



# Astrocytomas IDH-mutant of posterior cranial fossa, clinical presentation, imaging features and onco-functional balance in surgical management

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## Abstract

IDH-mutant astrocytomas (AIDHmut) in the posterior cranial fossa (PCF) are rare and present substantial diagnostic and therapeutic challenges due to their location. We analyzed patients with PCF AIDHmut from our institutions, treated between December 2021 and September 2024. Additionally, we conducted a systematic literature review (from January 2021 to September 2024) using PubMed, Ovid MEDLINE, and Ovid EMBASE to identify cases of PCF AIDHmut. We identified a total of 19 cases, including one institutional case. Most patients were young adults, with a male predominance (15 males, 4 females). Tumors primarily originated from the brainstem (94.7%), with only one case involving the cerebellum. Clinical presentations frequently included cranial nerve deficits, with diplopia being the most common symptom (47.4%). Adjuvant radiotherapy (IMRT, DT 54 Gy/27 fractions, 78.9%) and chemotherapy (temozolomide, 68.4%) formed the mainstays of treatment. Tumor grading revealed 63.2% (12/19) were WHO grade 2, 21% (4/19) were WHO grade 3, and 15.8% (3/19) were grade 4. The mean follow-up period was 45 months. PCF AIDHmut are rare but pose significant treatment challenges due to their location and infiltrative nature. Multimodal treatment—comprising surgery, radiotherapy, and chemotherapy—is essential for achieving long-term disease control. Subtotal resection followed by adjuvant therapies provides a favorable balance between tumor control and functional preservation.

**Keywords** IDH-mutant Astrocytomas · Posterior cranial fossa · WHO grade II-III-IV gliomas · Temozolomide · Onco-functional balance

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## Background

According to the fifth edition of the WHO Classification of Tumors of the Central Nervous System (WHO CNS-5, 2021), gliomas are divided into adult-onset or pediatric-onset. In the adult type, diffuse gliomas include astrocytoma (IDH-mutant), oligodendroglioma (IDH-mutant and 1p/19q-co-deleted), and glioblastoma (IDH-wildtype). These categories are further graded according to their malignancy potential, with astrocytomas ranging from WHO grades II to IV, oligodendroglioma ranging from WHO grades II to III, and glioblastomas being classified as WHO grade IV [1–3]. While glioblastomas make up approximately 55% of all gliomas, the remaining 45% comprise a mix of distinct histological subtypes [4, 5]. These new categories have been understudied, not only due to time constraints but also because much of the existing literature has yet to fully adopt the current nomenclature, hence the need for this paper.

Glial tumors of the posterior cranial fossa (PCF) are rare and primarily arise in the cerebellum or brainstem. Among these, brainstem gliomas (BSGs) are significantly more common in the pediatric population, accounting for up to 20% of all pediatric brain central nervous system (CNS) tumors. In contrast, brainstem gliomas are much rarer in adults, representing only 1–2% of adult brain gliomas [6]. The prognosis of BSGs varies significantly between pediatric and adult patients. Based on MRI characteristics, BSGs are categorized as either focal brainstem glioma (FBSGs), in 20% of cases, or diffuse pontine gliomas (DIPGs), in 80% of cases [7]. In adults, FBSGs are more frequent, allowing for more aggressive surgical treatment. However, in children, DIPGs are more common, making surgical resection more difficult, with radiotherapy often being the main palliative treatment, providing transient symptomatic improvement, and improves the overall survival (OS) duration by 3–6 months [8].

The PCF, the deepest compartment of the skull base, accommodates the cerebellum, brainstem, and associated cranial nerves (CNs III–XII). The most common PCF neoplasms are extra-axial tumors such as vestibular schwannomas (70–80%), followed by meningiomas (10–15%) and epidermoid cysts (5%) [9]. In the pediatric population, PCF tumors remain rare and frequently arise as secondary extensions from intrinsic neoplasms of the brainstem, cerebellar peduncle, or cerebellum, or from direct extensions from the fourth ventricle and lateral recess [6]. In children, the PCF may also harbor atypical tumors such as sarcomas, medulloblastomas, and ependymomas. Unlike in adult patients, clinicians should expect a higher likelihood of malignant histology in pediatric PCF tumors, especially in infants and young children, further highlighting the importance of thorough evaluation and timely intervention [7].

Unfortunately, because of the rarity and neuro-radiological features of PCF gliomas, such lesions are often misdiagnosed until confirmation by histological examination. The clinical relevance of the PCF tumors stems from the numerous types of lesions that can affect this region, often presenting with a variety of unclear symptoms, the most typical of these include tinnitus, hearing loss and balance disturbances such as dizziness [8].

In diffuse gliomas, a definitive cure remains elusive. The primary objective in managing these tumors is to achieve maximal resection, as the extent of resection is closely linked to patient prognosis [10, 11]. However, given the tumor's location within the brain parenchyma, it is critical to avoid removing excessive amounts of normal brain tissue to maintain an optimal onco-functional balance. This balance is particularly challenging in the PCF, a region densely packed with vital neurovascular structures. Additionally, there is ongoing debate regarding the most effective adjuvant therapy for IDH-mutant gliomas, specifically whether temozolomide (TMZ) or the combination of procarbazine, lomustine, and vincristine (PCV) is superior [12–14].

To address these issues, we conducted a systematic review of AIDHmut gliomas in the PCF, with a focus on prognosis, adjuvant therapy, and the impact of specific mutations. In this study, we present also a case of AIDHmut located in the PCF to shed light on the clinical presentation, diagnosis, and management of these rare lesions.

## Materials and methods

### Literature review

#### Literature search

The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [15]. A comprehensive literature search of the databases PubMed, Ovid MEDLINE, and Ovid EMBASE was conducted. The search was limited to the period from June 2021 to September 2024 to include only papers that incorporated the WHO V<sup>th</sup> classification. The search was last updated on September 21, 2024. A combination of keyword searches was performed to generate a string. The search keywords, including “posterior cranial fossa”, “astrocytoma”, “grade II-III-IV”, “IDH-mutant”, “cerebellar”, “brainstem” and “pons” were used in both “AND” and “OR” combinations. Studies were found using the Medical Subject Heading (MeSH) terms and Boolean operators. Other pertinent articles were identified through reference analysis of selected papers.

All studies were selected based on the following inclusion criteria: (1) case series or case reports, (2) lesions located in the PCF, (3) glial lesions of astrocytic nature, and (4) grade 2 to 4 astrocytomas according to the WHO V<sup>th</sup> classification. Exclusion criteria were: (1) meta-analysis and literature reviews, and (2) articles not reporting sufficient data on the presentation, diagnosis, or management. The list of identified studies was imported into Endnote X9, and duplicates were removed. The coauthors (M.D.S. and A.C.) independently performed the screening of abstracts for eligibility. Discordance between authors was resolved by the consensus of senior authors (A.S. and G.I.).

### Risk of bias assessment

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the included studies [16]. Quality assessment was performed by assessing the selection criteria, comparability of the study, and outcome assessment [17]. The ideal score was 9. Higher scores indicated better quality of studies. Studies receiving 7 or more points were considered high-quality studies. Two authors (A.C. and C.R.) performed the quality assessment independently. When discrepancies arose, papers were re-examined by a third author (M.D.S.).

### Data extraction

For the institutional case and each study included in our systematic review, we extracted the following baseline information: number of patients, age, gender, and anamnesis of cancer familiarity or genetic disease. As for the age stratification, we adopted the recommended classes of the Adolescent and Young Adult Oncology Progress Review Group (AYAO PRG): children (0–15 y), young adults (16–39 y), adults (40–64 y), and elderly ( $\geq 65$  y) [18]. Regarding the clinical presentation, we collected the following information: initial suspected diagnosis, pre-treatment Karnofsky Performance Status (KPS), histotype and molecular characteristics, tumor origin (i.e., pons, cerebellum), presenting symptoms and their duration, pre-treatment VII cranial nerve (CN) function [i.e., House-Brackmann (HB) grade]. As for the treatment, we extracted information regarding the surgical approach, type of resection [i.e., biopsy, sub-total resection (STR), near-total resection (NTR), gross-total resection (GTR)], and adjuvant therapy [i.e., chemotherapy (CHT) and/or radiotherapy (RT)]. For the outcomes, the post-treatment KPS and post-treatment VII CN function (HB grade), the time to recurrence (TTR), and the mean length of imaging and clinical follow-up were abstracted.

### Outcomes

Clinical presentation, diagnostic features, and management strategies were our primary objectives. Diagnostic features of AIDHmut of the PCF were examined, including clinical presentation, imaging findings, and differential diagnoses. The review also investigated the management strategies, including surgery, CHT, and/or RT. The secondary objectives were to assess the efficacy of these approaches based on clinical outcomes, survival, and recurrence rate.

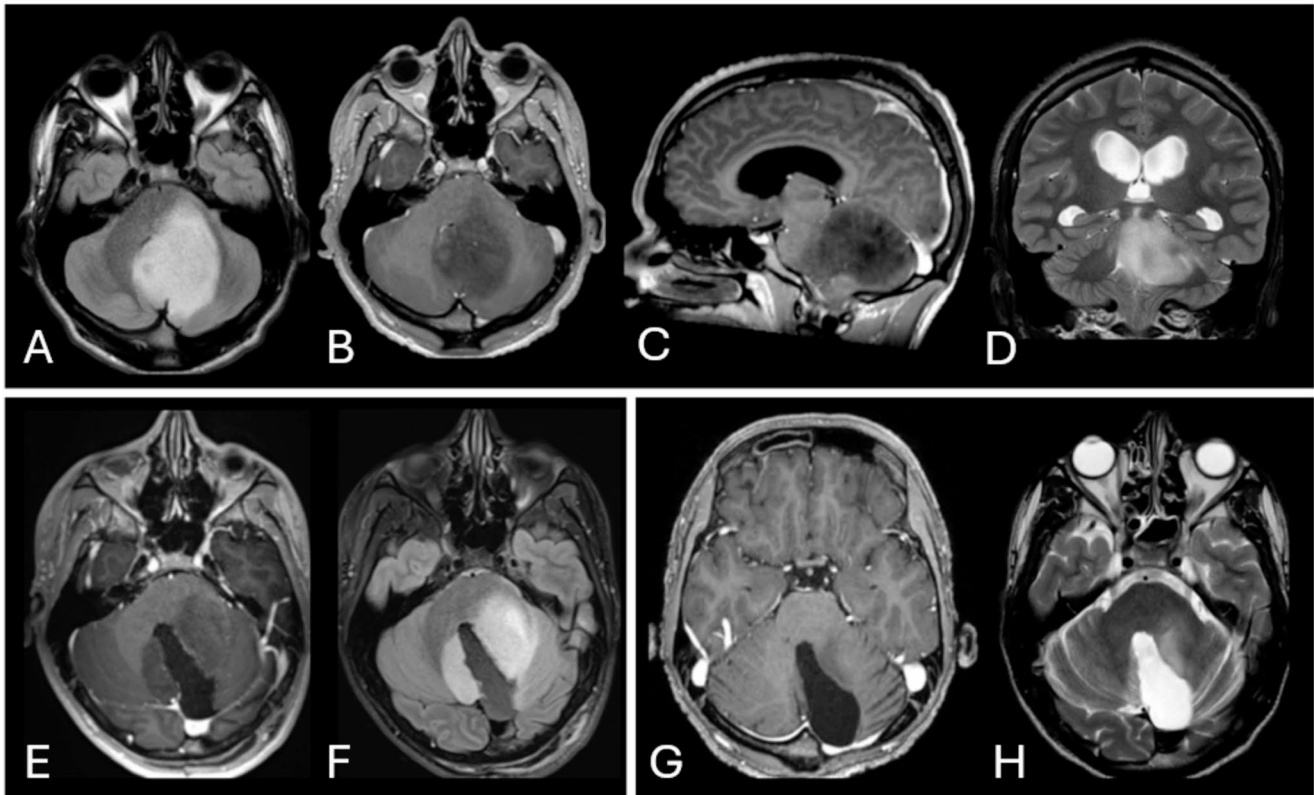
### Statistical analysis

Descriptive statistics were reported including means and proportions. No formal statistical comparisons were performed due to small sample sizes and insufficient power to detect differences between groups.

## Results

### Illustrative case

An 18-year-old male with no prior medical history presented with progressive intracranial hypertension and gait disorder over three weeks. His family history was notable for a cerebral rhabdomyosarcoma for her mother, treated 30 years earlier. Clinical examination showed cerebellar ataxia, adiadokokinesia predominantly on the left side, and subtle nystagmus. Ophthalmological assessment revealed mild bilateral papilledema. Brain MRI demonstrated an extensive left cerebellar lesion with pontine infiltration. The lesion appeared hypointense on T1-weighted sequences without tumoral enhancement after gadolinium injection – hyperintense on T2 and T2 FLAIR sequences (Fig. 1, A, B, C & D). There was associated triventricular hydrocephalus. The patient underwent urgent surgical intervention, first with third ventriculostomy followed by a subtotal resection of the cerebellar lesion a few days later. Histopathological and molecular analysis confirmed the diagnosis of WHO grade III anaplastic astrocytoma. Molecular findings included the absence of an IDH1 R132H mutation but revealed a minor IDH1 mutation (IDH1 R132G). There was a TP53 mutation, loss of nuclear ATRX expression, and unmethylated MGMT. The Ki-67 proliferation index was 50%. Genetic counseling ruled out Li-Fraumeni syndrome, the patient does not have genetic condition. Following a multidisciplinary tumor board discussion, the patient underwent six cycles of chemotherapy (procarbazine, lomustine, and vincristine [PCV]) with adjuvant radiotherapy (60 Gy in 33 fractions) initiated between the third and fourth chemotherapy cycles. Post-treatment, the patient remained



**Fig. 1** Preoperative (A, B, C & D), one-year postoperative (E & F), and two-year postoperative Brain MRI. (G & H). A preoperative axial T2-FLAIR MRI. B preoperative axial contrast-enhanced (CI) T1-weighted imaging (WI) MRI. C preoperative sagittal CI T1-WI

MRI. D preoperative coronal T2-WI MRI. E one-year postoperative axial CI-T1-WI MRI. F one-year postoperative axial T2-FLAIR MRI. G two-year postoperative axial CI T1-WI MRI. H two-year postoperative axial T2-WI MRI

radiologically and clinically stable. PET-CT showed no hypermetabolism, and MRI revealed no concerning contrast enhancement (Fig. 1E, F, G & H). To this day, at 36 follow-up, the patient is working with accommodations for residual deficits, including exertional fatigue, noise intolerance, and mild residual cerebellar ataxia.

## Literature review

### Literature search

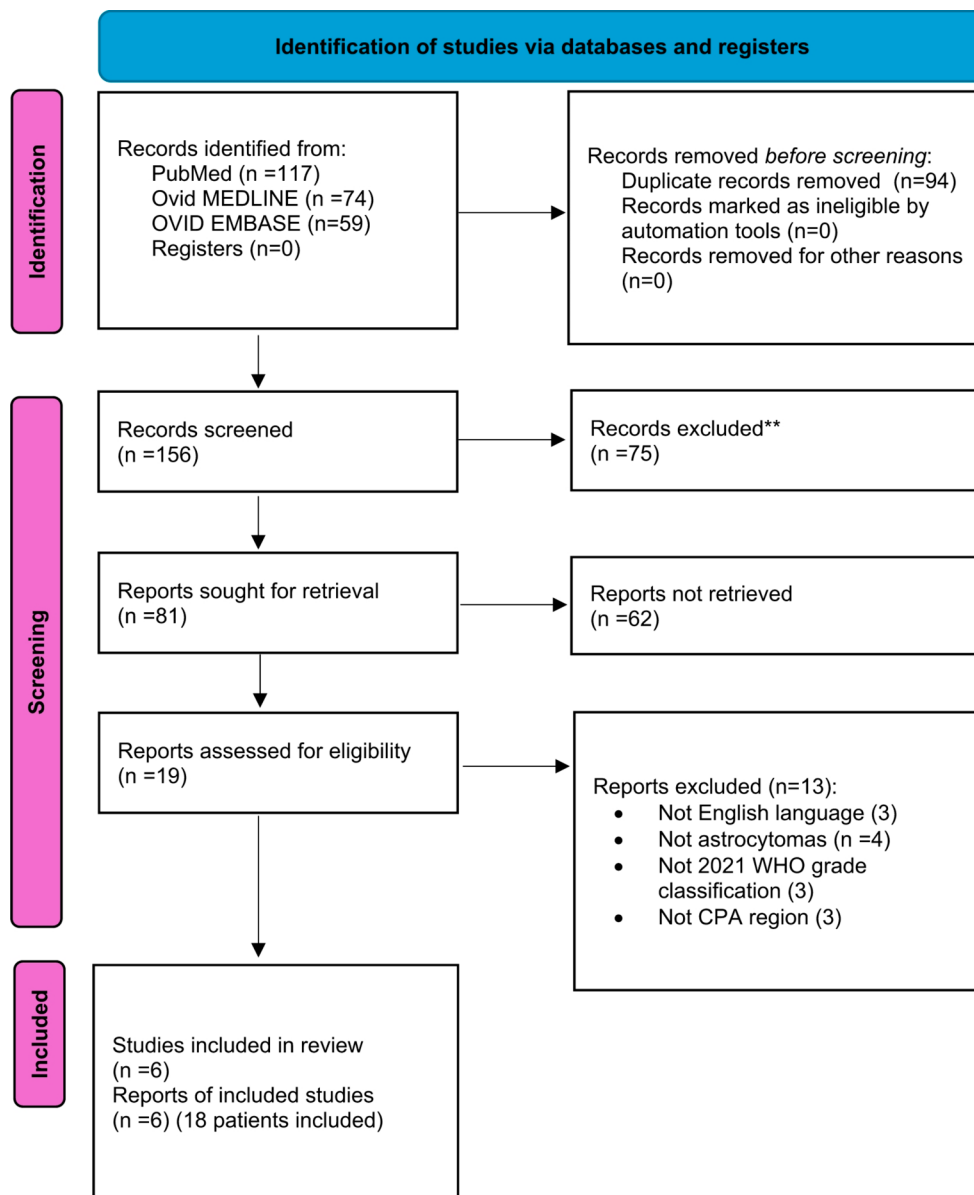
A total of 156 papers were identified after duplicate removal. After title and abstract analysis, 19 articles were identified for full-text analysis. Eligibility was ascertained for 6 articles. The remaining 13 articles were excluded for reasons including (1) language other than English (3 articles), (2) glial lesions other than astrocytomas (4 articles), (3) lack of 2021 WHO grade classification (3 articles), (4) lesions not located in the CPA region (3 articles). Figure 2 shows the flow chart according to the PRISMA statement [19–24].

### Pooled analysis

Including our Institutional case, a total of 19 patients harboring IDH-mutated astrocytoma in the posterior cranial fossa were studied in our systematic review. A male predilection (15:4) was observed. The median age was 31 years (range 17–52). According to the recommended age groups of the AYA0 PRG [18], the series included 1 pediatric patient (17 years), 13 young adults (18–35 years: 18, 19, 21, 23, 24, 24, 27, 29, 32, 32, 33, 34, 35 years), 5 adults (36–49 years: 36, 38, 43, 49, 52 years). The median pre-treatment Karnofsky Performance Score (KPS) across the 19 patients, excluding the two with ‘not reported’ values, was calculated to be approximately 80.6.

Considering the histotype, the integrated diagnosis included astrocytoma, IDH-mutant, WHO grade 2 in 63.2% (12/19) of cases, WHO grade 3 in 21.1% (4/19) of cases, and WHO grade 4 in 15.8% (3/19) of cases. The IDH1 R132H mutation was the most frequent, occurring in 57.9% (11/19) of cases, followed by the IDH1 R132S mutation, which was found in 15.8% (3/19) of cases. The IDH1 R132G and IDH2 R172G mutations were each observed in 5.3% (1/19). In

**Fig. 2** PRISMA flow diagram depicting the literature search process



15.8% (3/19) of cases, the mutation status was not reported (NR).

The origin of the tumor was most frequently in the brainstem, occurring in 94.7% (18/19) of cases, while only 1 case involved the cerebellum (1/19). The Ki-67 labeling index ranged from less than 1–50%, with an average of 10.9% (12/19). The index was not reported in 7 cases (7/19). Positivity for the TP53 mutation was observed in 73.7% (14/19) of cases, while it was not reported in 21.1% (4/19) of cases. Wilde-type TP53 was found in only one case (1/19). Loss of ATRX was observed in 26.3% (5/19) of cases, while in the remaining 73.7% (14/19) of cases, the status was not reported.

Analyzing the clinical presentation at diagnosis, diplopia was observed in 47.4% (9/19) of patients, while a broad

category of other symptoms, including intracranial hypertension and impaired visual function, was present in 63.2% (12/19). Facial palsy or paralysis occurred in 36.8% (7/19), headache in 31.6% (6/19), and ataxia in 31.6% (6/19). Limb weakness or paralysis was noted in 26.3% (5/19), dizziness in 21.1% (4/19), and hearing loss, dysarthria, and hoarseness/dysphagia were each reported in 10.5% (2/19) of the cases. Diagnostic procedures varied, with open biopsy being the most common, performed in 26.3% (5/19) of cases.

Navigation-guided open biopsy was used in 15.8% (3/19) of cases. Other techniques included brainstem excision and decompression procedures. The most common radiotherapy protocol utilized was IMRT (DT 54 Gy/27 fractions), applied in 78.9% (15/19) of cases. The most common chemotherapy agent used was temozolomide (TMZ),

administered in 68.4% (13/19) of cases. The most frequent protocol involved TMZ (75 mg/m<sup>2</sup>) followed by continuous TMZ (150–200 mg/m<sup>2</sup>, day 1–5, every 4 weeks), for a total of 24 cycles, used in 15.8% (3/19) of cases. PCV (6 cycles) and a combination of TMZ, carboplatin, and vincristine were each used in 5.3% (1/19) of cases, for a total of 10.5% (2/19). Chemotherapy was not reported in 21.1% (4/19) of cases. The follow-up period was not reported in 21.1% (4/19) of cases, while it was available in 78.9% (15/19) of cases. Patients were followed up with a Gd-enhanced MRI. The median follow-up was 45 months (range 12–201 months) (Table 1; Fig. 3).

## Discussion

AIDHmut of the PCF are epidemiologically rare [9]. Only 19 cases of AIDHmut are described in the literature in this region. Patients of all age groups are included in this review (17–52 years). A predominance of distribution in the young adult group was observed. The medical history was negative for genetic syndromes in all cases. Their management is challenging, and the treatment strategies include surgery, CHT, and RT in different combinations. Based on our analysis of 19 cases, including the institutional case, several critical insights into clinical presentation, diagnosis, management, and outcomes can be drawn.

### Clinical presentation and diagnosis

All the patients reported had a pre-treatment KPS (reported or calculated) of 70 or more meaning that they had disabling symptoms but not such as to result in significant loss of independence. These findings are likely attributable to an early onset of symptoms resulting in rapid assessment by neuroradiological imaging. Early diagnosis of a disease can positively influence KPS in several ways. Early diagnosis often enables the initiation of timely and targeted treatments [25]. Treating a disease at an earlier stage can help reduce the impact on a patient's overall function and preserve his or her quality of life. Besides, in cases where a disease is diagnosed early, there are generally fewer associated complications. The patient may have fewer severe symptoms or comorbidities, contributing to better functional capacity. Treatments such as CHT, RT, or surgery may be better tolerated when applied at an early stage of the disease. This may positively affect KPS, as the patient may maintain better function during and after treatment. In these types of tumors, preserving quality of life (QoL) is a clear priority. The surgeon's role is becoming more like that of a judge, tasked with balancing the extent of tumor resection against the risk of neurological damage that may result from an

aggressive approach. This requires evaluating the “onco-functional balance” on a case-by-case basis [26].

AIDHmut originating from pons tended to have a shorter duration of symptoms than those originating from the cerebellum [27]. The earliness of symptoms associated with pons AIDHmut compared with cerebellar AIDHmut could be attributed to several factors related to the anatomical location of the two brain regions and the functions they control. The pons is located in the brainstem, a critical region of the brain that regulates many vital functions, such as breathing, heart rate, and swallowing. Pons gliomas can involve and compress nerve pathways crucial for motor and sensory control. This can cause symptoms such as weakness, coordination problems, and sensory disturbances early on. It should also be considered that brain bridge gliomas, especially those with high aggressiveness, can progress rapidly and cause more pronounced mass effects than cerebellar gliomas. The more rapid growth and mass effects may lead to greater compression of neural structures, generating earlier symptoms. Radiologically, diffuse or nodular enhancement of the meninges can be observed, indicating infiltration by tumor cells. T1- and T2-weighted images may show areas of variable signal intensity in the meninges, which may be related to tumor infiltration, inflammation, or cerebrospinal fluid accumulation. Involved meninges may appear thickened, and irregular, and may show signs of irritation. It is common for PCF tumors, especially in pediatric patients, to present with intracranial hypertension caused by hydrocephalus [28–29]. Notably in the work of Won et al. brainstem compression (OR 5.4) was confirmed as an independent predictor of hydrocephalus in pediatrics. In general, the incidence of PFT-associated hydrocephalus at presentation is believed to be higher in children (70–90%) than in adults (10–21%) [30].

Despite the challenges associated with treating AIDHmut in the PCF, the median follow-up in this series was approximately 45 months, with no significant deterioration in KPS in most cases. Importantly, the institutional case demonstrated stable disease with no signs of recurrence at 36 months post-treatment. However, some cases in the literature reported recurrence or progression, emphasizing the importance of vigilant long-term follow-up, especially given the infiltrative nature of these tumors and their potential for malignant transformation. A large study with 20 years of follow-up on posterior cranial fossa tumors, published in 2020, reported that residual tumors were found in 40.2% of cases, with 10.9% of patients experiencing symptoms of disease progression. Tumor recurrence was observed in 14.3% of patients, while 6.0% developed severe disability. The overall mortality rate was 11.4% within the first year after surgery, rising to 18.9% in patients with malignant tumors. The 1-year event-free survival (EFS) was 66.0%

**Table 1** Data collection of cases included

Author, Year	Age	Sex	Integrated diagnosis (or Histologic diagnosis)	KPS	IDH mutation type	TP53 Mutation	ATRX loss	Ki-67 labelling Index (%)	Tumor Location	Presenting symptoms	Diagnostic method (biopsy, STR, GTR)	SRS/RT (Gy/ rads and No. of fractions if reported)	CHT (agent and No. of cycles if reported)	Follow-up (months)
Institutional case	18	M	Astrocytoma, IDH-mutant, WHO grade 3	90	IDH1 R132G	+	+	50%	Cerebellum	.Intracranial hypertension for 3 weeks .Cerebellar Ataxia .Gait Disturbance	Third ventriculostomy then STR	RT (1 cycle: 60gy 33fractions). The RT was performed between the 3rd and 4th PCV cycle)	PCV (6 cycles)	36
Okie et al., 2024	32	M	Astrocytoma, IDH-mutant, WHO grade 3	80	IDH1 R132H	-	NR	NR	Brainstem	.Left-sided facial tightness, headache; .Later developed diplopia; .Left facial palsy; .Ataxia	Two needle biopsies	IMRT (DT 54 Gy/27 fractions)	TMZ (150–200 mg/m <sup>2</sup> , day 1–5, every 4 weeks)	47 (death)
Okie et al., 2024	21	M	Astrocytoma, IDH-mutant, WHO grade 3	90	IDH2 R172G	+	NR	NR	Brainstem	.Left-sided deafness; .Two episodes of paralysis in the right upper extremity	.Open biopsy	IMRT (DT 54 Gy/27 fractions)	TMZ (75 mg/m <sup>2</sup> , followed by continuous TMZ (150–200 mg/m <sup>2</sup> , day 1–5, every 4 weeks), total of 24 cycles	NR
Okie et al., 2024	35	M	Astrocytoma, IDH-mutant, WHO grade 4	70	IDH1 R132H	+	+	NR	Brainstem	.Left facial palsy; .Hoarseness; .Diplopia; .Dysphagia; .Left ear hearing loss	.Autopsy diagnosis	IMRT (DT 54 Gy/27 fractions)	TMZ (75 mg/m <sup>2</sup> , followed by continuous TMZ (150–200 mg/m <sup>2</sup> , day 1–5, every 4 weeks), total of 24 cycles	28.8 (death)
Okie et al., 2024	36	M	Astrocytoma, IDH-mutant, WHO grade 4	90	IDH1 R132H	+	+	NR	Brainstem	.Headache; .Diplopia	Open Biopsy	IMRT (DT 54 Gy/27 fractions)	TMZ (75 mg/m <sup>2</sup> , followed by continuous TMZ (150–200 mg/m <sup>2</sup> , day 1–5, every 4 weeks), total of 24 cycles	31 (death)
Iwahashi et al., 2023	27	M	Astrocytoma, IDH-mutant, WHO grade 2	80*	IDH1 R132G	NR	NR	3%	Brainstem	NR	Komai stereotactic biopsy	IMRT (DT 54 Gy/27 fractions)	TMZ	63
Iwahashi et al., 2023	24	M	Astrocytoma, IDH-mutant, WHO grade 2	80*	IDH1 R132S	NR	NR	3%	Brainstem	NR	Navigation-guided open biopsy	IMRT (DT 54 Gy/27 fractions)	NR	64

**Table 1** (continued)

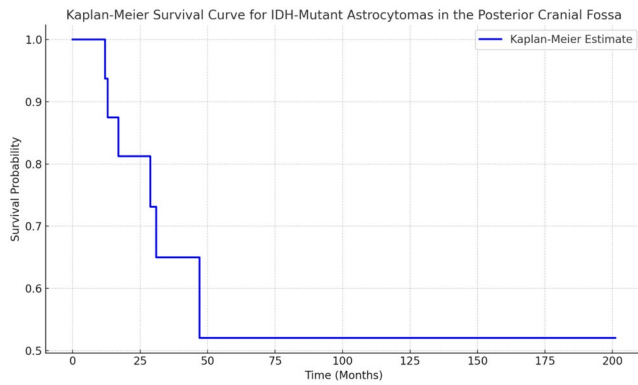
Author, Year	Age	Sex	Integrated diagnosis (or Histologic diagnosis)	KPS	IDH mutation type	TP53 Mutation	ATRX loss	Ki-67 labelling Index (%)	Tumor Location	Presenting symptoms	Diagnostic method (biopsy, STR, GTR)	SRS/RT (Gy/ rads and No. of fractions if reported)	CHT (agent and No. of cycles if reported)	Follow-up (months)
Iwashi et al. 2023	33	F	Astrocytoma, IDH-mutant, WHO grade 2	80*	IDH1 R132H	NR	NR	< 1%	Brainstem	NR	Navigation-guided open biopsy	IMRT (DT 54 Gy/27 fractions)	NR	26
Iwashi et al. 2023	38	M	Astrocytoma, IDH-mutant, WHO grade 2	90*	IDH1 R132S	NR	NR	10%	Brainstem	NR	Navigation-guided open biopsy	IMRT (DT 54 Gy/27 fractions)	NR	201
Nagase et al., 2023	23	F	Astrocytoma, IDH-mutant, WHO grade 2	100	IDH1 R132H	+	+	NR	Brainstem	.Headache (lasting 6 months); .Impaired visual function; .Congested papillae .Dizziness; .Diplopia; .Hearing loss in the right ear; .Dextral numbness;	Stereotactic biopsy and foramen magnum decompression (FMD) (relieve obstructive hydrocephalus) GTR	NR	NR	12
Zhou et al., 2022	34	M	Astrocytoma, IDH-mutant, WHO grade 2	70*	IDH1 R132H	+	+	5%	Brainstem	.Limb Weakness; .Dysarthria; .Ataxia; .Dizziness	GTR	IMRT (DT 54 Gy/27 fractions)	TMZ (120 mg)	NR
Zhou et al., 2022	49	M	Astrocytoma, IDH-mutant, WHO grade 2	60*	IDH1 R132H	+	NR	2%	Brainstem	.Limb Weakness; .Dysarthria; .Ataxia; .Dizziness	biopsy	IMRT (DT 54 Gy/27 fractions)	TMZ (75 mg/m <sup>2</sup> )	17
Zhou et al., 2022	29	M	Astrocytoma, IDH-mutant, WHO grade 2	70*	IDH1 R132H	+	NR	4%	Brainstem	.Episodic dizziness; .Diplopia; .Facial palsy	Robot-guided biopsy	IMRT (DT 54 Gy/27 fractions)	TMZ (75 mg/m <sup>2</sup> )	NR
Zhou et al., 2022	52	F	Astrocytoma, IDH-mutant, WHO grade 2	80*	NR	+	NR	7%	Brainstem	.Dizziness; .Ataxia; .Mild headache	.Brainstem glioma excision .Decompressive craniectomy .Extra-ventricular drainage	Conformal radiotherapy	NR	13
Zhou et al., 2022	32	M	Astrocytoma, IDH-mutant, WHO grade 2	80*	NR	+	NR	NR	Brainstem	.Weakness in the right limb	.Brainstem glioma excision .Dura mater reparation .Cranioplasty	IMRT (DT 40 Gy/20 fractions)	TMZ (120 mg) with 6 cycles (340 mg)	28



Table 1 (continued)

Author, Year	Age	Sex	Integrated diagnosis (or Histologic diagnosis)	KPS	IDH mutation type	TP53 Mutation	ATRX loss	Ki-67 labelling Index (%)	Tumor Location	Presenting symptoms	Diagnostic method (biopsy, STR, GTR)	SRS/RT (Gy/rads and No. of fractions if reported)	CHT (agent and No. of cycles if reported)	Follow-up (months)
Sano et al., 2021	43	M	Astrocytoma, IDH-mutant, WHO grade 4	NR	IDH1 + R132H		NR	NR	Brainstem	Diplopia (worsening over 24 months); Right-sided sensory disturbance; Left-sided Facial Paralysis	Open biopsy (initially) Subtotal tumor removal (following progression)	IMRT (DT 54 Gy/27 fractions) Stereotactic radiotherapy (36 Gy/9 fractions) after progression	TMZ (75 mg/m <sup>2</sup> /day for 43 days) with radiotherapy, followed by 24 cycles of adjuvant TMZ (150–200 mg/m <sup>2</sup> /day)	NR
Chang et al., 2021	19	F	Astrocytoma, IDH-mutant, WHO grade 3	NR	IDH1 + R132S		NR	20%*	Brainstem	Left ptosis Left facial palsy Headache Diplopia Ataxia	Open Biopsy	IMRT (DT 54 Gy/27 fractions) Focal Radiation	TMZ, carboplatin, vincristine	62
Chang et al., 2021	17	M	Astrocytoma, IDH-mutant, WHO grade 2	80*	IDH1 + R132H		NR	<5%*	Brainstem	Left leg weakness Headache Diplopia Ataxia Left facial palsy	Open biopsy	IMRT (DT 54 Gy/27 fractions)	TMZ	36
Chang et al., 2021	24	M	Astrocytoma, IDH-mutant, WHO grade 2	80*	IDH1 + R132H		NR	7%*	Brainstem	Right facial palsy Diplopia	Open Biopsy	IMRT (DT 54 Gy/27 fractions)	TMZ	18

KPS=Karnofsky Performance Score; IDH=Isocitrate dehydrogenase; STR=subtotal resection; GTR=Gross total resection; CHT=chemotherapy; SRS/RT=Stereotactic Radiosurgery/Radiotherapy; Gy=Gray; DT=Dose Total; PCV=Procarbazine; TMZ=Temozolomide; IMRT=Intensity-Modulated Radiotherapy; NR=Not Reported



**Fig. 3** Kaplan-Meier survival curve for patients with IDH-mutant astrocytomas in the posterior cranial fossa

for all patients. For those with malignant tumors, the 1-year EFS was 47.7%, compared to 87.7% for patients with benign tumors [31].

The pooled analysis further highlights the complexity of managing IDH-mutated astrocytomas in the PCF. The average Ki-67 labeling index (LI) was 10.9%, which may correlate with the overall favorable outcomes seen in this series. However, in cases with higher Ki-67 indices or more aggressive histopathological features, recurrence rates may be higher, necessitating more aggressive postoperative monitoring and potentially adjunctive therapies. Yang et al. demonstrated that morphological MRI (mMRI), SWI, DWI and SDC-PWI have the potential to predict Ki-67 LI and ATRX mutation status in AIDHmut. The combination of mMRI and SWI can improve the diagnostic performance for the prediction of Ki-67 LI and ATRX mutation status [32]. Regarding mutations, The IDH1R132H mutation was found in over 80% of supratentorial AIDHmut, while it was present in only 24% of infratentorial cases, where IDH1R132C/G mutations were more commonly observed [24, 26–33]. Mu et al., in a study of 55 patients, regarding mutations, found that patients with IDH1 R132H mutation had a longer recurrence free period (RFP) than the subgroup with IDH1 wild type ( $p < .01$ ), but OS had no statistical difference between the two subgroups ( $p > .6$ ). In addition, the IDH1 R132H mutation independently predicted a long RFP in patients with low grade remedial glioma (HR 1.073, 95% CI 0.151–0.775,  $p < .01$ ) [34]. Regarding extent of resection (EOR), a recent retrospective study of 138 patients supplemented the molecular data with a survival analysis in pts with high-grade tumors. Patients with  $EOR \geq 88\%$  experienced 44% prolonged overall survival (OS) in multivariable analysis (hazard ratio: 0.56,  $P = .030$ ). Patients with TP53 pathway alterations and  $EOR < 89\%$  showed reduced OS compared with patients with TP53 pathway alterations and  $EOR > 89\%$  (10.5 vs. 18.8 months; HR: 2.78,  $P = .013$ ); however, EOR/RTV was not associated with OS in patients without TP53 pathway alterations. Meanwhile, in all

patients with  $EOR < 88\%$ , PTEN -altered had significantly worse OS than PTEN -wildtype (9.5 vs. 15.4 months; HR: 4.53,  $P < .001$ ).

## Management and outcomes

Surgery is a useful strategy in many brain tumors. For some of these it is always the first choice, think of meningiomas. For the surgical management of posterior cranial fossa AIDHmut, the choice of approach is crucial for optimizing outcomes while minimizing risks. In the study by Bal et al. (2021) [35], eight patients with posterior incisural space lesions were treated using the suboccipital transtentorial (SOTT) approach. Gross or near-total resection (GTR or NTR) was achieved in 75% of cases, with no patient experiencing visual field deficits, and only one developing temporary trochlear nerve palsy. These results highlight the safety and efficacy of this approach in providing excellent access to deep-seated tumors, particularly when careful case selection is applied. Furthermore, Mahmoud et al. [36] reported on the surgical management of exophytic brainstem gliomas, achieving near-total excision in 87% of cases. They found that the telovelar approach, used in 17 out of 23 patients, allowed for significant tumor removal with minimal complications.

Similarly, Rady et al. (2024) [37] analyzed pediatric brainstem and peduncular low-grade gliomas (LGGs), demonstrating that gross total resection was achieved in 40% of cases, with near-total resection in 34%. The study also found a clear difference in outcomes based on the extent of resection: the 3-year progression-free survival rate was 100% for GTR cases, compared to 88.2% for NTR, highlighting the importance of maximal safe resection in improving long-term outcomes.

Cinibulak et al. (2024) [38] compared the transmastoid infralabyrinthine approach (TI-A) techniques for jugular fossa pathologies and found that the short-rerouting technique significantly increased the exposed area (169.1 mm<sup>2</sup> vs. 151.0 mm<sup>2</sup>) and surgical freedom (19,650 mm<sup>2</sup> vs. 17,233 mm<sup>2</sup>) compared to the non-rerouting technique. However, tailored steps to the non-rerouting approach provided comparable access, making it a valuable option for select cases, particularly for class C1, C2, and C3 lesions.

Regarding extent of resection (EOR), a recent retrospective study of 138 patients supplemented the molecular data with a survival analysis in pts with high-grade tumors [39]. Patients with  $EOR \geq 88\%$  experienced 44% prolonged overall survival (OS) in multivariable analysis (hazard ratio: 0.56,  $P = .030$ ). Patients with TP53 pathway alterations and  $EOR < 89\%$  showed reduced OS compared with patients with TP53 pathway alterations and  $EOR > 89\%$  (10.5 vs. 18.8 months; HR: 2.78,  $P = .013$ ); however, EOR/RTV was

not associated with OS in patients without TP53 pathway alterations. Meanwhile, in all patients with EOR < 88%, PTEN -altered had significantly worse OS than PTEN -wildtype (9.5 vs. 15.4 months; HR: 4.53,  $P < .001$ ).

In an article, predating the latest classification, the authors related the extent of resection to survival in a retrospective cohort of 74 patients with low-grade gliomas [40]. Stratifying by IDH status, showed that higher EOR independently prolonged malignant progression-free survival (MPFS) and OS for wild type IDH patients (hazard ratio [HR]=0.002 [95% confidence interval {CI} 0.000-0.074] and HR=0.001 [95% CI 0.00-0.108], respectively), but not for IDH-mutant patients (HR=0.84 [95% CI 0.17–4.13] and HR=2.99 [95% CI 0.15–61.66], respectively). The role of EOR on OS in grade 3 tumors was recently analyzed in a retrospective cohort of 246 patients, and it was shown that extended resection benefits only a portion of patients with WHO grade 3 IDH-mutant gliomas; in particular, stratifying for age, no survival benefit from total resection was found in patients with astrocytoma older than 45 years [41].

Those interesting findings makes it clear that the biology of these tumors is complex, and the role of surgery is not sufficient, which is why adjuvant treatment modalities are increasingly emerging and finding a venue. In fact, in this regard, TMZ-based chemoradiotherapy is associated with a survival benefit in patients with grade 2 AIDHmut. Chemoradiotherapy can be deferred until the time of progression in younger patients undergoing extensive resection, while early treatment should be recommended in high-risk patients [42]. These debates represent research areas of keen interest; beyond this is the discourse of molecular understanding that is also increasingly prominent in brain tumors, which is why immunotherapeutic strategies may be useful. The latter have shown potential in various cancer types, but their efficacy in gliomas has been limited by tumor heterogeneity and an immunologically “cold” microenvironment. However, promising results from recent studies exploring vaccines, T-cell therapies, and IDH-mutant inhibitors offer hope for improved treatment outcomes in AIDHmut gliomas [4, 43, 44].

Considering this evidence, it is imperative to plot prospective studies aimed at understanding what treatment is most appropriate and what the surgical timing is, and it will also be essential to determine what the goal of surgery will be in these cases.

## Limitations

This paper was primarily based on retrospective studies and thus has limitations inherent to retrospective studies. Because of the small number of studies responding to the inclusion criteria, our paper was limited to descriptive

statistics. Nonetheless, to the best of our knowledge, we reported 19 cases of IDH-mutant astrocytoma in the PCF region, and we provide a comprehensive synopsis of the presentation, clinical challenges, and management of these tumors. The systematic review also included a risk of bias assessment using the Newcastle-Ottawa Scale (NOS). The NOS allowed for the evaluation of the quality of the included studies based on selection criteria, comparability of the study, and outcome assessment.

## Conclusions

AIDHmut tumors of the PCF are rare but present significant clinical and surgical challenges. Recent updates in classification have highlighted the importance of multimodal treatment, including subtotal resection followed by adjuvant chemotherapy and radiotherapy, which appear to offer favorable outcomes while minimizing functional deterioration. Although surgical intervention is often limited, earlier diagnosis allows patients to benefit more from adjuvant therapies. The delicate balance between maximizing tumor resection and preserving neurological function—known as the ‘onco-functional balance’—is crucial in guiding treatment decisions on an individual basis. The results of this study highlight that the nosological entity *AIDHmut* when located in the PCF, requires specialized diagnostic and management approaches. Our analysis identified a male predominance (15:4) with a median age of 31 years, spanning pediatric to adult groups. The tumor was predominantly located in the brainstem (94.7%), with only one case involving the cerebellum. Most cases were classified as WHO grade 2 (63.2%), followed by grade 3 (21.1%) and grade 4 (15.8%). Molecularly, the IDH1 R132H mutation was the most common (57.9%), while TP53 positivity was observed in 73.7% of cases, and ATRX loss in 26.3%. Treatment primarily included IMRT-based radiotherapy (78.9%) and temozolomide chemotherapy (68.4%), underscoring a targeted approach in managing this rare tumor. This finding opens the door to potential advancements in the implementation of the WHO classification. Further research, involving larger patient cohorts and longer follow-up, is necessary to refine therapeutic strategies and improve overall patient outcomes.

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## Declarations

**Ethical approval and consent to participate** All principles in the Declaration of Helsinki were followed, and the Italian laws on privacy (Art. 20–21, DL 196/2003) as published in the Official Journal, volume 190, 14 August 2004, which explicitly waives the need for ethical approval for the use of anonymous data, were respected.

**Consent for publication** Consent for publication was obtained from the patient, and their anonymity is guaranteed.

**Submission** This manuscript is original and has not been submitted elsewhere in part or in whole.

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