Prediction of *BRAF* mutation status of craniopharyngioma using magnetic resonance imaging features

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OBJECTIVE Treatment with a *BRAF* mutation inhibitor might shrink otherwise refractory craniopharyngiomas and is a promising preoperative treatment to facilitate tumor resection. The aim of this study was to investigate the noninvasive diagnosis of *BRAF*-mutated craniopharyngiomas based on MRI characteristics.

METHODS Fifty-two patients with pathologically diagnosed craniopharyngioma were included in this study. Polymerase chain reaction was performed on tumor tissue specimens to detect *BRAF* and *CTNNB1* mutations. MRI manifestations—including tumor location, size, shape, and composition; signal intensity of cysts; enhancement pattern; pituitary stalk morphology; and encasement of the internal carotid artery—were analyzed by 2 neuroradiologists blinded to patient identity and clinical characteristics, including *BRAF* mutation status. Results were compared between the *BRAF*-mutated and wild-type (WT) groups. Characteristics that were significantly more prevalent ($p < 0.05$) in the *BRAF*-mutated craniopharyngiomas were defined as diagnostic features. The minimum number of diagnostic features needed to make a diagnosis was determined by analyzing the receiver operating characteristic (ROC) curve.

RESULTS Eight of the 52 patients had *BRAF*-mutated craniopharyngiomas, and the remaining 44 had *BRAF* WT tumors. The clinical characteristics did not differ significantly between the 2 groups. Interobserver agreement for MRI data analysis was relatively reliable, with values of Cohen κ ranging from 0.65 to 0.97 ($p < 0.001$). A comparison of findings in the 2 patient groups showed that *BRAF*-mutated craniopharyngiomas tended to be suprasellar ($p < 0.001$), spherical ($p = 0.005$), predominantly solid ($p = 0.003$), and homogeneously enhancing ($p < 0.001$), and that patients with these tumors tended to have a thickened pituitary stalk ($p = 0.014$). When at least 3 of these 5 features were present, a tumor might be identified as *BRAF* mutated with a sensitivity of 1.00 and a specificity of 0.91. The area under the ROC curve for the sum of all 5 diagnostic criteria was 0.989 ($p < 0.001$).

CONCLUSIONS The *BRAF* mutation status of craniopharyngiomas might be predicted using certain MRI features with relatively high sensitivity and specificity, thus offering potential guidance for the preoperative administration of *BRAF* mutation inhibitors.

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KEY WORDS craniopharyngioma; *BRAF*; diagnosis; magnetic resonance imaging; oncology

CRANIOPHARYNGIOMAS are intracranial epithelial neoplasms with an estimated incidence of 0.13 per 100,000 cases per year. A bimodal age distribution, with peaks at 5–14 and 50–74 years, is present, and no difference in incidence by sex has been reported.⁵ The tumors may be entirely suprasellar, or they may exhibit intrasellar involvement. The prominent symptoms in patients

diagnosed with craniopharyngioma include visual deficits, endocrine deficiencies (such as diabetes insipidus), and headache.²⁷ As the majority of craniopharyngiomas show benign biological behavior, surgery, via either craniotomy or endoscopy, remains the first choice for treatment due to its advantages in tumor debulking and intracranial decompression.¹¹ However, craniopharyngiomas arise adjacent to

ABBREVIATIONS AUC = area under the curve; FFPE = formalin-fixed and paraffin-embedded; ICA = internal carotid artery; ROC = receiver operating characteristic; WT = wild type.

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the pituitary gland, hypothalamus, and optic chiasm and sometimes infiltrate into the third ventricle, adding to operative difficulties and causing substantial postoperative complications, such as hypothalamic disturbance, visual loss, or even death.²⁵

In efforts to develop less-invasive interventions for craniopharyngioma, molecular characteristics of the tumor as well as underlying mechanisms responsible for tumorigenesis have been investigated for years. *BRAF* is the most widely studied molecular characteristic of craniopharyngioma, and its V600E mutation is present in nearly all squamous-papillary craniopharyngiomas.^{4,8,12,22} Treatment with inhibitors targeting the *BRAF* V600E mutation, which has exhibited satisfactory efficacy for several malignancies,^{9,13} has been recently reported to be associated with shrinkage of recurrent craniopharyngiomas.^{1,3} If primary craniopharyngiomas could be diagnosed as *BRAF* V600E mutated via noninvasive methods, the inhibitors might serve as first-line treatment instead of surgery, or at least partially reduce the tumor size to facilitate subsequent surgery. Moreover, a precise pretreatment diagnosis of *BRAF* V600E-mutated craniopharyngioma is necessary for further clinical trials to assess the inhibitors' efficacy in a larger population.

The purpose of this study was to investigate the non-invasive diagnosis of *BRAF*-mutated craniopharyngioma. Since MRI is now the standard tool for preoperative diagnosis of craniopharyngioma, we compared the MRI manifestations of these tumors based on *BRAF* mutation status and tried to summarize diagnostic criteria for *BRAF*-mutated ones. The results may pave the way for administration of *BRAF* mutation inhibitors in the future.

Methods

Patient Population and Tissue Samples

This single-center retrospective study was approved by the local institutional review board. The inclusion criteria were preoperative MRI, including both nonenhanced and contrast-enhanced sequences, performed in our hospital; formalin-fixed and paraffin-embedded (FFPE) tumor tissues available in our tissue archive; and histological diagnosis of craniopharyngioma, reviewed and confirmed by 2 neuropathologists in consensus according to WHO 2007 criteria. The exclusion criteria were incomplete preoperative MRI data or MRI data electronically stored at other hospitals and insufficient FFPE tissue for analysis. Between January 2013 and August 2015, 59 patients underwent resection of intracranial tumors in our hospital and received a pathological diagnosis of craniopharyngioma. A total of 52 patients (35 men and 17 women; mean age 41 years, range 7–70 years) met the criteria and were included in the study.

Polymerase Chain Reaction and Mutation Analysis

DNA was extracted from FFPE tissue as follows. Tissues from the representative area of 90% tumor content were scraped off deparaffinized sections into tubes and treated in 10-mM Tris-HCl buffer with proteinase K at 55°C for 12 hours and then at 98°C for 10 minutes. The cell lysate was centrifuged, and supernatant was col-

lected for polymerase chain reaction (PCR). Primer pairs were used for gene amplification of *BRAF* V600E and beta-catenin (*CTNNB1*) exon 3. The primer sequences are shown in Supplemental Table 1, and the PCR procedure is described in detail in the Supplemental Methods.

Clinical Data Collection

Electronic medical records were reviewed for patient demographic characteristics, presenting symptoms, laboratory data, therapeutic strategies, and pathological manifestations. The patients' chief complaints and associated symptoms were classified into 4 categories. Intracranial hypertension usually caused headache, vomiting, and papilledema. Optic nerve-related symptoms such as blurred vision and visual field deficit were always further determined by ophthalmological examinations. Signs of hypothalamic dysfunction included diabetes insipidus, adipsia, weight gain, drowsiness, and cognitive disorders. Signs of hypopituitarism included developmental retardation, impotence, amenorrhea, and hypotension. Levels of hypothalamic-pituitary axis hormones were also scanned. Therapeutic strategies were established according to the above information combined with radiological data, and all patients in this study received surgical treatment via either craniotomy or the transsphenoidal approach.

Imaging Data Acquisition and Analysis

MR images were obtained with a 3.0-T MR scanner (Discovery 750, GE Healthcare). Patients were positioned supine, and an 8-channel head coil was used as the signal receiver. Imaging parameters of axial, sagittal, and coronal T1-weighted sequences were as follows: TE 9.1 msec, TR 2000 msec, FOV 20 × 20 cm, slice thickness 2.5 mm, and matrix size 256 × 256. Enhanced sagittal and coronal T1-weighted images were acquired with the same parameters after Gd-DTPA injection (0.2 ml/kg). Two neuroradiologists—one with 28 years of experience and one with 5 years of experience—first reviewed all MR images (blinded to patient identity and clinical characteristics, including *BRAF* mutation status) and then resolved their discrepancies in consensus. Quantitative measurements were made on a picture archiving and communication system (PACS). MRI characteristics evaluated were as follows: tumor location, size, shape, and composition; signal of tumor cysts on T1-weighted MRI; enhancement pattern; pituitary stalk morphology; and internal carotid artery (ICA) encasement. Lesions were divided into 2 subgroups based on location: 1) those located entirely within the suprasellar space, and 2) those located in the suprasellar region with sellar extension. Tumor size was measured as the maximum diameter on midsagittal contrast-enhanced T1-weighted MR images. Lesion shape was evaluated on sagittal and coronal MR images and described as spherical, lobular, or irregular. Lesion composition was defined as predominantly solid (if the solid component represented more than 50% of the total tumor volume on both sagittal and coronal sequences) or predominantly cystic (if the solid component was less than 50% of the total tumor volume). The signal intensity of tumor cysts on T1-weighted images was described as hyper-, iso-, or hypointense.

The patterns of contrast enhancement were described as homogeneous, heterogeneous, marginal enhancement, or no enhancement. Pituitary stalk thickening was defined as a diameter of the infundibulum ≥ 4 mm on contrast-enhanced sagittal T1-weighted MR images. Encasement of the ICA was confirmed when the ICA flow void was totally or partially within the tumor.

Statistical Analysis

Comparisons of continuous variables between groups were conducted by means of the Mann-Whitney U-test. Categorical variables were compared using the Fisher exact test. Interobserver agreement between the 2 readers was evaluated according to the Cohen κ statistic ($\kappa < 0$, poor agreement; $\kappa = 0$ –0.20, slight agreement; $\kappa = 0.21$ –0.40, fair agreement; $\kappa = 0.41$ –0.60, moderate agreement; $\kappa = 0.61$ –0.80, substantial agreement; $\kappa = 0.81$ –1.00, almost perfect agreement).¹⁵ Receiver operating characteristic (ROC) curves were constructed to test the sensitivity and specificity of the diagnostic criteria. The area under the curve (AUC) was estimated. The Youden index (sensitivity + specificity – 1) was calculated to assess the performance of each diagnostic criterion. A *p* value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS software version 21.0 (IBM Corp.).

Results

Clinical, Genetic, and Pathological Findings

Fifty-two patients with craniopharyngioma were included in this study. In 8 of these 52 cases, the tumor tissue exhibited the *BRAF* V600E mutation (Table 1, Supplemental Fig. 1). *CTNNB1* mutation, another common mutation in craniopharyngioma, was found in 25 tumors in the *BRAF* wild-type (WT) group (Supplemental Fig. 2, Supplemental Table 2). The patients' mean age at diagnosis did not differ significantly between the group with *BRAF*-mutated tumors and the group with *BRAF* WT tumors (48.5 ± 10.6 vs 39.3 ± 18.2 years, *p* = 0.149). Seven (87.5%) of the 8 patients with *BRAF*-mutated tumors and 28 (63.6%) of the 44 with *BRAF* WT tumors were male (*p* = 0.248). Optic nerve–related symptoms were the most common complaint for patients in both groups, followed by intracranial hypertension in patients with *BRAF*-mutated tumors (present in 5 of 8 cases) and hypothalamic dysfunction in patients with *BRAF* WT tumors (present in 20 of 44 cases). Overall, the distribution of patients' clinical symptoms did not vary significantly according to the *BRAF* status of their tumors (*p* = 0.880). In the *BRAF*-mutated group, 6 (75%) of 8 tumors were pathologically classified as squamous-papillary, 1 (12.5%) was classified as adamantinous, and 1 (12.5%) was classified as mixed type. Conversely, in the *BRAF* WT group, most of the tumors (41 of 44) were classified as adamantinous, indicating a potential correlation between *BRAF* mutation and pathological classification.

MRI Findings

MR images were analyzed for tumor location, size, shape, and composition; presence of cysts on noncontrast

TABLE 1. Demographics and clinical characteristics of 52 cases of craniopharyngioma stratified by *BRAF* V600E mutation status

Characteristic	<i>BRAF</i> Mutation (n = 8)	<i>BRAF</i> WT (n = 44)	<i>p</i> Value
Mean pt age (yrs)	48.5 $\pm$ 10.6	39.3 $\pm$ 18.2	0.149
Sex			0.248
Male	7	28	
Female	1	16	
Symptoms			0.880
Intracranial hypertension	5	18	
Optic nerve–related symptoms	6	29	
Hypothalamic dysfunction	3	20	
Hypopituitarism	2	14	
MRI features			
Location			<0.001
Suprasellar (only)	7	10	
Intrasellar involvement	1	34	
Mean size (mm)	27.1 $\pm$ 9.8	35.0 $\pm$ 13.5	0.180
Shape			0.005
Spherical	8	17	
Lobulated	0	12	
Irregular	0	15	
Composition			0.003
Predominantly solid	6	8	
Predominantly cystic	2	36	
Enhancement pattern			<0.001
Homogeneous	7	0	
Heterogeneous	1	26	
Marginal	0	14	
Nonenhanced	0	4	
Tumor cysts on noncontrast T1WI*			0.121
Hyperintense	0	20	
Hypointense	4	22	
Encasement of ICA			0.573
Yes	0	6	
No	8	38	
Pituitary stalk			0.014
Thickened	4	4	
Normal	4	40	
Pathological subtype			<0.001
Squamous-papillary	6	3	
Adamantinous	1	41	
Mixed	1	0	

Pt = patient; T1WI = T1-weighted MR imaging.

Values are numbers of cases or patients unless otherwise indicated. Mean values are presented with SDs.

* Cysts only existed in 4 *BRAF*-mutated tumors and 42 *BRAF* WT tumors.

T1-weighted images; enhancement pattern; pituitary stalk morphology; and ICA encasement (Table 1). The interobserver agreement between the 2 readers was satisfactory

FIG. 1. Representative coronal (A, C, E, and G) and sagittal (B, D, F, and H) T1-weighted contrast-enhanced MR images obtained in 2 patients with *BRAF*-mutated completely solid craniopharyngiomas (A and B, Case 1; C and D, Case 2) and 2 patients with *BRAF*-mutated mixed solid-cystic craniopharyngioma (E and F, Case 3; G and H, Case 4). In each image, the arrow indicates the tumor.

(Supplemental Table 3), with Cohen κ ranging from 0.65 to 0.97 ($p < 0.001$ for all parameters). Most of the *BRAF*-mutated tumors were located completely above the sellar region, while more than three-quarters of the *BRAF* WT tumors demonstrated intrasellar extension ($p < 0.001$).

The mean maximum diameter of the *BRAF*-mutated tumors was 27.1 mm, and that of the *BRAF* WT tumors was 35.0 mm. All *BRAF*-mutated tumors exhibited a spherical shape, which was also the most common shape in the *BRAF* WT group. However, 12 (27.3%) of the 44 *BRAF*

FIG. 2. Representative coronal (A, C, E, and G) and sagittal (B, D, F, and H) T1-weighted contrast-enhanced MR images obtained in 4 patients with *BRAF* WT craniopharyngioma (A and B, Case 5; C and D, Case 6; E and F, Case 7; G and H, Case 8). In each image, the arrow indicates the tumor.

TABLE 2. Diagnostic criteria of *BRAF*-mutated craniopharyngioma

Parameter	Manifestation on MRI
Location	Completely suprasellar
Shape	Spherical
Composition	Predominantly solid
Enhancement pattern	Homogeneous
Pituitary stalk	Thickened

WT tumors were lobulated and 15 (34.1%) were irregular, leading to a statistically significant difference in shape between the 2 groups ($p = 0.005$). Half of the *BRAF*-mutated tumors were completely solid, and 2 were mixed solid-cystic with a higher proportion of the solid component (Fig. 1). In contrast, 36 (81.8%) of the 44 *BRAF* WT tumors were predominantly cystic; thus, predominantly cystic tumor composition was significantly more common in the *BRAF* WT tumors than in the *BRAF*-mutated tumors ($p = 0.003$). Since the signal of cyst on noncontrast T1-weighted MR images has been reported to vary between different pathological types,²¹ we further investigated MR signal intensity in cases with tumor cysts and found hypointense signal in all 4 of the *BRAF*-mutated tumors with a cystic component on nonenhanced T1-weighted MR images and 22 (52.4%) of the 42 of *BRAF* WT ones. On postcontrast T1-weighted MR images, 7 *BRAF*-mutated tumors (87.5%) showed homogeneous enhancement, while only 1 (12.5%) showed heterogeneous enhancement. In contrast, 26 (59.1%) of the 44 *BRAF* WT tumors presented with a heterogeneous enhancement pattern ($p < 0.001$ for comparison with the percentage of *BRAF*-mutated tumors); 14 (31.8%) showed marginal enhancement, and 4 (9.1%) showed no enhancement (Fig. 2). Pituitary stalk thickening was present in half of the *BRAF*-mutated tumors but in only 4 (9.1%) of the 44 *BRAF* WT ones, serving as another significant parameter for differential diagnosis ($p = 0.014$). With regard to the tumor's relationship with vital vessels, the ICA was encased by tumor in none of the cases of *BRAF*-mutated tumors and in 6 (13.6%) of the 44 cases of *BRAF* WT tumors.

Considering that *CTNNB1* is also frequently mutated in craniopharyngioma,^{6,14,24} we further divided the *BRAF* WT group by *CTNNB1* status and made comparisons between *BRAF*-mutated, *CTNNB1*-mutated, and WT cases (Supplemental Table 4). Concordant with the above results, *BRAF*-mutated cases showed statistically significant differences in tumor location, shape, composition, and enhancement pattern and the pituitary stalk in comparison with either *CTNNB1*-mutated or WT cases. Moreover, the latter 2 groups shared more common MRI manifestations, implying that they might be related in tumorigenesis and pathology. As a result, we treated the *BRAF* WT cases as a single group and continued to dichotomize by *BRAF* status in subsequent studies.

Diagnostic Criteria for *BRAF*-Mutated Craniopharyngioma

Based on comparisons between the 2 groups, we suggested MRI characteristics of *BRAF*-mutated craniopharyngiomas as suprasellar location, spherical shape, predominantly solid composition, homogeneous enhancement, and association with pituitary stalk thickening (Table 2). These features were explored as potential diagnostic criteria for *BRAF*-mutated craniopharyngiomas, and ROC curves were created for each one (v. 3). No feature significantly surpassed others in AUC (Supplemental Table 5). The threshold number of features needed to make a diagnosis was further investigated. In 21 of the 52 cases, none of the features were present; and 1, 2, 3, 4, or 5 features were present, respectively, in 11, 8, 6, 3, and 3 cases. Accordingly, ROC curves were drawn to analyze the validity of diagnostic criteria using various combinations of features. For diagnostic criteria based on the presence of at least 1, 2, or 3 features, the sensitivities were all 100%, while the specificities were 47.7%, 72.7%, and 90.9%, respectively (Table 3). For diagnostic criteria based on the presence of at least 4 or 5 features, the specificities were 100% (for both), while the sensitivities were 75% and 37.5%, respectively. For criteria based on the presence of at least 1, 2, 3, 4, or 5 features, the Youden indexes were 0.477, 0.727, 0.909, 0.750, and 0.375, respectively, suggesting the diagnostic criterion of having at least 3 features as the optimal choice. In this context, the positive predictive

TABLE 3. Validity of diagnostic criteria with various numbers of features

Result	No. of Features				
	≥1	≥2	≥3	≥4	5
No. of true-pos results	8	8	8	6	3
No. of false-pos results	23	12	4	0	0
No. of true-neg results	21	32	40	44	44
No. of false-neg results	0	0	0	2	5
Sensitivity (95% CI)	1.00 (0.68–1.00)	1.00 (0.68–1.00)	1.00 (0.68–1.00)	0.75 (0.41–0.93)	0.38 (0.14–0.69)
Specificity (95% CI)	0.48 (0.34–0.62)	0.73 (0.58–0.84)	0.91 (0.79–0.96)	1.00 (0.92–1.00)	1.00 (0.92–1.00)
PPV (95% CI)	0.26 (0.14–0.43)	0.40 (0.22–0.61)	0.67 (0.39–0.86)	1.00 (0.61–1.00)	1.00 (0.44–1.00)
NPV	1.00 (0.85–1.00)	1.00 (0.89–1.00)	1.00 (0.91–1.00)	0.96 (0.85–0.99)	0.90 (0.78–0.96)
Youden index	0.48	0.73	0.91	0.75	0.38

Neg = negative; NPV = negative predictive value; pos = positive; PPV = positive predictive value.

FIG. 3. ROC curves for each characteristic feature of *BRAF*-mutated craniopharyngioma—suprasellar location (A), spherical shape (B), predominantly solid composition (C), homogeneous enhancement (D), and thickened pituitary stalk (E)—and for the combination of the features (F).

value and negative predictive value were 66.7% and 100%, respectively. The area under the ROC curve was 0.989 ($p < 0.001$), indicating relatively satisfactory performance of the diagnostic criterion (Fig. 3).

Discussion

Although neoadjuvant treatment such as *BRAF* V600E mutation inhibitor therapy shows a promising craniopharyngioma shrinkage effect, application will be limited until minimally invasive or noninvasive diagnostic methods are established. In this study we summarized common features of *BRAF* V600E-mutated craniopharyngiomas on MRI and proposed a novel set of diagnostic criteria.

Classically, craniopharyngiomas are divided into 2 histological subtypes: squamous-papillary and adamantinous.^{16,20} The squamous-papillary craniopharyngiomas arise from squamous-cell nests formed by metaplastic cells of the pars tuberalis of the adenohypophysis and are characterized by well-differentiated, nonkeratinizing squamous epithelium and little adhesion to surrounding tissues (Supplemental Fig. 3). In contrast, the adamantinous craniopharyngiomas originate from cell remnants of the craniopharyngeal duct and are characterized by multicystic components, nodules containing wet keratin, and invasion into the brain parenchyma (Supplemental Fig. 3). The

pathological differences contribute to various presentations on MRI.¹⁸ It has been reported that spherical shape, hypointense cysts on T1-weighted images, and predominantly solid appearance in squamous-papillary craniopharyngiomas are statistically differential manifestations from lobulated shape, large hyperintense cysts on T1-weighted images, and encasement of vessels in adamantinous tumors.²¹ However, awareness of pathological subtype does not alter surgical strategy, with total resection always being the preferred treatment. Moreover, no obvious difference in the recurrence rate, postoperative outcome, or mortality has been discovered between the 2 subtypes,²⁶ leaving the MRI differentiating criteria rarely applied in clinical practice.

Studies in the emerging field of tumor genetics may shed light on craniopharyngioma tumorigenesis and the biological behavior of these lesions. The *BRAF* protein is from the RAF kinase family and regulates cell growth through the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) signaling pathway. Its mutations,¹² among which V600E is the most common, are discovered in a variety of tumors and are considered to promote tumor progression as oncogenic drivers.⁸ It has been reported that nearly all squamous-papillary craniopharyngiomas harbor the *BRAF* V600E mutation.^{4,22} Mutation of *CTNNB1*, which encodes β -catenin protein in a Wnt pathway, was detected in adamantinous craniopharyngiomas.

ryngiomas with a prevalence reported at 16% in one study¹⁹ and 100% in another.²⁴ Although the coexistence of the *CTNNB1* and *BRAF* mutations has been reported in rare cases,¹⁷ some researchers have suggested that these mutations may be mutually exclusive, clonal, and specific to each subtype.² Confirming these earlier findings, our study showed that the *BRAF* V600E mutation was expressed in 6 (66.7%) of 9 squamous-papillary craniopharyngiomas, while the *CTNNB1* mutation was detected in 24 (57.1%) of 42 adamantinous craniopharyngiomas, indicating that reactivation of Wnt and MAPK/ERK pathways may play important roles in tumorigenesis of these pathological subtypes, respectively. Moreover, 19 cases in our series were found to be WT for both *BRAF* and *CTNNB1*, implying the existence of other genetic drivers for craniopharyngiomas that have not yet been identified.

Since the *BRAF* V600E mutation was first detected in craniopharyngiomas in 2014,⁴ no study had, until now, explored MRI manifestations of *BRAF*-mutated craniopharyngiomas, let alone their differentiation from *CTNNB1*-mutated tumors or other subtypes. Although our study is based on a relatively small sample, we addressed characteristic features of *BRAF*-mutated craniopharyngiomas and propose a novel diagnostic criterion (of having at least 3 features) with a sensitivity of 100% and a specificity of 90.9%. The reasons that would explain why *BRAF*-mutated craniopharyngiomas commonly share these features are unclear, because few studies have focused on the mechanisms underlying the contribution of *BRAF* mutation to the tumorigenesis of craniopharyngiomas. Taking into account that *BRAF*-mutated craniopharyngiomas present features similar to those of squamous-papillary craniopharyngiomas and that *BRAF* mutation is highly prevalent in the squamous-papillary subtype, we speculate that there may be a 2-step process, with *BRAF* mutation first inducing the origination of squamous-papillary craniopharyngioma from the pars tuberalis and then promoting the histological presentations, such as discrete architecture and well-differentiated epithelium, resulting in a characteristic macroscopic appearance on MRI.

In our study, *BRAF* WT craniopharyngiomas also tended to share certain MRI characteristics regardless of *CTNNB1* status. They were predominantly cystic and usually multicystic, presented with heterogeneous signal on T1-weighted imaging, and infiltrated into the sellar region more frequently. Reactivation of the Wnt pathway through *CTNNB1* mutation leads to whorl-like arrays and morule-like structures, as seen on histological examination, and regulates cytokeratin expression toward hair follicle differentiation.¹⁴ In addition to being seen in craniopharyngiomas, *CTNNB1* mutation is also seen in calcifying odontogenic cysts.²³ These data partially explain the heterogeneous composition of *CTNNB1*-mutated craniopharyngiomas, which include cholesterol, triglycerides, protein, and desquamated epithelium. The tumors free of both *BRAF* and *CTNNB1* mutations in our study showed a tendency toward a more irregular shape, but further investigation of molecular mechanisms is needed.

The development of *BRAF* mutation inhibitors, including vemurafenib and dabrafenib, has strikingly advanced the fight against malignant tumors.¹⁰ In a Phase III trial

focusing on melanoma, the objective response rate (ORR) was elevated from 5% in the control cohort to 48% in the vemurafenib cohort, bringing great hope to patients with *BRAF*-mutated tumors.⁷ An ongoing Phase II study enrolling patients with nonmelanoma cancers revealed that vemurafenib treatment resulted in an ORR of 42% in non-small cell lung cancer and an ORR of 43% in Erdheim-Chester disease and Langerhans cell histiocytosis.¹³ So far 2 reports have addressed the application of vemurafenib in craniopharyngiomas. Aylwin et al.¹ administered vemurafenib to a patient with recurrent craniopharyngioma and reported marked tumor shrinkage. Considering that monotherapy tends to induce tumor resistance, Brastianos et al.³ combined dabrafenib with the mitogen/extracellular signal-regulated kinase (MEK) inhibitor trametinib to treat a patient with recurrent *BRAF* V600E craniopharyngioma and achieved a dramatic response. These data highlight the potential of *BRAF* mutation inhibition as a novel chemotherapy for recurrent *BRAF*-mutated craniopharyngioma. Additionally, according to our findings, this kind of craniopharyngioma is predominantly solid, which adds to the surgical difficulty and increases the risk of iatrogenic injury to surrounding tissues. Preoperative treatment with a *BRAF* mutation inhibitor may reduce the tumor's size, reduce its blood supply, and release adhesion, thus facilitating subsequent surgery or radiotherapy.

Study Limitations

Our study has some limitations. First, although 52 cases were analyzed, only 8 of the tumors were *BRAF* mutated, adding to potential bias caused by a limited sample size. Second, since our center primarily treats adults, few cases involving children were included; in light of the craniopharyngioma incidence peak in adolescence, this may constitute a selection bias. Third, this study retrospectively examined features of *BRAF*-mutated craniopharyngiomas based on cases with definite pathological diagnosis. However, other lesions, including pituitary adenoma, Rathke cleft cyst, and germ cell tumor, may confound preoperative diagnosis, and such lesions should be included in future studies.

Conclusions

Craniopharyngiomas with the *BRAF* V600E mutation share common features on MR images, including suprasellar location, spherical shape, predominantly solid composition, homogeneous enhancement, and association with pituitary stalk thickening. Our results indicate that when at least 3 of these 5 features are present, a pretreatment diagnosis of *BRAF*-mutated craniopharyngioma may be established. After further testing in a larger population, this diagnostic method may provide complementary genetic information for treatment planning and thus offer a potential reference for preoperative treatment with a *BRAF* mutation inhibitor to facilitate tumor resection.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Chen, Shi, Yao. Acquisition of data: Yue, Shi, Wang, Zhu, Du. Analysis and interpretation of data: Yue, Yu, Du. Drafting the article: Yue, Yu. Critically revising the article: Chen, Yue, Yu, Yao. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Chen. Statistical analysis: Yue, Yu. Administrative/technical/material support: Chen, Shi, Wang, Zhu, Yao, Mao. Study supervision: Chen, Mao.

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