



Clinical impact of craniopharyngioma classification based on location origin: a multicenter retrospective study

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Background: An assessment of the clinical impact for craniopharyngiomas (CPs) classification based on origin location has not been reported. The aim of this study was to determine the clinical impact of the site of tumor origin in primary CPs.

Methods: Patients from six national institutions who had undergone resection for primary CP were enrolled. Based on the point of origin and surrounding membranous structures, the location of the tumor origin was labelled as Q, S, or T, where Type Q CPs originated below the diaphragmatic area; Type S CPs originated from Rathke's pouch precursor cells; and Type T CPs originated from the Rathke's pouch precursor cells located above the pars tuberalis. Clinical characteristics, surgical approach, and outcome were evaluated according to the location of the tumor origin.

Results: Among the 529 patients with primary CP, symptoms, age, histopathology type, tumor size, the incidence of hydrocephalus, survival rates, and recurrence-free survival rates were significantly different among tumors originating in different locations. Patients with type T CPs had higher symptom rates of intracranial hypertension and hypothalamic dysfunction, while those with type Q CPs had higher rates of hormone deficits during pre-and post-operative management. Type S CPs were correlated with better outcomes and lower recurrence rates. The location of origin and primary therapy with survival and recurrence in CP were independent factors for survival and recurrence in multivariate analysis.

Conclusions: The identification of the different location of origin of CPs is of great significance in understanding the relationship between tumors and peripheral tissues. The origin of tumors effects the choice of surgical approach and prognosis.

Keywords: Craniopharyngioma (CP); classification; origin location; outcome

Submitted May 19, 2021. Accepted for publication Jun 28, 2021.

doi: [10.21037/atm-21-2924](https://doi.org/10.21037/atm-21-2924)

View this article at: <https://dx.doi.org/10.21037/atm-21-2924>

Introduction

Although craniopharyngioma (CP) is a benign tumor, it is challenging to treat due to the nature of its location relation to peripheral structures (1). Surgical resection is the treatment of choice for CP, and the extent of resection

plays a major role in the outcome of surgery. Performing complete resection at presentation offers an optimal choice for tumor control and potential cure with an acceptable morbidity rate (2-4). Hence, a suitable surgical approach can improve survival. The choice of operative approach

for total resection should be determined according to the mode of tumor growth and as the site of origin of a tumor often has dense adhesions, locating this can predict likely difficulties to be encountered during surgery and aid in the selection of an appropriate surgical approach. Whilst this might lead to differences in the prognosis and recurrence, there have been few investigations to verify this (4,5), and the clinical significance of three different origin types of CP tumors has not yet been clarified. Hence, in this study, we aimed to determine the impact of tumor location origin on the surgical approach, survival, and tumor recurrence in patients undergoing resection of primary CP. We present the following article in accordance with the STROBE reporting checklist (available at <https://dx.doi.org/10.21037/atm-21-2924>).

Methods

Study cohort and clinicopathological variables

We included all patients who were histologically identified and underwent resection of CPs between March 1997 and December 2012 at six major neurosurgery centers. Patients who underwent surgery for recurrent tumors were excluded due to alterations in the anatomy of the tumor origin site during the first surgery making it difficult to precisely identify. Patients with incomplete records or who were lost to follow-up were also excluded to reduce the bias. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of Nanfang Hospital, Southern Medical University (No.: NFEC201096). Individual consent for this retrospective analysis was waived.

Follow-up material and basic surgical approach

All patients underwent exhaustive preoperative and postoperative endocrine examinations involving the pituitary and hypothalamus (6-9). Visual evaluation included corrected and uncorrected visual acuities with visual field examinations in the Ophthalmologic department before and after surgery. All surgical records, image data, and videos were reviewed to help assess the extent of resection and tumor location.

The approaches attempted for gross-total resection in this study included the frontal base interhemispheric, pterional, lateral ventricle, transcassal, and transsphenoidal. The

surgical approach was selected according to the origin of the tumor.

The recurrence-free survival rate, total survival rate, imaging features, and pituitary hypothalamic functions were analyzed using long-term follow-up data. The outcome was divided into good and poor according to the system outlined in the study of Duff *et al.* as follows (10); good (alive, with functional vision, no major motor deficit in connection with the treatment or tumor progression, Karnofsky Performance Scale score of not less than 80, Katz grade of A, employability for adults at working age, school status of no more than 1 year behind the expected grade for young adults and children, no debilitating emotional or psychological problems), or poor (all patients not meeting the “good” criteria).

Histopathological evaluation and definition of tumor location

The diagnosis of CP in all patients was confirmed by histology. Preoperative imaging was reviewed by Dr. Jun Pan and Dr. Yun Bao in each case to ascertain the location of the tumor origin for determining the potential for study inclusion in a blinded fashion. If consensus could not be reached, Dr. Songtao Qi was assigned to make the final decision. The pituitary stalk (PS) was divided into four segments in accordance with the folds of the arachnoid sleeve around the pituitary stalk (ASPS) (11). Accordingly, we categorized the tumors into three types (3,5). The origin site of type Q CP is located below the diaphragmatic area and the extra-arachnoidal, intra-arachnoidal, and sub-arachnoidal segments of the PS as situated above the tumor. The dura mater, arachnoid, pituitary stalk and the third ventricle floor (3VF) were located above the tumor. These tumors are surrounded by the suprasellar arachnoid and dura mater. Type Q tumors usually demonstrate marked enlargement of the pituitary fossa and a large rounded and symmetrical extension to the suprasellar space. Type S CPs originate from Rathke’s pouch precursor cells, that are to the extra- and intra-arachnoidal segments of the PS, and the main body of these tumors is in the suprasellar arachnoid around the PS. The arachnoid and the 3VF are located above the tumor, the PS is located beside the tumor, the dura mater is below the tumor. Although type S tumors can grow into one or various subarachnoid cisterns, and/or into the pituitary fossa, they tend not to expand the pituitary fossa, and the diaphragm, basal arachnoid, and pituitary can be found below the tumor. If the tumor grows upward, the third ventricle floor can be pushed up. Type T CPs

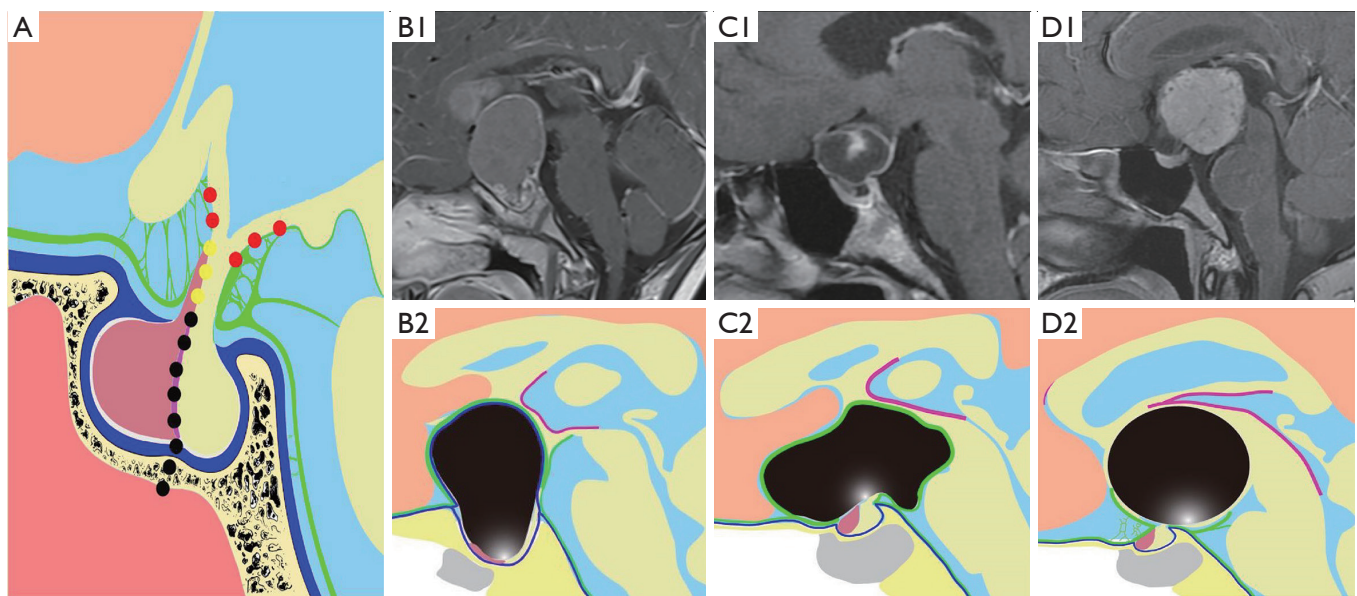


Figure 1 Classification of CPs based on origin location. (A) Several possible sites of tumor origin are indicated as Q (black dots), S (yellow dots), and T (red dots); (B1) preoperative contrast-enhanced MR images of type Q CP; (B2) the relationship between type Q tumors and surrounding structures; (C1) preoperative contrast-enhanced MR images of type S CP; (C2) the relationship between type S tumors and surrounding structures; (D1) preoperative contrast-enhanced MR images of type T CP; (D2) the relationship between type T tumors and surrounding structures. White dots represent the origin point, green lines represent the arachnoid membrane, blue lines represent the dura mater, and violet lines represent the ependyma.

originate from the Rathke's pouch precursor cells, which are at the top of pars tuberalis. 3VF is pushed up, and the third ventricle cavity is often occupied by the tumor. The PS, arachnoid sleeve, and basal arachnoid are beneath type T tumors (*Figure 1*).

The main differences in the tumors originating from the different sites are as follows: type Q tumors are found below the diaphragm, while type S are located on the extra-arachnoidal and intra-arachnoidal segments of the stalk, and type T tumors are situated at the pars tuberalis.

Statistical analysis

Statistical analysis was performed using IBM SPSS software (version 26.0, SPSS Inc., Chicago, IL, USA). Medians and ranges of continuous variables were compared using the Mann-Whitney U test and categorical variables were compared using Fisher's exact test or Pearson's chi-squared test. The overall survival (OS) was calculated based on the time from surgery until the last follow-up or death. Survival curves were generated using the Kaplan-Meier method and were compared by the log-rank test, and Cox regression

analysis was performed to explore possible determinants of outcomes. The value for significance was set at $P \leq 0.05$.

Results

Clinical characteristics

We excluded 213 patients with recurrent tumors and/or radiotherapy and 19 patients with incomplete data or who were lost to follow-up. A total of 529 patients were enrolled from six national institutions. Of these, 209 patients were treated at Nanfang Hospital of Southern Medical University, 87 at the Fuzhou General Hospital of Nanjing Military Area Command, 73 at the Affiliated Hospital of Southwest Medical University, 59 at the First Affiliated Hospital of Fujian Medical University, 51 at the General Hospital of Ningxia Medical University, and 50 at the First Affiliated Hospital of Suzhou University.

The median age of patients with CP was 23 years (range, 2–72 years), and 329 (62.2%) were men. There were 220 (41.6%) children and 309 (58.4%) adults when the tumor was detected. The median follow-up period was 83.0 months (range, 28–236 months) excluding the patients who died, who

Table 1 Preoperative clinical characteristics of patients, stratified according to growth pattern types

Parameter	Type Q (n=142)	Type S (n=115)	Type T (n=272)	Total (n=529)	P value
Age at diagnosis					
Mean	15.18±14.96	34.90±18.97	29.30±19.89	26.73±19.86	<0.001
Range	2–60	3–67	2–72	2–72	
Children, ≤14 yrs n (%)	93 (65.5)	24 (20.9)	103 (37.9)	220 (41.6)	<0.001
Adults, >14 yrs n (%)	49 (34.5)	91 (79.1)	169 (62.1)	309 (58.4)	
Sex, n (%)					
Male	93 (62.7)	63 (55.7)	173 (64.7)	329 (62.2)	0.168
Female	49 (37.3)	52 (44.3)	99 (35.3)	200 (37.8)	
Tumor size (cm)	3.7±1.3	3.9±1.0	3.6±1.0	3.7±1.1	0.028
Follow-up (months)					
Mean	106.8±48.0	102.8±38.4	100.0±43.8	102.4±43.9	0.325
Range	17–236	56–196	3–232	3–236	
Hydrocephalus, n (%)					
None	128 (90.1)	98 (85.2)	139 (51.1)	365 (69.0)	<0.001
Yes	14 (9.9)	17 (14.8)	133 (48.9)	164 (31.0)	
Tumor consistency, n (%)					
Solid	18 (12.7)	15 (13.1)	36 (14.0)	71 (13.4)	0.695
Mixed	93 (65.5)	77 (66.9)	164 (60.3)	334 (63.1)	
Cystic	31 (21.8)	23 (20.0)	70 (25.7)	124 (23.4)	
Pathology, n (%)					
Adamantinomatous	142 (100.0)	102 (88.7)	235 (86.4)	479 (90.5)	<0.001
Papillary	0 (0.0)	13 (11.3)	37 (13.6)	50 (9.5)	

numbered 86 (16.3%) at the time of analysis (*Table 1*).

QST classification and histopathological features

A total of 142 patients (26.8%) had type Q tumors, 115 (21.7%) had type S tumors, and 272 (51.4%) had type T tumors, and there were significant differences in the pathological subtypes among the three different types of tumors ($P<0.001$). The proportion of patients with adamantinomatous CP (ACP) was 100% (142/142), 88.7% (102/115), and 86.4% (235/272) among patients with types Q, S, and T tumors, respectively (*Table 1*).

Symptoms and signs

The location of the tumor origin and the main symptoms

in patients with CP are summarized in *Table 2*. The tumor location was inferred according to the protocol described above, and the most common symptoms were headache, reduced vision, reduced visual field, and growth retardation. There were significant differences in the frequency of symptoms including headache, nausea or vomiting, diplopia, reduced vision, reduced visual field, seizures, loss of appetite, polyuria, growth retardation, weight gain, altered personality, memory impairment, concentration impairment, and reduced consciousness among the three tumor types.

Treatment and surgical approach

Of the 529 patients, 403 (76.2%) were treated with gross total resection (GTR), 81 (15.3%) with subtotal resection

Table 2 Presenting symptoms in craniopharyngioma, stratified according to growth pattern types

Symptoms (No.)	Type Q (n=142)	Type S (n=115)	Type T (n=272)	Total (n=529)	P value
Headache	57 (40.1)	39 (34.0)	162 (59.6)	258 (48.8)	<0.001
Nausea or vomiting	9 (6.3)	14 (12.2)	89 (32.7)	112 (21.2)	<0.001
Diplopia	32 (22.5)	13 (11.3)	10 (3.7)	55 (10.4)	<0.001
Reduced vision	75 (52.8)	75 (65.2)	98 (36.0)	248 (46.9)	<0.001
Reduced visual field	47 (33.1)	63 (54.8)	80 (29.4)	190 (35.9)	<0.001
Seizures	5 (3.5)	4 (3.5)	8 (2.9)	17 (3.2)	<0.001
Loss of appetite	10 (7.0)	8 (7.0)	8 (2.9)	26 (4.9)	<0.001
Weight loss	4 (2.8)	3 (2.6)	8 (2.9)	15 (2.8)	0.984
Polyuria	17 (12.0)	6 (5.2)	41 (15.1)	64 (12.1)	0.025
Growth retardation*	78 (83.9)	9 (37.5)	46 (44.6)	133 (60.5)	<0.001
Weight gain	5 (3.5)	4 (3.5)	34 (12.5)	43 (8.1)	0.001
Insomnia	5 (3.5)	0 (0.0)	10 (3.7)	15 (2.8)	0.117
Altered personality	1 (0.7)	2 (1.7)	10 (3.7)	13 (2.5)	0.008
Memory impairment	5 (3.5)	4 (3.5)	30 (11.0)	39 (7.4)	0.004
Concentration impairment	1 (0.7)	4 (3.5)	26 (9.6)	31 (5.9)	0.001
Reduced consciousness	0 (0.0)	4 (3.5)	20 (7.4)	24 (4.5)	0.002

*, only in age ≤ 14 years group, n=220 (type Q =93, type S =24, type T =103).

(STR) without radiation therapy (RT), and 45 (8.5%) with STR with RT. Details of the surgical procedures are summarized in *Table 3*. The results showed significant differences in the surgical approach among the three different types of tumors ($P < 0.001$).

Pituitary function and functional outcome

The cumulative probability for each deficit in all patients is shown in *Table 3*. There were significant differences in the number of pituitary axes with insufficiencies (0 axes, 1–2 axes, and 3–4 axes) among types Q, S, and T tumors at presentation and after surgery ($P < 0.001$). Of the remaining 336 patients, new anterior hypopituitarism occurred in 94 (17.8%), with at least one intact axis preoperatively. The overall clinical outcome was good and poor in 81.9% and 18.1% of patients, respectively, and final functional outcomes are shown in *Table 3*. Patients with type T CPs had a worse outcome than those with type S and type Q CPs (*Table 3*).

Recurrent factors for patients with CP

Among the 529 patients who underwent surgery, 136 were

found to have tumor recurrence during follow up and the overall recurrence rate was 25.7%. The median recurrence time was 23 months (range, 1–98 months).

Multivariate analysis was performed to identify the recurrent factors and survival factors for patients with CP, and we selected seven potential candidate factors for analysis including age ($>14/\leq 14$ y), sex (male/female), origin location of the tumor (Q, S, and T), primary therapy (GTR/STR/STR + RT), pathology (ACP/PCP), calcification status (big/small/no), and size status ($>5/\leq 5$ cm).

The recurrence rate was affected by the size ($P = 0.023$), primary therapy ($P < 0.001$), and origin location ($P < 0.001$) in the univariate analyses, and the primary therapy [$P < 0.001$ B=1.137 Exp (B) =3.116, CI (2.568–3.781)], size [$P = 0.001$ B=0.763 Exp (B) =2.144, CI (1.381–3.329)], and origin location [$P < 0.001$ B=0.396 Exp (B) =1.485, CI (1.194–1.847)] were factors for recurrence in the multivariate analysis. The recurrence rate was not affected by age ($P = 0.082$), sex ($P = 0.343$), pathology ($P = 0.694$), and calcification status ($P = 0.615$) in the univariate analyses.

The recurrence rate after resection was significantly lower for type S tumors (13/115, 11.3%) than for type Q ($P = 0.002$), and type T tumors ($P < 0.001$). Kaplan-Meier

Table 3 Presenting symptoms and surgical outcome in craniopharyngioma, stratified according to growth pattern type

Parameter	Type Q (n=142)	Type S (n=115)	Type T (n=272)	Total (n=529)	P value
Preoperative Pituitary dysfunction axes, n (%)					
0 axis	4 (2.8)	51 (44.3)	72 (26.5)	127 (24.0)	<0.001
1–2 axes	35 (24.6)	44 (38.3)	130 (47.8)	209 (39.5)	
3–4 axes	103 (72.5)	20 (17.4)	70 (25.7)	193 (36.5)	
Preoperative polyuria	17 (12.0)	6 (5.2)	41 (15.1)	64 (12.1)	0.025
Postoperative pituitary dysfunction axes, n (%)					
0 axis	1 (0.01)	31 (27.0)	51 (18.6)	83 (15.7)	<0.001
1–2 axes	22 (15.5)	57 (49.6)	121 (44.5)	200 (37.8)	
3–4 axes	119 (83.8)	27 (23.5)	100 (36.8)	246 (46.5)	
Postoperative polyuria	82 (57.7)	47 (40.8)	137 (50.4)	266 (50.3)	0.027
Surgical approach, n (%)					
Frontal base interhemispheric	50 (35.2)	25 (21.7)	161 (59.2)	236 (44.6)	<0.001
Pterion	54 (38.0)	73 (63.5)	69 (25.4)	196 (37.1)	
Transsphenoidal	38 (26.8)	7 (6.1)	6 (2.2)	51 (9.6)	
Lateral ventricle	0 (0.0)	2 (1.7)	4 (1.5)	6 (1.1)	
Transcallosal	0 (0.0)	8 (7.0)	32 (11.8)	40 (7.6)	
Functional outcome, n (%)					
Good	121 (85.2)	103 (89.6)	209 (76.8)	433 (81.9)	0.006
Poor	21 (14.8)	12 (10.4)	63 (23.2)	96 (18.1)	

curves showed that the classification of tumors effectively stratified patient recurrence (*Figure 2A*). Recurrences appeared in 39 of 403 patients (9.7%) after total resection, in 77 of 81 patients (95.1%) after incomplete resection, and in 20 of 45 patients (44.4%) in incomplete resection plus radiotherapy. GTR was associated with a lower recurrence rate than STR ($P<0.001$) or STR with RT ($P<0.001$), and STR with RT was also associated with a lower recurrence rate than STR without RT ($P<0.001$). Kaplan-Meier curves showed that the classification of tumors effectively stratified patient recurrence (*Figure 2B*).

Survival factors for patients with CP

The total OS rate was affected by the primary therapy ($P<0.001$), origin location ($P=0.013$), and calcification ($P=0.036$) in the univariate analyses. The primary therapy [$P<0.001$ B=0.795 Exp (B) =2.215, CI (1.684–2.914)] and the origin location of the tumor [$P=0.011$ B=0.351 Exp (B) =1.420 CI, (1.085–1.859)] were factors for OS in the

multivariate analysis. The total OS was lower in type T participants than in type Q ($P=0.026$) and type S ($P=0.020$) tumors. Kaplan-Meier curves showed that the classification of tumors effectively stratified patient prognosis (*Figure 2C*). The total OS was higher in GTR tumors than in STR ($P<0.001$) and STR with RT ($P<0.001$) tumors, and was not significantly different between STR and STR with RT tumors (*Figure 2D*).

The main reasons for the 86 deaths in our study cohort were tumor progression, hypothalamic-pituitary dysfunction, and intracerebral vascular complications.

Discussion

CP is a benign tumor that arises from Rathke's pouch and accounts for 1–4% of all brain tumors, and the overall incidence of CP is 0.13 per 100,000 person years (12,13). Surgical resection is the first choice for CP followed Yaşargil's view (14). CPs are clinically relevant tumors of the sellar region (15). The management of patients

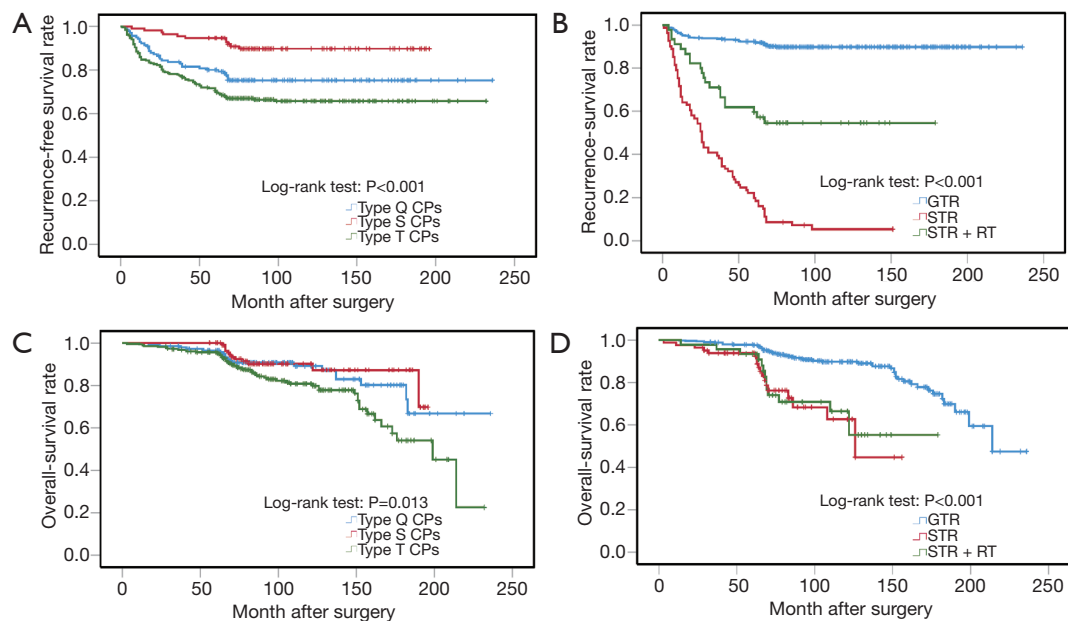


Figure 2 Graph depicting survival times in patients. All P values are based on log-rank test. (A) The image is related to the recurrence-free survival rate based on tumor origin location; (B) the image is related to the recurrence-free survival rate based on treatment modality; (C) the image is related to the overall-free survival rate based on tumor origin location; (D) the image is related to the overall-free survival rate based on treatment modality in Type T CP. GTR, gross total removal; STR, subtotal removal; RT, radiotherapy.

with CP is complex and has attracted the attention of many researchers in different fields. To improve the understanding and outcome of CP, several classifications have been put forward including those based on their relationship with the diaphragm or stalk (14), tumor extension (16), endoscopic views of the infundibular region (17,18), and the degree of hypothalamic involvement (19). However, as it is difficult to classify large tumors according to the aforementioned classifications, and all primary CPs were classified based on the location of their origin in the present study.

Although CPs are benign tumors, they are likely to involve the hypothalamic-pituitary axis and surrounding structures, which may limit surgical options to partial resection or lead to severe postoperative complications after total resection, especially severe hypothalamic reactions. To ensure safe surgical resection and avoid severe hypothalamic injury, understanding the pattern of gliosis is essential (2-4,11). The classification based on the origin of the tumor details the relationship of the surrounding structures to CPs and purports to predict and identify the intraoperative anatomical stratification. At the same time, it is not easy to expose the origin of CPs as the lesions have circumferential adhesions with surrounding structures, and the exposure

of this area is a priority factor in the choice of surgical approach (20,21).

According to the classification based on the location of the origin point and the relationship between the tumor and arachnoid structures (11), CPs can be divided into three types (5): type Q, type S, and type T. The location of origin of type Q tumors is below the diaphragm, type S is on the intra-arachnoidal and extra-arachnoidal segment of the stalk, and type T is in the pars tuberalis and sub-arachnoidal space. The key differences between type Q and type S/T are the presence of an enlarged pituitary fossa or whether the tumor is above the diaphragm. The main difference between type S and type T tumors is that the PS sits beside or at the bottom of the tumor, where the tumor extends into the subarachnoid space or the third ventricle, and whether the arachnoid is separated from the tuberoinfundibular and the tumor.

In this study, we analyzed the influence of the location of the tumors origin on clinical characteristics, functional outcome, long-term survival, and recurrence-free survival in patients with primary CP. Our findings show the classification of CP according to the location of tumor origin effectively stratifies the prognosis of patients after undergoing curative resection of the tumor and that

hypothalamus involvement is correlated with a higher OS rate (22). Type T tumors were strongly correlated with a higher incidence of hypothalamus involvement, resulting in a worse functional outcome and worse survival rate compared to patients with type Q and S tumors.

Significant endocrine dysfunction is seen in most patients with CP, and in this study, we found that pituitary dysfunction in CP was largely related to the location of its origin point. It is common to find three or more hormone deficits in patients with type Q tumors, which might be due to the direct effect of the pituitary on tumor compression and inflammation (23). Endocrine replacement after GTR also offers a chance of cure in type Q tumors. As Type S tumors mainly grow in the subarachnoid space, which usually has a mild or moderate effect on the PS and 3VF, pituitary dysfunction in patients is usually not serious. Type T tumors usually extend to the 3VF and occupy the space of the third ventricle, resulting in hypothalamus damage. Owing to this, hypothalamic-pituitary dysfunction occurs frequently in this tumor type.

In addition, we found that the symptoms, age, histopathology type, tumor size, and incidence of hydrocephalus were significantly different in the different types of tumors. Patients with type Q tumors were more likely to be younger compared to those with type S and T tumors. Several studies have described the symptoms of CPs (7,24,25), which include headache, nausea, vomiting, and symptoms related to hypothalamic function. These symptoms were more frequently observed in patients with type T tumors, which may be associated with intracranial hypertension. Memory deficits, behavioral abnormalities, and psychosocial impairment frequently occur early after the diagnosis of CP (8,26), and were especially seen in patients with type T CP in the present study, while reduced vision and visual field symptoms were more frequently observed in patients with type S and Q tumors than in those with type T tumors.

As some authors have reported cases in which an erroneous classification of the type of CPs has resulted in an incorrect surgical approach (15,27,28), it is particularly important to consider the classification of the tumor based on its origin site (29), before surgery. The initial site of the tumor is usually the closest to the surrounding tissue, and the relationship between the tumor and the surrounding tissue (such as the hypothalamus) differs in different tumor types. The transsphenoidal approach is the most appropriate corridor to treat some types of Q tumors, as it avoids injury to the optic chiasm and third

ventricle. The continuity of the 3VF-stalk-pituitary gland can be well protected in type S tumors via extra-axial approaches, while for type T tumors, if the upper edge of the tumor exceeds the mass intermedia, the trans-lamina terminalis approach can be selected to allow for additional exposure of the tumor. In addition, the classification of CP according to its site of origin can predict the adherent point and possible difficulties to during the course of the surgery. It is also important to predict the risk of CP adherence to the hypothalamus (29). Type T tumors are a strong predictor of adherence to the hypothalamus because of their origin point and radical resection becomes highly challenging because of their tenacious adherence to the infundibulo-tuberal region and the hypothalamus. Radical resection of type S tumors is easier than the other two tumor types, as well as a Grade V tumor in the classification system based on vertical extension (16), and the arachnoid between the tumor and 3VF should be a reliable boundary.

Recently, progress in molecular biology has unravelled creative, potentially druggable molecular pathways in CPs that provide new prospective therapeutic options. The treatment of ACP with vismodegib, a sonic hedgehog pathway inhibitor, results in a substantial reduction in median survival in murine models and further research is needed to effectively translate these laboratory findings to clinical settings (30). BRAF inhibitors have been demonstrated to show effectiveness against BRAF-mutated papillary CP. Related drugs are already in clinical trials, but are currently only used for recurrent CPs (31,32).

Limitations

The limitations of this study include its retrospective nature and associated biases. However, CPs are relatively rare, and the study is one of the largest series to analyze the tumor. Moreover, the current data were obtained from six high-volume centers in the East, South, West, and North of China. The proposed definitions of origin location offer a simple and reliable method to evaluate the prognosis of patients with CP.

Conclusions

Identification of the tumor origin site is crucial in the management of primary CP. The classification of primary CP into Q, S, and T tumors provides a useful tool for selecting the surgical approach and predicting its outcome.

Acknowledgments

The authors wish to thank Dezhi Kang (The First Affiliated Hospital, Fujian Medical University, Fujian province, China), Ligang Chen (Affiliated Hospital of Southwest Medical University, Sichuan province, China), Zongzheng Li (General Hospital of Ningxia Medical University, Ningxia province, China), Shousen Wang (Fuzhou General Hospital of Nanjing Military Area Command, Fujian Province, China), and Zhengquan Yu (The First Affiliated Hospital to Suzhou University, Jiangsu Province, China) for providing critical clinical data.

Funding: This work was supported by the National Natural Science Foundation of China (81972352); National Natural Science Foundation of Guangdong Province of China (2017A020215048); Clinical Research Startup Program of Southern Medical University by High-level University Construction Funding of Guangdong Provincial Department of Education (LC2016PY012); and Clinical Research Program of Nanfang Hospital, Southern Medical University (2018CR029).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://dx.doi.org/10.21037/atm-21-2924>

Data Sharing Statement: Available at <https://dx.doi.org/10.21037/atm-21-2924>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://dx.doi.org/10.21037/atm-21-2924>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of Nanfang Hospital, Southern Medical University (No.: NFEC201096). Individual consent for this retrospective analysis was waived.

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- (English Language Editor: B. Draper)

Cite this article as: Hu W, Qiu B, Mei F, Mao J, Zhou L, Liu F, Fan J, Liu Y, Wen G, Qi S, Bao Y, Pan J. Clinical impact of craniopharyngioma classification based on location origin: a multicenter retrospective study. *Ann Transl Med* 2021;9(14):1164. doi: 10.21037/atm-21-2924