of Resection, Cerebrospinal Fluid Leak, Return to Preoperative Productivity, and Body Mass Index	NEUROSURGERY	Leng, Lewis Z.	2012	111	Q1	4.653
7	Endoscopic endonasal surgery for craniopharyngiomas: surgical outcome in 64 patients Clinical article	JOURNAL OF NEUROSURGERY	Koutourousiou	2013	109	Q1	5.111
8	Pituitary Magnetic Resonance Imaging for Sellar and Parasellar Masses: Ten-Year Experience in 2598 Patients	JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM	Famini	2011	108	Q1	5.958
9	Gasket Seal Closure for Extended Endonasal Endoscopic Skull Base Surgery: Efficacy in a Large Case Series	WORLD NEUROSURGERY	Garcia-Navarro	2013	103	Q3	2.103
10	The endoscopic endonasal approach for the management of craniopharyngiomas: a series of 103 patients	JOURNAL OF NEUROSURGERY	Cavallo, Luigi Maria	2014	102	Q1	5.111

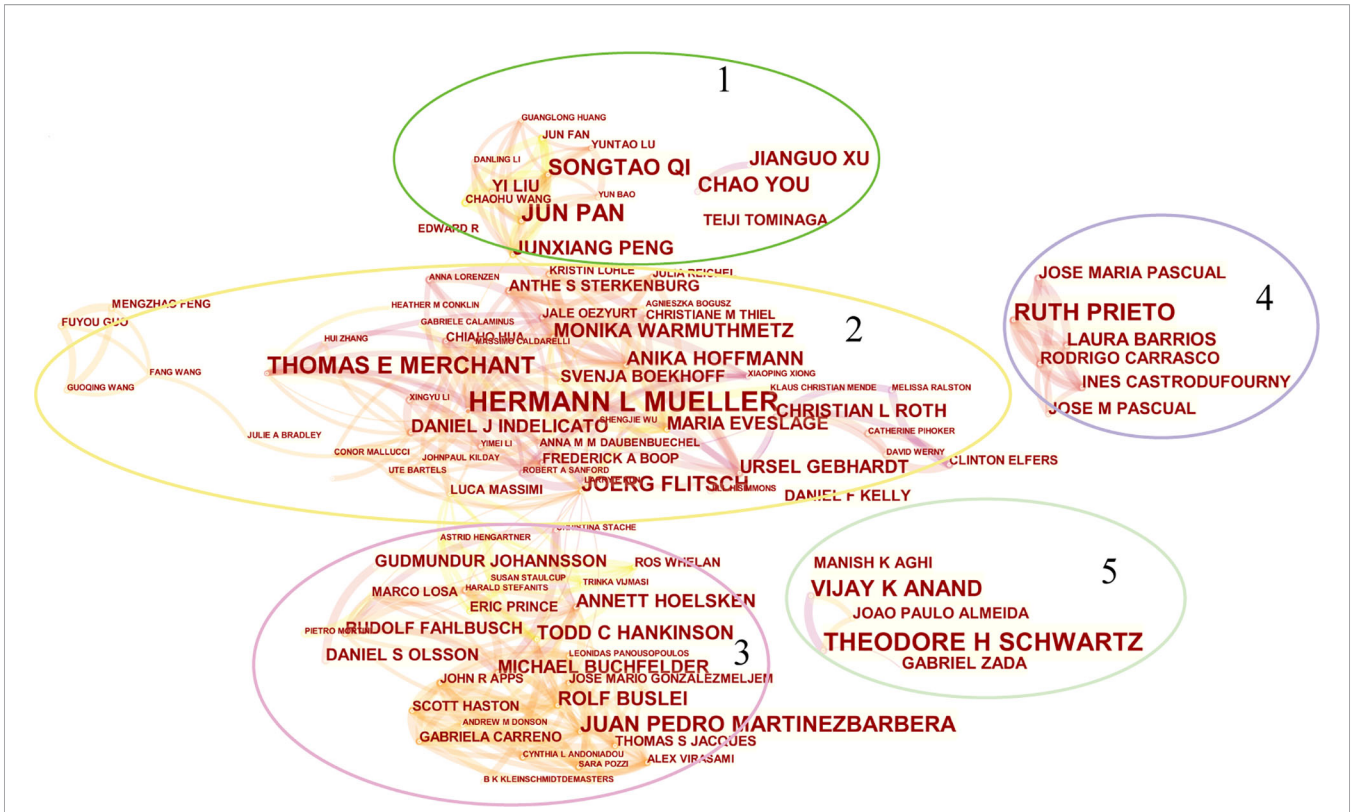

FIGURE 4 | The network map of productive authors. Conducted by CiteSpace (version 5.7.R3, Drexel University).

Cluster 0 mainly highlights (0) Surgery and radiotherapy of CP. CPs are located in the sellar region. Surgical treatment may damage the optic chiasma and hypothalamus-pituitary axis, so surgeons need enough experience and good surgical skills to complete the operation. At present, there are many surgical methods, whether radical surgery or limited surgery, with an emphasis on protecting the hypothalamus and visual integrity and quality of life after treatment (9–12). When surgeons are experienced and consider the highest recurrencefree survival (13), safe gross-total resection remains the goal (14). Endoscopic transnasal and microscopic transcranial surgery have become the standard methods for the treatment of CP. However, the approach selection mode of CP is still a discussion point. The main surgical approaches for CP can be divided into five categories: anterolateral transcranial, midline transcranial, extended endoscopic transnasal, intraventricular and lateral transcranial. Each method has its advantages and limitations. The personalized surgical scheme customized for individual CP patients based on multiple factors is an important research direction to improve the prognosis in the future (15). However, surgical treatment alone, sometimes, may not be appropriate for tumors invading the hypothalamus (16). Radiotherapy alone (17) or radiotherapy combined with limited surgical treatment has become an option for some doctors. Advances in fractionated radiotherapy have made treatment more accurate, thereby reducing the volume of normal brain structures receiving high doses of radiation. Although its purpose is to reduce the toxicity caused by late radiation, this potential advantage has not been confirmed in prospective studies, and it is also a direction that needs further verification in the future (18).

Cluster 1 mainly highlights (I) Early diagnosis of CP. The diagnosis of child CP is usually made late, with nonspecific symptoms characterized by elevated intracranial pressure (such as nausea and headache). These manifestations usually occur years after the initial symptoms (19, 20). Further progress can lead to visual impairments (62–84% of patients) and endocrine deficits (52–87% of patients) (21). Sexual dysfunction caused by hypothalamic-pituitary gonadotropin deficiency and hyperprolactinemia is a special symptom in adult CP (22, 23). Complications such as visual impairment, central diabetes insipidus, hypothalamic obesity, reduced sexual function, and psychiatric alterations seriously affect the quality of life of patients. So far, studies on history before diagnosis and the prognostic relevance of duration of history and specific clinical manifestations have been limited to the pediatric age group. Improving the relevant research of other age groups plays a great role in the comprehensive understanding of CP, so it will become an indispensable focus of CP research in the future. On this basis, according to the characteristics of different age groups, formulate corresponding early diagnosis schemes to realize the early intervention of CP, and finally reduce the

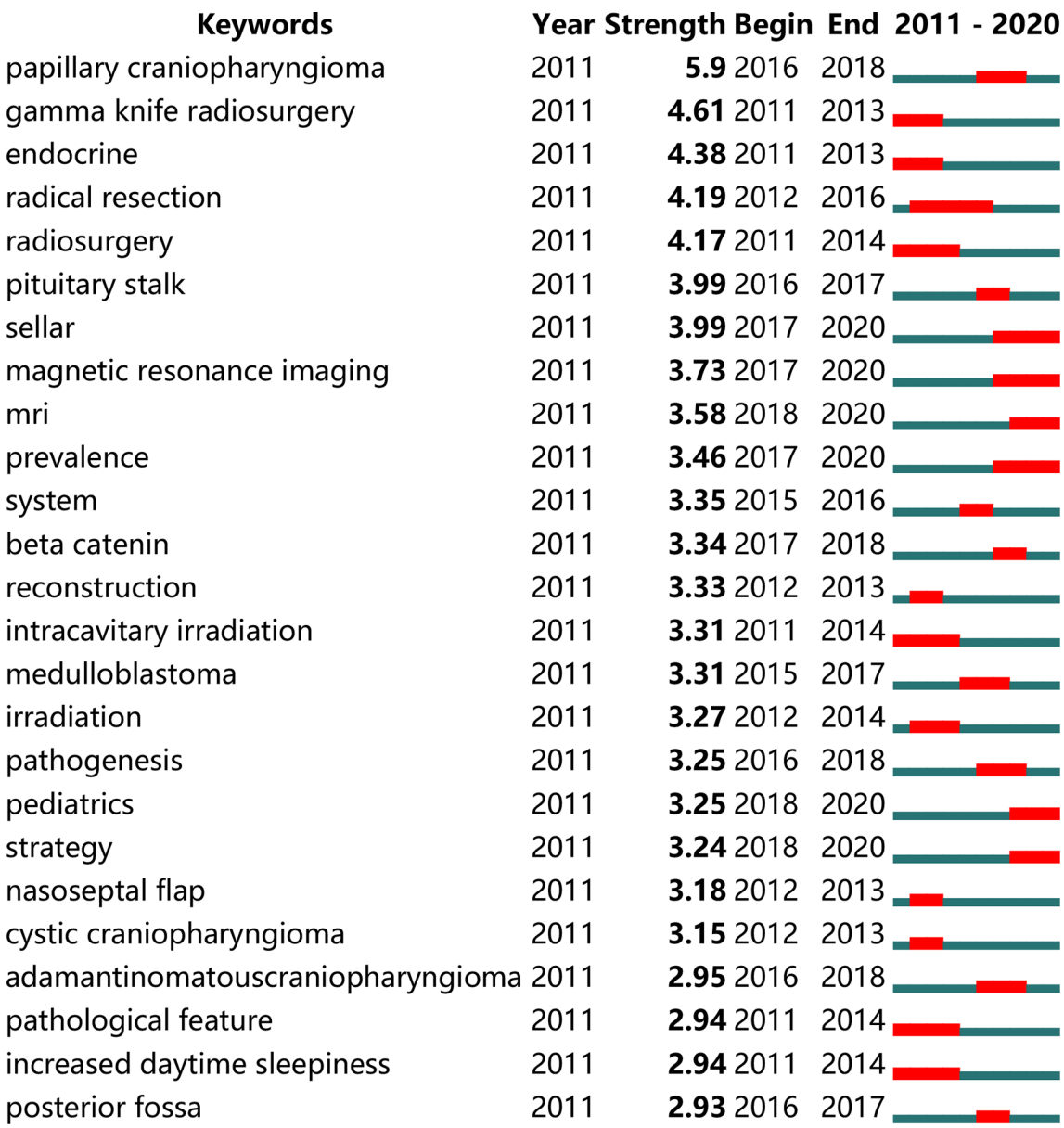

FIGURE 5 | The top 25 terms with the strongest citation bursts during 2011 to 2020. Conducted by CiteSpace (version 5.7.R3, Drexel University).

occurrence of complications and improve the prognosis of patients.

Cluster 2 mainly highlights (II) Mechanisms/pathophysiology of CP. CP is an epithelial tumor that occurs along the craniopharyngeal duct. In this regard, it is particularly essential to improve our understanding of the pathogenesis/pathophysiology of CP to develop targeted therapies that effectively prevent progression and hypothalamic involvement. Histopathologically, it consists of ACP and papillary PCP. ACPs are driven by somatic mutations of CTNNB1, which causes the β-catenin pathway not to be degraded effectively, accumulates in cells, and further leads to overactivation of the Wnt-β-catenin pathway (24, 25). A single cell or cell mass in which β-catenin accumulates causes the tumor to secrete too many growth factors and cytokines, activating specific pathways in surrounding nearby tumor cells (26–28). This secretory phenotype is consistent with the activation of the tumor senescence-associated secretory phenotype (SASP). And some studies have proved that SASP plays a vital role in the pathogenesis of ACP (26, 29, 30). Inflammatory mediators are also the key points of CP. Many inflammatory mediators, chemokines, and cytokines are expressed in the cystic and solid components of human ACP (31–34). These molecules may facilitate the escape of immune surveillance. By contrast, only somatic BRAFV600E mutations

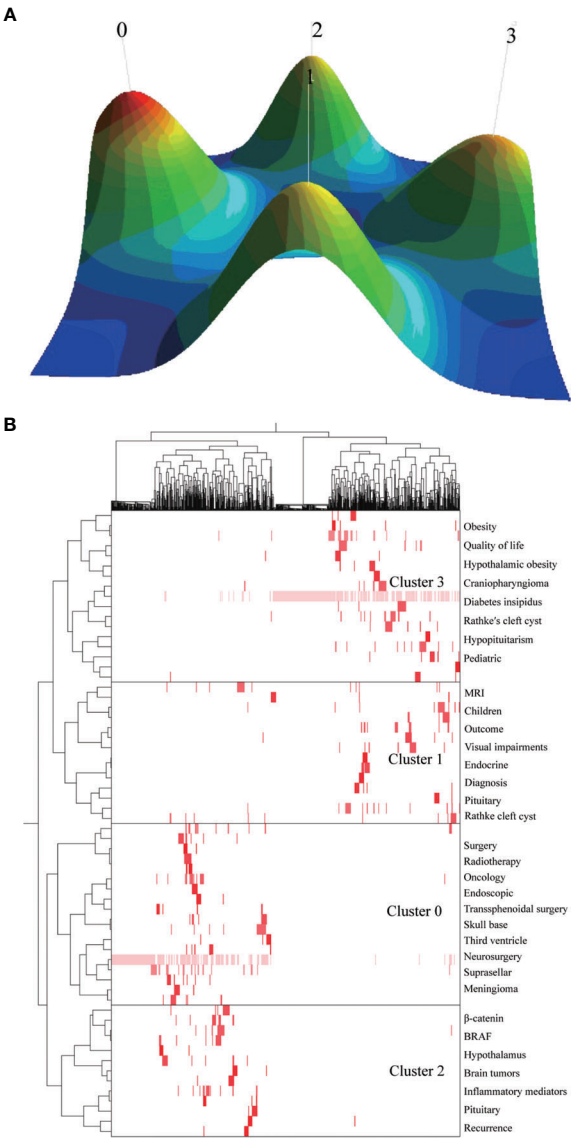

FIGURE 6 | Biclustering of highly frequent major keywords and literatures on craniopharyngioma. Mountain visualization **(A)** and matrix visualization **(B)** Conducted by gCLUTO (version1.0, University of Minnesota).

have been found in PCP (35, 36). Through MAPK activation, the mutation can transform normal SOX2+ stem cells in the pituitary into PCP tumor initiation cells (37). The potential role of cell senescence in PCP has not been determined, nor has the expression of inflammatory mediators in PCP been investigated. However, some studies (38, 39) have shown that the influence of inflammation and cell senescence on CP has become a focus and hotspot in this field, and there are still huge deficiencies in these two aspects. In the future, researchers engaged in CP related research are still needed to further explore these two aspects, so as to achieve effective treatment to prevent CP progression and hypothalamic involvement. At the same time, targeted therapy for CP specific mutation points (CTNNB1 and BRAF) is also an exciting research direction. Many of the top 100 cited case reports are about this aspect (40–43).

Cluster 3 mainly highlights (III) Treatment of complications of CP. No matter what kind of treatment for CP patients, the prevention of long-term morbidity should be a major strategic consideration. The functional and social independence of patients is the goal of treatment (39). With the development of medical technology, the rational use of corticosteroids and antibiotics to reduce inflammation and infection, the perioperative morbidity and mortality of CP patients have been greatly improved. Moreover, most of the complications of CP and its treatment can be managed through drugs and psychological, psychiatric and emotional care (44, 45). In recent years, our understanding of the neuropsychological adverse effects of CP has been dramatically improved. However, the treatment effect is not available for hypothalamic syndrome and its main clinical manifestations (obesity and neuropsychological defects). In order to improve the therapeutic effect, we must further understand how CP causes hypothalamic syndrome and its main clinical manifestations, and further explore the pathogenesis of these complications. In short, we need to keep exploring in the future to avoid these complications as much as possible and get effective treatment when symptoms appear.

Although we have analyzed the literatures on CP from 2011 to 2020 as comprehensively as possible, and analyzed top 100 cited case reports in the past 10 years as a supplement, there are still some limitations. Some literatures [such as Craniopharyngioma (46), Q1, IF=52.322] published recently, through the analysis of citation information, cannot well highlight its importance. Simultaneously, the database is still constantly updated, and there may be differences between our bibliometrics analysis and the actual publishing conditions. For any bibliometric analysis of CP, it should also be pointed out that there is a limitation, that is, only positive and excellent results are usually published in the most prestigious journals, so true, non-excellent results obtained in most patients still hidden in scientific analysis. Most of the published CPs surgery series are just the final work of a very prestigious surgeon/clinician working in a specialized center for decades. This process limits the opportunity to mix the treatment ideas/results of different institutions/authors for collaborative or collaborative research.

CONCLUSIONS

We summarized the literatures related to CP from 2011 to 2020, including source countries and institutions, authors, published journals, etc. Then, based on these publications, we analyze research hotspots and predict future trends. Reviewing the previous studies on CP, we discussed the four aspects of CP and found the key research. Subsequently, we included the top 100 cited case reports in the analysis to enrich our discussion. We fully and specifically discussed the shortcomings of these

priorities and the importance of achieving breakthroughs in these priorities for the treatment of CP patients. We believe that our research will help to determine the valuable future direction for CP research, and the mentioned hot spots will make major breakthroughs in the future.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

YL led the team and was responsible for all aspects of the project. TL and AY substantially contributed to the methods, data acquisition, results, and interpretation. SZ, YC, and BN participated in designing and writing the manuscript. GL revised this manuscript critically for important intellectual content. JF gave final approval of the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by grants from the Science and technology projects of Guangdong Province (2017A020215191).

ACKNOWLEDGMENTS

Thanks Bilibili up Masters for their guidance on the use of the softwares.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.744308/full#supplementary-material

Supplementary Table 1 | Top 100 cited case reports during 2011-2020.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 04 November 2021
doi: 10.3389/fneur.2021.753944

Impact of Pituitary Stalk Preservation on Tumor Recurrence/Progression and Surgically Induced Endocrinopathy After Endoscopic Endonasal Resection of Suprasellar Craniopharyngiomas

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Objective: To investigate the factors associated with recurrence/progression after endoscopic endonasal resection of suprasellar craniopharyngiomas. Special attention was paid to assess the impact of pituitary stalk preservation on tumor recurrence/progression and endocrinological outcomes.

Methods: We retrospectively recruited 73 patients with suprasellar craniopharyngiomas undergone endoscopic endonasal approach (EEA) surgery from September 2014 to May 2019 and assessed their clinical characteristics, surgical outcomes, and recurrence/progression. Stalk preservation or sacrifice was determined by reviewing operative records, videos, and post-operative magnetic resonance imaging.

Results: Gross total resection (GTR) was achieved in 51 cases (69.9%). Tumor recurrence was seen in 5 cases (9.8%) and progression was seen in 8 cases (36.4%), respectively. GTR (OR = 0.248 CI 0.081–0.759; $p = 0.015$) was the only independent factor influencing recurrence/progression. Kaplan-Meier survival analysis showed that the mean recurrence/progression-free survival were 53 (95% CI 48–59) and 39 (95% CI 28–50) months, respectively, in patients with and without GTR ($p = 0.011$). Pituitary stalk preservation was more common in cases with peripheral type tumors (83% vs. 30%, $p < 0.01$). Preserving the pituitary stalk does not appear to decrease the percentage of GTR (75.5% vs. 55.0%, $p = 0.089$), or increase the rate of tumor recurrence (12.5% vs. 0%, $p = 0.508$) or progression (46.2% vs. 22.2%, $p = 0.486$). However, surgically induced hypothyroidism (60.5%

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Edited by:
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Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Neurology

Received: *05 August 2021*
Accepted: *12 October 2021*
Published: *04 November 2021*

Citation:
Chen Z, Ma Z, He W, Shou X, Ye Z, Zhang Y, Zhang Q, Qiao N, Zhou X, Cao X, He M, Zhang Z, Ye H, Li Y, Li S, Zhao Y, Shen M and Wang Y (2021) Impact of Pituitary Stalk Preservation on Tumor Recurrence/Progression and Surgically Induced Endocrinopathy After Endoscopic Endonasal Resection of Suprasellar Craniopharyngiomas. Front. Neurol. 12:753944. doi: 10.3389/fneur.2021.753944

vs. 100%, $p = 0.041$) and diabetes insipidus (35.1% vs. 81.8%, $p = 0.017$) were significantly lower in patients with stalk preservation. For patients who had hypopituitarism before EEA, there was no difference between those with and without stalk preservation regarding post-operative hypopituitarism ($p > 0.05$).

Conclusion: GTR is the only independent predictor of recurrence/progression after EEA surgery for suprasellar craniopharyngiomas. Preserving the pituitary stalk does not appear to increase the risk of non-GTR and tumor recurrence/progression and might help reduce the risk of surgically induced hypothyroidism and diabetes insipidus. We recommend preserving the pituitary stalk in peripheral type suprasellar craniopharyngiomas with normal pituitary function, especially in cases without hypothyroidism or diabetes insipidus. On the other hand, stalk sacrifice could be considered in central type tumors with severe pre-operative endocrinopathy.

Keywords: craniopharyngioma, EEA surgery, pituitary stalk, recurrence, progression, endocrinopathy

INTRODUCTION

Craniopharyngioma is a common congenital tumor that constitutes about 2–6% of primary intracranial tumors, leading to visual disturbance, endocrine dysfunction, or cranial nerve palsy (1). Given its benign nature, craniopharyngioma is quite challenging due to its anatomical proximity to vital structures, including hypothalamic-pituitary axes, optical apparatus, and cranial nerves (2). It is ideal if gross total resection (GTR) with preservation of the hypothalamic function could be achieved (3). Otherwise, adjuvant radiotherapy is reserved in selected cases of residual or recurrent tumors (4).

Due to their origin from remnants of the craniopharyngeal duct epithelium, craniopharyngiomas may arise anywhere along the pituitary-hypothalamic axis. The pituitary stalk plays a crucial role in hypothalamic-pituitary functioning and is a vital structure during the surgical resection of suprasellar craniopharyngiomas. Damage to the pituitary stalk may lead to endocrine dysfunction, disruption of the water-electrolyte balance, central diabetes insipidus (DI), and other clinical manifestations (5). However, preserving the pituitary stalk might increase the risk of recurrence. Therefore, the choice of preserving or sacrificing the pituitary stalk is of great significance during surgical resection of suprasellar craniopharyngiomas. However, to the best of our knowledge, it still has controversies in literature (6). Several studies recommended preserving the pituitary stalk as much as possible, as the recurrence rate is not affected but might yield improved endocrinological outcomes (7–9). By contrast, some researchers found a weak association between stalk preservation and post-operative endocrinological benefits (10, 11). Moreover, stalk-preservation without achieving GTR will inevitably put patients at the risk of tumor recurrence.

Compared with transcranial approaches, the endoscopic endonasal approach (EEA) provides an ideal visualization of the ventral skull base, enabling early identification of the pituitary stalk (12, 13). Up to now, data reflecting the association between stalk preservation/sacrifice and post-operative recurrence and endocrinological outcomes in EEA is limited (14, 15). Does preserving the pituitary stalk lead to a higher risk of recurrence or progression? Does it contribute to a more favorable pituitary function? In the present study, we addressed these issues by evaluating the outcomes of EEA in 73 suprasellar craniopharyngiomas with a median follow-up time of 19 months.

MATERIALS AND METHODS

Patient Enrollment

We retrospectively collected data from patients treated in Huashan Hospital, the largest tertiary referral center in East China, between September 2014 and May 2019. The inclusion criteria were: (i) pathologically confirmed craniopharyngiomas; (ii) suprasellar type tumors based on MRI and intraoperative observation; (iii) treated by EEA. Patients who were followed up <6 months and those who were managed by prophylactic radiotherapy after surgery without evidence of recurrence/progression were excluded. The patients' medical records and imaging studies were reviewed after obtaining approval from the Huashan Institutional Review Board.

Endocrinological Evaluation

All patients were subject to endocrinological evaluation at baseline as well as post-operative follow-ups to screen for endocrinopathy. Morning free cortisol, adrenocorticotropin (ACTH), thyroid-stimulating hormone (TSH), total triiodothyronine (TT3) and thyroxine (TT4), free triiodothyronine (FT3) and thyroxine (FT4), prolactin, testosterone, estradiol, progesterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were tested. Hypopituitarism was diagnosed if hormones were lower than the normal range for each axis and not adequately responded to the stimulation test or already underwent hormone replacement therapy. The diagnosis of DI was based on thirst, urine output, serum electrolyte levels, urine specific gravity, and serum/urine osmolarity.

Neuroimaging

All patients underwent spin-echo sequence T1 post-contrast enhanced sagittal and coronal MRI pre-operatively, using a 3.0-T whole-body scanner (General Electric Medical Systems, 118 Milwaukee, MI). Certain patients had also undergone CT angiography. Tumor location, size, calcification, and cyst formation, were recorded. Tumors were classified into the central and peripheral types based on their relationship with the pituitary stalk (16). Central type refers to tumors that grow within the stalk, and no definite origin site can be identified. Peripheral type tumor arises from the stalk, extending laterally in an exophytic pattern, and the residual stalk is usually displaced. The resection degree was determined by reviewing post-operative MRI within 72 h after surgery. A GTR was achieved when complete removal of the tumor had been carried out, subtotal resection (STR) was achieved when more than 75% of the tumor was removed, and partial resection (PR) was achieved when <75% of the tumor was removed. Post-operative MRI was performed 3 months post-operatively and then at semi-annual or annual intervals during follow-up. Recurrence was defined as newly discovered neoplasms after GTR. Progression was defined as enlarged residual tumors after non-GTR.

Surgical Procedure, Follow-Up, and Adjuvant Therapy

All patients underwent an extended endoscopic endonasal transtuberculum approach. After sphenoidotomy and partial posterior ethmoidectomy, a wide exposure of the sellar and suprasellar area was achieved. The bone covering the sella turcica, the tuberculum, and the chiasmatic sulcus were widely opened to facilitate surgical freedom during suprasellar manipulations. Ligation of the superior intercavernous sinus was performed while opening the skull base dura. After opening the arachnoid membrane and releasing cerebrospinal fluid (CSF), the pituitary stalk could be recognized in most cases. Intracapsular debulking was carried out, followed by extracapsular dissection. We cut the tumor beside the pituitary stalk for peripheral type craniopharyngiomas and preserve the stalk as much as possible. However, if preserving the stalk hindered GTR, we sacrificed it. We vertically cut open the stalk for central type tumors, remove the tumor inside, and see if we could preserve some normal stalk tissues connecting the hypothalamus. However, there were no preservable stalk tissues in most central-type cases. We dissected tumors from the hypothalamus along the gliosis between them. If it was too adherent, this part of the tumor was reserved. The skull base reconstruction was performed using the standard multilayer technique, including a pedicled nasal septal flap.

All patients were closely followed up immediately and 1, 3, 6 months, and semi-annually or annually after surgery. Adjuvant radiotherapy was adopted for patients with recurrence after GTR or progression after non-GTR.

Statistical Analysis

Statistical analysis was performed using SPSS 22.0, and data were presented as mean ± SD (or median with interquartile range) for continuous variables normally (or not normally) distributed and as the frequency for categorical variables. Normality was tested using the Kolmogorov-Smirnov test. Means were compared using the unpaired *t*-test when data distribution was normal or by the Wilcoxon rank-sum (Mann-Whitney) test when variables were not normally distributed. For categorical variables, differences were analyzed by the Chi-square test or Fisher's exact-tests as appropriate. Cox regression analysis was used to determine the potential risk factors for predicting recurrence/progression. Recurrence/progression-free survival was estimated using the Kaplan-Meier method, and Kaplan-Meier survival curves were generated. A two-tailed P-value < 0.05 was considered significant.

TABLE 1 | Clinical characteristics of 73 patients with suprasellar craniopharyngiomas.

Characteristics	Value
Demographic features	
Gender (male)	38 (52.1%)
Age at diagnosis (years)	39 (16)
Follow-up time (months)	19 [12–36]
Previous treatment history	
Surgery	9 (12.3%)
Radiotherapy	5 (6.8%)
Clinical manifestation	
Visual impairment	41 (56.2%)
Headache	22 (30.1%)
Amenorrhea	19 (26.0%)
Drowsiness	13 (17.8%)
Polyuria/polydipsia	11 (15.1%)
Vomiting	5 (6.8%)
Developmental retardation	4 (5.5%)
Obesity	1 (1.4%)
Imaging and endocrinological features	
Maximum diameter (cm)	3.0 [2.0–3.8]
Tumor type	
Central type	23 (31.5%)
Peripheral type	50 (68.5%)
Pre-operative endocrinopathy	
Hypoadrenalism	24 (32.9%)
Hypothyroidism	26 (35.6%)
Hypogonadism	49 (67.1%)
Diabetes insipidus	25 (34.2%)
Treatment features	
Resection degree	
Gross total resection	51 (69.9%)
Subtotal resection	16 (21.9%)
Partial resection	6 (8.2%)
Pituitary stalk preservation	53 (72.6%)

Continuous variables with normal distribution were displayed as mean (standard deviation), continuous variables without normal distribution were displayed as median [interquartile range], categorical variables were displayed as count (proportion).

TABLE 2 | Comparison between patients with recurrence/progression and patients without.

Variable	Recurrence/progression group	Recurrence/progression-free group	*p*
Demographic features			
Patients (*n*)	13 (17.8%)	60 (82.2%)	-
Gender (male)	5 (38.5%)	33 (55.0%)	0.279
Age at diagnosis (years)	41 (11)	39 (16)	0.616
Follow-up time (months)	21 (12)	19 [12–36]	0.634
Previous treatment history			
Surgery	2 (15.4%)	7 (11.7%)	1.000
Radiotherapy	2 (15.4%)	3 (5.0%)	0.214
Imaging and endocrinological features			
Maximum diameter (cm)	2.8 (0.8)	3.0 [2.0–3.9]	0.865
Tumor type			0.018*
Central type	0 (0%)	23 (38.3%)	
Peripheral type	13 (100%)	37 (61.7%)	
Pre-operative endocrinopathy			
Hypoadrenalism	3 (23.1%)	21 (35.0%)	0.614
Hypothyroidism	6 (46.2%)	20 (33.3%)	0.578
Hypogonadism	9 (69.2%)	40 (66.7%)	1.000
Diabetes insipidus	5 (38.5%)	20 (33.3%)	0.975
Treatment features			
Gross total resection	5 (38.5%)	46 (76.7%)	0.017*
Pituitary stalk preservation	11 (84.6%)	42 (70.0%)	0.466
Recurrence/progression-free survival time (months)	15 (7)	19 [12–36]	0.074

Continuous variables with normal distribution were displayed as mean (standard deviation), continuous variables without normal distribution were displayed as median [interquartile range], categorical variables were displayed as count (proportion).
**P < 0.05.*

RESULTS

Patients Characteristics

The characteristic of 73 patients with suprasellar craniopharyngiomas who underwent EEA surgery was summarized in **Table 1**. There were 38 males and 35 females with a mean age of 39 ± 16 years. Nine patients (12.3%) had a history of surgery, and five patients (6.8%) had a history of fractionated radiotherapy or stereotactic radiosurgery, respectively. Forty-one patients complained of visual deterioration, 22 of headache, 19 of amenorrhea, 13 of drowsiness, 11 of polyuria/polydipsia, 5 of vomiting, 4 of developmental retardation, and one of obesity. There were 23 (31.5%) central type tumors and 50 (68.5%) peripheral type tumors. The percentage of pre-operative hypopituitarism was 32.9% of hypoadrenalism, 35.6% of hypothyroidism, 67.1% of hypogonadism and 34.2% of DI, respectively.

Surgical Outcomes and Complications

GTR, STR, and PR were achieved in 51 (69.8%), 16 (21.9%), and 6 (8.2%) patients, respectively. The pituitary stalk was morphologically preserved in 53 (72.6%) out of 73 patients. None of the patients died during the study period. All of them experienced intraoperative CSF leakage due to the extended approach. One (1.4%) patient experienced meningitis and was cured by antibiotics. Two (2.7%) patients had epistaxis. No incidents of intraoperative carotid injury, post-operative CSF leakage, or intracerebral hemorrhage occurred. Patients were followed up for 6–60 months with a median time of 19 months. At the last investigation, tumor recurrence was seen in 5 cases (9.8%) at 6, 12, 18, 20, and 24 months, respectively, after GTR. Tumor progression was seen in 8 cases (36.4%) at 6, 7, 8, 9, 18, 18, 24, and 24 months, respectively, after non-GTR. Six and seven patients with recurrence/progression were treated with reoperation and radiotherapy, respectively. For patients with normal pituitary function pre-operatively, surgically induced hypoadrenalism, hypothyroidism, hypogonadism, and DI developed in 55.1%, 68.1%, 37.5%, and 45.8% of them, respectively.

TABLE 3 | Cox regression analysis for predictors of recurrence/progression after surgery.

Feature	OR (95% CI)	*p*
Gross total resection	0.248 (0.081–0.759)	0.015*
Peripheral type tumor	3.270×10^5 (0.000–4.23×10^{195})	0.955

OR, odds ratio; CI, confidence interval.
**P < 0.05.*

Predictors of Recurrence/Progression

Patients were divided into the recurrence/progression ($n = 13$) and recurrence/progression-free ($n = 60$) groups (**Table 2**).

Compared to recurrence/progression-free cases, those who presented with recurrence/progression were of significantly higher percentage of peripheral type tumors (100% vs. 61.7%, $p = 0.018$) and lower percentage of GTR (38.5% vs. 76.7%, $p = 0.017$). No differences were found concerning age, gender, follow-up time, previous treatment history, tumor size, pre-operative endocrinopathy, pituitary stalk preservation, and recurrence/progression-free survival time between the two groups ($p > 0.05$). Cox regression analysis showed that GTR (OR = 0.248 CI 0.081–0.759; $p = 0.015$) was the only independent factor influencing recurrence/progression (**Table 3**). Kaplan-Meier survival analysis showed that the mean recurrence/progression-free survival was 53 (95% CI 48–59) and 39 (95% CI 28–50) months, respectively, in patients with and without GTR ($p = 0.011$; **Figure 1**).

Factors Related to Pituitary Stalk Preservation During Surgery

Patients were divided into the stalk-preserved ($n = 53$) and stalk-sacrificed ($n = 20$) groups (**Table 4**). Compared to the stalk-sacrificed group, the stalk-preserved group had higher percentage of peripheral type tumors (83.0% vs. 30.0%, $p < 0.001$), lower percentage of pre-operative hypoadrenalism (22.6% vs. 60.0%, $p = 0.002$), and hypothyroidism (28.3 vs. 55.0%, $p = 0.034$). There were no significant differences regarding gender, age, previous treatment history, tumor size, pre-operative hypogonadism, and DI between the two groups ($p > 0.05$). After multivariable logistic regression analysis (**Table 5**), stalk preservation was found to be more common in peripheral type tumors (OR = 10.505 CI 2.968–37.176; $p < 0.001$) and less common in cases with pre-operative hypoadrenalism (OR = 0.220 CI 0.062–0.786; $p = 0.020$).

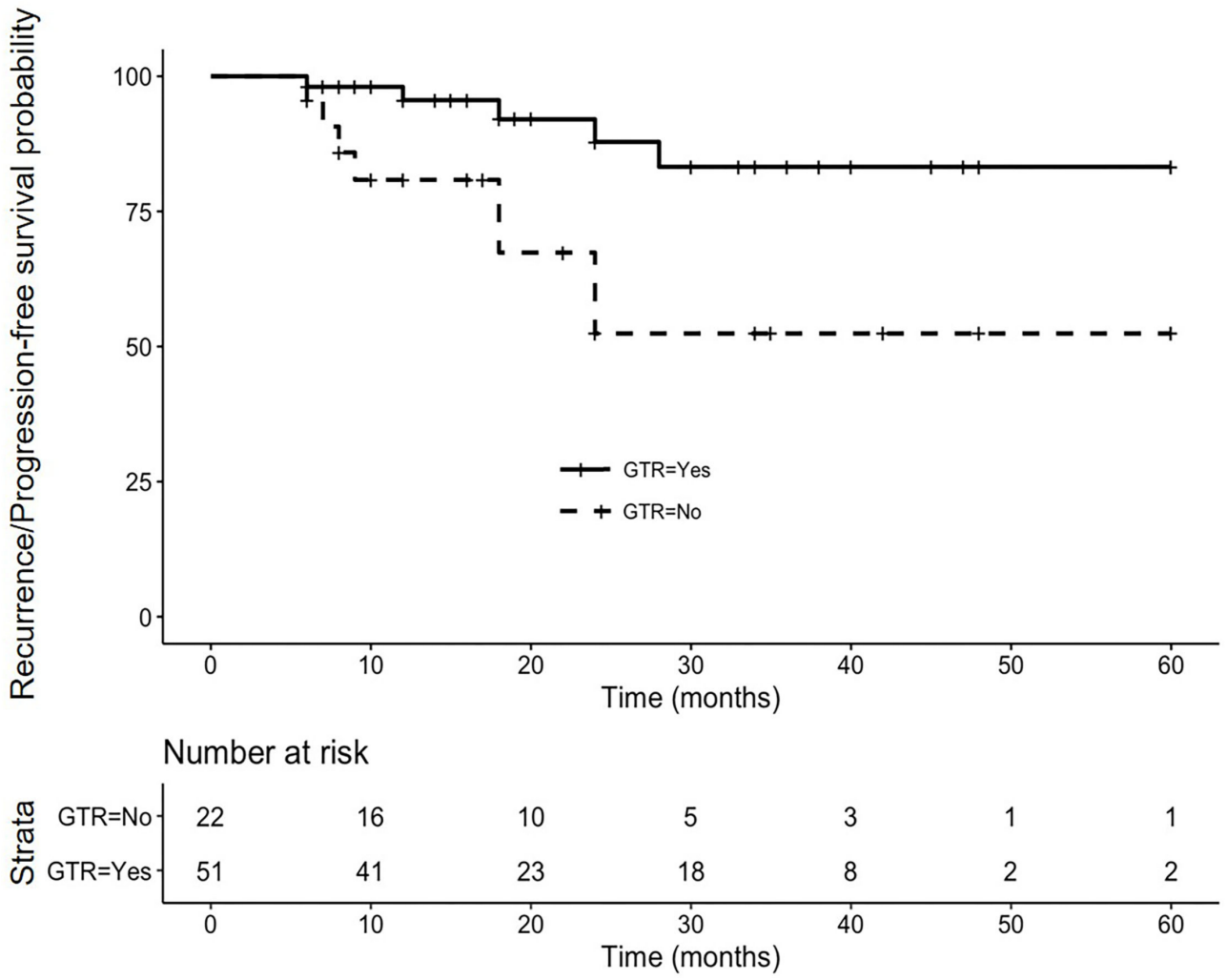

FIGURE 1 | Cumulative recurrence/progression-free Kaplan-Meier curve in 73 suprasellar craniopharyngiomas underwent endoscopic endonasal surgeries. The mean recurrence/progression-free survival time was 53 (95% CI 48–59) and 39 (95% CI 28–50) months, respectively, in patients with (the solid line) and without (the dotted line) gross total resection ($p = 0.011$).

TABLE 4 | Clinical characteristics between patients with pituitary stalk preservation and sacrifice.

Variable	Stalk-preserved group	Stalk-sacrificed group	*p*
Demographic features			
Patients (*n*)	53 (72.6%)	20 (27.4%)	-
Gender (male)	28 (52.8%)	10 (50.0%)	0.829
Age at diagnosis (years)	40 (16)	38 (15)	0.584
Previous treatment history			
Surgery	4 (7.5%)	5 (25.0%)	0.104
Radiotherapy	2 (3.8%)	3 (15.0%)	0.240
Imaging and endocrinological features			
Maximum diameter (cm)	3.0 [2.0–4.0]	2.8 (0.9)	0.879
Tumor type			0.000*
Central type	9 (17.0%)	14 (70.0%)	
Peripheral type	44 (83.0%)	6 (30.0%)	
Pre-operative endocrinopathy			
Hypoadrenalism	12 (22.6%)	12 (60.0%)	0.002*
Hypothyroidism	15 (28.3%)	11 (55.0%)	0.034*
Hypogonadism	32 (60.4%)	17 (85.0%)	0.086
Diabetes insipidus	16 (30.2%)	9 (45.0%)	0.234
Treatment features			
Gross total resection	40 (75.5%)	11 (55.0%)	0.089
Recurrence after gross total resection	5 (12.5%)	0 (0%)	0.508
Progression after non-gross total resection	6 (46.2%)	2 (22.2%)	0.486

Continuous variables with normal distribution were displayed as mean (standard deviation), continuous variables without normal distribution were displayed as median [interquartile range], categorical variables were displayed as count (proportion).
**P < 0.05.*

TABLE 5 | Multivariable logistic regression analysis of factors related to pituitary stalk preservation.

Feature	OR (95% CI)	*p*
Peripheral type tumor	10.505 (2.968–37.176)	0.000*
Pre-operative hypoadrenalism	0.220 (0.062–0.786)	0.020*

OR, odds ratio; CI, confidence interval.
**P < 0.05.*

Impact of Pituitary Stalk Preservation on GTR, Tumor Recurrence/Progression

In the stalk-preserved group, there were 40 (75.5%), and 13 (24.5%) cases achieved GTR and non-GTR, respectively. In the stalk-sacrificed group, 11 (55.0%) and 9 (45.0%) cases achieved GTR and non-GTR, respectively. Preserving the pituitary stalk does not appear to decrease the percentage of GTR (75.5% vs. 55.0%, $P = 0.089$), or increase the rate of tumor recurrence (12.5% vs. 0%, $P = 0.508$) or progression (46.2% vs. 22.2%, $P = 0.486$) (**Table 4**). Multivariable logistic regression analysis provided similar results after adjusting confounding factors ($p = 0.050$ and 0.595 for GTR and recurrence/progression, respectively).

Impact of Pituitary Stalk Preservation on Surgically Induced Endocrinopathy

At the last investigation, the overall percentage of hypopituitarism was 67.1% of hypoadrenalism, 76.7% of hypothyroidism, 77.0% of hypogonadism, and 58.9% of DI, which was higher than pre-operative status. Only individual cases experienced improved post-operative endocrine outcomes during follow-up.

Compared to the stalk-sacrificed group, post-operative endocrine outcomes were more favorable regarding hypoadrenalism (58.5% vs. 90.0%, $p = 0.023$), hypothyroidism (69.8% vs. 95%, $p = 0.05$), hypogonadism (68.2% vs. 100%, $p = 0.006$), and DI (49.1% vs. 85.0%, $p = 0.012$) in the stalk-preserved group.

Furthermore, surgically induced new-onset hypothyroidism (60.5% vs. 100%, $p = 0.041$) and DI (35.1% vs. 81.8%, $p = 0.017$) were significantly lower in patients with stalk preservation (**Figure 2A**). Notably, for 15 patients with normal pituitary function, 8 (53.3%) of them maintained uncompromised pituitary function after stalk preservation.

In contrast, for patients who already had hypopituitarism before EEA, there was no significant difference between patients with and without stalk preservation regarding post-operative hypoadrenalism (91.7% vs. 91.7%, $p = 1.000$), hypothyroidism (93.3% vs. 90.1%, $p = 1.000$), hypogonadism (88.4% vs. 100%, $p = 0.287$), and DI (81.2% vs. 88.9%, $p = 1.000$) (**Figure 2B**).

DISCUSSION

The pituitary stalk connects the pituitary gland with the hypothalamus, constitutes an important anatomical basis for maintaining the hypothalamic-pituitary function. Suprasellar

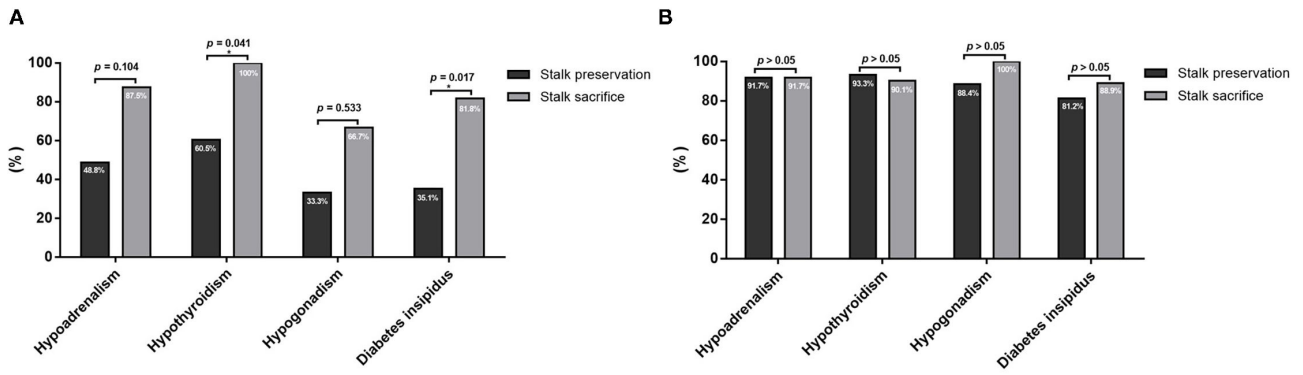

FIGURE 2 | Comparison of post-operative hypopituitarism between patients with pituitary stalk preservation and sacrifice. **(A)** For patients with normal pituitary function before surgery, stalk preservation significantly decreased the percentage of surgically induced new-onset hypothyroidism and diabetes insipidus. **(B)** For patients who already had pre-operative hypopituitarism before EEA, there were no significant differences in the rate of post-operative hypopituitarism between patients with pituitary stalk preservation and sacrifice. *$P < 0.05$.

craniopharyngiomas originate from the pituitary stalk. Damage to the stalk, either pathologically or iatrogenically, compromises the endocrinological function and seriously affects patients' quality of life. However, preserving the pituitary stalk during surgery might shield the seed of the tumor, resulting in a higher risk of recurrence. From a study conducted by Xiao et al., the ultra-electron microscope was used to determine whether pituitary stalk specimens were invaded with tumor cells. The results revealed that all pituitary stalk samples (15/15, 100%) showed tumor invasion (9). Furthermore, a morphologically preserved pituitary stalk might not be functional. So, whether to sacrifice or preserve the stalk is still an issue of importance facing neurosurgeons.

Currently, two contradictory opinions existed in the intraoperative management strategy of the pituitary stalk. Honegger et al.'s series of 92 transcranial cases demonstrated that the post-operative endocrine status was generally better in patients with stalk preservation (7). The authors also recommended preserving the stalk as much as possible because it didn't seem to increase the risk of recurrence. By contrast, Jung et al. treated 17 pediatric craniopharyngiomas *via* transcranial approaches and found that preserving the pituitary stalk did not benefit post-operative endocrinological outcomes but significantly increased the risk of recurrence (10). Also, Xiao et al. recommended total resection of the tumor along with the pituitary stalk if the stalk was intraoperatively invaded (9). Sometimes, it is hard to say whether the pituitary stalk is preserved due to its deep location and the limited exposure of microscopic view during transcranial approaches. We might experience a "missing" pituitary stalk, but it is compressed to a corner that is difficult to observe under the microscope. On the contrary, we might think the pituitary stalk is preserved, but it has been transected at some site out of the surgical view. This makes one of the explanations of the different results mentioned above.

Compared with microscopic transcranial approaches, the EEA provides an ideal visualization of the ventral skull base, enabling early identification of the pituitary stalk (12, 13). The EEA is a perfect model to study the impact of pituitary stalk management on surgical and endocrinological outcomes of suprasellar craniopharyngiomas because the judgment of stalk preservation vs. sacrifice is very reliable in most cases. In a study conducted by Ordonez-Rubiano et al., the authors reported that stalk preservation during EEA reduced the rate of post-operative endocrinopathy but compromised GTR achievement with a higher rate of tumor recurrence or residual tumor regrowth (14). The authors recommended that stalk preservation should be considered if GTR could be achieved. In the present study, we demonstrated that GTR (OR = 0.248 CI 0.081–0.759; $p = 0.015$) was the only independent factor influencing recurrence/progression. We found a four-fold higher possibility of recurrence/progression in patients with non-GTR. Furthermore, preserving the pituitary stalk does not appear to decrease the percentage of GTR (75.5% vs. 55.0%, $p = 0.089$), or increase the rate of tumor recurrence (12.5% vs. 0%, $p = 0.508$) or progression (46.2% vs. 22.2%, $p = 0.486$). However, surgically induced hypothyroidism (60.5% vs. 100%, $p = 0.041$) and DI (35.1% vs. 81.8%, $p = 0.017$) were significantly lower in patients with stalk preservation. Most of our results were comparable to Ordonez-Rubiano et al.'s study. However, we didn't find stalk preservation decreased the rate of GTR. One explanation is that stalk preservation was found to be more common in peripheral type tumors in our study, which made GTR easier to achieve than in cases with central type tumors.

Regarding the endocrinological outcomes, the present study revealed a large proportion of post-operative hypopituitarism after EEA, even in patients with stalk preservation, which is similar to previous studies (17, 18). Patients should be informed and agreed with that. Attempt to preserve the stalk is time-consuming, but it is rewarded with improved post-operative pituitary function. However, for patients who already had severe hypopituitarism before EEA, stalk preservation

didn't improve post-operative endocrinological outcomes. We recommend preserving the pituitary stalk as much as possible in peripheral type suprasellar craniopharyngiomas with normal pituitary function, especially in cases without hypothyroidism or DI. On the other hand, stalk sacrifice could be considered in central type tumors with severe pre-operative endocrinopathy.

Interestingly, we found there was one patient (5.0%) recovered adrenal function, one patient (5.0%) recovered thyroidal function, and one patient (5.0%) recovered posterior pituitary function even after stalk sacrifice. Ogawa and Nishizawa et al. also noticed that endocrinopathy could be partially reversible even with stalk sacrifice (11, 19). Further researches are needed to address this issue.

There are several limitations to our study. Firstly, because of the study's retrospective nature, the conclusion we draw may not be solid enough, and a prospective observational study is needed to strengthen our opinion further. Secondly, a limitation of comparison between studies is that not the same tumor location classification was used, and we had a relatively short follow-up period to estimate the long-term outcomes. We speculated that the short follow-up period might be related to the fact that ∼80% of our patients come from other cities outside of Shanghai. It is difficult for everyone to visit us after 1–2 years of stable disease after surgery.

CONCLUSION

GTR is the only independent predictor of recurrence/progression after EEA surgery for suprasellar craniopharyngiomas. Preserving the pituitary stalk does not appear to increase the risk of non-GTR and tumor recurrence/progression and might help reduce the risk of surgically induced hypothyroidism and DI.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee, Huashan Hospital, Fudan University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

ZC, ZM, MS, and YW: study design, implementation and supervision, and draft organization. YW and YZhao: surgical procedure. MS, WH, ZY, XZ, XS, XC, SL, and YZhan: patient recruitment. MH, ZZ, HY, and YL: endocrinological evaluation. ZM and QZ: radiological examination. NQ and ZM: statistical analysis. ZC and MS: clinical data collection. All authors draft final review.

FUNDING

This work was supported by the National Natural Science Foundation of China (81602191), received by MS; the National Project in promoting the diagnosis and treatment of major diseases by MDT, received by YZhao; and the CAMS Innovation Fund for Medical Sciences (CIFMS, 2019-I2M-5-008), received by YW. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

ACKNOWLEDGMENTS

We thank and acknowledge all of the participants in this study.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.753944/full#supplementary-material

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frontiers in Neurology

ORIGINAL RESEARCH
published: 15 November 2021
doi: 10.3389/fneur.2021.755784

Intraventricular Craniopharyngiomas—Overcoming Their Relative Inaccessibility: Institutional Experience With a Review of Literature

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Introduction: Craniopharyngiomas constitute 2–4% of intracranial neoplasms. Intraventricular craniopharyngiomas (IVCrs) are the rarely encountered varieties of these lesions.

Objective: The objective of the study was to study the special features in clinical presentation, imaging, management, and surgical outcome of IVCrs.

Materials and Methods: This retrospective analysis included the combined experience from two tertiary care institutions. Medical records of histopathologically proven cases of IVCrs from January 1994 to June 2021 were assessed, and images were analyzed based on the criteria by Migliore et al. for inclusion of solely intraventricular lesion with the third ventricular ependyma demarcating it from the suprasellar cistern.

Results: Among the 25 patients included (mean age: 35.4 years), the most common presentation included headache (n = 21, 84%), vomiting and other features of raised ICP (n = 18, 72%), visual complaints (n = 12, 48%), and endocrinopathies (n = 11, 44%). Fifteen had predominantly cystic tumors, two were purely solid, and eight were of mixed consistency. Primary open microsurgical procedures were performed in 18 (72%) patients, of which four (16%) were endoscope-assisted. Seven (28%) underwent a purely endoscopic procedure. One underwent a staged surgery with endoscopic cyst fenestration and intracystic interferon (IFN)-alpha therapy, followed by microsurgical excision. Complete excision was achieved in 10 patients, near-total in nine, and partial excision in six. Four patients underwent a ventriculoperitoneal shunt (one before the definitive procedure). At a median follow-up of 36 months (range:11–147 months), five patients developed a recurrence, and one had a stable small residue. This patient and two others with small cystic recurrences were observed. One patient was managed with radiotherapy alone. Another underwent re-surgery after a trial of radiotherapy, and the last patient developed a local recurrence, which was managed with radiotherapy; he then later developed an intraparenchymal recurrence, which was operated.

OPEN ACCESS

Edited by:
Paolo Cappabianca, University of Naples Federico II, Italy

Reviewed by:
Domenico Solari, Federico II University Hospital, Italy
Teresa Somma, Federico II University Hospital, Italy

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Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Neurology

Received: *09 August 2021*
Accepted: *22 September 2021*
Published: *15 November 2021*

Citation:
Deopujari C, Behari S, Shroff K, Kumar A, Thombre B, Karmarkar V and Mohanty C (2021) Intraventricular Craniopharyngiomas—Overcoming Their Relative Inaccessibility: Institutional Experience With a Review of Literature. Front. Neurol. 12:755784. doi: 10.3389/fneur.2021.755784

Conclusion: Purely IVCrs present with raised intracranial pressure, and visual disturbances are less common. Their deep-seated location and limited surgical field-of-view makes minimally invasive endoscopic-assisted surgery most suitable for their excision. The thin-walled cystic lesions may be occasionally adherent to the ependymal wall in close vicinity to the thalamus–hypothalamus complex, making complete excision difficult. Their responsiveness to radiotherapy, often leads to a gratifying long-term outcome.

Keywords: craniopharyngioma, intraventricular craniopharyngioma, intraventricular tumor, adult craniopharyngioma, hydrocephalus

INTRODUCTION

Craniopharyngiomas are benign tumors, originating either from squamous epithelial cell that rests in the Rathke's pouch, located along its path from the nasopharynx to the infundibulum, or as a result of squamous metaplasia from the pars tuberalis of the pituitary gland (1–4). They constitute 2–4% of all intracranial tumors (3, 5–12). Multiple classification systems (based on their imaging features) have been proposed to help in choosing the appropriate management strategy (13). Purely intraventricular variety of craniopharyngiomas are infrequent, with the reported incidence varying from 0.5 to 14% of all craniopharyngiomas (3, 5, 8, 12, 14). As IVCrs originate from ectopic remnants present within the neuraxis, they are generally seen in older patients and present more often with features of raised intracranial pressure, rather than with visual or endocrinological disorders, as compared with their sellar/suprasellar or suprasellar–intraventricular counterparts (5, 11, 12, 15). Their deep-seated location, proximity, and often adherence to the walls and floor of the third ventricle and the hypothalamus, makes their surgical excision challenging. In this study, we discuss the clinical and radiological features, and management nuances of purely IVCrs.

METHODOLOGY

Patient Selection

The medical records of operated and histologically proven (**Figure 1**) cases of craniopharyngiomas, managed between January 1994 to June 2021 (The experience of the senior author from the first institution, and the departmental experience from the second institution is reported) were assessed. The purely intraventricular tumors were selected based on the radiological inclusion criteria suggested by Migliore et al. (16). This includes an intraventricular location of the tumor with the ventricular ependyma being intact inferiorly, clearly demarcating the tumor from the unoccupied suprasellar cistern (**Figure 2**). The demographic, clinical, endocrinological, and radiological features of these purely IVCrs were analyzed. The surgical approaches undertaken, their merits and demerits, and the subsequent adjuvant therapy administered, were assessed.

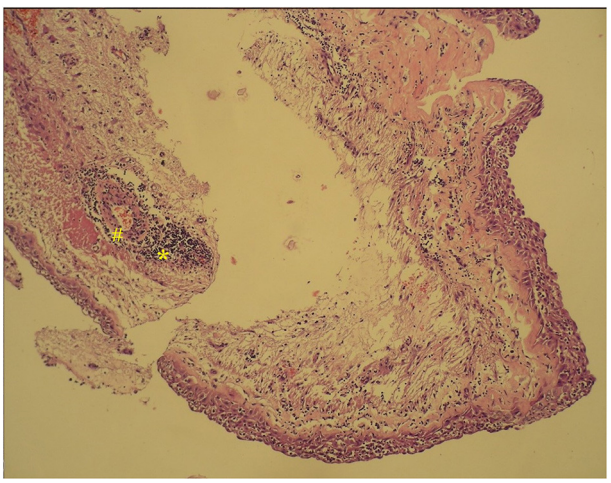

FIGURE 1 | Histopathology section of an adamantinomatous intraventricular craniopharyngioma, showing areas of wet keratin (#) with calcification (*).

Follow-Up

The follow-up data regarding visual/endocrine status, postoperative complications, postoperative radiotherapy administered, and the recurrence rate were also analyzed.

Statistics

A descriptive analysis of the data obtained has been reported.

Review of Literature

A search was made on the PubMed database using the keywords "intraventricular craniopharyngioma," and the articles which were intended for the reporting of cases of purely intraventricular craniopharyngiomas were selected, and their findings are summarized in **Table 1**. The data of similar such case series were used for comparison with the results obtained from our series of patients.

Abbreviations: IVCr, intraventricular craniopharyngioma; MBs, mamillary bodies; MBA, mamillary body angle; FLAIR, fluid attenuated inversion recovery sequence; MRI, magnetic resonance imaging; DVT, deep venous thrombosis; ICP, intracranial pressure.

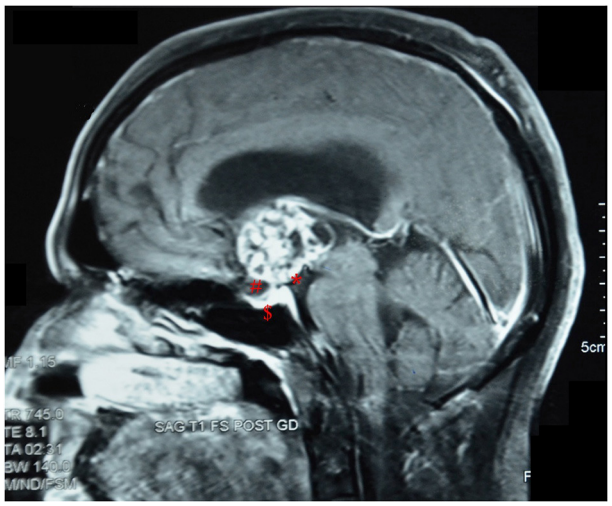

FIGURE 2 | Post-contrast sagittal MRI image of a patient with an intrinsic third ventricular craniopharyngioma, showing features as described by Migliore et al. (16). *, an intact third ventricular floor; #, a patent suprasellar cistern; $, absence of sellar abnormalities.

RESULTS

Demographics

The 25 patients (mean age 35.4 years; age range 6–74 years; male: female ratio = 11:14) with a purely IVCr formed 4.27% (25/585) of all craniopharyngioma patients operated during the same time frame. The six cases of IVCrs presented in the study by Behari et al. have been included in this study (5).

Clinical Presentation

The clinical signs and symptoms at presentation are summarized in **Table 2**. Headache (either bifrontal or holocranial) was the most common (84%) symptom at presentation. Other features of raised intracranial pressure like vomiting and transient blurring of vision (due to intermittent abducent nerve palsy brought about by brainstem distortion) were noted in 18 (72%) patients. Three (12%) patients had loss of consciousness attributable to sudden increase in intracranial pressure due to cerebrospinal fluid pathway obstruction at the foramen of Monro.

Vision was affected in 12 (48%) of the patients. Homonymous hemianopia was seen in two, and bitemporal hemianopia was seen in two patients. Two patients presented with secondary optic atrophy. Six patients had decreased vision with no overt field deficits, and vision could not be evaluated in one patient who presented with altered sensorium. Gait apraxia was present in five (20%) of the patients. Some form of hypopituitarism was present in 11 (44%) of the patients. These endocrinopathies included hypothyroidism, hypocortisolism, diabetes insipidus, irregular menstrual cycle, or loss of libido. Sleep disturbances, changes in appetite or behavior, and cognitive disturbances, as a form of hypothalamic syndrome, was seen in 3/25 (12%) patients.

Imaging Characteristics

As shown in **Table 3**, 60% of the tumors were cystic, 8% were solid, and the rest (32%) were of mixed consistency. The cystic component was hyperintense on T2-weighted MRI. Their imaging intensity was distinctly different from the cerebrospinal fluid (CSF) intensity, as noted on FLAIR sequences. Tumors with a predominantly solid component had a more heterogeneous appearance and were most often associated with intramural calcification. In cystic tumors, calcification of a part of the wall was present in six (24%) of the patients (**Figure 3**). As can be noted in the image shown, in consonance with our selection criteria, the floor of the third ventricle was bulging inferiorly toward the suprasellar cistern in each of the cases due to the mass effect of the tumor but was not breached in any of the cases.

Surgical Management

While choosing the surgical approach, the factors considered included the age of the patient, the size and site of tumor, the degree of associated hydrocephalus, and the type of visual deterioration. As noted in **Table 4**, an open craniotomy was used in 18 (72%) patients. Seven patients were operated using the transcortical–transventricular route (**Figure 4**), of which three underwent an endoscopy-assisted procedure. The interhemispheric-transcallosal approach was used in four patients (of which one was operated using an endoscopy-assisted procedure); the interhemispheric lamina terminalis approach was used in five patients; and, two patients underwent the pterional, trans-sylvian, lamina terminalis approach. In the translateral–third ventricular approaches (transcortical–transventricular and interhemispheric–transcallosal–transventricular; $n = 11$), the foramen of Monro was usually sufficiently dilated to access the third ventricle through the transforaminal route ($n = 10$). The subchoroidal approach was used in one patient in whom the tumor was situated posterior to the foramen of Monro in the body of the third ventricle. Ommaya reservoir placement was done within the cyst in two tumors.

Among those who underwent a purely endoscopic procedure (mainly those with a cystic tumor in whom a transcortical–transventricular approach was adopted; $n = 7$), cyst fenestration (**Figure 5**) along with wall biopsy was performed in four patients. Endoscopic third ventriculostomy was performed along with cyst fenestration in one patient. Two patients underwent a purely endoscopic procedure, *via* a keyhole craniotomy. One patient underwent a staged procedure with endoscopic cyst fenestration and intracystic interferon (IFN)-alpha therapy, followed by microsurgical excision.

Complete excision of the tumor was possible in 10 (40%) of the patients, while in nine (36%), near-total excision was possible. In the latter cases, the capsule of the tumor, densely adherent to the ventricular wall, was left *in situ*. Only a partial or subtotal removal of the tumor was done in six (24%) patients, with a predominantly cystic tumor having a very thin wall. In the cystic tumors, cholesterol crystals were noted, with the presence of machine-oil colored fluid, after cyst fenestration.

Post-operative Course

In the immediate postoperative period, diabetes insipidus (DI) was present in seven (28%) of the patients. The DI was transient in five (20%) patients, and two patients

TABLE 1 | Prior reports and series of purely intraventricular craniopharyngiomas in literature.

Reference	No. of cases	Age (years)	Sex	Clinical presentation	Preoperative visual status	Preoperative hormonal status	Imaging appearance	Extent of surgical excision	Outcome	Recurrence
Cashion and Young (17)	2	46	Male	Headache, malaise, papilloedema	-	-	-		Died	-
		26	Male	Headache, lethargy, episodes of syncope, papilloedema	-	-	-	Underwent ventriculojugular shunt	Died	-
King (18)	4	68	Female	Gradual diminution of vision especially in left eye, early somnolence, decline in memory	Visual acuity-6/12 right eye and 6/18 left eye, bitemporal hemianopia, more severe in left eye	-	Pneumoencephalogram-third ventricular mass	Subtotal excision	Improved and remained well over following 6 years	No
		10	Male	Headaches, vomiting, papilloedema	Visual acuity of 6/12 in either eye with incomplete left homonymous hemianopia	Had diabetes insipidus, decreased sexual characteristics	Pneumoencephalogram-calcified tumor in third ventricle	Underwent ventriculocisternotomy followed by radiotherapy initially, on progression underwent subtotal excision	Developed memory deficits, poikilothermia, visual fields improved postoperatively	No
		54	Male	Progressive diminution of vision, intellectual dullness	Visual acuity of 6/9 in right eye and finger counting in left eye, visual fields showed bitempoal hemianopia, scotomatous on the left, fundi showed optic atrophy		Pneumoencephalogram-showed tumor in third ventricle	Subtotal excision	Euphoria, developed homonymous hemianopia, visual acuity-6/9 in right eye and finger counting in left eye, required ventriculo-atrial shunting due to persistent ventricular enlargement, underwent radiotherapy, hypopituitarism treated with supplementation	No

(Continued)

TABLE 1 | Continued

Reference	No. of cases	Age (years)	Sex	Clinical presentation	Preoperative visual status	Preoperative hormonal status	Imaging appearance	Extent of surgical excision	Outcome	Recurrence
		47	Male	Headaches and loss of vision	Visual acuity of 6/60 in right eye and recognition of hand movements in left eye	On thyroxine supplementation	Calcified cystic intraventricular craniopharyngioma	Subtotal excision leaving behind a small piece attached to floor of the third ventricle just behind the optic chiasm	Postoperatively developed some confusion, serum hyperosmolarity requiring antidiuretics, tendency to poikilothermia, visual acuity 6/18 on right and 3/60 on left, also required steroid replacement	
Goldstein et al. (19)	1	57	Female	Severe bifrontal headaches and left facial paraesthesia	Normal vision, no papilloedema	-	Solid tumor, no calcification or cyst	Subtotal excision leaving behind only a small tumor in the posteroinferior aspect of the third ventricle	Developed a subgaleal CSF leak which required a secondary procedure to close a small dural defect, underwent adjuvant radiotherapy	No
Matthews (10)	1	65	Female	Dementia, two episodes of syncope, mental status changes, no headache, vomiting or papilloedema	No papilloedema	-	Solid tumor, no calcification	Complete excision	Dementia and hydrocephalus remained unchanged after surgery, patient underwent a ventriculoperitoneal shunt and mental status improved steadily	-

(Continued)

TABLE 1 | Continued

Reference	No. of cases	Age (years)	Sex	Clinical presentation	Preoperative visual status	Preoperative hormonal status	Imaging appearance	Extent of surgical excision	Outcome	Recurrence
Sole-Llenas et al. (20)	1	33	Female	Frontonuchal headache, asthenia, drowsiness, vomiting, occasional psychomotor agitation, attacks of loss of consciousness lasting several min, one episode of urinary incontinence; examination showed left abducent paresis, bilateral exophthalmos, and paresis of gaze, generalized hyper-reflexia, bilateral Babinski sign and vesical incontinence	-	-	Third ventricular tumor with cystic component	Complete excision	Worsening of clinical symptoms 11 months after surgery, CT scan done-intraventricular tumor in anterior third ventricle with extraventricular extension noted	Yes, detected 11 months after surgery, underwent surgery for recurrence
Chin (21)	1	56		Signs and symptoms of raised intracranial pressure	-	-	Mass lesion in the third ventricle on CT scan	-	-	-
Sacher et al. (22)	1	34	Male	Worsening bifrontal headaches	Normal	Normal	CT scan-non-calcified cystic lesion	-	-	-
Fukushima et al. (14)	1	28	Male	Headache, nausea; examination revealed drowsiness, mild optic atrophy and left upper and right lower temporal quadrantanopia	-	-	CT scan-enhancing isodense mass with low density spots in the third ventricle	Partial excision and decompression of optic chiasm	Transient diabetes insipidus, no neurological deficit, visual fields improved	No
Migliore et al. (16)	1	11	Female	Headache, nausea, and vomiting; examination showed bilateral papilloedema and marked bradycardia	-	-	CT scan-spherical hyperdense non-enhancing mass lesion	Complete excision	Uneventful, no cortisone or thyroxine therapy necessary	No

(Continued)

TABLE 1 | Continued

Reference	No. of cases	Age (years)	Sex	Clinical presentation	Preoperative visual status	Preoperative hormonal status	Imaging appearance	Extent of surgical excision	Outcome	Recurrence
Iwasaki et al. (23)	2	39	Male	Progressive headache; examination showed mild papilloedema	Normal	Normal	Solid mass, no cyst/calcification	Complete excision	Headache resolved, no neurological deficit, postoperative hormonal examinations normal	No
		49	Male	Headache	-	Normal	Lesion in third ventricle, no cystic regions/calcification	Complete excision	Transient mild disorientation, normal endocrinological reports	No
Davies et al. (6)	6	45 (Mean)	3 males 3 females	Headache-4/6, visual symptoms-6/6, hypopituitarism in 3/6, memory disturbances 1/6	Visual symptoms in all patients, homonymous hemianopia in 3/6 patients, bitemporal defect in 1/6, left central scotoma and right temporal defect in 1/6 and transient obscuration in 1/6	Hypopituitarism in 3/6, DI in 1/6	-	Complete excision—1/6, subtotal excision-3/6, partial excision—2/6	Normalization of vision in 3/6, improvement in 2/6 and improvement with later deterioration in 1/6, hypopituitarism in 3/6, DI with adypsia in 2/6, memory loss which recovered in 2/6 and impaired memory in 1/6, obesity in 2/6, all received radiotherapy at some stage	-

(Continued)

TABLE 1 | Continued

Reference	No. of cases	Age (years)	Sex	Clinical presentation	Preoperative visual status	Preoperative hormonal status	Imaging appearance	Extent of surgical excision	Outcome	Recurrence
Maira et al. (24)	8	33.63 (Mean)	3 males, 5 females	Amenorrhoea 2/8, psychological disturbances 2/8, hydrocephalus 2/8, headache 1/8, hypopituitarism 1/8	-	Panhypopituitarism in 4/8, gonadotropin deficiency in 1/8, hyperprolactinaemia in 2/8	Solid tumor in all patients, no cysts/calcifications	Complete excision—7/8, partial excision in 1/8	No patient received adjuvant radiotherapy, visual functions preserved for all patients, confusion and fluid-electrolyte imbalance in one patient requiring prolonged ICU stay who later recovered but had persistent panhypopituitarism (requiring replacement therapy) and a defective thirst mechanism	1 recurrence
Pascual et al. (25)	1	47	Male	Headache, psychiatric disturbances, memory disturbances	Normal	Normal	Cystic	Cyst decompression and partial excision	Complete recovery, normal neurological examination	No
Madhavan et al. (26)	1	56	Male	Headache, fever, generalized lethargy, drowsiness; on examination there was neck stiffness and papilloedema with left lower limb hypertonia and extensor Babinski response	-	Normal	Solid	Complete excision	Recovered uneventfully after surgery but died before discharge on 12th postoperative day due to acute myocardial infarction	-

(Continued)

TABLE 1 | Continued

Reference	No. of cases	Age (years)	Sex	Clinical presentation	Preoperative visual status	Preoperative hormonal status	Imaging appearance	Extent of surgical excision	Outcome	Recurrence
Agrawal et al. (27)	1	10	Female	Headache, diminution of vision in the left eye, bilateral papilloedema	Finger counting at 2 feet left eye, right eye normal	-	Cystic, no calcification	Complete excision	Improvement in vision	-
Tayari et al. (15)	1	22	Female	Headache, nausea, and vomiting, one episode of generalized tonic-clonic seizure, fundoscopy showed mild bilateral papilloedema	Normal	-	No calcification	Complete excision	-	No
Pan et al. (2)	17	37.3 ± 14.3 (Mean)	13 males, 4 females	Raised ICP-11/17, cognitive disturbances-8/17, visual deficits-8/17, diabetes insipidus-3/17, somnolence - 3/17	Visual deficits-8/17	Hypoadrenalism in 8/17, hypothyroidism in 6/17, hypogonadism in 14/15 adults, GH deficiency in 9 patients, panhypopituitarism in 3/17	Solid tumor - 6/17, cystic or mixed variety-11/17	Complete excision−13/17, subtotal excision−4/17	One patient died, one patient developed contralateral epidural haematoma, one patient developed postoperative frontal lobe dysfunction, 16 patients underwent resolution of their postoperative hypothalamic symptoms, deterioration of anterior pituitary function seen in all patients (adrenocorticotrophic disturbance in 4/17, thyrotrophic disturbance in 5/17, panhypopituitarism in 3/17, transient DI in 16/17, permanent DI in 5/17)	3/17 patients, all 3 underwent reoperation followed by adjunctive radiotherapy

(Continued)

TABLE 1 | Continued

Reference	No. of cases	Age (years)	Sex	Clinical presentation	Preoperative visual status	Preoperative hormonal status	Imaging appearance	Extent of surgical excision	Outcome	Recurrence
Yu et al. (12)	24	40.2 (Median), range 15–61 years	M:F ratio-10.5:1	Headache-16/24, visual deficits - 10/24, sexual dysfunction or amenorrhoea-8/24, mental disturbances or drowsiness-8/24, diabetes insipidus-5/24, intracranial hypertension-3/24	Visual deficits-10/24	Sexual dysfunction/ amenorrhoea-8/24	Solid tumor-20/24 cases, cystic tumor-2/24 cases, mixed solid-cystic-2/24 cases	Complete excision—19/24, subtotal excision—5/24	No perioperative mortality, seizure in one patient, mental disturbances, and memory dysfunction in one patient, panhypopituitarism in 8/24, corticotroph insufficiency in 13/24, diabetes insipidus in 15/24	6/24 patients, 1 underwent reoperation, 1 received stereotactic interstitial radiation, 1 patient radiosurgery, 3 patients managed conservatively
Yano et al. (28)	1	52	Male	Headache, fatigue and lethargy, memory disturbances	Left temporal visual field defect	Hypopituitarism with GH deficiency and polyuria	Solid	Complete excision	-	-
Rambarki and Rajesh (11)	2	50	Male	Raised ICP	-	-	Solid-cystic	-	-	-
		27	Male	Raised ICP	-	-	Solid-cystic	-	-	-
Diniz et al. (8)	1	36	Female	Headache, photophobia, phonophobia, vomiting, bilateral papilloedema	-	-	Solid-cystic, no calcification	-	-	-

(Continued)

TABLE 1 | Continued

Reference	No. of cases	Age (years)	Sex	Clinical presentation	Preoperative visual status	Preoperative hormonal status	Imaging appearance	Extent of surgical excision	Outcome	Recurrence
Kehayov et al. (9)	1	43	Male	Intermittent severe headache and progressive visual loss, obesity	Bitemporal field loss, predominantly for right eye		Solid-cystic	Complete excision	Diabetes insipidus and hypocortisolaemia, complete recovery of vision	No
Guadagno et al. (29)	1	45	Male	Polyuria, polydipsia, polyphagia, severe headache, loss of consciousness	Visual impairment in left eye	Normal	Solid with calcified spots	Near-total excision (>90%)	Death due to meningitis and multi-organ failure	-
Hung et al. (3)	5	46(mean)	1 female, 1 male, the rest not mentioned	Headaches and visual disturbances	Visual disturbances in all five patients	-	Mixed components-2/5, Solid tumors-3/5, no calcification seen in any tumor	Complete excision for 3/5, extent of resection not mentioned for two patients	-	-
Our series	25	35.4	11 males, 14 females	Headache 21/25, vomiting and other features of raised ICP 18/25, memory disturbances 6/25, gait apraxia 5/25, urinary/fecal incontinence 4/25	Visual disturbances in 12/25	Preoperative endocrinological disturbances in 11/25	Cystic-15/25, mixed-8/25, solid-2/25	Complete excision—10/25, near-total excision—9/25, subtotal/partial excision—6/25	DI-7/25 (transient 5/25, permanent 2/25), meningitis 2/25, hydrocephalus requiring VP shunt 4/25, death 3/25	Recurrence 5/25, residual lesion 1/25

TABLE 2 | Clinical presentation.

	N = 25	%
Clinical symptoms and signs		
Headache	21	84
Features of raised ICP	18	72
Visual complaints	12	48
Gait apraxia	5	20
Loss of consciousness	3	12
Urinary/fecal incontinence	4	16
Memory disturbances	6	24
Hypothalamic syndrome	3	12
Others	4	16
Pre op hormonal status		
Hypothyroidism	6	24
Hypocortisolism	5	20
Diabetes insipidus	4	16
Sexual dysfunction	2	8

TABLE 3 | Imaging characteristics.

	N = 25	%
Type of lesion on imaging		
Cystic	15	60
Solid-cystic	8	32
Solid	2	8
Other findings		
Hydrocephalus	11	44
Calcification	6	24

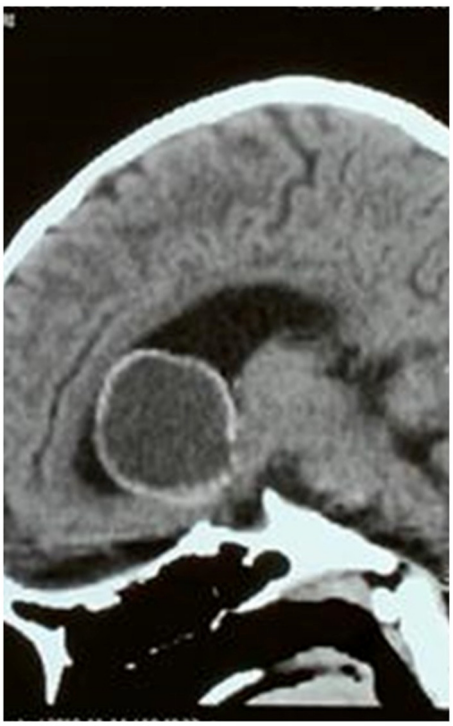

FIGURE 3 | Sagittal section CT scan of a patient with a cystic intraventricular craniopharyngioma showing peripheral calcification, and a bulge in the floor of the third ventricle.

TABLE 4 | Surgical details.

Procedure type(*n*)	**Approach**	***N***	**%**
Open (18)	Trans-cortical trans-ventricular	7 (3 endoscope-assisted)	16
	Inter-hemispheric trans-callosal	4 (1 endoscope-assisted)	12
	Inter-hemispheric lamina terminalis	5	20
	Pterional trans-sylvian lamina terminalis	2	8
Purely endoscopic (7)		7	28
Extent of resection		**N**	**%**
Complete		10	40
Near-total		9	36
Subtotal/partial		6	24

(8%) developed permanent DI and requiring long-term vasopressin (desmopressin) supplementation. The postoperative complications are summarized in **Table 5**. Features of new-onset hypothalamic dysfunction after surgery were seen in one patient. Three patients expired in the series. One of them developed postoperative septicaemia, the second developed central DI with adipsic hypernatraemia, and the third expired due to pulmonary embolism secondary to deep vein thrombosis after second surgery for recurrence, 6 years after primary excision.

Follow-Up

The median follow-up period was 36 months, with a range of 11–147 months. In 17 patients (68%), the follow-up MRI revealed no recurrence; while five patients had a recurrence (**Figure 6**) and, one patient had a small residual tumor. The patient with the small residue and two others with small cystic recurrences, were observed. Among the other three patients with recurrences, one patient who had a recurrence in the region of the hypothalamus was managed with radiotherapy alone. Another patient underwent re-surgery after a trial of radiotherapy. The last patient with a recurrent lesion, developed a local recurrence which was managed with radiotherapy; and later developed an intraparenchymal ectopic recurrence for which he underwent surgery. The residual cystic collection of two patients was managed conservatively by tapping of the Ommaya reservoir. In all, four out of 11 patients with preoperative hydrocephalus underwent a ventriculoperitoneal shunt (of which, one was before the definitive procedure). One patient with mild transient hydrocephalus was managed conservatively with acetazolamide.

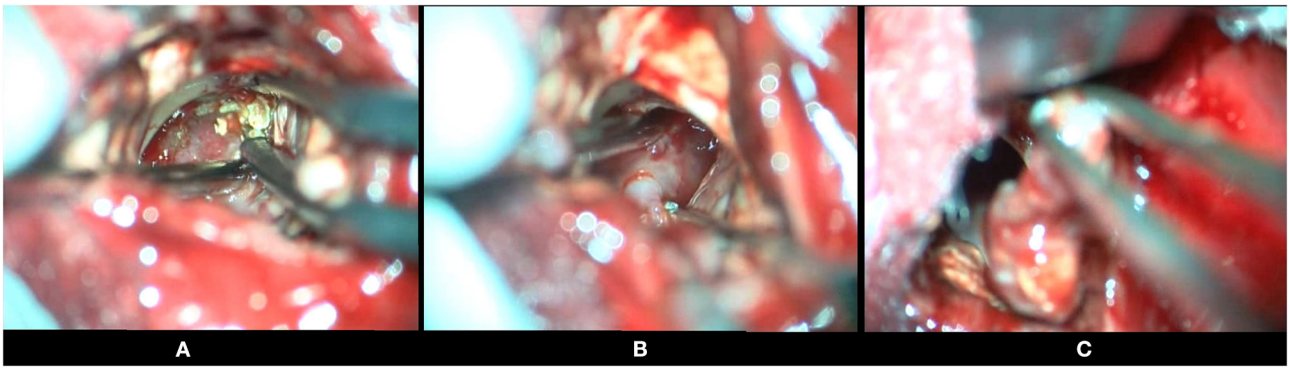

FIGURE 4 | Intraoperative photographs of a patient with an intraventricular craniopharyngioma, undergoing a frontal transcortical-transventricular approach, for tumor excision. **(A)** Tumor being dissected from the walls of the third ventricle (calcifications visualized in the wall of the tumor). **(B)** Tumor being separated from the floor of the third ventricle. **(C)** Solid tumor being removed, after dissection.

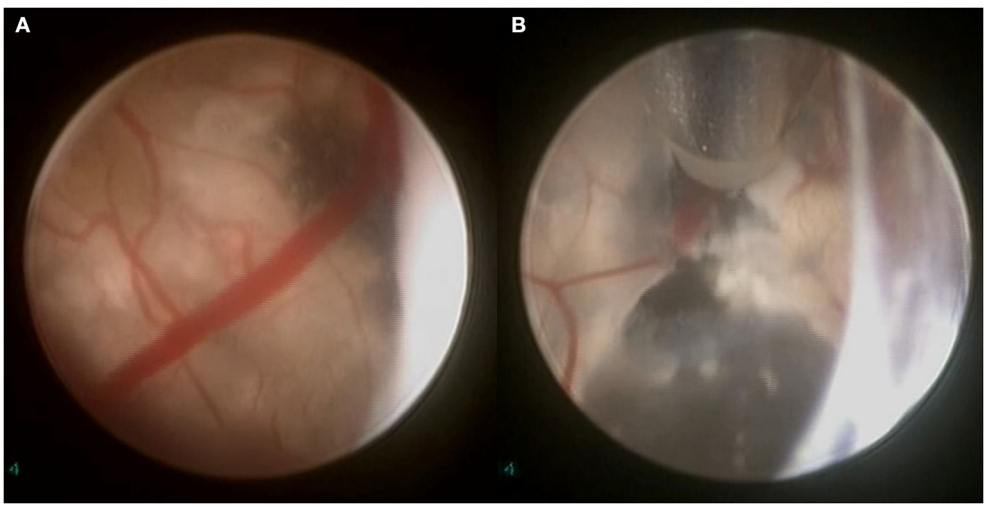

FIGURE 5 | Intraoperative endoscopic view of a cystic intraventricular craniopharyngioma in a 6-year-old child. **(A)** Craniopharyngioma cyst wall (with calcifications) visualized. **(B)** Using bipolar diathermy, a fenestration is made into the cyst wall for draining its contents and insertion of a ventricular catheter connected to an Ommaya reservoir (through which alpha-interferon was administered).

The remaining patients did not require any other intervention for CSF diversion.

Radiotherapy of 4,500–5,400 rads was given in eight (32%) patients. Two of them received radiotherapy after developing a recurrence. A maintenance dose of prednisolone (5 and 2.5 mg daily) was given in all patients for a period of 6 weeks, and supplemental thyroxine (0.1 mg/day) was given in the six patients who were preoperatively hypothyroid. On follow up at 6 weeks, a complete hormonal evaluation was done to assess for hypopituitarism, which was accordingly treated with the necessary supplemental therapy. In our series, we observed the development of new-onset hypocortisolism in two (8%) patients, and new-onset hypothyroidism in two (8%) patients, after surgery. Documented postoperative improvement in vision was seen on formal assessment in 6/12 (50%) of the affected patients. Documented formal assessment was not charted for the other five patients but clinical assessment notes show better or stable vision. No further deterioration in vision occurred for any of the patients.

DISCUSSION

Cushing described craniopharyngiomas as "the most formidable of intracranial tumors" (1). The intraventricular variety is the least common and poses special challenges (5). IVCrs were first reported in 1953 by Dubos et al. and subsequently by Cashion and Young (5, 16, 17, 20, 25). It is widely believed that the adamantinomatous variety originates from epithelial cell rests in the Rathke's pouch and that the papillary variety originates from the squamous metaplasia within the pars tuberalis of the pituitary gland (2). Previously, Atwell had suggested that the

TABLE 5 | Postoperative complications and follow-up.

	N	%
Postoperative complications		
Transient DI	5	20
Permanent DI	2	8
Hydrocephalus requiring VP shunt	4	16
New-onset hypothyroidism	2	8
New-onset hypocortisolism	2	8
New-onset hypothalamic dysfunction	1	4
Meningitis	2	8
CSF Leak	1	4
Septicaemia	1	4
Follow up		
Post-op radiotherapy	8	32
Recurrence	5	20
Residual lesion	1	4

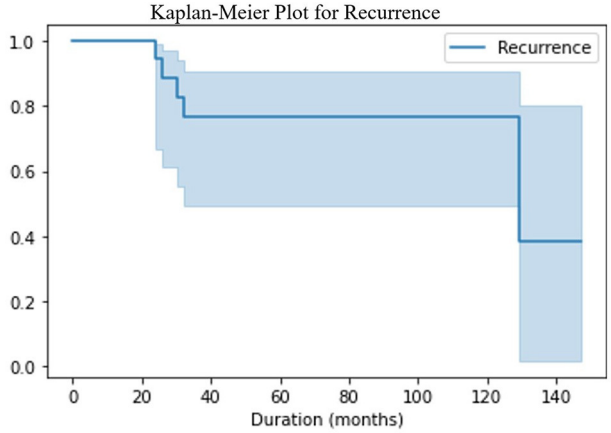

FIGURE 6 | The Kaplan- Meier survival plot showed that majority of the recurrences are detected in the first 36 months, but the risk of recurrence still exists even at 10 years of follow up.

pars tuberalis could rarely grow forward or backward, and that it could sometimes extend to the infundibulum or the tuber cinereum; and this was believed to be the cause of the location of these tumours being exclusively in the third ventricle (23, 30). However, it is now known that the pial membrane serves as a barrier preventing the Rathke's pouch cells from coming into direct contact with the developing cerebral vesicle (the precursor of the third ventricular floor and infundibulum). If the development of this pial membrane is delayed, the cells of the Rathke's pouch come into direct contact with the neuroectoderm of the developing cerebral vesicle. These cells, when they grow to form a tumor, give rise to a purely intraventricular craniopharyngioma (5, 8, 24).

The incidence of purely IVCrs among craniopharyngioma patients in our series was 4.27% (25 purely intraventricular craniopharyngiomas out of a total of 585 craniopharyngioma patients who underwent surgery). The incidence reported in other major series is 2.89% (by Yu et al.) and 8.72% (by Pan et al.) (2, 12).

The importance of the location of craniopharyngiomas with respect to the third ventricle has long been recognized, as can be seen from the various classification schemes proposed. Steno (1985) classified craniopharyngiomas into the intrasellar and suprasellar types. Suprasellar types were further classified into three groups (extraventricular, intra–extraventricular, and intraventricular), based on their relationship to the third ventricular floor (31). Yasargil classified craniopharyngiomas into purely intrasellar–infradiaphragmatic; intra and suprasellar, infra and supradiaphragmatic; parachiasmatic, extraventricular; intra- and extraventricular; paraventricular with respect to their location relative to the third ventricle; and purely intraventricular (13, 32). Samii and Tatagiba graded craniopharyngiomas into five types based on the extension of the tumor. Grade I tumors were intrasellar or infradiaphragmatic; grade II tumors were occupying the cistern with/without an intrasellar component; grade III tumors were in the lower half of the ventricle; grade IV tumors were in the upper half of the ventricle; and, grade V tumors were reaching the septum pellucidum or the lateral ventricles (13, 33). Kassam et al. classified craniopharyngiomas after the advent of the endonasal endoscopic route, in terms of their relation to the pituitary stalk, into the preinfundibular, transinfundibular, and retroinfundibular types with a separate isolated intraventricular (type IV) variety, defined as being unsuitable for this approach (13, 34).

However, it was Pascual et al. who described the intricate relationship of the IVCrs relative to the third ventricular floor. The lesions were classified into: the suprasellar tumor pushing the intact third ventricular floor upwards (*pseudo-intraventricular*); suprasellar mass breaking through the third ventricle floor and invading the third ventricle cavity (*secondarily IVC*); intraventricular mass within the third ventricle cavity and floor, the latter being replaced by tumor (*non-strictly IVC or infundibulo-tuberal craniopharyngiomas*); and intraventricular mass completely located within the third ventricle cavity and with the intact floor lying below its inferior surface (*strictly IVC*) (13, 25). We believe that such a topographical classification is necessary to help in choosing the appropriate surgical approach.

IVCrs, though rare, have been reported to occur predominantly in adults (5, 8, 11, 12, 15, 35). The oft cited reason for this predominant occurrence in adult patients is the slow growth of these tumors along with their location in the third ventricle lumen, whereby the symptom onset may be delayed till infiltration into the walls of the ventricle or obstructive hydrocephalus occurs (8, 15). The clinical presentation of IVCrs has been predominantly that of raised intracranial pressure (headache, nausea, vomiting, and papilloedema). In older patients, clinical manifestations of normal-pressure hydrocephalus (cognitive disturbances, gait imbalance, and urinary incontinence) may occur. In our series, we had a mix of pediatric (eight patients) and adult cases (17 patients).

The absence or paucity of the effects of local compression on the optic apparatus or the pituitary stalk/gland (visual symptoms or endocrinological disturbances) is noted in IVCrs (5, 6, 8,

10, 14, 15, 19, 25, 35, 36). In our series, visual symptoms on presentation were seen in 12/25 (48%) of patients. In two of our patients, homonymous hemianopia was observed, which was, likely due to the pressure effect on the optic tract. The two patients who showed bitemporal hemianopia, perhaps manifested this sign due to the bulging of the chiasmatic recess of the third ventricle leading to chiasmatic compression. In some of the other series as well (Yu et al. and Pan et al.) visual deficits were noted in 10/24 and 8/17 patients, respectively (2, 12). Preoperative hypopituitarism was noted in 11 (44%) of our patients, whereas in the series by Yu et al. it was seen in 8/24 (33%) of patients (12). This could be explained by the pressure effect of the tumor on the pituitary stalk or the hypothalamus.

Diabetes insipidus, behavioral changes, autonomic nervous system disturbances such as disturbances in sleep rhythm, appetite, body core temperature, and disturbances in memory, may also be observed (due to hypothalamic dysfunction as a result of the tumor invasion into the lateral wall or floor of the third ventricle) (3, 37–39). Cognitive or psychological disturbances can be due to primary hypothalamic involvement by the tumor, (40) hydrocephalus, or forniceal involvement due to pressure. In our series, we observed memory disturbances, in 6/25 (24%) patients.

The integrity of the third ventricular floor has long been recognized as an important radiologic criterion which helps to differentiate between a purely IVCr and one that is primarily suprasellar but with an intraventricular extension (41). Migliore et al. described the other commonly accepted radiologic criteria for purely IVCrs: a patent suprasellar cistern, an intact pituitary stalk, and the absence of sellar abnormalities (8, 16). Pascual et al. proposed that two important signs can significantly correlate with the topographical type of craniopharyngioma-third ventricle relationship. The first of these radiological signs was the identification of the mamillary bodies (MBs) and measurement of the mamillary body angle (MBA, the angle subtended between the intersection of one plane tangential to the base of one of the MBs and the plane tangential to the fourth ventricular floor) on preoperative midsagittal MRI images; and the second sign was the relative position of the hypothalamus with respect to the tumor on coronal preoperative MRI images (42). Chiasmal distortion has been evaluated and found to be a prominent feature that may help in differentiating varieties of IVCrs. It has been found to be stretched upward in *pseudo-intraventricular* tumors, stretched forward in *secondarily IVCs*, compressed forward in *non-strictly IVCs*, and compressed downward in *strictly IVCs* (18, 42, 43). Prieto et al. suggested six characteristics of strictly IVCrs based on the conventional T1 and T2-weighted MR images: a typical rounded shape; the downward deviation of the optic chiasm; a well-observed pituitary stalk; a free chiasmatic cistern; an MBA between 30° and 60° (**Figure 7**); and the hypothalamus being situated below the lower-third of the tumor (3, 43). These lesions have been described as being predominantly solid tumors in some reports (3, 19) and calcifications are only rarely reported in IVCrs (5, 6, 8, 15). In our series of 25 patients, however, 60% of tumors were predominantly cystic in nature. This could be because most series report cases in adults, whereas our series represents a good mix of children (eight patients) and adults (17 patients).

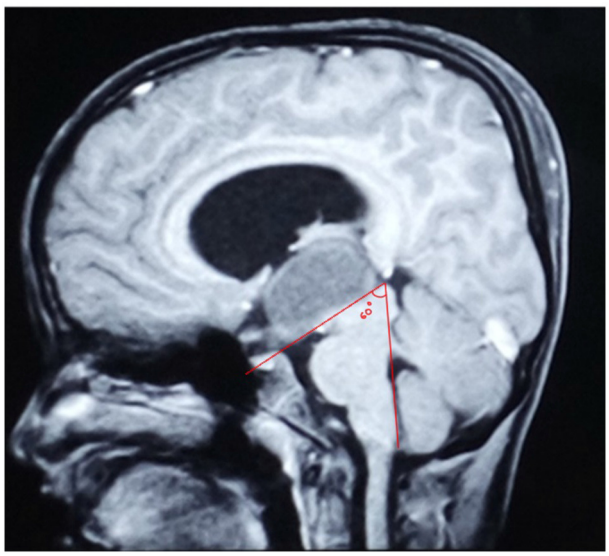

FIGURE 7 | Mid-sagittal MRI image of an 8-year-old boy with a purely intraventricular craniopharyngioma showing the Mamillary Body Angle being 60 degrees.

The differential diagnoses of IVCs includes other lesions of the third ventricle such as colloid cysts, ependymoma, choroid plexus papilloma, hypothalamic glioma, meningioma, germinoma, and lymphoma (3, 5, 8, 10, 15, 19, 23).

On histopathology, purely IVCrs have been classically reported to be of the squamous papillary variety, lacking calcification (3, 10, 12, 23, 26, 27); any associated calcification is in the form of microcalcifications (26). However, Davies et al. Pascual et al. and Yu et al. have found an even distribution between the adamantinomatous and papillary histological varieties of these tumors (6, 12, 25).

The indications for surgical treatment of IVCrs include: a. the need for a tissue diagnosis; and b. the relief of preoperative symptoms with the goal of maximal safe decompression of the lesion. The need for further adjuvant therapy (brachytherapy or radiotherapy, as the case may be) can be decided depending upon the clinical status of the patient and the extent of residual lesion, either in the immediate postoperative period, or on periodic follow-up visits. Stereotactic radiation utilizing gamma knife radiosurgery can also be considered for residual or recurrent cases (3). Proton beam therapy has also shown a great potential (44, 45).

The risks of surgical intervention in the region of the third ventricle poses challenges because of the complexity and critical location of the surrounding structures including the hypothalamus, infundibulum, optic pathway, limbic system, adjacent vascular structures, and fornix (5, 46). Often, the tumor cannot be excised completely, and subtotal excision followed by radiotherapy has been the treatment of choice (6).

Classical approaches used for primary intraventricular tumors have all been described for the management of

these lesions (23). These can be broadly divided into the transventricular approaches from the roof of the ventricle, and the lamina terminalis approaches along the floor of the third ventricle. The lamina terminalis corridor can be approached *via* a sub-frontal/anterior interhemispheric route or a pterional trans-sylvian approach. The transventricular corridor (through the lateral ventricle) can be divided into the transcortical–transventricular–transforaminal approach and the interhemispheric–transcallosal–transventricular approach. From the lateral ventricle, entry into the third ventricle can be *via* the transforaminal, subchoroidal, or interforniceal routes (4). The use of neuronavigation as an adjunct, can enhance surgical safety and results (3). Endoscopic or assisted approaches have added a new dimension to the surgical excision of these lesions.

The trans-lamina terminalis approach was first described by (47) in 1936 for the treatment of tumor-related hydrocephalus (24). The lamina terminalis is accessible *via* an anterior interhemispheric approach or a sub-frontal corridor or *via* a more lateral corridor through a pterional craniotomy (4, 9, 18, 24, 48). During the pterional (fronto-temporal) approach, due to the angulation of the surgical trajectory, it may be difficult to visualize the posterior-most region of the third ventricle. Moreover, tumors that are adherent to the lateral wall or floor of the third ventricle may be difficult to excise via this corridor. According to Prieto et al. the strictly intraventricular topography of craniopharyngiomas is associated with a moderate level of severity of adherence (49). The anterior interhemispheric approach on the other hand provides a more direct trajectory and a view of the entire third ventricle via the lamina terminalis. It helps in visualizing the third ventricle posteriorly right up to the aqueduct, and in avoiding hypothalamic injury (2, 5). The lamina terminalis approach was essentially described for retrochiasmal tumors of the extra- as well as intraventricular variety situated predominantly in the midline (50). It is ideal for tumors located predominantly in the inferior part of the third ventricle. It is, however, not suitable for large lesions, for which a transventricular approach is more appropriate (4, 5, 9, 12, 16, 51, 52). The risks associated with the translamina terminalis approach include a retraction injury or perforator damage involving the optic pathway, columns of fornix, supraoptic nuclei, organum vasculosum, and tuber cinereum (5, 9, 53).

Tumors with extensions into the lateral ventricles or those projecting through the foramen of Monro should be considered for an interhemispheric–transcallosal–transventricular approach, or a transcortical–transventricular approach (4, 48). When the lateral ventricle is dilated and the foramen of Monro is enlarged, a natural corridor opens for access to the third ventricular craniopharyngioma. With the transcortical–transventricular approach, the tumor can be dissected from the walls of the third ventricle posteriorly and laterally. A limitation to effectively visualize and dissect the antero-superior aspects and the parts of the lesion adherent to the third ventricular wall ipsilateral to the side of surgical approach arises if the foramen of Monro is not enlarged. In this scenario, a neuroendoscope may help visualize this part of the tumor, and facilitate its excision (54). The other advantages in the use of a neuroendoscope include the confirmation of hemostasis at the end of surgery and the determination of extent of resection on the operating table itself, prior to the performance of a postoperative imaging study. As compared with the transcortical–transventricular–transforaminal route, the interhemispheric–transcallosal–transventricular route may be associated with less tissue damage (and therefore, oedema) and a lower incidence of seizures (4, 5). The interhemispheric–transcallosal approach is advantageous because of the minimal brain retraction and limited division of the corpus callosum needed (5, 16, 28).

Endoscopic fenestration/marsupialisation of cystic craniopharyngiomas in the third ventricle is often done, especially for patients presenting with acutely raised intracranial pressure. The part of the cyst wall emerging at the foramen of Monro, as well as its floor blending with the third ventricular floor, may be fenestrated to gain access to the interpeduncular cistern. This "triple fenestration" (twice of the cyst wall and once of the third ventricular floor) not only helps in decompression of the cyst contents but also in relieving the coexisting hydrocephalus due to the simultaneous performance of the third ventriculostomy (**Figure 8**). This initial endoscopic treatment can stabilize the neurological condition of the patient and makes the brain less tense for a more invasive microsurgical procedure (55–58). Though a few reports of chemical meningitis are known to occur, it is not a common occurrence (58, 59). An Ommaya reservoir may be placed (60, 61), and instillation of chemotherapy (interferon-alpha) into the cyst may be undertaken for local disease control, if considered appropriate in young children (62, 63). Proponents of this type of therapy favor it, as surgical intervention (either by a trans-cranial or an endonasal trans-sphenoidal approach), has been shown to have a higher rate of postoperative endocrinological disturbances than minimally invasive techniques such as the Ommaya reservoir insertion and cyst aspiration/intracystic therapy (64).

The traditional trans-sphenoidal route has been restricted to intrasellar subdiaphragmatic tumors that extend upwards from an enlarged sella or only partially involve the anteroinferior portion of the third ventricle (as per Grades I and II of Samii's classification) (65). The extended endonasal trans-sphenoidal corridor (extended endonasal approach or EEA) has changed this traditional notion. The latter approach is useful in the management of primarily suprasellar lesions that have an intraventricular extension, especially if the chiasma–pituitary window is not narrow (48, 66–69). The position of the optic chiasm is considered the most important factor in approaching the ventricle via the endonasal route. An anteriorly placed prefixed chiasm provides a good window; however, when this corridor is narrow, techniques such as "pituitary transposition" may help in providing space for the surgical corridor to the subarachnoid cisterns above the optic apparatus and the third ventricle (70). The surgeon must approach the tumor working alternatively from both sides of the stalk. In this manner, these tumors, which often do not cause sellar enlargement, can be successfully removed (65). The benefits of this approach include direct access to ventral midline structures with only minimal handling and/or manipulation of the adjacent neurovascular structures. The major drawback is the lack of a natural corridor

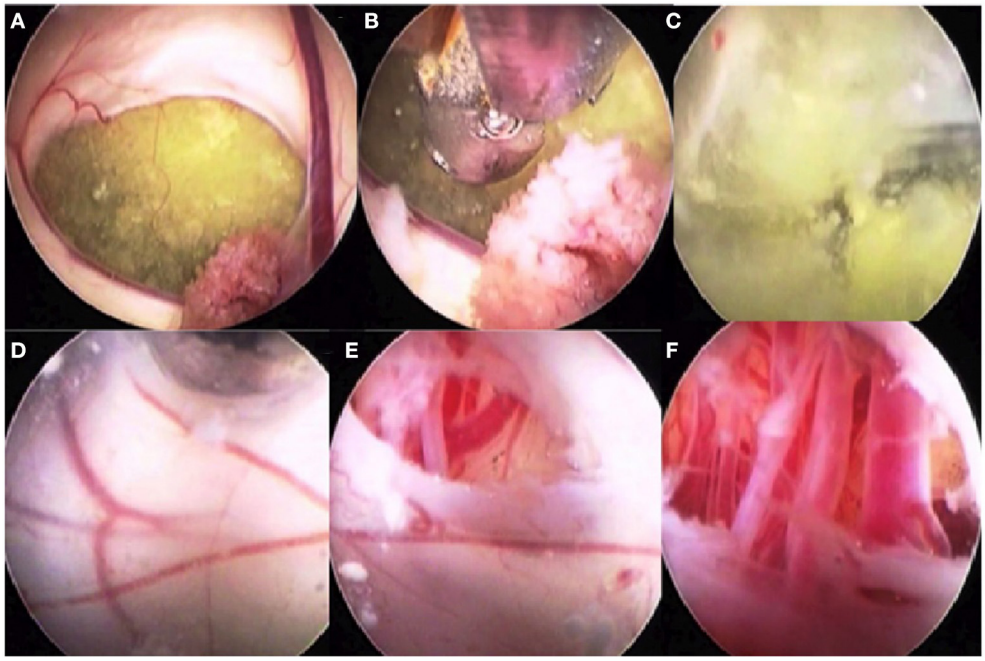

FIGURE 8 | Intraoperative images of a patient with a cystic intraventricular craniopharyngioma undergoing endoscopic cyst fenestration and third ventriculostomy. **(A)** Intra-third ventricular craniopharyngioma cyst seen through foramen of Monro. Choroid plexus is also seen. **(B)** The cyst is being fenestrated using an endoscope through the frontal, transcortical, transforaminal approach. **(C)** The machinery oil fluid of the craniopharyngioma cyst is well seen. **(D)** The inner wall of the craniopharyngioma cyst blended with the third ventricular ependymal floor is seen after drainage of the cyst contents. The cyst wall along with the third ventricular floor is being fenestrated. **(E)** The arterial blood vessels in the interpeduncular cistern are visible. **(F)** The endoscope tip is taken through the inferior cyst wall and the ventricular ependyma to see the blood vessels of the interpeduncular cistern.

in the absence of a suprasellar component of the tumor, and the significant risk of a postoperative CSF leak and its consequences (53, 71).

Perhaps the most important utility of all the classification systems discussed in the context of IVCs, lies in the prediction of the relationship of the third ventricle margins to the tumor (25). In this respect, the classification system proposed by Pascual et al. seems to be the most useful one in planning of surgical approach as it is dependent upon tumor topography and its relationship to the third ventricle. Nine (36%) patients in the current series had adherence of the tumor to the walls of the third ventricle, hence near-total excision was performed to preserve the ventricular walls. Though one can transgress the floor of the third ventricle, as splaying of the floor occurs in retrochiasmal tumors extending into the ventricle (*secondarily IVCr*); in *purely IVCrs,* it is essential that integrity of the third ventricle floor is maintained as there is no splaying of the hypothalamus (48). The exception to the rule may be an extremely thinned-out floor in a cystic tumor where an endoscopic cyst fenestration/removal may be complemented by a third ventriculostomy, as was done in two of our patients. This may rationalize the occasional use of endoscopic endonasal route for purely IVCr (4).

The concept of "maximum safe resection," traditionally described in neurosurgery for the management of gliomas, has now been adopted in the management of craniopharyngiomas as well, which we know are benign tumors; especially so in children, who have a longer life expectancy and in whom the consequences of hypothalamic dysfunction (and postoperative hormonal disturbances) can significantly impair the quality of life. Most experts nowadays consider subtotal resection to be an acceptable surgical outcome (with the indispensable tool of adjuvant therapy in our armamentarium), provided that most of the tumor is removed, just short of its hypothalamic component or that which is adhered to critical neurovascular structures (72).

Hypothalamic syndrome is an often-described clinical feature in literature, for IVCrs. Children and adolescents usually develop growth failure and disorders of puberty (which may be delayed or precocious). Adults present with cognitive disturbances, disturbances of sleep and appetite, and hormonal disturbances (73). In our series of 25 patients with purely IVCr, we observed preoperative hypothalamic dysfunction in three patients and new-onset postoperative hypothalamic dysfunction in one patient. A total of 4/25 (16%) of our patients with IVCrs, had the hypothalamic syndrome.

It is imperative to pay careful attention to the postoperative fluid balance and body temperature charts as the patients may develop diabetes insipidus and disturbances of body temperature regulation, due to hypothalamic injury (18, 24). Patients may require long-term supplementation of corticosteroid, thyroid,

and other pituitary hormones; and diencephalic insufficiency (due to damage to hypothalamic nuclei) may even occur in a delayed fashion even months or years after surgery (18, 24). In our series, two patients (8%) developed permanent diabetes insipidus and five patients (20%) developed transient diabetes insipidus, after surgery.

Adamson et al. have shown that there is a rare chance of recurrence of the squamous papillary variety after complete microsurgical resection. This is because a clear demarcation is usually present between the tumor and the adjacent brain (23, 26, 74). Maira et al. and Pierre-Kahn et al. have shown that a worse postoperative outcome is obtained where there is a disappearance of the third ventricular floor (24, 25, 75). Anatomic preservation of the third ventricular floor and walls and of the infundibulum is truly of significant importance for a good postoperative outcome (2). A good postoperative visual outcome is also generally reported (5, 6).

CONCLUSION

IVCrs present predominantly with symptoms of raised intracranial pressure and hydrocephalus. A careful study of the preoperative imaging is necessary to identify them and decide the appropriate surgical approach. The relationship of the tumor to the third ventricle walls and floor, as well as the presence or absence of infiltration of the tumor in the hypothalamus, are important factors in deciding the surgical strategy. Serial clinical and radiological follow-up, with appropriate adjuvant therapy, when necessary, are essential in the management of these patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Ethical review and approval was not required for this study on human participants in accordance with local legislation and institutional requirements since this was a retrospective study and there was no deviation from standard of care that was provided to the patients. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

KS wrote the manuscript primarily and also contributed to data collection. AK and BT contributed to data collection and formation of the results and assisting with writing the manuscript. VK and CM were part of the surgical team and have contributed with the technical discussion. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.755784/full#supplementary-material

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ORIGINAL RESEARCH
published: 17 November 2021
doi: 10.3389/fneur.2021.754349

Clinical Analysis of Risk Factors of Postoperative Psychiatric Disorders in Patients With Adult Craniopharyngioma

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Edited by:
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Reviewed by:
Hermann Lothar Mueller,
Klinikum Oldenburg, Germany
Yubo Wang,
First Affiliated Hospital of Jilin University, China

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Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Neurology

Received: 06 August 2021
Accepted: 13 September 2021
Published: 17 November 2021

Citation:
Zhao R, Lu P, Fan Y, Li C, Liu C, Zhao P, Cao L, Gao H and Gui S (2021) Clinical Analysis of Risk Factors of Postoperative Psychiatric Disorders in Patients With Adult Craniopharyngioma. Front. Neurol. 12:754349. doi: 10.3389/fneur.2021.754349

Objective: To analyze the risk factors relative to postoperative psychiatric disorders in adult patients with craniopharyngioma.

Methods: A retrospective case-control study design was used in this study. The Neuropsychiatric Inventory–Questionnaire (NPI-Q) assessment tool was used to assess psychiatric disorders in postoperative patients with craniopharyngioma at Beijing Tiantan Hospital from January 2018 to December 2020. The relationship between the psychiatric disorders and basic demographic data as well as several risk factors, such as the tumor characteristics (tumor location, tumor size, pathological finding of the tumor, etc.) and treatment-related factors (the extent of the resection), were analyzed.

Results: A total of 173 patients were included in this study. The prevalence of psychiatric disorders was 14.5% among adult craniopharyngioma patients. Irritability represented the most common type of psychological symptom (64%, $n = 16$), followed by agitation (36%, $n = 9$), and delusions (28%, $n = 7$). The risk factors relative to postoperative psychiatric disorders that were identified were a tumor volume larger than 7 cm^3 (HR = 3.292, $P = 0.042$), tumor location ($P = 0.003$), hypothalamic invasion (HR = 9.766, $P = 0.036$), and gross-total resection (HR = 0.085, $P = 0.042$).

Conclusion: Neurocognitive assessment and intervention before and after surgery are important in patients with larger tumors, invading the third ventricle, and tumors with hypothalamic invasion. Prediction of these risk factors is essential for the treatment.

Keywords: craniopharyngioma, psychiatric disorders, risk factors, hypothalamic invasion, tumor location

INTRODUCTION

Craniopharyngiomas are rare, benign, and slow-growing tumors of the sellar and/or parasellar region. Due to their close anatomical proximity to the hypothalamus, the pituitary, and the optic nerves, craniopharyngiomas are frequently associated with visual, endocrine, and neurobehavioral deficits which may seriously limit functional capacity

and quality of life (1, 2). Within the past three decades, advances in treatment strategies and techniques have led to decreasing mortality and less severe morbidity (3). Improved outcomes have encouraged researchers to increasingly focus attention on issues related to neurobehavioral, social, and emotional dysfunctions and quality of life, including cognitive functions (4–6).

There have been several researches focusing on pediatric patients psychiatric, cognitive, and behavioral outcomes following craniopharyngioma and pituitary adenoma surgery (7–10). Due to the different diagnostic criteria and the selection of specific populations, the incidence of postoperative psychiatric disorders in patients with craniopharyngioma is between 24 and 75% (6, 9). Following surgical intervention, the psychiatric disorders may manifest Korsakoff-like memory deficits, behaviors/personality changes, impaired emotional control, cognitive impairment, mood alteration, and psychotic symptoms (11, 12).

Previous studies have identified several risk factors of psychiatric disorders in patients with craniopharyngioma. Giese et al. (6) described a cohort of 36 patients with craniopharyngiomas; the risk factors that were found include: a tumor volume larger than 9 cm^3, tumor extension toward/into the third ventricle or the brainstem, and resection using a bifrontal translamina terminalis or left-sided approach. A systematic review by Pascual confirms that: the histological type of the tumor, age, and postoperative treatment with chemotherapy and radiotherapy are also potentially associated with psychological deficits (13).

Psychiatric disorders are associated with the patient's reduction of quality of life, impairment in social relationships, longer rehabilitation time, poor adherence to treatment, and abnormal illness behavior (14). However, the current research is mainly focused on pediatric patients, and there is almost no research on psychiatric disorders in adult patients with craniopharyngiomas through the endoscopic endonasal approach. Therefore, in the current study, we systematically assessed the postoperative psychiatric disorders and risk factors of patients with adult craniopharyngioma.

PATIENTS AND METHODS

This study includes a total of 173 patients who underwent craniopharyngioma surgery between January 2018 and December 2020. The inclusion criteria were as follows: a histological diagnosis of craniopharyngioma, medically fit to complete the assessment, include adult cases (defined as age $\geq$14 years old at time of craniopharyngioma diagnosis and treatment), and surgical approaches were endonasal approach. The exclusion criteria were as follows: a history of psychiatric disorders before the diagnosis of brain tumor and a history of head trauma. This study was approved by the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University. Informed consent was obtained from all participants or their legal guardians.

Data Collection

Complete medical records were retrospectively reviewed. Patient demographic and images and details of the surgery were recorded. We recorded basic demographic information regarding age, sex, course, pathological type (adamantinomatous and squamous papillary), tumor character (calcification or not, solid or cystic), primary or recurrent surgery, tumor location (All craniopharyngiomas were simply classified into the following four subtypes based on the anatomical location for surgical approach selection: intrasellar type, intra-suprasellar type, suprasellar type, and intra-third ventricle type) (15), tumor size, hypothalamic invasion [Puget's grading system is used as the standard for hypothalamic invasion. Specifically, grade 0 (no hypothalamic damage), grade 1 (negligible hypothalamic damage or residual tumor displacing the hypothalamus), or grade 2 (significant hypothalamic damage with the floor of the third ventricle not identifiable)] (16), and extent of resection. The extent of tumor resection was confirmed by intraoperative findings and postoperative MR images acquired within 48 h after surgery. Gross-total resection (GTR) was deemed as the absence of residual tumor by these criteria, and cases in which there was any small residual tumor were classified as subtotal resection (STR).

Psychiatric Disorders

The psychiatric disorders were assessed with the Neuropsychiatric Inventory–Questionnaire (NPI-Q), a

TABLE 1 | Characteristics of the patients.

Variables		*N*	%
Age (y)	42.03 ± 13.70		
Course of disease (d)	5 (2, 12)		
Gender	Male	88	50.9
	Female	85	49.1
Pathological type	Adamantinomatous	131	75.7
	Squamous papillary	42	24.3
Calcification	No	64	37.0
	Yes	109	63.0
Tumor character	Solid	39	22.5
	Cystic	61	35.3
	Cystic and solid	73	42.2
Recurrent tumor	No	129	74.6
	Yes	44	25.4
Tumor location	Intrasellar type	5	2.9
	Suprasellar type	111	64.2
	Intra-suprasellar type	40	23.1
	Intra-third ventricle type	17	9.8
Tumor size	$\leq$7 cm^3	96	55.5
	>7 cm^3	77	44.5
Hypothalamic invasion	No	63	36.4
	Yes	110	63.6
Tumor resection	Gross-total resection	150	86.7
	Subtotal resection	23	13.3
Psychiatric disorders	No	148	85.5
	Yes	25	14.5

retrospective questionnaire that measures the presence of a number of neuropsychiatric symptoms (0 = present; 1 = not present) and their severity (1 = mild; 2 = moderate; 3 = severe). It includes the items hallucinations, delusions, agitation, depression, anxiety, elation, apathy, disinhibition, irritability, motor disturbance, night-time behavior, and appetite. The NPI-Q has been accepted as a brief, reliable, informal-based assessment of neuropsychiatric symptoms assessment.

Follow-Ups

Regular follow-ups were performed at 6 months postoperatively by outpatient, rehospitalization, or a telephone call.

Statistical Analysis

Statistical analyses were performed using SPSS software 23.0. Univariate descriptive statistics were applied to describe the sociodemographic characteristics of study participants, as well as their tumor characteristics and treatment-related factors. For the normal distribution and equal variances data, the statistical analyses of categorical variables between two groups [the psychiatric group (cohort with craniopharyngioma with psychiatric symptoms) and non-psychiatric group (cohort with craniopharyngioma without psychiatric symptoms)] were carried out using *t*-test. A chi-square test and Fisher's exact test were used to analyze relationships or compare proportions. The correlation of risk factors and psychiatric disorders was evaluated by binary logistic regression. Statistical significance was defined as a $p < 0.05$.

RESULTS

Patient Characteristics

The average age of the patients in this study was 42.03 ± 13.70 years. Of all 173 patients, 88 (50.9%) were male and 85 (49.1%) were female. In histopathological analysis, 131 (75.7%)

TABLE 3 | Psychiatric disorders of the patients.

Variables	Mild	Moderate	Severe	Total
Delusions	3	1	3	7
Hallucinations	2	3	1	6
Agitation	4	2	3	9
Depression	2	2	1	5
Anxiety	1	2	2	5
Elation	2	2	0	4
Apathy	1	2	0	3
Disinhibition	0	0	1	1
Irritability	3	5	8	16
Motor disturbance	2	1	0	3
Night-time behavior	1	1	0	2
Appetite	0	1	1	2

TABLE 2 | Comparison of the two groups regarding the psychiatric disorders.

Variables		No	Yes	t/χ2	*P*
Age (y)		41.59 ± 13.93	44.60 ± 12.21	−1.015	0.312
Course of disease (d)		4.00 (2.00, 12.00)	6.00 (3.00, 10.50)		0.278
Gender	Male	77 (52.0)	11 (44.0)	0.551	0.458
	Female	71 (48.0)	14 (56.0)		
Pathological type	Adamantinomatous	113 (76.4)	18 (72.0)	0.220	0.639
	Squamous papillary	35 (23.6)	7 (28.0)		
Calcification	No	56 (37.8)	8 (32.0)	0.157	0.692
	Yes	92 (62.2)	17 (68.0)		
Tumor character	Solid	34 (23.0)	5 (20.0)	0.405	0.817
	Cystic	53 (35.8)	8 (32.0)		
	Cystic and solid	61 (41.2)	12 (48.0)		
Recurrent tumor	No	109 (73.6)	20 (80.0)	0.455	0.500
	Yes	39 (26.4)	5 (20.0)		
Tumor location	Intrasellar type	4 (2.7)	1 (4.0)	14.399	0.002
	Suprasellar type	97 (65.5)	14 (56.0)		
	Intra-suprasellar	38 (25.7)	2 (8.0)		
	Intra-third ventricle	9 (6.1)	8 (32.0)		
Tumor size	≤7 cm^3	89 (60.1)	7 (28.0)	8.942	0.003
	>7 cm^3	59 (39.9)	18 (72.0)		
Hypothalamic invasion	No	61 (41.2)	2 (8.0)	8.807	0.003
	Yes	87 (58.8)	23 (92.0)		
Tumor resection	Gross-total resection	126 (85.1)	24 (96.0)	1.349	0.245
	Subtotal resection	22 (14.9)	1 (4.0)		

TABLE 4 | Factors associated with psychiatric disorders—Univariate analysis.

Variables		HR	95% CI	*P*
Age (y)		1.017	0.985∼1.050	0.311
Course of disease (d)		0.994	0.956 1.033	0.757
Gender	Male	1		
	Female	1.380	0.588∼3.239	0.459
Pathological type	Adamantinomatous	1		
	Squamous papillary	1.256	0.485∼3.252	0.639
Recurrent tumor	No	1		
	Yes	0.699	0.245∼1.989	0.502
Tumor size	≤7 cm^3	1		
	>7 cm^3	3.879	1.526 9.861	**0.004**
Calcification	No	1		
	Yes	1.293	0.524∼3.193	0.577
Tumor character	Solid	1		
	Cystic	1.026	0.310∼3.399	0.966
	Cystic and solid	1.338	0.435∼4.118	0.612
Tumor resection	Gross-total resection	1		
	Subtotal resection	0.239	0.031∼1.856	0.171
Hypothalamic invasion	No	1		
	Yes	8.063	1.833∼35.475	**0.006**
Tumor location	Intrasellar type	1		**0.003**
	Suprasellar type	0.577	0.060∼0.5543	0.634
	Intra-suprasellar type	0.211	0.015∼2.869	0.242
	Intra-third ventricle type	3.556	0.326 38.777	0.298

patients showed an adamantinomatous craniopharyngioma and 42 (24.3%) a papillary craniopharyngioma. Calcification occurred in 109 (63.0%) cases. Thirty-nine (22.5%) cases were entirely solid; 61 (35.3%) cases were predominately cystic, and 73 (42.2%) cases were mixed cystic/solid. A total of 74.6% of the surgeries were primary, and 25.4% were repeat surgery for tumor recurrence. Based on preoperative MRI and CT scans, all tumors were classified into four subtypes: intrasellar type (type I, 5 cases), intra-suprasellar type (type II, 40 cases), suprasellar type (type III, 111 cases), and intra-third ventricle type (type IV, 17 cases). Tumor sizes were quantified by volumetric MRI measurements; small tumors had a volume of <7 cm^3 ($n = 96$), and large tumors a volume more than 7 cm^3 ($n = 77$). Hypothalamic invasion was found in 110 cases. The extent of tumor resection was divided into GTR and STR. GTR was achieved in 150 (86.7%) of the patients as confirmed by postoperative MRI (**Table 1**).

Patients were divided into two groups: the psychiatric group (cohort with craniopharyngioma with psychiatric symptoms) and non-psychiatric group (cohort with craniopharyngioma without psychiatric symptoms). The psychiatric disorders rate of the group with tumor extension toward/into the third ventricle was higher than that of the group with the tumor in other locations ($\chi^2 = 14.399$, $P = 0.002$). In addition, the tumor size was classified as a categorized variable; the psychiatric rate increased significantly as the tumor in larger size 7.3% (≤7 cm^3 group) vs. 23.4% (>7 cm^3 group) ($\chi^2 = 8.942$, $p = 0.003$). Moreover, the psychiatric rate of the group with hypothalamic invasion was higher than that without hypothalamic invasion ($\chi^2 = 8.807$, $p = 0.003$; **Table 2**).

Psychiatric Disorders

The results of NPI-Q showed that 14.5% of the craniopharyngioma patients had at least one psychological symptom after operation. **Table 3** shows the distribution of psychiatric disorders within the 12 major categorical axes considered among the 173 patients. A total of 12 psychiatric symptoms were reported in these series. Forty percent of patients manifested symptoms corresponding to two or three psychiatric categories. The most common symptoms were irritability (64%, $n = 16$), followed by agitation (36%, $n = 9$), and delusions (28%, $n = 7$; **Table 3**).

Neuropsychological Outcome

We tracked down the recovery of psychiatric symptoms in patients with craniopharyngioma who developed a psychiatric disorder after surgery. After a 6-month follow-up, we found that in all of the patients, the psychiatric disturbances significantly improved or disappeared, allowing them to resume their previous activities.

Factors Associated With Psychiatric Disorders

According to univariate analysis, the patient's age, sex, as well as several risk factors such as course, pathological

TABLE 5 | Factors associated with psychiatric disorders -Multivariate analysis.

Variables		HR	95% CI	*P*
Age (y)		1.019	0.974∼1.065	0.415
Course of disease (d)		0.995	0.947 1.045	0.835
Gender	Male	1		
	Female	2.036	0.733∼5.658	0.173
Pathological type	Adamantinomatous	1		
	Squamous papillary	2.432	0.733∼5.658	0.344
Recurrent tumor	No	1		
	Yes	0.561	0.126∼2.505	0.449
Tumor size	≤7 cm^3	1		
	>7 cm^3	3.292	1.045 10.370	**0.042**
Calcification	No	1		
	Yes	2.414	0.420∼13.877	0.323
Tumor character	Solid	1		0.758
	Cystic	0.778	0.159∼3.812	0.756
	Cystic and solid	1.260	0.296∼5.357	0.755
Tumor resection	Gross-total resection	1		
	Subtotal resection	0.085	0.008∼0.919	**0.042**
Hypothalamic invasion	No	1		
	Yes	9.766	1.163∼82.002	**0.036**
Tumor location	Intrasellar type	1		**0.005**
	Suprasellar type	0.014	0.000∼0.488	**0.018**
	Intra-suprasellar type	0.008	0.000∼0.355	**0.013**
	Intra-third ventricle type	0.089	0.002 3.512	0.197

type, tumor character, primary or repeat surgery, tumor location, tumor size, hypothalamic invasion, and extent of resection were set as independent variables and whether a psychiatric disorder occurred was set as a dependent variable. Logistic regression analysis showed that tumor location (HR 0.577, 95% CI 0.060∼0.5543, HR 0.211, 95% CI 0.015∼2.869, HR 3.556, 95% CI 0.326 38.777, $p = 0.003$), tumor size (HR 3.879, 95% CI 1.526 9.861, $p = 0.004$), and hypothalamic invasion (HR 8.063, 95% CI 1.833∼35.475, $p = 0.006$) were correlated with post-operative psychiatric disorder (**Table 4**).

According to multivariate analysis, tumor location (HR 0.014, 95%CI 0.000∼0.488, HR 0.008, 95% CI 0.000∼0.355, HR 0.089, 95% CI 0.002 3.512, $p = 0.005$), tumor size (HR 3.292, 95% CI 1.045 10.370, $p = 0.042$), hypothalamic invasion (HR 9.766, 95% CI 1.163∼82.002, $p = 0.036$), and extent of resection (HR 0.085, 95% CI 0.008∼0.919, $p = 0.042$) had a strong correlation with post-operative psychiatric disorder, whereas age, course, pathological type, tumor character, and primary or repeat surgery did not show correlation with post-operative psychiatric disorder (**Table 5**).

DISCUSSION

There are few studies on postoperative psychiatric disorders in adult patients with craniopharyngioma, and the exact mechanism is still unclear. This study provides a detailed investigation on psychiatric disorders following surgical removal of craniopharyngiomas in adult patients. Specifically, it systematically assesses risk factors and long-term psychological outcomes. Our results showed that the incidence of postoperative psychiatric disorders in patients with craniopharyngioma is 14.5%. Patients with larger size tumor, hypothalamic invasion, and GTR had more risk of psychiatric disorder. In addition, tumor location also influenced the postoperative psychiatric symptoms.

NPI-Q is a sensitive cognitive function assessment scale, which is commonly adapted by researchers. Previous studies reported a high prevalence of postoperative psychiatric disorder, with 24–75% of patients showing neuropsychological deviations in at least one test item (6). However, our study found a relatively lower incidence than the previous reports. It is possible due to the differences in surgical approaches. There have been studies comparing the outcomes and complications between endoscopic endonasal approach and craniotomy for pediatric craniopharyngioma. Results showed that: patients in the open surgical group had a 33.3% rate of developing psychological and cognitive deficits during follow-up, while it was 18.5% in the endoscopic endonasal surgery group (17). Studies have demonstrated that endoscopic endonasal surgery can achieve a comparable or superior extent of resection over craniotomy while having a significantly lower potential of cerebrovascular injury (18).

In our research, irritability is the most common type of psychological symptom (64%, $n = 16$), followed by

agitation (36%, $n = 9$) and delusions (28%, $n = 7$). This result is different from pediatric patients to some extent. Many researches have focused on the cognitive, emotional, and social behavior of children and adolescents following operations for craniopharyngioma. Children after removal of craniopharyngioma had experienced many difficulties in daily life regarding social relationships, emotion control, and learning (9). The most frequent problems in children's daily functioning included inability to control emotions, difficulties in learning, unsatisfactory peer relationships, and unattractive appearance resulting from hormonal disorders (short height and obesity). One-third of parents had problems with pathological appetite in some reports (4, 7).

In our study, tumor volume is an independent risk factor for postoperative psychiatric disorder. The psychiatric disorder rate was 23.4% in the group who had tumor volume >7 cm^3, while 7.3% in tumor volume ≤7 cm^3 ($\chi^2 = 8.942$, p = 0.003). This result is consistent with the study by Giese et al. (6). The reason may be that larger tumor volume is more aggressive to the surrounding brain tissue, which causes severe damage to the function of normal structures. Tumor location or extension in/toward the third ventricle is the risk factor for postoperative mental disorders, which are consistent with the results of previous studies (6, 13). A greater frequency of hypothalamic dysfunction has been reported for craniopharyngiomas invading the third ventricle (**Figure 1**) (19, 20).

Hypothalamic invasion is considered to be an independent risk factor in our study. The exact mechanism of psychiatric disorder is still unclear; however, hypothalamus injury is a relatively recognized reason (21). The central position of the hypothalamus around the third ventricle serves as the convergence point of numerous neural pathways connecting different brain areas. This diencephalic region hosts the headquarters of the brain circuitry involved in monitoring the continuous changes of the internal medium as well as external conditions to coordinate the appropriate neuroendocrine responses and active behaviors to restore body homeostasis and mental balance. Therefore, any lesion invades into the hypothalamic centers that participate in the integration of emotional and behavioral responses, which would cause potentially structural and functional damage, resulting in the development of numerous psychiatric disorders (13, 21–23). This mechanism may explain why the rate of psychiatric disorders in the group of patients with hypothalamic invasion was higher than that without hypothalamic invasion ($\chi^2 = 8.807, p = 0.003$) (**Figures 2**–**4**).

Multivariate logistic regression analysis showed that total tumor resection is the risk factor for the psychological disorders. The choice of optimal treatment strategies for

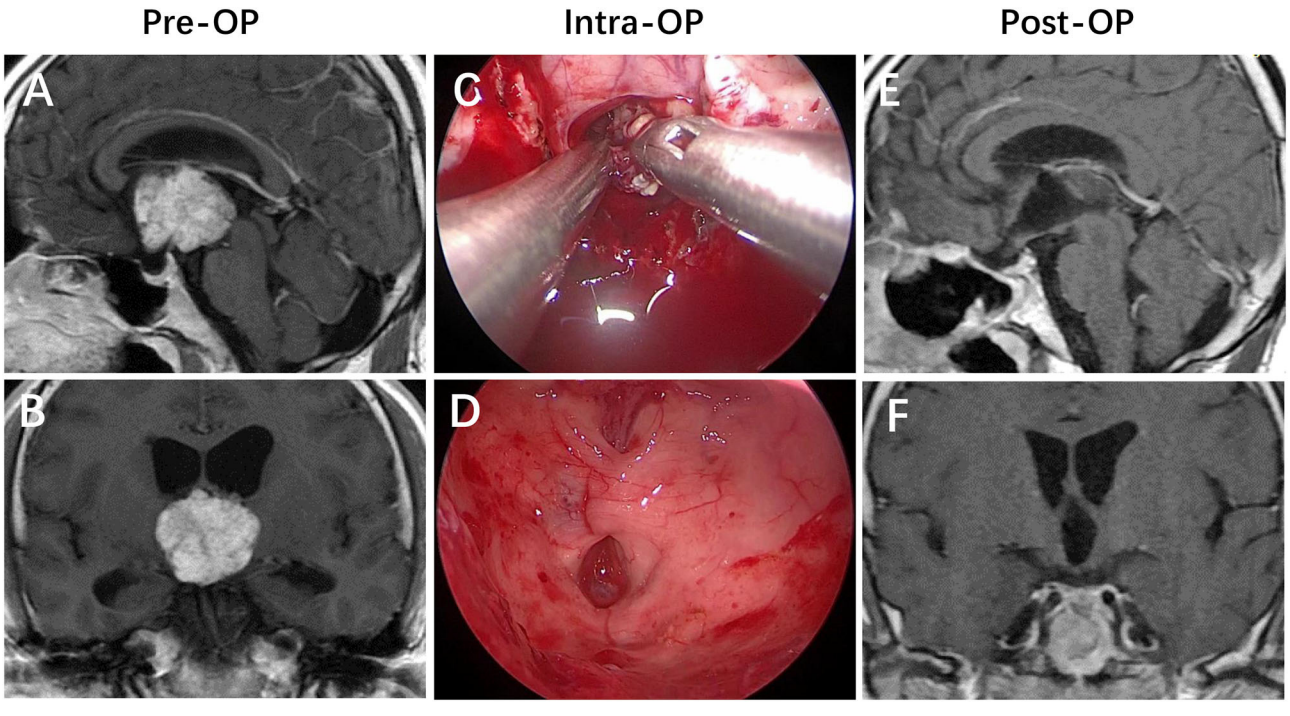

FIGURE 1 | Strictly intraventricular craniopharyngioma. **(A,B)** Preoperative enhanced MRI demonstrated a mass that is localized in the third ventricle cavity with an intact floor lying below its inferior surface. **(C,D)** Intraoperative findings revealed that the patient achieved a gross-total resection of the lesion *via* the endoscopic endonasal suprachiasmatic trans-lamina terminalis corridor. **(E,F)** Postoperative enhanced MRI revealed that the lesion was totally removed, with the posterior wall of the third ventricle preserved intactly.

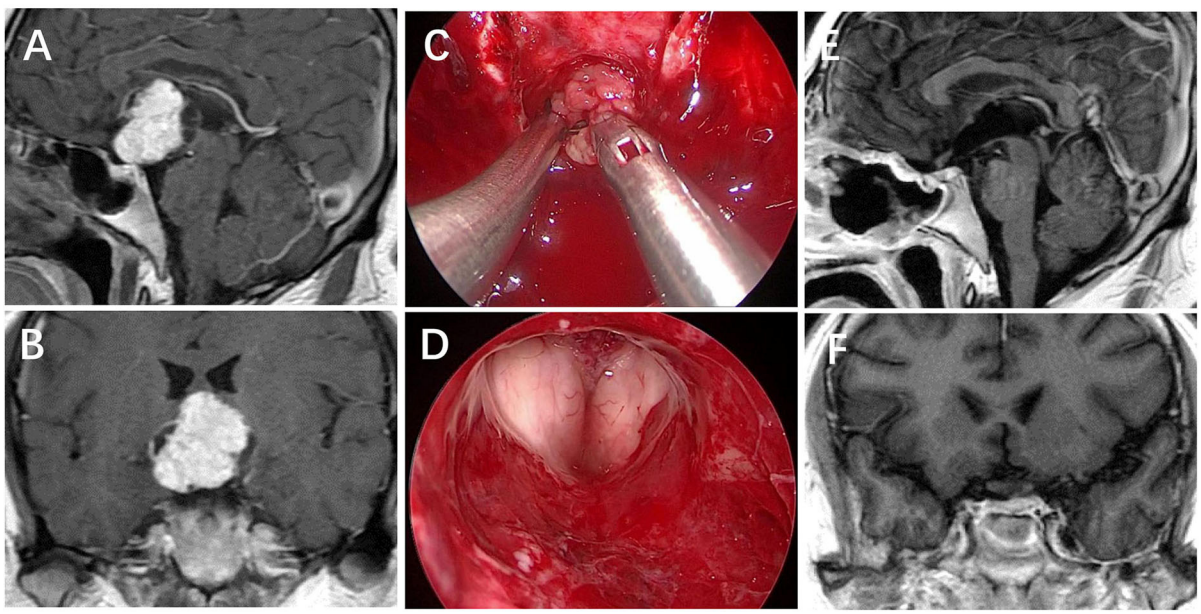

FIGURE 2 | Not strictly intraventricular craniopharyngioma. **(A,B)** Preoperative enhanced MRI demonstrated that a mass had primarily developed within the neural tissue of the third ventricle floor (TVF), progressively replacing part of the floor while expanding into the third ventricle cavity, in which expansion of the tumor has breached the TVF. **(C,D)** Intraoperative views revealed that the patient achieved a gross-total resection of the lesion *via* the endonasal endoscopic endonasal infrachiasmatic corridor. **(E,F)** Postoperative enhanced MRI revealed that the lesion was totally removed, with the posterior wall of the third ventricle and the pituitary stalk preserved intactly.

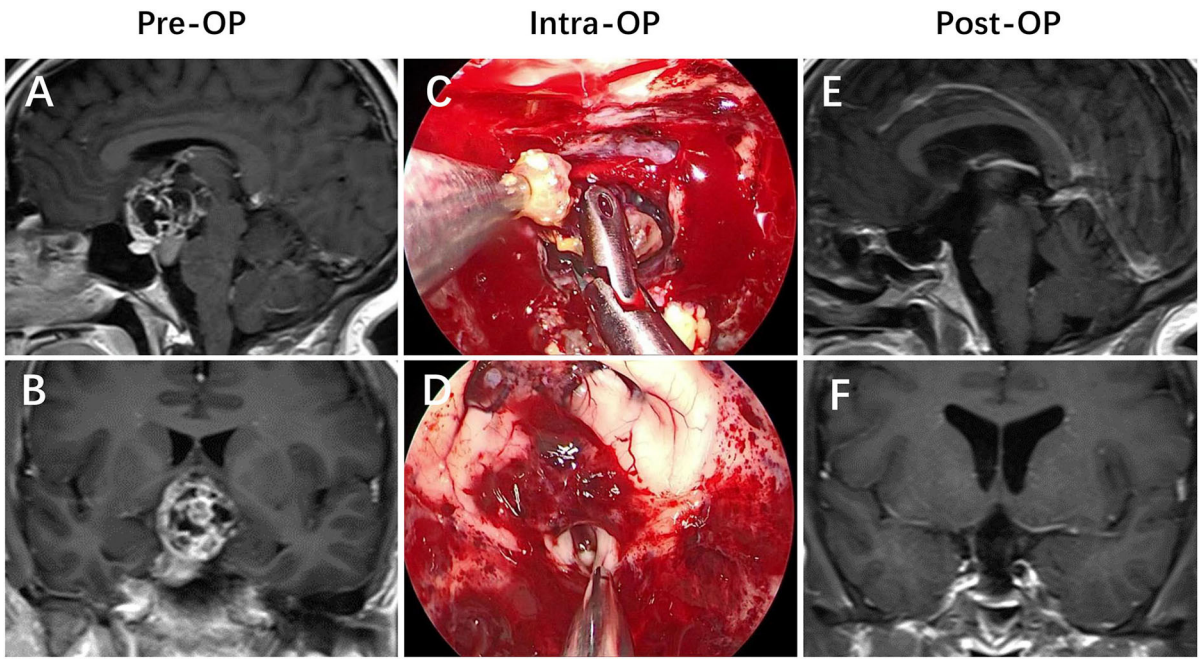

FIGURE 3 | Craniopharyngioma with hypothalamic invasion. **(A,B)** Preoperative enhanced MRI demonstrated that an extraintraventricular mass developed from the pituitary gland and/or the pituitary stalk that had invaded the third ventricle after breaking through the third ventricle floor. **(C,D)** Intraoperative views revealed that the patient achieved a gross-total resection of the lesion *via* the endonasal endoscopic endonasal infrachiasmatic corridor. **(E,F)** Postoperative enhanced MRI revealed that the lesion was totally removed, with the TVF opened.

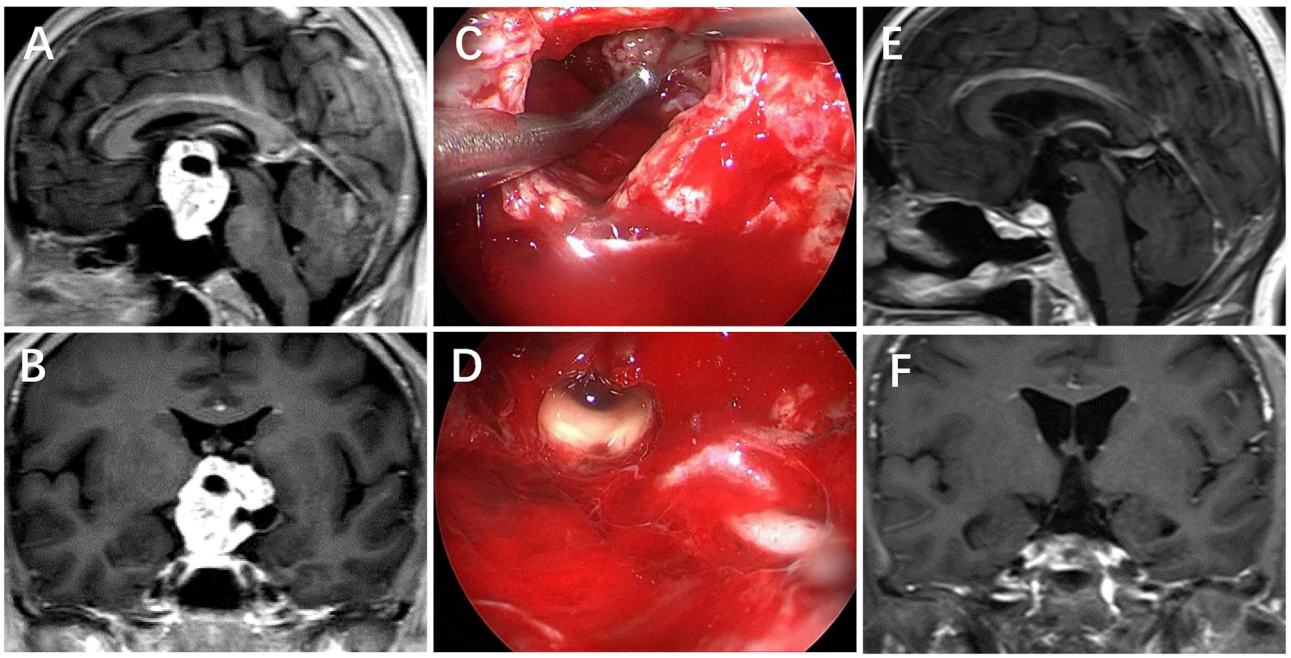

FIGURE 4 | Craniopharyngioma with a large volume. **(A,B)** Preoperative enhanced MRI demonstrated that a giant suprasellar mass developed from the pituitary stalk that pushed the TVF upward, mimicking an intraventricular position. **(C,D)** Intraoperative views revealed that the patient achieved a gross-total resection of the lesion *via* the endonasal endoscopic endonasal infrachiasmatic corridor. **(E,F)** Postoperative enhanced MRI revealed that the lesion was totally removed, with the TVF opened.

craniopharyngioma remains a controversial subject (15). Because of the local recurrence that has highly occurred after partial surgical resection, total resection is advocated by many authors. But other reports also revealed that radical surgery and irradiation can result in severe damage to the optic pathway and hypothalamic–pituitary axis, thus, decreasing the prognosis of postoperative psychological outcomes. Previous studies also have found that total tumor resection affects patients' long-term quality of life (24). Based on these reports, when selecting the best treatment strategies for patients with craniopharyngiomas, it is important for surgeons to consider not only the tumor resection extents and surgical treatment outcomes but also the functional and psychological complications or long-term quality of life of the patients.

Nursing staff and a multidisciplinary team (MDT) should take the individualized and professional care of patients with mental disorders from the following aspects. Firstly, the neurosurgeons work closely with the nursing staff to identify early enough the cognitive impairment of the patient through daily observation or testing. Secondly, endocrinologists and clinical neuropsychologists should be involved in the perioperative management of patients as soon as possible. Thirdly, it is important to create a safe, comfortable treatment environment for the patients. In addition. different nursing and communication skills should be adopted for patients with different mental disorders. For irritable patients, nursing staff should avoid verbal and behavioral stimulations to these patients. And for patients with delusions and hallucinations, even if the patient's description of certain situations is not in line with the reality, nurses should be good at listening, expressing belief, and facilitating the establishment of a good nursing relationship. Furthermore, proper restraint can ensure the safety of patients; however, improper measures to restrict the activities of patients will result in obviously rebellious psychology, such as increased restlessness, loss of dignity, fear, and other changes. Therefore, when the patient's condition improves, nurses should remove the restraints on the patients in time. Finally, moderate psychotropic drugs were used for patients with severe cognitive dysfunction.

The treatment and care for craniopharyngioma is multidisciplinary, involving the cooperation of oncological surgery, medical oncology, radiotherapy, chemotherapy as well as psycho-social support and rehabilitation and, when cancer is not treatable, palliative care (14). The management of psychological disorders also relies heavily on the decision-making process in MDT, composed of dedicated experienced neurosurgery specialists and neuropsychologists, assisted by specialists from adjoining branches. A mutual exchange of specialist opinions in such fields can reach a more satisfactory treatment strategy in accordance with the scientific community standards.

CONCLUSION

This exploratory study is a first experimental study toward the identification of factors predicting psychological disorders

after craniopharyngioma resection in adult patients in our center. The results of this study may provide the surgeon a reference to optimize the treatment plan of craniopharyngioma while maintaining a functional and psychological balance. Recommendations for assessment and intervention to psychiatric and psychosocial disorders across the trajectory of cancer are therefore considered essential in every cancer center, institute, hospital, and community service, in order to warrant the reasonable psychological outcomes and qualities of life for craniopharyngioma patients. Furthermore, our study may also provide a unique opportunity to further our understanding on the role of hypothalamus in the integration of emotional and behavioral information.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

RZ and PL: analyzed the data and drafted the manuscript for intellectual content. SG: surgery treatment, interpreted the data, and revised the manuscript for intellectual content. HG: patients management and follow-up and design and conceptualized study. LC: surgery treatment and revised the manuscript for intellectual content. PZ, CLiu, and CLi: surgery treatment and patients management and follow-up. YF: design and conceptualized study. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by the Beijing Municipal Science & Technology Commission (Z19110700660000) and Beijing Hospitals Authority Clinical Medicine Development of Special Funding Support (XMLX202108). The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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frontiers in Neurology

REVIEW
published: 02 December 2021
doi: 10.3389/fneur.2021.737743

Endocrine Disorder in Patients With Craniopharyngioma

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Craniopharyngioma is an intracranial congenital epithelial tumor growing along the pathway of the embryonic craniopharyngeal tube. The main clinical symptoms of patients with craniopharyngioma include high intracranial pressure, visual field defect, endocrine dysfunction, and hypothalamic dysfunction. At present, the preferred treatment remains the surgical treatment, but the recovery of endocrine and hypothalamic function following surgery is limited. In addition, endocrine disorders often emerge following surgery, which seriously reduces the quality of life of patients after operation. So far, research on craniopharyngioma focuses on ways to ameliorate endocrine dysfunction. This article reviews the latest research progress on pathogenesis, manifestation, significance, and treatment of endocrine disorders in patients with craniopharyngioma.

Keywords: craniopharyngioma, endocrine disorders, pituitary hormone deficiency, treatment, risk

OPEN ACCESS

Edited by:
Edward Raymond Laws, Brigham and Women's Hospital and Harvard Medical School, United States

Reviewed by:
Andrea Saladino, Carlo Besta Neurological Institute (IRCCS), Italy
Manjari Pandey, Geisinger Commonwealth School of Medicine, United States

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Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Neurology

Received: *07 July 2021*
Accepted: *13 October 2021*
Published: *02 December 2021*

Citation:
Zhou Z, Zhang S and Hu F (2021) Endocrine Disorder in Patients With Craniopharyngioma. Front. Neurol. 12:737743. doi: 10.3389/fneur.2021.737743

INTRODUCTION

Craniopharyngioma is a rare solid or mixed cystic epithelial tumor in the sellar and suprasellar region, accounting for 2–4% of intracranial tumors, which can be found in each age group (1). Patients with craniopharyngioma frequently exhibited hypothalamic–pituitary axis dysfunction, including growth hormone deficiency (GHD), adrenocortical insufficiency, central hypothyroidism, hypogonadism, precocious puberty, hyperprolactinemia, central diabetes insipidus, and hypothalamic obesity (2). In the 15 years ago, pituitary hormone deficiencies have been reported in 54–100% of patients (3, 4). Recent studies have shown that hormone deficiencies occurs in 65–92% of patients, in which childhood-onset is significantly higher than adult-onset (5–8). The current standard treatment is surgery followed by adjuvant radiation therapy (9). However, patients did not return to comparable life-quality scores as a healthy patient collective even after successful treatment (10). Pituitary hormone deficiency is an essential factor affecting long-term quality of life (11) and is associated with poor outcomes (12). Over the last decade, patients with craniopharyngioma have received increased attention concerning specific aspects of their disease, like hormonal deficiencies (10). This article reviews the latest research progress on pathogenesis, manifestation, significance, and treatment of endocrine disorders in patients with craniopharyngioma. In addition, we provide a new perspective and method for diagnosing, treating, and managing hormone deficiency in patients with craniopharyngioma.

THE PATHOGENESIS OF ENDOCRINE DISORDERS

In the nineteenth century, an increasing number of young patients exhibited unexplained physical and mental symptoms, including loss or delay of sexual maturity, progressive obesity, abnormal somnolence, and dementia-like behavioral changes. These patients were reported to have large solid cystic tumors, characterized by dilatation in the funnel and third ventricle, exceeding the

anatomically intact pituitary gland. Cushing chose the term "craniopharyngioma" to refer to these lesions (13). Recent research indicates that tumor mass effect, surgical invasion, radiotherapy, and pituitary fibrosis contribute to the development of endocrine disorders in patients with craniopharyngioma. Consequently, it is beneficial to understand the pathophysiology of endocrine disorders to develop appropriate treatment programs.

Primary Tumor

Hypothalamic dysfunction caused by the tumor space-occupying effect is a risk factor for developing endocrine disorders (14), and the damage to the hypothalamus–pituitary system caused by the tumor itself is probably permanent (15). The tumor space-occupying effect is closely related to the origin, location, and growth pattern of tumor. Based on tumor origin and the presence of an arachnoid envelope around the pituitary stalk, Pan established a QST typing system for craniopharyngioma (16). Since Q-type tumors originate below the sellar diaphragm, they are classified as epidural tumors; however, as these tumors grow, suprasellar structures are invaded; in extreme cases, the level of the floor of the third ventricle, or even higher, is affected (17). Because tumors vary in their origin, location, and growth pattern, Q-type tumors are theoretically more likely to oppress the neurohypophysis and attack the hypothalamus–pituitary system. Similarly, craniopharyngiomas originating from the subsellar diaphragm have been linked to an increased risk of pituitary dysfunction (16). In addition, the commonest hormonal deficiency in each craniopharyngioma type based on size is different (18): (1) size $\leq$9 mm: 50% in GHD; (2) size 10–19 mm: 73% in secondary hypothyroidism (SHT); (3) size 20–29 mm: 88% in secondary hypogonadism (SHG); and (4) size $\geq$30 mm: 86% in SHG. It is obvious that larger and more aggressive tumors are more likely to cause pituitary dysfunction (19), especially when it grows more than 20 mm. In recurrent craniopharyngioma, the recurrence site directly affects the growth pattern of recurrent craniopharyngioma and significantly affects hypothalamus–pituitary function (20).

Surgery

The surgical treatment strategy of craniopharyngioma remains controversial (21). Because of the high recurrence rate of craniopharyngioma, one opinion advocates radical surgery to remove the tumor completely to prevent recurrence and eventually to perform a higher risk operation (22). Another, more conservative approach is that limited and safer excision is supplemented by radiotherapy or radiosurgery for lesions targeting key important structures, especially the hypothalamus (23). Prieto et al. (24) described the status of 500 patients with postoperative craniopharyngioma: the operation-associated mortality rate was 30%, another 15% of patients suffered from severe sequelae, and most of which were correlated with hypothalamic injury. In the perioperative period of craniopharyngioma, the most serious period of endocrine dysfunction is 1–2 weeks after surgery (8), we deduce that postoperative endocrine dysfunction is delayed, which is related to the cycle of pituitary hormone metabolism. It has also been reported that the proportion of postoperative pituitary hormone deficiency, such as diabetes insipidus (DI), hypothyroidism, GHD, adrenocortical dysfunction, and sexual dysfunction, is higher than those before operation (10). DI is the most frequent endocrinopathy following transsphenoidal surgery or transcranial surgery for craniopharyngiomas (25), whereas it is often transient and can be recovered after drug treatment. Common postoperative long-term complications are hypothalamus–pituitary–thyroid (HPT) axis and hypothalamus–pituitary–adrenal (HPA) axis endocrine dysfunction (8). Craniopharyngioma originates from the sellar region and is anatomically connected to the hypothalamus and pituitary. As a result of cystic degeneration and calcification of tumor, adhesion between tumor and the surrounding tissue is quite common (26). The pituitary stalk connects the pituitary and hypothalamus and is mainly composed of nerve fiber bundles, which are easily injured or even ruptured during operation due to overstretching, resulting in impaired hormone secretion. The incidence and severity of injuries are determined by their location and severity (27). Compared with partial resection, total and subtotal resection are more likely to cause damage to hypothalamus, pituitary, and pituitary stalk (28), which is associated with poor prognosis of neuroendocrine in adults (29). Invasive surgery is associated with a high incidence of postoperative hormone defects but has no impact on anterior pituitary function (30). The type of surgery can also affect endocrine outcomes, the ratio of endocrine dysfunction after craniotomy is significantly higher than that after transsphenoidal surgery (31).

Radiotherapy

Craniopharyngiomas often involve the anterior part of the third ventricle, and its surrounding structures, such as the hypothalamus, are important. When total resection of craniopharyngiomas is difficult, adjuvant radiotherapy after subtotal resection is an effective method to control tumor growth (32). At present, pituitary dysfunction is the most common complication of radiotherapy and chemotherapy. The largest long-term study of children receiving chemotherapy and radiotherapy (748 participants with an average follow-up period of 27.3 years) revealed that cumulative incidence of growth hormone (GH), thyroid-stimulating hormone (TSH), adrenocorticotrophic hormone (ACTH), and gonadotropin (Gn) deficiency at the age of 40 was 72.4, 11.6, 5.2, and 24.4%, respectively (33). Another study reported that a group of 10 patients with craniopharyngioma who received multiple radiotherapies exhibited hormone defects in cortisol and thyroid axes (34). In addition, during the long-term follow-up of more than 100 pituitary tumors or closely related anatomic tumors, it was discovered that most of the GH and Gn deficiency occurred within 5 years after radiotherapy (35). Xu et al. (36) explained the mechanism of radiotherapy-induced endocrine disorders and verified it in mouse experiments: overactivation of p53 signal pathway can induce growth arrest or apoptosis of living cells, whereas Hippo pathway is necessary to induce apoptosis and reduce cell differentiation during the development. Therefore, by activating p53 pathway and inhibiting Hippo pathway, brain

radiotherapy can increase apoptosis, decrease cell proliferation, and eventually cause pituitary injury.

Pituitary Fibrosis

Pituitary fibrosis is also a factor in developing endocrine disorders in patients with craniopharyngioma, especially in GHD. The fact that ameloblastic craniopharyngioma secretes a range of pro-inflammatory cytokines distinguishes it from other sellar tumors (37). Pro-inflammatory cytokines derived from tumor cells infiltrate the brain tissue surrounding ameloblastic craniopharyngioma, potentially producing an inflammatory microenvironment (38). Local inflammatory environmental responses can result in tissue fibrosis, which impairs organ function (39). A significant positive correlation was reported between GHD and pituitary fibrosis, that the cross-talk between craniopharyngioma cells and pericytes in the pituitary plays a critical function in forming GHD, and that interleukin (IL)-1α activates pericytes through IL-1R1-related signaling pathway and then causes pituitary fibrosis, finally leading to decreased GHD levels in craniopharyngioma (40).

PITUITARY HORMONE DEFICIENCY

Pituitary hormones include GH, ACTH, Gn, TSH, oxytocin (OT), antidiuretic hormone (ADH), and so on. These hormone deficiencies are critical in the maintenance of normal physiological function. Unfortunately, such hormones are often deficient in patients with craniopharyngioma, impairing their quality of life.

Commonly used methods for determining hormones are radioimmunoassay and chemiluminescent immunoassays. Diagnostic criteria for hypopituitarism: (1) gonadal axis dysfunction: testosterone (TEST) decreased with abnormal follicle-stimulating hormone (FSH), luteinizing hormone (LH), and prolactin (PRL) levels in adult male patients, estradiol (E2) decreased with normal or decreased FSH and LH or abnormal PRL in female patients, and decreased FSH and LH in children (41). (2) The function of GH axis decreased: the insulin growth factor-1 (IGF-1) of the corresponding sex and age group decreased, or when the blood glucose of insulin tolerance test (ITT) was <400 mg/L, the GH was <5 μg/L (42, 43). (3) Central hypothyroidism: the decrease of free thyroxine (FT4) was accompanied by normal or decreased thyrotropin (44). (4) Central adrenocortical dysfunction: when cortisol (COR) < 30 μg/L in the morning, or ITT blood glucose < 400 mg/L, COR < 200 μg/L (45). And (5) DI is defined as the concomitant presence of inappropriate hypotonic polyuria (urine output >3 L/24 h and urine osmolality <300 mOsm/kg) in the presence of high or normal serum sodium (46). When IGF-1 was normal or morning COR > 30 μg/L and <180 μg/L, ITT was performed to determine GH axis function and cortisol reserve function (47, 48).

In the related literature reports, the incidence of various hormone defects in patients with craniopharyngioma is slightly different. We searched PubMed for keywords such as craniopharyngioma, endocrine, and hormone, and the subjects were identified as children or adults, and 11 related literatures (2, 8, 10, 11, 14, 20, 49–53) were obtained. We sorted out the literature to find out the incidence of endocrine dysfunction in craniopharyngioma (**Table 1**). The most affected hormones in children were GHD (62%) > HPT (60%) > HPA (54%) > DI (42%) > HPG (41%). The most affected hormones in adults were HPT (56%) > HPG (48%) > GHD (38%) > DI (34%) > HPA (33%).

Growth Hormone Deficiency

Growth hormone is a peptide hormone secreted by the anterior lobe of human pituitary composed of 191 amino acids and is critical in human physiology, including bone and organ growth, calcium homeostasis, fat decomposition, and weight regulation (54). After our analysis, GHD is more common in children than in adults. Adult GHD is characterized by decreased muscle mass, increased body fat, reduced energy, and well-being (55). GHD in craniopharyngioma children impacts their growth pattern, and their growth rate decreases significantly 1.5–6 years following operation (56). Pituitary dwarfism caused by GHD is the most common pathogenesis in children with short stature, adversely affecting their health (57). GH plays an important role in healthy growth, development, and maintenance of quality of life (58). Once GHD occurs, the GH replacement therapy (GRHT) is the only effective goal-oriented therapy (59). Although there is no clear evidence that GRHT negatively impacts tumor growth, the risk of tumor recurrence remains a critical safety issue (55). Numerous studies have demonstrated that GRHT does not increase the risk of recurrence in patients with craniopharyngioma (55, 60, 61): Smith et al. (60) found that 50 recurrences in these 739 surgically treated patients were recorded, recurrence rate was 6.8%, with a median follow-up time of 4.3 years (range 0.7–6.4 years); Losa et al. (55) researched 89 patients with craniopharyngioma, 49 patients in GRHT, the 5- and 10-year recurrence-free survivals were 92.9 and 84.5%, as compared with 74.5 and 65.2% in the control group, this difference was significant ($p = 0.024$ by the log-rank test), but the significance was only borderline in the sensitivity analysis ($p = 0.06$). A meta-analysis showed that overall craniopharyngioma recurrence rate was lower among children who were treated by GHRT (10.9%, $n = 3{,}436$) compared with those who were not (35.2%, $n = 51$), the p-value comparing the two groups was <0.01 (59).

Clinical trials demonstrate that GRHT positively influences body composition, blood lipids, bone mineral density, and mental health (62). However, even after GRHT, craniopharyngioma mortality remains high; a recent Pfizer International Metabolic Database (KIMS) analysis found that lower IGF-1 measurements at the last terminal sampling were associated with higher mortality, implying that the poor compliance or discontinuation of GRHT in advanced diseases may possess an impact on clinical data in this area (63). In addition, it has been reported that high expression of GH receptor in patients with craniopharyngioma is associated with the short time of postoperative stability. Therefore, if the surgical specimen is craniopharyngioma with high GH expression, GH should be supplemented cautiously (64) even if the tumor volume is uncertain.

TABLE 1 | The reports of endocrine dysfunction in the literature.

References	Object	Time	Number	GHD	HPG	HPT	HPA	DI
Qi et al. (8)	Children	2001–2012	98	75 (77%)	38 (39%)	46 (47%)	53 (54%)	29 (25%)
	Adults	2001–2012	114	39 (34%)	63 (55%)	35 (31%)	37 (33%)	26 (27%)
Qi et al. (49)	Children	1996–2012	109	52 (48%)	–	50 (46%)	35 (32%)	24 (22%)
Tan et al. (50)	Children	1973–2011	185	147 (80%)	118 (64%)	140 (76%)	127 (69%)	115 (62%)
Wijnen et al. (11)	Children	1978–2015	63	31 (53%)	10 (56%)	19 (32%)	17 (28%)	4 (7%)
	Adults	1978–2015	65	17 (27%)	39 (61%)	35 (56%)	25 (39%)	4 (6%)
Bao et al. (20)	Children	1997–2009	20	14/18 (78%)	14 (70%)	8 (40%)	11 (55%)	5 (25%)
	Adults	1997–2009	32	25/27 (93%)	20 (63%)	7 (22%)	17 (53%)	11 (34%)
Mende et al. (10)	Adults	Not mentioned	148	41/135 (30%)	69/136 (51%)	106/136 (78%)	96 (71%)	70/135 (52%)
Guo et al. (14)	Children	2011–2016	185	–	90 (49%)	130 (70%)	115 (62%)	–
Huang et al. (2)	Children	1995–2019	35	–	–	10/26 (39%)	7/17 (41%)	5 (14%)
Sun et al. (51)	Adults	2012–2015	20	–	10 (50%)	12 (60%)	–	12 (60%)
Sowithayasakul et al. (52)	Children	2015–2016	17	8 (47%)	–	11 (65%)	–	–
	Adults	2015–2016	19	16 (84%)	–	14 (74%)	–	–
Boekhoff et al. (53)	Children	2007–2014	215	100 (46.5%)	47 (21.9%)	138 (64.2%)	137 (63.7%)	30 (14.0%)
Total	Children	–	924	427/688 (62%)	317/766 (41%)	552/918 (60%)	486/892 (54%)	212/510 (42%)
	Adults	–	398	138/360 (38%)	176/367 (48%)	209/376 (56%)	175/525 (33%)	123/366 (34%)

GHD, growth hormone deficiency; HPG, hypothalamus-pituitary-gonad axis; HPT, hypothalamus–pituitary–thyroid axis; HPA, hypothalamus pituitary adrenal axis; DI, diabetes insipidus.

Adrenocorticotrophic Hormone Deficiency

Adrenocorticotrophic hormone is a peptide hormone produced in the pituitary gland that stimulates the formation and secretion of adrenocortical glucocorticoids (especially cortisol) (65). In a non-stressed state, signs and symptoms of adrenal insufficiency may be so subtle that they are not recognized, but they may alternatively include anorexia, nausea, shakiness relieved by eating, hypoglycemia, poor weight gain, poor stamina, or easy fatigability (66). Patients with craniopharyngioma is often identified by symptomatic hyponatremia secondary to ACTH deficiency (67). Adrenocortical dysfunction may greatly impact the rehabilitation of patients, and the hormone replacement therapy is a key step in craniopharyngioma treatment (68). Although the corticosteroid replacement therapy reduces the incidence of hypocortisol (51), risks are concurrently observed. It is stated that in patients with ACTH deficiency, a daily dose of more than 25 mg hydrocortisone is linked to increased mortality compared to lower doses (69). Research by Hammarstrand et al. (70) demonstrated that patients with nonfunctioning pituitary adenoma and adrenal insufficiency receiving a daily dose of more than 20 mg hydrocortisone have increased mortality. The possible explanation is that patients on high doses of (more than 20 mg/day) hydrocortisone replacement have increased total cholesterol, triglycerides, waist circumference, and glycosylated hemoglobin; all these factors are associated with increased cardiovascular morbidity (71). Okinaga et al. (72) reported a high risk of osteoporosis following operation of pituitary tumors, especially craniopharyngiomas. Consequently, it is recommended to reduce the dose of adrenocortical hormone replacement therapy to avoid bone destruction and take measures to protect bone.

Gonadotropin Deficiency

Following craniopharyngioma growth, the secondary mass effect can oppress the normal pituitary and stalk and lead to a deficiency of important pituitary hormones such as Gn (73), resulting in delayed puberty in children and hypogonadism in adults (4). Clinical evidence of their gonadotropin deficiency includes menstrual disorders, impaired sexual function, and loss of secondary sexual characteristics or lack of evolution in more than half of female patients (15). Gn deficiency may be an early warning sign of cardiovascular risk in adults (74). Pereira emphasized that estrogen deficiency in premenopausal women with craniopharyngioma may increase the risk of cerebrovascular events, requiring appropriate endocrine replacement (75). If left untreated, it will significantly worsen the prognosis (76). Emmert et al. (77) reported a case of secondary Gn dysfunction in patients with craniopharyngioma, suggesting that endocrine pathology may affect gender identity and cause psychological and cognitive impairment in children. It has currently been found that female patients with craniopharyngioma exhibit significantly lower bone mineral density than their matched control group, which may be due to insufficient sex hormone supplementation because sex hormones can mediate the effect on bone and adipose tissue by interacting with neuronal pathways (78). The KIMS database analysis also revealed that sex hormone deficiency might be linked to low standardized bone mineral density (79). In addition, hypopituitarism is associated with pregnancy complications, such as abortion, anemia, pregnancy-induced hypertension, placental abruption, preterm delivery, and postpartum hemorrhage (80). Post-craniopharyngioma pregnancy is rare: 133 female patients with childhood craniopharyngioma were followed up, only six cases became

successfully pregnant, but no serious pregnancy complications were observed (81).

Thyroid-Stimulating Hormone Deficiency

The TSH deficiency can cause central hypothyroidism. Typical hypothyroidism symptoms include cold intolerance, constipation, dry skin, sparse or fragile hair, weight gain, loss of energy, and bradycardia (82). TSH deficiency is critical in diagnosing craniopharyngioma in patients with Hashimoto's thyroiditis (83). The subclinical state of hypothyroidism may have adverse clinical effects on cardiovascular system, lipid, and bone metabolism, and increased mortality, underlining the importance of strict hormone supplementation regulation (84). In patients with TSH and ACTH deficiency, hydrocortisone replacement should precede levothyroxine replacement because levothyroxine increases the metabolic clearance rate of glucocorticoids, and L-thyroxine replacement before hydrocortisone may result in adrenal crisis (82).

Oxytocin Deficiency

Social and emotional impairment, school dysfunction, and neurobehavioral impairment are highly prevalent in survivors of childhood craniopharyngioma and negatively affect the quality of life. Post-operative deficiency of hormone OT may be the etiology of social/emotional impairment (85). OT is a pituitary neuropeptide hormone synthesized from hypothalamic paraventricular nucleus and supraoptic nucleus (86). OT is critical in regulating a wide range of functions (childbirth and lactation) and complex behaviors (memory, positive social bonds, and stress reduction) (87). Salivary OT levels are lower in patients with anterior pituitary dysfunction than in healthy people (88). The level of OT is positively correlated with psychopathological symptoms, and the level of endogenous OT may be increased in patients with severe depression (89). At present, the effect of OT replacement therapy remains unclear. Gebert et al. (90) believes that the replacement therapy is unnecessary for treating anxiety in patients with craniopharyngioma because patients only exhibit a higher level of state anxiety than the control group ($p > 0.05$). Cook et al. (85) stated that treatment with low-dose intranasal OT resulted in increased desire for socialization and improvement in affection toward family, and the potential of intranasal OT to restore social and behavioral function to pediatric craniopharyngioma survivors should be further explored. Reduced postprandial OT saliva concentrations were observed to be associated with weight problems in childhood-onset craniopharyngioma and adverse eating behavior and symptoms of eating disorders in both childhood-onset craniopharyngioma and controls (91). The OT supplementation may be a therapeutic option for patients with craniopharyngioma with hypothalamic obesity and/or neurobehavioral disorders caused by particular lesions in the anterior hypothalamus (92).

Antidiuretic Hormone Deficiency

Antidiuretic hormone is a non-peptide hormone produced in the hypothalamus and released into circulation *via* the posterior pituitary in response to an increase in plasma osmotic pressure (93). Central DI occurs when ADH secretion is partially or completely absent (94). DI is a prevalent symptom in patients with craniopharyngioma, with an incidence of 14–18% before operation and 80–93% following tumor resection (95). In DI cases, many electrolytes are lost through the urine, resulting in an out-of-control imbalance of fluid and electrolytes, and in severe cases, they cause slowness, discomfort, and even coma. Severe dehydration and hypernatremia can be fatal (26). Patients with craniopharyngioma with DI have a higher risk of type 2 diabetes, cerebral infarction, severe infection, and a higher mortality rate than the general population (19). The hypernatremia and hyperosmotic state associated with DI have several physiological consequences, including neuronal atrophy, muscle weakness, rhabdomyolysis, decreased ventricular contractility, and impaired glucose utilization, which may be the causes of high mortality in patients with DI (96). Prophylactic administration of ADH can effectively reduce the incidence of early DI and hyponatremia following skull hemangioma microsurgery (97).

MANAGEMENT

Perioperative Management

Perioperative management of craniopharyngioma is an important factor affecting neurological function and quality of life of patients (98). A comprehensive preoperative assessment of pituitary hormones should be performed, usually by basic determination (GH/IGF-1, LH, FSH/E2-TEST, TSH/T4, and ACTH/COR) and by routine measurements of 24-h urine volume, 24-h free cortisol, urine-specific gravity, urine osmotic pressure, and electrolytes (99). Certain hormonal changes, such as decreased cortisol, hypothyroidism, and altered water and electrolyte balance, should be corrected before surgery (100).

The onset of polyuria is usually abrupt, occurring within the first 12–24 h after surgery. Acute disorders of water metabolism can manifest in a triphasic pattern (in ∼3% of patients): an initial polyuric phase, a subsequent antidiuretic phase (the patients can temporarily concentrate urine and syndrome of inappropriate ADH secretion (SIADH) and hyponatremia develops), and a final polyuric phase that is usually chronic (101). To screen for potential development of postoperative DI and SIADH, patients after surgery undergo assessments of serum sodium and urine-specific gravity every 6 h (102).

Hypernatremia and hyponatremia often occur postoperatively due to DI and SIADH. Treatment strategies for hyponatremia (103): (1) mild or moderate hyponatremia: fluid restriction alone if cause rapidly reversible; otherwise, hypertonic saline solution at 1 ml/kg/h until substantial normalization symptoms. (2) Severe hyponatremia: rapidly increase [Na+] by 4–6 mEq/L with up to three 100-ml boluses of hypertonic saline solution given over 10 min at a time, followed by hypertonic saline solution at 1 ml/kg/h until substantial normalization. If rapid spontaneous correction occurs, it need not be constrained. Treatment strategies for hypernatremia (103): identification of the cause of hypernatremia and its correction. Central DI is usually the cause of hypernatremia, specific replacement therapy for central DI is usually straightforward and primarily aims at ameliorating symptoms (polyuria and polydipsia) by replacing ADH (104).

The urine volume is reduced 1–2 h after administration, and the action time varies from 6 to 18 h (105). Nasal feeding purified water is recommended to correct hypernatremia when necessary. The goal of treatment is to adjust the amount of input and the ratio of input fluids to electrolytes to maintain the basic water and electrolyte balance during the acute period after surgery.

The use of glucocorticoids is the most important in the perioperative period of patients with craniopharyngioma. Patients after surgery undergo assessments serum cortisol daily morning (102). At most centers, all patients are given stress doses of hydrocortisone (100 mg IV) or other glucocorticoid at the time of surgery, and this dose is tapered quickly over 2–3 days for a total of about five doses (106–108). Hydrocortisone is then administered orally and tapered down to the preoperative regimen of patients (typically 20 mg in the morning and 10 mg in the evening for hydrocortisone, or 5 mg in the morning and 2.5 mg in the evening for prednisone) (108). Patients who do not have preoperative cortisol deficiency (or are less likely to have one) should generally receive hydrocortisone replacement therapy if their cortisol levels fall below 8 μg/dL twice in a row, with ongoing cortisol replacement needs assessed at follow-up (108). As for the determination of postoperative pituitary hormone, our experience is to perform 3 and 7 days after the operation (increase frequency as necessary). Individualized treatment is taken based on the results of the test. Note that cortisol replacement is superior to thyroid hormone.

Follow-Up

Follow-up can find tumor recurrence in time, correct and treat water electrolyte, and endocrine state in time. Endocrine, electrolyte, liver and kidney function, and saddle MRI should be performed 14, 30 days, 3, 6 months, and 1 year postoperatively (follow-up frequency should be increased if necessary).

Glucocorticoid Supplementation

The glucocorticoid most widely used for the cortisol replacement therapy worldwide is oral hydrocortisone in daily divided doses. At present, the clinical evaluation of the glucocorticoid replacement therapy is mainly based on the clinical evaluation. Too low glucocorticoid doses increase the risk of adrenal crisis and reduce well-being, whereas too high doses increase the risk of complications such as osteoporosis, obesity, and impaired glucose tolerance (109). Given the cortisol production rate and the practicality of use of oral formulations, adults are generally prescribed hydrocortisone 15–20 mg/day (110). Dose adjustment is mainly based on clinical experience and whether patients have new symptoms or remission of symptoms after adjustment (109).

Thyroid Hormone Supplement

Compared with primary hypothyroidism, patients with TSH deficiency have more difficulty obtaining the best thyroid hormone replacement because they cannot be guided by serum TSH levels (111). Certain guidelines recommend using free tetraiodothyronine (FT4) as a standard for monitoring central hypothyroidism (112). Daily levothyroxine (L-T4) requirement is 0.8–1.6 mcg/kg, and starting doses typically vary between 50 and 125 mcg/day (113). It is widely recommended that FT4 levels should be maintained within the upper-middle normal range, free triiodothyronine (FT3) should be kept within the normal range, and L-T4 dose should be further adjusted according to clinical reactions and cholesterol levels (111). Combined therapy with L-T4 and liothyronine (L-T3) is not routinely recommended. Evidence from controlled trials has shown no added benefit of combined therapy over L-T4 monotherapy in terms of quality of life, mood, or psychometric measures (114).

Growth Hormone Supplement

There is no sign of recurrence 1–2 years after surgery, and GRHT may be considered. As mentioned earlier, GRHT does not promote tumor recurrence. In patients with permanent or confirmed GHD, a starting low rhGH dose (0.01–0.03 mg/day) to be adjusted according to IGF-1 concentrations is also widely accepted (115). Molitch et al. (58) suggest that during GH treatment, patients be monitored at 1- to 2-month intervals during dose titration and semiannually thereafter with a clinical assessment and an evaluation for adverse effects, IGF-1 levels, and other parameters of GH response (including blood pressure, weight and waist circumference, lipid profile, serum glucose, and bone age). The dose should be lowered, or treatment should be discontinued in case of side effects such as arthralgia, headache, and hyperglycemia (115). Some studies have shown that GH replacement caused a lowering of serum free T4 levels and a lowering of serum cortisol levels (116–118); thus, thyroid and adrenal function should be monitored during GH therapy of adults with GHD.

Sex Hormone Supplement

Female children are recommended to start the estrogen replacement therapy between the ages of 11 and 12 to mimic average physiology (119). Low doses of estrogen should be used to induce puberty, which is essential to maintain growth potential, and estradiol transdermal is the preferred route (equivalent of 3–7 mcg/day) (120). The estrogen dose is then increased once every 6 months, which will last for about 2–3 years until the girl reaches adult replacement level (121). In male children, pubertal development is induced at age 12, and a slow and gradual increase in serum steroids is obtained. For a monthly intramuscular injection of 25–50 mg of TEST, the dose should be kept as low as possible and increased every 6–12 months until the adult dose is given (122).

Adult male patients with central hypogonadism should be accepted the TEST replacement therapy to reduce fat mass and improve bone mineral density, libido, sexual function, energy levels, sense of well-being, and muscle mass and strength (47). The conventional use of TEST is as follows (122): (1) injectable preparations: TEST esters (enanthate and cypionate) 250 mg can be administered i.m. every 2–3 weeks; (2) oral preparations: multiple daily doses are required (160–240 mg/day in 3–4 doses); and (3) transdermal preparations: the daily doses vary between 5 and 10 g, each delivering 5–10 mg TEST. Hemoglobin, hematocrit, liver function, blood lipids, and prostate antigen should be followed up during treatment.

Hormonal replacement consists of an estrogen component and a progestogen component, in females possessing a uterus

(122). Replacement aims to promote and maintain secondary sexual characteristics and to reduce the risk of developing long-term complications such as cardiovascular disease and osteoporosis (123). In premenopausal women, the hormonal replacement therapy as oral estrogen or combined estrogen and progestogen therapy is recommended, assuming that no contraindications are present (47). An average daily dose of 1–2 mg or equivalent of estradiol is required; transdermal preparations are usually applied twice weekly and provided 50–100 μg of E2 daily in a cyclical combination with a progestogen (124). Either sequential transdermal systems with a progestogen component added to estradiol in the second phase of the menstrual cycle (where regular cyclical bleeding is expected) or a continuous combined system with both estradiol and the progestogen delivered throughout is available (125).

Diabetes Insipidus

Adequate fluid replacement, treatment of the underlying condition, and desmopressin administration are the mainstays of management (126). We think it is better to control the urine volume at 200 ml/h. The level of blood electrolyte was examined every week within 1 month after operation. The levels of electrolyte and muscle intoxication were checked every month from 1 to 6 months after operation (strengthen the monitoring frequency if necessary). Adjust the appropriate dose and interval according to plasma osmotic pressure and serum sodium concentration. Mild (134–125 mmol/l) hyponatremia can be treated in outpatient setting with fluid restriction and frequent sodium checks, whereas more severe hyponatremia (<125 mmol/l) requires hospitalization with possible short-time use of hypertonic saline or ADH receptor antagonist drugs, being careful to avoid over-correction (127).

TARGETED THERAPY

Although the standard treatment for craniopharyngioma, including surgical resection and radiotherapy, can achieve local tumor control, active local treatment often declines quality of life due to permanent neuroendocrine and neuroendocrine defects. The maintenance of quality of life is preferred over complete resection of tumor (128), and reasonable treatment for craniopharyngioma can be supplemented with targeted therapy by reducing the scope of resection or the necessity for follow-up radiotherapy, significantly reducing the incidence of primary diseases and current treatments (129). Targeted genotyping revealed that 95% of papillary craniopharyngiomas had BRAFV600E mutations, and 96% of ameloblastic craniopharyngiomas had CTNNB mutations suggesting that molecular targeted therapy for craniopharyngiomas may be effective (130). Mutations in BRAF kinases activate RAS/RAF/MEK/ERK signaling pathways, which are abnormally activated in many human tumors (131). In addition, *CTNNB1* gene abnormality results in imbalanced Wnt pathway and nuclear β-catenin accumulation, contributing to tumor invasiveness (132). Brastianos et al. (133) reported the treatment of a 39-year-old man having recurrent BRAFV600E craniopharyngioma with dabrafenib (150 mg, twice a day) and trametinib (2 mg, twice a day); after 35 days of treatment, the tumor size was reduced by 85%. Dabrafenib is a BRAF inhibitor and has a good anti-tumor effect in BRAFV600E mutated cancer (131), whereas MEK inhibitor trametinib can enhance the inhibitory effect of BRAF (134). Although Wnt pathway/β-catenin inhibition may be a promising treatment for craniopharyngioma, the potential non-target effect limits its application in current intervention regimens (132). The combined utilization of systemically administered tocilizumab and bevacizumab may be effective in pediatric patients with primarily cystic craniopharyngioma because tocilizumab, a humanized monoclonal antibody, acts against soluble and membrane-bound IL-6R, which has been proved to contain a high level of cystic and solid tumor components in craniopharyngioma (135).

SUMMARY

Craniopharyngioma is a catastrophic brain tumor, often accompanied by endocrine disorders. Endocrine disorders significantly impair quality of life of patients. Endocrine disorders are caused by primary tumor growth, surgical invasion, radiotherapy, pituitary fibrosis, etc. If left untreated, gonadotropin deficiency in patients with craniopharyngioma increases the risk of poor prognosis; DI increases the risk of mortality and other complications. At present, the replacement therapy remains the treatment option for endocrine disorders, but it must be utilized prudently, and an individualized treatment plan should be developed. The development of targeted therapy may provide a new perspective for improved hormone deficiency.

AUTHOR CONTRIBUTIONS

ZZ completed the part of each hormone deficiency. SZ completed the part of mechanisms of hormone deficiency and treatment. FH provided writing ideas and references. All authors contributed to the article and approved the submitted version.

FUNDING

Funding from the third level scientific research project of 333 Project of Jiangsu Province Foundation is gratefully acknowledged (BRA2018292).

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frontiers in Neurology

ORIGINAL RESEARCH
published: 03 December 2021
doi: 10.3389/fneur.2021.753902

Prediction of Post-operative Visual Deterioration Using Visual-Evoked Potential Latency in Extended Endoscopic Endonasal Resection of Craniopharyngiomas

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Background: The current study aimed to investigate the predictive value of visual-evoked potential (VEP) latency for post-operative visual deterioration in patients undergoing craniopharyngioma resection via extended endoscopic endonasal approach (EEEA).

Methods: Data from 90 patients who underwent craniopharyngioma resection *via* EEEA with intraoperative VEP monitoring were retrospectively reviewed. P100 latency was compared between patients with and without post-operative visual deterioration, and the threshold value of P100 latency for predicting post-operative visual deterioration was calculated by the receiver operating characteristic curve analysis. In addition, other potential prognostic factors regarding post-operative visual outcomes were also analyzed by multivariate analysis.

Results: Patients with post-operative visual deterioration showed a significantly longer VEP latency than those without ($p < 0.001$). An extension over 8.61% in VEP latency was identified as a predictor of post-operative visual deterioration ($p < 0.001$). By contrast, longer preoperative visual impairment duration and larger tumor volume were not significant predictors for post-operative visual deterioration.

Conclusions: The current study revealed that intraoperative VEP monitoring in EEEA is effective for predicting post-operative visual deterioration, and an extension over 8.61% in VEP latency can be used as a critical cut-off value to predict post-operative visual deterioration.

Keywords: craniopharyngioma, extended endoscopic endonasal approach, optic nerves, visual evoked potential (VEP), post-operative visual deterioration

OPEN ACCESS

Edited by:
Paolo Cappabianca,
University of Naples Federico II, Italy

Reviewed by:
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Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Neurology

Received: *05 August 2021*
Accepted: *25 October 2021*
Published: *03 December 2021*

Citation:
Tao X, Yang X, Fan X, You H, Jin Y, Liu J, Guo D, Li C and Qiao H (2021) Prediction of Post-operative Visual Deterioration Using Visual-Evoked Potential Latency in Extended Endoscopic Endonasal Resection of Craniopharyngiomas. Front. Neurol. 12:753902. doi: 10.3389/fneur.2021.753902

BACKGROUND

Craniopharyngioma represents around 1.2–4.6% of all intracranial tumors. It is originated from the remnant of Rathke's pouch and histologically benign (Grade I according to the 2016 World Health Organization Classification). Nowadays, radical resection is still the preferred treatment for craniopharyngioma. However, due to its complex anatomical relationships with optic nerves

and chiasm, pituitary stalk, gland and hypothalamus, complete resection is usually difficult, and the risk of relevant post-operative complications is quite high (1, 2). Microscopic transcranial surgical approaches were considered as classic operative strategy for craniopharyngiomas, but in recent decades, extended endoscopic endonasal approach (EEEA) has revolutionized the surgical treatment of craniopharyngiomas. It has proved that the EEEA could provide the shortest direct corridor and also maximal exposure without any brain retraction. Although the EEEA could provide an improved visual field of the optic nerves and chiasm, and hypothalamus, injury of optic pathways is still the most common surgical complication (3–5).

Over the past decades, intraoperative neurophysiological monitoring (IONM) has become a crucial component for modern neurosurgery. Specific to visual function protection, visual-evoked potential (VEP) is proved to be an effective modality for reflecting the integrity of visual pathway from retina to pulvinar cortex, and has been applied to surgeries with the risk of visual pathway damage (6–9). To our knowledge, in the research field of VEP monitoring, most studies have focused on the predictive value of VEP amplitude for post-operative visual deterioration. By contrast, few studies have been designed to identify the relationship of VEP latency with post-operative visual outcome (10). In the current study, we aimed to investigate the predictive value of P100 latency of VEP for post-operative visual deterioration in patients undergoing EEEA, and to attempt to calculate an appropriate threshold of P100 latency prolongation to avoid post-operative visual deterioration.

METHODS

Patients

Data of 124 craniopharyngioma patients undergoing EEEA from June, 2019 to February, 2021 at Beijing Tiantan Hospital were retrospectively reviewed. The inclusion criteria were as follows: (i) aged from 16 to 65 years old; (ii) received VEP monitoring. The exclusion criteria were as follows: (i) severe visual impairment preoperatively (blindness or severe visual field defect); (ii) with a pathological diagnosis not consistent with craniopharyngioma. This study was approved by the ethics committee of Beijing Tiantan Hospital. All patients provided informed consent for participation in the study.

Anesthesia

Total intravenous anesthesia was induced by propofol (2–2.5 mg/kg) and sufentanil (0.3–0.4 μg/kg) and was maintained by continuous infusion of propofol (4–12 mg/kg/h) and remifentanil (0.05–0.2 μg/kg/min). The BIS values were maintained between 40 and 60 using a dual spectral index sensor (VISTA monitoring system, Massachusetts, USA). The patient's heart rate, blood pressure, blood oxygen, and carbon dioxide levels were continuously monitored during surgery.

Neurophysiological Monitoring

A monitoring protocol including ERG and VEP monitoring was applied to all patients enrolled in the study. A photostimulation device consisting of a white LED (NimEclipse; Medtronic) served as the stimulator, flashing at a frequency of 0.7–1.2 Hz. The brightness of the LED was set to 500–10,000 Lx, and the duration of each stimulus was 84 ms. Goggles were applied to both closed eyelids. The needle electrodes for ERG were placed 2 cm from the external canthus. For VEP monitoring, the recorded sites were O1, O2, and Oz, and the reference electrodes were placed on Fz, according to the International EEG Electrode Placement 10–20 System Standard, with bilateral recording using monocular stimulation. The recording electrodes were corkscrew electrodes. The bandpass filter was set from 1 to 100 Hz and stacked <50 times. The analysis times were 300 ms. VEP data were collected and evaluated by one of the two experienced IONM technicians with corresponding equipment (NIM-ECLIPSE Nerve Monitoring System, Medtronic, Medtronic, Minneapolis, MN, USA). VEP were recorded once after anesthesia and recorded at least three times to ensure repeatable waveforms. The stable VEP waveform after opening the dura was considered as the baseline. For uncoupling of the optic canal and removal of the tumor, intraoperative VEP monitoring was performed every 2 min until the end of the skull base reconstruction. Intraoperatively, we focused on the latency of the large positive peak (P100) at around 100 ms. A warning is purely given according to the presence of P100 latency prolongation. The neurosurgeon will change the surgical strategy, such as stopping the retraction of the optic nerve or adjusting the filler position, to restore the P100 latency. The degree of P100 latency prolongation was calculated by the following formula: (post-operative latency—baseline)/baseline*100%. **Figure 1** shows VEP waveforms acquired during the surgery.

Clinical Assessment and Follow-Up

Preoperative computed tomography and magnetic resonance imaging (MRI) were performed for preoperative evaluation and used to examine the tumor volume. Tumor volume was calculated using the following formula: volume $= 4/3\pi$ (a/2 $\times$ b/2 $\times$ c/2), where a, b, and c represent the diameter dimensions of the three. Post-operative MRI was performed within 2 weeks after surgery to confirm the extent of tumor removal. Gross total removal was defined as resection without visible remnant tumor according to intraoperative assessment and post-operative MRI.

All patients underwent best-corrected visual acuity (BCVA) examinations preoperatively and at least 3 months after surgery. BCVA (normal $\geq$ 1.0) was assessed by a trained and certified research optometrist using a logarithmic visual acuity (VF) scale at a distance of 5 m under standard illumination. BCVA in decimal units was converted to the logarithm of the minimum angle of resolution (logMAR) for analysis. A change of <1 line was defined as no deterioration in visual acuity, and a loss of at least one line was defined as deterioration in visual acuity.

Adhesion forces between neoplasms and optical nerves were classified into two categories according to the intraoperative findings of the surgeon: (1) no or loose adhesion if the tumor can be easily separated from the optic apparatus with gentle blunt dissection using dissectors; or (2) tight adhesion if separation of the tumor needed sharp dissection using scissors (11, 12).

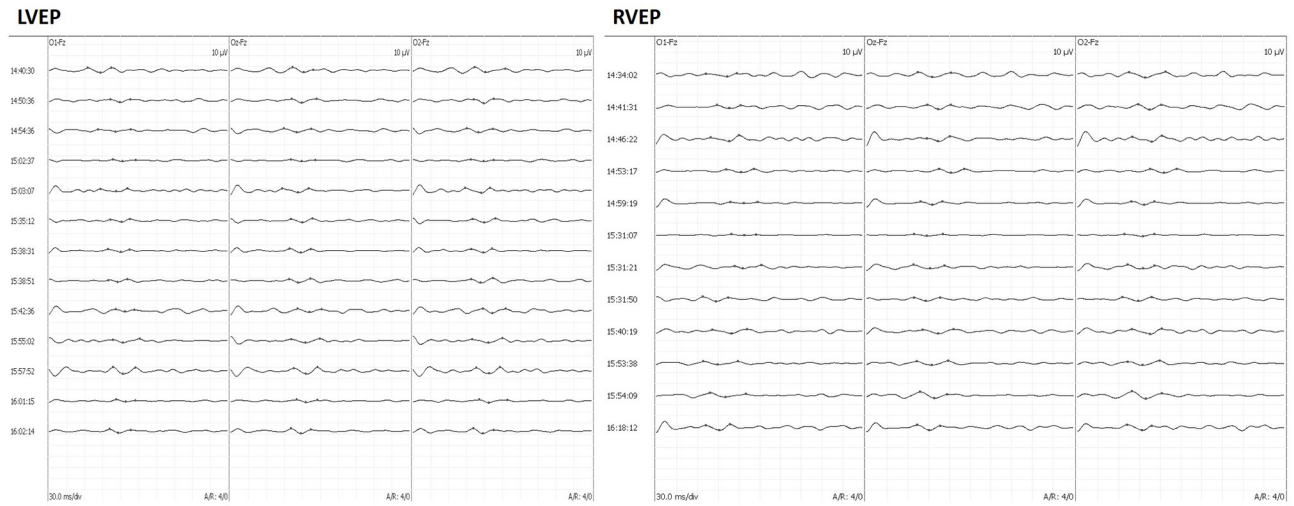

FIGURE 1 | A 49-year-old man complained of vision loss for 6 months. Intraoperatively, the patient underwent craniopharyngioma resection through EEEA with VEP monitoring. The left VEP latency was prolonged until the end of surgery, and the right VEP latency was prolonged intraoperatively and returned to baseline levels by the end of surgery. Follow-up at 3 months after surgery showed a decrease in visual acuity in the left eye and no change in the right eye, respectively. EEEA, extended endoscopic endonasal approach; VEP, visual-evoked potential.

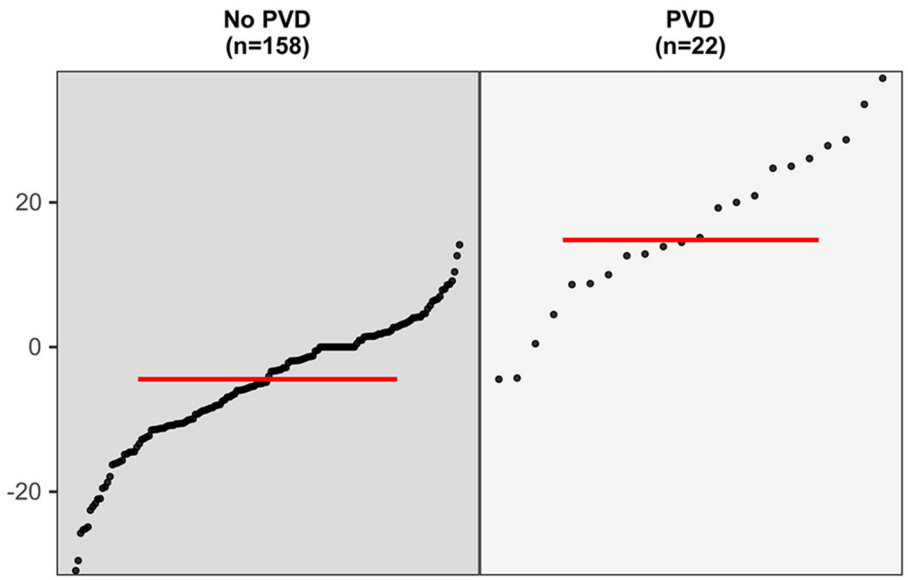

FIGURE 2 | The comparison in the degree of P100 latency prolongation between eyes with post-operative visual deterioration and those without (Mann–Whitney *U*-test, $p < 0.001$).

Statistical Analysis

All statistical analyses were performed with the SPSS software version 22.0 (SPSS Inc., Chicago, Illinois, USA) and GraphPad Prism (version 8.0.1 for Windows, GraphPad Software, San Diego, California, USA). Normally distributed samples were expressed as the mean ± standard deviation, median [with interquartile range (IQR)] for non-normally distributed samples. The degree of P100 latency prolongation between patients with post-operative visual deterioration and those without was compared by the Mann–Whitney *U*-test. A $p < 0.05$ was considered statistically significant.

Receiver operating characteristic curve analysis was used to calculate the optimal threshold for the degree of prolongation of P100 latency to avoid post-operative visual dysfunction. A chi-square test was used to compare patients with a prolonged P100 latency less than or greater than the threshold. Univariate logistic regression was used to describe the correlation between the parameters of interest and post-operative visual function deterioration.

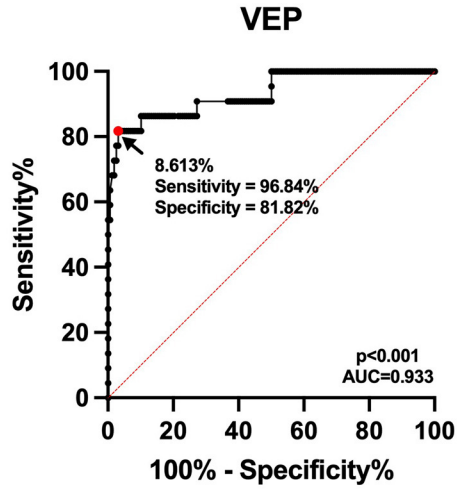

FIGURE 3 | Receiver operating characteristic curve for the prediction of post-operative visual deterioration. The continuous line shows the sensitivity, and dashed line shows identity. The area under the curve is 0.933.

TABLE 1 | Relationship between intraoperative P100 latency prolongation and post-operative visual outcome.

Visual deterioration (*n*)	P100 latency prolongation		Total (*N* = 180)	*P*-Value
	Yes	No		
Yes	18	4	22	<0.001
No	5	153	158	

TABLE 2 | Univariate logistic regression analysis of potential predictors.

Variable	Post-operative visual deterioration		
	OR	95% CI	*P*-Value
Gender	0.51	0.16–1.65	0.26
Age	1.02	0.97–1.06	0.49
Volume	1.02	0.99–1.05	0.13
Recurrence	1.00	0.29–3.50	1.00
Pathology	0.40	0.08–1.91	0.25
Visual impairment duration	1.00	0.94–1.05	0.89
Tight adhesion	0.90	0.29–2.77	0.85

RESULTS

Clinical and Demographic Characteristics of Craniopharyngiomas Patients

Ultimately, 90 patients (48 men and 42 women) were enrolled. The mean age of the enrolled patients was 42 years (range, 16–65). Craniopharyngiomas of adamantinomatous type were histopathologically diagnosed in 48 cases (73.8%), whereas papillary type was identified in 17 cases (26.2%). Among the 90 tumors, 66 (73.3%) were primary craniopharyngiomas and 24 (26.7%) were recurrent craniopharyngiomas. The median duration of preoperative visual impairment was 4 months (range, 1–72 months). The median tumor volume was 7.59 cm^3 (3.32–17.80 cm^3). Craniopharyngiom were loose or unattached in 52 cases (57.8%) and adherent tight in 38 cases (42.2%). Of the 10 cases with residual tumors, six were observed without further treatment, and four were treated with gamma knife after 3 months.

P100 Latency of VEP

Reproducible and stable VEP monitoring results were obtained in all 180 (100%) eyes of the enrolled 90 patients. The preoperative P100 latency was 101.50 ms (94.00–109.50 ms) and 101 ms (90.50–107.50 ms) post-operatively. The post-operative P100 latency was significantly shorter than the preoperative one, with a statistically significant difference ($p < 0.001$, Wilcoxon test).

Prolonged P100 Latency and Post-operative Visual Deterioration

In the 180 eyes of 90 patients included in this study, the degree of P100 latency prolongation was 14.81% (8.75–25.27%) in the 22 (12.22%) eyes with post-operative visual deterioration and −4.45% (−10.84 to −1.41%) in 158 (87.78%) eyes without post-operative visual deterioration. The degree of P100 latency prolongation was significantly higher in patients with post-operative visual deterioration than in those without deterioration (Mann–Whitney *U*-test, $p < 0.001$, **Figure 2**).

The optimal threshold value for avoidance of post-operative visual deterioration was 8.61% (AUC = 0.933, 95% CI 0.869–0.997, $p < 0.001$, **Figure 3**). The 23 eyes had post-operative P100 latency prolongation ≥8.61%, 15 eyes had no changes, and 142 eyes had P100 latency prolongation <8.61% or varying degrees of shortening. In 23 eyes with prolonged P100 latency, 18 eyes showed post-operative visual deterioration, and five eyes did not show those. Out of 157 eyes with shortened or unchanged P100 latency, four eyes showed post-operative visual deterioration, and 153 eyes did not show post-operative visual deterioration. Patients with a prolonged post-operative P100 latency ≥8.61% had a significantly higher risk of worsening post-operative visual function (chi-square test, $p < 0.001$, **Table 1**).

Other Potential Predictors

Logistic regression analysis was performed to further investigate other potential predictors for post-operative visual deterioration. Variables such as gender, age, whether recurrence, preoperative visual impairment duration, pathology type, tumor volume, the degree of adhesion, and the extent of resection were analyzed. As in all 70 patients with prolonged post-operative P100 latency <8.61% for both eyes, post-operative visual deterioration was not observed, and prolonged post-operative P100 latency was not applied to logistic regression analysis; so was the extent of resection (in all 10 patients who received total resection, post-operative visual deterioration was not observed). The results of univariate logistic regression analysis showed that none of the above variables could be used to predict post-operative visual deterioration (**Table 2**).

DISCUSSION

With the remarkable development of neurosurgery, the concept of protecting neurological function while treating diseases has become deeply rooted. IONM, as an important method to protect neurological function during surgery, has been widely used in various neurosurgical procedures. At present, EEEA is the optimal surgical approach for craniopharyngioma surgery without significant lateral invasion (11, 12). As the tumor is adjacent to the optic nerve and chiasm, the surgical removal of the tumor may lead to strain damage to the optic nerve and chiasm, and thus result in new or intensified deterioration of visual function post-operatively, which can significantly decrease the quality of life of the patients. VEP is a long latency-evoked potential recorded in the occipital region of the visual primary cortex after performing flash stimulation on the human eyes, and it can reflect the functional integrity of visual pathway. Accordingly, it is of great clinical importance to apply VEP monitoring to EEEA to protect the visual function of patients.

The main objective of this study was to determine the relationship between intraoperative P100 latency changes and post-operative visual deterioration. Although the relationship between the prolonged P100 latency and visual loss has been reported previously (13, 14); however, to our knowledge, this is the first large sample study on this issue. From the present findings, the incidence of post-operative visual deterioration was significantly higher in patients with prolonged post-operative P100 latency than in patients without prolonged P100 latency, the degree of prolonged post-operative visual deterioration of P100 latency was significantly higher in patients with deteriorated visual acuity than in patients without deterioration, and using a P100 latency prolongation degree of 8.61% as the critical threshold can refine the current warning criteria of VEP monitoring. This finding is of clinical significance, and can further reduce the incidence of post-operative visual deterioration. It is clear that a threshold value of 8.61% will be difficult to grasp in clinical practice, and the application of automatic recognition methods is needed in the coming era of precision medicine.

As early as 1973, Wright et al. first attempted to apply VEPs for intraoperative monitoring under general anesthesia, and the waveforms elicited were unstable due to the conditions at that time (15). In recent years, the development of total intravenous anesthesia techniques and light-emitting diode technology has led to the stable generation of VEP. To date, many clinical studies have explored and confirmed a good correlation between intraoperative VEP and post-operative visual function, but most of them are limited to the relationship between VEP amplitude changes and visual function (16–20), and VEP is reliable in predicting new visual damage at 50% alarm criteria (16, 20). Previous studies have paid less attention to P100 latency in VEP, and none of them could summarize the threshold for the degree of P100 latency in VEP prolongation (21). In the present work, data from 180 eyes in 90 patients were analyzed, and 8.61% was determined as the threshold for the degree of P100 prolongation for predicting post-operative visual deterioration. The incidence of post-operative visual deterioration was significantly higher in patients with a degree of P100 prolongation $\geq$8.61%. The results of this work may further refine the alarm criteria for VEP monitoring in predicting new visual impairment.

Visual-evoked potential is a routinely applied intraoperative optic nerve monitoring technique that can continuously monitor the integrity of the visual conduction pathway in real time and assess the status of intraoperative optic nerve function, which is done without interference to the operator. After intraoperative stimulation of the optic nerve by traction, cautery, and compression, the P100 latency will be prolonged. At this time, timely adjustment of the surgical strategy will enable some patients to have a certain degree of recovery of the P100 latency and no significant deterioration of post-operative visual acuity. Hayashi and Kawaguchi concluded that hypocapnia likewise leads to prolonged VEP latency, and therefore, hypocapnia is avoided as much as possible during total intravenous anesthesia procedures (22). Since P100 latency varies greatly among individuals, the degree of P100 latency prolongation was used as the judgment index, but there is still the possibility of false negatives and false positives. In this work, we found that the P100 latency was shortened in two eyes after surgery compared with the preoperative period, and the post-operative visual function still deteriorated, and a false negative result occurred. The reason for post-operative visual deterioration was analyzed as ischemia caused by vasospasm. After monitoring 100 cases by Sasaki et al. (16) and 53 surgeries by Kodama et al. (17) it was found that the sensitivity of using VEP amplitude to predict visual dysfunction was up to 87.5% and the specificity was 98.8%. These two studies found high specificity, but slightly lower sensitivity for monitoring VEP amplitude changes. By comparison, here we obtained a higher sensitivity (96.8%) and a slightly lower specificity (81.8%) in the VEP latency.

Our study has limitations. First, the sample size was still relatively small, and it is still unclear whether P100 delay can be used as an independent predictor. Secondly, our study was limited by retrospective nature. Future sample size expansion and prospective studies are needed to validate our results.

CONCLUSION

This study revealed that intraoperative VEP monitoring is an effective method for preventing visual deterioration during EEEA. P100 latency in VEP prolongation of 8.61% can be used as a critical cutoff to predict post-operative visual deterioration.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Beijing Tiantan Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

XT and HQ: study concept, design, and writing—review and editing. XT, XY, DG, and HY: data acquisition and analysis. XF, YJ, and JL: formal analysis and investigation. XT: writing—original draft preparation. HQ: funding acquisition. CL and HQ: supervision. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by the Beijing Municipal Science & Technology Commission (Grant No. Z191100006619087).

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frontiers in Oncology

ORIGINAL RESEARCH
published: 08 December 2021
doi: 10.3389/fonc.2021.761281

Expanded Transsphenoidal Trans-Lamina Terminalis Approach to Tumors Extending Into the Third Ventricle: Technique Notes and a Single Institute Experience

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OPEN ACCESS

Edited by:
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Reviewed by:
Joao Paulo Almeida, University of Toronto, Canada
Emanuele La Corte, University of Bologna, Italy

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Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: *19 August 2021*
Accepted: *15 November 2021*
Published: *08 December 2021*

Citation:
Cao L, Wu W, Kang J, Qiao H, Yang X, Bai J, Zhu H, Zhang Y and Gui S (2021) Expanded Transsphenoidal Trans-Lamina Terminalis Approach to Tumors Extending Into the Third Ventricle: Technique Notes and a Single Institute Experience. Front. Oncol. 11:761281. doi: 10.3389/fonc.2021.761281

Object: The trans lamina terminalis approach (TLTA) has been described as a way to remove third ventricular tumors. The aim of this paper was to analyze the feasible outcomes of TLTA applied to tumors extending into the third ventricle in our institute.

Methods: Suprasellar tumors (n = 149) were treated by the extended endonasal approach from September 2019 to December 2020 in Beijing Tiantan Hospital. Eleven of the tumors were treated by TLTA or TLTA *via* the trans-chiasm-pituitary corridor (TCPC). The surgical technique notes of TLTA were described and indications and outcomes of the approach were analyzed.

Results: There were 11 patients enrolled in the study, six with papillary craniopharyngiomas, two with adamantinomatous craniopharyngiomas, one with a germinal cell tumor (GCT), one with cavernous malformation and one with chordoid glioma. Four of the patients received a radical resection by TLTA alone, while seven of them received TLTA *via* the TCPC. Gross total resection was achieved in eight patients (72.7%), and partial resection in three patients (27.3%). Visual function was improved in four of the 11 patients (36.4%), was unchanged in five patients (45.5%), and deteriorated in two patients (18.2%). New-onset hypopituitarism occurred in seven patients (63.3%) and new-onset diabetes insipidus occurred in two patients (18.2%). Electrocyte imbalance were observed in six patients (54.5%) at post-operative week 2. There were no surgery-related deaths or cerebrospinal fluid leaks. Postoperative intracranial infection was observed in one patient (9.1%), and during the follow-up period, tumor recurrence occurred in one patient (9.1%).

Conclusion: The expanded TLTA provides a feasible suprachiasm corridor to remove tumors extending into the third ventricle, especially for craniopharyngiomas. Sound understanding of the major strengths and limitations of this approach, as well as strategies for complication avoidance, is necessary for its safe and effective application.

Keywords: trans-lamina terminalis approach, craniopharyngioma, third ventricle, chiasm pituitary corridor, expanded transsphenoidal

INTRODUCTION

Tumors located in the third ventricle behind the chiasma, such as craniopharyngiomas, are technically challenging due to their proximity to vital neurovascular structures including the hypothalamus, optic apparatus and anterior cerebral artery (ACA) complex. Access to these tumors is very difficult due to their deep location. King (1) described a trans-lamina terminalis approach (TLTA) through pterional craniotomy as a safe corridor to access these third ventricular lesions, as well as some other access options such as the transcallosal interforniceal approach (2, 3) and transcortical transforaminal approach (4). Compared to other approaches, TLTA provides direct access to the retro-chiasmatic portion of the tumor with little optic nerve retraction.

Expanded endonasal approaches (EEA) (5–7) can provide direct access to the midline skull base, including access to suprasellar tumors. However, reports on how to resect tumors involving the third ventricle have been limited. Kitano (8) reported extended transsphenoidal surgery for 20 suprasellar craniopharyngiomas using infrachiasmatic access, combined with or without a suprachiasmatic trans-lamina terminalis approach. Seo (9) also reported a series of 82 cases of tumors involving the third ventricle resected by EEA. Most of these cases were treated *via* the infrachiasm corridor or chiasm-pituitary corridor. However, resection of the tumor in the third ventricle *via* TLTA by extended transsphenoidal approach was seldom reported. In the present study, we share our experience with resection of tumors located in the third ventricle by TLTA in our single institute. The surgical technique notes and outcomes of TLTA are discussed as well as its advantages and disadvantages.

METHODS

Patient Selection

A total of 149 patients with suprasellar tumors underwent surgery using EEA between September 2019 and December 2020 in the Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, by G.S.B. Eleven of the 149 tumors extended behind the chiasma into the third ventricle and were removed *via* TLTA with or without access through the trans-chiasm-pituitary corridor (TCPC) by EEA. This study was performed under an institutional review board-approved protocol in compliance with regulations set by our institution for the study of human subjects with their informed consent and was approved by ethics committee of Beijing Tiantan Hospital, Capital Medical University (KY 2021-041-02).

Preoperative MRI Evaluation

All patients preoperatively received enhanced MRI examinations. All tumors were located retrochiasm in the third ventricle. A line between the nasal apex and the chiasm on the sagittal MRI (nasal-chiasm line, NCL) was used to evaluate the supra- and infrachiasm corridors available for tumor resection. The NCL divided the tumors into two areas, the upper supra-NCL region and the lower infra-NCL region. If the percent of the supra-NCL region included over 20% of the tumor, then the lamina terminalis corridor was used to remove this part of the tumor. At the same time, if the area of the tumor in the infra-NCL region was over 10%, both TLTA and TCPC were used (**Figure 1**).

Surgical Techniques

All 11 patients underwent tumor resection using the expanded transsphenoidal approach. An intraoperative visual evoked potential (VEP) monitor was used to monitor visual function. According to the preoperative MRI evaluation, if TLTA could be used to access the supra-NCL part of tumor, then bone of the bilateral optic canal was fully removed to increase optic nerve mobilization during optic nerve retraction so as to reduce damage to the nerve. The dura mater was opened to fully expose both the suprachiasm and infrachiasm corridors. The arachnoid membrane surrounding the chiasm was dissected sufficiently to release the optic nerves. When dissecting the suprachiasmatic space, we took care to protect the anterior communicating artery complex and its branches to the optic chiasm. We then opened the lamina terminalis with scissors to expose the tumor in the third ventricle. First, the tumor was decompressed piece by piece patiently to gain sufficient surgical space. Then the extracapsular portion of the tumor was dissected away from the optic chiasm, hypothalamus and surrounding artery system, especially the posterior cerebral artery, *via* careful microdissection between the tumor capsule and arachnoid plane, and the tumor was removed piece by piece until finally achieving complete resection. For tumors with more than 10% of their area under the NCL, after the upper tumor was removed, the degree of optic chiasm mobilization increased significantly. The infrachiasmatic corridor then widened significantly to expose the tumor. Sometimes, when the bottom of the third ventricle was intact, it was necessary to open the capsule from the weakest part of the tumor surface and resect the residual tumor. It was also necessary to protect the pituitary stalk, superior pituitary artery, circle of Willis and its branches. Finally, the tumor was completely resected. The skull base reconstruction was performed according to our previous work (10). These technique notes were showed in Video 1 for Case 9.

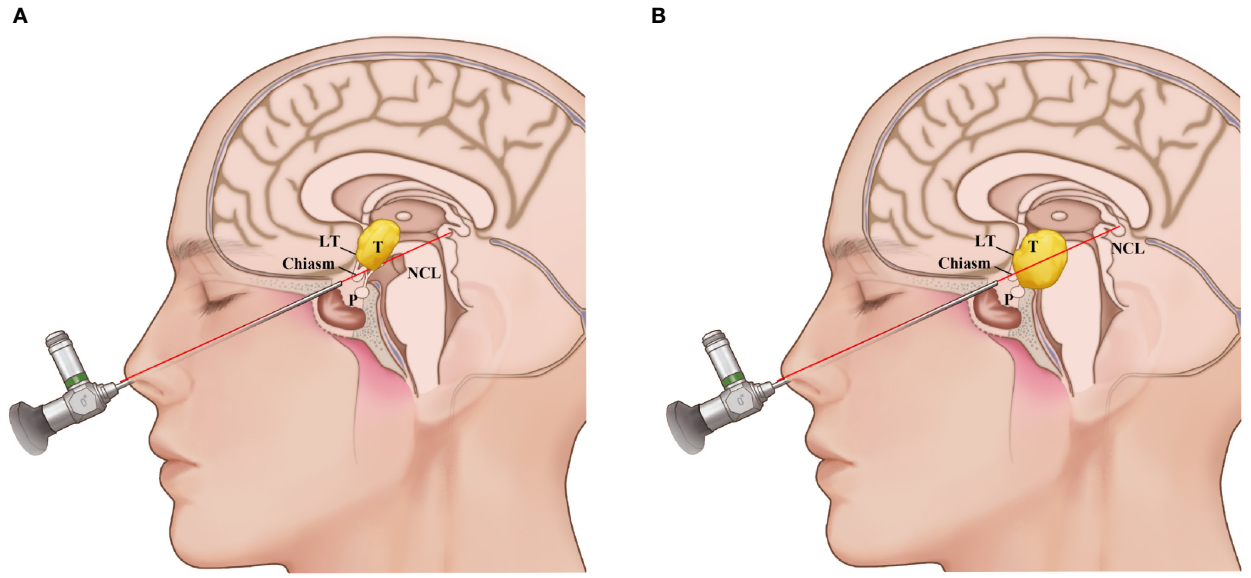

FIGURE 1 | Schematic representation of the use of the nasal-chiasmic line for corridor selection in third ventricle lesion. **(A)**, If the percent of the supra-NCL region included over 20% of the tumor, then the lamina terminalis corridor was used to remove this part of the tumor. **(B)** If the area of the tumor in the infra-NCL region was over 10% and the area of the tumor in the infra-NCL region was over 20%, both lamina terminalis corridor and infrachiasmic corridor were used. NCL, nasal-chiasmic line; T, tumor; P, pituitary; LT, laminal terminalis.

All patients received intraoperative VEP monitoring to predict visual outcomes, as referred to in our previous work (11). More attention was given to VEP variations during the three stages of unroofing the optic canal, removing the tumor and reconstructing the skull base.

Extent of Tumor Resection

The extent of resection was determined by pre- and postoperative volumetric analysis of MR images. Gross total resection (GTR) was defined as 100% tumor removal, subtotal total resection (STR) was defined as tumor removal of over 90%, and partial total resection (PTR) was defined as tumor removal less than 90%, but greater than 50%. Tumor recurrence during the follow-up period was defined as the appearance of new pathological tissue on MR images or the growth of tumor remnants. Follow-up MR imaging was performed at 3 months after surgery and then at regular intervals of 6–12 months.

Visual Function

Visual acuity and visual field examinations were evaluated by an ophthalmologist before and after surgery.

Endocrine Status

The endocrine status of all patients was assessed pre- and postoperatively according to adenohypophysis function and diabetes insipidus. Adenohypophysis function was assessed using complete serum pituitary hormone panels. Diabetes insipidus was defined as urine volume greater than 50 ml/kg/d. Electrocyte imbalance was defined as serum sodium level over 145 mmol/L or lower than 135 mmol/L, and serum potassium level over 5.5 mmol/L or lower than 3.5 mmol/L 2 weeks after surgery.

All patients BMIs were assessed at time of surgery and at the last visit. Obesity was defined as BMI > 30 kg/m^2 or 9% BMI gain after surgery compared with the preoperative BMI (12).

RESULTS

Demographic and Clinical Factors

From September 2019 to December 2021, 11 patients (ten males, one female) with tumors extending into the third ventricle, which were resected by TLTA participated in this study (details in **Table 1**). The average patient age was 45.1 ± 11.5 years, ranging from 25–68 years. In total, seven patients (63.6%) had vision impairment preoperatively. Additionally, three patients (27.3%) had polydipsia or polyuria, and one patient suffered from epilepsy. According to the histological characteristics, they were six papillary craniopharyngiomas, two adamantinomatous craniopharyngiomas, one cavernous malformation, one germinal cell tumor (GCT) and one chordoid glioma. Based on the NCL, tumors extending more than 50% supra-NCL were observed in all 11 patients, while tumors extending more than 10% infra-NCL were observed in eight patients. Intraoperatively, TLTA was used alone in 4 patients (**Figure 2**) while the TCPC was combined with TLTA in 7 patients (**Figure 3**). In a patient with an infra-NCL tumor of over 20%, only TLTA was used as the surgical strategy to achieve partial resection, followed by radiotherapy and chemotherapy; in this case, the frozen histological report indicated a GCT (Case 3).

TABLE 1 | Clinical data of tumors extended into third ventricle.

Case	Patho.	CTNNB1/ BRAFV600E Mutation	Gender/ age	symptoms	Approach	Supra-NCL/ sub-NCL	Extent of resection	Pre-op.Visual deficit	Post-op.Visual deficit	Intra-op. VEP	Pre-op. hypopituita-rism	Post-op. hypopituita-rism	Pre-op. DI	Post-op. DI	Pre-op. BMI	Pre-op. BMI	Adjunc-tive therapy	Recur-rent
1	PCP	-/+	M/40	Tongue numbness	TLTA +TCPC	50%/ 50%	GTR	Nor.	Nor.	No-change	Nor.	N	N	N	29.4	31.2	N	N
2`	CM	NA	M/43	epilepsy	TLTA +TCPC	80%/ 20%	PTR	Nor.	Nor.	No-change	Nor.	Y	N	Y	24.7	25.3	N	N
3	GCT	NA	F/25	Polydipsia, polyuria, visual deficit	TLTA	80%/ 20%	PTR	Visual deficit	Worse	Worse	Nor.	Y	Y	Y	26.7	24.7	R+C	N
4	CG	NA	M/37	Polydipsia, polyuria, visual deficit	TLTA	95%/ 5%	GTR	Visual deficit	Improved	Improved	Nor.	Y	Y	Y	26.7	28.9	N	N
5	PCP	-/+	M/43	visual deficit	TLTA +TCPC	50%/ 50%	GTR	Visual deficit	No-changed	No-changed	Nor.	Y	N	Y	24.3	24.7	R	Y
6	ACP	NA*	M/46	visual deficit	TLTA +TCPC	70%/ 30%	GTR	Visual deficit	improved	Improved	Nor.	Y	N	N	23.4	24.3	N	N
7	PCP	-/+	M/55	visual deficit	TLTA +TCPC	70%/ 30%	GTR	Visual deficit	No-changed	No-changed	Nor.	Y	N	N	26.8	24.9	N	N
8	ACP	+/-	M/52	visual deficit	TLTA +TCPC	55%/ 45%	PTR	Visual deficit	Worse	Worse	Nor.	Y	N	N	32.4	28.7	Y	N
9	PCP	-/+	M/68	polydipsia, polyuria, visual deficit	TLTA	95%/ 5%	GTR	Visual deficit	Improved	Improved	Nor.	N	Y	Y	27.2	29.4	N	N
10	PCP	-/+	M/42	visual deficit	TLTA +TCPC	55%/ 45%	GTR	Visual deficit	Improved	Improved	Nor.	N	N	N	29.4	18.5	N	N
11	PCP	-/+	M/57	Memory disorder, visual deficit	TLTA	90%/ 10%	GTR	Visual deficit	Improved	Improved	Nor.	N	N	N	26.1	26.4	N	N

*Patho., Pathology; PCP, papillary craniopharyngioma; CM,cavernous malformation; CG, chordoid glioma; TLTA, translamina terminalis approach; TCPC, trans chiasm-pituitary corridor; GTR, gross total resection; PTR, partial total resection; GCT, germinal cell tumor; ACP, adamantinomatous craniopharyngioma; DI, diabetes insipidus; Nor, normal; Y, yes; N, No; R, radiotherapy; C, chemotherapy; NA, Not available; *, specimen was not enough for detection of CTNNB1 and BRAFV600E mutation.*

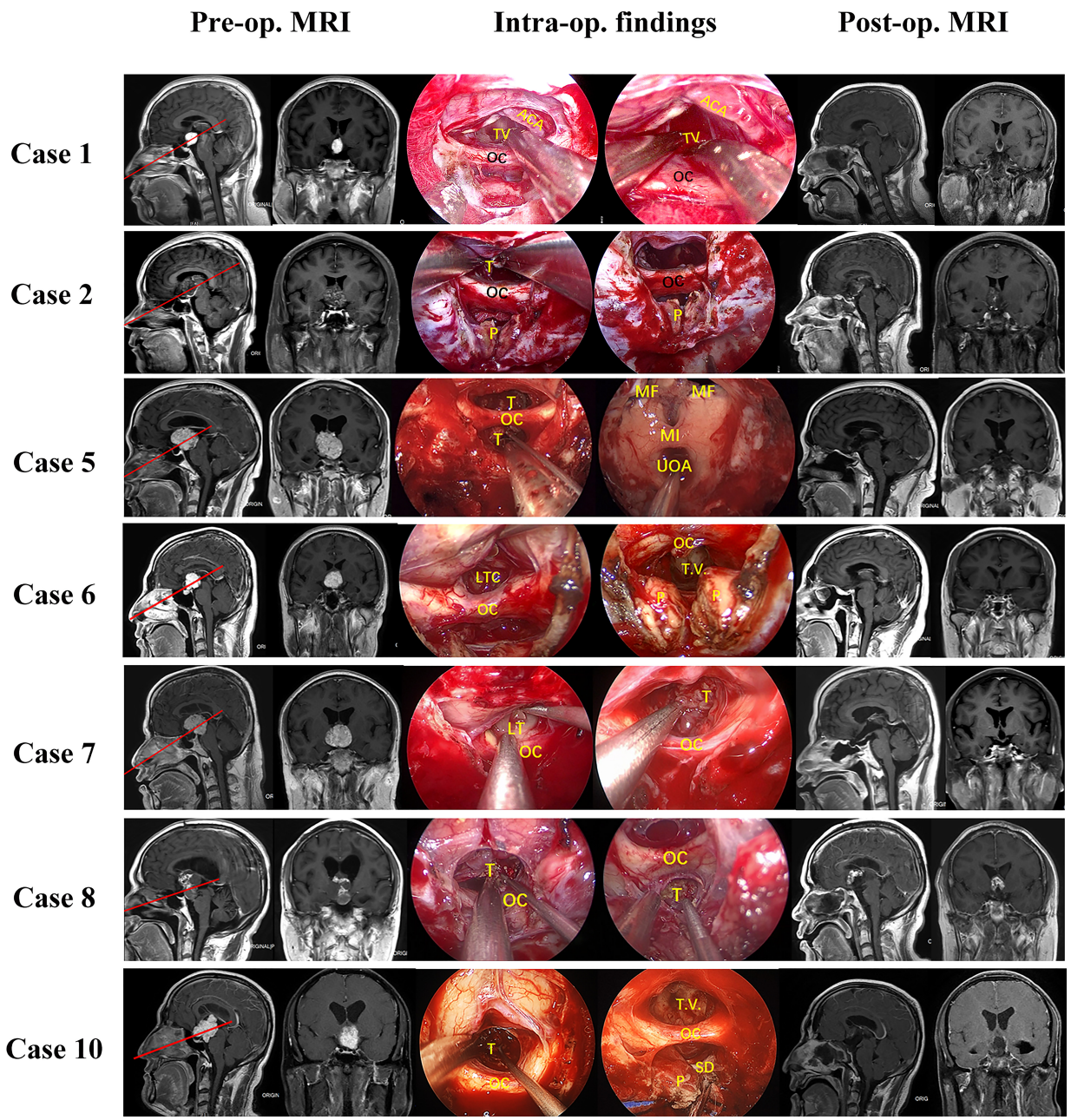

FIGURE 2 | Pre- and post-operative MRI and intraoperative findings of 11 patients treat by trans-lamina terminalis approach combined with trans-pituitary-chiasm corridors. Case 1, a papillary craniopharyngioma located in the 3rd ventricle with supra-NCL part about 50%. Removing the tumor through EEA with two corridors: suprachiasm trans-lamina terminalis corridor and infrachiasm chiasm-pituitary corridor. The tumor was gross total removed and lateral wall of third ventricle can be seen clearly. Case 2, a cavernous malformation located in the 3rd ventricle with supra-NCL part about 80%. the tumor was solid with a large draining vein. Both TLTA and TCPC were used to remove the tumor. the tumor was partial removed for protection of the draining vein. Case 5, a papillary craniopharyngioma extended into the 3rd ventricle with supra-NCL part about 95%. Removing the tumor through EEA with supra-chiasm corridor (trans-lamina terminalis). After the tumor was totally removed, the posterior wall of third ventricle, Monro foramen, and upper outlet of aqueduct can be seen clearly. Case 6, an ACP extended into the 3rd ventricle with supra-NCL part about 70%. Both TLTA and TCPC were used to remove the tumor totally. Case 7, a papillary craniopharyngioma with supra-NCL part about70% were removed by both TLTA and TCPC. Case 8, an ACP with supra-NCL part about 55% were removed by both TLTA and TCPC. the tumor was adhered internal cerebral vein tightly and encased AComA complex, the superior part of tumor was left for gamma knife. Case 10, a papillary craniopharyngioma with supra-NCL part about 55% were removed totally by TLTA combined with TCPC. Case 11, a papillary craniopharyngioma with supra-NCL part about 90% were removed totally by TLTA. OC, optic chiasm; PS, pituitary stalk; ON, optic nerve; T, tumor; P, pituitary; ICA, internal carotid artery; T.V., 3rd ventricle; LT, lamina terminalis; HT, hypothalamus; MF, Monro's foramen; TLTA,trans-lamina terminalis approach; TCPC,trans pituitary-chiasm corridor.

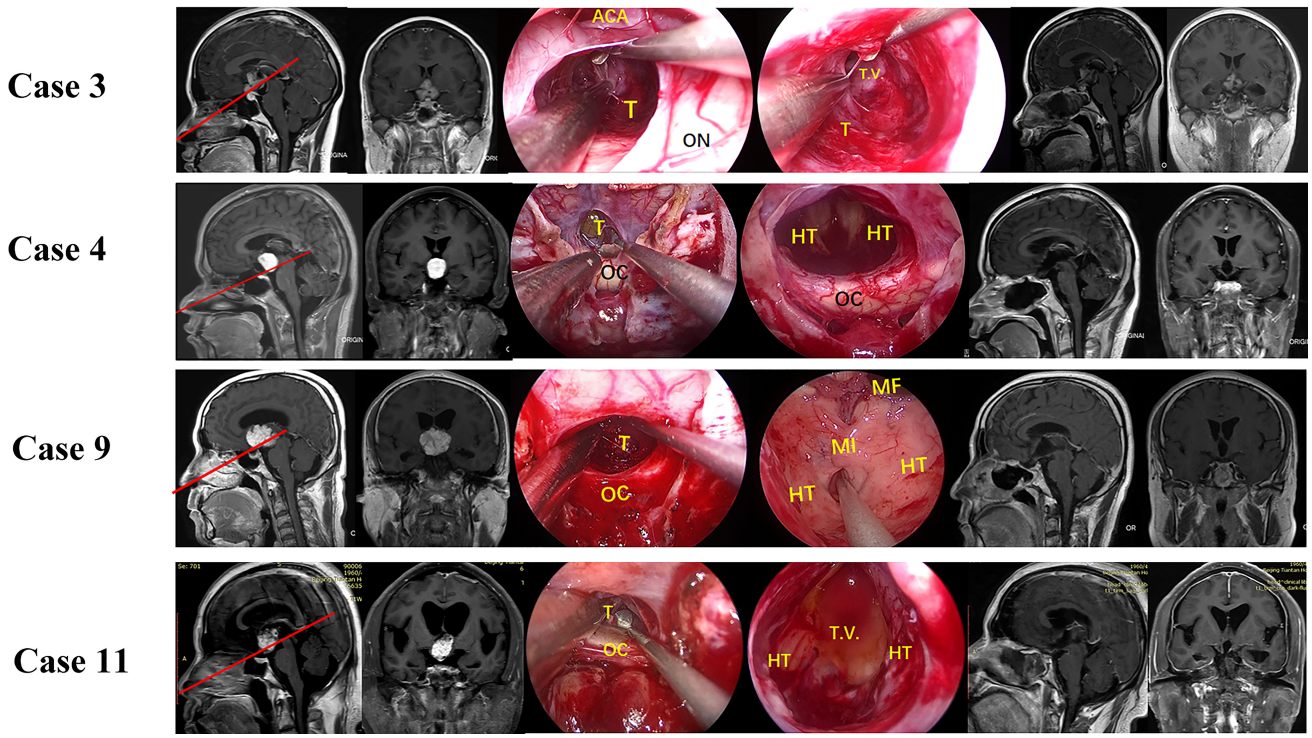

FIGURE 3 | Pre- and post-operative MRI and intraoperative findings of 11 patients treat by combined trans-lamina terminalis and trans-pituitary-chiasm corridors. Case 3, a germinoma with supra-NCL part about 80% were partial resected *via* a TLTA and a radiotherapy and chemotherapy were followed. Case 4, a chordoid glioma with supra-NCL part about 95% were total removed by TLTA. Case 9, a papillary craniopharyngioma with supra-NCL part about 95% were removed totally by TLTA. Case 11, a papillary craniopharyngioma with supra-NCL part about 90% were removed totally by TLTA. OC, optic chiasm; PS, pituitary stalk; ON, optic nerve; T, tumor; P, pituitary; ICA, internal carotid artery; T.V., 3rd ventricle; LT, lamina terminalis; HT, hypothalamus; MF, Monro's foramen; TLTA,trans-lamina terminalis approach.

Extent of Tumor Resection

GTR was achieved in eight (72.7%) patients. Partial resection was achieved in three patients. One patient with GCT achieved partial resection as the surgical outcome, followed by radiotherapy and chemotherapy. Another case was a cavernous malformation in which partial resection was used to protect an adherent large draining vein. A third case was craniopharyngioma in which the internal cerebral vein adhered tightly and the ACA was encased.

Ophthalmologic and Endocrine Outcomes

Prior to surgery, nine patients with tumors extending into the third ventricle had visual deficits. After surgery, visual improvement was observed in four patients (36.4%), no change was seen in five patients (45.5%), and some deterioration occurred in two patients (18.2%). The ophthalmologic outcomes were consistent with the intraoperative VEP amplitude improvement.

Seven of 11 patients (63.6%) developed new adenohypophysis deficits postoperatively (**Table 2**) and three patients were unchanged. For most patients, the diabetes inspidus symptoms did not change in eight patients and new-onset symptoms occurred in two patients. Only one patient developed hypothalamic obesity with BMI of 31.2 (**Table 2**).

Postoperative Complications and Outcomes

No postoperative cerebral spinal fluid leakage occurred. No patients died. One patient (Case 7) suffered from meningitis and was cured by administration of vancomycin and meropenem. Post-operative electrocyte imbalance including hypo- or hypernatremia and hypo- or hyperkalemia was observed in six patients (60%) after 2 weeks.

The mean follow-up period of this study was 12.16 ± 3.40 months (range, 6–22 months). One patient (case 3) with GCT who underwent PTR was treated with gamma knife therapy. One patient (case 7) with tumor recurrence received adjunctive gamma knife therapy. No tumor recurrence was observed in other patients.

Illustrative Case

A 37-year-old male patient (case 4) presented with polydipsia, polyuria and visual impairment for 1 year. Preoperative MRI

TABLE 2 | Clinical outcomes of 11 patients with tumor resection by TLTA.

	NO.	Percentage
Extent of tumor resection		
GTR	8	72.7%
PTR	3	27.3%
Visual outcome		
Improved	4	36.4%
Not changed	5	45.5%
Worse	2	18.2%
Adenohypophysis function		
Improved	1	9.1%
Not changed	3	27.3%
Worse	7	63.6%
Diabetes insipidus		
Improved	0	0
Not changed	9	81.2%
Worse(new-onset)	2	18.2%
Post-op BMI>30 or 9% more BMI gained		
Yes	1	9.1%
Not	10	90.9%
Complications		
CSF leaks	0	0
Infections	1	9.1%
Electrolyte imbalance (in post-op. 2w)	6	54.5%
Mortality	0	0
Recurrent	1	9.1%

indicated a solid lesion located in the third ventricle (**Figure 4**). Based on the NCL, the supra-NCL portion was over 90%. TLTA alone without TCPC was used to remove the tumor. Intraoperative VEP monitoring showed the VEP amplitude (N75 to P100) was gradually reversed and finally improved in both sides of the eyes after the tumor was totally removed. Postoperative ophthalmic examination showed that visual acuity and visual field improved significantly. The postoperative histological examination showed the tumor as a chordoid glioma and no tumor recurrence was observed 9 months post-operatively.

DISCUSSION

Feasibility of Using TLTA for Tumors Extending Into the Third Ventricle by EEA

Tumors that are deep-seated mostly within the third ventricle are often considered for a midline approach such as endoscopic endonasal, subfrontal trans-lamina terminalis (13), anterior interhemispheric trans-lamina terminalis (14) or anterior transcallosal (15) approaches to gain optimal access and minimize hypothalamic disruption. EEA has become popular in recent decades to resect suprasellar tumor, but some authors do not support the use of EEA for tumors located in the third ventricle because the intact floor of the third ventricle may be at least partially violated by using the infrachiasmatic corridor (16). Recently, several authors have reported the outcomes of EEA for third ventricle tumors (17–21). In these studies, GTR ranged from 66.7%–90%, with newly developed endocrinopathy ranging from 18%–67% for panhypopituitarism, and the improvement rate for visual functions ranging from 56%–86%. The CSF leakage rate ranged from 3.8%–69%, with a recurrence rate ranging from 18%–34.4%. In our study, we report our successful experience in treating 11 patients with tumors located in the third ventricle by an expanded endoscopic transnasal approach *via* TLTA combined with or without access through TCPC. GTR was achieved in eight cases (72.7%). Visual impairments were improved or unchanged in nine cases (81.8%), with two new-onset diabetes inspidus, seven new onset cases of hypopituitarism, no surgical-related deaths and no CSF leaks. Only one patient had recurrent craniopharyngioma in 12 months. The results imply that it is feasible to remove deep-seated tumors in the third ventricle *via* TLTC by EEA.

The major finding of this report was that the patients achieved GTR after undergoing tumor resection *via* EEA even though a large amount of tumor extended up into the third ventricle above and behind the chiasm. Preoperatively, we evaluated the tumor topography using MRI. The suprachiasmatic and infrachiasmatic corridors were first evaluated with sagittal MRI. The NCL was used to divide the tumor into two-regions described as supra-NCL and infra-NCL. The surgical strategy was formulated in advance by evaluating the predominance of the supra-and infra-NCL regions. For tumors located in the third ventricle, the chiasm was likely to be compressed anterior-inferiorly, resulting in a chiasm-pituitary corridor too narrow to gain access to the tumor. For tumors with a supra-NCL region less than 20%, the chiasm was more likely to be compressed superiorly; thus, tumor resection could often be performed through the chiasm-pituitary corridor (22). With tumor decompression, the upper part of the tumor settled into the surgical field to be easily removed from the interface between tumor and hypothalamus. For tumors with a supra-NCL region more than 20%, the chiasms were more likely be compressed inferiorly, and the lamina terminalis provided good access to the upper part of the tumors. During the process of tumor depression, the chiasm resettled upward, so that TCPC was accessed to remove the lower part of the tumor. Therefore, the combination of TLTA *via* the TCPC was needed for this subtype of tumor. However, if the tumor region below the NCL was less than 10%, then the tumor could be removed by TLTA alone because the lower region could be moved upward by slight manipulation of the chiasm. For tumors in the third ventricle, intraoperative frozen pathology was needed to confirm the histological results. For germ cell tumors or optic gliomas, partial resection after tumor decompression was sufficient to reconstruct the cerebrospinal fluid circulation, and postoperative adjuvant radiotherapy and chemotherapy were then combined. For tumors with tight adhesion to important blood vessels such as the ACA or internal cerebral veins, a small amount of residual tumor was accepted if the tumor could not be separated, and adjuvant postoperative radiotherapy was employed to reduce tumor recurrence.

The limitation of TLTA is that higher surgical manipulation through the lamina terminalis may have a higher incidence of injury to the optic chiasm or anterior communicating artery (AComA) complex, because most of the blood supply to the optic apparatus comes from the branches of the ACA and AcomA (22, 23). Also, the AComA sometimes blocked the suprachiasmic corridors to expose the lesions in the third

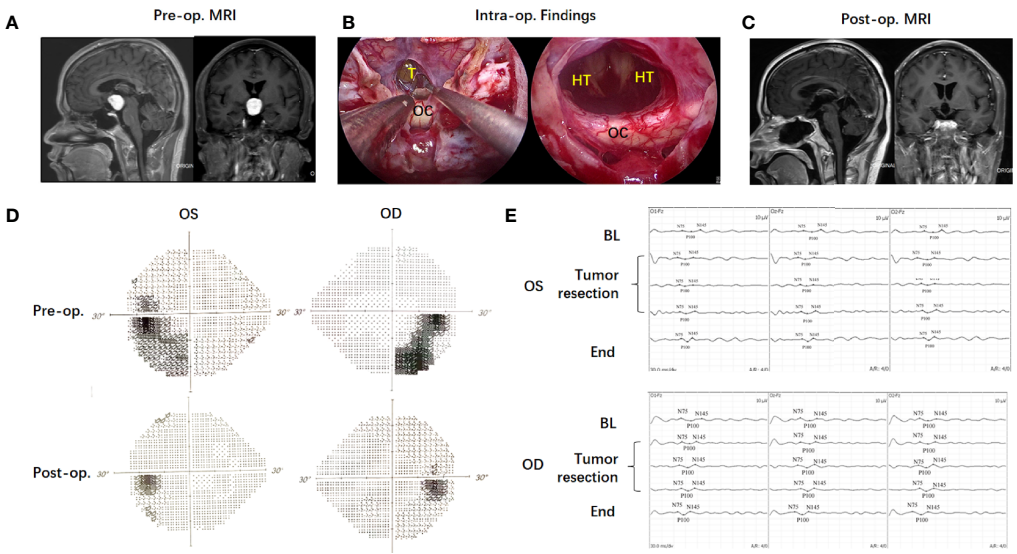

FIGURE 4 | Case illustration of endoscopic transnasal translamina terminalis approach. A 37-year-old male patient (Case 4) with a solid lesion located in the third ventricle in preoperative MRI **(A)**. Based on the NCL, the Supra-NCL part was over 90%. Translamina terminalis approach was used to remove the tumor **(B)**. Postoperative MRI showed the tumor was totally removed **(C)**. The intraoperative VEP monitoring showed the VEP amplitude (N75 to P100) was gradually reversed and finally improved in both sides of eyes after the tumor was totally removed **(D)**. Postoperative ophthalmic examination showed the visual field improved significantly **(E)**.

ventricle. So, some authors advocated the surgical clipping and division of the AComA in selected patients through the bifrontal basal interhemispheric approach or the anatomical feasibility through the endoscopic endonasal corridor to achieve a better visualization (24, 25). In our study, visual function worsened in 18.2% of the patients. We also used intra-operative VEP monitoring to assess manipulation of the optic nerve in order to avoid surgical damage to visual function (11). We also tried to remove more bone from the optical canals to increase the mobilization of the optic chiasm, which can reduce manipulation injuries though TLTA (26). The indications and complications of EEA TLTA for tumors extended into third ventricle were summarized in **Table 3**.

Comparison of Different Approaches to Tumors Extending Into the Third Ventricle

Currently, transcranial approaches such as the transcallosal interforniceal approach, transventricular approach and translamina terminalis approach are commonly used to remove tumors extending into the third ventricle. The indications and pros and cons of these approaches are summarized in **Table 4**.

The transcallosal interforniceal route provides an excellent window for the dissection of tumors from the hypothalamus bilaterally, especially for larger tumors and tumors that favor the posterosuperior aspect of the third ventricle. However, direct visualization of the third ventricle floor and displaced optic chiasm from this superior viewpoint is unsatisfactory. Thus, tumor tissue in the anterior third ventricle and suprasellar cistern can be difficult to dissect safely given the working angle and depth, and resection can cause inadvertent damage of the third ventricle floor involving infundibulum/stalk disconnection and surrounding arteries. Furthermore, the transcallosal approach may cause cognitive decline in adults (27, 28).

In the transventricular approach, access into the third ventricle is performed *via* enlargement of the Monro foramen. However, the Monro foramen is more likely to be small in the absence of a dilated ventricular system, which will increase the risk to the ipsilateral fornix and deep venous structures. Additionally, the long working depth and blind spots in the transventricular approach can also complicate efforts to dissect the deep margin of the tumor from neurovascular structures when adherence is present.

TABLE 3 | The indications and complications of EEA TLTA for tumors extended into third ventricle.

	Details
Indications	All tumors were located retrochiasm in the third ventricle with the percent of supra-NCL part over 20 percent.
Complications	Visual impairment, endocrinological disorders, CSF leaks, electrocyte imbalance
Complications avoidance techniques	1.Protect the blood supply to chiasm, intra-operative VEP monitoring, reduce retraction of optic chiasm, remove the bone of optical canals to increase the optic nerve mobilization. 2.Skull base reconstruction using nasal septal flap. 3.Monitor the water and electrocyte balance.

TABLE 4 | Indications and pros and cons of different surgical approaches to the tumors extended to third ventricle.

Surgical approaches	Indications	Advantages	Disadvantages
Transcallosal interforniceal approach	Tumors favor the middle line and posterosuperior aspect of the third ventricles	1. Better for larger tumors and tumors that favor the posterosuperior aspect of the third ventricle 2. Excellent window for the dissection of tumor from the hypothalamus bilaterally	1. Long work distance 2. Cognitive impairment 3. Limited visualization of the third ventricle floor and displaced optic chiasm from this superior viewpoint
Transventricular approach	Tumors favor the posterosuperior aspect of the third ventricles with dilated Monro's Foramen or tumors extended into the lateral ventricle	1. Excellent visualization for larger tumors and tumors that favor the posterosuperior aspect of the third ventricle	1. Risk to the ipsilateral fornix and deep venous structures 2. Long work distance 3. Limited visualization of deep margin of the tumor
Anterior interhemispheric approach *via* TLTA	Tumors occupying the anteroinferior portion of the third ventricle without ACoA complex blocking lamina terminalis	Excellent visualization of tumors through lamina terminalis	1. Risks to the adjacent optic pathways, supraoptic nuclei of the hypothalamus, and columns of the fornix 2. ACoA complex block TLTA
Subfrontal or pterion approach *via* TLTA	Tumors occupying the anteroinferior portion of the third ventricle without ACoA complex blocking lamina terminalis	Excellent visualization of contralateral wall of hypothalamus and third ventricle floor thought lamina terminalis	1. Limited visualization of the superior extent of tumor extension and ipsilateral wall of hypothalamus 2. ACoA complex and ipsilateral A1 block TLTA
EEA *via* TCPC	Tumors favors sub-NCL part of the third ventricle	1. Excellent visualization of the infrachiasmic tumor 2. little traction of optic chiasm	1. Long work distance 2. Bad visualization of upper tumor to roof of third ventricle 3. TCPC is narrow when chiasm prefixed 4. CSF leaks
EEA *via* TLTA	Tumors favor supra-NCL part of the third ventricle without extending into lateral ventricle	Excellent visualization of the suprachiasmic tumor	1. 1.High risk to optic chiasm for traction 2. Limited visualization of infrachiasmic tumors 3. Long wok distance 4. CSF leaks

TLTA, translamina terminalis approach; TCPC, trans chiasm-pituitary corridor; EEA, extended endoscopic approach; ACoA, artery communicating artery; CSF, cerebrospinal fluid.

The trans-lamina terminalis approach is suggested for tumors occupying the anteroinferior portion of the third ventricle. Entry through the lamina terminalis is associated with risks to the adjacent optic pathways, supraoptic nuclei of the hypothalamus and columns of the fornix. The small trans-lamina terminalis corridor is biased toward the inferior aspect of the third ventricle. There are various approaches for access to the lamina terminalis, such as the transcranial and transnasal approaches. When approached from the pterional corridor, lateral subfrontal and/or midline subfrontal interhemispheric corridor, limited visualization of the superior extent of tumor extension makes it difficult to reach tumors that extend posteriorly and superiorly. Elevation of the ACA also limits the superior trajectory of the exposure. Generally, the interface between the tumor and hypothalamus cannot be directly visualized through transcranial approaches, so it is often necessary to remove the tumor by traction. The damage to the hypothalamus caused by tumor traction is far greater than that caused by sharp dissection under direct vision. Therefore, if the tumor is integrated into the walls of the hypothalamus, many surgeons advocate forgoing total resection, leaving the part that adheres to the hypothalamus to avoid postoperative functional complications.

EEA has improved our ability to perform a cleaner dissection of the tumor away from the hypothalamus, with direct visualization of the interface between the tumor and hypothalamus. This can decrease damage to the hypothalamus caused by tumor traction, which means that EEA may be worthwhile to achieve GTR of the tumor with less damage to the hypothalamus (29, 30). Furthermore, radiotherapy to treat these tumors can also be damaging. In addition, the risk of re-operation for recurrent tumors after radiotherapy is higher, and the total resection rate can be significantly lower (31–33), especially for large cystic craniopharyngiomas, which tend to adhere more tightly to the hypothalamus, and from which a small residue may quickly grow into a large cyst tumor. Therefore, we attempt total resection whenever possible by careful sharp dissection between the tumor and hypothalamus to avoid these postoperative complications.

CONCLUSIONS

TLTA provides a feasible suprachiasmatic corridor to remove lesions extending into the third ventricle by EEA. Sound understanding of the major strengths and limitations of this approach, as well as strategies for complication avoidance, is necessary for its safe and effective application.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethic committee of Beijing Tiantan Hospital, Capital Medical University (KY 2021-041-02). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Conception and design: SG, LC, and YZ. Surgical Intervene: LC, JK, HZ, and JB. Data Collection and Analysis: LC, WW, and JK. Technique support: HQ and XY. Drafting the article: LC and SG. Critically revising the article: all authors. Approved the final version of the manuscript on behalf of all authors: SG. Study supervision: all authors. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by the Capital's Funds for Health Improvement and Research (grant no.2020-4-1077), the Beijing Municipal Science & Technology Commission (Z19110700660000) and Beijing Hospitals Authority Clinical Medicine Development of Special Funding Support (XMLX202108).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.761281/full#supplementary-material

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frontiers in Neurology

ORIGINAL RESEARCH
published: 13 December 2021
doi: 10.3389/fneur.2021.704130

A Novel Immune Classification for Predicting Immunotherapy Responsiveness in Patients With Adamantinomatous Craniopharyngioma

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Edited by:
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Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Neurology

Received: 01 May 2021
Accepted: 12 November 2021
Published: 13 December 2021

Citation:
Yuan F, Cai X, Zhu J, Yuan L, Wang Y, Tang C, Cong Z and Ma C (2021) A Novel Immune Classification for Predicting Immunotherapy Responsiveness in Patients With Adamantinomatous Craniopharyngioma. Front. Neurol. 12:704130. doi: 10.3389/fneur.2021.704130

Adamantinomatous craniopharyngioma (ACP) is the most common tumor of the sellar region in children. The aggressive behavior of ACP challenges the treatment for it. However, immunotherapy is rarely studied in ACP. In this research, we performed unsupervised cluster analysis on the 725 immune-related genes and arrays of 39 patients with ACP patients in GSE60815 and GSE94349 databases. Two novel immune subtypes were identified, namely immune resistance (IR) subtype and immunogenic (IG) subtype. Interestingly, we found that the ACPs with IG subtype (34.78%, 8/23) were more likely to respond to immunotherapy than the ACPs with IR subtype (6.25%, 1/16) *via* tumor immune dysfunction and exclusion (TIDE) method. Simultaneously, the enrichment analysis indicated that the differentially expressed genes (DEGs) ($p < 0.01$, FDR < 0.01) of the IG subtype were chiefly involved in inflammatory and immune responses. However, the DEGs of the IR subtype were mainly involved in RNA processing. Next, immune infiltration analysis revealed a higher proportion of M2 macrophage in the IG subtype than that in the IR subtype. Compared with the IR subtype, the expression levels of immune checkpoint molecules (PD1, PDL1, PDL2, TIM3, CTLA4, Galectin9, LAG3, and CD86) were significantly upregulated in the IG subtype. The ssGSEA results demonstrated that the biofunction of carcinogenesis in the IG subtype was significantly enriched, such as lymphocyte infiltration, mesenchymal phenotype, stemness maintenance, and tumorigenic cytokines, compared with the IR subtype. Finally, a WDR89 (the DEG between IG and IR subtype)-based nomogram model was constructed to predict the immune classification of ACPs with excellent performance. This predictive model provided a reliable classification assessment tool for clinicians and aids treatment decision-making in the clinic.

Keywords: adamantinomatous craniopharyngioma (ACP), immune microenvironment (IME), classification, immunotherapy, nomogram

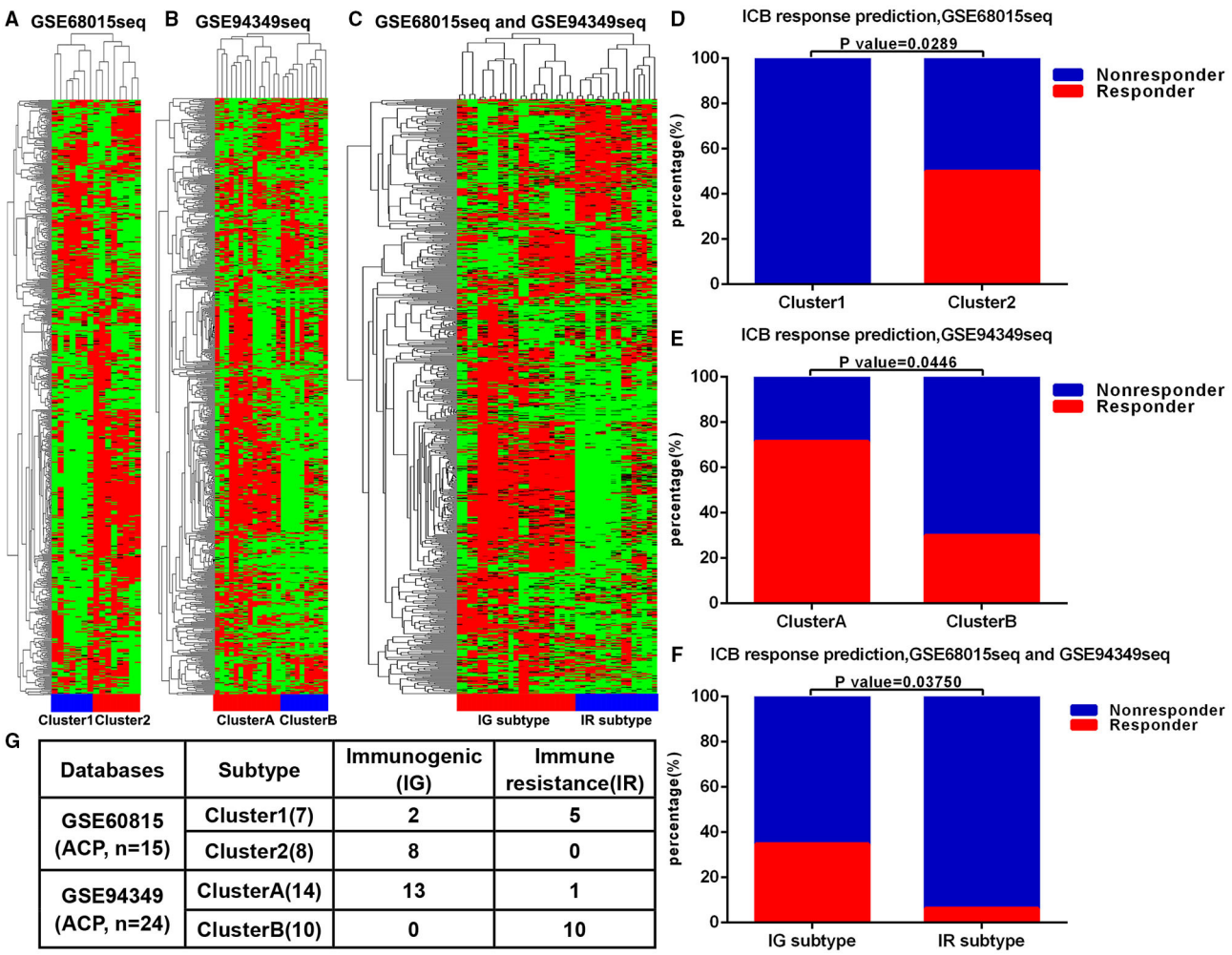
INTRODUCTION

Craniopharyngioma (CP) constitutes 1.2–4.6% of all intracranial tumors, accounting for 0.5–2.5 new cases per 1 million population per year globally, of which 30–50% are diagnosed during childhood and adolescence (1–3). The two histological subtypes of CP, adamantinomatous CP (ACP) and papillary CP (PCP) differ in their genesis and age distribution (4). ACP has a bimodal age distribution, with peak incidences in children aged 5–15 years and adults aged 45–60 years. In the childhood and adolescent age group, the APC histological type with cyst formation is the most common. PCPs occurs almost exclusively in adults, at a mean patient age of 40–55 years, and no sex differences have been observed (1, 2, 5, 6).

The current standard treatment for CP is surgery with or without radiotherapy. Although CP is considered histologically benign (WHO grade I), the prognosis and outcomes of CPs are frequently impaired due to the hypothalamus–pituitary location of the CP and tumor-related and/or treatment-related injury to these important structures (7, 8). There is an urgent need for safe and effective alternative therapies to reduce side effects and improve quality of life.

In recent years, cancer immunotherapy has experienced remarkable advances and shifted the paradigm for the treatment of malignancies. Impressive clinical responses have been achieved for several types of solid cancers (such as melanoma, non-small cell lung cancer, and bladder cancer) after treatment with immune checkpoint blockade (ICB) therapy (9). However, cancer immunotherapy is rarely studied in patients with CP.

Through in-depth analysis of the genomic, transcriptomic, and proteomics of patients with ACP, researchers found that the immune response process plays an important role in the



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Databases	Subtype	Immunogenic (IG)	Immune resistance(IR)
GSE60815 (ACP, n=15)	Cluster1(7)	2	5
	Cluster2(8)	8	0
GSE94349 (ACP, n=24)	ClusterA(14)	13	1
	ClusterB(10)	0	10

FIGURE 1 | ACPs classification based on immune infiltration. **(A)** The immune microenvironment (IME) of ACPs in the GSE68015 database could be divided into two different clusters, namely cluster 1 and cluster 2. **(B)** The IME of ACPs in the GSE94349 database could also be divided into two different clusters (cluster A and cluster B). **(C,G)** After merging these two databases, ACPs in the cluster 1 group could be matched with ACPs in the cluster B group well, and ACPs in the cluster 2 group could be matched with ACPs in the cluster A group well. **(D–F)** The accumulative bar diagram showed that the ACPs with cluster 2 and cluster A (50%, 4/8; 71.43%, 10/14) were more likely to respond to ICB immunotherapy than the ACPs with cluster 1 and cluster B (0%, 0/7; 30%, 3/10). **(G)** Immune classification and naming of ACPs. ICB, immune checkpoint blockade; IG, immunogenic; IR, immune resistance.

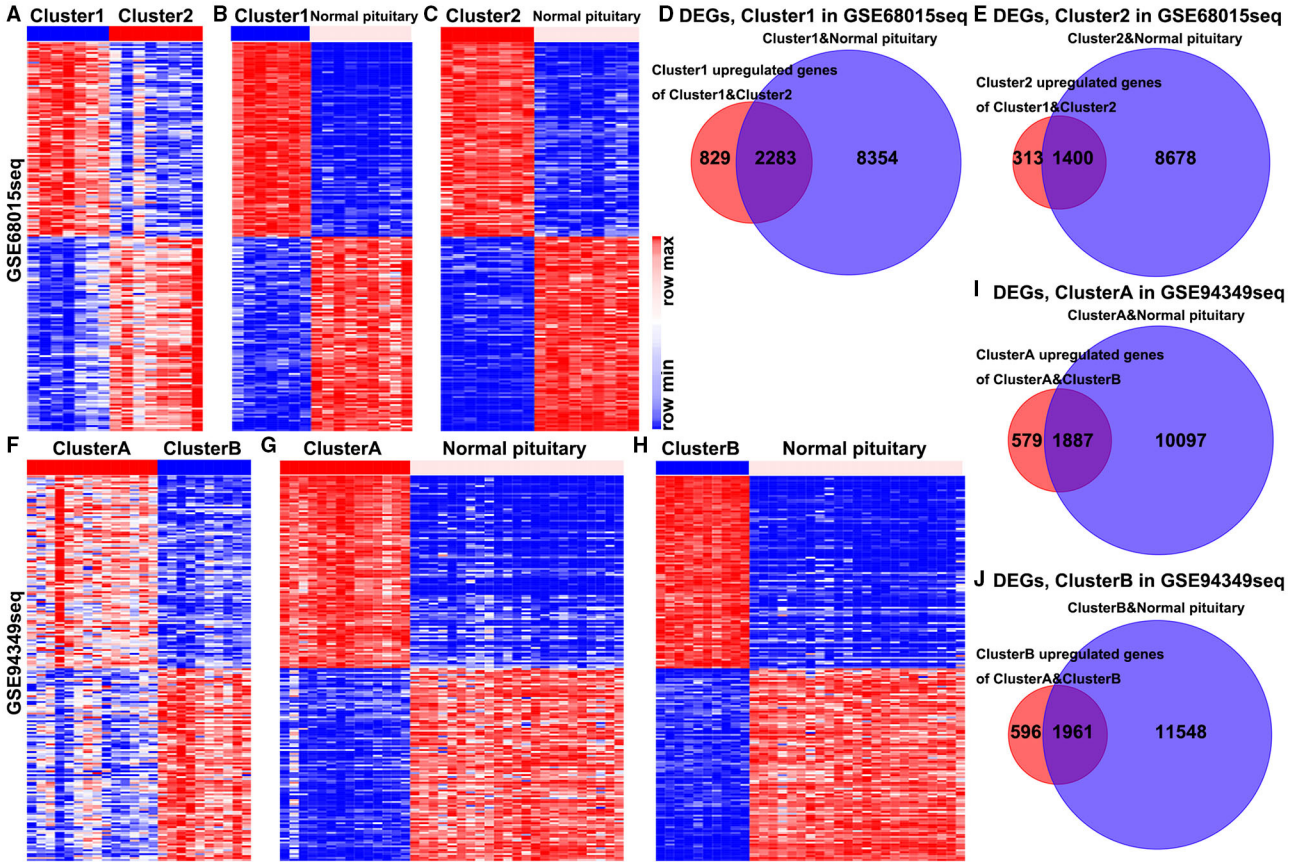

FIGURE 2 | Identification of DEGs in the IG and IR subtypes of ACPs. **(A)** Heat map displaying the DEGs between-group cluster 1 and cluster 2 ACPs in the GSE68015 database. The heat maps display the DEGs between **(B)** cluster 1 and normal pituitary, **(C)** cluster 2 and normal pituitary. **(D)** A total of 3,112 cluster 1 upregulated genes were compared with 10,637 DEGs between the cluster 1 and normal pituitary groups, yielding a set of 2,283 overlapping genes. **(E)** A total of 1,713 cluster 2 upregulated genes were compared with 10,078 DEGs between the cluster 2 and normal pituitary groups, yielding a set of 1,400 overlapping genes. **(F)** Heat map displaying the DEGs between-group cluster A and cluster B ACPs in the GSE94349 database. The heat maps display the DEGs between **(G)** cluster A and normal pituitary, **(H)** cluster B and normal pituitary. **(I)** A total of 2,466 cluster A upregulated genes were compared with 11,984 DEGs between cluster A and normal pituitary groups, yielding a set of 1,887 overlapping genes. **(J)** A total of 2,557 cluster B upregulated genes were compared with 13,509 DEGs between the cluster B and normal pituitary groups, yielding a set of 1,961 overlapping genes.

pathogenesis of ACP (10). The tumor immune process (or the tumor-immunity cycle) is the basis of immunotherapy and the key to treatment strategies and drug development (11). Therefore, patients with CP have the potential to benefit from cancer immunotherapy.

In this research, we collected a total of 401 samples, including 210 RNA-sequencing data from the GSE68015 database and 110 RNA-sequencing data from the GSE494349 database to investigate the intratumoral immune profile of ACP and explore a novel immune classification for predicting immunotherapy responsiveness. Subsequently, we constructed a gene-based classification prediction model to guide clinical diagnosis and treatment.

PATIENTS AND METHODS

Databases

We collected a total of 401 samples, including 210 RNA-sequencing data from the GSE68015 database and 110 RNA-sequencing data from the GSE494349 database. GSE68015 and GSE94349 databases were downloaded from Gene Expression Omnibus (GEO) (http://www.ncbi.nlm.gov/geo). GSE68015 database (n = 210) contains 15 ACP tumor samples, nine normal pituitary tissue samples (controls), 16 normal brain tissue samples, and 170 other primary pediatric and adult brain tumor samples. GSE94349 database (n = 191) includes 24 ACP tumor samples, 23 normal pituitary samples, 27 normal brain tissue samples, and 117 surgical tumor samples of other primary pediatric and adult brain tumor types. Gene expression profiles were performed using Affymetrix HG-U133plus2 chips (Platform GPL570).

Bioinformatic Analysis

ESTIMATE algorithm was applied to calculate the fraction of stromal and immune cells with the R package "estimate" (12). The proportion of tumor-infiltrating immune cell (TIC) was explored using the CIBERSORT algorithm (13). The differentially expressed genes (DEGs) between cluster 1 and cluster 2 groups

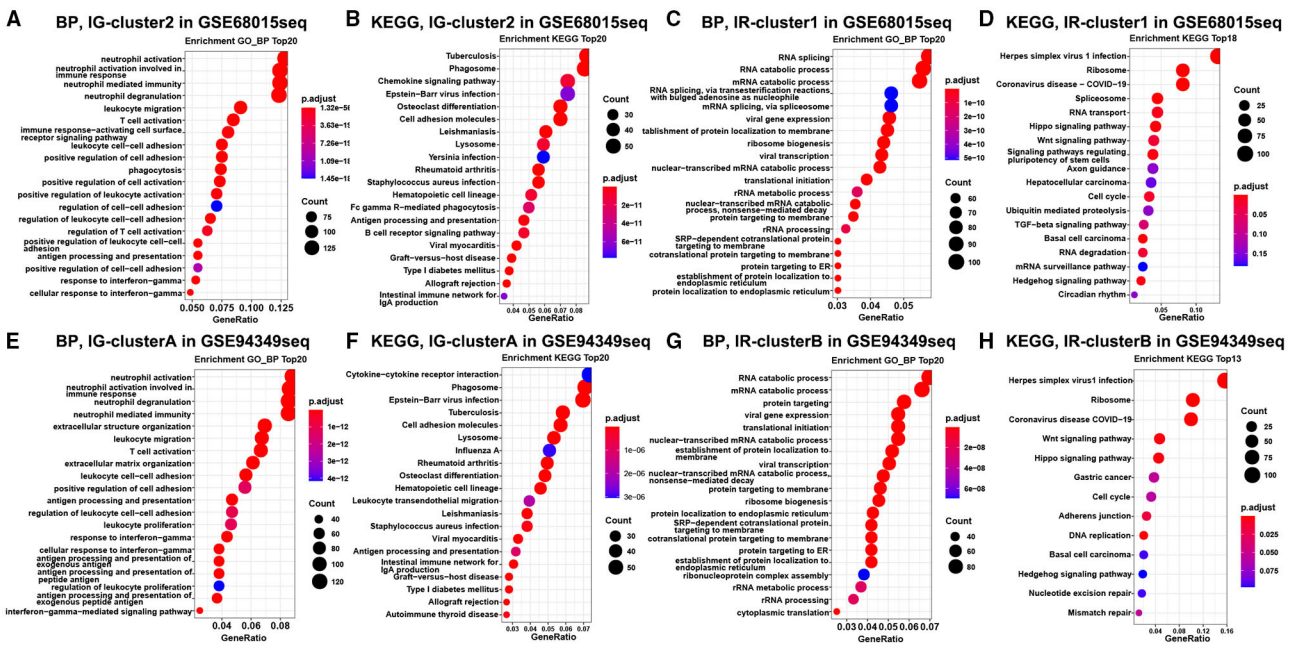

FIGURE 3 | Enrichment analysis in the IG and IR subtypes of ACPs. GO and KEGG enrichment analysis of DEGs in the cluster 1 **(A,B)** and cluster 2 **(C,D)** groups. Enrichment analysis of DEGs in the cluster A **(E,F)** and cluster B **(G,H)** groups. The top 20 items were displayed in the bubble chart.

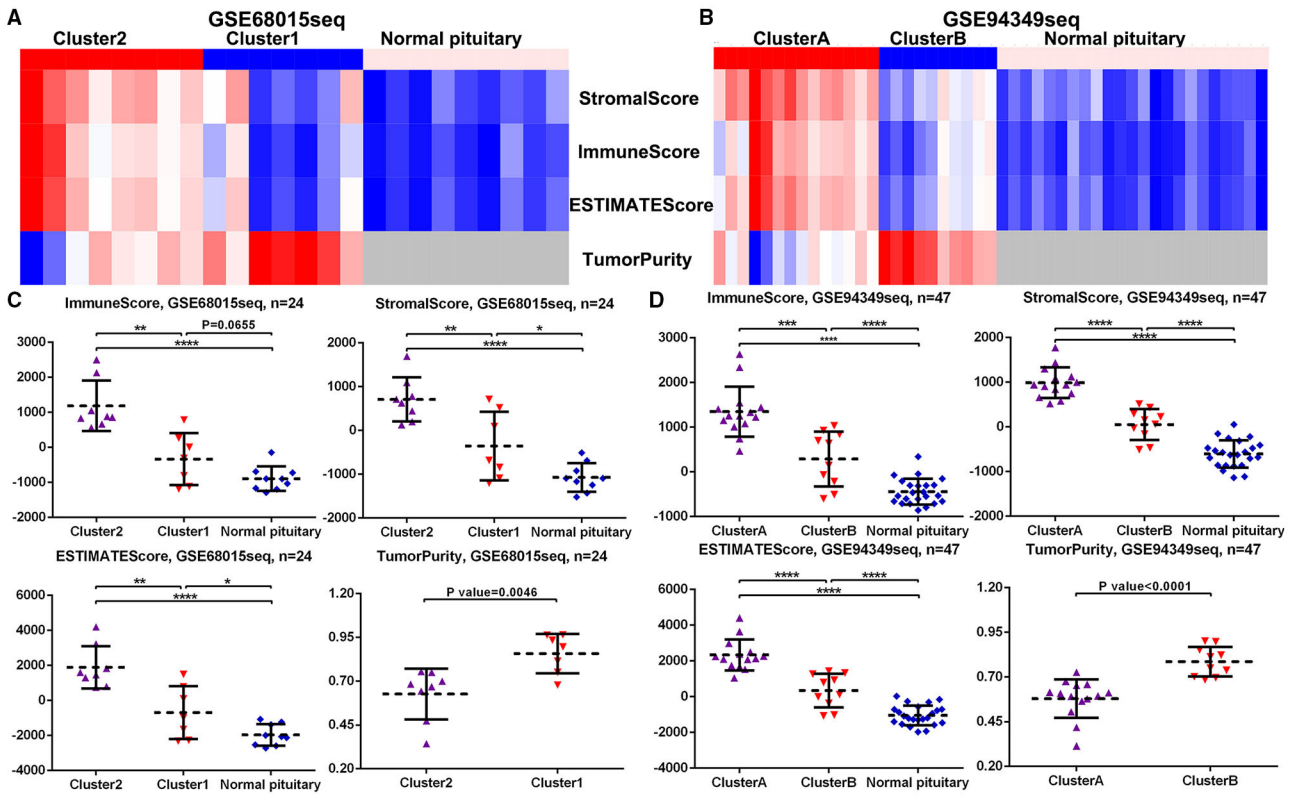

FIGURE 4 | Scores in the IG and IR subtypes of ACPs. **(A,B)** Heat map displaying the distribution of scores among cluster 1/2, cluster A/B and normal pituitary groups in the GSE68015 and GSE94349 databases. **(C,D)** The Scatter plot demonstrated the ratio differentiation of scores and TumorPurity among cluster 1/2, cluster A/B and normal pituitary groups in the GSE68015 and GSE94349 databases. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$.

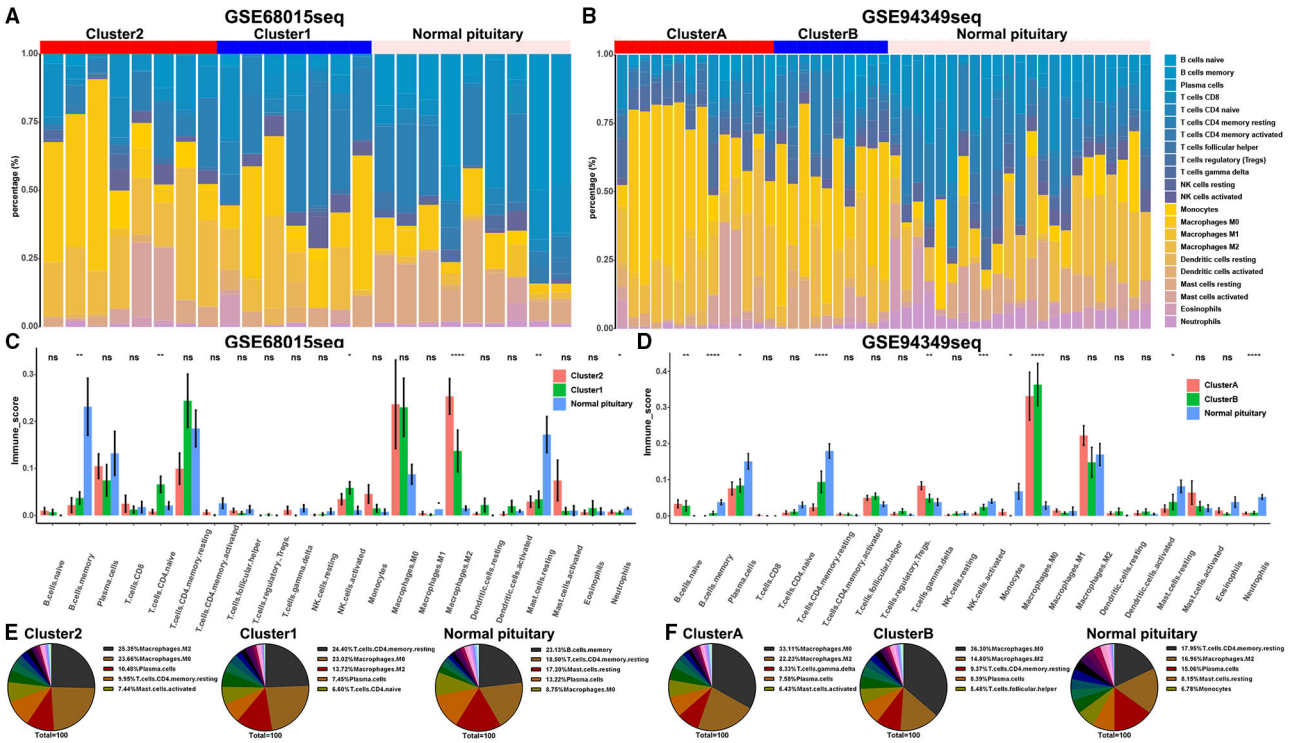

FIGURE 5 | Proportion of TICs in the IG and IR subtypes of ACPs. **(A,B)** Barplot showing the proportion of 21 kinds of TICs in ACPs and normal pituitary in the GSE68015 and GSE94349 databases. Column names of the plot were sample ID. **(C,D)** The bar chart showed the ratio differentiation of 21 kinds of immune cells among cluster 1/2, cluster A/B and normal pituitary groups. **(E,F)** Pie charts showed the distribution of the immune cells among cluster 1/2, cluster A/B and normal pituitary groups. *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001.

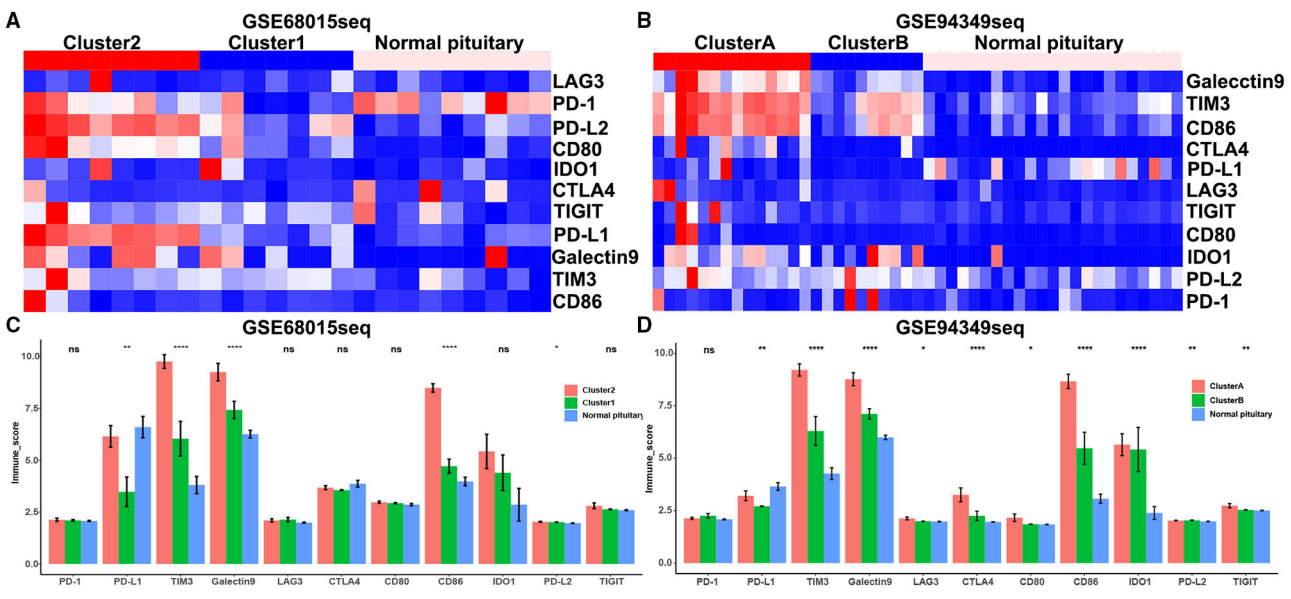

FIGURE 6 | Expression of immune checkpoint molecules in the IG and IR subtypes of ACPs. **(A,B)** Heat map displaying the distribution of immune checkpoint molecules (PD1, PDL1, PDL2, TIM3, CTLA4, Galectin9, LAG3, and CD86) among cluster 1/2, cluster A/B and normal pituitary groups in the GSE68015 and GSE94349 databases. **(C,D)** The bar chart showed the ratio differentiation of immune checkpoint molecules among cluster 1/2, cluster A/B and normal pituitary groups. *p < 0.05,**p < 0.01, ****p < 0.0001.

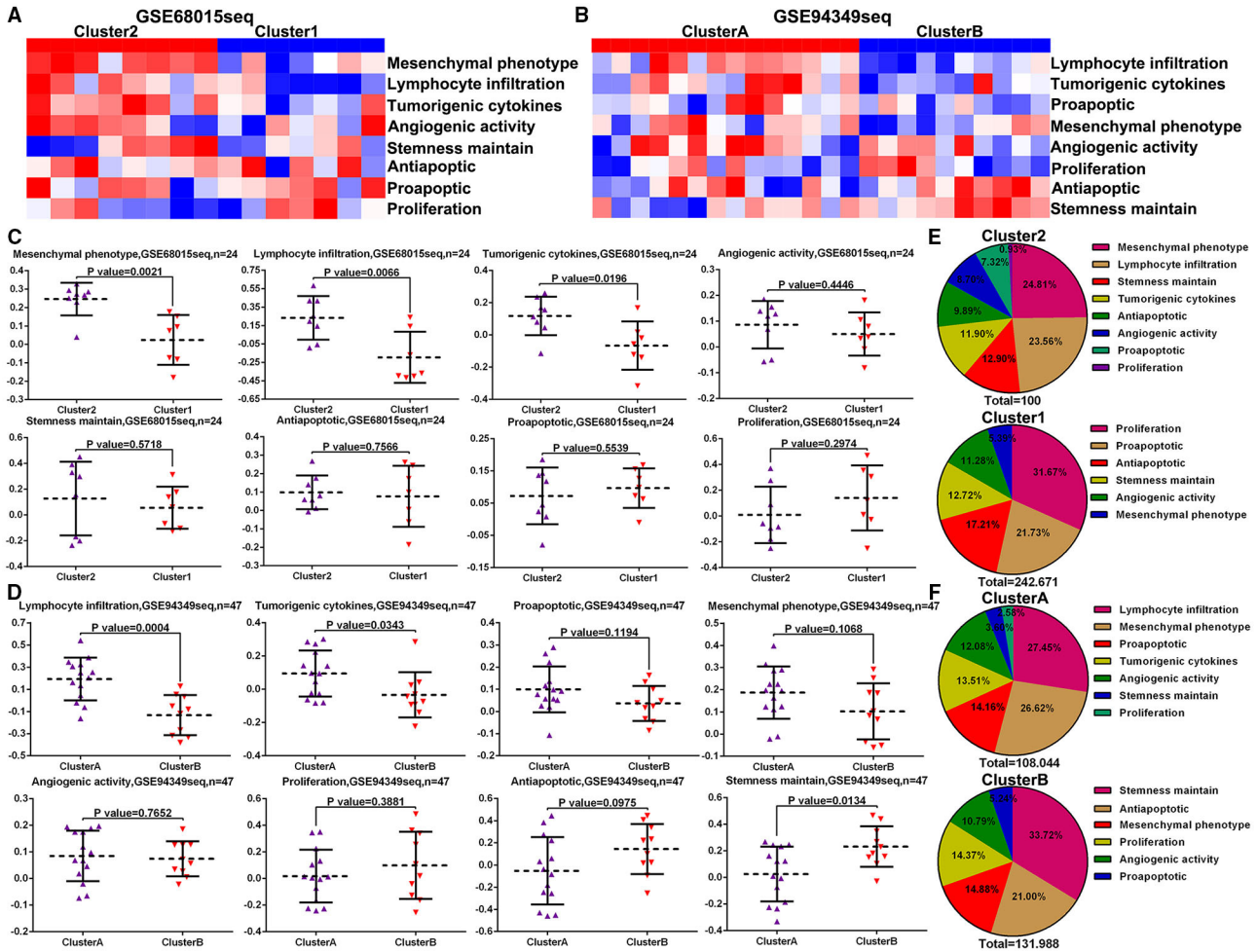

FIGURE 7 | ssGSVA between the IG and IR subtypes of ACPs. **(A,B)** Heat map displaying the distribution of eight biofunctions (proliferation, proapoptic, antiapoptic, stemness maintain, angiogenic activity, tumorigenic cytokines, lymphocyte infiltration, and mesenchymal phenotype) between cluster 1/2 and cluster A/B groups in the GSE68015 and GSE94349 databases. **(C,D)** The Scatter plot indicated the ratio differentiation of eight biofunctions among cluster 1/2, cluster A/B and normal pituitary groups. **(E,F)** Pie charts displayed the distribution of these biofunctions between cluster 1/2 and cluster A/B groups.

were determined using a threshold *p*-value of 0.05 by Morpheus online software (https://software.broadinstitute.org/morpheus/) (14). Pearson correlation analysis was applied to identify genes correlated with WDR89 (Pearson $|R| > 0.5$). Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis were applied for DEGs and genes that were most correlated with WDR89 (15). We obtained the metagene signatures for angiogenic activity (16), antiapoptotic and proapoptotic (17), tumorigenic cytokines (18), mesenchymal phenotype (19), lymphocyte infiltration (20), proliferation (20), and stemness maintain (21). Single-sample gene set enrichment analysis (ssGSVA) was performed to acquire the enrichment score of each biofunction signature using the "GSVA" R package (22).

Construction of Immune Classification Predicted Model

The least absolute shrinkage and selection operator (LASSO) method and logistic regression analysis were used to identify the best predictive genes (23). A gene-based nomogram model was constructed to predict the classification of ACPs using the "rms" R package (24).

Prediction of the Immunotherapy Response

Tumor immune dysfunction and exclusion (TIDE) is a computational method developed in 2018 to predict the ICB response (25). A Bonferroni-corrected *p*-value < 0.05 was considered statistically significant.

Statistical Analysis

R language (version 3.6.1, http://www.r-project.org) was used as the principal tool for statistical analysis and graphic work.

RESULTS

ACPs Classification Based on Immune Infiltration

First, we performed unsupervised cluster analysis on the 725 immune related genes and arrays of 15 patients with ACP in the

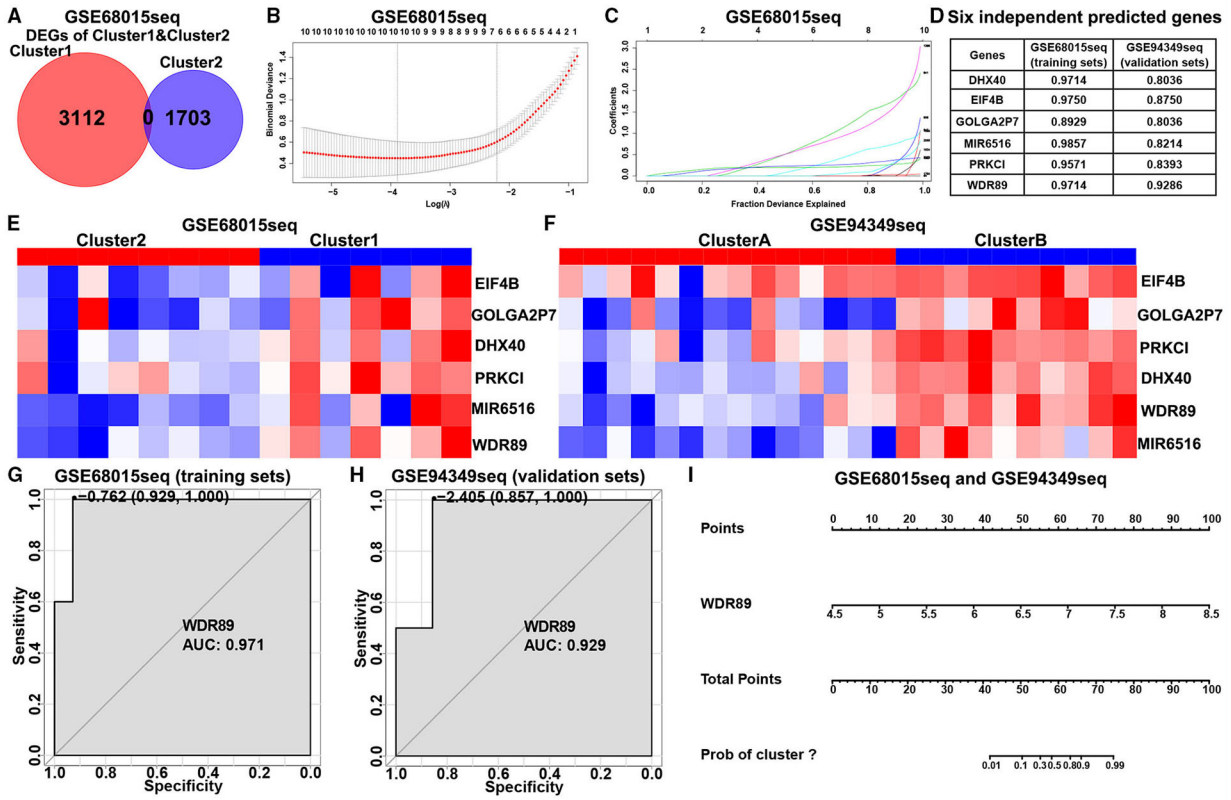

FIGURE 8 | Construction of the classification prediction model. **(A)** Venn diagram showed the DEGs between-group cluster 1 and cluster 2 ACPs in the GSE68015 database. **(B)** LASSO coefficients profiles of 4,815 DEGs in the GSE68015 database. **(C)** LASSO regression with tenfold cross-validation obtained optimal prognostic genes using minimum lambda value. **(D)** Logistic analysis was used to evaluate the best six independent predicted genes. **(E,F)** Heatmap of the expression profiles of the six independent predicted genes between cluster 1/2 and cluster A/B in the GSE68015 and GSE94349 databases. **(G,H)** ROC curves showed WDR89-based predictive model could provide a more reliable classification assessment in the training sets (AUC = 0.971) and validation sets (AUC = 0.929). **(I)** WDR89-based nomogram model to predict the immune classification of ACPs in the GSE68015 and GSE94349 databases.

GSE60815 database. The immune microenvironment (IME) of ACPs was divided into two different clusters, namely cluster 1 and cluster 2 (**Figure 1A**). Similarly, unsupervised cluster analysis was performed on the 725 immune related genes and arrays of 24 patients with ACP in the GSE94349 database, ACPs were also divided into two different clusters (cluster A and cluster B) (**Figure 1B**). After merging these two databases, we performed unsupervised cluster analysis on the 725 immune related genes and arrays of 39 patients with ACP again. The results showed that cluster 1 matched well with cluster B, and cluster 2 matched with cluster A (**Figures 1C,G**). The TIDE results showed that the ACPs with cluster 2 and cluster A (50%, 4/8; 71.43%, 10/14) were more likely to respond to immunotherapy than the ACPs with cluster 1 and cluster B (0%, 0/7; 30%, 3/10) (**Figures 1D–F**). Therefore, we defined cluster 2/cluster A as the immunogenic (IG) subtype and cluster 1/cluster B as the immune resistance (IR) subtype (**Figure 1G**).

Enrichment Analysis in the IG and IR Subtypes of ACPs

In the GSE68015 database, we found 4,825 DEGs (3,112 upregulated genes of cluster 1 and 1,713 upregulated genes of cluster 2) between the cluster 1 and the cluster 2 groups (**Figure 2A**), 10,637 DEGs that were identified between cluster 1 and the normal pituitary groups (**Figure 2B**) and 10,078 DEGs between the cluster 2 and the normal pituitary groups (**Figure 2C**). Then, we compared the above-mentioned genes. A total of 2,283 and 1,400 overlapped DEGs specific to the cluster 1 and cluster 2 groups were yielded, respectively (**Figures 2D,E**). Simultaneously, in the GSE94349 database, we found 5,023 DEGs (2,466 upregulated genes of cluster A and 2,557 upregulated genes of cluster B) between the cluster A and the cluster B groups (**Figure 2F**), 11,984 DEGs between cluster A and the normal pituitary groups (**Figure 2G**), and 13,509 DEGs between the cluster B and the normal pituitary groups (**Figure 2H**). Then, we compared the above-mentioned genes, and a total of 1,887 and 1,961 overlapped DEGs specific to the cluster A and cluster B groups were detected, respectively (**Figures 2I,J**).

Finally, the enrichment analysis results indicated that the DEGs of the IG subtype were chiefly involved in various inflammatory and immune responses, as well as a chemokine signaling pathway, antigen processing, and presentation (**Figures 3A,B,E,F**). However, the DEGs of the IR subtype were mainly involved in RNA splicing, RNA catabolic process, cell cycle, Wnt, and Hippo signaling pathway (**Figures 3C,D,G,H**).

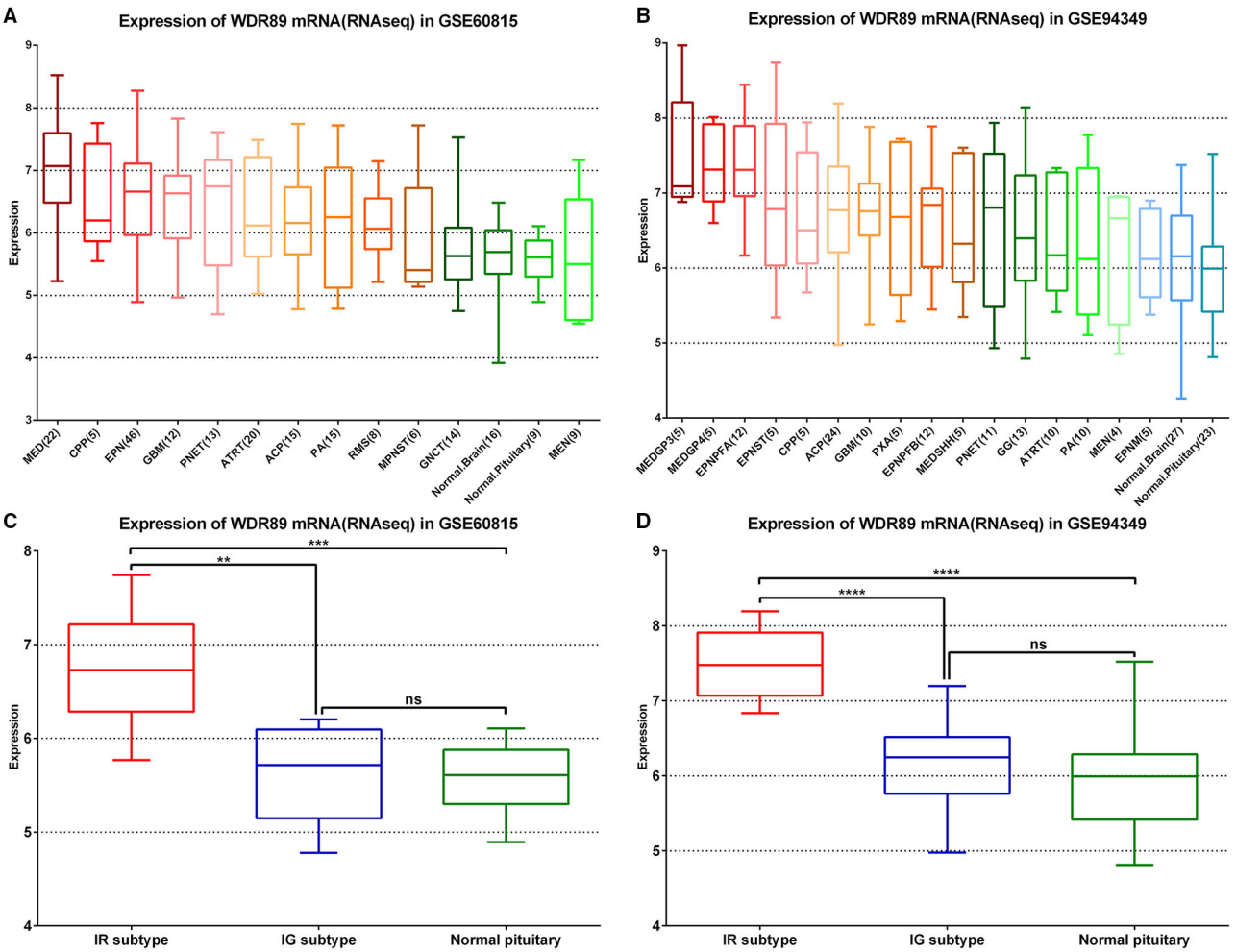

FIGURE 9 | WDR89 related expression profile in ACPs relative to a broad range of pediatric and adult brain tumor types. **(A,B)** WDR89 mRNA expression in ACPs relative to a broad range of pediatric and adult brain tumor types in the GSE68015 and GSE94349 databases. **(C,D)** Expression of WDR89 in the IG and IR subtype of ACPs, and normal pituitary group. **p < 0.01, ***p < 0.001, ****p < 0.0001.

Scores in the IG and IR Subtypes of ACPs

In both GSE60815 and GSE94349 databases, the ESTIMATE results suggested that compared with the normal pituitary group, ACPs had higher immune and stromal scores. In ACPs, compared with IR subtype (cluster 1 and cluster B groups), ACPs in IG subtype (cluster 2 and cluster A groups) had higher immune and stromal scores, while the purity of tumors was lowered (**Figures 4A–D**).

The Proportion of TICs in the IG and IR Subtypes of ACPs

The CITICSORT results found that compared with the normal pituitary group, the proportion of M0 and M2 macrophages was significantly higher in ACPs. The proportion of M2 macrophage in the IG subtype (cluster 2 and cluster A groups) was higher than that in the IR subtype (cluster 1 and cluster B groups). However, the proportion of T cell CD4 memory resting and mast cell resting in the normal pituitary group was distinctly higher than that in the ACPs (**Figures 5A–F**).

Expression of Immune Checkpoint Molecules in the IG and IR Subtypes of ACPs

We also discovered that the expression levels of immune checkpoint molecules (PD1, PDL1, PDL2, TIM3, CTLA4, Galectin9, LAG3, and CD86) were significantly increased in IG subtype (cluster 2 and cluster A groups) compared with IR subtype (cluster 1 and cluster B groups) (**Figures 6A–D**).

ssGSVA Between the IG and IR Subtypes of ACPs

To further investigate the different biofunctions between the IG and IR subtypes of ACPs, the ssGSEA analysis demonstrated that the biofunction of carcinogenesis, such as lymphocyte infiltration, mesenchymal phenotype, stemness

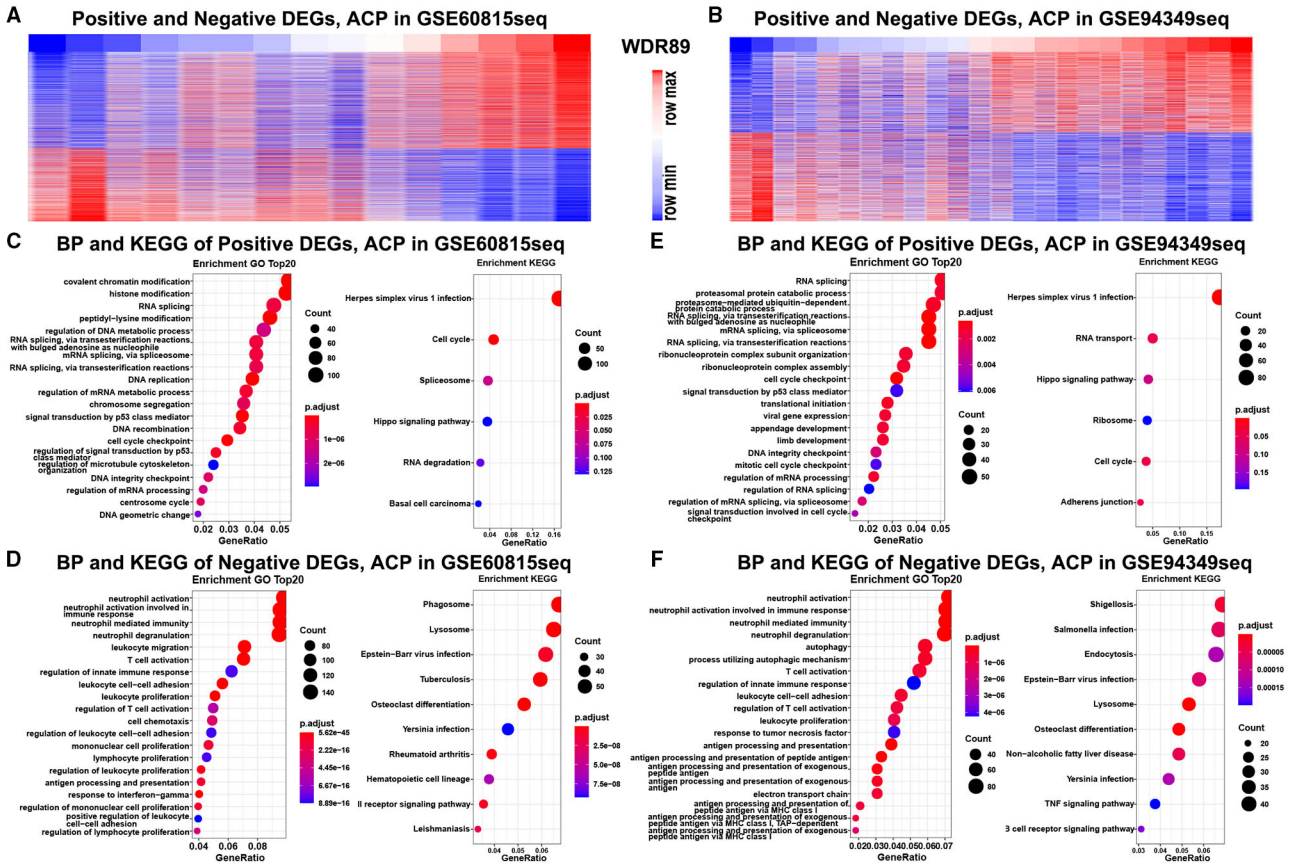

FIGURE 10 | GO and KEGG analysis of WDR89-associated genes in ACPs. **(A,B)** Heatmap for genes most relevant to WDR89 generated by Pearson correlation analysis in the GSE68015 and GSE94349 databases. **(C–F)** GO and KEGG enrichment analysis of genes most relevant to WDR89.

maintenance, and tumorigenic cytokines, in IG subtype were significantly enriched compared with IR subtype (**Figures 7A–D**). Moreover, the proportion of lymphocyte infiltration and mesenchymal phenotype in the IG subtype of ACPs was obviously higher than that in the IR subtype of ACPs (**Figures 7E,F**).

Construction of the Classification Prediction Model

In the GSE60815 database, we identified 4,825 DEGs (3,112 upregulated genes of cluster 1 and 1,713 upregulated genes of cluster 2) for LASSO and logistic analysis and identified the best six independent predicted genes (WDR89, PRKCI, DHX40, EIF4B, GOLGA2P7, and MIR65161) (**Figures 8A–F**). A gene-based classification prediction model was constructed afterward. ROC curves showed that the WDR89-based predictive model provided a reliable classification assessment in the training sets (area under curves (AUC) = 0.971) and validation sets (AUC = 0.929) (**Figures 8G,H**). Finally, we developed a WDR89-based nomogram model to predict the classification of ACPs (**Figure 8I**).

WDR89-Related Expression Profile in ACPs Relative to a Broad Range of Other Primary Pediatric and Adult Brain Tumor Types

In the GSE60815 and GSE94349 databases, expression profile analysis suggested that compared with the normal brain group (including pituitary) and most other primary pediatric and adult brain tumors (including MEN, GNCT, MPNST, RMS, PA), WDR89 was highly expressed in ACPs (**Figures 9A,B**). In addition, the expression of WDR89 in the IR subtype of ACPs is higher than that in patients with the IG subtype of ACP (**Figures 9C,D**).

GO and KEGG Analysis of WDR89-Associated Genes in ACPs

Functional enrichment analysis demonstrated that genes negatively relevant to WDR89 (Pearson $|R| > 0.5$) were mostly involved in neutrophil activation, T cell activation, leukocyte proliferation, and TNF signaling pathway (**Figures 10A,C,D**). However, genes positively relevant to WDR89 were associated with RNA splicing, DNA replication, cell cycle, and Hippo signaling pathway (**Figures 10B,E,F**).

DISCUSSION

Cancer immunotherapy has completely revolutionized the treatment landscape of malignant tumors, which is a new type of treatment that has emerged after surgery, chemotherapy, radiotherapy, and targeted therapy (26, 27). Although cancer immunotherapy has been widely used in many tumors, there are still many challenges, such as limited efficacy and serious side effects (27, 28). Relevant studies have shown that only about 13% of patients could benefit from ICB therapy, and it is not yet possible to accurately determine which patients could benefit from immunotherapy (29).

Adamantinomatous craniopharyngiomas mostly have large cystic components. The rapid growth of the cystic component will compress and destroy the neighboring key structures. Therefore, the study of the pathogenesis of ACP cysts is particularly important. Up to now, studies have found that the expression of many inflammatory molecules in the cystic component of ACP are upregulated, such as alpha-defensins 1-3, IL6R, IL2RB, IL-1B, IL-6, CXCL1, CXCL8 (IL-8), IL-10, CXCR2, CXCL1 (GRO), IDO-1, IL-18, TNF, and IFNG (30–33). At the same time, related studies have also found that the expression of inflammatory molecules in the solid components of ACP is also upregulated, which further supports the important role of immune response in the pathogenesis of ACP (32, 34). A recent study found that immune checkpoint molecules PD-1 and PD-L1 are overexpressed in epithelial cell clusters in ACP (35), and these clusters of epithelial cells were found to play an important role in the growth of ACP (36–38). This research provides theoretical support for the treatment of ICB in ACPs.

Immune cells can induce excessive activation of intracellular signaling pathways or activation of abnormal signaling pathways by secreting proinflammatory factors and chemokines, and ultimately promote tumor proliferation, invasion, and metastasis (39, 40). A related study found that there was a large number of immune cell infiltrations between ACPs and important structures such as the hypothalamus, and there is also tight adhesion formation. The degree of inflammatory response is significantly positively correlated with the incidence and severity of the hypothalamus–pituitary deficiency (41). Therefore, we inferred that the inflammatory response between the tumor and important structures may cause the difficulty of tumor dissection during the operation, which may lead to the occurrence of serious postoperative complications and tumor recurrence. The inflammatory response may be one of the important factors for the worse prognosis of ACPs.

In summary, it has been discovered and verified that many inflammatory molecules and cytokines in ACP are overexpressed, and the IME of ACP plays an important role in the development of tumors (32). Therefore, cancer immunotherapy, such as ICB therapy, is a promising therapy for ACPs, but there is still a long way to go to fully explain the potential of immunotherapy in ACPs.

In this research, we summarized the immune profile of ACP and identified two novel immune subtypes (namely IR subtype and IG subtype), which showed completely different immunotherapy responsiveness rates. Compared with the IR subtype, the IG subtype is involved in various inflammatory and immune responses. Simultaneously, the expression of immune checkpoint molecules in the IG subtype is higher than that of the IR subtype, and the IG subtype showed a better response to immunotherapy. We also constructed a WDR89-based model to predict the immune classification of ACPs with excellent performance. The related study demonstrated that the degree of inflammatory response is significantly positively correlated with the incidence and severity of the hypothalamus–pituitary deficiency (41). Therefore, this subtype of ACPs is in urgent need of immunotherapy. However, the lack of *in vitro*, *in vivo,* or clinical validation of these findings is a major limitation in this study. In the future, our team will work on an in-depth analysis of the IME of ACPs through *in vitro* and *in vivo* methods, and provide theoretical and practical support for the application of immunotherapy in ACPs.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found at: National Center for Biotechnology Information (NCBI) Gene Expression Omnibus (GEO), https://www.ncbi.nlm.nih.gov/geo/, GSE60815 and GSE94349.

AUTHOR CONTRIBUTIONS

FY: conceived the project. CM and FY: supervised the project. FY, XC, and JZ: downloaded the data and performed the statistical analysis. CM, FY, LY, YW, CT, and ZC: interpreted the results. All listed authors read and approved the final manuscript.

ACKNOWLEDGMENTS

We appreciate the generosity of the GEO network for sharing a huge amount of data.

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frontiers in Oncology

ORIGINAL RESEARCH
published: 06 January 2022
doi: 10.3389/fonc.2021.764582

Prognostic Utility of Optical Coherence Tomography for Visual Outcome After Extended Endoscopic Endonasal Surgery for Adult Craniopharyngiomas

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OPEN ACCESS

Edited by:
Francesco Doglietto, University of Brescia, Italy

Reviewed by:
Joao Paulo Almeida, University of Toronto, Canada
Matteo Zoli, IRCCS Institute of Neurological Sciences of Bologna (ISNB), Italy

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Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: *25 August 2021*
Accepted: *10 December 2021*
Published: *06 January 2022*

Citation:
Qiao N, Li C, Xu J, Ma G, Kang J, Jin L, Cao L, Liu C, Zhang Y and Gui S (2022) Prognostic Utility of Optical Coherence Tomography for Visual Outcome After Extended Endoscopic Endonasal Surgery for Adult Craniopharyngiomas. Front. Oncol. 11:764582. doi: 10.3389/fonc.2021.764582

Introduction: Owing to the close vicinity of the optic chiasma, visual dysfunction is known as one of the most common surgical indications and postoperative complications in adult patients with craniopharyngiomas, probably leading to poor quality of life. Historically, very few consistent predictive factors associated with the visual outcome are identified, which may not be helpful for patient counseling and preoperative decision making. Recently, optical coherence tomography (OCT) serving as a novel high-resolution imaging technique can assess the retinal morphology by measuring the circumpapillary retinal nerve fiber layer (cpRNFL) and macular ganglion cell complex thickness. However, few studies have examined the prognostic utility of OCT parameters for visual outcome after surgery for craniopharyngiomas. This study aims to use the largest series to evaluate the association between OCT parameters and visual outcome after extended endoscopic endonasal surgery (EEES) for primary craniopharyngiomas in adults.

Material and Methods: From October 2018 to October 2020, one hundred and seventy eyes in 88 adult patients with newly confirmed craniopharyngiomas were retrospectively reviewed and pertinent prognostic factors were analyzed.

Results: Gross total resection was performed in 82 (93.2%) patients. The median postoperative follow-up time was 10.9 months. Multiple logistic regression analysis showed that increased temporal cpRNFL thickness was associated with higher odds of visual acuity (VA) improvement and maintenance (OR = 1.070; 95% CI, 1.005–1.140; p = 0.035), and greater inferior cpRNFL thickness was significantly associated with visual field (VF) improvement and maintenance (OR = 1.034; 95% CI, 1.001–1.068; p = 0.046). Furthermore, tight adhesion between optic nerves and craniopharyngiomas was demonstrated as an independent adverse factor for either postoperative VA or VF (p = 0.048, p = 0.030, respectively). The ROC results further verified the robustness of the prediction model either in VA (AUC = 0.843; 95% CI, 0.734–0.952; p < 0.001) or VF (AUC = 0.849; 95% CI, 0.741–0.958; p < 0.001).

Conclusion: Preoperative OCT can effectively predict visual outcome after EEES for adult craniopharyngiomas. It can also serve as a reliable alternative to evaluate preoperative visual field defects, especially for patients with lower compliance. Tight adhesion was confirmed as an independent risk factor for postoperative visual outcome. The OCT-based multivariable prediction models developed in the present study may contribute to patient counseling on visual prognosis.

Keywords: optical coherence tomography, prognosis factors, visual outcomes, extended endoscopic endonasal surgery, craniopharyngiomas

INTRODUCTION

Craniopharyngiomas are rare brain tumors originating from any point along with the pituitary–hypothalamic axis, accounting for 1.2%–4.6% of all intracranial tumors (1, 2). Because of the close vicinity of optic chiasma, visual deterioration is known as a common complication following surgery for craniopharyngiomas (3–7). Prognostic factors related to postoperative visual outcome, including age (8–10), symptoms duration (11), tumor size and volume (12), preoperative visual function (10), and optic atrophy (13), have been studied extensively, but results are not consistent.

Retrograde axonal degeneration caused by chronic optic nerve compression secondary to craniopharyngiomas often leads to thinner circumpapillary retinal nerve fiber layer (cpRNFL) and macular ganglion cell complex (mGCC), thus leading to irreversible visual dysfunction (14). Hence, visual recovery largely relies on timely removal of optic nerve compression and the amount of viable axions (14, 15). Optical coherence tomography (OCT) can serve as a non-invasive *in vivo* method to quantitatively and objectively measure cpRNFL thickness and mGCC parameters (14, 16). The clinical efficiency of OCT as a predictor of visual recovery after surgery for pituitary adenomas, meningiomas, or pediatric craniopharyngiomas has already been verified (13, 14, 16–21). Differing from pituitary tumors and meningioma, craniopharyngiomas often directly adhere to optic nerves, with a higher risk of postoperative visual deterioration. Compared with pediatric craniopharyngiomas, adult craniopharyngiomas more frequently cause visual impairment before surgery (5, 22). Therefore, investigating reliable predictive indicators of postoperative visual outcome may be beneficial for patients counseling on visual prognosis. However, there is limited evidence on the prognostic utility of OCT for visual outcome after surgery for adult craniopharyngiomas (16, 18).

This is the first study to systematically evaluate the association between OCT parameters and visual outcome after the extended endoscopic endonasal surgery (EEES) for adult craniopharyngiomas.

MATERIALS AND METHODS

Patient Population

From October 2018 to October 2020, a total of 118 adult patients underwent EEES for primary craniopharyngiomas at Beijing Tiantan Hospital of Capital Medical University. Inclusion criteria were as follows: (1) adult patients aged ≥18 years, (2) newly confirmed diagnosis of craniopharyngioma, (3) computed tomography (CT), magnetic resonance imaging (MRI), and ophthalmologic tests before and after surgery. The exclusion criteria were (1) past medical history of treatment including radiotherapy and surgery, (2) any ophthalmic condition other than compressive optic neuropathy caused by craniopharyngiomas, (3) any medical illness (including glaucoma, diabetes mellitus) known to affect optic apparatus, (4) ineligible OCT parameters, (5) unreliable visual field (VF) and best-corrected visual acuity (BCVA) testing (fixation losses more than 20%, false-negative error more than 20%, and false-positive error more than 20%), (6) myopia greater than −6.00 diopters, (7) and papilledema on fundoscopy. Consequently, 88 (74.6%) of 118 patients with primary craniopharyngiomas were retrospectively analyzed in this study. The flowchart for study inclusion and exclusion is described in **Figure 1**. All participants signed an informed consent form. The study was approved by the ethics committee of Beijing Tiantan Hospital of Capital Medical University.

Radiological Evaluations

The MRI examinations were performed preoperatively and at 3 and 9 months after surgery. Subsequent MRI scans were executed annually. Gross total removal (GTR) was defined as the resection without visual residual enhancing tumor according to postoperative MRI (5). Tumor recurrence during follow-up was defined as the development of a pathological lesion on MRI that had not previously been observed or the regrowth of tumor residuals (5). Tumor volume was calculated by using the following formula (23): volume = $4/3\pi$ ($a/2 \times b/2 \times c/2$) (where a, b, and c represent the diameters in the three dimensions).

Visual Evaluation and Definition

The ophthalmologic tests were performed preoperatively and at least 3 months after surgery. The BCVA was evaluated using a logarithmic visual acuity chart and then converted to the logarithm of the minimum angle of resolution (logMAR) for analysis. The VF examinations, including mean deviation (MD), pattern standard deviation (PSD), and visual field index (VFI), were performed using the Humphrey field analyzer (24-2 SITA-fast program, Carl Zeiss Meditec, Dublin, California, USA). OCT measurements, including cpRNFL thickness and mGCC parameters, were conducted using spectral-domain OCT (Optovue, Freemont CA, USA). OCT parameters were also analyzed based on a decade of age: ≤20, 21–30, 31–40, 41–50, 51–60, and 61–70 years (24, 25). For the analysis, improvement

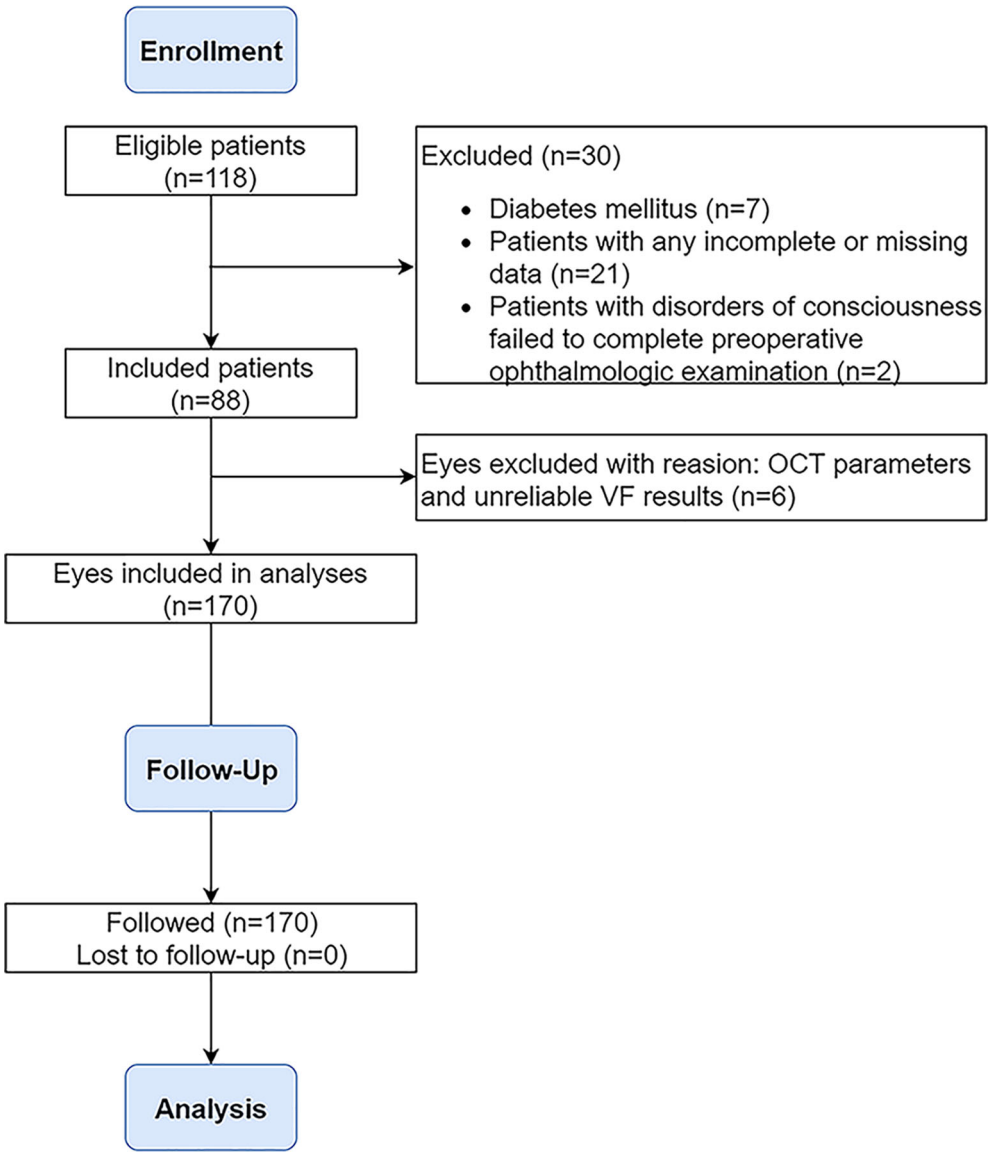

FIGURE 1 | Flowchart demonstrating the inclusion/exclusion criteria used in the selection process. OCT, optical coherence tomography; VF, visual field.

or worsening in BCVA (normal ≥ 1.0) was defined as a change of greater than 0.1 in LogMAR visual acuity (26). The VF improvement or worsening was defined as a change of MD [normal ≥ -2 decibels (dB)] greater than -3 dB (27).

Spectral-Domain Optical Coherence Tomography

Subjects underwent spectral-domain optical coherence tomography (SD-OCT) scanning without pupillary dilation using Avanti RTVue XR (Optovue, Fremont, California, USA) by experienced examiners on the same day as the ophthalmic evaluation. This equipment with an axial scan speed of 100 kHz using an 840-nm-wavelength laser has a resolution of 5.3 mm axially and 18 mm laterally. Three consecutive scans were performed on each eye. The scanning protocol for peripapillary RNFL thickness was acquired using the optic nerve head map, with a scanning range covering centered on the optic disc and covering a circle 3.45 mm in diameter. The GCC thickness was obtained using the GCC scanning protocol, which generates the data through the scans of a square grid (7 mm × 7 mm) on the central macula centered 1 mm temporal to the fovea and covered. Criteria for acceptable images included signal intensity level greater than 7 of 10, signal strength index ≥40. The normal RNFL and GCC thickness was defined as within the 95% percentile of age-, sex-, and race-matched normative values obtained from the manufacturer's database.

Surgical Procedures

All extended endoscopic endonasal approaches were performed by one surgeon (SG). Firstly, a right middle turbinectomy, nasoseptal flap harvesting, posterior septal resection, and an enough opening of the sphenoid sinus were performed. Subsequently, the tuberculum sellae is removed using a Kerrison rongeur and a high-speed drill, and the bony removal was extended anteriorly toward the planum sphenoidale and laterally to the medial optic-carotid recess bilaterally. When the dura mater was opened, the arachnoid membrane was sharply dissected, and the tumor was exposed between the upper surface of the pituitary gland and the optic chiasm (28). If the pituitary stalk was confirmed to suffer from obvious tumor invasion, it was sacrificed (29). After assessment of the pituitary stalk, the tumor was debulked adequately. When necessary, sharp separation of the tumor from neurovascular structures like optic nerves, optic chiasma, and hypothalamus was performed. After the removal of the tumor, skull base reconstruction was performed according to our earlier literature (30).

Classification of Adhesion

Compared to pituitary adenomas, craniopharyngiomas posed challenges mainly owing to their tendency to adhere to vital neurovascular structures, such as optic nerves and optic chiasma (31), with a higher risk of postoperative visual deterioration. The adhesion strength between optic apparatus and the tumor was classified into two categories according to intraoperative findings by the surgeon: (1) no or loose adhesion if the tumor can be easily separated from the optic apparatus by gentle blunt dissection using dissectors or (2) tight adhesion if the separation of the tumor required sharp dissection using scissors (**Figure 2**).

Statistical Analysis

We performed all statistical analyses with SPSS statistics software version 23 (IBM Corp). The data were presented as the mean ± standard deviation (SD) or median (with interquartile range (IQR)) for normally distributed and non-normally distributed samples, respectively. Differences between the pre- and postoperative visual outcomes were assessed by using the Wilcoxon signed-rank test. Spearman's rank correlation coefficients were used to evaluate the relationship between OCT and VF parameters. The prognostic factors for visual outcome were analyzed by binary logistic regression. Variables were selected into the multivariate analysis according to a statistically significant association in univariate analysis ($p < 0.05$) or previous studies and professional knowledge (32). Independent predictors in multivariate analysis and other variables selected by referring to previous studies and professional knowledge were used to establish the multivariable prediction models. Receiver operating characteristic (ROC) curves were used to determine the performance of the prediction model. The area under the curve (AUC) with 95% confidence interval (CI) and the associated p-value were both calculated. $p < 0.05$ was considered statistically significant.

RESULTS

Patient Characteristics

The present cohort included 37 (42.0%) male patients, and the mean age was 44.0 years old (range, 19–68 years). The most common preoperative symptom was visual impairment (78 patients; 88.6%), and the mean duration of such symptom was 6.2 months (range, 1–24 months). The median tumor volume was 6.5 cm^3 (IQR, 3.4-14.0 cm^3). The clinicoradiological data of 88 patients are shown in **Table 1**.

Preoperative Visual Function

One hundred and twenty-three eyes (72.4%) had VA impairment preoperatively. The median BCVA was 0.2 logMAR (IQR, 0 to 0.5). VF defects occurred in one hundred and forty-nine eyes (87.6%). MD, PSD, and VFI on VF testing were -9.3 (IQR, -14.8 to -4.9), 7.7 (IQR, 3.5 -11.4), and 77.5 (IQR, 56.5-90), respectively. The mean global RNFL thickness was 97.05 ± 13.17 μm. It was 121.72 ± 19.36 μm in the inferior quadrant, 124.66 ± 20.24 μm in the superior quadrant, 70.53 ± 13.96 μm in the nasal quadrant, and 70.28 ± 12.42 μm in the temporal quadrant, respectively. Inner average, superior, and inferior mGCC thicknesses were 91.68 ± 9.15 μm, 91.00 ± 9.34 μm, and 92.36 ± 9.49 μm, respectively (**Table 1**). The associations between the mGCC parameters, cpRNFL thickness parameters, and VF parameters in the 170 eyes are shown in **Table 2**. mGCC parameters significantly correlated with MD, PSD, and VFI. All cpRNFL thickness parameters were significantly associated with MD except for the superior quadrant, PSD except for the nasal quadrant, and VFI except for the inferior and nasal quadrant, respectively.

Overall Surgical Results

GTR was performed in 82 (93.2%) patients. Of the six cases with residual tumors, three were observed without further treatment, and three received gamma-knife radiosurgeries postoperatively without causing new visual defects. Tight adhesion was observed in 31 (35.2%) patients. Adamantinomatous craniopharyngiomas were confirmed in 67 (76.1%) patients. After a median follow-up duration of 10.9 months, recurrence occurred in 2 (2.3%) patients. Of these patients, one did radiotherapy, and the other was observed without adjuvant therapy. There was no new visual impairment occurred in these two patients.

Postoperative Visual Outcome

The follow-up time was 10.9 (IQR, 7.2–16.2) months. Among 123 eyes with preoperative VA impairment, VA improved in 78.0% but worsened in 4.9% postoperatively. Five (10.6%) of the 47 eyes with normal preoperative VA had postoperative VA deterioration. Of the 149 eyes with preoperative VF impairment, 83 (55.7%) experienced improved or normalized VF, with no change in 58 (38.9%), and 8 (5.4%) experienced deterioration after surgery. Eighteen (85.7%) of 21 eyes with normal preoperative VF showed no change, and 2 (9.5%) experienced worsening. The median BCVA after surgery was 0.1 logMAR (IQR, 0 to 0.2), which was significantly lower than the

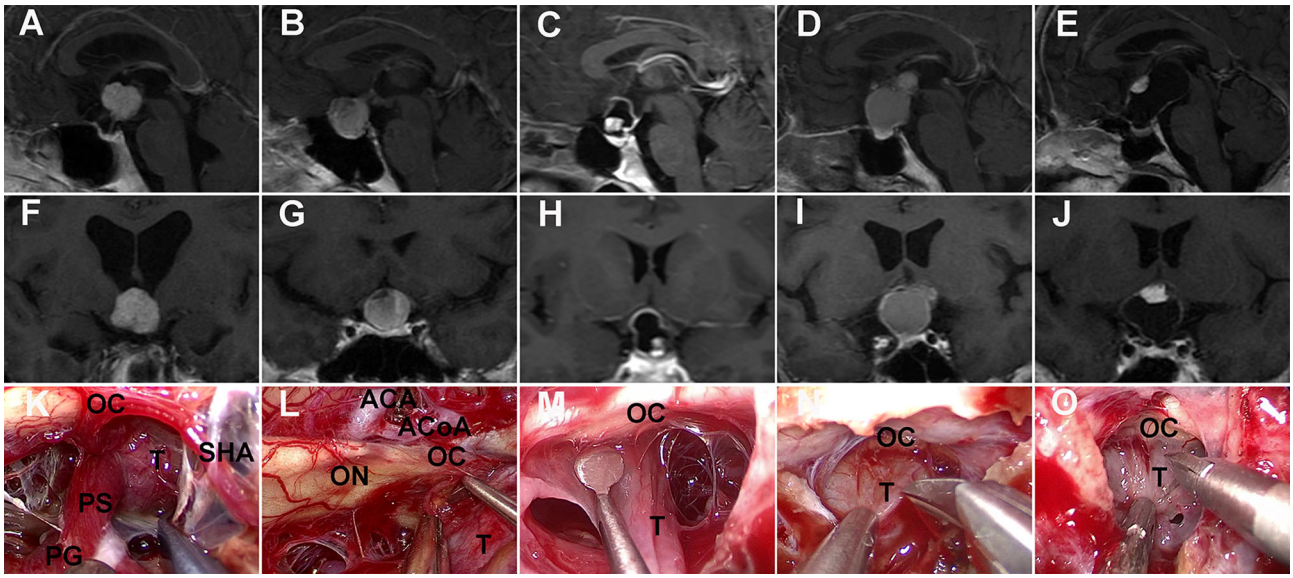

FIGURE 2 | Adhesion strength between craniopharyngioma and optic nerves was intraoperatively evaluated. **(K, L, M)** No or loose adhesion. Contrast-enhanced T1-weighted MRI scans **(A, F)** showing an intrinsic third ventricular solid tumor compressing forward the optic chiasm. Intraoperative view **(K)** revealing that the proximal part of the pituitary stalk extending from the gland could be identified as intact and at a normal size before tumor resection. Preoperative MRI scans **(B, C, G, H)** showing a sellar-suprasellar/suprasellar cystic-solid tumor stretching upward the optic chiasm. Surgical view **(L, M)** showing that the tumor can be easily separated from the optic nerves by dissector. **(N, O)** Tight adhesion. Preoperative MRI scans **(D, E, I, J)** showing sellar-suprasellar cystic-solid tumors displacing the optic chiasm. Intraoperative video-captured photographs **(N, O)** showing tight adhesion between the tumor and the optic apparatus needing sharp dissection using scissors. OC, optic chiasma; ON, optic nerve; T, tumor; PG, pituitary gland; PS, pituitary stalk; SHA, superior hypophysial artery; ACA, anterior cerebral artery; ACoA, anterior communicating artery.

preoperative 0.2 logMAR (IQR, 0 to 0.5) (p <0.001). The MD (IQR) showed a significant improvement from -9.3 (IQR, -14.8 to -4.9) preoperatively to -5.3 (IQR, -9.9 to -2.5) postoperatively (p < 0.001).The mean global RNFL thickness after surgery was 86.99 ± 13.99 μm. It was 112.81 ± 18.37 μm in the inferior quadrant, 112.02 ± 20.41 μm in the superior quadrant, 60.46 ± 14.03 μm in the nasal quadrant, and 62.67 ± 12.26 μm in the temporal quadrant, respectively. Inner average, superior, and inferior mGCC thicknesses were 87.19 ± 10.26 μm, 86.33 ± 10.85 μm, and 88.08 ± 10.12 μm, respectively. While overall visual function showed significant improvement following surgery, all postoperative OCT parameters mentioned above significantly decreased compared with preoperative data (each p < 0.001).

Prognostic Factors for Visual Prognosis

Univariate logistic regression analysis for visual improvement and maintenance by OCT parameters are summarized in **Table 3**, and increased temporal (p = 0.001) and inferior cpRNFL thickness (p = 0.004) proved to be independent prognostic factors. Clinicoradiological factors were also assessed, and the univariate analysis results revealed that tight adhesion and gender were associated significantly with postoperative visual outcome. In the multivariate analysis, increased temporal (OR, 1.070; 95% confidence interval [CI], 1.005–1.140; p = 0.035) and inferior cpRNFL thickness (OR, 1.034; 95% CI, 1.001–1.068; p = 0.046) proved to be independent favorable factors for VA (**Figure 3A**) and VF (**Figure 3B**) improvement and maintenance after surgery, respectively (**Figures 4**, **5**). Moreover, tight adhesion was confirmed as an independent risk factor for VA (OR, 0.188; 95% CI, 0.036–0.986; p = 0.048) or VF (OR, 0.162; 95% CI, 0.032–0.836; p = 0.030) after surgery for craniopharyngiomas.

As for predictors of postoperative VA, the AUC was 0.791 (95% CI, 0.667–0.914; p = 0.001) for temporal cpRNFL thickness and 0.746 (95% CI, 0.605–0.887; p = 0.007) for tight adherence, respectively. In terms of predictive factors of postoperative VF, the AUC with was 0.674 (95% CI, 0.459–0.890; p = 0.065) for inferior cpRNFL thickness and 0.734 (95% CI, 0.583–0.886; p = 0.013) for tight adherence, respectively. Multivariable prediction models developed for postoperative VA and VF recovery and maintenance, including age, gender, cpRNFL thickness, and adhesion strength, showed AUC of 0.843 (95% CI, 0.734–0.952; p < 0.001) and 0.849 (95% CI, 0.741–0.958; p < 0.001), respectively (**Figure 6**).

DISCUSSION

Retrograde axonal degeneration resulting from chronic compression of optic chiasma can result in cpRNFL and mGCC thinning, consequently leading to irreversible visual impairment (14). OCT allows quick, non-invasive, *in vivo* cross-sectional imaging of the retinal layers, acting as an important tool for objective quantification of cpRNFL and mGCC (18). There is

TABLE 1 | Clinicoradiological characteristics of the 88 enrolled patients.

Parameters	Values, n (%)
Total number	88
Sex	
Male	37 (42)
Female	51 (58)
Age, y	44.0 ± 13.1
Preoperative manifestations	
Visual disturbance	78 (89)
Menstrual disorder/impaired sexual function	70 (80)
Headache	58 (66)
Fatigue	43 (49)
Polyuria/polydipsia	33 (38)
Preoperative visual acuity	
Normal	23 (26)
Abnormal	65 (74)
Preoperative visual field	
No defect	10 (11)
Defect	78 (89)
Size of tumor	
Volume (cm)	6.5 (IQR,3.4-14.0)
Characteristics of tumor	
Solid	12 (14)
Cystic	31 (35)
Solid and cystic	
Cystic component >50%	29 (33)
Solid component >50%	16 (18)
With hydrocephalus	33 (37.5)
With calcification	49 (55.7)
Preoperative cpRNFL parameters (μm)	
Average thickness	97.05 ± 13.17
Superior quadrant	124.66 ± 20.24
Inferior quadrant	121.72 ± 19.36
Nasal quadrant	70.53 ± 13.96
Temporal quadrant	70.28 ± 12.42
Preoperative mGCC parameters (μm)	
Inner average	91.68 ± 9.15
Superior	91.00 ± 9.34
Inferior	92.36 ± 9.49
GCC FLV (%)	3.19 ± 2.94
GCC GLV (%)	6.49 ± 5.88

Values are presented as number (%), mean ± standard deviation, or median [with interquartile range (IQR)]. cpRNFL, circumpapillary retinal nerve fiber layer; mGCL, macular ganglion cell layer; GLV, global loss volume; FLV, focal loss volume.

increasing evidence suggesting that preoperative OCT parameters can serve as excellent prognostic indicators of visual outcome after surgery for parasellar lesions, such as meningioma, pituitary adenoma, and craniopharyngioma (14, 18, 33–35). Among these tumors, craniopharyngiomas often directly adhere to the undersurface of optic nerves or chiasm, with a higher risk of postoperative visual deterioration (36). Hence, it is helpful for patients with craniopharyngiomas to establish reliable multivariable prediction models to give them good counsel on visual prognosis. In this paper, the authors present the largest series to date to systematically analyze the prognostic utility of OCT parameters for visual outcome after EEES for adult craniopharyngiomas.

In keeping with the results reported in the previous studies (14, 18, 33–35), our research showed that preoperative OCT parameters can effectively predict visual outcome after EEES for adult craniopharyngiomas. Interestingly, increased inferior cpRNFL thickness was significantly associated with higher odds of VF recovery and maintenance ($p = 0.046$) in the present study, which was consistent with the results reported in the earlier literature (16, 37). Compression of retinal ganglion cell axons at the chiasm usually first cause VF defects because it preferentially damages the ventral fibers from the inferonasal and inferotemporal retina (38). Axonal shrinkage caused by such longstanding compression can bring about the inferior cpRNFL thinning, therefore resulting in irreversible VF defects after decompression. In addition, greater temporal cpRNFL thickness was confirmed as a significant favorable factor for VA recovery and maintenance ($p = 0.035$) in our study, which was similar to the findings by Kawaguchi and colleagues (26). Within the retina, the axons from the macula project to the disc at the temporal poles, forming the papillomacular bundle responsible for central visual acuity (16, 38). The authors discuss that the potential mechanisms might be that the temporal cpRNFL thinning caused by chiasmal compression secondary to craniopharyngiomas might affect the papillomacular bundle, thus leading to the decreased VA recovery following surgery. In consideration of different tissue types mentioned above,

TABLE 2 | Relationship between GCC parameters, RNFL thickness parameters, and preoperative visual field parameters.

Variable	MD		PSD		VFI	
	r	p value	r	p value	r	p value
cpRNFL parameters						
Average thickness	0.226	0.003*	-0.342	<0.001*	0.245	0.001*
Superior quadrant	0.266	<0.001*	-0.347	<0.001*	0.288	<0.001*
Inferior quadrant	0.140	0.069	-0.225	0.003*	0.124	0.106
Nasal quadrant	-0.039	0.611	-0.086	0.266	0.003	0.971
Temporal quadrant	0.327	<0.001*	-0.356	<0.001*	0.325	<0.001*
mGCC parameters						
Inner average	0.264	0.001*	-0.293	<0.001*	0.239	0.020*
Superior	0.288	<0.001*	-0.318	<0.001*	0.267	<0.001*
Inferior	0.235	0.002*	-0.259	<0.001*	0.203	0.008*
Focal loss volume	-0.342	<0.001*	0.367	<0.001*	-0.356	<0.001*
Global loss volume	-0.332	<0.001*	0.334	<0.001*	-0.317	<0.001*

cpRNFL, circumpapillary retinal nerve fiber layer; mGCL, macular ganglion cell layer; MD, mean deviation; VFI, visual field index; PSD, pattern standard deviation.
The asterisk indicates statistical significance, $p < 0.05$.

TABLE 3 | Univariate logistic regression for visual improvement and maintenance by OCT parameters.

Variable	VA improvement and maintenance		VF improvement and maintenance	
	OR (95% CI)	p value	OR (95% CI)	p value
cpRNFL thickness (μm)				
Average	1.036 (0.990–1.083)	0.127	1.012 (0.965–1.061)	0.630
Superior	1.012 (0.982–1.043)	0.440	0.990 (0.960–1.021)	0.509
Inferior	1.019 (0.989–1.051)	0.216	1.049 (1.016–1.083)	0.004*
Nasal	1.020 (0.976–1.066)	0.375	1.018 (0.972–1.066)	0.444
Temporal	1.104 (1.041–1.172)	0.001*	1.027 (0.975–1.082)	0.313
mGCC parameters (μm)				
Inner average	1.056 (0.988–1.128)	0.109	1.049 (0.979–1.124)	0.175
Superior	1.056 (0.991–1.126)	0.091	1.041 (0.974–1.112)	0.235
Inferior	1.046 (0.983–1.113)	0.152	1.049 (0.983–1.119)	0.146
GCC FLV (%)	0.860 (0.723–1.022)	0.087	0.958 (0.781–1.175)	0.681
GCC GLV (%)	0.933 (0.855–1.019)	0.122	0.950 (0.865–1.044)	0.290

OCT, optical coherence tomography; VA, visual acuity; VF, visual field; BCVA, best-corrected visual acuity; MD, mean deviation; cpRNFL, circumpapillary retinal nerve fiber layer; mGCL, macular ganglion cell layer; GLV, global loss volume; FLV, focal loss volume.
The asterisk indicates statistical significance, p < 0.05.

namely, pituitary adenomas (16), meningiomas (38), and craniopharyngioma (17, 20), which belonged to slow-growing benign tumors (WHO grade 1), preoperative cpRNFL thinning might be mainly due to longstanding mechanical compression of the optic apparatus and/or supporting vascular structures, thereby leading to visual impairment. The most noteworthy characteristic of visual impairment with chiasmal compression was that decompression could contribute to immediate visual improvement. Such rapid recovery was not observed in other forms of optic nerve injury (38). However, in terms of functional pituitary adenomas and malignant tumors in the sellar region, the issue of whether disease-related specific factors may affect the OCT parameters and visual outcome or not still required further advanced research.

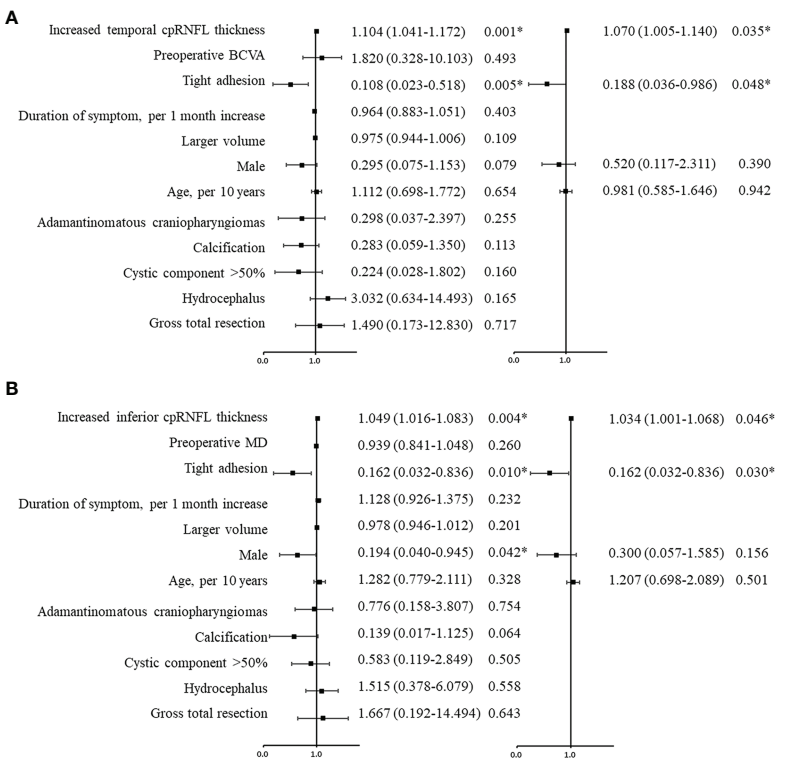

FIGURE 3 | Univariate and multivariate logistic regression analyses were used to evaluate the predictive factors for visual prognosis following surgery for craniopharyngiomas. The black squares indicate the OR values, error bars represent 95% CIs, and *p < 0.05. According to the analysis, increased temporal **(A)** and inferior **(B)** cpRNFL were favorable factors for postoperative visual acuity and visual field, respectively. Tight adhesion was an adverse factor for visual recovery. cpRNF, circumpapillary retinal nerve fiber layer; BCVA, best corrected visual acuity; MD, mean deviation.

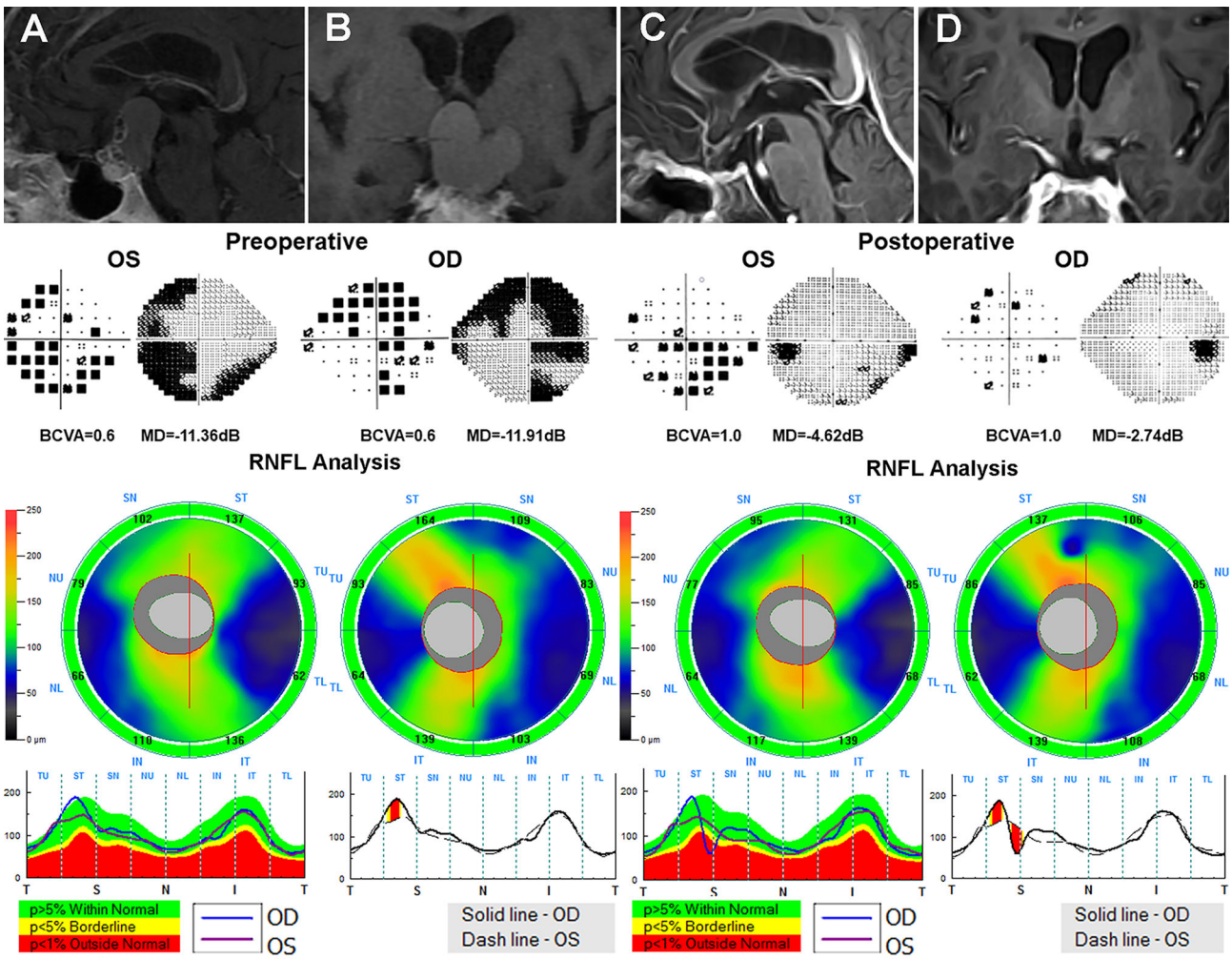

FIGURE 4 | A 59-year-old male patient who underwent the EEES for craniopharyngiomas was examined preoperatively and 3 months after surgery. Contrast-enhanced T1-weighted MRI scans **(A, B)** suggested a suprasellar cystic-solid lesion compressing downward the optic chiasma. Preoperative Humphrey VF test showed mainly temporal VF defects in both eyes. Preoperative OCT suggested normal cpRNFL thickness in both eyes. After total resection of the tumor **(C, D)**, the optic nerves were sufficiently decompressed, the VA and VF in both eyes dramatically improved after surgery. EEES, extended endoscopic endonasal surgery; OCT, optical coherence tomography; cpRNF, circumpapillary retinal nerve fiber layer; BCVA, best-corrected visual acuity; MD, mean deviation; VA, visual acuity; VF, visual field.

Noticeably, Yoo et al. (35) argued that the validity of the mGCC thickness measured by SD-OCT in predicting the postoperative visual outcome of parasellar tumors was superior to cpRNFL thickness. Some patients with mild VF defects were reported to have normal cpRNFL thickness, and the benefits of cpRNFL analysis were limited because of axonal overlap around the optic nerve head which did not allow to properly evaluate the topographic arrangement of the retinal ganglion cells (39–41). At present, the mGCC thickness can be measured separately by using SD-OCT. In a series of 79 consecutive patients, Yoo and colleagues (35) pointed out that the mGCC thickness can serve as an excellent predictor of visual recovery after chiasmal decompression. Furthermore, Ohkubo and colleagues (34) declared that preoperative mGCC parameters measured by SD-OCT, particularly focal loss volume (FLV), were shown to be a reliable predictor of visual outcome following surgical decompression of chiasmal compression. Our findings also suggested that the superonasal quadrant mGCC thicknesses ($p = 0.091$) and FLV ($p = 0.087$) showed statistical tendencies for VA recovery and maintenance in univariate analysis, although they were not statistically significant. This may be explained by the potential impact of the selection bias on results obtained from the present series.

Interestingly, in our findings, cpRNFL and mGCC thickness showed a significant decrease after surgery while postoperative visual function improved overall, which was consistent with results reported in the series by Lee (37) and Chung (42). An ongoing decline in RNFL thickness without recovery over 6 months following surgery was reported by Lee et al. In another study, Chung and colleagues observed that the RNFL thickness

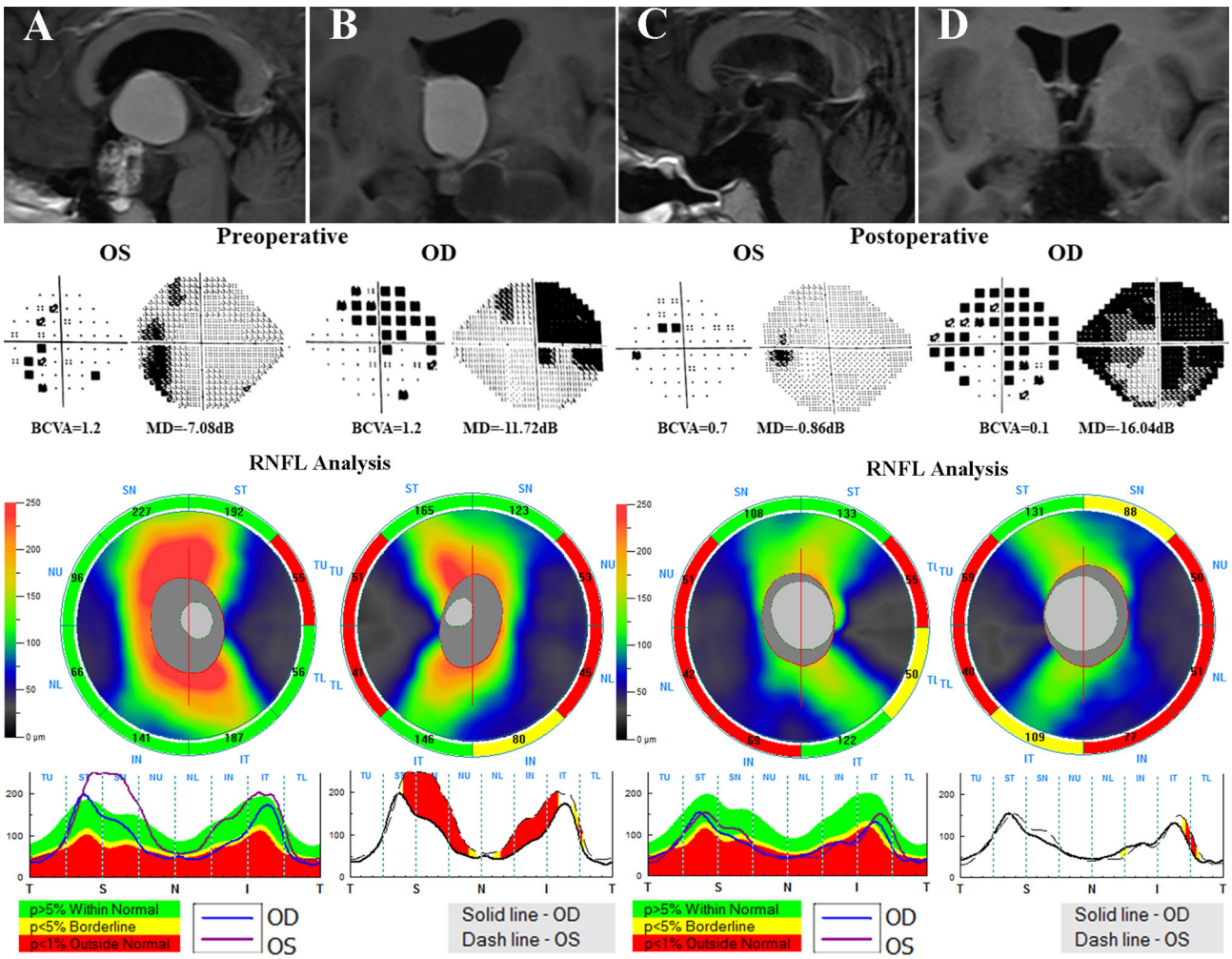

FIGURE 5 | A 21-year-old male who underwent endoscopic surgery for craniopharyngiomas was evaluated before and after surgery. Preoperative MRI scans **(A, B)** reveals a suprasellar cystic-solid tumor involving the third ventricle compressing the optic chiasma. Preoperative visual field examination suggested bitemporal VF defects. Preoperative OCT showed decreased temporal cpRNFL thickness in both eyes and inferior cpRNFL thinning in the right eye. After surgery **(C, D)**, the deterioration of VA in both eyes and VF in the right eye were observed. OCT, optical coherence tomography; cpRNF, circumpapillary retinal nerve fiber layer; BCVA, best-corrected visual acuity; MD, mean deviation; VA, visual acuity; VF, visual field.

continuously decreased over 12 to 36 months although the visual field recovered. This might be explained by the nerve edema to a certain extent, which potentially contributed to a false increase in OCT results at the preoperative testing, followed by a normalization of OCT parameters after surgery. Based on this, we supported that excluding cases with papilledema on fundoscopy from the analysis probably made it possible to control the possible confounding effect in our study. Another potential mechanism was that permanent ischemia to the outermost layer may lead to gradual thinning although satisfactory decompression of the optic nerve fiber (42). However, the discrepancy between anatomic change and functional recovery still necessitated advanced research in the future.

Moreover, the present study pointed out that tight adhesion between craniopharyngiomas and optic nerves was demonstrated as an independent risk factor for visual outcome following EEES for primary craniopharyngiomas, which was similar to our previous results (36). In the current series, tumors with tight adherence were observed in 31 (35.2%) of all patients. Poor visual outcomes were more likely to happen in patients with tight adherence (35.5%) compared with the rest of patients (1.8%). This could be explained by tumor adherence to the undersurface of optic nerves or chiasm, which can predispose the optical apparatus to mechanical and ischemic injury during the tumor resection.

Operative trauma can be a confounder to postoperative visual outcome (14). Compared with transcranial approaches (5), the extended endoscopic endonasal approach can provide a close-up view with better visualization of optic nerves and facilitate a lower visual deterioration after surgery (4, 6, 7), probably because

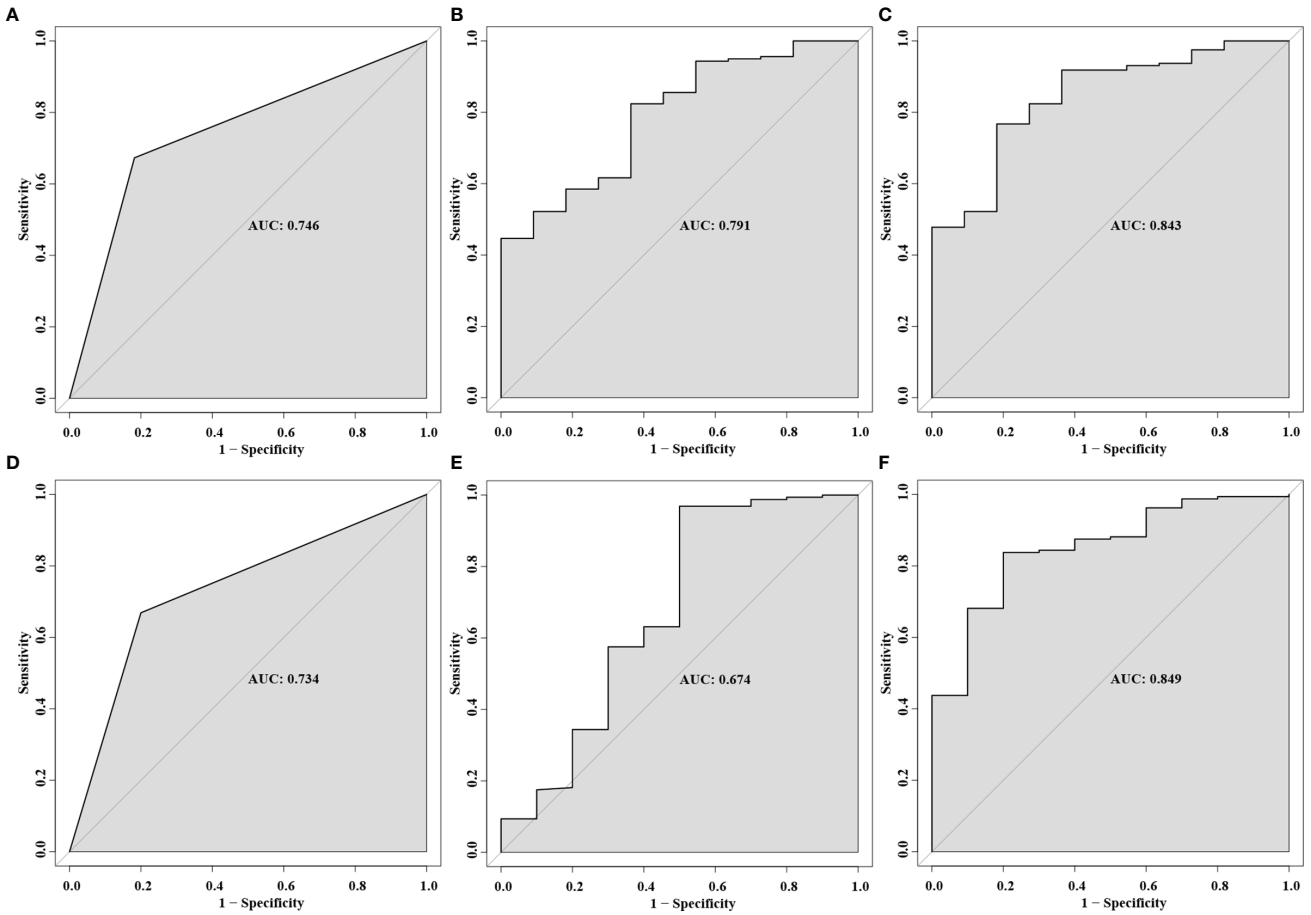

FIGURE 6 | Receiver operating characteristic (ROC) curves for the predictor of multivariable prediction models developed for postoperative VA: tight adhesion **(A)**, increased temporal cpRNFL **(B)**, and the combination of all predictors **(C)**. ROC curves for the predictor of multivariable prediction models developed for postoperative VF: tight adhesion **(D)**, increased inferior cpRNFL **(E)**, and the combination of all predictors **(F)**.

there was less surgical trauma. Besides, this potential limitation was overcome by using the data of only one neurosurgeon (SG). In addition, in our series, the mean follow-up time was 12.0 months (range, 3–28 months), which is longer than the period reported in the series by Danesh-Meyer that the majority of visual recovery was inclined to happen within the first 6–10 weeks (19). Considering the biological characteristic of craniopharyngiomas, the degree of the adhesion strength between optic nerves and the tumor was evaluated according to intraoperative findings and included in multivariate analysis, which made it possible to control the possible confounding effect.

In our study, the advancing age and gender failed to be predictors of postoperative visual outcome, which was inconsistent with the results of previous studies (8, 13, 43), presumably because of the selection and referral bias of the study population. However, considering the age-related changes and sexual differences in OCT parameters, these factors still needed to be included in multivariate analysis when using cpRNFL thickness to make clinical prediction models (24, 25, 44, 45). Overall, clinical prediction models established in the present study, incorporating age, gender, cpRNFL thickness, and adhesion strength, suggested moderate discriminative abilities of VA (AUC = 0.843) or VF (AUC = 0.849) recovery and maintenance. It may be helpful to patient counseling on visual prognosis.

Our study also showed a statistically significant association between OCT parameters and MD/PSD/VFI, which was in line with the findings reported in the series by Ohkubo (34) and Chung (42). That means OCT parameters can excellently act as an alternative to assess preoperative visual field defects resulting from chronic chiasmal compression, particularly for patients with lower compliance.

Limitation

The single-center setting and a retrospective study design have the potential to introduce selection bias, and our results required external validation in the future. In addition, the comparison of the extent of long-term visual recovery after surgery among the

patients with normal and thin RNFL thickness was limited by the present follow-up time, and ophthalmologic examinations should continue to be termly performed after surgery in the future.

CONCLUSION

Preoperative OCT proved to have an independent predictive value in visual outcome after extended endoscopic endonasal surgery for adult craniopharyngiomas. It can also serve as a reliable alternative to evaluate preoperative visual field defects, especially for patients with lower compliance. Tight adhesion was also a strong predictor of postoperative visual outcome. The OCT-based multivariable prediction model developed in the current study may be beneficial to patient counseling on visual prognosis.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of Beijing Tiantan Hospital of Capital Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors take responsibility for the integrity and the accuracy of this manuscript. Study concept and design: NQ and SG. Draft of the manuscript: NQ, CZL and JX. Acquisition of data: NQ, CHL, GM, JX, JK, and LJ. Statistical analysis: NQ and LC. Edit: NQ. Supervision: CHL and YZ. Revision: NQ and SG. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by the Beijing Municipal Science & Technology Commission (Z19110700660000) and Beijing Hospitals Authority Clinical Medicine Development of Special Funding Support (XMLX202108).

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

REVIEW
published: 06 January 2022
doi: 10.3389/fneur.2021.752119

Application of Artificial Intelligence in Diagnosis of Craniopharyngioma

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Craniopharyngioma is a congenital brain tumor with clinical characteristics of hypothalamic-pituitary dysfunction, increased intracranial pressure, and visual field disorder, among other injuries. Its clinical diagnosis mainly depends on radiological examinations (such as Computed Tomography, Magnetic Resonance Imaging). However, assessing numerous radiological images manually is a challenging task, and the experience of doctors has a great influence on the diagnosis result. The development of artificial intelligence has brought about a great transformation in the clinical diagnosis of craniopharyngioma. This study reviewed the application of artificial intelligence technology in the clinical diagnosis of craniopharyngioma from the aspects of differential classification, prediction of tissue invasion and gene mutation, prognosis prediction, and so on. Based on the reviews, the technical route of intelligent diagnosis based on the traditional machine learning model and deep learning model were further proposed. Additionally, in terms of the limitations and possibilities of the development of artificial intelligence in craniopharyngioma diagnosis, this study discussed the attentions required in future research, including few-shot learning, imbalanced data set, semi-supervised models, and multi-omics fusion.

Keywords: craniopharyngioma, tumor, diagnosis, machine learning, deep learning

OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Neurology

Received: *02 August 2021*
Accepted: *12 November 2021*
Published: *06 January 2022*

Citation:
Qin C, Hu W, Wang X and Ma X (2022) Application of Artificial Intelligence in Diagnosis of Craniopharyngioma. Front. Neurol. 12:752119. doi: 10.3389/fneur.2021.752119

1. INTRODUCTION

1.1. Introduction of Craniopharyngioma

Craniopharyngioma is a common skull congenital tumor in clinical which accounts for 1.2–4.0% of all primary skull tumors (1). Its annual incidence rate is reported about 0.05–0.2 per 100,000 individuals (2). Craniopharyngioma has a wide range of age at onset even in the prenatal and neonatal period (3, 4). Craniopharyngioma occurs in a bimodal age distribution, with peak onset ages ranging from 5 to 14 years and 50 to 74 years (5).

The embryonic remnant theory is generally accepted for the pathogenesis of craniopharyngiomas. This theory believes that craniopharyngioma arises from the embryonic enamel primordium, which is located between the Rathke capsule and the oral craniopharyngeal tube, and is formed by residual epithelial cells remaining from craniopharyngeal duct insufficiency (6, 7).

The clinical manifestations of craniopharyngioma are diverse, depending on the tumor location, size, growth pattern, and the relationship with adjacent brain tissue. Craniopharyngioma grows slowly along the suprasellar, sphenoid sinus, posterior nasopharyngeal wall to the third ventricle, thereby forming compression on adjacent brain tissue and causing clinical manifestations

including: (1) Symptoms of increased intracranial pressure, such as headache, vomiting, etc. (8). (2) Sudden changes in visual field and vision (9), which are caused by compression of the optic chiasmatic nerve because of suprasellar lesion. (3) Growth and developmental disorders, and decreased basal metabolic rate (10, 11), which are caused by insufficient secretion of growth hormone and gonadotropins because of the compression of the anterior pituitary gland. (4) As the tumor grows up to the suprasellar even to the bottom of the third ventricle, the hypothalamus is compressed and damaged. As a result, lethargy or even coma (12), electrolyte disturbance (13), diabetes insipidus (14), obesity (15), alterations of BcT ° (body core temperature) and sleep wake cycle rhythms (16), and other atypical symptoms may occur.

1.2. Radiomics

Although it is defined as a benign tumor by the World Health Organization (WHO), craniopharyngioma may cause significant morbidity and mortality due to its locally aggressive growth pattern (17). Therefore, early and accurate diagnosis of craniopharyngioma has important significance for the formulation of therapeutic schemes. Surgical pathological diagnosis is the current golden standard for diagnosing craniopharyngiomas, but it is lowly accepted by patients due to its invasive, high expense and complex operation. Besides, it is not easy to detect brain tissue invasion by histopathology because of the lack of brain tissue samples (18). The inaccurate diagnosis may affect the patient's therapeutic schemes and prognosis, and thus histopathology is difficult to apply to routine clinical examination. Instead of focusing on local tiny tissues, medical imaging can provide a more comprehensive view of the tumor. At present, medical imaging examinations mainly rely on neuroradiologists' subjective judgement on tumor tissues, they are time-comsuming, inefficient, and have subjective bias. With the development of artificial intelligence, radiomics can extract a large amount of image information through imaging methods, such as computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and transformation of visual image information into deep-level features, which can quantitatively describe the image (19, 20). The deeper mining and analysis of numerous image information can assist neuroradiologists to make accurate diagnoses. The combination of radiomics and artificial intelligence methods have the advantages of being non-invasive, economical, efficient, and reproducible, thus can be widely used in tumor diagnosis, treatment, monitoring, and individualization of treatment.

1.3. Artificial Intelligence

Artificial intelligence (AI) is a multidisciplinary and interdisciplinary research on the basis of computer science, which applies the theory and method of simulating and expanding human intelligence to every field of life (21). The application of AI in the field of medical imaging can shorten the image processing time and improve the reliability of diagnostic results leveraging big data (22, 23). AI falls into the categories of traditional machine learning (ML) and deep learning (DL). The ML method inputs training data into the computer, gradually learns rules and recognition patterns based on big data, and finally analyzes the characteristic indicators to predict on new data. ML is characterized by the need to manually design a feature extractor to transform the original data into appropriate feature vectors, which has great influence for the prediction of new data (24). As an important branch of machine learning, deep learning has shown excellent performance in the field of image recognition (25). DL is a multi-level neural network model that combines low-level features to form high-level features, and then discovers the inherent characteristics of the data. It relies on the deep neural network to simulate human brain learning and analyzing data. Meanwhile, DL is also an algorithm highly dependent on big data, whose performance is enhanced with the increase in the amount of data and training intensity.

Although some attempts in the field of intelligent diagnosis of craniopharyngioma have emerged in recent years, the research of artificial intelligence in the diagnosis of craniopharyngioma is still in the preliminary stage. To this end, this study reviewed the existing research on intelligent diagnosis methods for craniopharyngioma, and introduced these applications of artificial intelligence technology in the diagnosis of craniopharyngioma from the aspects of differential classification, tissue invasiveness, gene mutation, and postoperative prediction. With reference to literature of AI in craniopharyngiomas and other similar tumors, this study proposed the technical route for intelligent diagnosis of craniopharyngiomas, focusing on MRI-based machine learning and deep learning methods. In the future research, it requires attentions, but not limited to, few-shot learning, imbalanced data set, semi-supervised learning, and multi-omics research.

The rest of this review was structured as follows: section 2 reviewed the applications of artificial intelligence in the diagnosis of craniopharyngioma from three aspects: differential classification, tissue invasion and gene mutation prediction, and prognosis prediction. Section 3 discussed in depth the intelligent diagnosis route of craniopharyngioma, including traditional machine learning and deep learning models, and a mixture of the two. Section 4 expounded the factors that affect the development of artificial intelligence technology in this field, and the attentions required for future research. Finally, the conclusion of the article was given in the last section.

2. THE APPLICATIONS OF AI IN CRANIOPHARYNGIOMA DIAGNOSIS

Owing to the diversity of tumor shapes and types, craniopharyngiomas have different pathogeneses, degrees of malignancy, and therapeutic schema. Manual diagnosis is time-consuming in clinical practice, and may produce inconsistent results due to individual differences in patients and doctors' experience. Some research into the diagnosis of craniopharyngiomas based on artificial intelligence has emerged in recent years. In this retrospective study, Web of Science, Google Scholar and PubMed electronic databases were searched up to July 15, 2021. Other possible articles were searched manually from the citation list provided

with each article. The potential literature searches were performed using the following keywords: "craniopharyngioma" AND "Artificial intelligence," "craniopharyngioma" AND "machine learning," "craniopharyngioma" AND "deep learning," "craniopharyngioma" AND "non-invasive," "craniopharyngioma" AND "MRI," "craniopharyngioma" AND "diagnosis."

2.1. Differential Classification

(1) Tian et al. (26) employed statistical methods to investigate the role of qualitative features and texture features on MRI between craniopharyngioma and meningioma. The study cohort was a single institutional database consisting of 127 patients with craniopharyngioma or meningioma. Doctors from relevant departments collaborated to evaluate MRI features qualitatively, which include signal intensity, heterogeneity, cystic changes, unenhanced area, the presence of air-fluid level, and the size and location of the tumor. Besides, LifeX medical software was used to extract texture features, including histogram-based matrix (HISTO), gray-level co-occurrence matrix (GLCM), gray-level run length matrix (GLRLM), etc. In this study, according to the previous reports, 10 of the most commonly used texture features were selected for analysis. IBM SPASS software and MedCalc were utilized for statistical analysis. Chi-square tests, Fisher exact test, and the Mann-Whitney *U*-test were used to evaluate the differences between two types of tumors. Additionally, binary logistic regression was adopted to predict the probability of texture feature as an independent predictor. The statistical results demonstrated that there were significant differences in five features between the two types of tumor, including HISTO-Skewness, GLCM-Contrast, GLCM-Dissimilarity on contrast-enhanced images, HISTO-Skewness, and GLCM-Contrast of T2-weighted imaging (T2WI). Later, in the logistic regression experiment, it was found that HISTO-Skewness, GLCM-Contrast on contrast-enhanced images, and HISTO-Skewness of T2WI can be used as independent predictors. The statistical methods facilitate better understanding of the data used for training, and enhance the interpretability of the machine learning model.

(2) Zhang et al. (27) reviewed the data of 126 patients with craniopharyngioma or pituitary adenoma from a single institution. Qualitative MRI features mentioned in previous reports were analyzed. Meanwhile, LifeX software was used to extract 46 texture features of the tumor, including HISTO, GLCM, GLRLM, GLZLM (gray-level zone length matrix), and NGLDM (Neighborhood gray-level dependence matrix). MRI features were evaluated by using chi-square test or Fisher test, while texture features were evaluated by using Man-Whitney test. Subsequently, binary logistic regression analysis was used to evaluate whether the significant features could be used as independent predictors. All statistical analyses were performed with SPSS software. The analysis results showed that the qualitative and textural features of MRI were of potential value in the differential diagnosis of craniopharyngioma and pituitary adenoma, which was helpful for clinicians to make decisions. The main limitation of the study appeared as a small database in a single institution with the exception of inevitable selection bias. On the other hand, the results may be affected by the different image characteristics between two types of craniopharyngioma. Besides that, the study did not evaluate the correlation between texture characteristics and pathology of tumor.

(3) Zhang et al. (28) adopted a machine learning model to identify common lesions presented in the anterior skull base with radiological parameters and clinical parameters. A single-institution database of 235 patients with pathologically proven pituitary adenoma, craniopharyngioma, meningioma, or Rathke fissure cyst were involved in the study cohort. Doctors from relevant departments utilized LifeX software to extract 40 texture features from an MRI, combined with clinical parameters (age, gender, etc.) to identify tumor types. In order to screen out more relevant feature sets, five feature selection methods were adopted, including distance correlation, random forest (RF), least absolute shrinkage, and selection operator (Lasso), extreme gradient boosting and gradient boosting decision tree (GBDT). In addition, nine classification models were employed for classification, including linear discriminant analysis (LDA), support vector machine (SVM), RF, Adaboost, k-nearest neighbor (KNN), Gaussian Naive Bayes (GaussianNB), logistic regression (LR), GBDT, and decision tree (DT). To evaluate the performance of machine learning models, indicators such as ROC, accuracy, sensitivity, and specificity were adopted. The SPSS software was utilized for statistical analysis, and the Python platform and the Scikit-Learn package were utilized to simulate machine learning algorithms. Among the 45 diagnostic models, the combination of LASSO and LDA achieved the best comprehensive effect, which had been reported in previous studies with good classification performance. However, the study cohort, simply from a single institution, was relatively small. In addition, radiomics analysis only adopted contrast-enhanced T1WI without other subsequences. Multi-model imaging statistics should be integrated into the study in future research.

(4) Prince et al. (29) tried adopting deep learning to identify craniopharyngiomas. The imaging data were obtained via Children's Hospital in Colorado. Experiments were conducted by using CT scan images and contrast-enhanced T1-weighted MRI. In order to overcome the disadvantages of small data sets, the study adopted a transfer learning method to obtain the pre-training model of ImageNet through the TensorFlow application module. Another measure to solve over-fitting problems was a three-term loss function comprised of sigmoid focal cross-entropy, triplet hard-loss, and CORellation alignment, also the effectiveness of the modified loss function was verifed in this study. In addition, a meta-heuristic parameter optimization method was adopted to mitigate the calculation loss of the model. The StandardScale function of Scikit-Learn was used to preprocess the image, and the Long Short-Term Memory model (LSTM) was employed for classification of adamantinomatous craniopharyngioma with other sellar/suprasellar tumors. The deep learning algorithm was based on the TensorFlow framework, which was written and executed by Python 3.6. The experimental results provided a transferable and extensible computing framework for intelligent diagnosis of rare diseases. Further optimization of classifiers will be the next potential. Also, training on MRI and CI

simultaneously may acquire a more robust classification model. Furthermore, the integration of classification model into a lightweight web-based application will accelerate deployment to the clinical medical community.

(5) Prince et al. (30) studied a series of optimization methods to address small data sets and subsequently adopted deep learning algorithm to identify the pediatric adamantinomatous craniopharyngioma. Transfer learning was an effective technique to deal with overfitting of small data sets, which was verified in the study. In addition, two data augmentation techniques were utilized to expand the data set. One was the random data augmentation technique, which used random probability thresholds to transform the image, through cutting, rotation, blurring, etc. The other method was transformation adversarial networks for data augmentation (TANDA), which was an unsupervised image generation mode based on generative adversarial networks (GAN). Moreover, a meta-heuristic parameter optimization was applied to reduce the computational time. The experimental cohort involved a small data set from Children's Hospital Colorado and St. Jude Children's Research Hospital. The program was developed in the virtual environment of python 3.6. The results showed that the performance of the optimal model was comparable to the average of radiologists, and the deep learning network achieved the best performance with the combination of CT and MRI data sets. Potential next steps include optimization of TANDA algorithm and synthetically expanding the data set which could leverage pre-trained feature extraction. Besides that, the study adopted only one type of classification model. Other additional classifiers should be explored in future research.

2.2. Prediction of Tissue Invasion and Gene Mutation

(1) Although Craniopharyngioma is a benign tumor, it is still possible to invade adjacent brain tissue which results in incomplete surgical resection and poor prognosis. Therefore, preoperative evaluation of the tissue invasion of craniopharyngioma is helpful to formulate a more individualized surgical scheme. Ma et al. (31) used a machine learning algorithm combined with radiological characteristics to predict preoperative craniopharyngioma invasiveness. The study cohort consisted of 325 patients in a single institution. The researchers utilized MRIcron software to manually delineating the region of interest, and applied Z-score transformation on the images to avoid heterogeneity bias. A total of 1,874 features were extracted in this study. After being screened by using the Lasso feature selection method, an optimal feature subset of 11 features was finally selected and fed into the SVM model for invasion prediction. The experiments used the ROC curve to evaluate the performance of the learning model. The results suggested that this non-invasive radiomics approach could predict the invasiveness of craniopharyngioma, aid clinical decision making, and improve patient prognosis.

(2) Craniopharyngiomas are classified into two histologic subtypes: Adamantinomatous craniopharyngioma (ACP) and papillary craniopharyngioma (PCP). BRAF and CTNNB1 mutations are found to be strongly correlated with the pathological subtypes of craniopharyngiomas, which means the diagnosis of pathological subtypes and gene mutations has great significance for the effective adjuvant targeted therapy. Chen et al. (32) discussed the prediction of BRAF and CTNNB1 mutations through radiomics method based on MRI. The study reviewed the preoperative MRI data of 44 patients with craniopharyngioma from a single study institution. In this study, 464 local features were obtained using quantitative location evaluation methods, and another 555 high-throughput features including intensity, shape, texture, and wavelet features were extracted by using MATLAB tools. In order to reduce the redundancy and computational complexity of features, a three-stage feature selection method was adopted. In the first stage, High-throughput texture features were evaluated according to intra-class correlation coefficients (ICC), and the features with ICC greater than 0.8 remained. In the second stage, the data set was sampled 100 times by the bootstrap, and the feature selection method embedded in Random Forest model was adopted to preserve the highest average of results. In the third stage, sequence forward selection strategy was applied to evaluate the prediction effect of candidate feature subsets according to the performance of Random Forest classification. Finally, the most relevant feature subset was screened out and fed into the Random Forest model, and then the performance of the classification model was evaluated by 10-fold cross-validation. The method proposed in this study achieved considerable accuracy in the prediction of pathological subtypes and the classification of gene mutation status.

(3) The cystic part of craniopharyngioma can easily aggress adjacent brain tissue, making complete surgical removal difficult. Since CTNNB1 mutation has been proved to be related to tumor recurrence, the prediction of CTNNB1 mutation in craniopharyngioma can facilitate surgical treatment and reduce postoperative recurrence rates with molecular targeted drugs. Zhu et al. (33) adopted the preoperative MRI data of children with cystic ACP from a institutional database, quantitatively measured the MRI by the picture archiving and communication system (PACS), and extracted the location, quantity, shape, maximum diameter, internal signal, cyst wall, and other characteristics. Continuous data were assessed through Mann-Whitney *U*-test, categorical data were analyzed through Fisher's exact test, and all the statistical analyses were carried out by using SPASS software. The study confirmed the differences in MRI features between patients with CTNNB1 mutation and the control group. Through the identification of gene mutations, appropriate preoperative inhibitors may prevent the formation of cystic tumors and reduce the size of tumors, thereby providing the best opportunity for surgical treatment.

(4) Prediction of BRAF mutation before surgery and treatment with inhibitors may shrink the tumor and improve the success rate of surgical resection. Yue et al. (34) dedicated their research to the study of the non-invasive diagnosis method of BRAF mutation in craniopharyngioma. The study reviewed the information of patients with craniopharyngioma from a single institution, and MRIs (including non-enhanced sequences and contrast-enhanced sequences) of 52 patients were involved in the

study. The study assessed MRI features including tumor location, size, shape, composition, tumor cysts signal, enhancement pattern, pituitary stalk morphology, and internal carotid artery encasement. A Mann-Whitney test was adopted to evaluate the continuous variables, Fisher's exact test was used to compare the categorical variables, and these statistical analyses were carried out by using SPSS software. The results showed that five features of the MRI were related to BRAF mutation, and this non-invasive diagnostic approach provided a reference for the use of targeted inhibitors before surgery.

(5) Due to the heterogeneity in clinical expression, topography, and pathological features of craniopharyngioma, the diagnosis and surgical treatment of craniopharyngioma are still challenging in the clinic. Craniopharyngioma (CP) may occur at any point from the sella to the third ventricle, along the vertical hypothalamic-pituitary axis. The anatomical relationship between craniopharyngioma and the third ventricle is a vital factor for surgical schemes. Prieto et al. (35) discussed the topographic classification of craniopharyngioma with preoperative MRI. In the study, the tumors were classified into five major categories, including sellar-suprasellar CPs, suprasellar-pseudoventricle CPs, secondary intraventricular CPs, infundibulo-tuberal CPs, and strictly intraventricular CPs. The study retrospected the MRI of 200 craniopharyngiomas selected from a recent publication, and analyzed radiologic features related to tumor size, shape, consistency, the occupation of the tumor of intracranial compartments, the distortions of anatomic structures along the sella turcica–third ventricle axis, etc. The correlations between pairs of categorical variables were evaluated by using chi-square or Monte Carlo validation, then the topographic classification of craniopharyngioma was explained through multiple classification and regression tree growing method. The statistical analysis was carried out by using SPSS software. The experiment result identified seven radiologic features on preoperative MRI which should be analyzed to accurately define the topography of CP. A further step may be the integration of specific MR imaging sequences which can offer high-resolution.

2.3. Prognosis

Due to the tissue invasion, surgical resection of craniopharyngioma is often incomplete, which leads to tumor recurrence and poor prognosis. The prediction models of prognosis require complex and abundant data, hence artificial intelligence technology is appropriate to traditional statistical methods. In this field, some research on the prognosis of brain tumors such as pituitary tumors have been emerging. Inspired by these attempts, some researchers studied the postoperative prediction of craniopharyngioma. Hollon et al. (36) predicted early outcomes of pituitary adenoma surgery with a machine learning model. In the study, a retrospective review was constructed for a cohort of 400 consecutive pituitary adenoma treated at a tertiary care center. Naive Bayes, logistic regression with elastic net (LR-EN) regularization (linearly combined L1 and L2 regularization penalties), SVM, and random forest were adopted to predict early postoperative outcomes in pituitary adenoma patients. The experiment selected twenty-six characteristics as predictive variables, used a grid search for the selection of model hyperparameters, and performed a 10-fold cross-validation for each model. After model training, LR-EN best predicted early postoperative outcomes with 87% accuracy. Additionally, risk factors for postoperative complications after pituitary adenoma surgery were explored. Moreover, these results provided insight into how to use machine learning models to improve the perioperative management of pituitary adenoma patients.

Shahrestani et al. (37) developed a multilayered neural network (NN) to estimate predictors of postoperative complications and outcomes in patients with functional pituitary adenomas (FPAs). Three hundred forty-eight patients with FPAs in a single center were included in the analysis. First, the study performed multivariate regression model to test the correlation between patient-specific characteristics and good outcomes. Then, the NNs with strong ability in non-linear models were trained on significant variables obtained in multivariate analysis. Weights and bias terms were calculated from these back-propagation models. The NN models were tested and confirmed by using ROC curve, AUC value, and confusion matrices. The study developed a robust prediction algorithm for recurrence, progression, and hormonal non-remission in patients with FPAs.

Since craniopharyngioma is structurally close to the optic nerve, visual dysfunction occurs in 53–93% of patients. Kopparapu et al. (9) collected preoperative, intraoperative, and postoperative variables of craniopharyngioma in a single institution, including demographics, radiology information, surgical approach, etc. Meanwhile, radiographic, operative, and perioperative characteristics were qualified in this study. Besides, the patient's visual characteristics such as visual acuity (VA) and visual fields (VFS) were standardized according to the guidelines defined by the German Ophthalmological Society. Statistical analyses were performed by using Stata software. Categorical variables were analyzed through chi-square test, and continuous variables were analyzed through independent-sample *t*-test. Furthermore, multivariate analysis was carried out by using logistic regression for significant variables. The analysis result demonstrated that patients with reduced preoperative visual acuity, specific readiographic vascular involvement, and total surgical resection had more possibility of achieving improved postoperative visual acuity. In addition, statistical analysis also found that the translaminar surgical approach was related to visual deterioration. Postoperative vision prediction is helpful for counseling between patients and surgeons and may facilitate the customization of surgical schemes. The limitations of the study are consistent with other similar retrospective reviews. A relatively small sample size affected the results of study and resulted in non-significant findings on bivariate and multivariate analysis.

3. STRATEGIES OF ARTIFICIAL INTELLIGENCE IN CRANIOPHARYNGIOMA DIAGNOSIS

In the field of clinical medical imaging, subjective diagnosis of radiologists has inevitable bias and is time-consuming. Moreover, it is a challenge for medical staff to address

numerous data and high-dimensional features manually. With the development of artificial intelligence technology and its successful applications in many fields, more and more research has been performed on the application of artificial intelligence in the medical field. As shown in section 2 above, some attempts emerged in differential classification, prediction of tissue invasiveness and gene mutation, and prognosis detection of craniopharyngioma. However, these works represent an initial exploration in the diagnosis of craniopharyngioma. Glioma and lung adenocarcinoma, similar to craniopharyngioma in tissue invasion, with which difficulties in diagnosis and individualization of treatment are also associated. Glioma is one of the most aggressive brain tumors with poor prognosis compared with other brain cancers. Diffuse invasion of tumor cells into normal brain is a big challenge in diagnosis and individualization of treatment (38). Lung cancer is a common cause of cancer incidents worldwide, comprising 1/3 to 1/2 of incidents being attributed to adenocarcinoma. Due to an increased degree of invasion with poor prognosis, evaluation of invasion of lung nodules is important to customize the appropriate clinical-decision scheme (39). Thus, many studies have been dedicated to developing a new, non-invasive method that provided a reference for accurately diagnosis before surgery to reduce tumor recurrence and improve patients prognosis. Inspired by this research, the study referred to the achievements of AI diagnostic techniques for tumors (e.g., glioma, lung adenocarcinoma), and furthermore proposed the diagnosis route of craniopharyngioma based on artificial intelligence technology.

At present, imaging examinations are common methods for clinical diagnosis of craniopharyngioma. Compared with CT, MRI can clearly display the tumor location and the anatomical relationship of adjacent tissues through multi-directional imaging. The aforementioned studies also found that the features extracted from MRI have significant difference for the diagnosis of craniopharyngioma (26, 35). Therefore, the artificial intelligence diagnosis route discussed in this study is based on MRI.

3.1. Machine Learning Mode

While deep learning has become the technology of choice for most AI problems, it relies excessively on large data sets, which are difficult to collect, expensive, and time-consuming, especially for scarce tumors like craniopharyngioma. For small data sets, classical machine learning methods sometimes outperform deep learning models, with lower computational cost, and unnecessary high-end hardware. On the other hand, deep learning is a "black box." In comparison, machine learning algorithms are more explanatory. The diagnostic route based on machine learning method is shown in **Figure 1**, which mainly includes image pre-processing, image region of interest (ROI) segmentation, feature extraction, feature selection, machine learning modeling, and other steps.

(1) Image pre-processing: As the acquisition of image data is dependent on device manufacturer, device parameters and patient position, pre-processing techniques can correct and normalize original images to weaken the interference information, and also improved the quality of core areas in the image. For brain MRI, the general pre-processing techniques usually include noise suppression, skull stripping, non-uniform correction, intensity normalization, and so on.

Noise suppression and non-uniformity correction can reduce the individual differences of the collected objects and the MRI brightness differences caused by the deviation of the instrument and the scanning process. For image sequences with various intensity ranges of the same image, such as T1WI and T2WI, intensity normalization is required for preprocessing. Skull stripping as an important part of brain image analysis can mitigate non-uniform distribution of intensity due to fat tissue. Skull stripping can be automatically implemented base on contour or histogram except for when using manual methods. Some of the pre-processing techniques in literature are as follows: Al-Saffar and Yildirim (40) performed skull stripping with a threshold-based method, and adopted median filtering technology to reduce image noise. Gutta et al. (41) used BrainSuite software for resampling all images and skull-stripping, and used the FMRIB Software Library (FSL) toolbox for co-registration. Analogously, Ahammed et al. (42) also performed skull stripping by using BrainSuite software, which adopted a brain surface extraction algorithm (BSE) to operate the skull stripping. Aiming to solve the non-standardization of MRI intensity, Chen et al. (43) used bias correction and Z-score normalization which were implemented in Statistical Parametric Mapping (SPM12) for pre-processing. Siakallis et al. (44) performed log-transformation, normalization, bias field correction and intensity matching on skull stripping images. Kandemirli et al. (45) conducted pre-processing operations including gray-level normalization and discretization. The commonly used techniques and tools in representative literature are listed in **Table 1**.

(2) ROI segmentation: Image ROI segmentation has an important impact on the final result of medical classification. ROI segmentation can remove surrounding tissues of the lesion and irrelevant interference information in the background, and identify the lesion area by describing the density, shape and other characteristics of the ROI. In many research studies, neuroradiologists manually delineate the ROI which requires deliberations to demonstrate the effectiveness of the segmentation and reach a consensus on the differences. In addition, semi-automatic or automatic segmentation algorithms are also feasible. Threshold segmentation, as a commonly used method, takes the gray value of the pixel as the feature description, and uses the threshold to distinguish background information and segmentation targets (46). A common method based on region, the image starts from a certain point and merges the surrounding pixel points with the same attribute (including gray value, texture and other features) (47). There are also some segmentation algorithms based on specific theories, such as minimized graph cut algorithm based on energy (48), conditional random field method based on statistics (49), and clustering analysis method based on fuzzy sets (50), etc. In addition, the deep learning network can automatically obtain features from the training data and achieve good segmentation performance (51, 52).

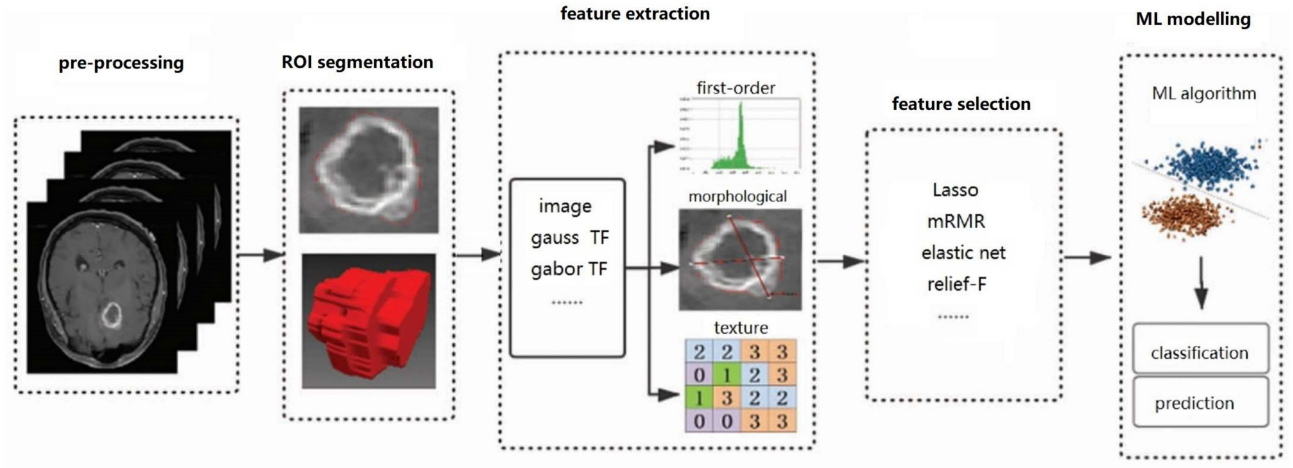

FIGURE 1 | Flow chart of diagnostic craniopharyngioma based on ML: the steps include pre-processing, ROI segmentation, feature extraction, feature selection, and ML modeling. "TL" is the abbreviation of transformation.

Part of the research performed manual segmentation by using ITK-SNAP, MRIcron, LifeX, and other softwares. Tekawa et al. (53) performed semi-automatic image segmentation by using the Analysis of Functional Neuro Images software (NUMH Scientific and Statistical Computing Core; Bethesda, MD, USA). In the semi-automatic segmentation procedure, the neuroradiologist manually selected the intensity threshold to extract the high-intensity areas of T2-weighted FLAIR images. In addition, there were some auto-segmentation methods adopted in retrieved literature. Al-Saffar and Yildirim (40) adopted the LDI-means clustering algorithm for image automatic segmentation. Ahammed et al. (42) combined k-means and fuzzy-c-means clustering method for automatic segmentation. Gutta et al. (41) performed segmentation with a fully automated tumor segmentation tool, which came from the Brain Tumor Segmentation Challenge. The aforementioned automatic segmentation methods also achieved good performance.

Different ROI segmentation techniques in representative literature are summarized in **Table 2**. Manual segmentation methods are simple and easy to master, but there are inevitably subjective differences. Some automatic segmentation algorithms with better performance can optimize the clinical diagnosis process, but their applications need to be evaluated with strict clinical tests.

(3) Feature extraction: This is a process of integrating, analyzing and calculating numerous features of ROI with various algorithms, which has a significant influence on the whole process. A high-quality feature set can not only simplify the complexity of the images sample, but also better represent the structural information, visual characteristics, and biological background knowledge of images, and directly affect the prediction effect of models. The features extracted from MRI commonly include first-order features, morphological features, texture features, and wavelet features (55), etc. First-order features, also known as histogram features, are extracted from the gray histogram of images. First-order features can only be used to describe the gray value distribution of ROI, but cannot describe the spatial relationship, interaction, and correlation between adjacent voxels. Morphological features can be used to quantitatively describe the geometric characteristics of ROI, which are good indicators of the anatomical changes of the tumor. Texture features represent the spatial arrangement between the image voxel gray levels, and facilitate evaluation of the heterogeneity inside the tumor. If two types of tumors have similar intensity distributions but different spatial correlations, second-order or higher-order texture features may be preferable to first-order features in such a situation. Texture features can also be obtained by the image Laplace transform, wavelet transform, Gabor transform, etc. Since a single feature set with insufficient information may lead to the risk of under-fitting in the training model, most literature use mixed feature sets in the research.

TABLE 1 | An overview of techniques for pre-processing based on MRI.

References	Pre-processing	Tool
Al-Saffar and Yildirim (40)	Skull stripping based on threshold, Median filtering for noise reduction	MATLAB
Gutta et al. (41)	Skull stripping	Brainsuite software
KV et al. (42)	Skull stripping	Brainsuite software
Chen et al. (43)	Bias correction, Z-score normalization	SPM12
Siakallis et al. (44)	Logarithmic transformation, normalization, Offset field correction, strength matching	
Kandemirli et al. (45)	Grayscale normalization, Discretization	

TABLE 2 | An overview of techniques for ROI segmentation based on MRI.

References	Manual/ semi-automatic/ automatic	Method/tool
Özyurt et al. (54)	Manual	MRIcron software
Tian et al. (26), Zhang et al. (27)	Manual	LIfeX software
Siakallis et al. (44)	Manual	ITK-SNAP 3.8
Tatekawa et al. (53)	Semi-automatic	Analysis of Functional Neuro Images software
Al-Saffar and Yildirim (40)	Automatic	LDI-means clustering algorithm
KV et al. (42)	Automatic	Combined k-means and fuzzy c-means
Gutta et al. (41)	Automatic	A tool from competition

TABLE 3 | An introduction of feature extracted from MRI.

Feature type	Feature family
First-order features	Mean, maximum, minimum, median, root mean square, energy, entropy, kurtosis, skewness, variance, standard deviation, uniformity, gray field, etc.
Morphological features	Density, 3D maximum diameter, spherical asymmetry, sphericity, surface area, ratio of surface to volume, volume, etc.
Texture features	Gray-level co-occurrence matrix, gray-level run matrix, gray-level area size matrix, gray-level correlation matrix, adjacent gray- level difference matrix, neighborhood gray-level dependence matrix and gray-level run length matrix, etc.
Common transformations	Laplace transform, wavelet transform, Gabor transform, etc.

Commonly used image features are briefly described in **Table 3**, and the single or mixed feature sets extracted in the representative literature are summarized in **Table 4**.

(4) Feature selection: The feature dimension obtained in the previous feature extraction process counts from tens to thousands, which leads to inevitable problems of computational complexity and overfitting. The feature selection method should be recommended to further optimize the high-dimensional features, eliminate redundant features, screen out the most relevant feature subsets, and avoid over-fitting. Commonly used feature selection methods include the criterion-based sorting methods that sort the features according to the evaluation criterion and select the feature with a higher score than the threshold. The general evaluation criteria include Fisher score (58), Pearson correlation coefficient (59), mutual information (60), etc. In addition, some heuristic rules can also be applied in selecting subsets, such as forward/backward search strategy (61), Markov chain (62), etc. It can also combine the criterion-based sorting method with the search strategy to form a two-step feature selection method, such as the feature selection method with maximum relation and minimum redundancy (63), which obtained good result in reports. There are also some learning algorithms with embedded feature evaluation, among which the decision tree is a typical algorithm (64).

Zhang et al. (28) verified five feature selection methods including distance correlation, random forest, Lasso, extreme gradient boosting and gradient boosting decision tree, of which Lasso achieved the best performance. And Ma et al. (31) also adopted Lasso for feature selection. Gutta et al. (41) used the importance score in the gradient boosting algorithm to select the features. Hybrid feature selection methods were adopted in some literature. Le et al. (56) employed a two-level feature selection method. In this method, the salient radiological features were evaluated with F-score criterion and ranked in descending order. Sequentially, the features were added to the model one by one, meanwhile the recursive feature culling technique was adopted to select the best cut-off point. Al-Saffar and Yildirim (40) adopted mutual information (MI) to evaluate the features, and used singular value decomposition (SVD) method to reduce feature dimension. Kandemirli et al. (45) firstly used the intraclass correlation coefficient to eliminate the features with score lower than 0.75, and then adopted the intrinsic feature selection method of XGBoost or additional feature selection methods (such as Boruta, low variance filter, and multicollinearity analysis) for further selection. Gao et al. (57) obtained the top 15 features according to Chi-square evaluate criterion, and drew a heatmap by using Seaborn library to identify the highly correlated features. Finally, the optimal feature subset was selected in terms of the feature importance of Random Forest algorithm. Chen et al. (32) proposed a three-stage feature selection method. In the first stage, intraclass correlation coefficients were used to screen robust variables. Sequentially, the robust texture features, location features, and clinical features were evaluated according to the feature score of Random Forest, and the top-ranked features were retained. In the third stage, a sequential forward search strategy was adopted to select the optimal feature subset.

The feature set and feature selection methods used in representative literature are compared in **Table 4**. Although there are a lot of mature feature selection methods, there are still problems involved in designing effective methods for specific scenarios. In the retrieved literature, Lasso is a linear regression model with the constraint term of L1 norm added behind the cost function. It carries out variable screening and complexity adjustment through the control parameter lambda, and is widely used in the medical field. In addition, the combination of different types of feature selection methods and the design of appropriate evaluation criterion according to specific scenarios are also required for further research.

(5) Machine learning modeling: In this procedure, a high-quality classifier is generated through sample training, and the feature vectors obtained after feature extraction and selection are fed into the classifier, thereby outputting the diagnosis results. Machine learning algorithms are classified as supervised learning and unsupervised learning. Supervised learning models are commonly used in the current medical field, such as random

TABLE 4 | An overview of features extracted from MRI and feature selection methods.

References	Original feature set	Dimension	Extraction tool	Selection method
Zhang et al. (28)	First-order features, GLCM, GLZLM, NGLDM, GLRLM, gender, age	40+2	LifeX	Distance Correlation, RF, Lasso, XGBoost, and GBDT
Ma et al. (31)	First-order statistics, shape, GLCM, GLRLM, GLSZM, NGTDM, GLDM, Wavelet features	1,874	MATLAB	Lasso
Gutta et al. (41)	First-order feature, shape, GLCM, GLRLM, GLSZM, NGTDM, GLDM	1,284	PyRadiomics	Importance score from gradient boosting algorithm
Le et al. (56)	Intensity, image derivative, geodesic, texture, posterior probability maps	704	Cancer Imaging Phenomics Toolkit	F-score evaluation criterion, recursive feature elimination
Al-Saffar and Yildirim (40)	GLCM, intensity	40		MI evaluation criterion, SVD
Kandemirli et al. (45)	Intensity, shape, GLCM, GLRLM, GLSZM, GLDM	3,255	Pyradiomics	Intraclass correlation coefficient, XGBoost's inherent feature selection and additional feature selection method
Gao et al. (57)	First order features, shape, GLCM, GLRLM, GLSZM	1,421	PyRadiomics	Chi2 verification, Seaborn library, inherent feature selection of RF
Chen et al. (32)	Local feature, intensity, shape, texture and wavelet features	1,091	MATLAB	Intraclass correlation coefficients, feature scores of RF, forward search strategy

gray-level co-occurrence matrix; GLZLM, gray-level zone length matrix; NGLDM, neighborhood gray-level dependence matrix; GLRLM, gray-level run length matrix; GLSZM, gray-level size zone matrix; NGTDM, neighboring gray tone difference matrix; GLDM, gray-level dependence matrix.

forest (RF), artificial neural network (ANN), support vector machine (SVM), logistic regression (LR), and so on.

The machine learning models used in representative literature are compared in **Table 5**. Based on the principle of maximum interval separation, SVM can mitigate the structural risk by minimizing the model complexity and training error, and has became an important tool for data classification in the field of pattern recognition. SVM can solve problems of high dimension and overfitting, and is often recommended in small sample classification scenarios.

TABLE 5 | An overview of ML model in literatures.

References	ML model	The best one
Le et al. (56)	KNN, NB, RF, SVM, XGBoost	XGBoost
Al-Saffar and Yildirim (40)	Multi-layer perceptron, RBF-SVM	
Kaplan et al. (65)	KNN, ANN, RF, A1DE, LDA	KNN
Kandemirli et al. (45)	XGBoost	
Tatekawa et al. (53)	SVM	
Gao et al. (57)	LR, SVM, RF	RF
Zhang et al. (66)	LR, SVM	LR
Siakallis et al. (44)	SVM	
Zhang et al. (28)	LDA, SVM, RF, Adaboost, KNN, GaussianNB, LR, GBDT, DT	Lasso+LDA
Chen et al. (32)	RF	
Ma et al. (31)	SVM	

3.2. Deep Learning Mode

A machine learning algorithm requires complex feature engineering, which needs to explore and analyze the data set, reduce dimension of the feature set, and finally select the optimal feature subset to feed to the machine learning model. In contrast, the deep learning method is a kind of end-to-end learning, which has a strong learning ability and is easy to be transplanted. In many fields, deep learning algorithms perform far better than machine learning algorithms based on large amounts of data. Herein, craniopharyngioma diagnosis based on deep learning includes data augmentation and design of models.

(1) Data augmentation: Data is the driving force for deep learning models. Feeding abundant data into the training process can significantly improve the performance of the deep learning model. Whereas, in the field of medical research, due to the difficulty of data collection and the high cost of data labeling, the training data are not so sufficient, which results in poor model generalization and insufficient credibility of deep learning models. Data augmentation technology generates new data by transforming existing data, which is an important measure to expand the number of samples and improve the generalization ability of deep learning models. Therefore, data augmentation is widely used in the training process of deep learning models in the medical field. Data augmentation techniques can be implemented by transforming a single image or mixing information of multiple images. The geometric transformation commonly used in medical images is a typical data deformation operation (67), which generates new samples through rotation, mirroring, translation, cropping, etc. In addition, SMOTE, mixup and other methods can mix information from multiple images and

synthesize new samples (68, 69). With the further development of artificial intelligence, novel data augmentation methods such as adversarial learning, meta-learning, and reinforcement learning have emerged and achieved good performance (70–72).

Data deformation technology was commonly utilized in most of the literature to achieve data augmentation, which can quickly and directly expand the data set. In (73), flips, rotation, shift, zoom, ZCA whitening, shearing, and brightness operations were used to achieve data augmentation. In (74), methods such as vertical flip, horizontal flip, image rotation of 90 degrees, 270 degrees, and image transpose were adopted to expand the data set by 6 times. In (75), Augmenter library was utilized to implement a cascade of rotation, zooming, shearing, and flipping techniques with certain probability, and elastic transformation was combined for data augmentation. As a result the training data set was increased by 20 times. In (76), eight different data augment techniques, including flip vertical, flip horizontal, rotate at 180 degree, rotation at 90 degree, noise, shear, blurr, and crop & scale were compared. The results showed that rotation at 90 degree and 180 degree achieved the best performance. In (77), contrast conversion, brightness conversion, sharpening and flipping were used to expand the data, and the training data was increased by four times. In (78), elastic transformation was used for data expansion. Autoaugment tool was used in (79), and multiple geometric transformation strategies were used to expand the data set to 23 times. In (80), the inversion technique in geometric transformation was adopted, and the classification accuracy was improved from 82.46 to 96.4% through data augmentation. In (81), data augmentation was carried out by using random clockwise rotation, counterclockwise rotation, and vertical flipping techniques.

Some literature also utilized GAN technology for data synthesis. For example, Carver et al. (82) used GAN network to generate high-quality images. Price et al. (30) employed two data augment techniques, one was a random process that used probability thresholds for sample transformations, and the other was a transformation adversarial network for data augmentation (TANDA). The relative simplicity of the image led to the advantage of random augment over TANDA. TANDA method was more advantageous for complex data sets where the target and background were indistinguishable.

Image deformation technology, as a basic image augmentation method, has been widely used for preprocessing in the field of image processing, and most of the methods are integrated into the machine learning library for deep learning applications. However, the transformation rules are not universal, and some of them only perform well on specific data sets. Data augmentation based on GAN which can generate the virtual image sample close to reality provides a new solution for data augmentation. More important, virtual images generated from noise images can enrich the randomness and diversity of samples, thus greatly improving the performance of the model. Nevertheless, the GAN training process is extremely complex and requires a large amount of computation, which limits its application in large image data sets. The techniques for data augmentation are listed in **Table 6**.

TABLE 6 | An overview of techniques for data augmentation.

References	Techniques for data augmentation
Ismael et al. (73)	Flips, rotations, shifting, zooming, ZCA whitening, shearing, brightness manipulation
Zhang et al. (74)	Flips, rotations, image transpose
Özcan et al. (75)	A chain of rotation, zooming, shearing, flippling, and elastic transforms
Safdar et al. (76)	Flips, rotations,noise, shear, blurr, crop and scale
Wu et al. (77)	Contrast & brightness conversion, sharpening, flippling
Diaz-Pernas et al. (78)	Elastic transformation
Zhuge et al. (79)	Geometric transformation
Mzoughi et al. (80)	Geometric transformation
Atici et al. (81)	Rotations, flippin
Carver et al. (82)	GAN
Prince et al. (30)	TANDA, random transformations

(2) Design of deep learning model : Deep neural networks are developed on the basis of the early artificial neural network. Through the deeper neural network structure, the expression ability and the performance of the whole network have been greatly improved. With the breakthrough of deep learning in the traditional image recognition field, many classical deep learning frameworks have emerged, especially since large-scale image data sets became open source. In deep learning models, convolutional neural network can be considered as one of the most classic network models (83), which is usually composed of convolutional layer, pooling layer, full connection layer, etc. The convolutional layer obtains the feature information of the image through convolution operations, and synthesizes the local features to global features. The pooling layer is used to reduce the dimension of features and improve computational efficiency of the network. The full-connection layer combines the pooled multiple groups of features into a group of signals, and performs classification and recognition tasks through the classifier. Many classic networks have evolved from the convolutional neural network. For example, the AlexNet network uses rectifying linear units (RELU) to introduce non-linearity, adopts dropout technology to selectively ignore some neurons to avoid overfitting, and stacks maximum pooling layers to improve the disadvantage of average pooling (84). As a result, AlexNet can learn more complex object and hierarchical architectures. In addition, the VGG network from the University of Oxford adopts continuous and multiple 3∗3 convolution to simulate the effect of larger convolution kernel (85). This technology can extract more complex features, but the drawback is the increase of parameter number and the requirement of computing power. Therefore, various network variants are derived to address this drawback. Typically, the ResNet adds cross-layer connections to form residual elements, which solves the problems of network degradation and gradient explosion caused by the deepening of the network layer (86). Additionally, in terms of the problem that a convolutional neural

network can not extract and retain the time series, the recurrent neural network (RNN) maintains the dependency relationship in data through the serial structure (87), which is suitable for time series data. There are also other variants of deep learning networks that have also achieved good performance in the field of medical imaging (88, 89). Deep learning models in the representative literature are summarized as follows:

Özcan et al. (75) adopted CNN network comprised of 7 convolution layers, a full connection layer, and a classifier of Softmax function. The proposed model obtained high performance and robustness in glioma grading. Chang et al. (90) used a CNN network to classify the gene mutation of glioma. Francisco et al. (78) adopted a CNN network to differential diagnosis of meningioma, glioma, and pituitary tumor, and achieved a high classification accuracy. Mehmet et al. (81) adopted a CNN network to automatically detect high-grade glioma and achieved good performance. Prince et al. (30) adopted a CNN network with parameter optimizer to realize the non-invasive diagnosis of adamantinomatous craniopharyngioma. Wu et al. (77) employed three CNN network models (AlexNet, ResNet, Inception-V3) to classify glioma and encephalitis. The results of the automatic classification were compared with the performance of the radiologists and acquired satisfying performance. Mzoughi et al. (80) graded glioma by using a 3DCNN network, which fused local and global context information through a small convolution kernel. Wang et al. (91) developed and validated a 3DCNN model for classification of different types of lung cancer. The performance of the proposed classification model was compared to radiologists and obtained a higher score. Ismael et al. (73) identified three types of brain tumors (meningiomas, gliomas, and pituitary tumors) on MRI with the Resnet50 framework that is a 50-layer variant of the residual network. Zhuge et al. (79) proposed two automatic methods for glioma grading, one of which was a 3DConvNet structure, and the other was a ResNet structure combined with a pyramid network. Safdar et al. (76) used YOLO3 model to assess the effect of data augmentation methods. Carver et al. (82) adopted a 2D-UNET network to evaluate the segmentation performance of the synthetic image. Baid et al. (92) segmented glioma images with a 3D-UNET network. Prince et al. (29) adopted the long short-term memory (LSTM) network to realize the non-invasive diagnosis of adamantinomatous craniopharyngioma.

3.3. Hybrid Model

The quality of the data set is pivotal to the performance of AI algorithms. The input data can be the feature vectors extracted by the algorithm, or the raw data directly entered into the end-to-end learning system. The imaging features mentioned in section 3.1 can express and quantify the hidden information in the image, while their ability to describe the global information of images is insufficient, and the ability to filter noise is weak. By contrast, CNN itself as an excellent feature extractor, can obtain global high-order features (93). Therefore, some researches developed a hybrid model of traditional machine learning and deep learning, which could better match multi-source heterogeneous medical data and obtain more comprehensive information.

Deepak and Ameer (94) employed the modified GoogleNet to extract deep CNN features, and subsequently fed these features into SVM and KNN classifier models. The performance of classification for brain tumors was improved with the proposed hybrid model. Ning et al. (95) fused the radiomics features with depth features extracted by the CNN network, and performed feature selection to screen out the optimal feature subset. Finally, SVM was used for grading gliomas. The results demonstrated that integrating radiomics features and deep features for gliomas grading is feasible. Zhang et al. (96) combined the depth features extracted from the pre-trained CNN with texture features and morphological features, and evaluated the effects of these features by machine learning classifier. The experimental results suggested that the combination of features extracted by deep learning and radiomics is superior to a single modeling method. Li et al. (97) proposed a feature learning method based on generative adversarial network. AlexNet was used as feature extractor, while SVM was used for classification. The experimental results achieved high classification precision. Xia et al. (98) developed models based on deep learning and radiomics features respectively, and then applied an information-fusion method to fuse the prediction performance of the two models. The proposed fusion model improved the classification performance of non-invasive adenocarcinoma and invasive adenocarcinoma.

4. DISCUSSION

4.1. Few-Shot Learning

At present, AI has achieved high performance in many fields, which rely on a mass of labeled samples and iterations of trained models. In the medical field, AI performs well in some scenarios where large amounts of training data are available, such as skin diseases and diabetic retinopathy (99, 100), etc. However, for most scenarios, the data collection and labeling are laborious and time-consuming. Besides that, some privacy ethics and obstacles are also difficult to overcome. All of these are real challenges for the applications of AI in the medical field.

According to the retrieved literature, the application of AI in craniopharyngioma has been emerging in the last 5 years. Data sets reported in most of the literature were from a single institution. The lack of standard databases and the small sample size of data sets affect the application of AI in diagnosis of craniopharyngioma. When experiments are carried out on small data sets, overfitting is inevitable and the generalization performance is often queried, especially in high-risk tasks like tumor diagnosis. Therefore, few-shot learning aiming to learn quickly from a small data set, is an issue worthy of further research. Several measures that can be implemented to deal with few-shot learning are discussed below.

(1) Data augmentation can expand a data set with transformation rules and prevent the over-fitting of the model. As a straightforward and simple solution, it has been commonly used in the retrieved literature. Common transformation rules include shift, rotation, scale, crop, flip, and other operations on a single sample. Other algorithms are also available to operate on multiple samples, such as SMOTE, mixup, etc. These methods

with minor changes to the original images, can quickly and simply obtain a large amount of new data.

(2) Data synthesis can synthesize new data through neural networks, among which generated adversarial network (GAN) is the most representative one. The GAN framework includes generators and discriminators (101). The goal of the generator is to generate a large number of samples close to reality, while the discriminator should correctly distinguish between real samples and simulated samples. The game theory and confrontation training mode of GAN endow it with a strong ability in data augmentation.

(3) Feature enhancement enriches the diversity of samples by augmenting the sample feature space, and consequently expands the data sets. Typically, Schwartz et al. (102) developed a network comprised of encoders and decoders to generate new data. The encoder learned to extract the transferable deformations between pairs of samples of the same category in the data set, while the decoder learned how to apply these deformations to the samples in the new category to generate new data.

(4) Other more advanced strategies include meta-learning strategy, measurement learning strategy, parameter optimization strategy (103, 104). Meta-learning strategy is currently a novel research framework. In few-shot learning, meta-learning strategy learns meta-knowledge from prior tasks, and uses prior knowledge to guide the model to learn quickly. Through calculating the distance between the samples to be classified and the known ones, measurement learning strategy acquires the adjacent categories to determine the results of the samples to be classified. This algorithm does not need to fine-tune labeled images, but compares the image to be classified with the known ones to perform classification. Another problem of few-shot learning is that the generalization ability of the network deteriorates due to iterations of few parameters on small data sets, which results in the lack of credibility in the classification performance of the models. The parameter optimization strategy focuses on optimization of the basic learner through an optimizer, thus improving the credibility and generalization ability of the classifier.

(5) Transfer learning is a common technique used in deep learning frameworks. Considering that most of tasks are correlated, transfer learning can accelerate and optimize the learning efficiency of the model by transferring the pre-trained model parameters to the new model, rather than learning from scratch. For deep learning models, the transfer method applies the pre-training model to a new task by fine-tuning (105). For the transfer learning method, the source domain and the target domain do not need the same distribution of data, which overcomes the shortcomings of traditional machine learning, and has a great advantage in the case of few samples in the target domain and sufficient samples in related fields.

4.2. Classification of Imbalanced Data Sets

Most data sets in the medical field are unbalanced, that is, the sample size of one category is much smaller than that of another. The imbalanced data set may cause the neglection of the minority category samples leading to underfitting, or the overemphasis of the minority category samples leading to overfitting. In order to design the learning model with more reliable ability, it is necessary to address the problem of the imbalanced data set.

(1) Data pre-processing is an effective method to solve this problem. It can be performed by deleting the samples of the majority category or adding to the samples of the minority category to reduce the difference in the sample number. According to the difference in sampling methods, over-sampling, under-sampling, and a combination of the two methods are all feasible (106).

(2) In an imbalanced data set, the costs of misclassification on the majority and minority categories are different, and the misclassification of the minority category should cost higher. Based on this premise, cost sensitive methods are feasible methods to deal with an imbalanced data set, which assign different costs to misclassification of different categories by introducing cost matrix, and then construct classifiers with the goal of minimizing cost value (107).

(3) Additionally, the ensemble learning method is another measure to mitigate the influence of an imbalanced data set. Ensemble learning models combine several different weak learners together to form a strong learner. The generalization performance of the model is improved by taking advantage of the differences between each base learner. A typical example is Adaboost algorithm (108). In the training process, the algorithm will assign higher weight to the samples with a large prediction error, and the model will pay more attention to these samples in the next iteration.

4.3. Research on Semi-supervised Learning

In the medical field, manual labeled data are expensive and scarce, while a large number of unlabeled image data resources are left idle. The semi-supervised learning method based on a small number of labeled samples and a large number of unlabeled samples is more suitable in such real conditions. The recommended techniques for semi-supervised learning are as follows:

(1) Generative models as the early semi-supervised learning methods, establish the relationship between prediction models and unlabeled data based on clustering assumption and manifold assumption, and assume that all data are "generated" by the same potential model. Typical algorithms include Gaussian mixture model, Expectation-Maximum method, Naive Bayes method, and others (109–111).

(2) The self-training method is an incremental algorithm (112) that firstly uses a small number of labeled data to train an initial classification model, and then adopts this model to predict all unlabeled data. Only the samples with high confidence will be added to the training set for re-training, and the iterations are repeated until the termination condition is satisfied.

(3) The co-training method consists of several classification models. First, each base classifier is initialized with labeled data, and then the classifier selects the "most confident" unlabeled data, assigns the predicted category of samples and adds them to the labeled data set. The labeled data set is updated and provided to another classifier, and the iterations are repeated until each classifier does not change (113).

(4) The graph-based method maps the data set into a composition that presents the organizational relationship between the sample data. In the graph, the nodes of the graph represent the sample points, and the edges represent the similarity relationship between two sample points. And then the labels are spread from labeled data to unlabeled data based on the adjacency relationship on the graph (114).

(5) Semi-supervised SVM is an extension of SVM on semi-supervised learning (115). After adding unlabeled data into the feature space, semi-supervised SVM tries to find a partitioning hyperplane that still divides the labeled data and passes through the low-density region of the samples.

4.4. Multi-Omics Model Research

Traditional single omics has some limitations in interpreting disease due to its complexity. The development of multi-omics technology provides abundant materials for the study of complex diseases. Genomics, epigenomics, transcriptomics, proteomics, and metabolomics are all important components of systems biology. Multi-omics research can study diseases more comprehensively by integrating the data of different omics effectively. Adding some clinical parameters such as gender and age to the feature set is a preliminary attempt. In addition, Guo et al. (116) graded glioma by utilizing radiomics and clinical parameters, such as age and markers of inflammation in the blood. Chen et al. (117) combined histology images and genomics to predict survival outcomes, and the results performed higher than single omics experiments. In the future, it will be an important research direction that comprehensively analyzes complex diseases like cancers by combining multi-omics data.

5. CONCLUSION

With the successful applications of AI in many fields, research on the application of AI in diagnosis of craniopharyngioma has emerged in recent years. This study reviewed the existing applications of artificial intelligence in craniopharyngioma from the aspects of differential classifications, brain tissue invasiveness and gene mutation prediction, and postoperative prediction. Leveraging the relevant literature on other similar tumors, the artificial intelligence-based diagnostic routes were further proposed. Traditional machine learning methods are more explanatory and less computation is required. Intelligent diagnosis of craniopharyngioma based on traditional machine learning included steps of image preprocessing, image segmentation, feature extraction, feature selection, machine learning modeling. Deep learning model is an end-to-end learning framework, which heavily relies on a mass of data. Therefore, diagnosis of craniopharyngioma based on deep learning is usually included steps of data augmentation and design of model. The study also proposed the methods that could be adopted in each step. The applications of artificial intelligence technology in the diagnosis of craniopharyngioma are still in the preliminary period. The lack of standard data sets and small data sets may affect the development of artificial intelligence technology in this field. In view of the existing research, this study discussed the attentions required for future research. Few-shot learning is one of the first works to be addressed. Data augmentation, data synthesis, feature enhancement, some advanced learning strategies, and transfer learning are available measures for learning on a small data set. In addition, future research should also pay attention to the problem of imbalanced data sets. Over-sampling or undersampling technology, cost sensitive method, and ensemble learning methods are recommended solutions. Another research direction should point to the semi-supervised learning model which is a suitable choice for the medical field with scarce labeled data. Additionally, multi-omics fusion mode can better describe complex diseases like cancers.

AUTHOR CONTRIBUTIONS

CQ wrote the manuscript draft, conducted the review of literature, and summarized the findings of the review. XW, WH, and XM discussed the review and edited the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This work has been partially supported by the National Key Research programs of China (2016YFA0100900, 2016YFA0100902), the Chinese National Natural Science Foundation Projects #82090051 #81871442, the Youth Innovation Promotion Association CAS(#Y201930), the Fujian Province Natural Science Foundation (2017J01779), and in part by the Shandong Province Natural Science Foundation (ZR2020KF016). Additionally, this work is partially supported by Fujian Key Lab of Agriculture IOT Application, IOT Application Engineering Research Center of Fujian Province Colleges and Universities, Digital Fujian Research Institute for Industrial Energy Big Data.

ACKNOWLEDGMENTS

We would like to acknowledge Lin Zhu for assistance with literature collection and post-processing.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

ORIGINAL RESEARCH
published: 26 January 2022
doi: 10.3389/fonc.2021.739714

Identification and Characterization of TF-lncRNA Regulatory Networks Involved in the Tumorigenesis and Development of Adamantinomatous Craniopharyngioma

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Edited by:
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Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: 11 July 2021
Accepted: 28 December 2021
Published: 26 January 2022

Citation:
Xu D, Guo Y, Lei S, Guo A, Song D, Gao Q, Zhao S, Yin K, Wei Q, Zhang L, Wang X, Wang J, Zhang Q and Guo F (2022) Identification and Characterization of TF-lncRNA Regulatory Networks Involved in the Tumorigenesis and Development of Adamantinomatous Craniopharyngioma. Front. Oncol. 11:739714. doi: 10.3389/fonc.2021.739714

Craniopharyngiomas (CPs) are rare tumors arising from the sellar region. Although the best outcome for patients with one subtype, adamantinomatous craniopharyngioma (ACP), is obtained by gross total resection, little is known about the roles of long noncoding RNAs (lncRNAs) and transcription factors (TFs) in ACP tumorigenesis. In total, 12 human ACP and 5 control samples were subjected to transcriptome-level sequencing. We built an integrated algorithm for identifying lncRNAs and TFs regulating the CP-related pathway. Furthermore, ChIP-Seq datasets with binding domain information were used to further verify and identify TF-lncRNA correlations. RT–PCR and immunohistochemistry staining were performed to validate the potential targets. Five pathways associated with ACP were identified and defined by an extensive literature search. Based on the specific pathways and the whole gene expression profile, 266 ACP-related lncRNAs and 39 TFs were identified by our integrating algorithm. Comprehensive analysis of the ChIP-Seq datasets revealed that 29 TFs were targeted by 12000 lncRNAs in a wide range of tissues, including 161 ACP-related lncRNAs that were identified by the computational method. These 29 TFs and 161 lncRNAs, constituting 1004 TF-lncRNA pairs, were shown to potentially regulate different ACP-related pathways. A total of 232 TF-lncRNA networks were consequently established based on differential gene expression. Validation by RT–PCR and immunohistochemistry staining revealed positive expression of the ACP-related TFs E2F2 and KLF5 in ACP. Moreover, the expression of the lncRNA RP11-360P21.2 was shown to be upregulated in ACP tissues. In this study,

we introduced an integrated algorithm for identifying lncRNAs and TFs regulating the ACP-related pathway. This is the first comprehensive study to systematically investigate the potential TF and lncRNA regulatory network in ACP. The resulting data serve as a valuable resource for understanding the mechanisms underlying ACP-related lncRNAs and TFs.

Keywords: craniopharyngiomas, LncRNA, transcription factors, RNA-seq, integrated algorithm

INTRODUCTION

Craniopharyngiomas (CPs) are benign suprasellar tumors and account for 2-4% of all intracranial tumors (1, 2). Despite their histological classification as WHO I tumors, CPs remain challenging to treat *via* total resection and postoperative management due to their specialized location and biological behavior, leading to increased mortality and poor functional results, similar to those of patients with severe endocrine disorders.

There are two types of CPs, namely, adamantinomatous craniopharyngiomas (ACPs) and papillary craniopharyngiomas (PCPs). ACPs exhibit a bimodal incidence, peaking in both childhood and at 45-60 years (1–3). The important genomic characteristics of ACPs are somatic mutations of CTNNB1, which encodes β-catenin, as revealed by widespread whole-exon sequencing, while PCPs are driven by mutation of p. BRAF-V600E (4). CPs harboring histological features of both ACP and PCP are extremely rare (5). Recently, multiple studies have provided new insight into the tumorigenesis of ACP and possible therapeutic targets. Mutation in exon 3 of CTNNB1, leading to overactivation of the Wnt/β-catenin signaling pathway, is considered the main oncogenic driver of ACP tumorigenesis. Moreover, other pathways, such as ERBB2 and SHH signaling, have also been shown to be related to tumor growth and proliferation (6–8). Gaston et al. constructed an ACP embryonic and inducible model to further confirm that cells in the β-catenin-accumulating cluster promote tumor growth by regulating paracrine cells with a series of related proteins, including bone morphogenic proteins (BMPs) and fibroblast growth factors (FGFs) (9, 10). Transcriptome sequencing of murine ACP models and human tumor samples using laser capture microdissection has revealed overactivated MAPK/ERK pathways in tumor components, implying that MEK inhibitors could be developed as a potential treatment (11). Grob et al. reported high expression of IL-6 in ACPs, and current therapies include IL-6 inhibitors and have shown satisfactory results in patients with cystic ACP (12). The differential genetic backgrounds and epigenetic factors of ACP and PCP lead to differences in targeted therapies. Therefore, further studies at the transcription level are essential for elucidating the potential molecular mechanism of ACP.

Long noncoding RNAs (lncRNAs) are a type of RNA exceeding 200 nucleotides in length that are not translated into proteins. Mounting evidence suggests that lncRNAs impact numerous biological processes, such as cell proliferation, invasion, differentiation, apoptosis and metastasis (13). Similarly, transcription factors (TFs) are thought to modulate the expression of lncRNAs, thereby mediating the expression of downstream molecules and promoting cancer development (14). Recently, Li et al. explored the regulatory roles of lncRNAs in different immune-related pathways in tumors using the GSEA method (15). Because ACP, which is considered a benign tumor, carries a low rate of somatic mutations, mounting evidence suggests that the TGF-β, ERBB2 and SHH signaling pathways are involved in tumor formation in an autocrine or paracrine manner. However, only a few studies focusing on the noncoding transcriptome of ACP tumors have been reported (16, 17).

To systematically identify the regulatory networks that are potentially associated with ACP, we utilized an integrated algorithm to specifically explore the TFs and lncRNAs regulating ACP. This is the first study to investigate TFs and lncRNAs that affect the biological behavior of ACP. In addition, we further constructed TF-lncRNA pairs, which provided new insights into the mechanism underlying ACP, and we demonstrated that the expression levels of E2F2, KLF5 and RP11-360P21.2 were significantly upregulated in ACP tissues. In conclusion, this comprehensive study on TFs and lncRNAs was performed to investigate the pathogenesis and underlying mechanism of ACP development.

METHODS AND MATERIALS

Clinical Samples

In total, 12 ACP samples and 5 normal brain tissue samples were collected from patients at the First Affiliated Hospital of Zhengzhou University, PR China. All procedures were approved by the Ethics Committee for Human Experiments of Zhengzhou University. Informed consent was obtained, and the University Review Board approved this study, which was conducted in accordance with the Helsinki Declaration. In this study, 12 ACP samples and 5 normal tissues were subjected to high-throughput RNA sequencing (RNA-seq) analysis, and 14 samples were subjected to further immunohistochemical staining. Five normal brain tissues were obtained from patients undergoing brain tissue resection due to severe traumatic intracerebral injury, and the ages and sexes of the patients in the two groups did not significantly differ.

Whole RNA Sequencing

RNA isolation and quantification were conducted according to previous reports (18). Briefly, a total of 3 μg of RNA per sample was used as input material for the RNA sample preparations.

First, ribosomal RNA was removed using an Epicenter Ribo-ZeroTM rRNA Removal Kit (Epicenter, USA), and rRNA-free residues were removed by ethanol precipitation. Subsequently, sequencing libraries were generated using rRNA-depleted RNA with an NEBNext UltraTM Directional RNA Library Prep Kit for Illumina (NEB, USA) in accordance with the manufacturer's recommendations. The total RNA was sequenced on a HiSeq 4000 platform (Illumina, USA) at a read length of 2 × 150 bp. Then, the limma R package was used to conduct differential gene expression analysis. The adjusted P values were analyzed to correct for false positive results in the datasets. An adjusted $P < 0.05$ and a log (fold change) >1 or log (fold change)< −1 were defined as the thresholds for screening differential mRNA expression.

Identification of lncRNAs and TFs in ACP-Related Pathways

Because the Wnt/β-catenin, SHH, TGF-β, ERK1/ERK2, MAPK and ERBB2 pathways are involved in the development of CP (6–8, 10), we defined the above pathways as ACP-related pathways. To identify potential lncRNAs in ACP-related pathways, we used a calculation method involving the integration of lncRNAs and whole gene expression data. We used the method described by Li et al. with some modifications to identify TFs and lncRNAs modulating ACP (15). In brief, all genes were ranked based on their correlation with lncRNA/TF expression. To determine whether the gene sets were enriched in ACP-related pathways, the ranked genes and related pathways were calculated. The lncRNA relative enrichment score (lncRES) of each lncRNA pathway was computed, and pairs with significant values were identified. For each lncRNA or TF, we computed its activity in ACP pathways (lncRES/or TFRES) based on modified gene set enrichment analysis (GSEA).

Based on the correlation of the expression of coding genes with lncRNAs/TFs, we ranked these lncRNAs/TFs in order. Each lncRNA/or TF i and coding gene j were defined as follows: lncRNA(i) = (lncRNA1, lncRNA2, lncRNAi, …, lncRNAm) and gene(j) = (gene1, gene2, gene3, …genej,… genem).

$$\mathrm{p}corValue(ij) = pearson(ij)$$

For each lncRNA-gene pair, the rank score (RS) was calculated as follows:

$$RS(\mathrm{ij}) = \log_{10}(p(ij)) \star pcorValue(ij)$$

where p(ij) is the Pearson's (ij) P value.

Genes were ranked according to the RES values and subjected to enrichment analysis. To analyze the regulatory network(s) between lncRNAs and ACP-related pathways, we mapped the genes to the rank list according to the principles of GSEA. Then, the enrichment score (ES) based on the GSEA was calculated. ES_{ik} was defined as the ES between the lncRNA i and ACP-related pathway k. Finally, we integrated the P value and the ES into lncRES values as follows.

$$LncRES(i,k) = \begin{cases} 1 - 2p; if \quad ES(ik) > 0 \\ 2p - 1; if \quad ES(ik) < 0 \end{cases}$$

Consequently, the lncRESs ranged from -1 to 1, and an absolute lncRES >0.995 and a false discovery rate (FDR) <0.05 were considered to indicate significant lncRNA-pathway pairs. The TF pathways were constructed with the same method described above. To acquire a relatively reasonable number of TFs, TFs with a RES >0.990 were considered significant.

Identification of TF-lncRNA Regulatory Interactions

To identify potential TF-lncRNA relationships, we downloaded a large number of ChIP-seq peak datasets of TFs from the ChIPBase database (http://rna.sysu.edu.cn/chipbase/) (14, 19). In ChIPBase v2.0, 10200 peak datasets generated from ChIP-seq, ChIP-exo and MNChIP-seq datasets were curated from the NCBI GEO database, ENCODE project, modENCODE project and NIH Roadmap Epigenomics project. We extracted the peak data of TFs from all lncRNA datasets and validated the peak information regarding lncRNA/TF regulators associated with ACP-related pathways. Specific TF-lncRNA pairs were established when a peak signal was observed between TFs and lncRNAs. A total of 1004 potential TF-lncRNA interactions among 29 TFs and 161 lncRNAs were generated based on the conserved TF binding sites and ChIP-Seq dataset. Consequently, we selected the significant TFs and lncRNAs from the differentially expressed genes, and a total of 232 TF-lncRNA pairs were constructed. The "OmicCircos" package (R) was used to visualize the severity of the gradients of the normalized fold changes in the expression levels of the top lncRNAs and TFs across all studies on ACP (20).

Quantitative Reverse Transcription PCR Analysis (RT–PCR)

The real-time RT–PCR method used was described in our previous study (21). Briefly, oligonucleotide primers and TaqMan probes for KLF5 and E2F2 were designed based on sequences available in the GenBank database. The PCR primer sequences designed for amplification of the target molecules are listed in the **Supplemental Table**. The conditions for real-time RT–PCR were as follows: preheating at 94°C for 2 min, followed by 35 cycles of 94°C for 20 s, 60°C for 40 s, and 72°C for 30 s. The quantity of the β-actin gene product, a representative housekeeping gene, was equivalent in all the samples. Relative changes in gene expression were quantified using the likelihood method ($2^{-\Delta\Delta Ct}$ method). The normalized value for each target cDNA reflected the expression level of the corresponding gene.

Immunohistochemistry Staining

The immunohistochemistry method used in the present study has been previously described (18, 21). Briefly, sections were incubated overnight at 4°C with the following primary antibodies: rabbit anti-KLF5 (1:1000, Proteintech, China) and rabbit anti-E2F2 (1:1000, Proteintech, China). After washing, a goat anti-rabbit antibody (1:200, Servicebio, China) was added and incubated at room temperature.

Statistical Analysis

Genes were considered differentially expressed if they had a fold change ≥ 2 and a P value < 0.05. Parametric data are presented as the mean ± standard deviation. The mean integrated optical density (IOD) was used to compare the immunohistochemical staining differences between the two groups. Differences between two groups were evaluated with the two-tailed Student's t test. All analyses were performed with R software (Version 3.6.3). P<0.05 was considered statistically significant.

RESULTS

Patients Characteristics and Grouping

In total, 12 primary ACP samples and 5 control brain tissues were subjected to RNA-seq analysis. The ACP group included 5 males and 7 females, 4 of whom were children and 8 were adults (5,7,10,13 years old vs 22,33,51,54,56,56,57,58 years old). The control group included 3 males and 2 females, with an average age of 40 years. There was no significant difference between the ACP and control groups.

Identification of lncRNAs/TFs in ACP-Related Pathways

Previous studies have indicated that the Wnt/β-catenin, SHH, TGF-β, Erk1/Erk2 MAPK and ERBB2 pathways play significant roles in the occurrence and development of CP. In the present study, the identification of lncRNAs/TFs was based on ACP-related pathways. To identify potential lncRNAs and TFs correlated with ACP-related pathways, an integrated algorithm was used to construct TF- and lncRNA-pathway networks (**Figure 1A**). First, the whole gene expression profiles of mRNAs and lncRNAs were obtained. Then, we calculated and ranked the RESs of genes for each lncRNA. Third, the activity of each lncRNA in the ACP-related pathway was calculated based on GSEA, and the P values were converted into lncRES values (**Figure 1B**). A lncRES >0.995 and an FDR <0.05 were considered significant. According to the relevant lncRNA-pathway pairs, the lncRNA-related pathways were in the following descending order: TGF-β, SHH, Erk1/Erk2 MAPK, ERBB2 and Wnt/β-catenin (**Figure 1C**). In addition, the TF-related pathways were in the following descending order: TGF-β, Wnt/β-catenin, Erk1/Erk2 MAPK, Shh, and ERBB2 pathways (**Figure 1D**).

Based on the integrated algorithm, we identified TFs and lncRNAs of the ACP-related pathway, and the expression of TFs/lncRNAs was significantly upregulated in ACP tissues (**Figures 2A, B**). First, 39 TFs and 266 lncRNAs were identified, and 161 of these overlapped with ChIP-Seq datasets and ACP profiles (Supplemental material, See TFRES and LncRES). Then, significant genes among the 5 signaling pathways were identified. The top 15 TF-pathway and lncRNA-pathway pairs are listed in **Table 1**. Finally, 1004

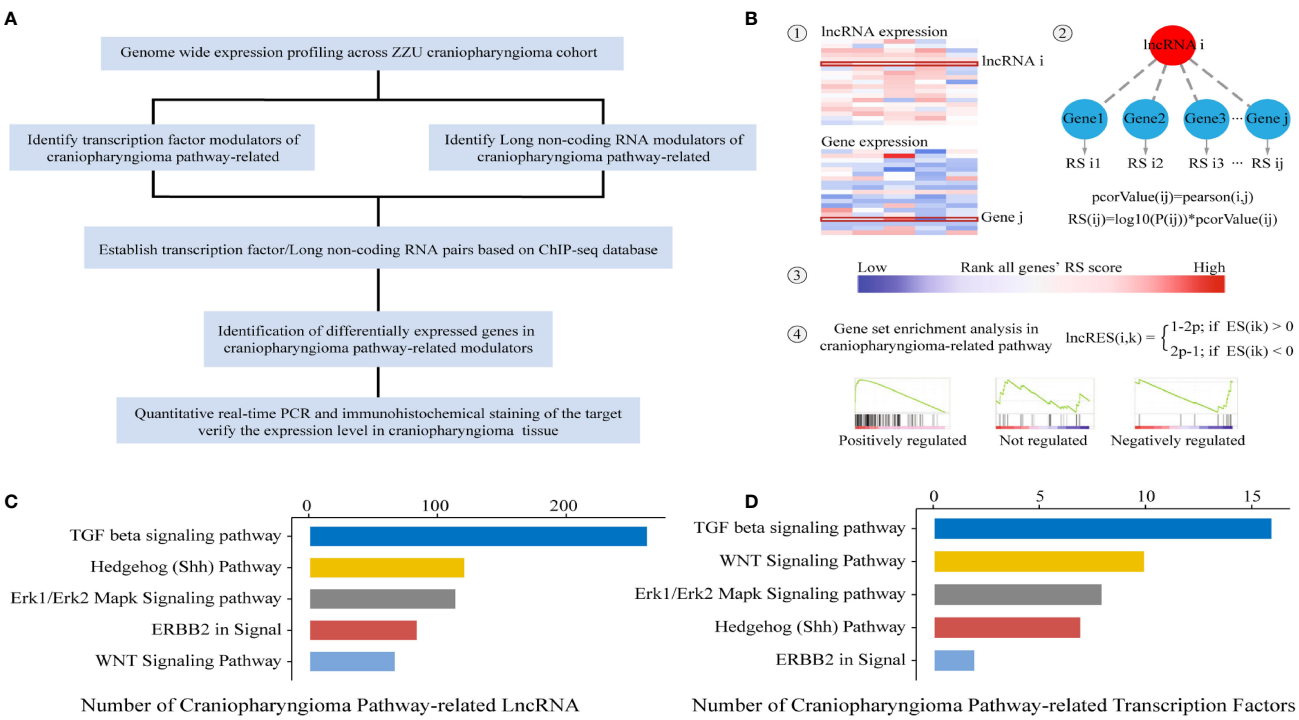

FIGURE 1 | Schematic of data generation and analysis **(A)**. Workflow patterns of lncRNA-pathway and TF-pathway network construction **(B)**. ACP pathway-related TFs and lncRNAs with significant RESs **(C, D)**.

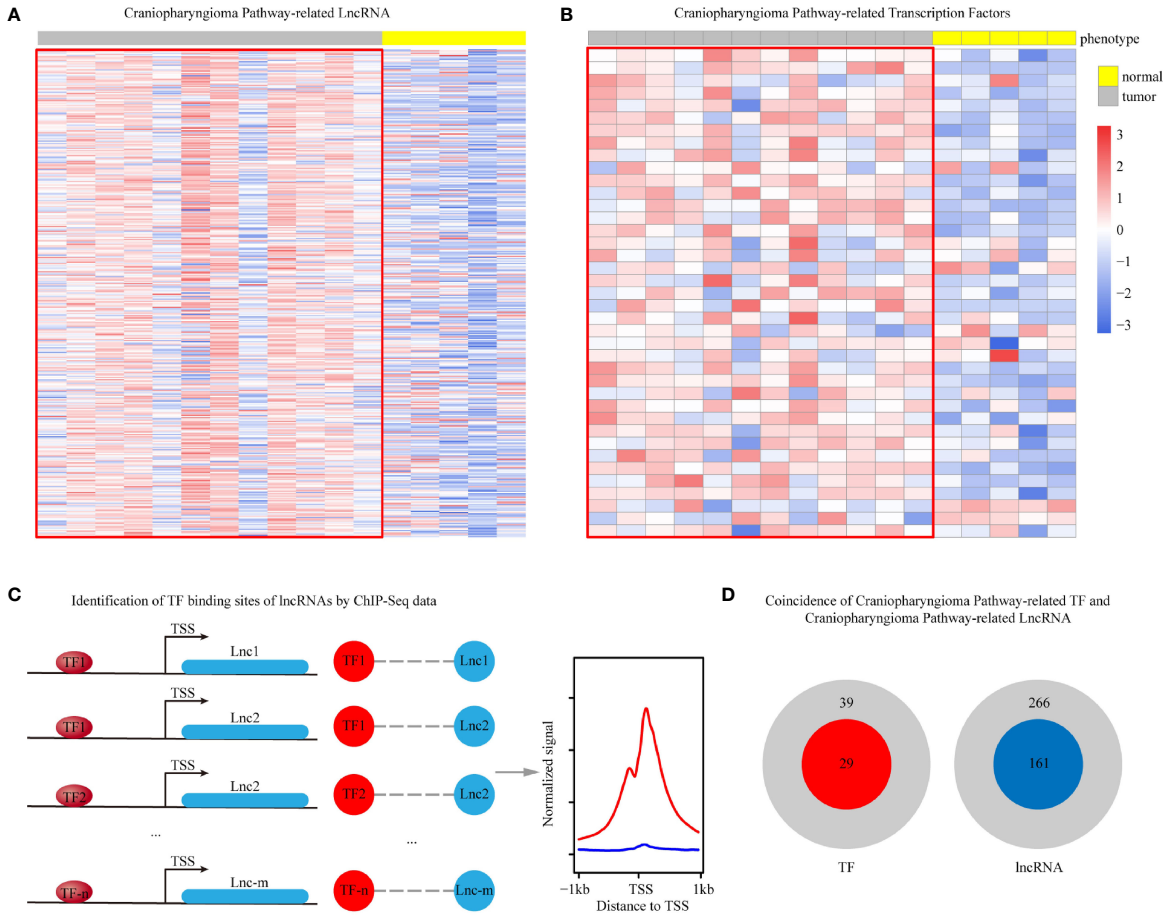

FIGURE 2 | Heatmap showing the differentially expressed ACP pathway-related lncRNAs **(A)** and TFs **(B)**. The schematic diagram shows the binding process of TFs and lncRNAs (**C**, red represents TFs and blue represents lncRNAs). In total, 266 lncRNAs and 39 TFs were identified. Of these, 161 lncRNAs and 29 TFs with binding domain information were ultimately verified through ChIP datasets (**D**, red represents TFs and blue represents lncRNAs).

TF-lncRNA interactions among 29 TF pathways and 161 lncRNA pathways were constructed using the ChIP-Seq datasets (Supplemental material, see TF-lncRNA) (**Figures 2C, D**). In addition, the positions of the top 30 TFs and the top 70 lncRNAs on the chromosome and their expression patterns are shown in **Figure 3**.

Gene Expression and Construction of TF-lncRNA Pairs

Differential gene expression analysis revealed a total of 293 RNAs that were differentially expressed. Of these RNAs, the expression levels of 59 RNAs were decreased, while the expression levels of the remaining RNAs were significantly increased (Supplemental material). The differential expression and Gene Ontology (GO) analysis were investigated between pediatric and adults (Supplemental material, see pediatric vs adults). The top 3 related biological processes (BP) were production of molecular mediator of immune response, humoral immune response and immune response-activating cell surface receptor signaling pathway (**Supplemental Figure**).

To explore the TF-lncRNA pairs potentially playing roles in the occurrence and development of ACP, we established a TF-lncRNA network based on the ChIP-seq database. In summary, a total of 232 TF-lncRNA pairs were finally established after matching significant RNAs in the profile (Supplemental material, see TF-lncRNA pairs). For example, the STAT4 TF targeted 10 lncRNAs, and KLF5 was correlated with 25 KLF5-lncRNA pairs. Of note, a pair could affect multiple pathways, and a pathway could also be affected by multiple pairs, indicating that the interaction was not one-to-one.

To further verify the reliability of the TF and lncRNA pathways we identified, we matched the data obtained from our center with those obtained from the GSE94349 dataset (**Figure 4A**) (22). Only the GEO cohort was used to quantify pathway activity. Although not completely significant in the ZZU dataset, which may have been due to data error and the small number of samples, all the data in the Gene Expression Omnibus (GEO) cohort were significantly correlated with the five pathways. The final TFs were exported based on the whole gene expression profile and significant differentially expressed genes (**Figure 4B**).

TABLE 1 | Top 15 TFs and lncRNAs of the ACP-related pathway.

	Gene	RES	FC	P	Pathway
TFs	KLF5	0.997719498	6.309701298	5.78715E-06	WNT signaling pathway
	RUNX1	0.99252802	4.835681265	5.29484E-07	TGF-β signaling pathway
	ISL1	0.997392438	4.460237557	4.11582E-05	Erk1/Erk2 Mapk signaling pathway
	GLI1	0.997775306	4.077460079	0.000782605	Hedgehog (Shh) pathway
	VDR	0.992217899	3.747748682	0.00040768	TGF-β signaling pathway
	DLX2	0.997329773	3.268986894	0.023339632	WNT signaling pathway
	AHR	0.994962217	3.267678968	1.86192E-06	TGF-β signaling pathway
	ESR1	-0.991404011	3.085325484	0.001337029	Erk1/Erk2 Mapk signaling pathway
	HAND2	-0.99488491	2.868591174	0.003974244	TGF-β signaling pathway
	HOXB6	-0.992471769	2.748524623	0.001430767	WNT signaling pathway
	MYC	0.994100295	2.410371459	0.000783643	Erk1/Erk2 Mapk signaling pathway
	ETS1	-0.99375	2.16777249	5.19216E-05	Hedgehog (Shh) pathway
	BHLHE40	0.997329773	2.012126829	0.001622299	TGF-β signaling pathway
	ARNT2	-1	-1.996219981	0.006013635	WNT signaling pathway
	E2F2	0.992277992	1.861109149	0.00236967	Hedgehog (Shh) pathway
LncRNAs	ZNF888	0.995979899	8.14568238	8.8122E-08	WNT signaling pathway
	RP11-356O9.2	-0.995584989	4.575635245	8.83516E-09	TGF-β signaling pathway
	RP11-65L19.4	-0.996779388	4.30060785	5.08636E-09	ERBB2 signaling pathway
	LINC00426	-0.996357013	4.274391208	5.22651E-09	Hedgehog (Shh) pathway
	RP11-373D23.3	0.997641509	4.248671731	6.69968E-07	TGF-β signaling pathway
	RP11-55L3.1	-0.997903564	3.846392873	3.67095E-07	WNT signaling pathway
	RP4-781K5.6	-0.997412678	3.673846446	1.65208E-06	ERBB2 signaling pathway
	CTB-1I21.1	-0.995085995	3.474261135	1.29922E-06	ERBB2 signaling pathway
	CTC-490G23.2	-0.997663551	3.437881709	1.65967E-06	WNT signaling pathway
	RP11-475I24.3	0.997894737	3.437581722	0.000789382	Hedgehog (Shh) pathway
	AC012363.13	-0.996621622	3.129375139	9.57969E-08	TGF-β signaling pathway
	RP11-452F19.3	0.997742664	3.117381748	5.30894E-06	Erk1/Erk2 Mapk signaling pathway
	CTC-529P8.1	-0.997572816	-3.107091438	0.000117385	ERBB2 signaling pathway
	CTC-529P8.1	-0.995203837	-3.107091438	0.000117385	Erk1/Erk2 Mapk signaling pathway
	RP11-360P21.2	-0.996632997	3.080472936	1.7834E-06	TGF-β signaling pathway

Confirmation of the Expression Changes in ACP-Related Genes

To confirm the real expression of TFs/lncRNAs in ACPs, highly significantly expressed TFs/lncRNAs of interest were detected, including 5 TFs (KLF5, E2F2, STAT4, ETS1 and ESR1) and 7 lncRNAs. qRT–PCR was performed, revealing that the expression levels of KLF5 and E2F2 were increased in the ACP group compared with the control group ($p<0.05$, **Figure 5A**). The expression levels of STAT4, ETS1, or ESR1 did not significantly differ between the tumor and control groups. Furthermore, the ACP samples were subjected to immunohistochemistry analysis, which demonstrated strong staining of KLF5 and E2F2 in the whole tumor tissues, especially in the cystic wall (**Figure 5B**). We further screened the top 5 lncRNA pairs with the top FC values among the TF-lncRNA pairs (**Table 2**). The expression of RP11-360P21.2 was significantly increased in ACP (**Figures 5C, D**). Thus, based on the PCR, immunohistochemistry, and integrated algorithm results, we established the KLF5-RP11-360P21.2 and E2F2-RP11-360P21.2 pairs in ACP.

DISCUSSION

In recent years, due to the development of high-throughput technology, research on CP has been transferred from the genome level to the transcriptome level, but research at the nontranscriptome RNA level is still lacking in this field. Mounting evidence suggests that lncRNAs are important modulators of tumorigenesis (23, 24), but no research on TF/lncRNA regulation in ACP has been performed. In this study, we established TF-lncRNA networks by using an integrated algorithm based on high-throughput sequencing data of ACP. We first summarized the ACP-related pathways and identified the pathway-related TFs and lncRNAs based on whole gene expression. Furthermore, we validated the TF-lncRNAs pairs based on exact binding domain information verified by ChIP-Seq data and found that RP11-360P21.2 was upregulated in ACP. Finally, the TF-lncRNA pairs were obtained by matching the significant differentially expressed genes. Increased KLF5 and E2F2 expression levels were observed in tumor tissues, especially in the palisading epithelium and the cyst wall. Therefore, the binding sites of KLF5-RP11-360P21.2 and E2F2-RP11-360P21.2 may become regulatory networks to mediate the expression of downstream genes playing roles in ACP development. To the best of our knowledge, this is the first study focusing on lncRNAs and TFs in ACP, and the results potentially provide pathological insight into the mechanism underlying the unique growth pattern of ACP.

The pathogenesis of CP is complex and involves not only driver mutations but also coding and noncoding RNAs. ACPs are a series of tumors that have low incidence rates, which limits our knowledge of these tumors at the transcriptome level, especially at the noncoding RNA level. Although our knowledge about ACP has increased, the specific regulatory

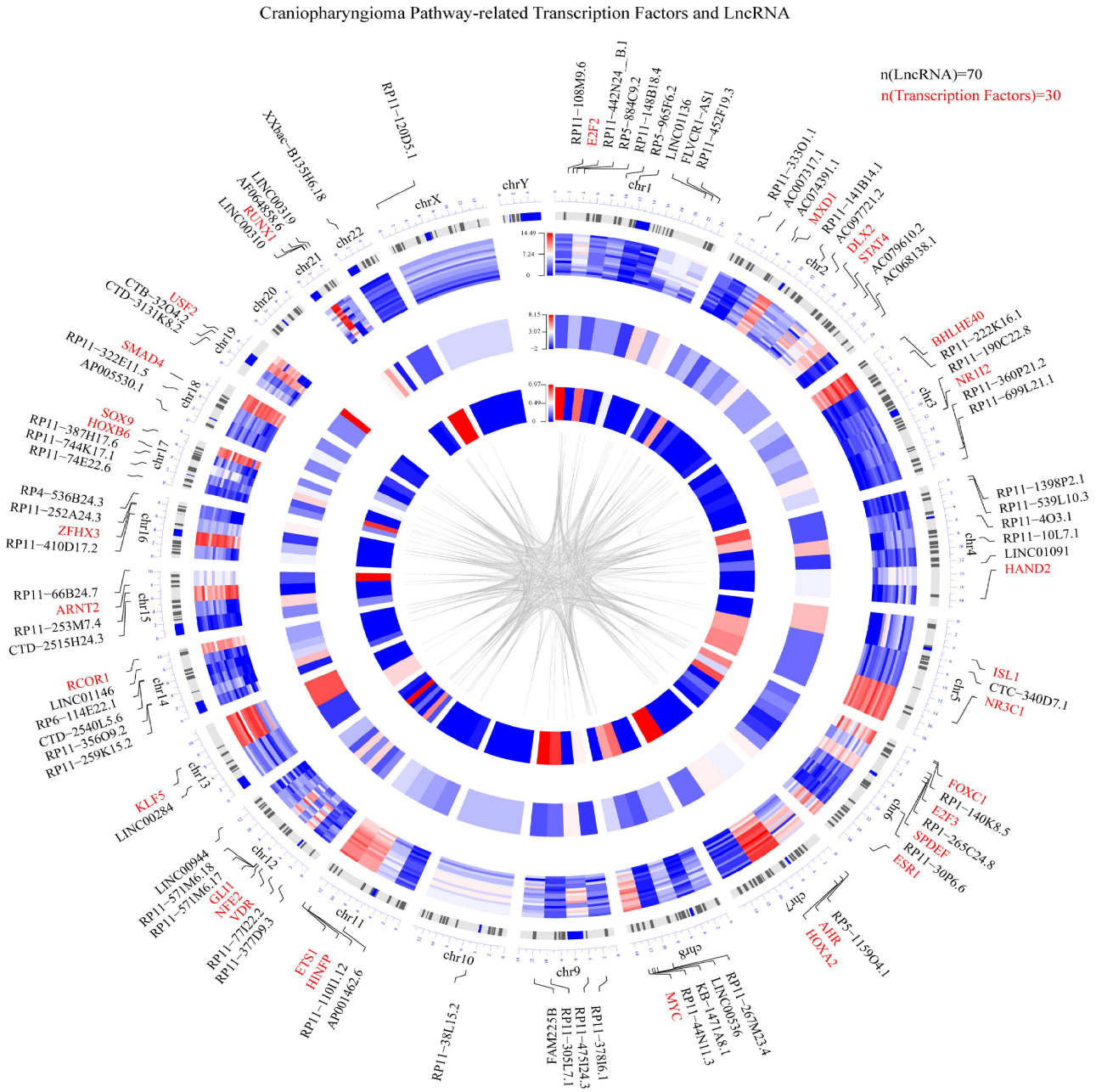

FIGURE 3 | Circular visualization of the chromosomal positions, differential expression levels and P values of the top 30 TFs and top 70 lncRNAs. The concentric circles representing different microarray datasets radiate outwards from the middle of the circle, with the P values shown in the innermost group, the fold changes shown in the middle group and the differential expression of each gene shown in the outermost group. The lines from each gene symbol represent its specific chromosomal location. A weighted heatmap image was constructed according to the log2-fold changes in gene expression regardless of significance. The gray lines in the center of the circle indicate a specific interaction between the TF and lncRNA based on the ChIP datasets (red represents upregulation, and blue represents downregulation).

network of the underlying mechanism is still unclear. Increasing evidence suggests that TFs and lncRNAs play key roles in the progression of multiple cancers (25, 26). Therefore, the identification of TFs and lncRNAs is critical for the construction of TF-lncRNA pairs. Although several studies on CPs utilized RNA-seq analysis, most of them were limited to the expression of a few genes and lack an overall profile. Previous studies have revealed that SOX2+ pituitary stem cells may cause tumorigenesis in a paracrine manner based on the ACP mouse model (9, 10, 23). Evidence indicates that the tumor as a whole is complex and that one or few molecules might not be sufficient to explore the nature of the tumor. Considering the low genomic

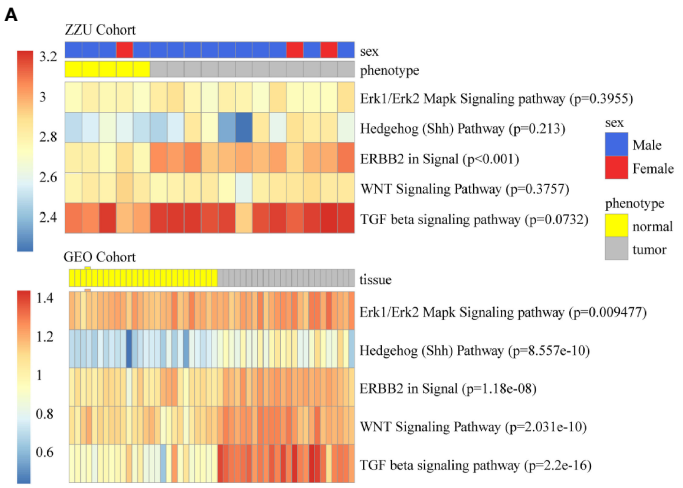

FIGURE 4 | Single-sample gene set enrichment analysis (ssGSEA) of the ZZU and GEO cohorts **(A)**. The volcano map shows the fold changes and P values corresponding to the differentially expressed TFs among different TF-pathway pairs. The volcano plot shows the differences in mean gene expression between the ACP and control samples on the x-axis and the corresponding –log10 transformed p values on the y-axis. The different colors represent the various related pathways, and the colors represent the pathway with the highest RESs (**B**, purple represents the TGF-β pathway, blue represents the Wnt pathway, green represents the Erk1/Erk2 pathway and brown represents the Shh pathway).

mutation rate in ACP, determining which factors among bulk gene sets that play essential roles in its biological process is difficult. Thus, we developed this method as a different validation process, and the results indicated its potential applications for prioritizing ACP-related pathway lncRNAs and TFs. The TF, lncRNA and TF-lncRNA networks have already provided novel biological insight into ACP. For instance, ESR1 yielded a high TFRES value in the ERK1/2 MAPK pathway (**Table 1**), indicating that it plays a preferential regulatory role in this pathway in ACP. ESR1, which is responsible for the maintenance of bone integrity, may play a key role in ACP osteogenesis. Generally, the increased activation of the ERK1/2 MAPK pathway is accompanied by the repression of ESR1 expression (27); however, the development of ACP involves the participation of both the ERK1/2 MAPK pathway and ESR1 (**Table 1**). This phenomenon may be attributed to the differential transcriptional backgrounds of different cell types. In addition, BMP2 was mainly expressed in the stellate reticulum and whorl-like array, while strong ERK1/2 staining was observed in the palisading epithelium. These observations suggest that these TFs and lncRNAs will be beneficial for prioritizing ACP-related lncRNAs and TFs, leading to the identification of several novel genes as potential targets in ACP. Notably, bulk RNA sequencing might allow us to ignore some specific cellular components, and more advanced sequencing such as single-cell sequencing should serve as a new tool to better understand the tissue components in craniopharyngioma in the future.

Noncoding RNAs are emerging as critical factors involved in posttranscriptional regulation, but only a few studies have focused on this field in ACP (16, 17). ACP exhibits a distinct pathological structure with differential expression levels. The activation of MAPK/ERK signals occurs mainly in the palisading epithelium and reactive glial tissues, whereas BMP signaling-activated cells lie within and adjacent to β-catenin cluster cells (10). Based on previous reports, we focused more on TFs related to the processes of epidermal development, keratinocyte differentiation and odontogenesis (28). In this study, two TFs, E2F2 and KLF5, were confirmed to be differentially expressed. KLF5 encodes a member of the Krüppel-like factor zinc finger protein family and is involved in a variety of physiological processes, including proliferation, differentiation and embryogenesis. Ng et al. reported that KLF5 promotes tumor epithelial development in patients with Barrett's esophagus (BE) and esophageal adenocarcinoma (29). Our study revealed that KLF5 may also play the same biological role in the development of ACP. KLF5 promotes the nuclear localization and transcriptional activity of β-catenin through a physical interaction (30), revealing its crucial role in the Wnt/β-catenin pathway. In addition, KLF5 binds to the RUNX2 promoter to mediate vascular smooth muscle cell calcification (31). E2F2 is a member of the E2F TF family and is mainly involved in regulating the cell cycle. Increased E2F2 expression is potentially predictive of a poor prognosis in hepatocellular carcinoma and of inflammatory cytokine upregulation (32, 33). In addition, several striking features were observed in the present study. Although the two TFs detected by RNA-seq are highly expressed in CPs, their expression levels differ depending on their pathological features. The expression of E2F2 and KLF5 was more prominent at the edge of the tumor cystic wall. Because the CP cyst is a unique feature, the cystic fluid may be a microenvironment that promotes CP growth. Previous studies have reported that inflammasomes are activated in ACP and that cholesterol crystals are potential activators, providing insight into the generation of cystic fluid and the growth pattern of ACPs (11, 23). The occurrence of CP may be related to several inflammatory factors, such as the IL-1- and IL-6-mediated

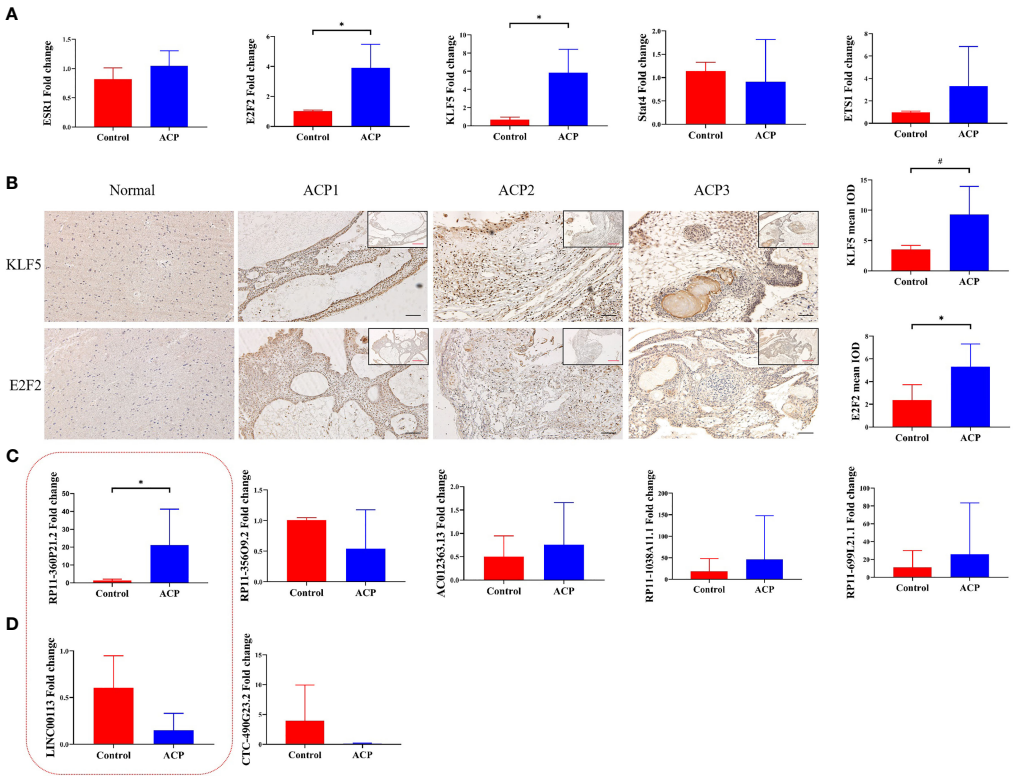

FIGURE 5 | RT–PCR analysis of ESR1, E2F2, KLF5, STAT4 and ETS1 at the transcript level. The expression of E2F2 and KLF5 was markedly increased in ACP tissues compared with normal brain tissues (**A**, n=5, * indicates $p < 0.05$). Representative immunochemistry images of KLF5 and E2F2 in ACP. Moderate staining of KLF5 and E2F2 was observed in normal tissues (**B**, n=14, * indicates $p < 0.05$, # indicates $p < 0.01$). RT–PCR analysis revealed the expression of related lncRNAs binding to KLF5- **(C)** and E2F2-lncRNA pairs **(D)**. The red box represents lncRNAs that bind to both KLF5 and E2F2. The results indicated increased expression of RP11-360P21.2 (n=8, * indicates $p < 0.05$, # indicates $p < 0.01$).

TABLE 2 | Top5 TF-lncRNA pairs.

TF-lncRNA pairs		
Pair	**logFC**	**adj. P. value**
KLF5-RP11-360P21.2	3.080472936	1.78E-06
KLF5-RP11-699L21.1	2.287542186	6.55318E-05
KLF5-LINC00113	2.055964371	0.000597201
KLF5-RP11-267M23.4	1.676662109	0.005338561
KLF5-RP11-110I1.12	1.122476444	0.016541618
E2F2-CTC-490G23.2	3.437881709	1.65967E-06
E2F2-RP11-360P21.2	3.080472936	1.7834E-06
E2F2-RP11-699L21.1	2.287542186	6.55318E-05
E2F2-LINC00113	2.055964371	0.000597201
E2F2-RP11-267M23.4	1.676662109	0.005338561
ETS1-RP11-360P21.2	3.080472936	1.7834E-06
ETS1-RP11-699L21.1	2.287542186	6.55318E-05
ETS1-RP11-267M23.4	1.676662109	0.005338561
ETS1-RP1-265C24.8	-1.279511209	0.021678162
ETS1-RP11-110I1.12	1.122476444	0.016541618
STAT4-RP11-699L21.1	2.287542186	6.55318E-05
STAT4-RP11-267M23.4	1.676662109	0.005338561
STAT4-RP1-265C24.8	-1.279511209	0.021678162
ESR1-ZNF888	8.14568238	8.8122E-08
ESR1-RP11-356O9.2	4.575635245	8.83516E-09
ESR1-LINC00426	4.274391208	5.22651E-09
ESR1-RP11-55L3.1	3.846392873	3.67095E-07
ESR1-CTB-1I21.1	3.474261135	1.29922E-06

senescence-associated secretory phenotype (SASP) phenotype (23). High E2F2 expression and E2F2-RP11-360P21.2 binding may mediate downstream inflammatory factors and thus mediate the growth of CP. Due to the limitation of TF-lncRNA domain information in the CHIP-seq database, the regulatory network in CPs can be further developed using the integrated algorithm with newly acquired information in the future.

This study had several limitations, including an in-depth study on differential expressions between adults and pediatric groups, a shortage of link between pathways and phenotypes such as epithelial-mesenchymal transition (34, 35). In addition, the expression of more TFs and lncRNAs needs to be validated in a larger independent cohort. Future studies need to further clarify the role of the KLF5-RP11-360P21.2 and E2F2-RP11-360P21.2 regulatory networks in the development of ACP.

CONCLUSION

In conclusion, this study identified the potential lncRNAs and TFs in ACP and established a TF-lncRNA regulatory network in ACP at the posttranscriptional level through RNA sequencing. The present study further clarified the regulation of ACPs at the posttranscriptional level. Targeting the KLF5-RP11-360P21.2 and E2F2-RP11-360P21.2 network may serve as a novel therapeutic strategy for ACP in the future. Together, these results suggest that the identification of critical lncRNAs/TFs involved in ACP can serve as a valuable resource in the development of precision medicine.

DATA AVAILABILITY STATEMENT

The datasets generated for this study can be found in The National Omics Data Encyclopedia (NODE). Datalink: https://www.biosino.org/node (Accession No: OER236537).

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Ethics Committee for Human Experiments of Zhengzhou University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

FG, DX, and YG designed the research. DX and YG performed the research and data analysis. DX, SL, QG, DS, SZ, KY, MZ, and LZ performed the basic studies. XW and JW collected the data. DX and YG wrote the paper. FG and QZ critically revised the paper. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by grants from the National Natural Science Foundation of China (U1204807), the Science and Technology Department of Henan Province (192102310113), the Medical Science and Technique Foundation of Henan Province (SB201901007) and the Educational Department of Henan Province (19B320017).

ACKNOWLEDGMENTS

We are grateful to the patients who gracefully donated their samples to this project. We would also like to thank Dr. Zhe Li at the Second Affiliated Hospital of Zhengzhou University for collecting data during the most difficult time in the pandemic. This unforgettable memory is a spiritual treasure worth cherishing forever, and I firmly believe that mankind will eventually win the war against COVID-19.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.739714/full#supplementary-material

Supplementary Figure | Enrichment analysis of differential genes between pediatric and adults. The size of the dot indicates the number of target genes, and the color represents the p value.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 31 January 2022
doi: 10.3389/fneur.2022.771236

Extended Neuroendoscopic Endonasal Approach for Resection of Craniopharyngioma in Children

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Objective: To explore the surgical approach and technique of neuroendoscopic endonasal resection of pediatric craniopharyngiomas and to further evaluate its safety and effect in children.

Methods: The clinical data of 8 children with craniopharyngiomas who were surgically treated by neuroendoscopy through an extended endonasal approach in our center from 2018 to 2021 were retrospectively analyzed. The related surgical approach and technique were evaluated to improve the surgical results and further reduce the surgical complications when removing craniopharyngioma in children.

Results: All 8 patients achieved a gross-total resection of the tumor under neuroendoscopy. Postoperatively, 2 cases of transient hyperthermia and 4 cases of transient hyper- and/or hyponatremia occurred within the first 2 weeks, all of which were quickly controlled. Seven patients had symptoms of diabetes insipidus to varying degrees after the operation, and 4 of them improved within 1–3 months after surgery, but 3 cases still needed oral pituitrin. There were no cases of coma or death, leakage of cerebrospinal fluid, or severe electrolyte imbalance after surgery. During the postoperative follow-up of 3 months to 2 years, no tumor recurrence was found. Among the 7 patients who suffered postoperative neuroendocrine deficiencies, 3 patients were found to be temporary during the follow-up, but 4 patients still required hormone replacement therapy. Particularly, postoperative visual deterioration and olfactory defect that occurred in patients were all improved during follow-up periods. In addition, 4 cases of obesity were noted at the last follow-up.

Conclusions: Extended neuroendoscopic endonasal resection of craniopharyngiomas may be used as a safe and effective approach for children. Due to the poor pneumatization of the sphenoid sinus and worse compliance of treatment in children, surgical techniques of exposing the sellar region, removing the tumor, and reconstructing the skull base, as well as postoperative management of patients was proposed. However, due to the limited surgical cases in the study, the surgical safety and effects of the extended neuroendoscopic endonasal approach for children with craniopharyngiomas need to be further studied in the future.

Keywords: craniopharyngioma, children, surgical technique, neuroendoscopy, endonasal approach

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Edited by:
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Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Neurology

Received: *06 September 2021*
Accepted: *03 January 2022*
Published: *31 January 2022*

Citation:
Wu D, Xu L, Xie S, Sun F, Xie M, Wang P and Xiao S (2022) Extended Neuroendoscopic Endonasal Approach for Resection of Craniopharyngioma in Children. Front. Neurol. 13:771236. doi: 10.3389/fneur.2022.771236

INTRODUCTION

Craniopharyngiomas are a rare and mostly benign epithelial tumor occurring in the sellar and suprasellar regions, which usually involve children and adolescents (1–3). Craniopharyngiomas are deeply located and tend to adhere to circumjacent neurovascular structures, such as optic nerves, hypothalamus, and pituitary stalk (1, 2). Thus, how to safely remove the tumor is a huge challenge for most neurosurgeons. Traditional microscopic surgery for craniopharyngiomas has been well-established and includes the pterion approach, subfrontal approach, presigmoid approach, and interhemispheric transcorpus callosal ventricular approach (4–8). However, these surgical approaches are almost from various supratentorial routes and each route has different degrees or angles of surgical blind areas, especially when operating on intrasellar or infradiaphragmatic tumors (6, 7, 9, 10).

Recently, with the gradual development and application of neuroendoscopy in adult craniopharyngiomas, neuroendoscopy has gradually been used for pediatrics with different tumor characteristics and different ages, which to some extent complement the defects of the simple transcranial microsurgery for craniopharyngiomas (10–12). Although some progress has been made, there are still insufficient reports in the literature for the treatment of children *via* extended neuroendoscopic endonasal resection of craniopharyngioma (6, 10, 13). Therefore, in this study, we would retrospectively summarize the surgical cases of pediatric craniopharyngioma in our center to further explore the surgical approach and technique of neuroendoscopic endonasal resection of craniopharyngioma in children and to evaluate its surgical safety and effect as well as the postoperative management of children with craniopharyngioma.

MATERIALS AND METHODS

Selection of Patients

The data of patients with craniopharyngioma who were surgically treated by extended neuroendoscopic endonasal approach at the Affiliated Hospital of Zunyi Medical University from 2018 to 2021 were retrospectively reviewed. Patients with age under 18 years were included in this study. A total of 8 children were diagnosed with craniopharyngiomas by imaging and pathology, with a median age of 9.5 years (range, 6–18 years). The main clinical manifestations include headache in 8 cases, vomiting in 3 cases, blurred vision or visual field defect in 6 cases, polydipsia and polyuria in 4 cases, and growth retardation in 5 cases.

Preoperative Examinations and Evaluations

Before the operation, all children underwent head CT examination, especially the three-dimensional CT under the thin-layer scan of the sphenoidal sella and the head CT angiogram (CTA) examination, and the head MRI with enhanced scan. The CT scans were used to understand the tumor calcification, the development or pneumatization of the sphenoid sinus, and whether there is an unruptured aneurysm in the intracranial arterial ring or whether the artery is pushed or wrapped by the tumor from CTA. The head MRI examination was to understand the tumor size, cyst changes, anatomical relationship with surrounding structures, or with or without hydrocephalus, etc. As regards the tumor location, one case was an intrasellar type, and 3 cases were intrasellar-suprasellar type, and 4 cases were suprasellar–ventricular type; among them, 4 cases were with poor pneumatization of sphenoid sinus, and 2 cases were with a turbinal sella (completely no pneumatization). All tumors were solid-cystic and calcified to varying degrees, and 5 cases suffered obstructive hydrocephalus. In this study, we calculated the longest diameter of the tumor to represent the tumor size, with the median diameter of 4 cm (range, 3–5 cm).

Preoperative laboratory examination revealed that 3 patients had reduced gonadal hormones, and 4 patients had low levels of growth hormone. Preoperative visual acuity and visual field examination revealed that 5 patients had decreased vision, and 7 patients had visual field defects. However, the neuropsychological and intelligent evaluations were only performed in one child, therefore, we did not show the data in the study.

The radiological criteria used for the selection of the trans-nasal approach: (1) The main body of the tumor grows along the midline; (2) The lateral growth of the tumor cannot exceed the radiating area by 30° endoscope (with a 30° angle of the intracranial tube opening of the optic canal on the coronal MRI); (3) In addition, a turbinal sella (completely no pneumatization), combined hydrocephalus, and tumor calcification are not contraindications for this trans-nasal approach.

Surgical Techniques and Procedures

After general anesthesia and endotracheal intubation, the patient was posed as supine, with the head slightly tilted backward and rotated laterally to face the right-side standing surgeon. The three-nail head holder (Mayfield, United States) could be used for children over 8 years of age to fix their heads. A 4-mm, 0° rigid neuroendoscope (Karlstorz, Germany) was used for lighting. Based on both sides of the nasal cavity, we used 1:100,000 adrenaline cotton pads to contract the blood vessels of the bilateral nasal mucosa. Routinely, we removed the right middle and upper turbinate and took the right nasal septum mucosal flap, except that one case was with nasal septum deviating to the right, so the left nasal septum mucosal flap was taken. An electric knife was used to incise the nasal septal mucosa near the right sphenoid crypt. Usually, the incision should avoid the nasal mucosa of the olfactory zone by extending the upper mucosal incision to the nasal vestibule, extending the lower mucosal incision from the posterior nostril and the bottom of the nose to the nasal vestibule, and merging with the upper incision. After peeling the pedicled nasal septum mucosa, it was pulled into the right lower nasal passage for subsequent use. The bony nasal septum was severed, and the left nasal septum mucosa was cut approximately 1.5 cm, and the anterior wall of the bilateral sphenoid sinuses was ground by a drill (Medtronic, United States) to expose the sphenoid sinus cavity. The anatomical landmarks of the sphenoid sinus in children are not always distinguishable, and thus the sellar base should be drilled strictly along the midline to both sides (**Figure 1**). After exposing the sellar dura mater, expanding the

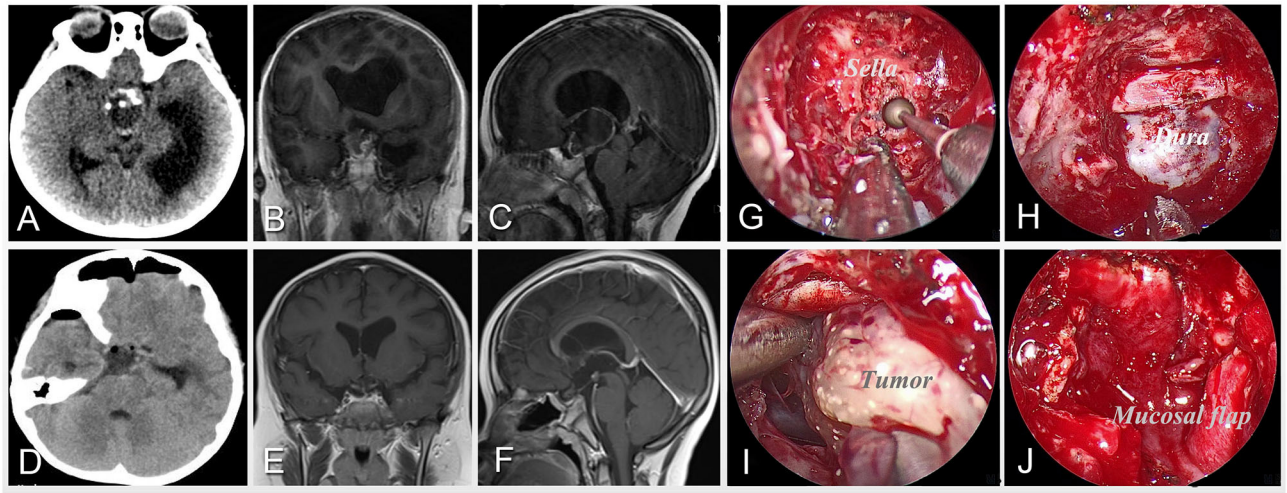

FIGURE 1 | Case 5 was an 8-year-old boy who presented with developmental retardation and headache before surgery. Preoperative imaging of CT **(A)** and MRI **(B,C)** shows a calcified and solid-cystic lesion located in the suprasellar region and invading the third ventricle with obstructive hydrocephalus. After careful preoperative evaluation, the extended neuroendoscopic endonasal approach was performed for the patient. The intraoperative pictures **(G–J)** illustrate the surgical procedures including drilling the sphenoid sella along the midline **(G)**, exposing the bone window for operation **(H)**, and separating the tumor along its boundary **(I)**, and reconstructing the skull base with pedicled mucosal flap after resection **(J)**. Postoperative imaging of CT **(D)** and MRI **(E,F)** demonstrates the gross-total resection of the tumor.

exposure to both sides as well as the upper and lower sides of the sellar floor. Those who are unfamiliar with anatomy in the early stage could use neuronavigation to help to remove the bony compartments of sphenoid sinus, sellar tuberosity, sphenoid plateau, etc. Doppler ultrasound (Hadeco smandop 45, Japan) probe was used to locate the bilateral internal carotid arteries. After that, we electrically coagulated and incised the anterior cavernous sinus, and the bleeding could be stopped with fluid gelatin (Surgiflo, United States). The dura mater of the anterior skull base was incised by 1.5 cm to form a dural window bound by the internal carotid artery above the clinoid process, with the posterior edge exposing one-third or all of the pituitary gland tissue and the anterior edge of exposing the tumor and the optic chiasm.

After fully revealing the operating field for the tumor and the adjacent structures based on preoperative imaging and neuronavigation, the subarachnoid space was opened above the pituitary gland and the superior pituitary artery was slightly pushed aside. First, we explored the pituitary stalk to observe the anatomical relationship between the tumor and the optic nerve, pituitary stalk, and third ventricle (**Figure 2**). Then, the capsule was incised to decompress the tumor first. If the tumor was calcified, we usually removed the calcified tissue in pieces, with attention to separating and protecting the perforating blood vessels that supply the optic nerve and hypothalamus from the superior pituitary artery. The tumor envelope was then lightly peeled from the optic chiasm and pituitary stalk under a directly close view of the neuroendoscope until it was separated to the gliosis zone at the bottom of the third ventricle. If the tumor is located in the third ventricle, it was necessary to enter the third ventricle through the suprachiasmatic and lamina terminalis. When operating, the papillary body and gray nodules, as well as the pituitary stalk should be protected as much as possible. In some cases of tumors that wrapped pituitary stalk, the pituitary stalk could be dissected early to reduce the difficulty of the operation if it could not be preserved safely.

After the removal of the tumor, the skull base was rebuilt and properly sealed with absorbable artificial meninges and porcine fibrin glue (Johnson & Johnson, United States), and then covered by the previously reserved pedicled nasal septum mucosal flap (**Figure 1**), with iodoform gauze packed and supported for 12–14 days. Patients without cerebrospinal fluid (CSF) leakage from the nasal cavity did not need lumbar cistern drainage after surgery. Endocrine tests were performed on the first, third, and seventh days after resection to inspect the changes of hypothalamic-pituitary hormones. On the tenth day after the operation, the pituitary MRI scan with the enhanced examination was performed to observe the growth of the mucosal flap as well as the tumor resection. Usually, the third-generation cephalosporin antibiotics were administered to patients for 10–12 days after the operation. The hypophysin was injected intramuscularly and then changed to oral dose to control symptoms of diabetes insipidus in patients after surgery; meanwhile, supplement the cortical and thyroidal hormones, and controlling the intake of salt within 3 days after the operation, with 24-h monitoring of intake-and-output fluid volume, were necessary to maintain the postoperative metabolic balance. Then, 3 days later, the physiological requirements sodium-containing fluids and hormones should be appropriately supplemented, with routinely monitoring of serum electrolyte and pituitary hormone levels as well as routinely preventing epilepsy.

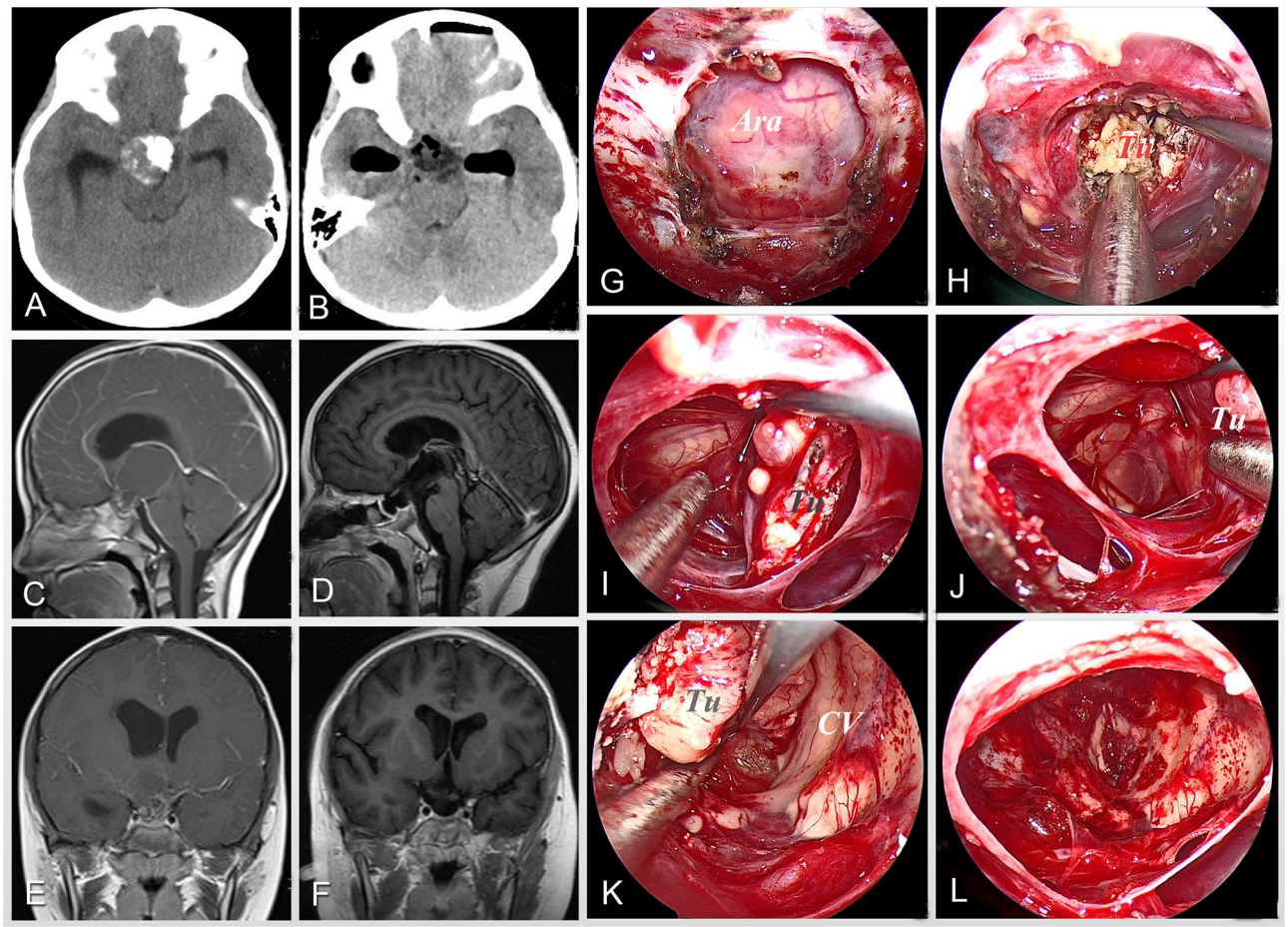

FIGURE 2 | Case 6 was an 8-year-old girl who complained of polyuria, impaired vision, headache, and vomiting on admission. Preoperative images of CT scan **(A)** and MRI scan **(C,E)** show a solid-cystic lesion with obvious calcification, involving the third ventricle with obstructive hydrocephalus. After careful preoperative evaluation, the extended neuroendoscopic endonasal approach was planned for the patient. The intraoperative pictures **(G–L)** illustrate the surgical procedures including exposing the bone window **(G)**, decompressing the tumor by sucking in the intratumor fluid oil **(H)**, separating the tumor along its boundary **(I,J)** and the third ventricular wall **(K)**, and gross-totally removing the tumor **(L)**. Postoperative imaging of CT **(B)** and MRI **(D,F)** demonstrates the complete resection of tumor and relief of hydrocephalus. Tu, tumor; Ara, arachnoid mater; CV, cerebral ventricular.

Follow-Up and Statistical Analysis

All patients were followed up closely after surgery. Follow-up data were collected by telephone and outpatient visits. During the follow-up period, patients were routinely performed with imaging and laboratory examinations and the results were reviewed.

Through a single-center retrospective summary of the clinical data of children with craniopharyngioma, the clinical factors affecting surgery, such as patient age, tumor location and size, and sphenoid sinus development, and the surgical results, including tumor resection extent, postoperative pituitary function, and surgical complications, were evaluated to further optimize the surgical methods and techniques of surgical resection of craniopharyngioma in children. In the study, all quantitative data (such as age and tumor size) were displayed with a median and range, and all qualitative data (such as gender, tumor resection, and incidence of complications) were exhibited with rates. All data analysis was calculated using SPSS 25.0 statistical software.

RESULTS

All 8 patients achieved a complete tumor resection under the direct sight of neuroendoscope, and postoperative imaging examinations further confirmed the complete resection. In particular, all 8 cases with tumors were histopathologically diagnosed as adamantinomatous. Postoperatively, 3 cases suffered transient hyperthermia, and 3 patients had early mild hypernatremia, and 2 patients had late hyponatremia after surgery, including one case experiencing both early hypernatremia and late hyponatremia, all of which were quickly corrected. Seven patients had symptoms of diabetes insipidus to varying degrees after surgery, including 4 patients with polyuria

before the operation; 2 of them improved within 1 week after surgery and returned to normal status at 2 weeks; 3 patients returned to normal within 1–3 months, and 3 patients still needed oral pituitrin therapy. The visual acuity was unchanged in 3 cases and improved in 2 cases, and there was no new case of visual impairment. One patient developed a slight fever after the resection, and the CSF test indicated the possibility of intracranial infection, which was well controlled after positive antibiotic treatment. There were no cases of coma or death, no CSF leakage, and no severe electrolyte disturbance after the operation. All patients did not enter the neuro-intensive care unit after surgery and received postoperative treatment in the general ward.

The 8 patients were followed up after surgery. The follow-up time ranged from 3 months to 2 years, with a median time of 12 months. During the follow-up, no tumor recurrence was found on MRI reexamination. The decreased visual acuity and visual field defects were recovered; 2 patients with hyposmia also improved 3 months after the operation. Six cases encountered postoperative pituitary–thyroid axis hypofunction, of which 3 cases improved within 1–3 months after surgery, and 3 patients still needed extra hormone replacement treatment; patients with pituitary–adrenal axis dysfunction was found in 7 cases, and among them, 3 cases improved to varying degrees, but 4 cases still needed extra oral drug therapy; in addition, 2 cases had hypogonadism and 4 cases had decreased growth hormone. At the last time of follow-up, 4 obese patients were noted (Details are shown in **Table 1**).

DISCUSSION

Craniopharyngiomas are benign intracranial tumors originating from embryonic malformations, which are categorized as adamantinomatous or papillary (1, 2). They are commonly found at the sellar or parasellar, suprasellar region, from sella turcica to the third ventricle along with the hypothalamic-pituitary axis (1, 7). The clinical manifestations include pituitary or hypothalamic deficiencies, visual impairment, and increased intracranial pressure, all of which can be attributed to the tumor mass impacting the optic nerve or chiasma, the hypothalamic-pituitary axis, and the CSF circulation (1, 14). Surgical resection of the craniopharyngiomas has been seen as the best choice to remove the mass and to improve symptoms. However, craniopharyngiomas occur in a deep location, adjacent to important endocrine structures of the hypothalamus and pituitary, and visual nerve tracts. How to safely and completely remove the tumor is still confusing for most neurosurgeons (1, 7, 14). Many scholars believe that subtotal resection and adjuvant radiotherapy could be an alternative for the treatment of craniopharyngiomas (8, 14, 15). Thus, the phenomenon of "malignant results of benign tumors" is also common in clinics (15–17).

Traditional microscopic surgery for children with craniopharyngiomas has been well developed and includes various supratentorial approaches (4, 5, 7, 10). However, these approaches are still limited due to their surgical blind areas when operating at sellar or parasellar regions, which may finally

TABLE 1 | The detailed data of all 8 cases with craniopharyngiomas, including demographic and tumor characteristics, surgical complications and follow-up outcomes.

Number	Age/y	Sex	Size/cm	calcification	Tumor location	Sphenoid sinus (pneumatization)	Hydrocephalus	Surgical Complications				Postoperative follow-up outcomes					
								Hyperthermia	Hyper- or hyponatremia	CSF leak	IC infection	Diabetes insipidus	Reduced cortin	Reduced thyroxin	Reduced gonadal hormone	Reduced somatotropin	Obesity	Follow-up/m
1	6	F	3.5	Y	Third ventricular	Well	Y	N	Y	N	N	N*	Y	N*	Y	Y	Y	24
2	18	M	4	Y	Suprasellar	Well	N	N	N	N	Y	N*	N*	N	Y	N	N	16
3	9	M	5	Y	Third ventricular	Poor	Y	Y	Y	N	N	Y	Y	Y	N	Y	Y	19
4	16	M	3.5	Y	Intrasellar	Well	N	N	N	N	N	N	N	N	N	N	N	26
5	8	M	4.2	Y	Third ventricular	Poor/turbinal	Y	Y	N	N	N	Y	Y	Y	N	Y	Y	6
6	8	F	4.5	Y	Third ventricular	Poor/turbinal	Y	Y	Y	N	N	Y	Y	Y	N	Y	Y	8
7	18	M	4	Y	Suprasellar	Well	N	N	Y	N	N	N*	N*	N*	N	N	N	5
8	10	M	3	Y	Suprasellar	Poor	N	N	N	N	N	N*	N*	N*	N	N	N	3

F, female; M, male; Y, yes; N, no; CSF, cerebrospinal fluid; IC, intracranial; y, year; m, month.

**Patients with transient symptoms that occurred in the early postoperative period and gradually improved during the follow up.*

TABLE 2 | The summary of surgical cases of pediatric patients with craniopharyngiomas removed by endoscopic trans-nasal approach from the literature since 2010*.

References	No. of case	GTR (%)	Surgical complication (n)	Tumor recurrence (%)	Mean follow-up period (months)
Madsen et al. (18)	28	85.7	Hypopituitarism (26), new obesity (6), mental disorder (5), CSF leak (2)	40.0	14
Kim et al. (19)	39	92.3	Decreased vision (1), hypopituitarism (18), aseptic or bacterial meningitis (5), delayed ventricular hemorrhage (1)	15.4	47
Giovannetti et al. (20)	12	100.0	Diabetes insipidus (2), CSF leak (2)	0.0	22
Schelini et al. (21)	20	70.0	CSF leak (1), hypopituitarism (11)	15.0	64
Javadpour et al. (22)	15	60.0	Decreased vision (1), hypopituitarism (10), diabetes insipidus (10), postoperative weight gain (1), mental disorder (1)	13.3	77
Patel et al. (23)	16	93.8	New obesity (6), CSF leak (3), meningitis (1), unilater injury of oculomotor nerve (2), hypopituitarism (7), diabetes insipidus (10)	6.3	56
Koumas et al. (24)	12	75.0	Vasospasm/stroke (3), hydrocephalus (1), new obesity (2), meningitis (1), diabetes insipidus (4), hypopituitarism (5)	0.0	39
Stapleton et al. (25)	20	100.0	CSF leak (4), meningitis (4), hydrocephalus (6), intracranial hemorrhage (1)	35.0	/
Alalade et al. (26)	11	45.0	Decreased vision (5), CSF (1), intracranial infection (1), new obesity (6), hypopituitarism (10), diabetes insipidus (7)	9.0	44
d'Avella et al. (27)	12	75.0	CSF leak (1), hypopituitarism (3), diabetes insipidus (4)	33.3	78
Yamada et al. (28)	65	91.0	New obesity (7), decreased vision (6), hypopituitarism (25)	13.8	94
Chivukula et al. (29)	16	56.2	CSF leak (3), hydrocephalus (2), diabetes insipidus (12), meningitis (2), stroke (3), diplopia (2)	43.8	29
Koutourousiou et al. (30)	17	100.0	CSF leak (2), hypopituitarism (13), diabetes insipidus (11), new obesity (3)	41.1	35
Locatelli et al. (31)	7	100.0	CSF leak (2), new obesity (1), hypopituitarism (3)	14.3	103

GTR, gross total resection, CSF, cerebrospinal fluid.

**Surgical cases in the literature with unavailable data and review articles were not presented in the table.*

compromise to incomplete resection, with residual tumor recurrence and postoperative severe complications caused by increased traction of brain tissue (10, 12). Recently, with great advance and increasing application of neuroendoscopy in adult craniopharyngiomas, neuroendoscopy has gradually been applied to the resection of craniopharyngiomas in children (**Table 2**) (5, 6, 9, 12). However, there are fewer surgical cases in pediatrics being reported, and the surgical techniques related to postoperative outcomes and complications as well as the postoperative management of pediatrics are not yet well defined (1, 7).

Surgical Exposure and Tumor Resection

The nasal cavity and paranasal sinuses of children have their special anatomic characteristics. The nostrils and nasal passages are relatively narrow, making it difficult to resect the tumor and make pedicled mucosal flaps (9). The procedure of putting in or out of surgical instruments may also increase the damage of the nasal mucosa. In addition, there are differences in sphenoid sinus development with different ages (9, 11, 12). The sphenoid cavity pneumatization first appears on the anterior inferior wall of the sphenoid bone. By the age of 6–7 years, all the anterior walls have been completely pneumatized, and then progresses to the bottom wall of the sphenoid bone, and reaches the sphenoid platform and finally the anterior wall of the sphenoid sella. After 10 years, pneumatization of the sphenoid sinus toward the back of the sphenoid body and clivus can be seen by imaging. Thus, the younger patients are always with poor pneumatization of the sphenoid sinus, which adds more difficulty in exposing the sella through nostrils with neuroendoscopy than adults (32–34). Usually, we chose to gradually expose the floor of the sella in strict accordance with its midline, and after the sellar dura is determined, it is gradually extended to both sides as well as top and bottom. The surgical areas, such as the dorsum sella, clival recess, sellar tuberosity, and sphenoid platform, can be exposed satisfactorily, without extra destruction of the bone at the base of the skull. For those who are unfamiliar with anatomy, the neuronavigation could help to determine the anatomical structures of the sella and its vicinity to avoid unnecessary injury.

After the operation channel is established, the operation space is sufficient, and it does not increase the difficulty of the operation and prolong the operation time compared with the adult operation. However, given the limitation of the narrow nostrils and nasal cavity in children, the patients' selection or surgical indication in children is still unknown and need to be further defined in the future, which may be partly based on the tumor characteristics and patients' age (6, 9). In our surgical group of 8 cases, craniopharyngiomas in children are mainly solid-cystic craniopharyngiomas with

obvious calcification, which may be attributed to the enamel type of craniopharyngiomas in this age group. For tumors with obvious cystic changes, decompressing the tumor first by sucking up the liquid oil could achieve more space for resection, with a gentle pull of the tumor capsule after determining the tumor boundary using the neuroendoscopy for close observation. When removing calcified lesions in a piecemeal way, the blood vessels, nerves, and brain tissues around the tumor should avoid being scratched.

According to the QST classification of craniopharyngioma (35–37), the Q-type craniopharyngiomas originate from below the diaphragma sellae, and it is easy to separate the tumor during surgery even if it grows large and invades the hypothalamus, because of the barrier formed by the diaphragm sellae, arachnoid and pial mater between the tumor and the hypothalamus. Some cases with sellar septal tumors should be removed together with the diaphragm to avoid tumor recurrence (35, 38). The S-type craniopharyngiomas on the diaphragm sellae grow from the pituitary stalk to the surrounding area usually with a relatively complete capsule. During the operation, the tumor must be separated from the pituitary stalk along the direction of the pituitary stem. If the pituitary stalk is in the center of the tumor, it must be incised to free the tumor and then try to protect the remaining pituitary stalk (36, 38, 39). For T-type craniopharyngiomas originating from the pars tuberalis, there is only a layer of pial mater between the tumor and the hypothalamus, which may adhere to the nerve tissue in the later stage and is not easy to be separated by surgery, and thus requires to find the boundary between the tumor and the normal tissue (35, 39). For the latter two types, partial tumors of the pituitary stalk cannot be preserved and could be dissected early to reduce the difficulty of tumor resection (35, 37). In addition, excising the tumor along the gliosis zone in the third ventricle may partly ensure that the neural tissue and the third ventricular walls are intact (5). When dealing with the adhesions between the tumor capsule and the optic chiasm, hypothalamus, and third ventricular wall under neuroendoscope, sharp separations should be performed, and a 1–2 mm suction device combined with a right-angle dissector or tumor forceps, with gently stretching or peeling off the tumor under direct views of neuroendoscope, always can remove tumor tissue completely (4, 5). For craniopharyngiomas that extend to the middle and lower clivus, removing the posterior clinoid process and part of the upper clival bone, and opening the membrane of the pituitary gland, and pulling down the tumors through the endoscope to obtain a certain space and angle, especially with the help of angle mirrors, the tumor and surrounding anatomical structures can be observed and then completely removed. Thus, pituitary dysfunction caused by pituitary displacement can be avoided in some cases (1, 4, 6).

Most of the tumors invading the third ventricle can block the CSF circulation and result in obstructive hydrocephalus (1, 3, 5). If patients with hydrocephalus before surgery are in need and have not yet prepared for tumor resection, the Ommaya capsules can be inserted into the ventricle to temporarily relieve high intracranial pressure and to buy time for surgery (3, 7, 14). External ventricular drainage is not recommended because it may increase the postoperative risk of intracranial infection. If the patient's hydrocephalus is not such an emergency, it is wise to directly remove the whole tumor to reconstruct the CSF circulation. During the operation, the Liliquest membrane of the interpeduncular pools can be opened to make the CSF circulation more secure (5). In our surgical group, 4 patients suffered preoperative hydrocephalus that was all caused by a tumor invading the third ventricle, and all of them were improved after the tumor resection. However, for patients with residual tumors that could not be easily removed and thus were left, close follow-up is needed, and generally, gamma knife treatment can be performed 3 months after the operation.

Skull Base Reconstruction and CSF Leakage

The younger the patients, the poorer postoperative compliance is confronted in children, and the prevention of postoperative CSF leakage is more difficult than that of adults (2, 5, 6, 12). Therefore, reliable skull base reconstruction is a vital part of neuroendoscopic endonasal resection of craniopharyngioma in children to avoid CSF nasal leaks and impossible postoperative intracranial infection (6, 12). During operating, we used the resorbable artificial dura mater to rebuild the first layer of skull base defect, which was inserted into the dura mater to seal the base of the skull, so that the high-flow CSF leak becomes the low-flow CSF leak. If the sphenoid sinus pneumatization is well, the bone flap *in situ* can be made to recover it. If there is no bone flap *in situ*, we attached and paved the pedicled mucosal flap of the nasal septum directly to the skull base defect as the second or third layer of reconstruction, and finally, the iodoform gauze was used to tightly pack and support the mucosal flap for 10–14 days (5, 11, 12). Fortunately, but confidently, there was no CSF effusion in all 8 children. Compared with the same period of adult cases of craniopharyngiomas in our center, the incidence of CSF leak after endoscopic endonasal surgery was relatively lower, which may be attributed to the smaller impact force of CSF flow on the faster-growing mucosal flaps in children to close early the meningeal defect.

Postoperative Complications and Management of Patients

The children in our surgical cohort had a mild response after resection, without convulsions, coma, and uncontrolled other complications. However, 3 patients presented with transient hyperthermia, and 4 patients had transient hypernatremia and/or hyponatremia after surgery. Particularly, 7 patients had diabetes insipidus after operations, but the degree of polyuria and the remission time was less than those of adults in the same period. The recovery time of children with diabetes insipidus in this group is shorter than that of adults in the same period, which may lie in that most of the tumors were intrasellar and hypothalamic origin in children in this group and thus the pituitary stalks were well protected, while adults in the same period had tumor originating from pituitary stalk. In addition, whether it takes a shorter time to establish

paracrine in children than in adults requires further study. Regarding whether patients with craniopharyngiomas should receive neurointensive care, many scholars believe that patients with craniopharyngiomas undergo drastic changes in their physiological and metabolic condition and should be closely monitored (1, 2, 7, 14). However, the children and adults of our center did not receive intensive care after the extended endoscopic endonasal resection. We had considered that all patients were conscious after the operations and could drink and eat on the second day after surgery, and recording the hourly urine volume as well as the physical intake and output volume are necessary and enough, and meanwhile, there may be CSF rhinorrhea or occult CSF rhinorrhea after the expansion of the endonasal approach (2, 3, 14), and the commonly planted bacteria in the intensive care unit may cause a potential risk of intracranial infection or cross-infection due to improper nasal cares. However, the on-duty doctors ought to be guided to deal with the changes in time.

In addition, children with craniopharyngioma need to pay special attention to water and electrolyte balance after surgery (2, 14). High sodium may occur 1–3 days after surgery, so sodium salt should be controlled. On the fourth day or later, low sodium may occur, and the physiological requirement of sodium can be supplemented and corrected in time based on monitoring blood electrolytes. It has been reported that a sharp change in blood sodium (>10 mmol/L) within 24 h is likely to induce epileptiform seizures, especially a sharp drop in blood sodium concentration (40, 41). The mechanism may be due to the rapid occurrence of hyponatremia after reaching a certain threshold, allowing water molecules to quickly enter the cells, and causing brain cell edema and convulsions or coma (14, 41). In this group of cases, 3 cases of transient hypernatremia in the early stage and 2 cases of transient hyponatremia in the late stage were quickly corrected, and no convulsions or coma occurred.

In addition, hypopituitary dysfunctions after endoscopic endonasal surgery were common and should be paid more attention to (2, 3, 14). These endocrine dysfunctions can reduce the quality of life of children and even shorten the life of patients (1, 2). Therefore, the evaluation and treatment of endocrine dysfunction in children before and after surgery, especially subsequently long-term hormone replacement after surgery, is an important principle of the treatment of patients with craniopharyngiomas (2). In our surgical cases in pediatrics, six cases encountered postoperative pituitary–thyroid axis hypofunction, and 7 patients suffered pituitary–adrenal axis dysfunction, and 2 cases had hypogonadism, and 4 cases had decreased growth hormone. At the last time of follow-up, half of the cases gradually improved within 1–3 months after operations, but 4 patients still needed long-term hormone replacement therapy. Furthermore, during the postoperative follow-up, the children's growth, development, and mentality should be regularly assessed, except for the review of tumor recurrence on imaging (2, 3, 14).

CONCLUSION

The advantages of the extended endonasal approach for resection of craniopharyngioma by neuroendoscopy are relatively safe and effective for children, with a few light postoperative adverse reactions that do not require intensive care treatment. Due to the poor pneumatization of the sphenoid sinus in pediatrics, surgical drilling of the sellar base along its midline to further expand the exposure of surgical fields was proposed. After the passage is completed, there is no significant difference in removing the tumor when compared with adult endoscopic surgery, and it does not increase the difficulty and time of the operation. After resection, watertight skull base reconstruction should be ensured to reduce postoperative CSF leaks and intracranial infection. Finally, careful postoperative managements of patients are the guarantee for patients who could safely live through the perioperative period. For children who survive for a long time after surgery, hormone level monitoring and hormone replacement therapy are important for postoperative long-term management. Due to the limited surgical cases in this study, the surgical techniques and outcomes of this approach in children need more clinical research in the future.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Affiliated Hospital of Zunyi Medical University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

DW, LX, and SXie: contributed equally to the article. DW, LX, SXie, and SXiao: wrote the manuscript. DW, LX, SXie, FS, MX, and PW: analyzed and interpreted the patients' data. All authors read and approved the final manuscript.

FUNDING

This work was supported by the Guizhou Province Science and Technology Plan (12520000429401122B) and Zunyi Municipal Science and Technology Plan (2019-102).

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Neurology

REVIEW
published: 09 February 2022
doi: 10.3389/fneur.2021.817257

Sleep Disorders in Patients With Craniopharyngioma: A Physiopathological and Practical Update

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OPEN ACCESS

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Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Neurology

Received: 17 November 2021
Accepted: 28 December 2021
Published: 09 February 2022

Citation:
Romigi A, Feola T, Cappellano S, De Angelis M, Pio G, Caccamo M, Testa F, Vitrani G, Centonze D, Colonnese C, Esposito V and Jaffrain-Rea M-L (2022) Sleep Disorders in Patients With Craniopharyngioma: A Physiopathological and Practical Update. Front. Neurol. 12:817257. doi: 10.3389/fneur.2021.817257

Sleep disorders (SDs) represent an important issue in patients with craniopharyngioma (CP). Nearly 70% of these patients complain of sleep-wake cycle alterations and/or excessive diurnal somnolence due to sleep-related breathing disorders, such as obstructive sleep apnea (OSA) and/or central hypersomnia, including secondary narcolepsy. SDs may severely reduce quality of life, increase disease-related cardiorespiratory and cardiovascular morbidity, and finally play a major role in increased long-term mortality reported on patients with CP. A major risk factor for SDs is represented by the hypothalamic syndrome, which may develop because of direct hypothalamic damage by the tumor itself and/or complications of the treatments, neurosurgery and/or radiotherapy, and typically includes permanent neuroendocrine dysfunctions, morbid obesity, and secondary metabolic disorders. Despite increasing attention to SDs in the general population, and in particular to OSA as a risk factor for cardio-metabolic diseases and excessive daytime somnolence, sleep evaluation is still not routinely proposed to patients with CP. Hence, SDs are often underdiagnosed and undertreated. The aim of this paper is to update current knowledge of the pathogenesis and prevalence of SDs in patients with CP and propose practical algorithms for their evaluation and management in clinical practice. Particular attention is paid to screening and diagnostic tools for appropriate characterization of SDs, identification of risk factors, and potential role of hypothalamic sparing surgery in the prevention of morbid obesity and SDs. Available tools in sleep medicine, including lifestyle interventions, drugs, and respiratory devices, are discussed, as well as the importance of optimal hormone replacement and metabolic interventions. Current limits in the diagnosis and treatment of SDs in patients with CP and possible future avenues for research agenda are also considered.

Keywords: craniopharyngioma, sleep disorder, hypothalamic syndrome, hypothalamic obesity, obstructive sleep apnea, hypersomnia, narcolepsy, circadian rythm disorders

INTRODUCTION

Craniopharyngiomas (CPs) are rare benign parasellar tumors derived from Rathke's pouch rests, and are classified into two subtypes (1). Most are adamantinomatous, typically presenting as mixed solid/cystic tumors with frequent calcifications, driven by somatic beta-catenin mutations, whereas papillary CPs are suprasellar, mostly solid, tumors with frequent BRAF mutations (2). CPs have a bimodal age distribution, with peaks of incidence occurring in pediatric (5–14 years, adamantinomatous) and adult patients (50–74 years, both) (1, 2). Despite benign histology and high overall survival (>90% in childhood-onset CP), the standardized mortality rate in patients with CP has been variably estimated from 2.88 to 9.28, with a 3- to 19-fold increase in cardiovascular mortality compared to the general population (3). Prognosis may vary according to tumor characteristics and treatment, secondary co-morbidities, and childhood vs. adult onset of the disease (1). Neuroendocrine dysfunctions include partial or complete hypopituitarism, hyperprolactinemia, and diabetes insipidus (DI). The most dramatic complication is the development of a hypothalamic syndrome (HS), which is typically associated with neuroendocrine disorders and includes neurocognitive changes (4) morbid hypothalamic obesity (HO) and related systemic complications (5), a variety of sleep disorders (SDs) including sleep-related breathing disorders (SBDs), central hypersomnia and abnormal wake-sleep circadian rhythms (6, 7), and less commonly abnormalities of thirst and central temperature or cardiovascular regulation. Hypothalamic damage may severely impair the quality of life (QoL) of patients and has an impact on long-term mortality (8). The extension and localization of hypothalamic injury due to the tumor itself, neurosurgery, and, in some cases, radiotherapy, contribute to the timing and severity of HS (5, 9). The optimal treatment for CP and related complications remains difficult and relies on a multidisciplinary approach, with increasing attention being paid in the last decades to the prevention of hypothalamic damage during surgery (2, 10).

Overall, SDs have received more attention in pediatric than in adult patients with CP, who include long-term survivors of childhood-onset CP and patients with an adult-onset disease. In pediatric cohorts, SDs have been heterogeneously reported as daytime sleepiness/hypersomnia, sleep disturbances such as difficulty to fall asleep or waking up during the night, and variably evaluated by self-assessment—specific questionnaires (11), items as a part of QoL assessment (12)—and more recently by means of sleep medicine tools aiming to better define entities such as SBDs, like obstructive sleep apnea (OSA) (7) or secondary narcolepsy (13). Within the methodological limits and heterogeneity of reported studies, the prevalence of SDs and/or excessive daytime sleepiness (EDS) approaches 70–80% (11, 13), with an adult prevalence of OSA around 40% (6). A common observation is the higher prevalence of SDs in the presence of hypothalamic involvement, with a bi-directional interplay between obesity and SDs. Indeed, SDs recognize a multifactorial pathogenesis: (1) a strict relationship with HO; (2) damage to the hypothalamic nuclei regulating sleep, wakefulness and circadian rhythm; (3) dysfunction of the pharyngeal/respiratory muscles; (4) suboptimal endocrine treatment; (5) fatigue, and psychosocial disorders (14). On the other hand, SDs contribute to and aggravate metabolic and cardiovascular co-morbidities. In fact, SDs increase the risk of insulin-resistance, obesity, and diabetes mellitus (DM) (15), and intermittent hypoxemia in OSA is an independent risk factor for cardiovascular and cardiorespiratory mortality (16). SDs may also represent a risk factor for neurocognitive decline (17) and cancer (18).

Nonetheless, SDs remain largely underdiagnosed in clinical practice, which may be explained by the complex clinical management of patients with CP and insufficient awareness or access to centers for sleep medicine. However, no guidelines are available for the diagnosis and management of SDs in such patients. Because increasing attention is currently being given to sleep health in the general population because of relevant health and socioeconomic consequences (e.g., reduced performance at work, driving safety, and social relationship), we wished to review the current knowledge of SDs in patients with CP and propose, based on our multidisciplinary experience, practical algorithms for the screening, diagnosis, and management of such conditions. Current limits and future therapeutic options will also be discussed.

CLASSIFICATION AND PATHOGENESIS OF SLEEP DISORDERS IN PATIENTS WITH CP

Sleep disorders (SDs) are classified according to the third edition of the International Classification of Sleep Disorders (ICSD-3) of the American Academy of Sleep Medicine (19), which identifies seven major categories of disorders: insomnia disorders, SBDs, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders (CRSWDs), sleep-related movement disorders, parasomnias, and other SDs. The most frequently reported SDs in CP are EDS (11, 20), central hypersomnia and secondary narcolepsy (13, 14, 21–27), SBDs (7, 24), and CRSWD (28–30), which require appropriate characterization and understanding of their underlying causes. Since clinical pictures may be complex and different elements may co-exist in the same patient, this may be achieved through a specific expertise in sleep diseases. Although the real prevalence of SDs before and after CP surgery/radiotherapy should be clarified, Mandrell et al. (13) showed that 45% of a large sample of pediatric patients with CP were affected by hypersomnia due to a medical disorder and 35% by narcolepsy, and that the main predictor of sleepiness was obesity. In addition, 80% of this cohort complained of EDS at diagnosis or after neurosurgery. This is in keeping with previous studies reporting that children and adolescents with CP complain of somnolence, fatigue, and sleep–wake disruption, which persist in 65–80% of the cases after treatment (20, 31). Similar data were reported in unselected adults with CP, with a prevalence of SDs around 70% (10). Of note, EDS may reduce work/education performance in 43% of patients with CP (6).

From a physiopathological point of view, sleep can be altered because of tumor growth toward structures involved in the control of sleep and wake, direct or indirect/vascular treatment-related injury to the same structures, or as a consequence of

HO. Therefore, hypothalamic dysfunction plays an essential role in the development of SDs. Damage to the suprachiasmatic nucleus (SCN), the central biological "master clock," leads to abnormal circadian rhythms and sleep-wake cycles. The SCN is on the neural way of control of the nocturnal pineal secretion of melatonin (32). It is composed of 20.000 neurons and glia that change their rate of firing in response to variation in light (33) and modulates several processes, such as sleep and food intake. Internal rhythm is strictly linked to external light cycle, and CRSWD develop when misalignment between light cycle and internal rhythm occurs. Circulating melatonin is mostly of central origin, and abnormally low nocturnal melatonin levels have been reported in patients with childhood-onset CP in association with daytime somnolence (34) and disrupted circadian rhythm (29). Similar findings were reported in a population of predominant adult-onset CP in association with reduced sleep time and efficiency, and a tendency for increased diurnal sleepiness and impaired physical health (30). Of note, chronobiotic effects of melatonin go far above sleep induction and include several systemic effects, leading to endocrine/metabolic dysfunctions in the presence of melatonin deficiency (32). Most of the master clock genes involved in circadian rhythmicity and circadian rhythm integrity are also tightly linked to metabolism and weight control (35, 36). Damage to the lateral hypothalamus, ventrolateral preoptic area, and median preoptic nucleus may impair the secretion of hypocretins, also called orexins, which are deficient in narcolepsy type 1 (37). Orexin/hypocretin-secreting neurons have broad projections to the brain and play an essential role in the promotion of wakefulness; their loss induce secondary REM sleep dysregulation, with excessive diurnal somnolence and sleep attacks by abrupt transitions from NREM to REM sleep leading to narcolepsy (38). Additional manifestations of narcolepsy (i.e., cataplexy, hypnagogic hallucinations, and sleep paralysis), an expression of fast intrusion of REM sleep or REM atonia, are less frequent in patients affected by secondary narcolepsy due to suprasellar tumors (39). Almost 38%, 15%, and 7% of patients with CP may develop cataplexy, sleep paralysis, and hallucinations, respectively (39).

Sleep-Related Breathing Disorders

Sleep-related breathing disorders (SBDs) are the most common SDs among children and adolescents (40, 41), with 1–4% of unselected children suffering from OSA, and rising up to 13–60% in obese children (42). SBDs are also highly prevalent in adults. OSA can be recognized by polysomnography (PSG) or home sleep apnea test (HSAT), based on the Apnea/Hypopnea Index (AHI, expressed in events/h). According to the Wisconsin Sleep Cohort, ∼13% of men and 6% of women have moderate-to-severe sleep apnea (AHI>15/h), and 14% of men and 5% of women have AHI $\geq$ 5/h plus symptoms of daytime sleepiness, both increasing with age and body mass index (BMI) (43). As a consequence, these estimates have grown substantially over the last two decades, largely because of the rising obesity epidemic (43). Adult and pediatric patients show different presentation, diagnostic criteria, course, and complications. According to the ICDS-3 (19), pediatric OSA is characterized by intermittent complete or partial obstruction (obstructive apnea or hypopnea); prolonged partial upper airway obstruction; or both prolonged and intermittent obstructions that disrupt normal ventilation during sleep, normal sleep patterns, or both (at least one obstructive, mixed apnea, or hypopnea per hour of sleep). The presence of SBD symptoms in combination with an AHI of $\geq$ 1/h has been applied to define pediatric OSA in most published studies (44). In adults, the definition is based on AHI $\geq$ 5/h, and OSA is characterized by predominant obstructive respiratory events (obstructive and mixed apneas, hypopneas, or respiratory effort related arousals). Of note, no specific criteria are considered for the definition of OSA in the "transitional" age from childhood to adulthood, which represents a significant proportion of adolescent/young adult patients with CP. The clinical presentation of OSA may differ between adult and pediatric patients. In adults, snoring and breathing irregularity in sleep may easily suggest the presence of OSA, whereas in children EDS is less perceived and may manifest as irritability, impulsivity, and distractibility (45). EDS manifests only in minority of children with OSA (46, 47). OSA is also more common in children with neurological impairment due to hypotonia of pharyngeal muscle or inability to change position during sleep (48).

SDs, in particular SBDs, may also be linked to HO, which in turn could be worsened by disrupted sleep patterns. Damage to the ventromedial hypothalamus and arcuate nucleus, which regulate hunger, satiety, and energy balance, is considered as the main determinant of HO (5). Increased energy intake and hyperphagia are not sufficient to explain HO, which is also due to imbalance between increased parasympathetic activity promoting hyperinsulinemia, reduced sympathetic activity leading to a reduced energy expenditure, and reduced daily activities because of somnolence, neurological sequelae such as visual loss, and psychological distress (5). Somnolence itself contributes to lower energy expenditure and increases appetite, leading to weight increase (49). Rapid and severe weight gain, which is typically maximal during the first 12 months following surgery, aggravates psychological distress, inactivity, and deleterious food intake, sustaining a dramatic vicious cycle in patients with CP, although BMI tends to stabilize later on. OSA has been reported in 5–46% of patients with CP (6, 7, 11, 13, 14, 23, 29, 50), depending on demographic characteristics (**Table 1**). Obesity is a well-known risk factor for OSA in the general population, and no significant difference was found in the prevalence of OSA between adults with CP (46%) and matched overweight and obese controls (61%) (6). However, BMI did not correlate with either the AHI or Epworth Sleepiness Scale (ESS), and diurnal somnolence was higher in adult patients with CP than in obese controls (71.5 vs. 17%), confirming that OSA is only one of several causes of somnolence in these patients, and that obesity alone does not explain the prevalence of OSA (6). Compared with adolescent obese controls, obese adolescents with CP fall asleep quicker (lower sleep onset latency), tend to sleep longer (trend toward higher total sleep time), and show more severe oxygen desaturation and present more severe AHI and central apnea index (7). Since unspecified diagnostic criteria

TABLE 1 | Sleep-related breathing disorders in patients with craniopharyngioma.

References	Patients (*n*)	Study design	Prevalence	Age	Diagnostic criteria	Diagnostic tool
Snow et al. (23)	5	C P	2/5 (40%)	11–19 yrs	Not reported	PSG
Lipton et al. (29)	3	C selected hypersomnolent patients	3/3 (100%)	15–22 yrs	Not reported	PSG
O'Gorman et al. (7)	15	CS C (obese CP vs. obese controls)	7/13 normal-mild (53.8%) 2/13 moderate (15.3%) 4/13 severe (30.6%)	10–21 yrs	Mild OSA AHI 1.5–5/h Moderate OSA AHI 5–10/h Severe OSA AHI >10/h Abnormal CAI >1/h	PSG
Crowley et al. (6)	28	C P (obese CP vs. obese controls)	11/28 (39.2%)	16–67 yrs	AHI ≥ 5/h	PSG
Manley et al. (11)	28	R U	3/7 (42%) (2/3 OSA and CSA)	Pediatric and Adult	Not reported	PSG
Mandrell et al. (13)	110	CS CO U	5/98 (5.1%)	Pediatric and Adult	AHI ≥ 2/h for pediatric patients AHI ≥ 5/h for adult patients	PSG
Niel et al. (50)	50	U P	2/10 (20%)	3–20 yrs	AHI ≥ 5/h	PSG

CS, cross sectional; C, controlled; U, uncontrolled; CO, consecutive; P, prospective; R, retrospective; OSA, obstructive sleep apnea; CSA, central sleep apnea; AHI, apnea hypopnea index (events/h); CAI, central apnea index.

or adult criteria were applied in many pediatric patients with CP, the pediatric prevalence of OSA may be underestimated (11, 23, 29, 50).

Central Hypersomnias

The second main group of SDs in patients with CP is represented by central hypersomnias, which can be recognized on PSG. Central hypersomnias are characterized by severe EDS, despite normal quality and timing of nocturnal sleep. ICSD-3 distinguishes three main subtypes: narcolepsy type 1, narcolepsy type 2, and idiopathic hypersomnia (19). Secondary narcolepsy and cataplexy are rare disorders described as a consequence of lesions of lateral hypothalamus orexinergic neurons (13, 24, 26, 39, 51–54). Narcolepsy is rare and characterized by EDS and REM sleep dysregulation manifesting as sleep paralysis, cataplexy, and hypnagogic and hypnopompic hallucinations (19). The diagnosis is based on clinical symptoms and a mean sleep latency of ≤ 8 min with two or more sleep onset REM periods (SOREMPs) on a Multiple Sleep Latency Test (MSLT) or low hypocretin-1 concentration in the cerebrospinal fluid (CSF) (≤110 pg/ml) (19). Cataplexy is defined as more than one episode of generally brief (< 2 min), usually sudden bilateral and symmetrical loss of muscle tone with retained consciousness. The episodes are induced by strong emotions, usually positive, with almost all patients reporting some episodes induced by emotions associated with laughter (19). Narcolepsy is strongly associated with obesity (24) and other SDs like REM sleep behavior disorders (55), periodic leg movements during sleep and restless leg sleep syndrome (56), and OSA (57). Jacola et al. (31) assessed EDS in a pediatric CP cohort using the Modified Epworth Sleepiness Scale (M-ESS) and MSLT. M-ESS is a quick screening tool derived from ESS to identify EDS in children by assessing their likelihood to fall asleep in different everyday situations (from 0, which is low probability to fall asleep, to 3, which is high probability to fall asleep). A cutoff of 10 is indicative for EDS (58). EDS was identified by M-ESS in 76% of pediatric CP and strictly related to hypothalamic involvement (31). However, M-ESS may not be sensitive enough to screen pediatric patients for EDS (58), so complete sleep evaluation is often recommended (25). In survivors of childhood brain tumors, hypersomnia/narcolepsy was diagnosed on a median of 6.1 years from diagnosis and 4.7 years from cranial irradiation, and tumor location and radiation therapy were potential risk factors (26). Stimulants improved wakefulness and school performance (26). **Table 2** summarizes central hypersomnias and EDS observed in patients with CP.

Circadian Rhythm Sleep-Wake Disorders

CRSWDs are characterized by alterations of the circadian time-keeping system or misalignment of the endogenous circadian rhythm and the external environment (19), associated with sleep-wake disturbances (EDS or insomnia) and distress (19). ICSD-3 distinguishes different types of CRSWDs: delayed sleep-wake phase disorder, advanced sleep-wake phase disorder, irregular sleep-wake rhythm disorder, non-24-h sleep-wake rhythm disorder, shift work disorder, jet lag disorder, and circadian sleep-wake disorder not otherwise specified (19). Patients with CP show frequent disruption of sleep-wake cycle and circadian rhythm (20, 27–30), typically caused by involvement of the hypothalamic SCN and alterations in melatonin transmission (62, 63). Melatonin can be measured in the peripheral blood to diagnose clock disruption, but this requires serial blood samples, and several variables may interfere with correct result interpretation (33), preventing routine use in clinical practice. Sleep logs, prolonged sleep-wake cycle monitoring by actigraphy, and circadian variations of salivary melatonin by dim-light melatonin onset are useful tools to establish a CRSWD diagnosis (64). Patients with CP lacking midnight melatonin peak had impaired sleep quality, increased EDS, and more general and mental fatigue (30). Obesity and EDS were also linked to low midnight-morning melatonin concentration (20). In addition, sleep fragmentation and EDS are frequently reported in CP with a circadian profile characterized by early morning

TABLE 2 | Excessive daytime somnolence and secondary narcolepsy in patients with craniopharyngioma.

References	Patients (*n*)	SD	Study design	Prevalence	Age	Diagnostic criteria	Diagnostic tools
Snow et al. (23)	5 (3 CF)	Daytime sleepiness	C P	5/5 (100%)	11–15 yrs	ESS > 12	ESS, MSLT
Poretti et al. (59)	21	Daytime sleepiness	P U	6/21 (28.5%)	Pediatric	ESS > 10	ESS
Müller et al. (60)	79	Daytime sleepiness	C P	28/79 (35.4%)	Pediatric and Adult	ESS > 10	ESS
van der Klaauw et al. (61)	27	Daytime sleepiness	C P	9/27 (33%)	Adult	ESS > 10	ESS
Lipton et al. (29)	3	Daytime Sleepiness	C (selected hypersomnolent patients)	3/42 (7.14%)	17–22 yrs	Self-Reported	Actigraphy
Crowley et al. (6)	28	Daytime Sleepiness	C P (obese CP vs. obese controls)	20/28 (71.4%)	16–67 yrs	ESS > 10	ESS
Manley et al. (11)	28	Daytime Sleepiness	R U	19/28 (67.8%)	Pediatric and Adult	Self-Reported	Self-Reported
Mandrell et al. (13)	110	Hypersomnia	CS CO U	39/86 (45.3%)	Pediatric and Adult	Tanner Prepubescent MSL ≤ 15; Tanner pubescent MSL ≤ 10	PSG; MSLT
		Narcolepsy		30/86 (34.8%)		Tanner Prepubescent MSL ≤ 15; Tanner pubescent MSL ≤ 10 AND ≥ 2 SOREMPs	PSG; MSLT

CS, cross sectional; C, controlled; U, uncontrolled; P, prospective; CO, consecutive; R, retrospective; ESS, Epworth sleepiness scale; PSG, polysomnography; MSLT, multiple sleep latency test; SOREMPs, sleep onset REM periods.

TABLE 3 | Sleep-wake cycle alterations in patients with craniopharyngioma.

References		Patients (*n*)	Study design	Prevalence	Age	Sleep findings	Diagnostic tools
Lipton et al. (29)	Sleep-Wake cycle alterations Melatonin deficiency	3	C (selected hypersomnolent patients)	3/3 mild OSA	17–22 yrs	(1) Irregular bed time; (2) Frequent night-time activity; (3) Inappropriate daytime episodes of rest; (4) Low melatonin level in patients compared to controls	Actigraphy and Melatonin plasma dosage vs. levels in Historical controls
Pickering et al. (30)	Melatonin deficiency Increased sleep Latency	15	C	Normal melatonin profile and no sleep alterations (6/14) Absent mid night peak of melatonin and impaired sleep quality; EDS and fatigue (6/14) Phase-shifted peak and no sleep alterations (2/14)	18–70 yrs	(1) Unchanged sleep onset (2) Wake up 1 h earlier (3) Higher global score in PSQI (impaired sleep quality, increased sleep latency and increased daytime dysfunction) (4) Lower melatonin (5) Low midnight melatonin associated with increased daytime sleepiness	Sleep Log, PSQI, ESS, SF-36, MFI Saliva melatonin dosage, blood cortisol dosage

C, controlled; OSA, obstructive sleep apnea; EDS, excessive daytime somnolence; PSQI, Pittsburgh sleep quality index; ESS, Epworth sleepiness scale; SF-36, short form health survey; MFI, multidimensional fatigue inventory.

awakening, followed by napping during the afternoon (11, 30, 58). Actigraphy may help to recognize different patterns of SDs and is a reliable tool to estimate total sleep time, sleep latency, sleep onset latency, sleep efficiency, awakenings, and wakefulness after sleep onset (65). Different hypothalamic lesions in obese children with CP may induce shorter (7) or longer sleep onset latency (30). The main CRSWDs in patients with CP are reported in **Table 3**.

DIAGNOSIS OF SLEEP DISORDERS IN PATIENTS WITH CP

In order to appropriately evaluate patients with CP for SDs, it is crucial to investigate suggesting symptoms such EDS, non-restorative sleep, and fatigue. Physicians should obtain a comprehensive clinical history on sleep behaviors, sleep hygiene from patients, and bed partners, even in the absence

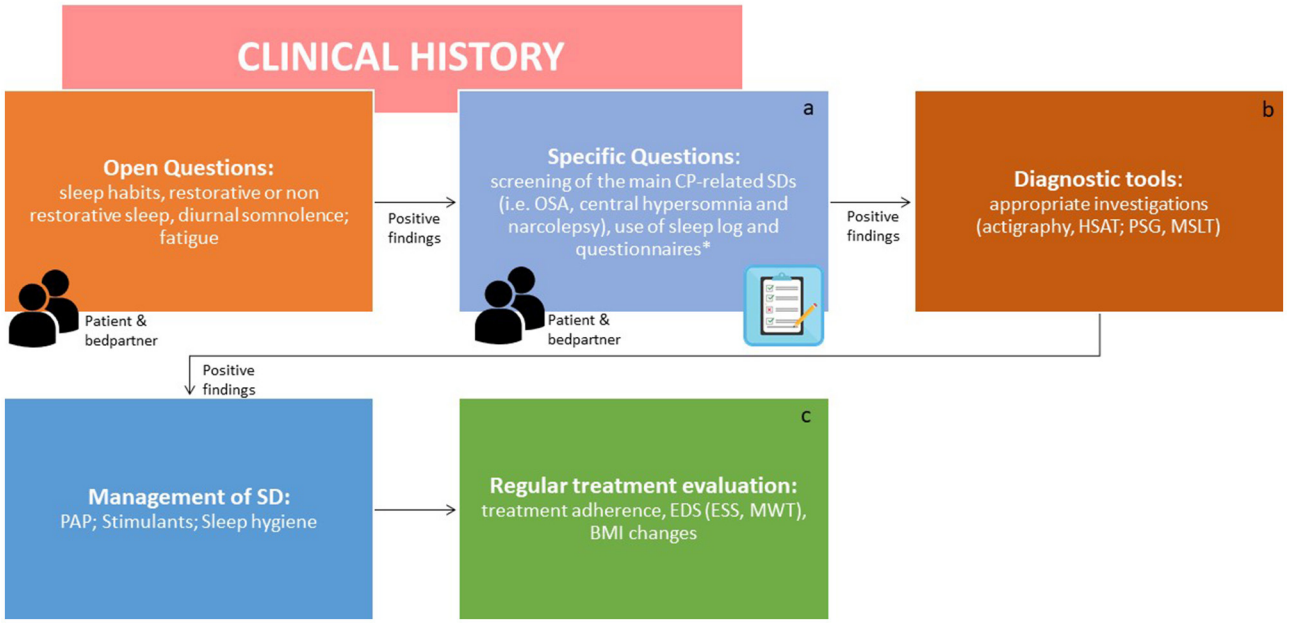

FIGURE 1 | Algorithm for the screening and identification of sleep disorders in patients with craniopharyngiomas. ICSD-3, International classification of sleep disorders version 3; CP, craniopharyngioma; SDs, sleep disorders; OSAS, obstructive sleep apnea syndrome; HSAT, home sleep apnea test; PSG, polysomnography; MSLT, multiple sleep latency test; CRSWD, circadian rhythm sleep-wake disorders. Endocrinologists and neurosurgeons should be involved in the screening step. The second step should be performed by a sleep specialist. [a]Diaries can help to obtain clinical points in a standardized manner. *The use of formal screening questionnaires for sleep disorders is advisable [i.e., STOP BANG for sleep apnea, Pittsburgh Sleep Questionnaire Index (PSQI) for SDs, Epworth Sleepiness Scale for EDS, Morningness-Eveningness Questionnaire to identify chronotype]. [b]SDs should be managed as per overall guidelines. [c]The effects of treatments should be regularly evaluated [adherence to PAP, EDS by ESS score or Maintenance Wakefulness Test (MWT) together with multidisciplinary evaluation of obesity and related cardiometabolic complications as well as appropriate hormone replacement, where present. In particular, body mass index (BMI) should be noticed at each visit].

of evident sleep complaints. Open questions regarding non-restorative sleep, history of observed snoring, apneas, obesity, and EDS should raise the suspicion of comorbid OSA and lead to further investigations. Special care should be paid to inattention, hyperactivity, high blood pressure, enuresis, and failure to thrive that are commonly reported in pediatric OSA (44). In addition, some questionnaires may help to suspect SBDs, EDS, and CRSWDs. Although specific guidelines for SDs in CP and other suprasellar tumors are lacking, the general indications for diagnostic tests should be applied based on clinical suspicion: HSAT for SBDs/OSA, PSG for hypersomnia and MSLT for narcolepsy and other central hypersomnias, and actigraphy for suspected SDs and more specifically CRSWDs and insomnia (19).

A clinical algorithm aimed to suspect SDs in patients with CP and summarize their approach and follow-up according to current sleep medicine guidelines (19) is proposed in **Figure 1**. Based on clinical suspicion, another algorithm is proposed in **Figure 2** to guide the diagnosis and treatment of the most frequently reported SDs. Examples of OSA, central hypersomnia and CRSWD observed in adult patients with CP in our institution and diagnosed by HSAT, PSG and actigraphy, respectively, are shown in **Figures 3–5**. Of note, all these patients had a supra- and retro-sellar extension at pre-operative magnetic resonance imaging (MRI). **Table 4** provides a glossary and abbreviation list of sleep terms reported in our study, and **Table 5** reports the current definition and diagnostic criteria of the most relevant SDs reported in patients with CP.

PREVENTION AND TREATMENT OF SLEEP DISORDERS IN PATIENTS WITH CRANIOPHARYNGIOMA

A multidisciplinary approach is crucial to target several factors involved in the onset and progression of SDs in patients with CP. The choice of a safe neurosurgical approach is the first step in the prevention of hypothalamic damage, and optimization of hormone replacement therapy is necessary in patients with hypopituitarism and/or DI to correct their potential contribution to SDs. In the presence of HS, complementary strategies should be put in place to simultaneously address sleep health (direct strategies) and HO (indirect strategies). We will, therefore, analyze risk factors for the development of HS and SDs, and focus on their prevention and treatment, pointing out the potential benefits of sleep medicine in such patients.

Neurosurgical Treatment

The optimal treatment of patients with CP is still a matter of debate due to difficulty in finding effective balance between an aggressive approach aiming for complete resection to prevent

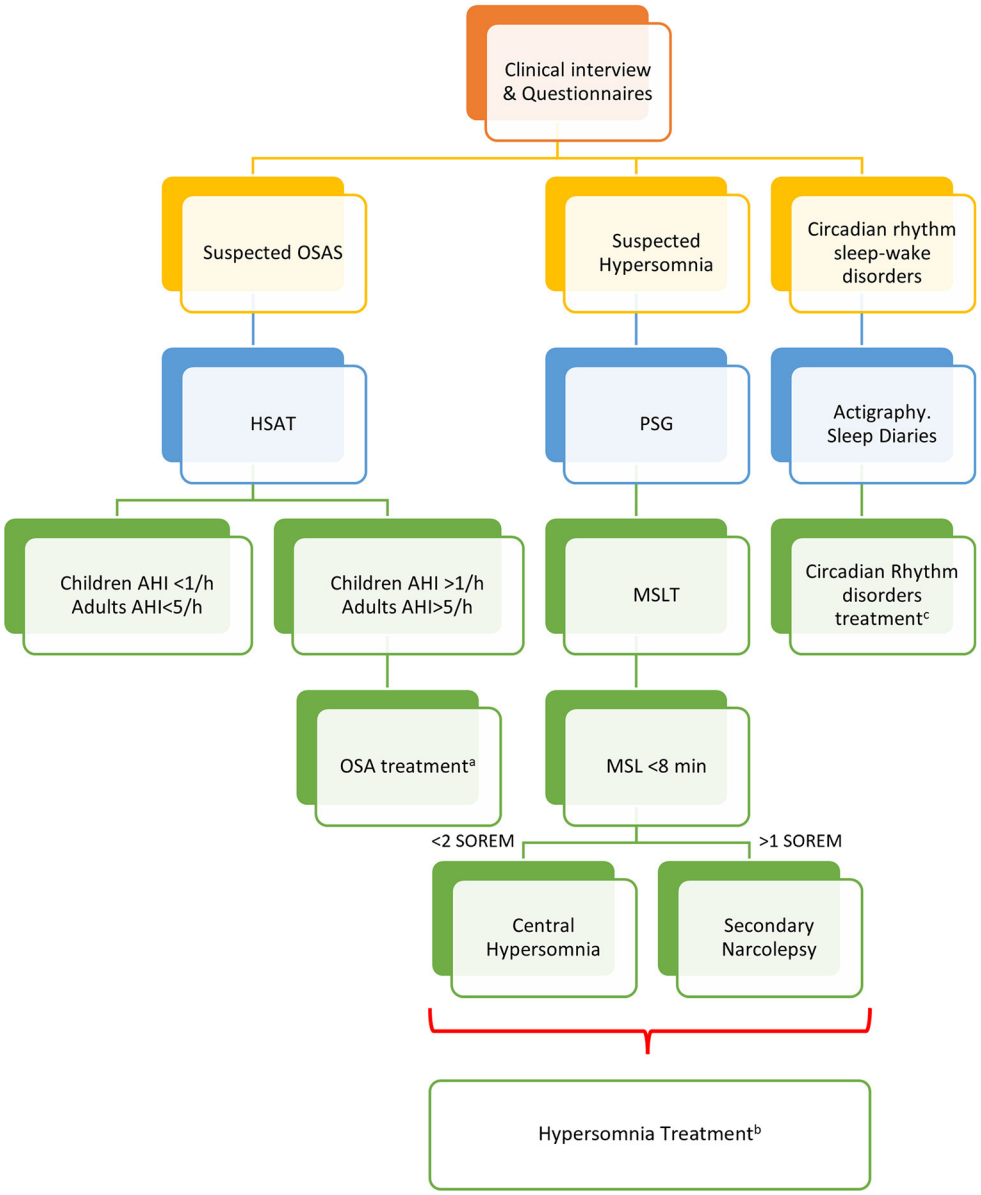

FIGURE 2 | Algorithm for the management of sleep disorders in patients with CP. PSG, polysomnography; OSAS, Obstructive Sleep Apnea (OSA) syndrome; HSAT, home sleep apnea test; AHI, apnea-hypopnea index per hour of sleep; MSLT, multiple sleep latency test; MSL, mean sleep latency; [a]The management of OSA should include weight loss, avoidance of alcoholic intake and smoking, sleep hygiene, and positional therapy. Positive Airway Pressure (PAP) is considered first-line treatment. Oral appliances may be suggested for mild to moderate OSA and surgery to correct anatomic obstructions (66). [b]The treatment of central hypersomnias and secondary narcolepsy should include cognitive behavioral therapy (CBT) and approved stimulants (i.e., modafinil, pitolisant, solriamfetol, and sodium oxybate) (67). [c]Sleep hygiene, CBT, and short-term pharmacologic approach should be considered for insomnia and CRSWD (68).

recurrences, and a more conservative approach aiming to reduce the risk of post-operative complications and long-term sequelae. The surgical approach itself has also significantly evolved in the last decades. Controversies about surgical objectives and techniques are related to the complexity of the anatomical location and extension of CP, which may arise anywhere along the craniopharyngeal duct. Nearly 95% have a suprasellar component, up to 75% are intra-suprasellar and only a minority are purely intrasellar (<10%) (1). Suprasellar CPs may occasionally extend to the anterior, middle, or posterior fossa, rarely they are completely situated within the 3rd ventricle, and hydrocephalus may be present more frequently in children than in adults (1). Radical resection has long been considered as the therapy of choice at any age for the primary treatment of CP, and several open transcranial microsurgical (TC) approaches have been developed, offering uni- or bilateral access to the tumor. TC surgery allows for good maneuverability but requires some degree of brain retraction

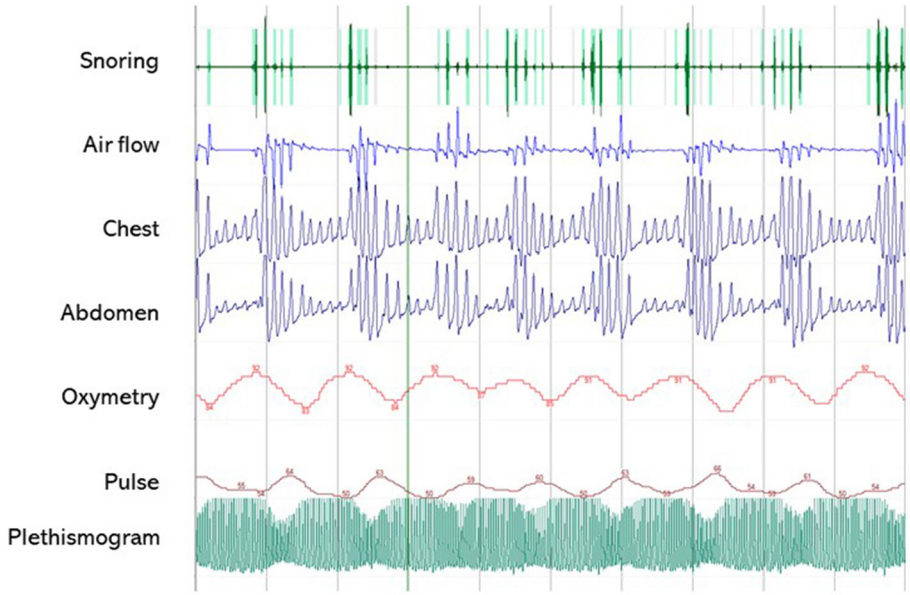

FIGURE 3 | A 5-min segment from home sleep apnea test (HSAT) in the diagnosis of sleep-related breath disorders in a 51-year old male patient with CP. The patient was operated on for a huge supra- and retrosellar craniopharyngioma with hydrocephalus and ataxia, achieving complete resection of an adamantinomatous lesion. He developed post-operative diabetes insipidus and partial hypopituitarism, and had severe weight gain (+50 kg) with snoring and markedly excessive daytime somnolence (EDS), confirmed by a high ESS score (16/24). HSAT confirmed the presence of severe OSA syndrome (AHI 58.8/h), characterized by several obstructive apneas. PAP treatment induced the disappearance of EDS (ESS score 7/24). Overall, the patient was very compliant to lifestyle interventions and endocrinological management, and significant weight loss (−30 kg) was also achieved.

and optic nerve and vascular manipulation, and increased resection rates have been associated with increased morbidity and mortality, in particular with neuroendocrine dysfunction and HO (1–3). Exposure of infra-chiasmatic, retrosellar, and interpeduncular extension of some midline tumors may also be limited. Conversely, microsurgical transsphenoidal approaches provide limited exposure and maneuverability in the suprasellar space and may cause CSF leak. In the last 15 years, the development of expanded endoscopic endonasal approaches (EEAs) in skull base surgery has changed the approach to CP (69–72). Although initially limited to resection of intrasellar tumors, with increasing experience and improved technology, EEAs are being increasingly used for suprasellar CP, and the incidence of CSF leaks has been reduced by the use of multilayer reconstruction techniques (69, 70). In experienced hands, EEAs may now be proposed for the treatment of midline infra-chiasmatic and suprasellar CP, and, in some cases extended to CP of the 3rd ventricle (70). A recent consensus statement of the European Association of Neurosurgical Societies (EANS), skull base section, recommends surgery in tertiary referral centers and further supports the role of EEAs as suitable to most adult CP (71). For anatomical reasons, endonasal surgery has been considered difficult in the pediatric population, but the place of EAAs in the treatment of pediatric CP may progressively increase with improved technology (73).

Preoperative neuroradiological imaging is essential for the diagnosis and surgical treatment of CPs, and their characteristics have been well-described (74). Adamantinomatous CP typically present as multilobulated mixed solid/cystic intra/suprasellar masses, with frequent calcifications (90%) on X-ray or computerized tomography (CT). The solid component is unevenly hypointense in T2 on MRI and, together with the peripheral component of the cysts, shows irregular contrast enhancement. Cystic components are hypointense on T1, and their intensity in T2 depends on their protein content. Papillary CPs are suprasellar and devoid of calcifications. Of note, perilesional edema in FLAIR may hardly be distinguished from the lesion when it infiltrates the chiasm, hypothalamus, or mammillary bodies. Identifying the hypothalamus and mammillary bodies is essential, although controversies remain about the relative impact of pre-operative hypothalamic involvement (HI) itself and surgical strategies on long-term post-operative outcome, including post-operative HO. Sainte-Rose et al. (75), Van Gompel et al. (76), and Muller et al. (77) have proposed different neuroradiological classifications of CP to define the grading of HI. The prognostic value of HI according to either classification, together with additional characteristics such as unidentified pituitary stalk, retrochiasmatic extension, and peri-tumoral edema, has been confirmed in a multifactorial analysis of risk factors for the development of HS and morbid HO (78).

Differences in CP management worldwide and across the last decades have been discussed in details elsewhere (2). As a general rule, experienced neurosurgeons currently advise gross total resection where presumably safe, and conservative approaches with subtotal tumor removal in the presence of risk

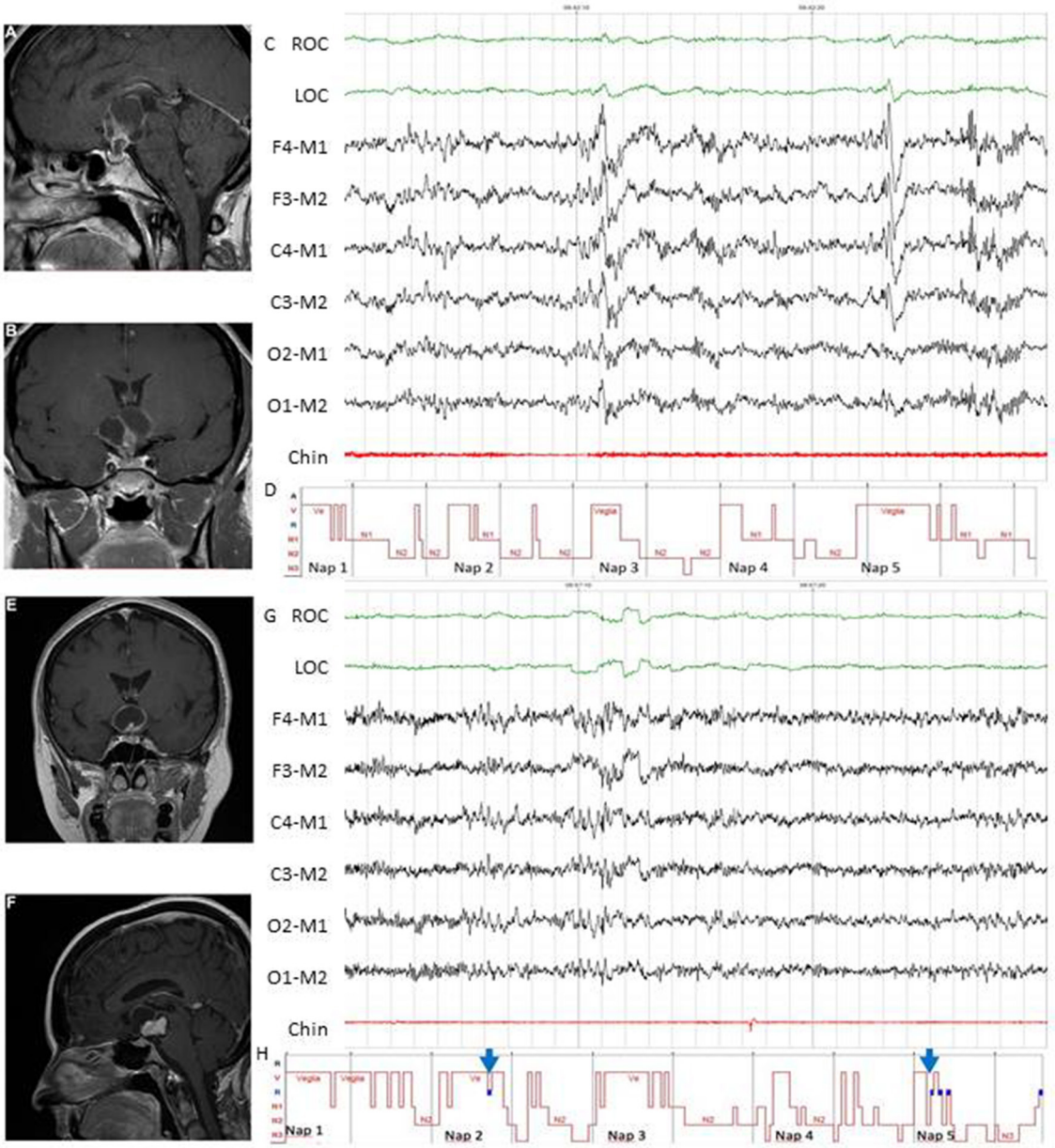

FIGURE 4 | Examples of MSLT in the diagnosis of central hypersomnias in two female patients with CP. Patient 1 **(A–D)**. Pre-operative evaluation of a 44-year-old woman who presented with spontaneous hypothalamic syndrome with severe weight gain (+30 kg) associated with headache, secondary amenorrhea, asthenia, insomnia, and diurnal somnolence. Contrast-enhanced T1-weighted magnetic resonance imaging (MRI) revealed a huge solid and cystic suprasellar lesion [**(A)**, coronal view] with posterior extension [**(B)**, sagittal view]. MSLT showed a 30-s epoch of NREM sleep (N2) **(C)** with hypnogram confirming severe excessive daytime somnolence (mean sleep latency 4.2 min) without sleep-onset REM in 5 of 5 nap periods **(D)**. A diagnosis of central hypersomnia was made. Patient 2 **(E–H)**. Post-operative evaluation of a 52-year-old woman affected by complex post-operative sleep disorders accompanied by diabetes insipidus, pan-hypopituitarism, ongoing severe weight gain (+7 kg before surgery, +30 kg after surgery) and asthenia. Preoperative contrast-enhanced T1-weighted MRI showed a huge solid and cystic suprasellar lesion [**(E)**, coronal view] with posterior extension [**(F)**, sagittal view]. Excessive daytime somnolence persisted on continuous PAP for documented post-operative OSA (data not shown), and MSLT was recently proposed. The MSLT showed a 30-s epoch of REM sleep **(G)**, with hypnogram confirming severe excessive daytime somnolence (mean sleep latency 2.3 min) with sleep-onset REM in 2 of 5 nap periods [**(H)**, see blue arrows]. A diagnosis of secondary narcolepsy was made, and a stimulant oral agent (modafinil) was started. In both patients, complete tumor resection was achieved, and pathological examination revealed adamantinomatous (patient 1) and papillary (patient 2) craniopharyngiomas. ROC, right oculogram; LOC, left oculogram; M1 and M2 reference electrodes placed on the mastoid process; Chin, Chin electromyogram.

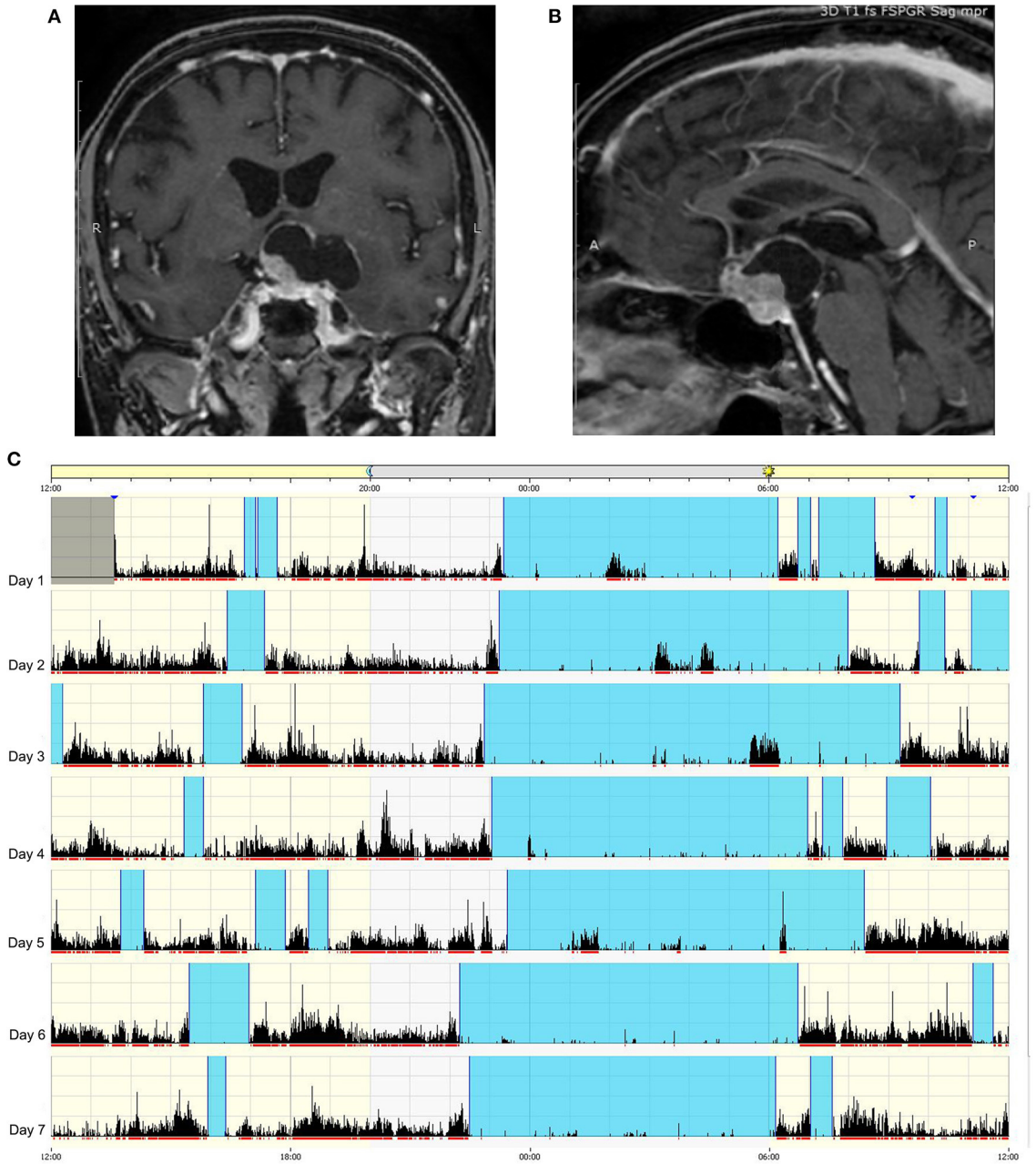

FIGURE 5 | Example of circadian sleep-wake alteration evaluation by actigraphy. A 75-year-old female patient came to our observation because of headache and visual loss in the context of recent and rapidly worsening neurological symptoms consisting of insomnia, excessive daytime somnolence, cognitive impairment, reduced appetite, and weight loss. No poliurodyspia was present, and basal pituitary function and electrolytes were normal. Contrast-enhanced T1-weighted MRI revealed a mixed cystic and solid tumor consistent with suprasellar craniopharyngioma **(A)** with retrosellar extension **(B)**. Sleep-wake patterns are displayed for individual days on actigraphy **(C)**: vertical black bars and the red line under each day indicate movement, and the absence of black bars indicates supposed sleeping periods. The blue band designates the sleep period. The actigram shows frequent nighttime activity, severe insomnia, sleep fragmentation, and frequent short diurnal naps. The patient is currently awaiting surgery.

factors for significant post-operative morbidity. Interestingly, according to a meta-analysis performed on adult patients with CP, conservative surgery itself was associated with reduced risk of post-operative hypopituitarism and DI but did not significantly prevent weight gain (79). Similar findings arise from a pediatric meta-data analysis in the United Kingdom (80), pointing out unresolved issues in the identification of individual risk factors and personalized surgery. An algorithm

TABLE 4 | Glossary of sleep terms included in the review.

Term	Abbreviation	Definitions
Actigraphy		A non-invasive technique that measures physical activity levels of a subject by means of a wristwatch-like motion-sensing device that can be worn for prolonged periods of time. Its use is considered useful to diagnose CRSWDs, insomnia and other sleep disorders (i.e., OSA, restless legs syndrome)
Apnea-Hypopnea index	AHI	A diagnostic tool for determining the presence and severity of OSA. It represents the average number of apneas and hypopneas by hour during sleep
Circadian rhythm sleep wake disorders	CRSWDs	Chronic or recurrent patterns of sleep-wake rhythm disruption primarily caused by an alteration in the endogenous circadian timing system or misalignment between the endogenous circadian rhythm and the sleep-wake schedule
Cognitive behavioral therapy of insomnia	CBTi	A short, structured, and evidence-based approach to improve symptoms of insomnia, by identifying and replacing thoughts and behaviors that cause or worsen sleep problems
Epworth sleepiness scale	ESS	A subjective questionnaire to measure daytime sleepiness in the past month
Home sleep apnea test	HSAT	An alternative simplified medical test for the diagnosis of OSA in uncomplicated adults presenting with signs and symptoms that indicate an increased risk of moderate to severe OSA. It does not include electroencephalography, electrooculogram, and electromyography
Maintenance wakefulness test	MWT	An objective measure of daytime vigilance that is used to quantify changes in the ability to stay awake
Morningness–Eveningness questionnaire	MEQ	A self-assessment tool that can provide details regarding an individual's subjective timing preferences
Multiple sleep latency test	MSLT	An objective measure of daytime sleepiness that is used to measure physiological sleep tendency in the absence of alerting factors among 5 diurnal naps. MSL (mean sleep latency) is the mean of each sleep latency
Obstructive sleep apnea	OSA	Obstructive sleep apnea (OSA) is a sleep-related breathing disorder that involves a decrease or complete halt in airflow despite an ongoing effort to breathe
Pittsburgh sleep quality index	PSQI	A self-rated, subjective, questionnaire to evaluate sleep quality, and disturbances over a 1-month time interval
Polysomnography	PSG	A comprehensive sleep study including electroencephalography, electrooculogram, chin and leg electromyography, body position, airflow, respiratory movement, oxygen saturation. PSG is considered the "gold standard" of sleep study
Positive airway pressure	PAP	PAP is the first-choice treatment for OSA involving devices to maintain upper airway patency by increasing the upper airway pressure
Sleep onset REM periods	SOREMPs	REM sleep period occurring $\leq$15 min after the onset of sleep on an overnight PSG or MSLT
Stop-BANG questionnaire	Stop-BANG	An easy to use, concise, effective, and reliable OSA screening tool including **S**noring, **T**iredness, **O**bserved a**P**nea, high **B**P, BMI, **A**ge, **N**eck circumference, and male **G**ender

for risk-adapted hypothalamic-sparing surgery (HSS) was first proposed by Sainte-Rose and Puget in pediatric CP, limiting the indications for extensive surgical resection (ESR) to CP presenting with no HI or with hypothalamic compression without invasion (75). In their experience, patients receiving risk-adapted HSS had similar relapse and progression rates, with a significant benefit in weight gain, when compared with their historical cohort of patients with CP treated by ESR (morbid obesity 28 vs. 54% and normal post-operative BMI at last follow-up 38 vs. 17%, respectively) (81). Although validation of this single-center observation in a prospective multicenter setting is still missing, additional studies have been conducted to evaluate the outcome of HSS in patients with CP. In a recent retrospective analysis of the German multicenter KRANIOPHARYNGIOMA 2007 cohort, neither pre-operative HI nor anterior hypothalamic surgical injury, but posterior hypothalamic surgical injury was significantly associated with increased risk of obesity and lower QoL (82). Hence, the authors proposed that HSS should particularly point to a "posterior HSS." However, the potential benefits of less aggressive surgical approaches to CP on SDs have deserved less attention than HO. Compared to TC surgery, EEA was recently reported to be associated with lower incidence of DI, but post-operative weight gain was not significantly lower and still depended on tumor volume and pre-operative BMI (83). SDs were not addressed in a large series of CP managed by HSS (81, 82). However, encouraging results were reported about potential improvement of sleep-wake cycle and body core temperature in a small series of CP of the 3rd ventricle managed by EEA (84). The recent consensus statement on the surgical treatment of adult CP by EANS skull base section suggests to systematically evaluate pre-operative hypothalamic function (regulation of weight, body temperature, and sleep-wake cycles) and encourages further attention to their post-operative evolution in the future (71).

A drawback of conservative approaches to CP is their potential to recur, and multiple recurrences are a serious concern after incomplete tumor resection, especially in children. The best results in terms of progression-free survival after conservative surgery have been reported in association with post-operative radiotherapy and are similar to those obtained by gross total resection. However, side effects of irradiation are delayed and may include hypothalamic complications (9). Among modern techniques, proton therapy may take an increasing place in the treatment of residual or recurrent CP because of the dosimetric characteristics of protons and limited off-target toxicity (2, 85).

TABLE 5 | Classification and definition of sleep disorders of interest in patients with craniopharyngioma (19).

Term (abbreviation)	Definition	Diagnostic criteria (ICSD-3)
Central disorders of hypersomnolence	A group of disorders in which the primary complaint is daytime sleepiness not caused by disturbed nocturnal sleep or misaligned circadian rhythms. Other sleep disorders may be present, but they must be adequately treated before a diagnosis in this category can be established. This group includes (a) Narcolepsy type 1 (b) Narcolepsy type 2 (c) Idiopathic hypersomnia (d) Kleine-Levin syndrome (e) Hypersomnia due to a medical disorder (f) Hypersomnia due to a medication or substance (g) Hypersomnia associated with a psychiatric disorder (h) Insufficient sleep syndrome	**Narcolepsy type 1** **Criteria A and B must be met** A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months B. The presence of one or both of the following: 1. Cataplexy (defined as more than one episode of generally brief (<2 min), usually bilaterally symmetrical, sudden loss of muscle tone with retained consciousness) and a mean sleep latency of ≤8 min and two or more sleep-onset REM periods (SOREMPs) on an MSLT performed according to standard techniques. A SOREMP (within 15 min of sleep onset) on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT 2. CSF hypocretin-1 concentration, measured by immunoreactivity, is either ≤110 pg/mLor <1/3 of mean values obtained in normal subjects with the same standardized assay **Narcolepsy type 2** **Criteria A and E must be met** A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months. B. A mean sleep latency of ≤8 min and two or more sleep-onset REM periods (SOREMPs) are found on a MSLT performed according to standard techniques. A SOREMP (within 15 min of sleep onset) on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT C. Cataplexy is absent D. Either CSF hypocretin-1 concentration has not been measured or CSF hypocretin-1 concentration measured by immunoreactivity is either >110 pg/mL or >1/3 of mean values obtained in normal subjects with the same standardized assay E. The hypersomnolence and/or MSLT findings are not explained more clearly by other causes such as insufficient sleep, obstructive sleep apnea, delayed sleep phase disorder or the effect of medication or substances or their withdrawal **Hypersomnia due to medical disorders Criteria A–D must be met** A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months B. The daytime sleepiness occurs as a consequence of a significant underlying medical or neurological condition C. If an MSLT is performed, the mean sleep latency is ≤ 8 min, and fewer than two sleep onset REM periods (SOREMPs) are observed D. The symptoms are not better explained by another untreated sleep disorder, a mental disorder, or the effects of medications or drugs. (a) If criteria for narcolepsy are fulfilled, a diagnosis of narcolepsy type 1 or type 2 due to a medical condition should be used rather than hypersomnia due to a medical condition; (b) In patients with severe neurological or medical disorders in whom it is not possible or desirable to perform sleep studies, the diagnosis can be made by clinical criteria
Circadian rhythm sleep wake disorders (CRSWDs)	Chronic or recurrent patterns of sleep-wake rhythm disruption primarily caused by an alteration in the endogenous circadian timing system or misalignment between the endogenous circadian rhythm and the sleep-wake schedule. This group includes 1. Delayed sleep–wake phase disorder; 2. Advanced sleep–wake phase disorder; 3. Irregular sleep–wake rhythm disorder; 4. Non-24 h sleep-wake rhythm disorder; 5. Shift work disorder; 6. Jet lag disorder; 7. Circadian sleep–wake disorder not otherwise specified	**General criteria for circadian rhythm sleep–wake disorder Criteria A–C must be met** A. A chronic or recurrent pattern of sleep–wake rhythm disruption due primarily to alteration of the endogenous circadian timing system or misalignment between the endogenous circadian rhythm and the sleep–wake schedule desired or required by an individual's physical environment or social/work schedules B. The circadian rhythm disruption leads to insomnia symptoms, excessive sleepiness or both C. The sleep and wake disturbances cause clinically significant distress or impairment in mental, physical, social, occupational, educational, or other important areas of functioning
Insomnia	A persistent difficulty with sleep initiation, duration, consolidation, or quality that occurs despite adequate opportunity and circumstances for sleep, and results in some form of daytime impairment	**Chronic Insomnia** **Criteria A–F must be met** **A. The patient reports, or the patient's parent or caregiver observes, one or more of the following**: 1. Difficulty initiating sleep

(Continued)

TABLE 5 | Continued

Term (abbreviation)	Definition	Diagnostic criteria (ICSD-3)
		2. Difficulty maintaining sleep 3. Waking up earlier than desired 4. Resistance to going to bed on appropriate schedule 5. Difficulty sleeping without parent or caregiver intervention **B. The patient reports, or the patient's parent or caregiver observes, one or more of the following related to the nighttime sleep difficulty**: 1. Fatigue/malaise 2. Attention, concentration or memory impairment 3. Impaired social, family, occupational, or academic performance 4. Mood disturbance/irritability 5. Daytime sleepiness 6. Behavioral problems (e.g., hyperactivity, impulsivity, aggression) 7. Reduced motivation/energy/initiative 8. Proneness for errors/accidents 9. Concerns about or dissatisfaction with sleep **C. The reported sleep/wake complaints cannot be explained purely by inadequate opportunity (i.e., enough time is allotted for sleep) or inadequate circumstances (i.e., the environment is safe, dark, quiet, and comfortable) for sleep** **D. The sleep disturbance and associated daytime symptoms occur at least three times per week E. The sleep disturbance and associated daytime symptoms have been present for at least 3 months** **F. The sleep/wake difficulty is not explained more clearly by another sleep disorder**
Sleep-Related breathing disorders (SDBs)	A range of conditions characterized by abnormal breathing during sleep; in many cases this is associated with narrowing or obstruction of the upper airway (pharynx). The disordered breathing ranges from intermittent, partial obstruction of the airway without sleep disturbance (snoring) to frequent apneas associated with repetitive hypoxaemia and arousals leading to sleep disruption and daytime sleepiness. This group includes obstructive sleep apnea (OSA) syndrome, central sleep apnea disorders, sleep-related hypoventilation disorders and sleep-related hypoxaemia disorders. OSA is a sleep disorder involving cessation or significant decrease in airflow in the presence of breathing effort	**OSA (ADULT)** **(A and B) or C satisfy the criteria** **A. The presence of one or more of the following**: The patient complains of sleepiness, non-restorative sleep, fatigue or insomnia symptoms The patient wakes with breath holding, gasping or choking The bed partner or other observer reports habitual snoring, breathing interruptions or both during the patient's sleep The patient has been diagnosed with hypertension, a mood disorder, cognitive dysfunction, coronary artery disease, stroke, congestive heart failure, atrial fibrillation, or type 2 diabetes mellitus **B. Polysomnography (PSG) or HSAT (Home Sleep Apnea Test) demonstrates:** Five or more predominantly obstructive respiratory events [obstructive and mixed apneas, hypopneas or respiratory effort-related arousals (RERAs)] per hour of sleep during a PSG or per hour of monitoring (HSAT) or **C. PSG or HSAT demonstrates:** Fifteen or more predominantly obstructive respiratory events (apneas, hypopnoeas, or RERAs) per hour of sleep during a PSG or per hour of monitoring (HSAT) **OSA (PEDIATRIC)** **Criteria A and B must be met** **The presence of one or more of the following**: 1. Snoring 2. Labored, paradoxical, or obstructed breathing during the child's sleep 3. Sleepiness, hyperactivity, behavioral problems, or learning problems **PSG demonstrates one or more of the following**: 1. One or more obstructive apneas, mixed apneas, or hypopneas, per hour of sleep 2. A pattern of obstructive hypoventilation, defined as at least 25% of total sleep time with hypercapnia ($PaCO_2 > 50$ mm Hg) in association with one or more of the following: (a) Snoring, (b) Flattening of the inspiratory nasal pressure waveform, (c) Paradoxical thoracoabdominal motion

ICSD-3: International Classification of Sleep Disorders - Third Edition (19).

Endocrine-Metabolic Treatments and Lifestyle Interventions

Although lifestyle and endocrinological/metabolic interventions are not resolutive in patients with HS, they still play a fundamental role in the control of homeostasis, optimization of SD treatment, and prevention of long-term cardio-metabolic/vascular complications. The essential role of short-term post-operative management of endocrine deficiencies and sodium/water imbalance is beyond the scope of this article. It should be remembered, however, that excessive post-operative fluctuations in serum osmolarity due to DI, SIADH, and/or salt wasting syndrome should be avoided, as excessively rapid corrections of hyponatremia may lead to irreversible neurological damage (86, 87). Patients should be clearly informed on the potential risks, clinical manifestations and timing of neuroendocrine alterations and HS following surgery, and the need for long-term endocrinological follow-up. Guidelines on the treatment of single or multiple pituitary deficiencies are currently available (88), and we will focus on the benefits and potential risks of hormone replacement therapy on SDs.

Hormone Replacement Therapy

The relationship between hormone replacement and sleep health is complex and bidirectional. Optimal hormone replacement therapy may have a beneficial effect on muscle function, including upper airway dilator muscles, body composition, and metabolism, as well as fatigue and mood. Conversely, overtreatment maybe deleterious for sleep, and worsens OSA or sleep-wake cycle and circadian rhythm. Even in the presence of undamaged hypothalamic-pituitary connections, sleep fragmentation and reduction in slow wave sleep impair circadian pituitary hormone regulation, in particular ACTH and GH (89). Therefore, fine-tuning of hormone replacement is needed to optimize metabolic, cardiovascular, and sleep issues in patients with CP.

Diabetes Insipidus

Diabetes insipidus (DI) may be transient or life-long and requires desmopressin replacement therapy according to current guidelines (87, 88). Uncontrolled DI is characterized by polyurodipsia (>50 mL/kg of body weight/24 h) with nycturia and deleterious consequences on sleep quality, increasing daytime sleepiness and fatigue (88, 90). Conversely, overtreatment results in hyponatremia and related neurological complications (86). A minority of CP patients with hypothalamic injury present an impaired sense of thirst, which should be promptly recognized by systematic evaluation of water balance. Adipsia complicates clinical management, reduces QoL (91, 92), and exposes patients to the risk of severe and potentially fatal dehydration (92). Patients and their families should be informed on such risks and the potential recovery of DI to optimize desmopressin treatment.

Glucocorticoid Replacement Therapy

Patients affected by either primary or secondary glucocorticoid deficiency complain of fatigue and impaired QoL with reduced daytime activities (93). Despite the risk of acute adrenal insufficiency being lower in patients with corticotroph deficiency because of a typically preserved mineral corticoid function, it may also occur and requires appropriate education of patients and their families. Because any available replacement therapy is unable to reproduce the physiological rhythm of cortisol secretion, patients are frequently exposed to supraphysiological evening levels of cortisol, which may impact on sleep quality, sleep latency, and daytime functioning (93, 94). It may be, therefore, be useful to prefer modified-release hydrocortisone to a standard replacement therapy with twice or trice daily oral hydrocortisone. Modified-release hydrocortisone replacement therapy best approaches physiological cortisol secretion and may have a favorable impact on body weight control, metabolism, immune function, and QoL (95). The single morning administration of modified-release hydrocortisone may also improve patient compliance in the setting of multiple treatments for hormone replacement and/or associated co-morbidities. We, therefore, suggest, where available, to consider modified-released hydrocortisone in the long-term treatment of patients with complex CP, including those with SDs.

Thyroid Hormone Replacement Therapy

Thyroid function and sleep also have a bidirectional relationship, influencing each other through the circadian clock (96). Hypothyroidism results in poor sleep quality and architecture (96), and may trigger or worsen preexisting OSA (97). This may occur as a consequence of impaired neural response to hypoxemia and hypercapnia, increased airway resistance due to mucoprotein deposition, increase in BMI, and changes in upper airway muscle activity (96). Conversely, over-replacement may favor insomnia, increase oxygen consumption, and impact on muscle and cardiovascular function as observed in hyperthyroidism (98). Therefore, optimizing thyroxine replacement therapy may contribute to improve sleep quality and architecture in patients with CP.

Testosterone Replacement Therapy

Because testosterone replacement therapy has pleiotropic benefits in hypogonadal men, including improvement in fatigue, lean mass, and hemoglobin concentration, it should be considered in hypogonadal male patients with CP according to current guidelines (88). The association between testosterone replacement and OSA is controversial and has not been specifically addressed in patients with CP, but the Endocrine Society recommends against testosterone replacement in patients with severe untreated OSA (99). In a large retrospective study, an elevated risk of OSA among testosterone users compared with controls was observed (100). Potential mechanisms include the impact of androgens on muscle contraction and neuromuscular control of upper airway muscles; increase in oxygen consumption leading to hypoxia, and changes in neural response to hypoxemia and hypercapnia (100). Thus, clinicians should be careful in prescribing testosterone replacement to patients CP and untreated OSA, and reevaluation during ventilation treatment may be useful. Of note, obesity in itself is frequently accompanied by functional hypogonadism. Because the cardiovascular risks and benefits of testosterone replacement

are also debated (101), a multidisciplinary evaluation is advisable in patients with complex CP.

Recombinant Human Growth Hormone Replacement Therapy

Growth hormone (GH) deficiency is generally the first to occur and the last to be replaced in patients with CP. The diagnosis of severe GH deficiency depends on patient age (childhood, transition, adult) and may be influenced by BMI and the presence and/or replacement of other pituitary deficits (88, 102). GH replacement has a beneficial effect on growth, body composition, and neurophysiological outcome (103), and does not influence the risk of CP relapse (104). Despite GH replacement being suspected to worsen OSA in adults, this remains controversial (105). In adults affected by the Prader Willi syndrome (PWS), a genetic disorder sharing with CP many features of hypothalamic dysfunction, including severe obesity and SDs, GH replacement was found to be safe and did not significantly impair sleep parameters in patients without SDs (106). However, consensus guidelines on PWS recommend to perform PSG before GH replacement and possibly to repeat the test within 3–6 months of treatment, with an ear, nose, and throat evaluation in the presence of OSA (107). Indeed, upper airway obstruction may occur because of GH/IGF1 effects on lymphoid tissue stimulation (107) and sodium/water retention with fibroblast stimulation, leading to soft tissue swelling (106); worsening of OSA in an adolescent patient during GH replacement resolved after tonsillectomy and adenoidectomy (108). GH replacement in adults may be limited by compliance issues and contraindications such as hyperglycemia, and overtreatment should be avoided as it may induce headache and long-term complications as reported in pathological GH/IGF1 excess, including cardiovascular and cardiorespiratory/OSA and neoplastic diseases (88).

Lifestyle and Metabolic Interventions

Personalized hypocaloric diet and daily physical activity should always be recommended to target energy expenditure and hyperinsulinemia, and counteract weight gain. Both should be started before surgery in the presence of preexisting obesity or HS and in the early post-operative period if hypothalamic injury is suspected. Several drugs have been proposed to patients affected by HO (1, 5, 109), and an individualized stepwise treatment algorithm has been recently proposed according to predominant clinical complications of HS (5).

The first-line pharmacological treatment of obesity is usually metformin, which increases insulin sensitivity. Metformin was found in a non-diabetic rat model to improve central sleep apnea (110) and some beneficial effects on sleep quality, efficiency, and duration have also been reported in patients with type 2 DM (111, 112). The underlying mechanisms remain unclear. However, as hypoxia increases the risk of lactic acidosis, a rare but severe side effect of metformin, hypoxic patients with CP should be recognized in order to adapt the daily dose of the drug, with prompt discontinuation in the presence of acute respiratory or systemic conditions. Antidiabetic drugs such as glucagon-like 1 (GLP-1) agonists and sodium-glucose contrasporter-2 (SGLT2) inhibitors may be considered to optimize weight loss and metabolic control. The GLP-1 receptor is expressed in several areas of the central nervous system, in particular the hypothalamic arcuate nucleus, where it directly stimulates POMC/CART neurons while indirectly inhibiting NPY/AGRP neurons, thereby increasing satiety and reducing hunger (113). Central effects, therefore, complete the peripheral action of GLP-1 agonists. Among them, exenatide and liraglutide have been used with some benefits in patients with CP (1, 5). Liraglutide 3 mg was studied in non-diabetic obese patients suffering from moderate or severe OSA, in the absence of positive airway pressure (PAP) therapy, and a significant reduction in weight and AHI was observed after 32 weeks of treatment, with a trend toward improved oxygen saturation, sleep architecture, and sleep/health-related QoL outcomes (114). Among SGLT2 inhibitors, empagliflozin has beneficial effects on cardiovascular and renal outcomes in type 2 diabetic patients and may reduce the risk of new-onset OSA (115), possibly mediated by weight loss and the diuretic/natriuretic action of the drug (115). It may, therefore, be attractive in diabetic patients with CP unless fluid and electrolytic imbalance is present, although experience is still lacking. An interesting perspective in patients with CP is the use of oxytocin, an hypothalamic peptide involved in the reduction of food intake and energy balance, with potential beneficial effects on body composition, and it is currently investigated as an intranasal drug for the treatment of obesity, including patients with PWS (116). Patients with CP and anterior hypothalamic damage may present with abnormal dynamic oxytocin secretion (117), and reduced oxytocin release has been associated with reduced emotion and social cognition (118). A preliminary experience with oxytocin treatment in patients with childhood-onset CP provided encouraging results in terms of neuropsychological and weight characteristics (119).

According to a recent systematic review of the American Academy Sleep Medicine, bariatric surgery may be proposed in obese patients with OSA to reduce important cardiovascular risk factors, like high BMI, DM, and hypertension, with a positive impact on sleep parameters, including AHI, snoring, and sleepiness (120). There is still limited experience with bariatric surgery in patients with CP. In a review of 21 cases who underwent bariatric surgery, maximal mean weight loss was achieved by Roux-en-Y gastric by-pass (RYGB), with an ongoing weight loss at 12 months (mean 33.7 kg), contrasting with a tendency to regain weight at 12 months after sleeve gastrectomy (121). A subsequent review of available studies further supported RYGB as a preferable option in patients with CP based on superior outcomes, which appear to be similar to unselected obese patients (109). Because only a small series is available and long-term follow-up is still lacking, bariatric surgery is currently limited to selected, mostly adult, patients with CP, and no recommendations are available concerning optimal age, timing, and general health conditions for surgery.

The Role of Central Stimulants

Central stimulants may simultaneously target HO and SDs. Stimulating drugs include dextroamphetamine, methylphenidate, mazindol, and caffeine/ephedrine, which may ameliorate the consequences of hypothalamic damage

on body weight and on sleep-wake cycle through inhibition of the reuptake of dopamine, norepinephrine, and serotonin, and increased release of these monoamines. A recent review evaluated their effects on body weight in few studies/case reports published and reported high percentages of weight reduction or stabilization in patients with CP: 88.2% for dextroamphetamine, and 100% for methylphenidate, mazindol, and caffeine/ephedrine (5). However, few data have been reported on SDs. Dextroamphetamine at low dose (5 mg twice daily) with a median therapy of 13 months was found to improve weight control (stabilization or weight loss) and/or daytime somnolence in 12 patients with childhood-onset CP (22). All the patients affected by daytime somnolence (8/12) improved during treatment, including 2 patients without beneficial effect on weight. Only one patient reported insomnia as adverse event, which was resolved by omission of the evening dose (22).

Sleep Medicine Strategies

EDS has a multifactorial basis in patients with CP and SBDs, central hypersomnias, and non-adherence with drug therapy (6) may play a critical role in inducing somnolence. In addition, for patients with CP and EDS, clinicians should confirm effective sleep hygiene and acceptable sleep opportunity. The American Academy of Sleep Medicine suggests a psychoeducational approach aiming to highlight habits that may adversely affect sleep and vigilance, and ameliorate approaches (so called "sleep hygiene rules") to avoid sleep fragmentation and EDS (122).

Few data are available regarding the approach of SBDs in patients with CP. Crowley et al. (6) reported benefit from PAP in 6 out 13 (46%) patients with CP and OSA. We found only a further small case series or single case report on PAP in patients with CP lacking data regarding efficacy and adherence (7, 123).

Stimulants have been used for fatigue and sleepiness in several neurological disorders. Although fatigue and EDS are common problems in patients with CP, there are few data regarding their treatment (6). Modafinil potentiates brain dopaminergic signals *via* dopamine transporter inhibition by acting at the same binding site of cocaine (124). A small case series demonstrated a positive effect of modafinil on EDS in patients with CP and secondary narcolepsy or OSA with residual sleepiness under PAP or not compliant with PAP use (6, 53). Besides modafinil, two other stimulants have been approved for narcolepsy and OSA with residual sleepiness: pitolisant and solriamfetol. Pitolisant is a first-in-class drug acting on histamine H3 receptors (H3Rs) as an antagonist/inverse agonist (125). Very recently, Cordani et al. (123) described a 19-year-old patient with CP and secondary narcolepsy responsive to pitolisant. Lastly, solriamfetol is a new dual dopamine and norepinephrine reuptake inhibitor approved for EDS in narcolepsy and OSA (126), with no clinical data on CP.

Some reports demonstrated fragmented sleep-wake cycles, EDS, and reduced melatonin levels in obese patients with CP (20, 29, 34). In a narrow sample, melatonin intake in 10 adults after CP therapy as children improved EDS and the amount of physical activity (60). On the contrary, other studies failed to demonstrate melatonin efficacy, particularly in patients who meet criteria for narcolepsy or hypersomnia (20). Lastly, Pickering et al. (30) described normal melatonin secretion in 40% of CP survivors, where its supplementation may be not effective.

However, given the probable effects on EDS of sleep habits, PAP, melatonin, and stimulants in comorbid SDs of CP survivors, future studies will be necessary to evaluate their potential role in managing EDS and sleep complaints in patients with CP.

CONCLUSION

Sleep disorders represent an important issue in patients with CP. Almost 70% of complaints of SDs and/or EDS are due to SBDs, central hypersomnias, and CRSWDs. SDs may affect QoL and increase respiratory and cardiovascular morbidity and long-term mortality. The main factor involved in SDs is HS due to direct hypothalamic tumor-related damage and/or complications of treatment. Despite the growing data regarding SDs and CP, sleep evaluation is still not routinely proposed, so SDs are often overlooked and undertreated in these patients. Although SDs are strongly related to the presence of HO and neuroendocrine dysfunction, which require dedicated long-life endocrinological management, there is an overwhelming body of evidence that supports the need of sleep management in patients with CP. Adequate sleep quality is crucial throughout the entire lifespan, and patients with CP may impair their QoL because of SDs and EDS. Nevertheless, despite this widely accepted clinical association, large clinical studies to improve clinical practice are lacking, and future studies are urgently needed. We, therefore, suggest to obtain clinical evaluation of sleep habits and SDs in clinical practice from CP survivors and their bed partners, and recommend an adequate diagnostic and therapeutic approach when SDs (SBDs, central hypersomnia, and CRSWDs) are suspected. Finally, considering the positive impact on EDS of sleep hygiene, ventilation, melatonin, and stimulants in comorbid SDs, future studies should be performed to clarify their potential role in managing EDS and sleep alterations in patients with CP. The management of patients suffering from HO and SDs should be multidisciplinary, and the development of new drugs for either condition may hopefully lead to bidirectional positive effects.

AUTHOR CONTRIBUTIONS

AR and M-LJ-R conceived, designed the study, revised, and edited the final version of the manuscript. AR, TF, SC, and M-LJ-R wrote the manuscript with contributions by MD, CC, and GV. GP contributed with data and references search, organization, and illustrations. MC and TF contributed with technical assistance to sleep explorations in illustrating cases. DC and VE critically reviewed the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This work was funded by Neuromed IRCCS, Current Research, by the Italian Ministry of Health.

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frontiers in Oncology

ORIGINAL RESEARCH
published: 10 February 2022
doi: 10.3389/fonc.2022.755342

Clinical Outcomes of Transcranial and Endoscopic Endonasal Surgery for Craniopharyngiomas: A Single-Institution Experience

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OPEN ACCESS

Edited by:
Edward Raymond Laws, Brigham and Women's Hospital and Harvard Medical School, United States

Reviewed by:
Matteo Zoli, IRCCS Institute of Neurological Sciences of Bologna (ISNB), Italy
Lei Cao, Capital Medical University, China

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Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: 08 August 2021
Accepted: 04 January 2022
Published: 10 February 2022

Citation:
Nie C, Ye Y, Wu J, Zhao H, Jiang X and Wang H (2022) Clinical Outcomes of Transcranial and Endoscopic Endonasal Surgery for Craniopharyngiomas: A Single-Institution Experience. Front. Oncol. 12:755342. doi: 10.3389/fonc.2022.755342

Objective: Craniopharyngioma has always been a challenge for the neurosurgeon, and there is no consensus on optimal treatment. The objective of this study was to compare surgical outcomes and complications between transcranial surgery (TCS) and endoscopic endonasal surgery (EES) of craniopharyngiomas.

Methods: A retrospective review of patients who underwent craniopharyngioma resection at Wuhan Union Hospital between January 2010 and December 2019 was performed. A total of 273 patients were enrolled in this retrospective study. All patients were analyzed with surgical effects, endocrinologic outcomes, complications, and follow-up results.

Results: A total of 185 patients underwent TCS and 88 underwent EES. There were no significant differences in patient demographic data, preoperative symptoms, and tumor characteristics between the two groups. The mean follow-up was 30.5 months (range 8–51 months). The EES group had a greater gross total resection (GTR) rate (89.8% EES vs. 77.3% TCS, $p < 0.05$) and lower rate of hypopituitarism (53.4% EES vs. 68.1% TCS, $p < 0.05$) and diabetes insipidus (DI) (51.1% EES vs. 72.4% TCS, $p < 0.05$). More postoperative cerebrospinal fluid (CSF) leaks occurred in the EES group (4.5% EES vs. 0% TCS, $p < 0.05$). More patients in the EES group with preoperative visual deficits experienced improvement after surgery (74.5% EES vs. 56.3% TCS, $p < 0.05$). There were statistical differences in the recurrence rates (12.5% EES vs. 23.8% TCS, $p < 0.05$) between the 2 groups.

Conclusion: These data support the view that EES is a safe and effective minimally invasive surgery compared to TCS. Compared to TCS, EES has fewer surgical complications and a lower recurrence rate.

Keywords: craniopharyngiomas, outcomes, transcranial surgery, endoscopic, surgery

INTRODUCTION

Craniopharyngioma is a rare benign tumor with a histologically low grade (WHO grade I) and mainly develops from remnants of the craniopharyngeal duct (1, 2). The annual incidence of craniopharyngioma is approximately 0.5–2.5 cases per million globally (3). Patients with craniopharyngiomas exhibit a bimodal age distribution of 5–14 years and 50–75 years (3). Although craniopharyngioma accounts for only 1.2%–4.6% of all intracranial tumors, it is considered to be the most common non-glial intracranial tumor in children, accounting for 10% of all brain tumors in children (4). The clinical manifestations of craniopharyngioma may occur due to compression or invasion by tumors, and the presenting symptoms may be different among children and adults. Symptoms of craniopharyngioma in children are often delayed, most of which are caused by the tumor growing to a considerable size. Children usually present with endocrine dysfunction, slowly progressive visual loss, and symptoms caused by increased intracranial pressure, while adults consistently have visual deficits (5, 6). The overall survival rates of childhood-onset craniopharyngiomas are 87%–95% at 20 years (2), and there are usually complications of hypothalamic–pituitary deficiencies, visual impairment, and neurologic dysfunction that led to a severe decline in long-term quality of life (1–3, 7). Craniopharyngioma is a surgical disease, and surgical management for craniopharyngiomas, especially in children, remains controversial (2, 8). The goal of treatment is permanent tumor control or cure without aggravating the symptoms. The aim of surgical resection is to achieve gross total resection (GTR) to reduce the risk of tumor residual and recurrence. Since the tumor is anatomically close to the optic nerve, third ventricle, and hypothalamus, it is critical to choose the appropriate approach to avoid serious postoperative complications like hypothalamic–pituitary dysfunction. Over the past decade, endoscopic endonasal surgery (EES) has been widely applied in the treatment of craniopharyngioma (9). Endoscopic surgery can provide a close high-definition view, which can clearly identify the anatomical structures, thus reducing intraoperative injuries. In contrast, traditional transcranial surgery (TCS) often requires retraction of brain and cranial nerves, especially the optic nerve, which often causes postoperative cerebral edema and cranial nerve impairment. Reports revealed that EES has significant advantages over TCS in intrasellar type of craniopharyngiomas (10, 11). However, for tumors located in the suprasellar region, there are relatively few studies directly comparing the surgical outcomes of EES and TCS. Both EES and TCS have their advantages, and there remains a lack of consensus on their benefits (12). In the current study, we retrospectively assessed outcomes of EES and TCS for suprasellar craniopharyngiomas.

METHODS

This retrospective study included all patients who underwent resection of craniopharyngiomas from January 2010 to December 2019 at Wuhan Union Hospital. All cases were pathologically confirmed as craniopharyngioma. Completely intrasellar craniopharyngiomas and recurrent cases were excluded. The medical records of all included patients were retrospectively reviewed. According to the records, patients were divided into the EES group and TCS group. Detailed patient records and follow-up reports were viewed to collect clinical data including symptoms; pathological, endocrinological, and ophthalmological assessments; and surgical outcomes. Ophthalmological assessments consisted of best corrected visual acuity and visual field examination. For both visual acuity and visual field, postoperative status was categorized as improved, stable, or deteriorated. To assess the visual acuity, the modified logMAR scale was used. To assess visual field deficits, an ordinal scale was used with the following scores: 6 indicates normal visual field; 5, slight constriction; 4, loss of a single quadrant; 3, loss of 2 quadrants; 2, loss of 3 quadrants; 1, severe constriction; and 0, blindness (13).

All the hypothalamic–pituitary axis hormones including plasma prolactin, thyroid function, growth hormone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, adrenocorticotropic hormone (ACTH), and plasma cortisol level were examined. All patients completed preoperative CT scans to detect the presence of calcifications. MRI was completed to identify detailed anatomy of the tumor and its relationship to the surrounding neurovascular structures. During the follow-up, MRI was performed at 1–2 days and 3–6 months after surgery. The tumor size was displayed as the largest diameter in all 3 dimensions (length, height, and width) on preoperative MRI. Tumor volume was calculated assuming a roughly spherical tumor configuration where tumor volume is in cubic centimeters (cm^3) = (anteroposterior × craniocaudal × transverse)/2. The consistency of tumor was assessed based on MR images and intraoperative records.

We defined the extent of tumor resection as GTR and subtotal resection (STR). GTR was only assumed if there were no tumor or capsule remnants postoperatively on MRI examination. All surgeries were performed by senior experts in our department. The pterional approach, providing short distance to parasellar region, was our first choice in TCS for craniopharyngiomas. In some cases, subfrontal approach was adopted to achieve good visualization of optic nerve and chiasm as well as ipsilateral carotid artery. For tumors extending into the third ventricle, lamina terminalis or transcallosal approach was performed. Within the EES cases, the key rule was to protect the pituitary stalk and hypothalamus. To avoid cerebrospinal fluid (CSF) leaks, the overlay technique with a pedicled nasoseptal flap was applied to reconstruct the skull base. A case example is shown in **Figures 1**, **2**. Among patients with severe hydrocephalus, emergency EES or TCS combined with lateral ventricle drainage surgery was done.

Statistical Analysis

Data were analyzed by SPSS 26.0. Descriptive statistics were used to analyze patient demographics. Continuous variables were described as means with SDs or medians as appropriate. Categorical variables were presented as frequencies or percentages. Group comparisons were assessed by the

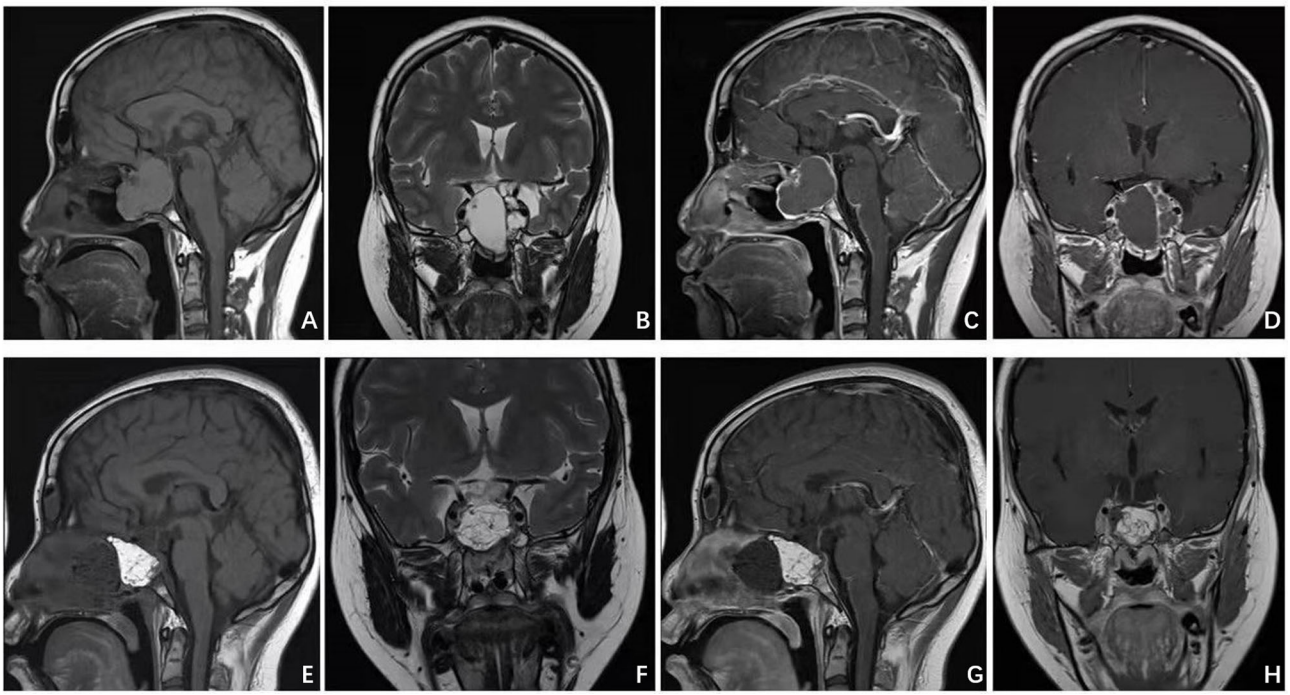

FIGURE 1 | Patient presented with visual deficit, pituitary and elevated intracranial pressure syndromes. Preoperative MRI **(A–D)** illustrated a giant intra-suprasellar craniopharyngioma. Postoperative MRI **(E–H)** confirmed gross total resection.

Student's T-test, chi-square test. Differences with $p < 0.05$ were considered statistically significant.

RESULTS

Clinical Characteristics

A total of 273 patients were enrolled in this study; 185 patients were assigned to the TCS group and 88 patients to the EES group.

The average age of the 273 patients in the study was 38.1 ± 12.9 years. The mean follow-up period was 30.5 months (8–51 months). The EES group included 41 (46.6%) males and 47 (53.4%) females, and the TCS group included 87 (47.0%) males and 98 (53.0%) females. In the EES and TCS groups, 51 (59%) of 88 patients and 118 (64%) of 185 patients were children, respectively, 37 (41%) and 67 (36.2%) were adults; headache occurred in 71 (80.7%) patients and 131 (70.8%) patients; symptoms of visual deficits presented in 47 (53.4%) and 87 (47.0%) patients; 9 (10.2%) patients and 15 (8.1%) patients presented with impaired cognition; 8 (9.1%) patients and 14 (7.6%) patients got obesity; hydrocephalus was noted in 11 (12.5%) patients and 28 (15.1%) patients; 33 (37.5%) patients and 75 (40.5%) patients had endocrine deficiencies before surgery. There were no significant statistical differences between these two groups with regard to the average age, sex, and preoperation symptoms. **Table 1** shows the demographic characteristics and clinical features in each group.

Tumor Characteristics and Extent of Resection

Pathological types, as well as tumor consistency, were similar between the two groups. The tumor characteristics and pathological types are listed in **Table 2**. There were no statistically significant differences noted. Among the 185 cases in the TCS group, GTR was achieved in 79 (89.8%) patients and subtotal resection in 9 (10.2%) patients. In the EES group, GTR was achieved in 143 (77.3%) patients; subtotal resection in 42 (22.7%) patients. The rate of GTR was statistically higher in the EES group, and the difference was statistically significant ($p < 0.05$).

Postoperative Complications

In this study, no surgery-related death occurred. Four (4.5%) of the 88 patients had postoperative leakage of CSF in the EES group and no patient in the TCS group. Two and 4 patients in the EES group and TCS group experienced meningitis, and no bacterial or fungal inflammations were found. All these differences were statistically significant with $p < 0.05$. Regarding other surgical complications, there were no significant differences in postoperative hemorrhage and seizures between the EES and TCS groups. **Table 3** demonstrates perioperative complications in the two groups.

Visual Outcome

Most patients with preoperative vision and visual field loss experienced improvement after the operation. Among the 47

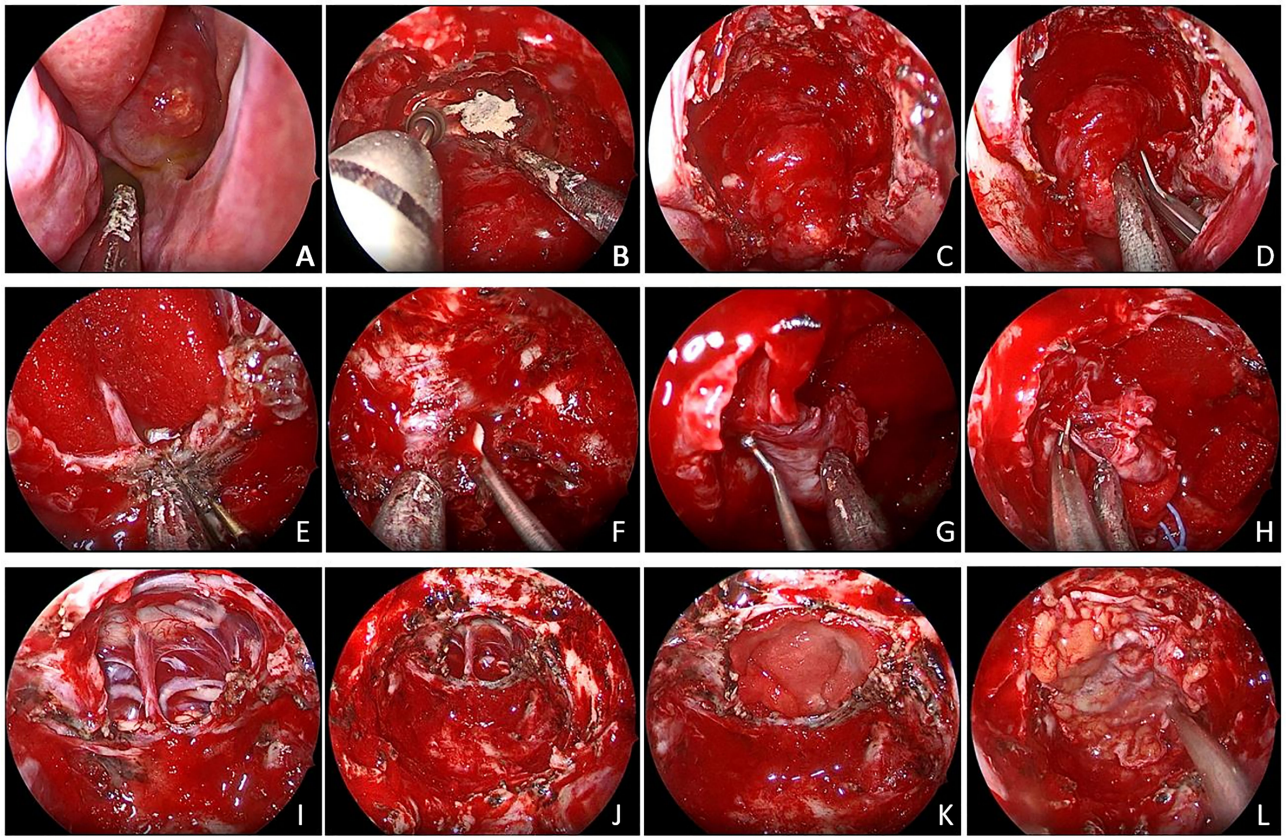

FIGURE 2 | **(A)** The tumor broke through the sphenoid sinus and grew to the nasal cavity. **(B, C)** An extended transnasal approach was performed. **(D)** Decompression inside the tumor. **(E)** Removal of the saddle septum attached to the base of the tumor. **(F–H)** Remove the adhesion tissue between the tumor and the cavernous sinus and internal carotid artery. **(I)** Pituitary stalk was preserved. **(J–L)** Tumor was gross total removed.

patients who had visual deficits preoperatively, 35 (74.5%) got visual improvement, and in the TCS group, 49 (56.3%) of 87 patients had improvement. The difference in remission rate was statistically significant ($p < 0.05$).

Two patients in the TCS group got blind in one eye. The remaining patients showed no change or slight deterioration in vision.

Hypopituitarism and Diabetes Insipidus

Postoperatively, 47 (53.4%) and 126 (68.1%) patients presented hypopituitarism in the EES and TCS groups. Among patients with endocrine deficits preoperatively, endocrine function improved in 21 (63.6%) of 33 patients in the EES group and 23 (30.7%) of 75 patients in the TCS group. These data showed statistically significant differences.

TABLE 1 | Main clinical manifestations of all the patients.

Variable	All cases	EES (%)	TCS (%)	p value
No. of cases	273	88 (32.2)	185 (67.8)	
Mean age (SD)	38.1 (12.9)	37.8 (13.8)	38.2 (12.3)	0.37
Male sex	128	41 (46.6)	87 (47.0)	1.00
Symptoms				
Headache	202	71 (80.7)	131 (70.8)	0.10
Impaired cognition	24	9 (10.2)	15 (8.1)	0.65
Visual deficits	134	47 (53.4)	87 (47.0)	0.37
Obesity	22	8 (9.1)	14 (7.6)	0.64
Hydrocephalus	39	11 (12.5)	28 (15.1)	0.71
Endocrine deficiencies	132	33 (37.5)	75 (40.5)	0.69

EES, endoscopic endonasal surgery; TCS, transcranial surgery.

TABLE 2 | Tumor size, histopathological subtype, and consistency.

	All cases	EES (%)	TCS (%)	p value
No. of cases	273	88 (32.2)	185 (67.8)	
Mean tumor vol in cm^3 (SD)	8.2 (7.9)	7.5 (8.4)	8.7 (7.1)	0.48
Tumor consistency				
Cystic	80 (29.3)	23 (26.1)	57 (30.8)	0.48
Solid	59 (21.6)	18 (20.5)	41 (22.1)	0.88
Mixed	134 (49.1)	47 (53.4)	87 (47.1)	0.37
Pathological type				
Adamantinomas	247 (90.5)	77 (87.5)	170 (91.9)	0.27
Papillary	26 (9.5)	11 (12.5)	15 (8.1)	0.27

EES, endoscopic endonasal surgery; TCS, transcranial surgery.

Diabetes insipidus (DI) occurred in 45 (51.1%) patients and 134 (72.4%) patients in the EES group and TCS group, respectively, and the difference was statistically significant ($p < 0.05$).

Tumor Recurrence

During the follow-up period, tumor recurrence occurred in 11 (12.5%) and 44 (23.8%) of the patients in the EES and TCS groups. The difference was significant ($p < 0.05$). The average time to recurrence was 8.3 months and 7.4 months in the two groups; no statistical difference was seen.

DISCUSSION

Craniopharyngioma is a tumor of low histological malignancy (WHO grade I) resulting from an anomaly of embryonic development (1). There are two clinicopathological subtypes (adamantinomas and papillary) with different characteristics, and the adamantinoma type (90%) is far more common than the papillary type (10%). Although craniopharyngioma is a benign tumor, it is among the most challenging brain tumors to manage regarding high rates of complications and recurrence. Surgery is the main method of treatment, and there remains controversy as to the optimal surgical treatment. Traditionally, craniopharyngiomas were operated on *via* a subfrontal, pterional, orbitofrontal, transcallosal, or transcortical approach. Recently, the endoscopic endonasal approach, wherein the tumor is resected transsphenoidal, has become more important during the past decade (14, 15). TCS and EES both have advantages and disadvantages. It should be noted that directly comparing TCS to EES is complicated regarding inherent selection bias (16, 17). Generally, the endoscopic endonasal approach is a better choice for intrasellar lesions and midline lesions. In contrast to the transcranial approach, the endoscopic approach can easily reach the sellar and parasellar regions, thus providing better close-up visualization of the optic nerve, optic chiasm, and pituitary stalk, and minimizes the retraction of the brain (18). Koutourousiou et al. (19) and Jane et al. (20) held the view that suprasellar craniopharyngiomas were better treated with craniotomy. Should craniopharyngioma extend too far laterally or posteriorly, the endonasal approach may not provide an entire view of the tumor, making maximal resection unlikely. Cavernous sinus or hypothalamic involvement may complicate the surgical resection and cause significant increases in mortality. In these suprasellar or intraventricular lesions, the extended endoscopic endonasal surgery (EEES) may be applied to better remove the sella turcica, the tuberculum sellae, and the posterior part of the planum sphenoidale (21). The combined use of endoscopic and microscopic may achieve better surgical effects through better visualization and protection of neurovascular structures.

Typically, the surgical outcome is closely associated with the extent of resection (3, 7, 22). Reports showed that the extent of resection is an independent predictor of tumor recurrence (7, 16, 17, 23–25). However, the close association of these tumors with critical neurovascular structures and locally aggressive characteristics make GTR difficult and lead to controversies surrounding the extent of resection in patients with craniopharyngiomas (10, 11, 26). Furthermore, radiosurgery has been proven to have the potential for better outcomes and decreasing mortality (3, 27–29). Subtotal resection surgery combined with radiotherapy has been advocated to protect hypothalamus–pituitary function and prevent tumor

TABLE 3 | Main postoperative and perioperative complications.

Complications	All cases	EES (%)	TCS (%)	p value
No. of cases	273	88	185	
Hypopituitarism	173	47	126	0.02
Diabetes insipidus	179	45	134	<0.01
CSF leaks	4	4	0	0.01
Wound infection	10	2	8	0.51
Meningitis	6	2	4	1.00
Hemorrhage	5	2	3	1.00
Seizures	5	1	4	0.67
Death	0	0	0	1.00

CSF, cerebrospinal fluid; EES, endoscopic endonasal surgery; TCS, transcranial surgery.

recurrence (23). In addition, neurosurgical expertise has an important impact on the extent of resection (24, 30–32), and tumor size may be a predictor of the postoperative functional outcome. Giant craniopharyngioma is associated with higher neurological, endocrinological, and hypothalamic morbidities postoperatively (33). In the present study, we prefer to achieve GTR if possible. The relationships between the tumor and the hypothalamus, pituitary, and optic chiasm were fully evaluated based on preoperative imaging, and an appropriate approach was chosen to allow adequate exposure of the tumor to the microscopic or endoscopic view. In some complicated cases, intraoperative ultrasound and MRI were applied to assess the extent of resection. Carai et al. (34) revealed that intraoperative ultrasound had a very good predictive value in neurosurgery to assist in intracerebral disease resection and improved the assessment ability of surgical resection (34, 35).

Visual Outcomes

Visual impairment is the most common clinical manifestation affecting the quality of life of patients with craniopharyngioma. Approximately 62%–84% of patients present preoperative visual impairments (36). Endoscopic endonasal approach may have tremendous advantage in protecting the optic nerve and chiasm. In the current study, 74.5% of patients got visual improvement in the EES group, and in the TCS group, 56.3% of patients had improvement. Two patients in the TCS group got blind in one eye. The results were comparable to others. Some reports have found visual improvement rates reach 63% to 89% after endonasal resection while a lower rate of 25% to 53% after transcranial resection (17, 37).

The tumor often locates behind the optic nerve and optic chiasm, and it is inevitable to avoid retraction following the transcranial approach. In contrast, the endoscopic endonasal approach through the skull base can remove the tumor under direct close-up vision, which greatly reduces the retraction of optic nerves and chiasm (38). Qiao et al. (35) suggested that intraoperative visual evoked potential (VEP) can provide real-time warning for surgeons during the operation. In addition, optical coherence tomography (OCT) has become widely available and correlates well with the loss of visual function (39). It will be a more reliable outcome measurement compared to visual function testing and dilated fundoscopy in future studies.

Cerebrospinal Fluid Leaks

CSF leakage remains one of the most common postoperative complications. Abrasion of the skull base and opening of the subarachnoid space make the transnasal approach more prone to CSF leakage than craniotomy. We routinely used autologous thigh broad fascia and vascularized flap to reconstruct the skull base in reducing postoperative leaks. In our study, CSF leaks occurred in 4.5% of patients in the EES group and none in the TCS group. Patients were then recovered through treatment of continuous lumbar drainage and antibiotics. The results are comparable to other studies that reported CSF leak rates of less than 10% (40, 41). A higher body mass index (BMI) and perioperative hydrocephalus may have an impact on the occurrence of CSF leakage (42).

Postoperation Endocrine Deficits

Injury to the hypothalamic–pituitary axis, naturally, will cause endocrine deficits. Regardless of craniotomy or transnasal approach, the protection of hypothalamus and pituitary is the basis for GTR. In our study, DI occurred in 45 (51.1%) patients and 134 (72.4%) patients in the EES group and TCS group, respectively, consistent with other reports. The rate of endocrine deficits was reported to reach 52%–87% (2, 7, 27). During the operation, take care to identify and protect the superior hypophyseal arteries and pituitary stalk. Kawamata et al. (43) reported that preserving the pituitary stalk could reduce the risk of DI, nevertheless, increasing the risk of tumor recurrence. When dealing with craniopharyngiomas, sufficient preoperative discussion and preparation must be done, and treatment plans need to be individualized according to patient and tumor characteristics. Furthermore, a solid foundational knowledge of anatomy is imperative for decreasing the risks of surgery.

Tumor Recurrence

There were statistical differences in the recurrence rates (12.5% EES vs. 23.8% TCS, $p < 0.05$) between the 2 groups in our study. It has been reported that the recurrence incidence was 0%–30% in cases of total resection (7, 10, 11, 44, 45). Komotar et al. (46) reported a recurrence rate of 18.4% and 28.2% in the endoscopic and transcranial group, with no statistical difference. Craniopharyngiomas characteristically tend to recur in patients with subtotal resection or partial resection. Patients received a second operation or radiotherapy when diagnosed with recurrence. Irradiation is considered efficient in preventing further growth or recurrence (27). Additionally, the calcified or cystic part may affect the effectiveness of radiotherapy. There are still concerns regarding radiation-induced toxicities and the potential risk of cyst enlargement that could cause severe compressive effects.

In summary, the endoscopic endonasal approach for resection of craniopharyngioma has a higher rate of total tumor resection and postoperative visual deficit recovery rate than the craniotomy approach. It is also better in terms of pituitary function protection, but the CSF leakage rate is slightly higher. Limitations to this study include selection bias and the development of surgical techniques. Due to the short follow-up period in this study, further study is needed in order to compare the therapeutic effects of the two surgical methods. With the development of neuroendoscopic technology and the accumulation of clinical experience of the surgeon, EES will be used more for the surgical treatment of craniopharyngioma.

CONCLUSION

EES is associated with a superior visual outcome and lower rates of DI but has a higher risk for postoperative CSF leaks. These data support the view that EES is a safe and effective minimally

invasive surgery, providing a viable alternative resection with less neurological injury and lower recurrence rates.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Wuhan Union Hospital. The patients/participants or their legal guardian/next of kin provided written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CN: conceptualization, data curation, project administration, resources, formal analysis, software, visualization, and writing the original draft. YY: conceptualization, data curation, project administration, resources, formal analysis, software, visualization, and writing the original draft. JW: conceptualization, resources, investigation, and resources. HZ: supervision and writing—review and editing. XJ: conceptualization, investigation, resources, supervision, and writing—review and editing. HW: methodology, validation, data curation, writing—original draft, writing—review and editing, visualization, supervision, project administration, funding acquisition, resources, and data verification. All authors read and approved the final version of the article.

FUNDING

This study has received funding from the National Natural Science Foundation of China (81974390).

ACKNOWLEDGMENTS

This study has received funding from the National Natural Science Foundation of China (81974390), and the funders had role in study design and data verification.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 09 March 2022
doi: 10.3389/fneur.2022.783737

Craniopharyngioma and Metabolic Syndrome: A 5-Year Follow-Up Single-Center Experience

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Patients with craniopharyngioma often have comorbidities, such as obesity and hypopituitarism. These two conditions affect each other and worsen the quality of life of patients, which lead to a higher risk of morbidity and mortality. In addition, abdominal obesity, measured as waist circumference (WC), is together with other parameters [arterial hypertension, hyperglycemia, hypertriglyceridemia, and reduced levels of high-density lipoprotein (HDL) cholesterol], one of the components of metabolic syndrome (MS). Each one of these morbidities occurs in patients with craniopharyngioma more frequently than in the remaining population. On these bases, we evaluated metabolic parameters in patients with craniopharyngioma at the time of diagnosis and after a 5-year follow-up, which compares these data with those of age-, gender-, WC-, and body mass index (BMI)-matched controls. In addition, we evaluated the prevalence of MS according to IDF criteria (MS-IDF) and the prevalence of MS according to ATP III (MS-ATPIII) criteria in patients and controls at baseline and after 5 years. We recruited 20 patients with craniopharyngioma (age 38.5 ± 15 years, 10 M) and 20 age-, gender-, WC- and BMI-matched controls (age 34.16 ± 13.19 years, 10 M). In all patients and controls, we evaluated the following: anthropometric features [height, weight, BMI, WC, hip circumference (HC) and waist-to-hip ratio (WHR)], systolic blood pressure (SBP) and diastolic blood pressure (DBP), lipid profile [total cholesterol (TC), HDL, low-density lipoprotein (LDL) cholesterol, triglycerides (TG)], and blood glucose at baseline and after 5 years. The prevalence of MS, according to IDF and ATPIII criteria, was calculated in the two groups at baseline and after 5 years. According to our results, at baseline, patients with craniopharyngioma had a worse metabolic profile than controls and a higher prevalence of MS. Besides, at a 5-year follow-up, patients still had impaired metabolic characteristics and more frequent MS (according to IDF and ATPIII criteria) when compared to controls. These data confirm that MS in patients with craniopharyngioma is unresponsive to life-changing interventions and to a common pharmacological approach. Other factors may be involved in the evolution of these conditions; so, further studies are needed to establish the correct management of these patients.

Keywords: craniopharyngioma, obesity, metabolism, cardiovascular, hypothalamic

OPEN ACCESS

Edited by:
Edward Raymond Laws, Brigham and Women's Hospital and Harvard Medical School, United States

Reviewed by:
Hermann Lothar Mueller, Klinikum Oldenburg, Germany
Brent T. Harris, Georgetown University, United States

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Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Neurology

Received: *26 September 2021*
Accepted: *31 January 2022*
Published: *09 March 2022*

Citation:
Scarano E, Solari D, Riccio E, Arianna R, Somma T, Cavallo LM, Romano F, Colao A and Di Somma C (2022) Craniopharyngioma and Metabolic Syndrome: A 5-Year Follow-Up Single-Center Experience. Front. Neurol. 13:783737. doi: 10.3389/fneur.2022.783737

INTRODUCTION

Craniopharyngiomas represent 1–15% of all primary intracranial neoplasms (1–3) and 5.6–15% of intracranial tumors of children (2). Although it is the most common lesion involving the hypothalamic–pituitary area in children, about half of cases are diagnosed in adults (1, 3, 4), with a peak incidence around 65–74 years. The symptoms associated with the presence of craniopharyngiomas are due to the development of a space-occupying mass in a non-expandable region and are characterized by headache, visual changes, hydrocephalus, pituitary deficits, and hypothalamic disease (diabetes insipidus, obesity, dysphoria, numbness, temporal-spatial disorientation and alterations in the sense of hunger or thirst, sleep–wake rhythm, and thermoregulation) (5–12). In particular, the hypothalamic obesity associated with this condition is believed to be due to an alteration of both the signals that reach the hypothalamus from the periphery, mainly mediated by leptin, an anorectic action protein that induces a reduction in the sense of hunger and an increase of energy expenditure, and the signal that goes from the hypothalamus to the periphery, with an increase in vagal tone, insulin secretion, and adipogenesis (13–15).

Obesity is associated with severe metabolic and psychological consequences, inducing comorbidities, reduced quality of life, and life expectancy (13, 14). Furthermore, abdominal obesity, measured as waist circumference (WC), is, with other parameters such as arterial hypertension, hyperglycemia, hypertriglyceridemia, and reduced high-density lipoprotein (HDL) cholesterol levels, one of the components of the metabolic syndrome (MS), the elements of which occur, in patients with craniopharyngioma, more frequently than in the remaining population (16, 17).

On these bases, this study aimed to evaluate metabolic status in patients with craniopharyngioma at the time of diagnosis and after a 5-year follow-up, which compares these data with controls.

MATERIALS AND METHODS

The study was approved by the local ethics committee and complied with the Declaration of Helsinki, in line with the Guidelines for Good Clinical Practice. All patients provided written informed consent before entering the study, with respect to study participation, and confidentiality statement of data collection according to the Italian privacy policy.

Patients and Controls

We consequently recruited 20 patients with craniopharyngioma (age 38.5 ± 15 years, 10 M) followed at the outpatient clinic of the Department of Clinical Medicine and Surgery, Section of Endocrinology, the University of Naples"Federico II," Italy, from 2012 to 2018. All patients underwent surgical treatment for craniopharyngioma. In five patients, a subsequent radiotherapy treatment was also necessary (**Table 1**). Multiple pituitary deficits developed following these treatments, and therefore, where necessary, patients underwent replacement therapy with glucocorticoids, rhGH, thyroid hormones, testosterone, estrogen and progestogen, and desmopressin. **Table 2** shows pituitary deficits found at baseline and after 5-year follow-up (**Table 2**).We also recruited 20 controls (age 34.16 ± 13.19 years, 10 M) followed at the Department of Clinical and Surgical Medicine, Section of Endocrinology, the University of Naples"Federico II" between 2012 and 2018 for outpatient checkups, in which no endocrinological disease was found.

The prevalence of MS, according to IDF and ATPIII criteria, was calculated in the two groups at baseline and after 5 years. In both groups, moreover, there were patients undergoing therapy for hyperlipidemia, impaired glucose tolerance, and hypertension. These criteria were considered for the diagnosis of MS.

The characteristics of patients with craniopharyngioma (group 1) and controls (group 2) at the time of recruitment for the study and after 5-year follow-up are shown in **Tables 3, 4**. The two groups were comparable in age, gender, WC, and body mass index (BMI) at baseline (**Table 5**).

Parameters

All parameters were evaluated at baseline and after 3 months during the first year of follow-up and every 6 months during the following 5 year follow-up.

In all patients and controls, we evaluated anthropometric features [height, weight, BMI, WC, hip circumference (HC), and waist-to-hip ratio (WHR), systolic blood pressure (SBP), and diastolic blood pressure (DBP)] at baseline and after 5-year follow-up.

Body weight was measured in the morning to the nearest 0.1 kg, and body height was measured to the nearest 0.01 m when the subject was wearing light indoor clothes without shoes. BMI was calculated as body weight (in kilograms) divided by squared height (in squared meters). WC was measured with a soft tape, midway between the lowest rib margin and the iliac crest, in the standing position. HC was measured over the widest part of the gluteal region, and then, WHR was calculated.

Blood pressure was measured at the right arm with the patient in the sitting position. The average of three measurements using a mercury sphygmomanometer was calculated. Hypertension was diagnosed when SBP exceeded 140 mmHg and DBP exceeded 90 mmHg.

We also evaluated in both groups: lipid profile [total cholesterol (TC), HDL, LDL (low-density lipoprotein) cholesterol, triglycerides (TG)], and blood glucose at baseline and after 5 years. Fasting venous blood sampling was performed between 8 and 12 a.m. The blood samples were immediately centrifuged, and the sera were stored at a temperature of −80°C until they were analyzed. Serum levels of TC, HDL, and triglycerides were determined by an enzymatic method on fasting serum. LDL was calculated according to Friedewald's formula adjusted to SI units (18). Serum LDL-C was excluded in patients with serum triglycerides >400 mg/dl. Blood glucose was measured by fasting on serum or plasma samples.

The presence of MS was evaluated in the two groups at baseline and after 5 years according to both the IDF and the ATPIII criteria. Thus, using the IDF criteria, the subject with abdominal obesity, defined as a WC >94 cm for men and WC >80 cm for women, was considered to have MS,

TABLE 1 | Patients' treatments.

Treatment	No. of Patients
Surgery	15
Surgery + Radiotherapy	5
Total	20

with at least two of the following factors: high values of TG value: >150 mg/dL or specific treatment for such dyslipidemia, reduced HDL-C values: <40 mg/dL in men and <50 mg/dL in women or hypercholesterolemia, high BP >130/85 mm/Hg or hypertension treatment, high fasting blood glucose: >100 mg/dL or diagnosis of type 2 diabetes mellitus (19, 20). Using the ATPIII criteria, the subject was considered to have MS if they had three of the following factors: abdominal obesity, defined as a WC >102 cm for men and WC >88 cm for women, high values of TG value: >150 mg/dL or specific treatment for such dyslipidemia, reduced HDL values: <40 mg/dL in men and <50 mg/dL in women or hypercholesterolemia, high BP > 130/85 mm/Hg or hypertension treatment, high fasting blood glucose: >100 mg/dL or diagnosis of type 2 diabetes mellitus (21). Hypopituitarism was diagnosed based on the clinical manifestations, the baseline assessment of pituitary function, and the stimulus test, according to the Clinical Practice Guidelines of the Endocrine Society (22). Peripheral venous blood samples were taken in the morning between 8 and 10 a.m., after fasting for at least 8 h and conserving at −80°C until processing. Hormonal profile evaluation [growth hormone (GH), insulin-like growth factor 1 (IGF-1), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), adrenocorticotropic hormone (ACTH), cortisol, and prolactin] was performed by chemiluminescence immunoassay (CLIA). We performed biochemical assays [GH, IGF-I, TSH, free thyroxine (FT4), free triiodothyronine (FT3), FSH, LH, estradiol, testosterone, ACTH, cortisol, and prolactin] and thyroid and abdomen ultrasound in controls to exclude endocrinological diseases.

Statistical Analysis

Data were reported as mean ± SD or as percentages. For all variables, within-group differences were calculated using a repeated-measures ANOVA, followed by a *post hoc* analysis performed using Bonferroni or Student–Newman–Keuls tests where applicable. The Student's *t*-test was used for intergroup–intragroup comparison. Then, the prevalence of MS according to both IDF and ATPIII criteria was calculated for the evaluation of intergroup–intragroup differences, with Fisher's exact test; significance was set at 5%. Data were analyzed using the SPSS Software (PASW version 21.0, SPSS Inc., Chicago, IL, USA) and MedCalc® package (version 12.3.0 1993-2012 MedCalc Software bvba-MedCalc Software, Mariakerke, Belgium).

TABLE 2 | Number of pituitary deficiencies in the study population at baseline and after 5-year follow-up.

No. of deficiencies	Baseline	5 years
Isolated deficiency	0	0
1 additional deficiency	1	1
2 additional deficiencies	8	3
>3 additional deficiencies/3+DI	11	16

DI, Diabetes insipidus.

TABLE 3 | Clinical features of patients (group 1) at baseline and after 5-year follow-up.

Parameters	Baseline	5 years	*P*
BMI (kg/m^2)	30.92 ± 8.19	32.74 ± 9.41	NS
WC (cm)	100.15 ± 18.63	101.95 ± 19.9	NS
HC (cm)	106.90 ± 13.39	110.35 ± 13.88	NS
WHR	0.91 ± 0.17	0.92 ± 0.14	NS
SBP (mmHg)	120.9 ± 12.58	120.8 ± 14.85	NS
DBP (mmHg)	73.35 ± 8.1	78.0 ± 11.4	NS
TC (mg/dL)	222.8 ± 39.56	203.0 ± 39.4	NS
LDL (mg/dL)	150.23 ± 39.38	133.63 ± 35.02	NS
HDL (mg/dL)	41.9 ± 10.18	40.5 ± 11.8	NS
TG (mg/dL)	152.3 ± 48.03	147.5 ± 51.06	NS
Fasting glucose (mg/dL)	98.3 ± 15.2	97.03 ± 12.87	NS

BMI, body mass index; WC, waist circumference; HC, hip circumference; WHR, waist-to-hip ratio, SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TG, triglycerides.

RESULTS

Body Composition and Blood Pressure

There was no statistical difference in the patient group and in the control group at baseline and after 5 years in body composition (weight, BMI, WC, HC, WHR) (**Tables 3**, **4**) and between patients and controls for the same parameters at the two study time points (**Table 5**). Some differences were found in blood pressure. In particular, SBP was higher in patients than controls at baseline and after 5-year follow-up ($p = 0.032$ and $p = 0.000$, respectively) (**Table 5**). Moreover, in the control group, SBP significantly increased after 5 year follow-up ($p = 0.000$) (**Table 4**). At the end of the study, DBP was higher in patients than controls ($p = 0.018$) (**Table 5**).

Lipid Profile and Glucose Metabolism

Total cholesterol and LDL were found higher in the patient group than the control group at baseline (TC; $p = 0.004$, LDL; $p = 0.000$) and after 5-year follow-up (TC; $p = 0.040$, DL; $p = 0.005$) (**Table 5**). HDL was found higher in controls than patients at the start and at the end of the study ($p = 0.004$ and $p = 0.000$, respectively) (**Table 5**). No differences

TABLE 4 | Clinical features of controls (group 2) at baseline and after 5-year follow-up.

Parameters	Baseline	5 years	*P*
BMI (kg/m^2)	29.17 ± 6.17	29.08 ± 6.18	NS
WC (cm)	99.22 ± 17.55	98.8 ± 17.16	NS
HC (cm)	106.87 ± 12.75	105.98 ± 11.73	NS
WHR	0.92 ± 0.08	0.93 ± 0.09	NS
SBP (mmHg)	114.3 ± 4.3	100.1 ± 13.3	0.000
DBP (mmHg)	72.8 ± 8.61	68.31 ± 13.42	NS
TC (mg/dL)	183.56 ± 41.59	180.4 ± 26.6	NS
LDL (mg/dL)	105.76 ± 38.5	101.6 ± 32.12	NS
HDL (mg/dL)	52.4 ± 11.51	54.62 ± 11.61	NS
TG (mg/dL)	128.04 ± 33.86	123.12 ± 38.41	NS
Fasting glucose (mg/dL)	92.33 ± 14.84	91.74 ± 10.32	NS

BMI, body mass index; WC, waist circumference; HC, hip circumference; WHR, waist-to-hip ratio, SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TG, triglycerides.

TABLE 5 | Comparison between patients (group 1) and controls (group 2) at baseline and after 5-year follow-up.

	Baseline	5 years
Parameters	***P* Group 1 vs. 2**	***P* Group 1 vs. 2**
BMI	NS	NS
WC	NS	NS
HC	NS	NS
WHR	NS	NS
SBP	0.032[a]	0.000[a]
DBP	NS	0.018[a]
TC	0.004[a]	0.040[a]
LDL	0.000[a]	0.005[a]
HDL	0.004[b]	0.000[b]
TG	NS	NS
Fasting glucose	NS	NS

a: 1 > 2; b 2>1.
*BMI, body mass index; WC, waist circumference; HC, hip circumference; WHR, waist-to-hip ratio, SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TG, triglycerides. NB, data of parameters of each group are shown in **Tables 3**, **4**.*

between the two groups were found for TG and blood glucose (**Table 5**).

Prevalence of MS

At baseline and after 5-year follow-up, no differences were found in the patient group (**Table 6**) and the control group (**Table 7**) regarding the prevalence of MS. At baseline, patients had a significantly higher prevalence of MS than controls according to IDF criteria and a near significantly higher prevalence according to ATPIII criteria ($p = 0.037$ and $p = 0.058$, respectively). At the end of the study, the prevalence of MS was higher in patients according to both IDF and ATPIII criteria ($p = 0.028$ and $p = 0.028$, respectively) (**Table 8**).

TABLE 6 | The prevalence of metabolic syndrome (MS) in patients (group 1) at study entry and after 5-year follow-up.

Patients		MS-IDF *n* (%)	MS-ATPIII *n* (%)
Group 1	Baseline	6 (30)	7 (35)
(20 patients)	5 years	8 (40)	8 (40)
	P	NS	NS

MS-IDF, metabolic syndrome according to IDF criteria; MS-ATPIII, metabolic syndrome according to ATPIII criteria.

TABLE 7 | The prevalence of MS in controls (group 2) at study entry and after 5-year follow-up.

Patients		MS-IDF *n* (%)	MS-ATPIII *n* (%)
Group 2	Baseline	1 (5)	2 (10)
(20 patients)	5 years	2 (10)	2 (10)
	p	NS	NS

MS-IDF, metabolic syndrome according to IDF criteria; MS-ATPIII, metabolic syndrome according to ATPIII criteria.

TABLE 8 | Differences in prevalence of MS at study entry and after 5-year follow-up between patients (group 1) and controls (group 2).

	Group	MS-IDF *n* (%)	MS-ATPIII *n* (%)
Baseline	1	6 (30)	7 (35)
	2	1 (5)	2 (10)
	p	0.037	0.058
5 years	1	8 (40)	8 (40)
	2	2 (10)	2 (10)
	P	0.028	0.028

Group 1, patients; group 2, controls; MS-IDF, metabolic syndrome according to IDF criteria; MS-ATPIII, metabolic syndrome according to ATPIII criteria.

DISCUSSION

This is a single-center retrospective observational study on the long-term prevalence of MS in adult patients with craniopharyngioma compared with age-, sex-, WC-, and BMI-matched controls.

Up to now, the studies that have investigated the metabolic aspect of this disease have been conducted above all in pediatric patients (16, 17, 23, 24). Some studies have evaluated the prevalence of MS in pediatric patients with craniopharyngioma (16, 17, 23, 24). Srinivasan et al. (16) and Sahakitrungruang et al. (17) found that children and adolescents treated for craniopharyngioma had a higher prevalence of altered MS parameters, in particular abdominal obesity and lipid profile, compared with healthy controls of the same age, sex, BMI, and pubertal status. Moreover, these conditions were directly correlated with age: the greater the age, the greater the alteration.

Metabolic impairments that appear in patients with craniopharyngioma are probably due to the hypothalamic involvement, because of the prevalent localization of craniopharyngiomas near the hypothalamus. In fact, the extension of tumor at this level can cause an alteration in the ventromedial portion of the hypothalamus and can induce, through a wrong regulation of hunger and satiety mechanisms, severe obesity (25, 26).

In particular, some authors (13, 25) have studied the pathogenetic mechanism that leads to "hypothalamic" obesity by identifying alterations both in the afferent signal, from the periphery to the hypothalamus, and in the efferent one, from the hypothalamus to the periphery. In fact, in these patients, leptin, a protein with an anorectic action that reduces the sense of hunger and increases energy expenditure, has an impaired function that is associated with increased insulin secretion, vagal tone, and adipogenesis (13, 15, 25). Moreover, a higher preoperative BMI seems to be an important risk factor for developing postoperative hypothalamic obesity (27).

On the other hand, it is known that obesity is linked to metabolic and psychological consequences, and it is also associated with arterial hypertension, hyperglycemia, hypertriglyceridemia, and reduced levels of HDL cholesterol, which are the components of the MS (28, 29).

Some authors focused metabolic attention on the adult population (30–33), and our results are in agreement with these, which confirm a higher prevalence of MS in patients with craniopharyngioma in adulthood. In particular, the major alterations regarded the lipid profile (30, 31).

In this study, at baseline, all subjects were selected to match BMI and WC as well as gender and age.

After 5 years of follow-up, although there was a higher prevalence of MS in patients than controls, weight and BMI were not different. This could be partially justified by the fact that MS in our patients is related not much to weight or BMI but to other parameters.

In fact, in our cohort, we found higher levels of TC and LDL values in patients at the first and the late evaluation compared with controls. In addition, in our study, patients had a worse HDL profile than controls.

Furthermore, in our sample, SBP and DBP were significantly higher in patients than controls after 5-year follow-up. These conditions contribute to the finding of higher MS prevalence in this group and are in line with literature data (31).

In our patients' group, metabolic parameters did not significantly improve during follow-up, despite the disease treatment and usual medical indications for metabolic impairments. Probably, other non-classical mechanisms are involved in the metabolic impairment of patients with craniopharyngioma. In this context, a new hypothesis spreads about the alterations of circadian rhythm (34).

Our findings reveal that patients with craniopharyngioma have a higher cardiometabolic risk than the control population. In fact, cardiometabolic risk is defined as a condition favorable to the development of type 2 diabetes mellitus and cardiovascular pathologies (35, 36). Key elements are abdominal obesity, insulin resistance, and metabolic abnormalities, such as high levels of triglycerides, total and LDL cholesterol levels, and low HDL cholesterol levels (37).

This is one of the few Italian studies to consider only patients with craniopharyngioma compared to the general population in a single center for a such long follow-up period. Points of the strength of this study are the presence of a control group, the absence of them in some of the studies analyzed (30, 32, 33), and the single-center recruitment reducing the possibility of any selection bias.

Limitations of this study are the absence of data on ethnicity, lifestyle factors, and histological subtypes of craniopharyngioma. Furthermore, the body composition and the percentage of fat have not been measured with dual-energy X-ray absorptiometry (DXA), which is considered the best predictor of the risk of developing cerebrovascular and cardiovascular events (38, 39).

Another limitation is the relatively small number of samples even though we are talking about a rare disease.

In conclusion, this study demonstrated a higher prevalence of MS in patients with craniopharyngioma compared with the general population.

An alteration in the lipid profile and blood pressure was evident in patients compared with controls, but there were no significant differences with the values recorded at baseline and at 5-year follow-up, by considering the two groups separately. It remains to be established whether, in patients with craniopharyngioma, other non-classical mechanisms are involved in metabolic impairment. In particular, there is some interest in the evidence of a correlation among circadian rhythm alterations, different chronotypes, and diseases. According to this evidence, the sleep–wake regulatory system and circadian rhythm synchronization could play an additional key role to provide new indications in the management of craniopharyngioma comorbidities. Further studies, therefore, appear necessary in this regard. It may be useful, in the future, for larger-scale and longer follow-up studies to analyze the increase in the prevalence of MS and mortality in adult patients with craniopharyngioma.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato Etico Università Federico II, Dipartimento di Medicina Pubblica e della Sicurezza Sociale-Sezione di Medicina Legale, Università Federico II, Naples Italy. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ES and CD were responsible for the concept of this paper and drafted the manuscript. DS, ER, RA, TS, LC, FR, and AC provided a critical review of the paper. All authors contributed to the article and approved the submitted version.

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frontiers in Oncology

OPINION
published: 22 March 2022
doi: 10.3389/fonc.2022.872689

Craniopharyngioma and the Third Ventricle: This Inescapable Topographical Relationship

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Keywords: craniopharyngioma, hypothalamus, papillary craniopharyngioma, pituitary infundibulum, third ventricle, third ventricle floor

INTRODUCTION

The Third-Ventricle Craniopharyngioma Surgical Challenge, a Hot Topic in Frontiers in Oncology

Craniopharyngiomas (CPs) are widely categorized as a group of benign epithelial tumors developed around the region of the sella turcica (1). However, from a surgical viewpoint, CPs have consistently been considered a particularly challenging intracranial tumor, owing to their close relationship to the hypothalamus and their biological infiltrating behavior (2, 3). The exceedingly heterogeneous CP topography and their usual extension into the third ventricle (3V) remain significant impediments to standardize a common management (4). Consequently, a wide array of surgical approaches, resection philosophies and adjuvant treatment guidelines have been employed and advocated, with no clear consensus being reached among authors (5, 6).

In the last decade, the experience gained from using the endonasal endoscopically assisted approach (EEA) has made this technique the gold standard for treating most sellar and suprasellar CPs (7, 8). Nevertheless, a high rate of CPs develop primarily at the infundibulo-tuberal region of the third ventricle floor (3VF) and expand within the 3V, above an intact pituitary gland and stalk (9, 10). The pervasive problem of identifying a "safe" cleavage plane through the tenacious adherence between the CP and the adjacent hypothalamus has remained the major obstacle for radical excision of infundibulo-tuberal CPs employing the EEA (11, 12) This difficulty becomes particularly delicate when dealing with papillary CPs (PCPs) having a strict or intrinsic 3V location, for which the EEA was originally regarded unsuitable and too risky, as it forced breaking through the seemingly functional 3VF, a maneuver that could potentially cause irreversible hypothalamic sequelae (13, 14). Therefore, transcranial-transventricular methods of approach have been employed to remove these intraventricular CPs, usually through the corpus callosum or by opening the lamina terminalis, a choice based on an accurate preoperative MRI diagnosis of the strict 3V topography (15–17).

Frontiers in Oncology's research topic, "*Advances in craniopharyngiomas: from physiology to clinical management*" gathers a series of papers specifically focused on the clinical assessment and surgical treatment of the subgroup of intrinsic or strictly 3V CPs (18–21). The studies by Deopujary

OPEN ACCESS

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Reviewed by:
Edward Laws,
Harvard University, United States

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Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: *09 February 2022*
Accepted: *28 February 2022*
Published: *22 March 2022*

Citation:
Pascual JM and Prieto R (2022) Craniopharyngioma and the Third Ventricle: This Inescapable Topographical Relationship. Front. Oncol. 12:872689. doi: 10.3389/fonc.2022.872689

Abbreviations: ACP, adamantinomatous craniopharyngioma; CP, craniopharyngioma; MRI, Magnetic Resonance Imaging; PCP, Squamous-papillary craniopharyngioma; 3VF, third ventricle floor; 3V, Third ventricle.

et al. and Zhao et al. direct their attention on the physiological and neuropsychological disturbances derived from the hypothalamic injury caused by resecting intra-3V CPs (18, 19). The feasibility of combining the extended endonasal endoscopically assisted approach (EEEA) with a trans-lamina terminalis (TLT) access to successfully remove strictly 3V CPs is the major objective of Cao et al. and Zhou et al. papers (20, 21). Potentially, a paradigm shift in the surgical method of choice to remove 3V CPs might occur from these studies, from the dominant use of transcranial-transventricular routes to a generalized use of the EEEA plus TLT (5, 22). Beyond that, however, all these works can shed light on the specific pathological features and hypothalamic alterations associated with infundibulo-tuberal and strictly 3V CPs, two topographical categories which need to be differentiated from the rest of sellar/suprasellar lesions (10).

The Craniopharyngioma-3V Relationship: Anatomical and Neuroradiological Evidence

For the last decades, our team has analyzed the anatomical relationships between CPs and the adjacent 3V that can be accurately defined in well-characterized individual CP reports (12, 23–25). Thus far, our research involves the exam of more than 1,000 autopsied CP specimens from non-operated patients and the correlation between the CP-3VF relationship observed on preoperative MRI scans and surgical findings in about 2,700 CP patients. This body of evidence has enabled us to differentiate four basic CP-3V relationships, which depend on the original site of CP development (beneath, within or above the 3VF) and the 3VF distortion pattern (3VF displaced upwards, expanded by the tumor or invaded by the tumor) (23, 24). In contrast to other CP classification methods, our scheme focuses on the way the 3V is affected by the lesion. Acknowledging the type of CP-3V relationship allows to define a set of clinical-pathological CP features specific to each topographical category. Even more importantly, a 3V-centered scheme also helps to predict the extension and strength of the CP-hypothalamic attachment, which largely determines the risk of radical removal (12, 26, 27). The works by Deopujarny et al., and Cao et al., whose surgical series encompass more than 800 CPs, have verified to a large extent our topographical concepts (18, 20). The attention that should be given to the hypothalamic symptoms caused by 3V CPs and the types of CP-hypothalamus attachment associated with this topography is the main message we wish to emphasize from these studies published in *Frontiers in Oncology*.

Craniopharyngiomas With a Primary Intra-3V Development: Types and Distinctive Features

Two major CP topographies primarily originate within the neural tissue of the infundibulum and tuber cinereum, the components of the 3VF: the not strictly intraventricular or infundibulo-tuberal, which expands within the 3VF itself and replaces it progressively; and the strictly intraventricular, which, owing to its subependymal origin, mostly expands within the 3V cavity above a stretched but anatomically intact infundibulum (9, 28) (**Figure 1**). Both types represent lesions primarily affecting the hypothalamus, which means that the tumor is partly or wholly embedded within the 3VF, often encircled by a band of non-functional gliotic tissue (10). Infundibulo-tuberal CPs constitute approximately 40% of lesions in the adult CP population. The majority belong to the adamantinomatous type (ACPs) and show the strongest and riskiest attachments to the hypothalamus (28). The scarcer subgroup of strictly 3V CPs only comprises about 5% of cases, also involves predominantly adults (92%) and largely includes lesions of the papillary type (82%). Strictly 3V PCPs characteristically present weaker, lower-risk attachments to the 3VF than not strictly intraventricular ACPs (12, 23). Interestingly, despite their more benign attachment, these PCPs with an intrinsic or strict intra-3V development very often cause a wide range of psychiatric disturbances (in up to 60% of patients), owing to the severe tumoral compression upon the hypothalamus (10, 29). These emotional, behavioral and cognitive alterations, poorly addressed in most surgical CP series, represent a true organic model of psychiatric disease of great potential relevance for elucidating the neurobiological basis of psychiatric disorders (29).

More recently, we were able to compile and analyze comprehensively the cohort of CPs with a verified strictly 3V topography (n=245), as well as the historical cohort of well-described papillary CPs published in the medical literature (n=350) (30, 31). Although the strictly 3V topography has remained controversial throughout history, some authors considering it an exceptional, ectopic location (32), while others even argue over its validity (33), the surgical series by Depoujarny (18), Cao (20), and Zhou (21) contribute to verify this particularly challenging location, confirming the anatomical integrity of the 3VF found in numerous strictly 3V CPs in prior studies (see **Table 1**) (34–49). The optimal surgical view of the brain undersurface obtained through the EEA unequivocally show the ballooned and stretched infundibulum wrapping around the lower pole of these lesions, which stay hidden within the 3V chamber (13, 14, 40, 46). In 5 out of 6 strict CP cases in the series by Cao (83%) and 6 out of 9 in Zhou's paper (66%), the lesions corresponded to the papillary type, percentages that fit well with the 82% rate of papillary lesions found in our systematic review (20, 21, 30). Depoujarny observed preoperatively symptoms related to hypothalamus dysfunction in 60% of their 3V CP patients overall, the most prominent being memory loss (25%), increased sleepiness (20%) and abnormal uninhibited behaviors, including hyperphagia (36%) (18). These figures also match with the rate of mental alterations in strictly 3V CPs (59%) and papillary CPs (50%) identified in our reviews (30, 31). Visual and endocrine symptoms, typical of ACPs with a suprasellar location below the 3V, were, however, rather low, in the range between 40-55% in both Depoujarny and Zhou studies (18, 21).

The Combined EEA-Translamina Terminalis Approach for Strictly 3V CPs: A Promising Surgical Strategy

The controversy about what should be the optimal surgical strategy for strictly 3V CPs has remained unresolved ever since. The complex problem of dealing with the CP-hypothalamus

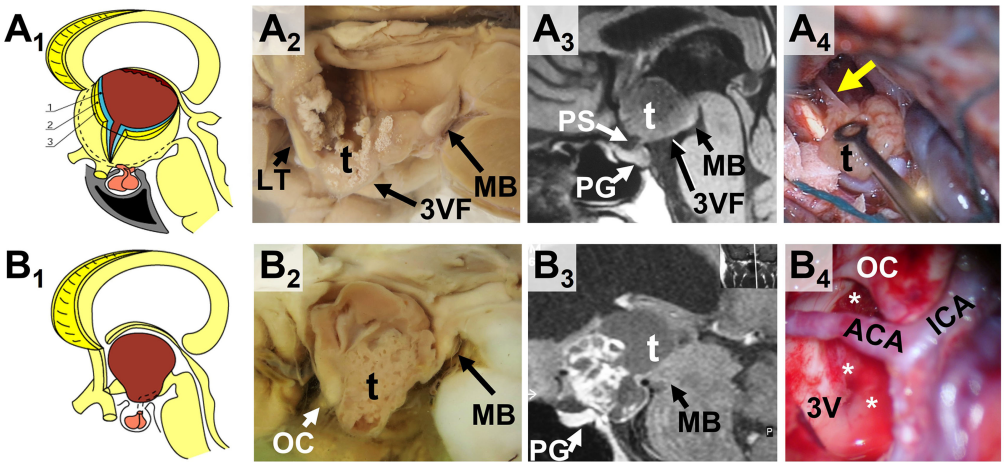

FIGURE 1 | Craniopharyngiomas with a primary third ventricle development (3V CPs): comparison between the two major 3V CP topographies. **(A_1-A_4)** The strictly 3V topography. The upper row panels show the anatomical **(A_1)**, gross pathological **(A_2)**, neuroradiological **(A_3)** and surgical **(A_4)** evidence for the strictly or truly 3V CP topography. **(A_1)** Anatomical sketch showing a CP wholly confined within the 3V cavity, above an intact third ventricle floor (3VF). The three layers that forms the 3VF, ependyma (1), the 3VF neural tissue including the median eminence and infundibulum (2) and the pia mater (3) remain intact below the tumor, originated at a subependymal position. **(A_2)** Midsagittal section of a gross pathological CP specimen with a strict 3V topography. A tenuous, but still present 3VF layer covers the basal boundary of the tumor. LT: Lamina terminalis; MB: mammillary body (Original brain specimen from the Vienna anatomical-pathological collection, housed at the Narrenturm). **A_3** T1-weighted MRI midsagittal scan of a strictly 3V CP diagnosed in a 46-year-old female patient showing headache, blurred vision with homonymous left inferior quadrantanopia, diabetes insipidus and a depressive disorder for 1 year. Notice how this largely solid tumor of the papillary type (t) is entirely confined within the 3V, above an intact 3VF and pituitary stalk (PS) and gland (PG). **(A_4)** Intraoperative image showing the narrow, pedicle-like CP attachment (yellow arrow) to the 3VF of a strict 3V papillary CP. **(B_1-B_4)** The infundibulo-tuberal or not strictly 3V topography. The lower row panels show the anatomical **(B_1)**, gross pathological **(B_2)**, neuroradiological **(B_3)** and surgical **(B_4)** evidence for the not strictly 3V CP topography, also known as infundibulo-tuberal. **(B_1)** Anatomical sketch showing a CP replacing the 3VF and largely occupying the 3V cavity. The lesion has primary developed at the neural layer of the 3VF (infundibulum and/or tuber cinereum) replacing progressively the 3VF while expanding into the 3V cavity. **(B_2)** Midsagittal section of a gross pathological CP specimen with an infundibulo-tuberal topography. The lower pole of this chiefly solid 3V CP (t) protrudes towards the suprasellar cistern after replacing the region of the infundibulum-tuber cinereum. The mammillary bodies (MB) are the only remaining structures of the 3VF. OC: optic chiasm (Original brain specimen from the Vienna anatomical-pathological collection, housed at the Narrenturm). **(B_3)** T1-weighted MRI midsagittal scan of an infundibulo-tuberal CP diagnosed in a 32-year-old male patient showing blurred vision with bitemporal hemianopia, progressive obesity, hyperphagia, unmotivated rage episodes, and memory disturbances for the last months. Notice how this large, solid-cystic CP of the adamantinomatous type (t) has replaced the 3VF and the infundibulum-pituitary stalk, occupying both the 3V cavity and the suprasellar cistern, above an intact pituitary gland (PG). **B_4** Intraoperative image of the 3V after total removal of the tumor through a trans-lamina terminalis approach. Notice the hemorrhagic border of the breached 3VF (white asterisks) corresponding to the ring-like band of tight attachment between the hypothalamus and the central CP region, often found for infundibulo-tuberal or not strictly 3V CPs. ACA, Anterior communicating artery; ICA, Internal carotid artery. OC, optic chiasm.

plane of adherence within the 3V under a good direct view has stimulated the use of multiple transcranial routes, mainly the frontal-transventricular, the transcallosal and the translaminar-terminalis (3, 5, 34, 36). Notably, Depoujarny found strong adherences between the CP capsule and the 3VF/3V walls in 36% of cases, mainly among pure cystic lesions in which the tumor capsule had merged with the 3V boundaries (18). These high-risk adherences in strictly or largely 3V CPs more often develop in the adamantinomatous type (58%) than in the papillary one (25%), the latter usually presenting either a small pedicle-like attachment or a sessile, flat patch adherence to the infundibulum (23, 31). Strong CP-hypothalamic attachments are the main obstacle precluding a safe radical removal of the lesion, a goal only reached in 40% of Depujany's series employing transcranial procedures (18). The more accurate assessment of the CP-3VF relationship achieved through the EEA over these open craniotomy-transventricular procedures, has changed the surgical paradigm towards the standard use of this approach to safely remove CPs involving the 3V (7, 8, 13, 40). Now, the expertise gained with the use of the EEEA allowed pituitary surgeons to incorporate the translaminar terminalis corridor to the technique to successfully remove strictly 3V CPs without mortality, as shown in the series by Cao (87.5% gross total removal, GTR) and Zhou (89% GTR) (20, 21). Accordingly, should this combination of EEEA plus TLT technique be considered the definitive method capable of overcoming the impediment of CP adherence and/or infiltration into the hypothalamus intrinsic to intra-3V development? (26, 28, 33, 50).

In our 2004 comparative analysis of the surgical approaches employed to remove intraventricular CPs up to that date, all performed through open craniotomies, we found that the TLT approach was superior to the others (transcallosal and frontal-transventricular) in terms of null postoperative mortality (23). Notably, partial degrees of tumor removal yielded poorer postoperative outcomes than total excisions, an apparently paradoxical result highlighting the damaging effect that unsuccessful attempts to dissect tight CP-hypothalamic adhesions had on the ultimate clinical outcome. The results of this research may be cautiously extrapolated to define the current indications for total removal of strictly 3V CPs employing the

TABLE 1 | Epidemiological, clinico-pathological and surgical characterization of third ventricle craniopharyngiomas (3V CPs) included in modern CP surgical series.

CP series/ Year [ref]	No. 3V CPs/ Adults Rate	Rate 3V CPs/ Total No. CPs	Histology Types	Hypothalamic/ Psychic symptoms	Main Approach/ GTR rate	Mortality/ Postop H.I. †	Recurrence/ Follow-up
Yasargil et al. (34)	7 100% A	4% 162	NA	NA	TC: 100% 100%	NA	NA
Davies et al. (35)	6 100% A	NA	3 pCP 3 aCP	16.5% Psychic: 16.5%	TLT: 100% 66%	0% 80%	50% 8 y
Maira et al. (36)	8 100% A	11% 72	2 pCP 6 aCP	25% Psychic: 25%	TLT: 100% 87.5%	12.5% (1y) 25%	14% 5 y
Behari et al. (37)	6 66% A	8% 75	NA	33% Psychic: 33%	TC: 50% 50%	16.6% 16.6%	0% 3 y
Pascual et al. (23)	105 85% A	NA	29 pCP 29 aCP	55% Psychic: 40%	FTV/TC: 68% 55%	29% 18%	NA
Sohma et al. (38)	5 4 A	NA	3 pCP 2 aCP	40% Psychic: 40%	TLT: 100% 100%	0% NA	20% 5 y
Shi et al. (39)	23 NA	8% 284	NA	NA	TLT: 56% 74%	NA	NA
Pan et al. (15)	17 15 A	8,7% 195	6 pCP 11 aCP	47% Psychic: 47%	TLT: 100% 76.5%	12% 12%	17.5% 4 y
Jung et al. (16)	4 100% A	NA	4 aCP	0%	TC: 100% 100%	0% 0%	50% 4y
Cavallo et al. (40)	12 92% A	29% 41	NA	16.6% NA	EEA: 100% 66.7%	8.3% 18%	9% 1y
Yu et al. (41)	24 100% > 15y	3% 830	10 pCP 14 aCP	33.3% Psychic: 33.3%	TC: 62.5% 79%	12.5% 8%	25% 4 y
Morisako et al. (42)	12 Mean age: 45	16.5% 72	2 pCP 10 aCP	33% Psychic: 25%	TLT: 100% 75%	0% 25%	0% 4 y
Zoli et al. (43)	10 100% A	NA	5 pCP 5 aCP	100% Psychic: NA	EEA: 100% 80%	0% 20%	10% 1 y
Nishioka et al. (44)	3 2 A	NA	2 pCP 1aCP	0% Psychic: NA	EEA: 100% 100%	0% 33%	0% 1 y
Mortini (45)	6 100% A	NA	NA	66.6% Psychic: 50%	TLT: 100% 100%	0% 33%	0% 2.5 y
Forbes et al. (46)	10 100% A	12.5% 80	3 pCP 7 aCP	40% Psychic: 20%	EEA: 100% 90%	0% 30%	20% 4 y
Seo et al. (47)	26 76% A	34% 76	11 pCP 15 aCP	23% Psychic: 19%	EEA: 100% 88.5%	0% NA	3.8% 3y
Fan et al. (48)	26 92% A	11.5% 223	5 pCP 19 aCP	34.5% Psychic: NA	EEA: 100% 92%	0% 34.5%	4% 1 y
Hung et al. (49)	5 100% A	NA	5 pCP	NA	FTV: 4; TLT: 1 NA	NA	NA
Deopujari et al. (18)	25 NA	4.3% 585	NA	60% Psychic: 44%	FTV: 56% 40%	8% 30%	20% 3y
Zhao et al. (19)	17 NA	10% 173	NA	NA Psychic: 47%	NA	NA	NA
Cao et al. (20)	8 100% A	5.3% 149 SS *	6 pCP 2 aCP	37.5% Psychic: 12.5%	EEA-TLT: 100% 100%	0% 12.5%	12.5% 1 y
Zhou et al. (21)	9 100% A	NA	6 pCP 3 aCP	33% NA	EEA-TLT 89%	0% 0%	0% 2.5y
Prieto et al. (30)	245 93% A	5.6% 3,821	182 pCP 33 aCP	65% Psychic: 59%	TLT: 41%; FTV/TC:41% 52%	3.3% ** 23%	14.5% 3 y

A, adults; aCP, adamantinomatous type; CP, craniopharyngioma; EEA, endonasal endoscopic approach; FTV, frontal transventricular approach; GTR, gross total removal; H.I., hypothalamic injury†; NA, not available; No., number; pCP, papillary type; postop, postoperative; TC, transcallosal; TLT, trans lamina terminalis; y, years; 3V, third ventricle.

**Suprasellar tumors; **Mortality rate for the tumors operated on in the most recent period between 2006-2021 (n=61).*

†Postoperative hypothalamic injury rates include any of the following worsening of and/or sequelae: severe obesity (> 30% of BMI) with hyperphagia, severe hydroelectrolytic or autonomic disturbances, hyperthermia/poikilothermic dysfunction, gait ataxia, sphincters incontinence, psychiatric disturbances, Korsakoff-like memory defects and/or cognitive decline, all preventing autonomous life.

trans-infundibular and translamina-terminalis corridors through the EEEA. Undoubtedly, in expert hands this procedure offers the great advantage over transcranial methods of allowing an easier sharp dissection of the CP-hypothalamic plane of adherence from the initial stages of surgery (13, 20, 40). It also ensures the preservation of the hypothalamus and chiasm blood supply through basal perforating vessels, which usually remain hidden from view when employing transcranial approaches. Avoiding mechanical and ischemic injuries to the hypothalamus caused by forceful blind pulling maneuvers on the intra-3V tumor bulk is essential for the postoperative improvement of psychiatric and neuropsychological disturbances, as is shown in the study by Zhao (19, 51). Nevertheless, the type of CP-hypothalamic attachment is the crucial factor determining the possibility of eventually accomplishing a successful total removal (4, 26).

CONCLUDING REMARKS

The infiltrative nature of CPs developed at the infundibulo-tuberal region, with finger-like tumor extensions protruding into the adjacent hypothalamus has been repeatedly confirmed on histological studies of CP boundaries (15, 26, 28, 33, 52). As is rightly noted by Depujarny, poorer clinical outcomes have been reported for CP patients showing a breached 3VF after radical removal of 3V CPs tightly attached to the 3VF (18, 36, 53, 54). Psychiatric disturbances due to hypothalamic injury can be truly devastating for the personal autonomy and social integration of CP patients (10, 55). Consequently, not all strict 3V CPs should undergo radical removal (6, 10). Regarding this, it is worth mentioning the lack of reliable information about the actual prevalence of long-term neuropsychiatric disturbances in large surgical series employing the EEA. The neuropsychiatry inventory-questionary (NPI-Q) used in the study by Zhao, taking into account the six fundamental categories of psychological disorders related to hypothalamic injury by CPs (emotional control loss, abnormal moods, odd behavioral changes, memory defects, dementia-like cognitive impairment; and/or psychotic symptoms), could well be incorporated into the standard battery of clinical tests to assess the postoperative long-term outcome of CP patients (19, 29). The concept of "maximum safe resection", which prioritizes the preservation of hypothalamic functions and psychological autonomy over the completeness of resection should guide surgical actions when dealing with such a complex lesion as a 3V CP, regardless of how sophisticated or technologically well-equipped the surgical procedure might be (10, 18).

AUTHOR CONTRIBUTIONS

Conception and design: JP. Acquisition of data: JP, RP. Analysis of data: JP, RP. Drafting the article: JP. Critically revising the article: RP. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

The authors wish to especially thank Crystal Smith and Liliya Gusakova, Reference Librarians of the National Library of Medicine, National Institutes of Healh (Bethesda, MD) for their kind assistance during the process of searching and retrieving articles and monographs consulted as background of this study. We are also grateful to Melissa Grafe, Librarian for Medical History Library, Yale University (New Haven, CT) and to Lucretia MacLure, Jack Eckert and the staff at the Francis Countway Medical Library at Harvard Medical School (Boston, MA) for their invaluable help in obtaining some of the original research material used during our research. Finally, we are grateful to George Hamilton for his critical review of the language and style of the manuscript.

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ORIGINAL RESEARCH
published: 19 May 2022
doi: 10.3389/fonc.2022.840572

Nomograms to Predict Endocrinological Deficiency in Patients With Surgically Treated Craniopharyngioma

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OPEN ACCESS

Edited by:
Songbai Gui,
Capital Medical University, China

Reviewed by:
Emanuele La Corte,
University of Bologna, Italy
Luiz Eduardo Armondi Wildemberg,
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Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: *21 December 2021*
Accepted: *15 April 2022*
Published: *19 May 2022*

Citation:
Wu J, Wu X, Yang L, Xie S, Tang B, Tong Z, Wu B, Yang Y, Ding H, Bao Y, Zhou L and Hong T (2022) Nomograms to Predict Endocrinological Deficiency in Patients With Surgically Treated Craniopharyngioma. Front. Oncol. 12:840572. doi: 10.3389/fonc.2022.840572

Objective: Postoperative hypopituitarism associated with increased risks of premature mobility and mortality is often encountered in craniopharyngioma patients. The aim of our study is to construct nomograms related to injury types of the hypothalamus–pituitary axis (HPA) to predict hypopituitarism 1 year after surgery.

Methods: Craniopharyngioma patients undergoing initial endoscopic endonasal surgery between December 2012 and March 2021 in our center were retrospectively reviewed, and injury types of the HPA were categorized according to intraoperative endoscopic observation. Included patients were randomly divided into a training group and a validation group. Nomograms were established based on the results of multivariate logistic analysis. The predictive performance of the nomograms was evaluated in the training and validation groups.

Results: A total of 183 patients with craniopharyngioma were enrolled, and seven injury types of the HPA were summarized. Relative to intact HPA, exclusive hypothalamus injury significantly increased the risk of anterior (OR, 194.174; 95% CI, 21.311–1769.253; $p < 0.001$) and posterior pituitary dysfunction (OR, 31.393; 95% CI, 6.319–155.964; $p < 0.001$) 1 year after surgery, while exclusively sacrificing stalk infiltrated by tumors did not significantly increase the risk of anterior (OR, 5.633; 95% CI, 0.753–42.133; $p = 0.092$) and posterior pituitary dysfunction (OR, 1.580; 95% CI, 0.257–9.707; $p = 0.621$) 1 year after surgery. In the training group, the AUCs of nomograms predicting anterior and posterior pituitary dysfunction 1 year after surgery were 0.921 and 0.885, respectively, compared with 0.921 and 0.880 in the validation group.

Conclusions: Intact hypothalamus structure is critical in maintaining pituitary function. Moreover, our preliminary study suggests that the pituitary stalk infiltrated by craniopharyngioma could be sacrificed to achieve radical resection, without substantially rendering significantly worse endocrinological efficiency 1 year after surgery. The user-friendly nomograms can be used to predict hypopituitarism 1 year after surgery.

Keywords: craniopharyngioma, nomogram, endocrinological deficiency, hypothalamus–pituitary axis, pituitary stalk

INTRODUCTION

Endocrinological deficiency associated with increased risks of premature mobility and mortality (1–3) is often encountered after surgery secondary to the injury of the hypothalamus–pituitary axis (HPA) in patients with craniopharyngioma (CP) (4–6). Meanwhile, it is well understood that the HPA plays a pivotal role in maintaining pituitary function. However, when evaluating endocrinological outcomes following surgery or addressing the issue that whether the pituitary stalk infiltrated by tumors can be sacrificed to achieve radical resection, previous studies only analyzed the effects of either the injury of the pituitary stalk (7–11) or the injury of the hypothalamus (12, 13) or the injury of the pituitary (14) on pituitary function, not mentioning any information about whether or not the other part of the HPA was injured. Given that the combined injury of the HPA is often encountered in patients with surgically treated CP due to different topographical characteristics of tumors, it is necessary to elucidate the impacts of combined injuries of the HPA on pituitary function, which is very helpful to comprehensively evaluate the impacts of the manipulation of the HPA on pituitary function and further tailor individual surgical strategies. Besides, risk factors associated with postoperative hypopituitarism in patients with CP are not well understood, which are pivotal to making informed decisions prior to and during surgery, aiming to improve endocrinological outcomes. Further, to date, there have been no prediction models to predict endocrinological deficiency for CP patients during follow-up, which is helpful to tailor individual endocrinological follow-up plans for patients with a high rate of postoperative endocrinological deficiency.

To address these gaps in the literature, we categorized the injury of the HPA into seven types based on intraoperative endoscopic observation and constructed nomograms incorporating independent risk factors to predict endocrinological deficiency 1 year after surgery.

MATERIALS AND METHODS

Patient Population

After obtaining the board approval of the local ethics committee, the medical files and imaging data of consecutive craniopharyngioma patients who underwent fully endoscopic endonasal approach (EEA) between December 2012 and March 2021 in our center were retrospectively reviewed. Inclusion criteria were listed as follows: (1) the diagnosis of craniopharyngioma was histologically confirmed; (2) medical records were complete, including demographic data, pre- and postoperative imaging data, preoperative assessment, tumor characteristics, intraoperative videos, surgical results and complications, postoperative management, follow-up, and endocrinological outcomes; and (3) endocrinological evaluation with a minimum 1-year follow-up was required. Patients undergoing reoperations were excluded because the possible initial manipulation of the HPA could affect the identification of the injury type of the HPA and the endocrinological outcomes. In addition, patients undergoing tumor recurrence or regrowth within 1 year of follow-up were excluded, because of possible effects on endocrinological outcomes. The manuscript conforms to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.

Tumor size estimated as the maximal tumor diameter, tumor location, tumor consistency, calcification, and hydrocephalus were determined by MR images and computed tomography (CT) scans before surgery. Regarding the extent of resection (EOR), gross total resection (GTR) was defined as no residual tumor evaluated by postoperative contrast-enhanced MR images acquired within 72 h after surgery. In contrast, cases in which ≥80% of the tumor was resected were deemed as subtotal resection (STR) (9).

Regarding the injury of the HPA, seven injury categories, including intact HPA (HPA-intact type; **Figure 1A**), exclusive pituitary stalk sacrifice (PSS) type (**Figure 1B**), hypothalamic injury combined with pituitary stalk sacrifice (HI+PSS) type (**Figure 1C**), hypothalamic injury combined with pituitary stalk sacrifice and pituitary gland injury (HI+PSS+PGI) type (**Figure 1D**), exclusive hypothalamic injury (HI) type (**Figure 1E**), exclusive pituitary gland injury (PGI) type (**Figure 1F**), and pituitary stalk sacrifice combined with pituitary gland injury (PSS+PGI) type (**Figure 1G**), were defined based on intraoperative videos. For the purpose of our study, we defined HI as the lack of the integrity of the hypothalamus, including mild HI, unilateral HI, and bilateral HI, which we have previously described elsewhere (15). Given that the pituitary stalk partly anatomically preserved may show function, only patients subjected to complete transection of the PS were included into the PSS group. Patients with intrasellar CP or supradiaphragmatic CP extending into the intrasellar were deemed as having PGI because of inevitable intraoperative manipulation of the pituitary gland. The confirmation of injury types was conducted by two independent neurosurgeons who were blinded for clinical outcomes. If they failed to reach consensus, a third neurosurgeon was assigned to make the final decision.

Endocrinological Evaluation

Presurgical and postsurgical endocrinological status was evaluated as described previously (16, 17). Partial hypopituitarism was defined as hormone deficiencies in one or two axes, and panhypopituitarism was defined as hormone deficiencies in three or more axes. Diabetes insipidus (DI) was evaluated preoperatively and postoperatively. Patients were diagnosed as having DI if they had polydipsia (excessive drinking; >3 l/day) and polyuria (excessive urination; >50 ml/kg body weight/24 h) combined with urine-specific gravity <1.005 and urine osmolality <300 mOsm/kg, as well as a positive response to desmopressin (15, 18). All the patients were recommended to receive imaging and clinical evaluation 3 months, 6 months, 12 months, and every 2 years subsequently after discharge. During follow-up, serum pituitary hormone levels were measured, and an endocrinologist analyzed the results. The protocol of hormone replacement was determined by the endocrinologist. Anterior pituitary dysfunction during follow-up was defined as replacement hormone required for at

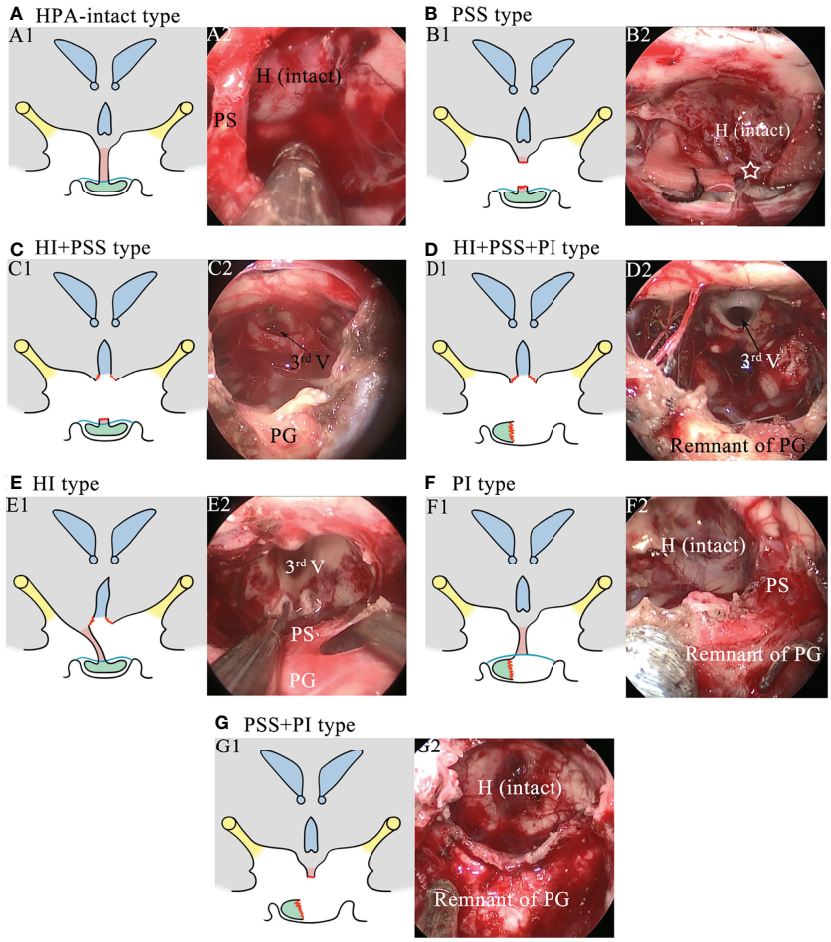

FIGURE 1 | Schematics and intraoperative images showing the injury types of the hypothalamus–pituitary axis. **(A)** Schematic of the HPA-intact type (A1) and the corresponding intraoperative image (A2). The hypothalamus, the pituitary stalk, and the pituitary gland are intact. H, hypothalamus; PS, pituitary stalk. **(B)** Schematic of the PSS type (B1) and the corresponding intraoperative image (B2). The pituitary stalk is resected, while the hypothalamus and the pituitary gland are intact. The white star represents the stalk proximal stump. **(C)** Schematic of the HI+PSS type (C1) and the corresponding intraoperative image (C2). The third ventricle floor is open, and the pituitary stalk is resected, while the pituitary gland is intact. 3rd V, the third ventricle; PG, pituitary gland. **(D)** Schematic of the HI+PSS+PGI type (D1) and the corresponding intraoperative image (D2). The third ventricle floor is open, the pituitary stalk is resected, and the pituitary gland is injured, rendering a remnant of the pituitary gland. **(E)** Schematic of the HI type (E1) and the corresponding intraoperative image (E2). The third ventricle floor is open, while the pituitary stalk and the pituitary gland are preserved. **(F)** Schematic of the PGI type (F1) and the corresponding intraoperative image (F2). The pituitary gland is injured, while the hypothalamus and the pituitary stalk are preserved. **(G)** Schematic of the PSS+PGI type (G1) and the corresponding intraoperative image (G2). The hypothalamus is intact, while the pituitary stalk is resected and the pituitary gland is injured, rendering a remnant of the pituitary gland.

least one anterior pituitary hormone axis (14). For the purpose of our study, we focused on the endocrinological outcomes at 1 year after surgery and permanent DI representing posterior pituitary function was defined as at least 1 year of the need for desmopressin therapy after surgery (19).

Surgical Procedure, Surgical Principle, and Adjuvant Treatment

All procedures were performed using an EEA. An image-guided neuronavigation system was employed for all procedures. All surgeries were performed by the chief surgeon (TH) and assisted by attending surgeons (BT, SHX, and LY). The surgical nuances of CP resection did not differ significantly from those described in the literature (20). After tumor resection, the closure was performed with a multilayered reconstruction, as described in previous literatures (21). Of note, the following surgical principles were strictly followed during CP resections. First, all procedures, especially in the process of tumor dissection, must be performed under direct visualization, avoiding pulling blindly. Second, carefully identifying and sharply combined with bluntly dissecting the cleavage plane between tumors and the HPA were warranted to

achieve radical resection of CP and preserve the anatomical integrity of the structure of the HPA involved in the attachment to the greatest extent. When the stalk was infiltrated by tumors and extremely thin, the stalk would be sacrificed to achieve a radical resection. In addition, less aggressive resection was performed for patients with the extensive involvement of the hypothalamus or with adherence of a thin CP cyst capsule to critical vessels to avoid the higher risk of hypothalamic damage and fatal complications. Radiotherapy was routinely performed in CP patients undergoing STR 3 months after surgery.

Statistical Analysis and Nomogram Construction

All patients were randomly divided into a training group and a validation group in a 7:3 ratio. Continuous variables were reported as mean (± standard deviation) or median with an interquartile range (IQR), which was determined by the Shapiro–Wilk test. Categorical data were reported as counts and proportions in each group. The baseline characteristics between the two groups were compared *via* the chi-square test (Fisher's exact test where appropriate) for categorical variables and two-tailed Student (Mann–Whitney U-test where appropriate) for continuous variables. Interrater reliability for classifying the injury type of the HPA was performed using Cohen's kappa, indicating a good level of agreement ($\kappa = 0.781$). Univariate and stepwise multivariate logistic regression was used to determine independent risk factors associated with the need for anterior pituitary hormone replacement 1 year after surgery and permanent DI in the training cohort. First, we performed univariate logistic regression analysis using all the clinical variables associated with endocrinological deficiency after CP surgery based on our subject matter knowledge and the established risk factors identified by previous literatures (7, 10, 14). Then, a stepwise multivariate logistic regression analysis was performed using variables with $p < 0.1$ in the univariate logistic regression analysis. A nomogram was drawn based on the results of the multivariate logistic regression analysis. To evaluate the discrimination efficiency and calibration power of the nomogram, the area under the receiver operating characteristic (ROC) curve (AUC) and calibration curve with 1,000 bootstrap samples were employed in the training cohort, respectively, and validated in the validation cohort. Regarding AUC, a value >0.8 was thought to have a good discrimination according to the grading guidelines (22). At last, for clinical use of the model, the total scores were calculated based on the nomogram for each patient. The procedures of conducting the nomograms followed the recommendations of "seven steps for development and an ABCD for validation" proposed by Steyerberg et al. (23).

SPSS (version 25.0; IBM Corp., Armonk, New York) was used to perform statistical analyses and plot ROC curves, while GraphPad Prism version 8 (GraphPad Software, La Jolla, CA) was used to plot histograms. R software (version 4.0.3; http://www.Rproject.org) was used to plot nomograms and calibration curves, with the "rms" package used. A two-sided level of $p < 0.05$ was considered statistically significant unless indicated otherwise.

RESULTS

Clinical Characteristics

According to the inclusion and exclusion criteria, after excluding the patients undergoing reoperations, cases with perioperative mortality or loss to follow-up, and patients with endocrinological evaluation after surgery less than 1 year, 183 CP patients (104 men and 79 women) were enrolled into the final study cohort. The median follow-up duration of the entire cohort was 29.0 months (IQR 19–46 months). The included patients were randomly divided into the training (138 cases) and validation cohorts (45 cases).

Clinical data associated with risk of need for anterior pituitary hormone replacement 1 year after surgery and permanent DI are listed in **Table 1**. The baseline characteristics between these two cohorts were similar without significant difference. The number of permanent DI and needs for anterior pituitary hormone replacement 1 year after surgery was 71 (51.4%) and 94 (68.1%) in the training cohort, respectively, while 22 (48.9%) and 30 (66.7%) in the validation cohort, respectively.

Risk Factors for Need for Anterior Pituitary Hormone Replacement 1 Year After Surgery

Variables including presurgical, surgical, and postsurgical factors were selected to determine candidate risk factors *via* univariate logistic regression analysis. In this step, preop pituitary function ($p = 0.001$), tumor location ($p = 0.012$), and injury type ($p < 0.001$) were identified as potential risk factors and further included into stepwise multivariate logistic regression analysis to determine independent risk factors associated with the need for anterior pituitary hormone replacement 1 year after surgery (**Table 2**). On multivariate analysis, with results reported as odds ratio (OR, 95% CI), preop pituitary function (for partial hypopituitarism vs. normal, 4.184 [1.225–14.292]; for panhypopituitarism vs. normal, 13.742 [1.345–140.417]) and injury type (for HI vs. HPA-intact, 194.174 [21.311–1769.253]; for HI+PSS vs. HPA-intact, 89.443 [13.642–586.416]; for HI +PSS+PGI vs. HPA-intact, 68.111 [4.975–932.565]; for PSS vs. HPA-intact, 5.633 [0.753–42.133]; for PGI vs. HPA-intact, 159.790 [11.974–2132.357]; for PSS+PGI vs. HPA-intact, 31.921 [3.320–306.873]) were determined as independent risk factors and further used to form a nomogram (**Table 3**). Intriguingly, the difference in the risk of need for anterior pituitary hormone replacement 1 year after surgery between PSS and HPA-intact did not reach statistical significance, although stalk sacrifice had a higher risk (OR, 5.633; 95% CI, 0.753–42.133; $p = 0.092$).

Risk Factors for Permanent DI

Similarly, through univariate (**Table 2**) and stepwise multivariate analyses, preop DI (yes vs. no, 8.997 [2.580–31.374]) and the injury type of HPA (for HI vs. HPA-intact, 31.393 [6.319–155.964]; for HI+PSS vs. HPA-intact, 12.820 [3.138–52.380]; for HI+PSS+PGI vs. HPA-intact, 62.934 [5.795–683.512]; for PSS vs. HPA-intact, 1.580 [0.257–9.707]; for PGI vs. HPA-intact,

TABLE 1 | Participant characteristic.

Variable	Cohort, no. (%)		P value
	Training (n = 138)	Validation (n = 45)	
Age in years (median with IQR)	41.0 (24.8–53.0)	45.0 (23.0–54.0)	0.651
Sex			0.842
Male	79 (57.2)	25 (55.6)	
Female	59 (42.8)	20 (44.4)	
Age group			0.595
Child (<18 years)	20 (14.5)	8 (17.8)	
Adult (≥18 years)	118 (85.5)	37 (82.2)	
Preop BMI in kg/m^2 (mean ± SD)	22.8 ± 3.7	23.1 ± 4.4	0.582
Preop hyperprolactinemia			0.636
Yes	68 (49.3)	24 (53.3)	
No	70 (50.7)	21 (46.7)	
Preop hydrocephalus			0.946
Yes	30 (21.7)	10 (22.2)	
No	108 (78.3)	35 (77.8)	
Preop DI			0.297
Yes	35 (25.4)	8 (17.8)	
No	103 (74.6)	37 (82.2)	
Preop pituitary function			0.897
Normal	47 (34.1)	14 (31.1)	
Partial hypopituitarism	67 (48.6)	22 (48.9)	
Panhypopituitarism	24 (17.4)	9 (20.0)	
Maximum diameter			0.573
≥3 cm	68 (49.3)	20 (44.4)	
<3 cm	70 (50.7)	25 (55.6)	
Tumor consistency			0.960
Solid	37 (26.8)	12 (26.7)	
Mixed	64 (46.4)	20 (44.4)	
Cystic	37 (26.8)	13 (28.9)	
Tumor location			0.071
Subdiaphragmatic	25 (18.1)	15 (33.3)	
Supradiaphragmatic	104 (75.4)	29 (64.4)	
Pure endoventricular	9 (6.5)	1 (2.2)	
Calcification			0.322
Yes	68 (49.3)	26 (57.8)	
No	7 0 (50.7)	19 (42.2)	
EOR			1.000
GTR	127 (92.0)	41 (91.1)	
STR	11 (8.0)	4 (8.9)	
Pathology			0.314
ACP	127 (92.0)	44 (97.8)	
PCP	11 (8.0)	1 (2.2)	
Postop hypernatremia			0.357
Yes	47 (34.1)	12 (26.7)	
No	91 (65.9)	33 (73.3)	
Postop radiotherapy			1.000
Yes	11(8.0)	4 (8.9)	
No	127 (92.0)	41 (91.1)	
Injury type			0.448
HPA-intact	26 (18.8)	5 (11.1)	
HI	25 (18.1)	8 (17.8)	
HI+PSS	36 (26.1)	10 (22.2)	
HI+PSS+PGI	12 (8.7)	6 (13.3)	
PSS	13 (9.4)	2 (4.4)	
PGI	17 (12.3)	8 (17.8)	
PGI+PSS	9 (6.5)	6 (13.3)	
Need for anterior pituitary hormone replacement 1 year after surgery			0.857
Yes	94 (68.1)	30 (66.7)	
No	44 (31.9)	15 (33.3)	
Permanent DI			0.765
Yes	71 (51.4)	22 (48.9)	
No	67 (48.6)	23 (51.1)	

IQR, interquartile range; BMI, body mass index; SD, standard deviation; DI, diabetes insipidus; GTR, gross total resection; STR, subtotal resection; ACP, adamantinomatous craniopharyngioma; PCP, papillary craniopharyngioma; HPA, hypothalamus–pituitary axis; HI, hypothalamic injury; HI+PSS, hypothalamic injury combined with pituitary stalk sacrifice; HI+PSS+PGI, hypothalamic injury combined with pituitary stalk sacrifice and pituitary gland injury; PSS, pituitary stalk sacrifice; PGI, pituitary gland injury; PGI+PSS, pituitary gland injury combined with pituitary stalk sacrifice.

0.980 [0.164–5.848]; for PSS+PGI vs. HPA-intact, 2.399 [0.335–17.192]) were determined as independent risk factors associated with permanent DI and were used to form a nomogram. Note that when we compared PSS vs. HPA-intact, PGI vs. HPA-intact, and PSS+PGI vs. HPA-intact, the significant difference in the risk of permanent DI was not found (**Table 3**).

Difference in Endocrinological Deficiency 1 Year After Surgery Between Injury Types

Further, we investigated the difference in endocrinological deficiency 1 year after surgery between the injury types of the HPA in the entire cohort (**Figure 2**). With regard to anterior pituitary dysfunction, the significant difference in the rate of need for anterior pituitary hormone replacement 1 year after surgery between injury types was found ($p < 0.001$). In addition, the rate of need for anterior pituitary hormone replacement 1 year after surgery was significantly lower in HPA-intact type and PSS type than HI type, HI+PSS type, HI+PSS+PGI type, PGI type, and PGI+PSS type ($p < 0.05$), whereas the difference between HPA-intact type and PSS type was not statistically significant ($p > 0.05$). Intriguingly, the difference in the rate of need for anterior pituitary hormone replacement 1 year after surgery between HI type, HI+PSS type, and HI+PSS+PGI type did not reach statistical significance ($p > 0.05$, **Figure 2A**). Regarding posterior pituitary dysfunction, there was a significant difference in the rate of permanent DI between injury types ($p < 0.001$). Moreover, the rate of permanent DI was significantly lower in HPA-intact type, PSS type, PGI type, and PGI+PSS type than HI type, HI+PSS type, and HI+PSS+PGI type ($p < 0.05$), whereas the difference between HPA-intact type, PSS type, PGI type, and PGI+PSS type was not statistically significant ($p > 0.05$). Likewise, the difference in the rate of permanent DI between HI type, HI+PSS type, and HI+PSS+PGI type did not reach statistical significance ($p > 0.05$, **Figure 2B**).

Nomograms and Model Performance

Nomograms based on the aforementioned independent risk factors to predict the probability of need for anterior pituitary hormone replacement 1 year after surgery and permanent DI are shown in **Figure 3**. The predicted probability of need for anterior pituitary hormone replacement 1 year after surgery and

TABLE 2 | Univariate logistic regression analysis of need for anterior pituitary hormone replacement 1 year after surgery and permanent diabetes insipidus (DI) based on pre-, intra-, and postoperative data in the training cohort.

Variable	Need for anterior pituitary hormone replacement 1 year after surgery			Permanent DI		
	OR	95% CI	p value	OR	95% CI	p value
Age, y	1.001	0.981–1.022	0.903	0.989	0.970–1.008	0.253
Age group (adult vs. child)	1.179	0.435–3.197	0.747	1.070	0.415–2.762	0.888
Sex (female vs. male)	1.117	0.541–2.310	0.764	1.216	0.618–2.390	0.571
Preop BMI, kg/m^2	1.006	0.913–1.109	0.903	1.052	0.959–1.153	0.281
Preop hyperprolactinemia (yes vs. no)	0.907	0.468–1.961	0.907	0.707	0.361–1.381	0.310
Preop hydrocephalus (yes vs. no)	1.712	0.672–4.360	0.259	1.557	0.684–3.542	0.291
Preop DI (yes vs. no)	1.813	0.747–4.402	0.188	9.073	3.253–25.305	**<0.001**
Preop pituitary function	–	–	**0.001**	–	–	0.646
Normal	1	–	NA	1	–	NA
Partial hypopituitarism	3.342	1.510–7.397	0.003	1.243	0.589–2.623	0.568
Panhypopituitarism	12.500	2.635–59.295	0.001	1.591	0.589–4.296	0.360
Maximum diameter (≥3 cm vs. < 3 cm)	0.839	0.409–1.717	0.630	1.002	0.514–1.953	0.996
Calcification (yes vs. no)	1.433	0.697–2.946	0.328	1.597	0.815–3.128	0.172
Tumor consistency	–	–	0.171	–	–	0.143
Solid	1	–	NA	1	–	NA
Mixed	1.440	0.591–3.510	0.422	0.823	0.362–1.869	0.641
Cystic	0.630	0.244–1.624	0.339	0.415	0.163–1.056	0.065
Tumor location	–	–	**0.012**	–	–	0.173
Subdiaphragmatic	1	–	NA	1	–	NA
Supradiaphragmatic	0.134	0.030–0.597	0.008	1.620	0.667–3.936	0.287
Pure endoventricular	0.696	0.055–8.748	0.789	5.250	0.900–30.621	0.065
EOR (STR vs. GTR)	0.532	0.153–1.847	0.320	0.512	0.143–1.835	0.304
Postop radiotherapy (yes vs. no)	0.532	0.153–1.847	0.320	0.512	0.143–1.835	0.304
Postop hypernatremia (yes vs. no)	1.862	0.837–4.140	0.127	1.880	0.917–3.854	**0.085**
Pathology (PCP vs. ACP)	0.805	0.223–2.906	0.740	0.770	0.224–2.653	0.679
Injury type	–	–	**<0.001**	–	–	**<0.001**
HPA-intact	1	–	NA	1	–	NA
HI	138.000	17.913–1063.110	<0.001	28.875	6.383–130.630	<0.001
HI+PSS	74.400	13.266–417.254	<0.001	16.500	4.473–60.872	<0.001
HI+PSS+PGI	132.000	10.789–1615.004	<0.001	60.500	6.019–608.126	<0.001
PSS	5.333	0.828–34.337	0.078	1.650	0.310–8.793	0.557
PGI	192.000	16.040–2298.245	<0.001	1.179	0.229–6.076	0.844
PGI+PSS	42.000	4.976–354.537	0.001	1.571	0.235–10.491	0.641

P value with bold font indicates significance.

DI, diabetes insipidus; OR, odds ratio; CI, confidence interval; BMI, body mass index; NA, not applicable; EOR, extent of resection; GTR, gross total resection; STR, subtotal resection; ACP, adamantinomatous craniopharyngioma; PCP, papillary craniopharyngioma; HPA, hypothalamus–pituitary axis; HI, hypothalamic injury; HI+PSS, hypothalamic injury combined with pituitary stalk sacrifice; HI+PSS+PGI, hypothalamic injury combined with pituitary stalk sacrifice and pituitary gland injury; PSS, pituitary stalk sacrifice; PGI, pituitary gland injury; PGI+PSS, pituitary gland injury combined with pituitary stalk sacrifice.

permanent DI for CP patients could be obtained, based on the sum of each variable score. Higher total scores calculated from the nomograms were associated with higher risk to suffer from endocrinological deficiency 1 year after surgery. For example, a CP patient with preoperative partial hypopituitarism, DI, and intraoperative pituitary stalk sacrifice would have a total of 110 scores (50 scores for partial hypopituitarism and 60 scores for pituitary stalk sacrifice) and a total of 92 scores (84 scores for preoperative DI and 18 scores for pituitary sacrifice), for a predicted need for anterior pituitary hormone replacement 1 year after surgery and permanent DI of 90.0% and 84.0%, respectively.

Further, ROC curves with AUCs and calibration curves were used to evaluate the performance of the nomograms. In the training cohort, for need for anterior pituitary hormone replacement 1 year after surgery and permanent DI predictions, the nomograms showed good discriminative abilities with AUCs of 0.921 and 0.885, respectively (**Figures 4A, B**). Calibration curves showed that the prediction curves were appropriately consistent with the ideal ones, which indicated that the nomograms had good calibration powers (**Figures 4C, D**). In addition, we validated the stability of the nomograms in the validation cohort. Similarly, good discriminative abilities with AUCs of 0.921 and 0.880 and moderate calibration powers of the nomograms were indicated by the ROC curves (**Figures 5A, B**) and calibration plots (**Figures 5C, D**), respectively.

DISCUSSION

Via categorizing the injury of the HPA into seven types, our study shows that although the stalk and the pituitary were anatomically preserved, relative to the HPA-intact type, the exclusive injury of the hypothalamus could significantly increase the risk of endocrinological deficiency 1 year after surgery. In addition,

TABLE 3 | Multivariate logistic regression analysis of need for anterior pituitary hormone replacement 1 year after surgery and permanent diabetes insipidus (DI) in the training cohort.

Variable	Need for anterior pituitary hormone replacement 1 year after surgery			Permanent DI		
	OR	95% CI	p value	OR	95% CI	p value
Preop DI (yes vs. no)	–	–	**–**	8.997	2.580–31.374	**0.001**
Postop hypernatremia (yes vs. no)	–	–	**–**	**–**	**–**	0.414
Preop pituitary function	–	–	**0.021**	**–**	**–**	**–**
Normal	1	–	NA	–	–	—
Partial hypopituitarism	4.184	1.225–14.292	0.022	–	–	–
Panhypopituitarism	13.742	1.345–140.417	0.027	–	–	–
Tumor location	–	–	0.955	–	–	–
Subdiaphragmatic	–	–	–	–	–	–
Supradiaphragmatic	–	–	–	–	–	–
Pure endoventricular	–	–	–	–	–	–
Injury type	–	–	**<0.001**			**<0.001**
HPA-intact	1	–	NA	1	–	
HI	194.174	21.311–1769.253	<0.001	31.393	6.319–155.964	<0.001
HI+PSS	89.443	13.642–586.416	<0.001	12.820	3.138–52.380	<0.001
HI+PSS+PGI	68.111	4.975–932.565	0.002	62.934	5.795–683.512	0.001
PSS	5.633	0.753–42.133	0.092	1.580	0.257–9.707	0.621
PGI	159.790	11.974–2132.357	<0.001	0.980	0.164–5.848	0.982
PGI+PSS	31.921	3.320–306.873	0.003	2.399	0.335–17.192	0.384

P value with bold font indicates significance.

DI, diabetes insipidus; OR, odds ratio; CI, confidence interval; NA, not applicable; HPA, hypothalamus–pituitary axis; HI, hypothalamic injury; HI+PSS, hypothalamic injury combined with pituitary stalk sacrifice; HI+PSS+PGI, hypothalamic injury combined with pituitary stalk sacrifice and pituitary gland injury; PSS, pituitary stalk sacrifice; PGI, pituitary gland injury; PGI+PSS, pituitary gland injury combined with pituitary stalk sacrifice.

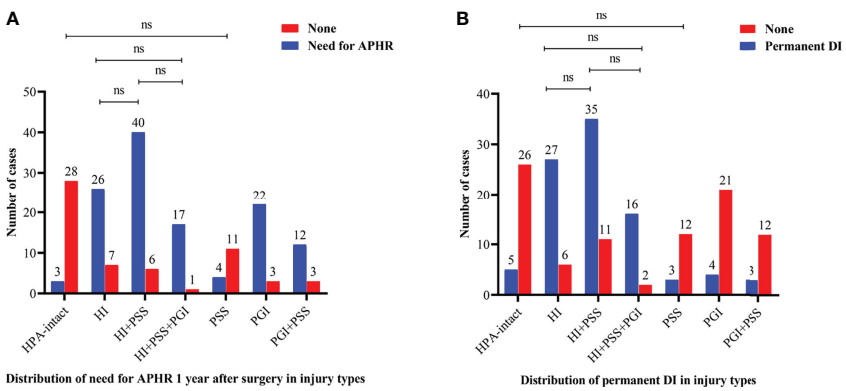

FIGURE 2 | Bar charts showing the distributions of need for anterior pituitary hormone replacement 1 year after surgery **(A)** and permanent DI **(B)** between injury types in the entire cohort. HPA, hypothalamus–pituitary axis; PSS, pituitary stalk sacrifice; PGI+PSS, pituitary gland injury combined with pituitary stalk sacrifice; HI +PSS+PGI, hypothalamic injury combined with pituitary stalk sacrifice and pituitary gland injury; HI+PSS, hypothalamic injury combined with pituitary stalk sacrifice; PGI, pituitary gland injury; HI, hypothalamic injury; APHR, anterior pituitary hormone replacement; DI, diabetes insipidus; ns, not significant.

when the hypothalamus and the pituitary were intact, relative to the HPA-intact type, sacrificing the stalk infiltrated by tumors did not significantly increase the risk of anterior pituitary dysfunction 1 year after CP surgery. Meanwhile, when the hypothalamus was intact, relative to HPA intact, sacrificing the PS infiltrated by CPs did not significantly increase the risk of permanent DI. By contrast, when the hypothalamus was injured, sacrificing the stalk infiltrated by CPs did not have a significantly worse pituitary function 1 year after surgery than stalk preservation. Based on aforementioned results, we conclude that the role of the hypothalamus in maintaining pituitary function is critical and the stalk infiltrated by CPs could be sacrificed to achieve GTR, not substantially resulting in significantly worse endocrinological efficiency 1 year after surgery. Additionally, *via* multivariate analysis, we found that preop pituitary function and the injury type of the HPA were independent risk factors for need for anterior pituitary hormone replacement 1 year after surgery, while preop DI and the injury type of the HPA were independent risk factors for permanent DI. At last, for the first time, we developed nomograms harboring good discriminations and calibration powers to predict endocrinological deficiency 1 year after CP resection.

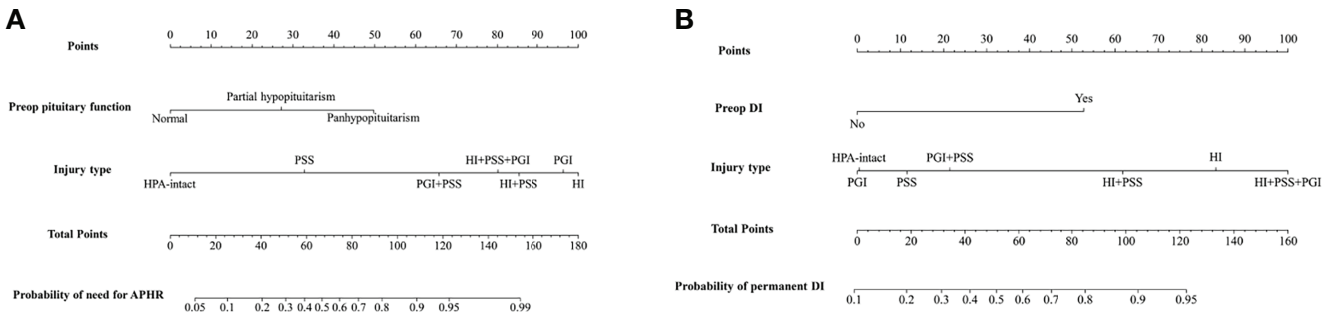

FIGURE 3 | Nomograms to predict the rate of need for anterior pituitary hormone replacement 1 year after surgery **(A)** and permanent diabetes insipidus **(B)** in patients with craniopharyngioma. HPA, hypothalamus–pituitary axis; PSS, pituitary stalk sacrifice; PGI+PSS, pituitary gland injury combined with pituitary stalk sacrifice; HI+PSS+PGI, hypothalamic injury combined with pituitary stalk sacrifice and pituitary gland injury; HI+PSS, hypothalamic injury combined with pituitary stalk sacrifice; PGI, pituitary gland injury; HI, hypothalamic injury; APHR, anterior pituitary hormone replacement; DI, diabetes insipidus.

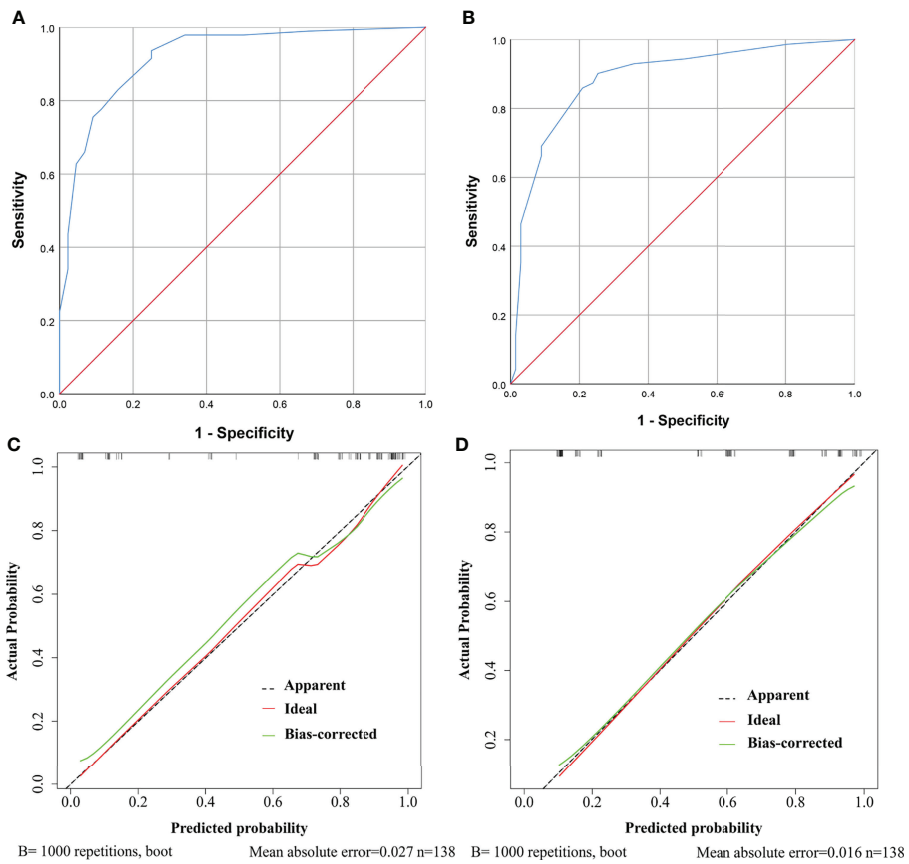

FIGURE 4 | ROC curves and calibration curves of the models showing predictive performance for need for anterior pituitary hormone replacement 1 year after surgery and permanent diabetes insipidus (DI) in the training cohort. **(A)** The AUC of the model for need for anterior pituitary hormone replacement is 0.921, with 95% CI ranging from 0.871 to 0.970. **(B)** The AUC of the model for permanent DI is 0.885, with 95% CI ranging from 0.827 to 0.943. **(C)** Calibration curve of the prediction model for need for anterior pituitary hormone replacement. The grey dashed line represents the apparent curve (non-correction), the green line represents the bias-correction curve, and the red line represents the ideal curve. B = 1,000 repetitions; n = 138, mean absolute error = 0.027. **(D)** As in **(C)** but for permanent DI.

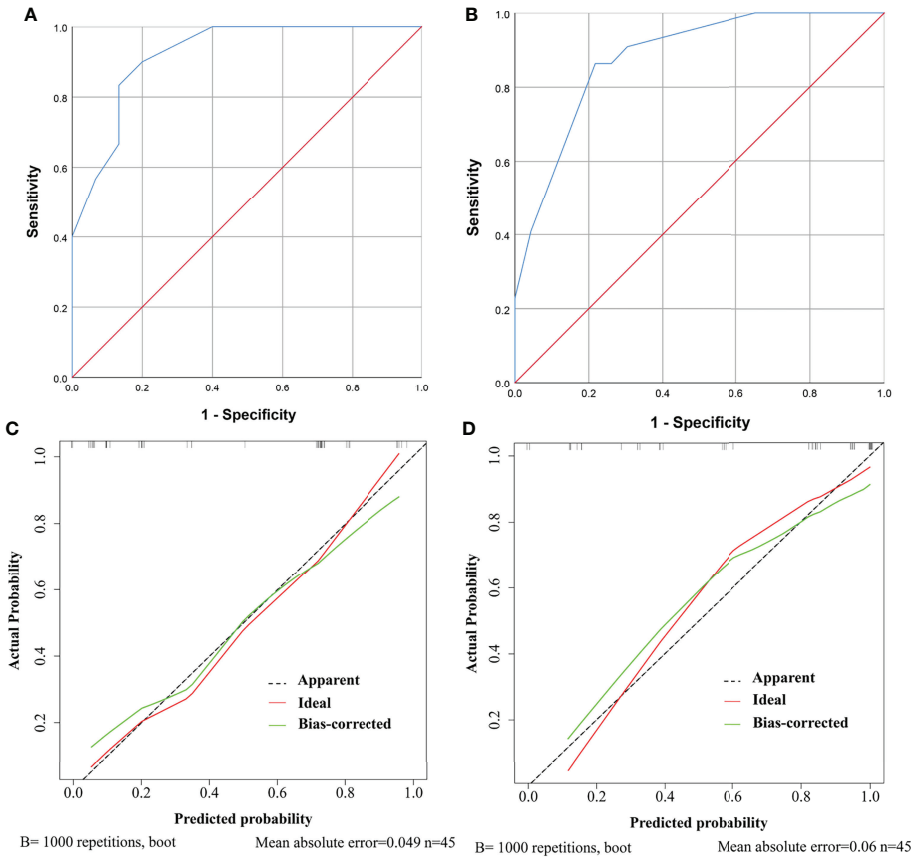

FIGURE 5 | ROC curves and calibration curves of the models showing predictive performance for need for anterior pituitary hormone replacement 1 year after surgery and permanent diabetes insipidus (DI) in the validation cohort. **(A)** The AUC of the model for need for anterior pituitary hormone replacement is 0.921, with 95% CI ranging from 0.834 to 1.000. **(B)** The AUC of the model for permanent DI is 0.880, with 95% CI ranging from 0.782 to 0.979. **(C)** Calibration curve of the prediction model for need for anterior pituitary hormone replacement. The grey dashed line represents the apparent curve (non-correction), the green line represents the bias-correction curve, and the red line represents the ideal curve. B = 1,000 repetitions; n = 45, mean absolute error = 0.049. **(D)** As in **(C)** but for permanent DI.

As published clinical literature evaluating the ramifications of the hypothalamus damage after CP surgery mainly focused on hypothalamic obesity, cognitive dysfunction, sleep disorders, and impaired temperature regulation, knowledge about the effects of exclusive hypothalamus injury on pituitary function is limited (12, 24, 25). *Via* focusing on the effects of exclusive injury of the hypothalamus on anterior pituitary function after surgery, we found that patients suffering from exclusive hypothalamus injury had a significantly increased rate of need for anterior pituitary hormone replacement 1 year after surgery, which shows a critical role of the intact hypothalamus in maintaining anterior pituitary function. Moreover, we also found that exclusively sacrificing the stalk infiltrated by tumors would not significantly increase the rate of need for anterior pituitary hormone replacement 1 year after surgery. Not completely consistent with our results, previous studies reported that sacrificing the stalk infiltrated by tumors could result in worse anterior pituitary function after CP surgery (7, 10, 11). The following reasons may account for this discrepancy. First, the results in our study are based on the premise that the hypothalamus and the pituitary are intact, which is not mentioned in aforementioned studies. Second, some previous studies do not report whether or not the difference in anterior pituitary function after surgery between stalk sacrifice and stalk preservation has reached statistical significance (10, 11). At last, the different duration of follow-up is another reason. The following underlying mechanisms are thought to account for our results. First, hypothalamic releasing factors (HRFs) produced in the hypothalamus are transported along neurons to the median eminence, where they are secreted into the portal vein and sequentially stimulate the anterior pituitary to synthesize and release anterior pituitary hormones (26–30). Second, previous studies have reported that when the stalk is resected, portal vein recanalization could occur over a long period of time demonstrated by MR images (31, 32). Thus, based on aforementioned evidence, we speculate that the maintaining of anterior pituitary function 1 year after stalk sacrifice is attributed to the fact that through the preserved median eminence, the HRFs are secreted into the reestablished portal vein and sequentially act on the preserved anterior pituitary lobe (32). At last, it must be highlighted that

according to our surgical strategies, the stalk sacrificed has been infiltrated or destroyed by CPs before surgery, so some degree of compensation may have existed. Nevertheless, our results require more multicenter clinical studies with a large sample size to validate.

Likewise, regarding posterior pituitary dysfunction after CP surgery, we found that the role of the intact hypothalamus in maintaining posterior pituitary function is critical and resecting the stalk below the level of the median eminence could not significantly increase the rate of permanent DI. In accordance with our results, many studies have reported that low-level stalk transection usually could not result in permanent DI (18, 32–36). The maintaining of posterior pituitary function after sacrificing stalk infiltrated by tumors may attribute to being hypersensitive to plasma-intrinsic antidiuretic hormone (ADH), occurrence of ectopic posterior lobe, and portal vein recanalization (31, 32, 35, 37). As to the underlying compensatory mechanism for DI, based on a rat experiment, Feng et al. (38) speculated that the functional ectopic posterior lobe increased the GAP-43 expression *via* PI3K/AKT pathways to alleviate DI after stalk sacrifice. Likewise, more clinical and laboratory studies are needed to elucidate the accurate compensatory mechanism for DI after stalk sacrifice.

In accordance with our results, preoperative pituitary dysfunction as a risk factor associated with endocrinological deficiency during follow-up has been widely reported, as preexisting endocrinological deficiency of CP patients undergoing surgery is usually only mildly improved during follow-up (9, 39, 40). There is an agreement in the literature that radiotherapy can worsen pituitary function (5, 7, 41, 42). Intriguingly, our statistical analysis excluded the role of radiotherapy as an independent risk factor associated with endocrinological deficiency 1 year after surgery. Limited sample size and relatively short time interval from receiving radiotherapy to the endpoint of our study may account for our results. In addition, some studies (43, 44) have reported that the EOR could affect endocrinological outcomes, which is not confirmed by our study. One possible explanation is that in the context that the goal of our surgery is to resect as much tumors as possible, the factors determining GTR or STR, such as adherence of CP to critical vessels, do not lead to a difference in the manipulation of HPA between GTR and STR. Thus, EOR (STR vs. GTR) has no significant difference in endocrinological outcomes, which is in accordance with previous studies (7, 10).

Identifying independent risk factors is of great importance to comprehensively understand the prognosis of a given disease. Further, a nomogram based on independent risk factors can provide more individual and accurate prognosis data for treating clinicians and patients or their relatives. In the last two decades, neurosurgical clinical prediction models have increased exponentially, for a variety of clinical outcomes (23, 45). This is the first study to construct models to predict postoperative endocrinological prognosis in patients with CP. Our nomograms were constructed following standard procedures and harbored good discriminations and calibration powers, which merits application in clinical works.

Limitations

First, due to the retrospective nature of the study, selection bias inevitably exists. Second, the present findings were based on limited data from a single center and on patients only undergoing EEA, it is necessary to validate them in multiple centers with a large sample size. Particularly, attention must be paid when interpreting our results that pituitary stalk infiltrated by tumors could be sacrificed, as only 15 patients underwent exclusive stalk sacrifice, warranting further investigation. Third, we defined endocrinological deficiency as the need for pituitary hormone replacement rather than objective measurement of pituitary hormone levels, which may underestimate the rate of pituitary deficiency, although it arguably gives a more clinically meaningful result (14). At last, the injury type of the HPA cannot be quantitatively defined, which may lead to bias when determining injury types between different neurosurgeons.

CONCLUSION

Collectively, our preliminary study suggests that the role of the intact hypothalamus in maintaining pituitary function is critical and the pituitary stalk infiltrated by CPs could be sacrificed to achieve GTR, not substantially resulting in significantly worse endocrinological efficiency 1 year after surgery. Moreover, our study highlights that more clinical and laboratory studies are required to elucidate the accurate mechanism and validate our results. The established nomograms with good predictive performance can provide a user-friendly tool to predict the rate of hypopituitarism 1 year after surgery, which is helpful for clinicians to better counsel patients and provide anticipatory guidance on postoperative expectations and management.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Ethics Committee of the First Affiliated Hospital of Nanchang University. For this retrospective study, formal consent was not required.

AUTHOR CONTRIBUTIONS

TH and JW contributed to the study's conception and design. Analysis of the data was performed by TH, JW, XW, and LY. Material preparation and data collection were performed by JW, XW, LY, SHX, BT, ZGT, BWW, HD, YYB, LZ, and YQY. The first draft of the manuscript was written by JW, and all authors commented on previous versions of the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by the National Natural Science Foundation of China (grant nos. 82060246 and 81460381), Ganpo555 engineering excellence of the Jiangxi Science and Technology Department (2013), and the Key Research and Invention Plan of Jiangxi Science and Technology Department (20192BBG70026).

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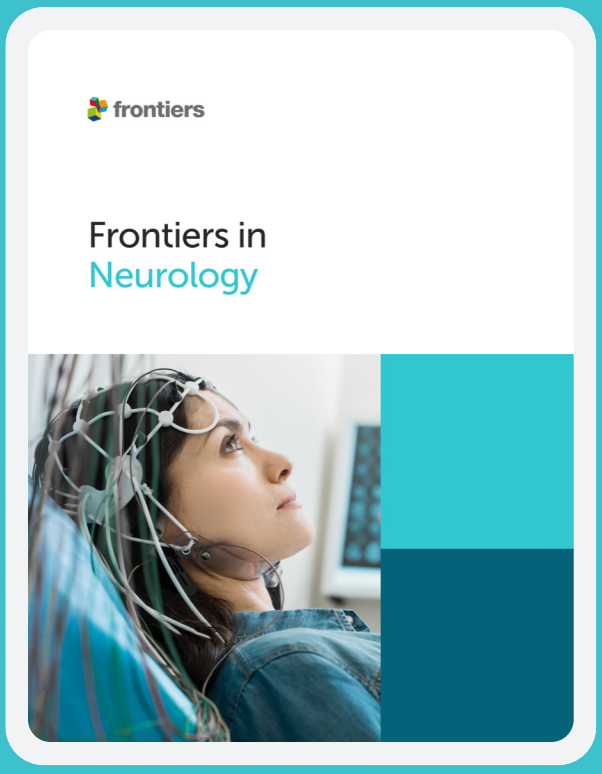

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