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Original Article

The Association of *BRAF* Single Nucleotide Polymorphism (rs113488022) with Clinical Characteristics and Postoperative Outcomes of Craniopharyngioma

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Abstract

Background: Craniopharyngiomas are benign but locally aggressive sellar tumors with high postoperative morbidity. The *BRAF V600E* mutation is a hallmark of the papillary subtype, yet its prognostic significance remains controversial. Most studies have focused on papillary craniopharyngiomas, while the potential role of *BRAF* gene variations in clinical outcomes across both subtypes has been underexplored. This study investigated the association of *BRAF* single nucleotide polymorphism with clinical characteristics and postoperative outcomes in patients with craniopharyngioma.

Methods: The current historical cohort study included 47 patients with histopathologically confirmed craniopharyngioma who underwent endoscopic endonasal resection. *BRAF* rs113488022 genotyping (TT, TC, CC) was performed on DNA extracted from formalin-fixed paraffin-embedded tumor specimens using real-time PCR. Associations between genotypes and histopathological subtype, tumor volume, calcification, lobulation, extent of resection, postoperative complications, recurrence, and mortality were analyzed.

Results: The patients included 26 males (55.3%) and 21 females (44.7%), with a mean age of 25.06 ± 17.17 years. The most frequent *BRAF* rs113488022 genotype was 'TC' (76.6%), followed by 'CC' (14.9%) and 'TT' (8.6%). A significant difference in genotype distribution was observed between adamantinomatous and papillary craniopharyngiomas (P=0.024), with the 'CC' genotype being more common in the papillary subtype. No significant associations were found between *BRAF* rs113488022 genotypes and tumor volume (P=0.93), calcification (P=0.61), lobulation (P=0.34), extent of resection (P=0.47), recurrence (P=0.55), mortality (P=0.13), or postoperative complications including diabetes insipidus, visual changes, and BMI changes (all P>0.05).

Conclusion: While *BRAF* rs113488022 genotype distribution differs significantly between histopathological subtypes and serves as a valuable diagnostic marker, it does not independently predict postoperative surgical outcomes, recurrence, or mortality in craniopharyngioma patients. Larger prospective studies are needed to further elucidate the prognostic significance of specific *BRAF* SNPs.

Keywords: BRAF; Craniopharyngioma; Polymorphism; Prognosis; Recurrence; rs113488022; Surgical Outcomes

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Introduction

Craniopharyngiomas are benign epithelial tumors arising from the sellar and parasellar region, accounting for approximately 1.2–4.6% of all intracranial neoplasms (1). Despite their benign histology, they often exhibit aggressive clinical behavior due to their proximity to critical structures including the optic pathway, pituitary gland, hypothalamus, and major cerebral arteries. The standard of care remains maximal safe surgical resection, often followed by radiation therapy for residual or recurrent disease. However, postoperative morbidity, including hypothalamic injury, panhypopituitarism, visual impairment, and diabetes insipidus, remains substantial as high as 50% (2).

Comprised of two main histopathological subtypes, adamantinomatous (ACP) and papillary (PCP), craniopharyngioma may demonstrate different etiologic and imaging features. The ACP is more common in adults and children, characterized by cystic components, calcifications, and activating mutations in *CTNNB1* (β-catenin). On the other hand, the PCP typically occurs in adults, is more often solid, and lacks calcifications (3). The discovery of *BRAF V600E* mutations and gene polymorphisms in nearly all PCP cases has dramatically influenced diagnostic and therapeutic approaches (4). This mutation leads to constitutive activation of the MAPK signaling pathway, driving tumor proliferation and survival.

The role of *BRAF* gene variations in craniopharyngioma prognosis remains incompletely understood. While some studies suggest that *BRAF*-mutant tumors may behave differently in terms of recurrence and response to therapy (5), others have found no independent prognostic value when accounting for extent of resection (6). In the meantime, all the prognostic studies, have focused on the role of *BRAF V600E* in PCP only, while it should be noted that each individual, even those with ACP harbor a genotype for this location, which could potentially play a role in disease prognosis. Furthermore, the emergence of BRAF/MEK inhibitor therapy has demonstrated remarkable efficacy, with up to 90% tumor volume reduction in newly diagnosed and recurrent PCP (7), raising the possibility of targeted therapy as a primary or neoadjuvant treatment.

Accordingly, understanding the association between *BRAF* single nucleotide polymorphisms (SNP) and clinical characteristics including tumor morphology, extent of resection, recurrence, and postoperative outcomes, is essential for optimizing patient management. In the current study, we investigated the distribution of *BRAF SNP rs113488022* (TT, TC, CC) in Iranian patients with craniopharyngioma and evaluated their relationship with histopathological subtype, tumor volume, calcification, lobulation, extent of surgical resection, postoperative complications, recurrence, and mortality.

Materials and Methods

Study Population

The historical cohort study was conducted in Tehran University of Medical Sciences (TUMS), Tehran, Iran. The patients with confirmed histopathologic diagnosis of craniopharyngioma who underwent endoscopic endonasal resection for treatment of tumor were eligible to be included. Accordingly, and after reconfirmation of the histopathologic diagnosis, the paraffin-block specimens were collected from the pathology department of Imam Khomeini Hospital Complex (IKHC), Tehran, Iran.

Clinical and demographic data (age, gender, histopathological subtype, tumor volume, calcification, lobulation, extent of surgical resection, postoperative complications, recurrence, and mortality) of patients were collected and recorded through reviewing patients' files.

This cohort study was approved by the Ethical Committee and Research Committee of Tehran University of Medical Sciences, Tehran, Iran.

Sample Preparation and DNA Extraction and Genotyping

The most suitable cross section of brain specimens by visual microscopic assessment (>70% neoplastic cells and <50% necrosis) were fixed by formalin-fixed paraffin embedded (FFPE) protocol.

The Phenol: Chloroform method was applied for DNA extraction from FFPE brain samples, followed by purity and yield assessment using a NanoDrop spectrophotometer. The *BRAF SNP (rs113488022)* mutation was genotyped through real-time PCR with TaqMan genotyping (allelic discrimination) using the ABI Real-Time PCR

System. Briefly, reagents including 10 µl Master-Mix, 0.5 µl AssayMix, 20 ng/µl of extracted DNA, and distilled water up to total volume of 20 µl were placed in each 96 microwell of the reaction plate. The primers were designed with TaqMan protocol and real-time PCR was conducted with TaqMan.

Statistical analysis

All the experimental data of the genotype frequency as well as the clinical data in patients were statistically evaluated using SPSS27.0. Qualitative variables were described using frequencies and percentage, and the quantitative ones were described using mean ± SD. The association of two qualitative variables were assessed using the Chi-square test, and the association of a qualitative and a quantitative variable were assessed using independent sample T-test or ANOVA, with a P-value of <0.05 considered statistically significant in all tests.

Results

After reviewing the data base and collecting the paraffin-fixed tumor blocks of 72 patients, DNA could be obtained from a total of 57 patients. After quality assessment the extracted DNA, PCR reactions were performed and the samples of 47 patients were successfully genotyped for the *BRAF SNP (rs113488022)*.

Patient Demographic and Clinical Characteristics

The patients included 26 males (55.3%) and 21 females (44.7%), with a mean age of 25.06 ± 17.17 years.The tumors included 41 ACP (87.24%) and 6 PCP (12.76%) subtypes. The most common genotype of *BRAF rs113488022* was 'TC' (76.6%), followed by 'CC' (14.9%), and the least common genotype was 'TT' (8.6%). The mean tumor volume was 22.77 ± 24.47 cm3. The majorities of tumors demonstrated calcification (70.2%), or lobulation (80.9%). Surgical resection resulted in GTR, NTR, STR, and PR of the tumors in 46.8%, 23.4%, 14.9%, and 4.3% of patients, respectively. A total number of 12 patients (25.5%), experienced recurrence and there was a mortality rate of 6.4% among these patients. Total rate of complications was 53.2%, with the most common complication being panhypopituitarism (42.6%). The details are demonstrated on **Table 1**.

The Association of *BRAF SNP (rs113488022)* Genotypes with Craniopharyngioma Histopathology

The most common genotype across both pathologies was the 'TC' genotype comprising 76.6% of all tumors. This genotype was more frequent in the Adamantinomatous type as well. However, the 'CC' genotype was more common in the Papillary type craniopharyngioma. There was significant difference in the genotype distribution of BRAF SNP between the Papillary and Adamnatinomatous Craniopharyngiomas (P=0.024) **(Table 2)**.

The Distribution of *BRAF SNP (rs113488022)* Genotypes in Pediatrics and Adults

The heterozygote 'TC' genotype was the most

Table 1. Demographics and clinical characteristics of patients

Variable (N=47)	Value
Age (Years)	25.06 ± 17.17
Gender	
Male	26 (55.3%)
Female	21 (44.7%)
Pathology	
Adamantinomatous	41 (87.24%)
Papillary	6 (12.76%)
BRAF V600E Genotype	
TT	4 (8.5%)
TC	36 (76.6%)
CC	7 (14.9%)
Tumor Volume (cm^3)	22.77 ± 24.47
Calcification	33 (70.2%)
Lobulation	38 (80.9%)
Extent of Resection	
GTR	22 (46.8%)
NTR	11 (23.4%)
STR	7 (14.9%)
PR	2 (4.3%)
Recurrence	12 (25.5%)
Mortality	3 (6.4%)
Surgical Complications (total)	25 (53.2%)
Panhypopituitarism	20 (42.6%)
Meningitis and Infection	3 (6.4%)
CSF Leak	1 (2.1%)

common among pediatrics and adults. The homozygote "TT' and 'CC' distributions were also comparable between two groups, as demonstrated on **Table 3** (P=0.79).

The Association of *BRAF SNP (rs113488022)* Genotypes and Tumor Calcification

As demonstrated in detail on **Table 4**, tumors with no calcification were found only among patients with 'TT' genotype. Therefore, the 'T' allele could potentially play a role in the absence of tumor calcification, however not significant (P=0.61).

The Association of *BRAF SNP (rs113488022)* Genotypes and Tumor Lobulation

Although most of the tumors demonstrated lobulation on MRI, those minorities without lobulation carried 'CC' genotype. It should be noted that genotype distribution among tumors with/without lobulation was not significant (P=0.34) **(Table 5)**.

Table 2. The association of *BRAF SNP (rs113488022)* genotypes with craniopharyngioma pathology

Histopathology	TT	TC	CC	P-value
Papillary	1 (16.7%)	2 (33.3%)	3 (50.0%)	0.024
Adamantinomatous	3 (7.3%)	34 (82.9%)	4 (9.8%)	

Table 3. The *BRAF SNP (rs113488022)* genotypes in pediatrics and adults

Age Group	TT	TC	CC	P-value
Pediatric	1 (2%)	19 (38%)	4 (8%)	0.79
Adults	3 (6%)	18 (36%)	5 (10%)	

Table 4. Tumor calcification among *BRAF SNP (rs113488022)* genotypes

		TT	TC	CC	P-value
Calcification	Yes	3 (9.1%)	26 (78.8%)	4 (12.1%)	0.61
	No	0	6 (75.0%)	2 (25.0%)	

Table 5. The association of tumor lobulation and *BRAF SNP (rs113488022)* genotypes

		TT	TC	CC	P-value
Lobulation	Yes	2 (5.3%)	30 (78.9%)	6 (15.8%)	0.34
	No	1 (25.0%)	3 (75.0%)	0	

The Association of *BRAF SNP (rs113488022)* Genotypes with Tumor Volume

The 'CC' genotype was associated with the highest tumor volume (25.42 ± 23.56), while patients with the 'TT' genotype has the lowest tumor volume (18.40 ± 8.82). The difference among genotypes was not statistically significant (P=0.93) **(Table 6)**.

The Association of *BRAF SNP (rs113488022)* Genotypes with Extent of Resection

The extent of resection across all the three genotypes of *BRAF SNP (rs113488022)* is demonstrated in detail on **Table 7**. Accordingly, it seems that the tumor genotype did not affect the extent of resection in craniopharyngiomas (P=0.47).

The Association of *BRAF SNP (rs113488022)* Genotypes with postoperative DI

As demonstrated in detail on **Table 8**, the distribution of *BRAF SNP (rs113488022)* genotypes among patients with and without postoperative DI was not significantly different (P=0.91).

The Association of *BRAF SNP (rs113488022)* Genotypes with postoperative VA Change

Homozygote genotypes (TT or CC) were not found in any of the patients with improved/dete-

riorated VA, however, the difference in the genotype distribution of *BRAF SNP (rs113488022)* was not statistically significant (P=0.75) **(Table 9)**.

The Association of *BRAF SNP (rs113488022)* Genotypes with postoperative VF Change

The homozygote 'TT' genotype was found in two patients with improved postop VF. The 'TT' genotype was more common among all the patients, and the *BRAF SNP (rs113488022)* genotype was not significantly associated with postoperative VF change (P=0.65) **(Table 10)**.

The Association of *BRAF SNP (rs113488022)* Genotypes with postoperative BMI Change

The 'TT' genotype was more common among all the patients, however, the genotypes of *BRAF SNP (rs113488022)* was not significantly associated with postoperative BMI change (P=0.95) **(Table 11)**.

The Association of *BRAF SNP (rs113488022)* Genotypes with Tumor Recurrence

As demonstrated on **Table 12**, *BRAF SNP (rs113488022)* genotypes were similarly distributed among patients with or without recurrence, and therefore, not to be considered as a prognostic factor (P=0.55).

The Association of *BRAF SNP (rs113488022)* Genotypes with Postoperative Complications and Mortality

BRAF SNP (rs113488022) genotypes were not associated with neither presence nor the type of postoperative complications in patients with craniopharyngioma. **Table 13** shows distribution of different types of surgical complications across the three genotypes of *BRAF SNP (rs113488022),* which was not remarkably different (P=0.33).

Table 6. The association of *BRAF SNP (rs113488022)* and tumor volume

Genotype	Number	Mean (cm^3)	SD	P-value
TT	3	18.3998	8.82435	0.93
TC	25	22.7648	26.38100	
CC	5	25.4255	23.56980	

Table 7. The association of *BRAF SNP (rs113488022)* genotypes and the extent of resection

		TT	TC	CC	P-value
Extent of Resection	**GTR**	1 (4.5%)	19 (86.4%)	2 (9.1%)	0.47
	STR	1 (14.3%)	5 (71.4%)	1 (14.3%)	
	PR	0	1 (50.0%)	1 (50.0%)	
	NTR	1 (9.1%)	8 (72.7%)	2 (18.2%)	

Table 8. The association of *BRAF SNP (rs113488022)* genotypes with postoperative DI

		TT	TC	CC	P-value
DI	**Yes**	1 (2.3%)	15 (34.9%)	3 (7%)	0.91
	No	2 (4.7%)	18 (41.9%)	4 (9.3%)	

Table 9. The association of *BRAF SNP (rs113488022)* with postoperative VA change

		TT	TC	CC	P-value
VA Change	**Improve**	0	8 (30.8%)	0	0.75
	Deteriorate	0	2 (7.7%)	0	
	No change	1 (3.8%)	13 (50%)	2 (7.7%)	

Table 10. The association of *BRAF SNP (rs113488022)* with postoperative VF change

		TT	TC	CC	P-value
VF Change	Improve	2 (6.3%)	12 (37.5%)	0	0.65
	Deteriorate	0	4 (12.5%)	0	
	No change	0	13 (40.6%)	1 (3.1%)	

Table 11. The association of *BRAF SNP (rs113488022)* genotype with postoperative BMI change

		TT	TC	CC	P-value
BMI Change	Increase	1 (5.9%)	11 (64.7%)	1 (5.9%)	0.95
	Decrease	0	3 (17.6%)	0	
	No change	0	1 (5.9%)	0	

Table 12. The association of *BRAF SNP (rs113488022)* genotype and tumor recurrence

		TT	TC	CC	P-value
Recurrence	Yes	0	10 (83.3%)	2 (16.7%)	0.55
	No	3 (10.3%)	23 (79.3%)	3 (10.3%)	

Table 13. The association of *BRAF SNP (rs113488022) g*enotypes and postoperative complications

		TT	TC	CC	P-value
Surgical Complications	No Complication	2 (4.3%)	16 (34.0%)	4 (8.5%)	-
	CSF Leak	0	1 (2.1%)	0	0.33
	Meningitis and Infection	0	1 (2.1%)	2 (4.3%)	
	Panhypopituitarism	2 (4.3%)	17 (36.2%)	1 (2.1%)	
	Others	0	1 (2.1%)	0	

Similarly, the mortality rate was not associated with the distribution of genotypes (P=0.13).

Discussion

In the current study, we investigated the association of the *BRAF SNP (rs113488022)* with clinical characteristics and postoperative outcomes in 47 patients with craniopharyngioma. Our findings demonstrated that the 'TC' genotype was the most prevalent (76.6%), followed by 'CC' (14.9%) and 'TT' (8.6%). Importantly, the distribution of *BRAF SNP (rs113488022)* genotypes differed significantly between Adamantinomatous (ACP) and Papillary craniopharyngiomas (PCP) (P=0.024), with the 'CC' genotype being more common in the PCP. It is worthwhile to note that prior studies have identified BRAF V600E mutations as a hallmark of PCP, often with a homozygous or heterozygous pattern (6, 7).

The *BRAF V600E* mutation results in a substitution of valine to glutamic acid at codon 600, leading to activation of the mitogen-activated protein kinase (MAPK) pathway, which promotes uncontrolled cellular proliferation and survival. In craniopharyngioma, this mutation is almost exclusively restricted to the papillary subtype and is believed to play a role in early tumorigenesis (3). Unlike ACP, which is characterized by *CTNNB1* mutations and aberrant β-catenin signaling, PCP lacks calcifications and cystic components, potentially due to differences in signaling pathway activation (5). The presence of *BRAF V600E* in nearly all PCP cases has led to its inclusion as a diagnostic criterion in the current WHO classification of central nervous system tumors (8).

Addressing the prognostic significance, we found that *BRAF* genotype was not significantly associated with tumor recurrence (P=0.55), extent of resection (P=0.47), mortality (P=0.13), or postoperative complications including diabe-

tes insipidus, visual changes, and BMI changes (P>0.05). Similarly, no significant associations were found between *BRAF SNP (rs113488022)* genotypes and tumor volume (P=0.93) or radiological features such as calcification (P=0.61) and lobulation (P=0.34).

Taking all together, the role of *BRAF* gene variations remains controversial. Some studies have suggested that *BRAF*-mutated PCP may have a lower recurrence rate compared to ACP when complete resection is achieved. However, other large cohorts have failed to demonstrate an independent prognostic role for *BRAF* mutation after adjusting for extent of resection and adjuvant therapy (6, 9). Our findings are consistent with the second group, as we observed no significant association between *BRAF SNP (rs113488022)* genotype and recurrence, mortality or postoperative complications. It is possible that while BRAF gene takes part in tumor initiation, clinical outcomes are predominantly influenced by surgical factors, tumor location, and hypothalamic involvement rather than the mutation itself.

Our finding that *BRAF SNP (rs113488022)* genotype did not independently predict postoperative surgical outcomes is consistent with several recent studies. A 2022 study by Xu et al., which included 61 craniopharyngioma specimens, demonstrated that while *BRAF V600E* was highly specific for papillary subtype, it did not offer prognostic significance for progression-free survival (PFS) (6). Similarly, a multicenter study published in 2025 comparing pediatric and adult PCP concluded that postoperative prognosis did not differ between these groups despite differences in tumor location, histology, and immune microenvironment. Both pediatric and adult PCP cases exhibited the *BRAF V600E* mutation with no differences in methylation patterns, yet the clinical outcomes following surgery were not statistically different (10). This supports our observation that BRAF mutation status alone does not serve as a surgical prognostic marker.

Reyes and colleagues reported that among *BRAF*-mutated craniopharyngioma patients, gross total resection (GTR) yielded significantly better PFS than subtotal resection (STR) with or without adjuvant radiation (P<0.01) (5). Importantly, their study demonstrated that for β-catenin-mutated tumors, GTR and STR ± XRT showed similar PFS outcomes, whereas for *BRAF*-mutated tumors, greater extent of resection was significantly associated with prolonged PFS (5). This suggests that the molecular subtyping may have prognostic value while being considered alongside treatment strategy rather than as an independent predictor. In contrast, a 2024 retrospective analysis by Fujio and colleagues found that among PCP patients, those with the *BRAF V600E* mutation did not show differences in recurrence-free survival compared to *BRAF*-wild-type PCP, further supporting that the mutation itself is not a strong prognostic factor (11).

Based on the results of a study involving 42 patients with craniopharyngioma, 12 patients harbored the *BRAF V600E* mutation. All mutation-positive patients were over 18 years of age, calcification was rarely observed in these tumors, and 92% exhibited a supradiaphragmatic location. Accordingly, patient age, calcification, and tumor location may serve as predictors of *BRAF V600E* mutation status (12). Notably, in a study of 30 patients with craniopharyngioma, 9 patients with the papillary subtype carried the *BRAF V600E* mutation, which was significantly associated with optic tract edema (55.6%). Furthermore, all patients demonstrating optic tract edema on MRI harbored this genetic mutation (13). The *BRAF V600E* mutation may also predict certain additional MRI features of craniopharyngioma. Tumors harboring the *BRAF V600E* mutation were more likely to have a suprasellar location, rounded morphology, a predominantly solid component, and homogeneous enhancement. Moreover, patients with this mutation had a thicker pituitary stalk compared to others. Based on these findings, the presence of these five aforementioned features could potentially predict *BRAF V600E* mutation (14). In another study, 94% of patients with PCP harbored the *BRAF V600E* mutation, whereas patients with the ACP subtype lacked this mutation (15). The *BRAF V600E* mutation showed 76.9% sensitivity and 96.4% specificity for PCP (16).

The results of our study differ from some of the published literature as we did not find *BRAF SNP (rs113488022)* genotype to be a prognostic factor for surgical outcomes (17). This disparity can be explained by several factors: First, the prognostic value of *BRAF* gene variations would be better elucidated through application of BRAF-MEK

inhibitors, while none of our patients received such treatment. Second, our cohort included both papillary and adamantinomatous subtypes, and the prognostic significance of *BRAF* gene variations may differ between these groups. However, it should be noted that as each individual has a genotype for this location, it could potentially play a role in pathogenesis and/or prognosis of disease. Third, our sample size (n=47) and limited number of events (12 recurrences, 3 deaths) may have been insufficient to detect associations, as suggested by the lack of statistical power for subgroup analyses.

Limitations

The limitations of our study include the retrospective design, relatively small sample size (especially for subgroup analyses), unequal distribution of histopathologic subtypes, and the absence of patients treated with BRAF/MEK inhibitors. Additionally, we did not assess the relationship between *BRAF* genotype and response to targeted therapy, as none of our patients received these agents. Future studies should prospectively evaluate the impact of *BRAF* genotype on both surgical and medical treatment outcomes (response to radiotherapy), as well as their response to targeted therapy.

Conclusions

In conclusion, while *BRAF* gene variations are highly prevalent in PCPs and serves as a valuable diagnostic marker, our findings suggest that it does not independently predict postoperative surgical outcomes including recurrence, mortality, or complications. Larger prospective studies are needed to further elucidate the prognostic significance of specific *BRAF SNP (rs113488022)* genotypes (TT, TC, CC) on long-term outcomes and to optimize the integration of targeted therapy into multimodal treatment strategies.

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References

1. Ostrom QT, Patil N, Cioffi G, Waite K, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2013–2017. Neuro-oncology. 2020;22(Supplement_1):iv1-iv96.
2. Müller H, Merchant T, Warmuth-Metz M, Martinez-Barbera J, Pugest S. Craniopharyngioma Nat Rev Dis Primer 5 (1): 75. 2019.
3. Brastianos PK, Taylor-Weiner A, Manley PE, Jones RT, Dias-Santagata D, Thorner AR, et al. Exome sequencing identifies BRAF mutations in papillary craniopharyngiomas. Nature genetics. 2014;46(2):161-5.
4. Larkin SJ, Ansorge O. Pathology and pathogenesis of craniopharyngiomas. Pituitary. 2013;16(1):9-17.
5. Reyes M, Kelly P, Kang K, Williams J, Sathe A, Kayne A, et al. Effect of Extent of Resection and Adjuvant Radiation on Recurrence of BRAF versus β-Catenin–Mutated Craniopharyngioma: A Single Institutional Case Series. Journal of Neurological Surgery Part B: Skull Base. 2025;86(05):570-6.
6. Xu C, Ge S, Cheng J, Gao H, Zhang F, Han A. Pathological and prognostic characterization of craniopharyngioma based on the expression of TrkA, β-catenin, cell cycle markers, and BRAF V600E mutation. Frontiers in Endocrinology. 2022;13:859381.
7. Brastianos PK, Twohy E, Geyer S, Gerstner ER, Kaufmann TJ, Tabrizi S, et al. BRAF–MEK inhibition in newly diagnosed papillary craniopharyngiomas. New England Journal of Medicine. 2023;389(2):118-26.
8. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro Oncol. 2021;23(8):1231-51.
9. Losa M, Mazza E, Pedone E, Nocera G, Liscia N, Reni M, et al. Targeted therapy in BRAF mutated aggressive papillary craniopharyngioma: a case report and overview of the literature. Journal of Endocrinological Investigation. 2024;47(11):2835-42.
10. Luo N, Lin Y, Feng J, Cai L, Zhang Y, Wang X, et al. Comparative analysis of clinical features, methylation and immune microenvironment in pediatric and adult papillary craniopharyngiomas: results from a multicenter study. Sci Rep. 2025;15(1):27422.
11. Fujio S, Ilmansyah R, Makino R, Juratli TA, Sugata J, Bakhtiar Y, et al. Prospects of BRAF/MEK Inhibitor Therapy in Papillary Craniopharyngiomas with the BRAF V600E Mutation: A Scoping Review. Neurologia medico-chirurgica. 2025;65(5):217-29.

12. Fujio S, Juratli TA, Arita K, Hirano H, Nagano Y, Takajo T, et al. A Clinical Rule for Preoperative Prediction of BRAF Mutation Status in Craniopharyngiomas. Neurosurgery. 2019;85(2):204-10.
13. Taguchi A, Kinoshita Y, Kojima M, Amatya VJ, Tominaga A, Takeshima Y, et al. Optic tract edema in craniopharyngioma as a predictor of BRAFV600E mutation presence. Jpn J Clin Oncol. 2023.
14. Yue Q, Yu Y, Shi Z, Wang Y, Zhu W, Du Z, et al. Prediction of BRAF mutation status of craniopharyngioma using magnetic resonance imaging features. J Neurosurg. 2018;129(1):27-34.
15. Goschzik T, Gessi M, Dreschmann V, Gebhardt U, Wang L, Yamaguchi S, et al. Genomic Alterations of Adamantinomatous and Papillary Craniopharyngioma. J Neuropathol Exp Neurol. 2017;76(2):126-34.
16. Marucci G, de Biase D, Zoli M, Faustini-Fustini M, Bacci A, Pasquini E, et al. Targeted BRAF and CTNNB1 next-generation sequencing allows proper classification of nonadenomatous lesions of the sellar region in samples with limiting amounts of lesional cells. Pituitary. 2015;18(6):905-11.
17. Iranmehr A, Esmaeilnia M, Afshari K, Sadrehosseini SM, Tabari A, Jouibari MF, et al. Surgical Outcomes of Endoscopic Endonasal Surgery in 29 Patients with Craniopharyngioma. J Neurol Surg B Skull Base. 2021;82(4):401-9.