Systematic Review of WHO Grade 4 Astrocytoma in the Cerebellopontine Angle: The Impact of Anatomic Corridor on Treatment Options and Outcomes

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Abstract

Background Despite advances in multimodal oncologic therapies and molecular genetics, overall survival (OS) in patients with high-grade astrocytomas remains poor. We present an illustrative case and systematic review of rare, predominantly extra-axial World Health Organization (WHO) grade 4 astrocytomas located within the cerebellopontine angle (CPA) and explore the impact of anatomic location on diagnosis, management, and outcomes.

Methods A systematic review of adult patients with predominantly extra-axial WHO grade 4 CPA astrocytomas was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines through December 2022.

Results Eighteen articles were included comprising 21 astrocytomas: 13 exophytic tumors arising from the cerebellopontine parenchyma and 8 tumors originating from a cranial nerve root entry zone. The median OS was 15 months with one-third of cases demonstrating delayed diagnosis. Gross total resection, molecular genetic profiling, and use of ancillary treatment were low. We report the only patient with an integrated isocitrate dehydrogenase 1 (IDH-1) mutant diagnosis, who, after subtotal resection and chemoradiation, remains alive at 40 months without progression.

Conclusion The deep conical-shaped corridor and abundance of eloquent tissue of the CPA significantly limits both surgical resection and utility of device-based therapies in this region. Prompt diagnosis, molecular characterization, and systemic therapeutic advances serve as the predominant means to optimize survival for patients with rare skull base astrocytomas.
Introduction

Fewer than 4% of World Health Organization (WHO) grade 4 astrocytomas occur in the posterior fossa, with rarer presentation at the lateral skull base. Infratentorial astrocytomas typically arise from the brainstem and/or cerebellar white matter, demonstrating overt infiltration and posing significant morbidity. They are clinically and biologically distinct from supratentorial astrocytomas, from prevalence of isocitrate dehydrogenase (IDH) variants, epigenetic profiling, and a trend toward shorter overall survival (OS), yet these differences remain uninvestigated in tumors appearing outside of the infratentorial parenchyma. Regardless of diagnostic and therapeutic advancements, prognosis for grade 4 astrocytomas remains suboptimal with median OS of 15 and 31 months after maximal treatment for IDH wild-type and mutant tumors, respectively.

Standard treatment emphasizes safe maximal resection of enhancing tumor followed by fractionated external beam radiation with concurrent and adjuvant temozolomide (TMZ) and tumor treating fields (TTFs). Tumor location in narrow skull base corridors surrounded by eloquent tissue, like the cerebellopontine angle (CPA), inherently restricts accessibility, thereby limiting extent of resection, and the ability to utilize TTF and to employ alternative therapeutic tools and regimens trialed in their supratentorial counterparts. Such emerging technologies span intraoperative tools to maximize cytoreduction, advanced radiotherapy techniques to minimize toxicity and/or treat recurrence, locoregional chemoradiation to bridge systemic therapies, and adjunct devices with novel anticancer mechanisms like thermal ablation. While the therapeutic benefits of some of these tools have been endorsed in clinical practice guidelines, they remain largely investigational for use in the posterior fossa.

Herein, we present the first report of a rare IDH-mutated grade 4 astrocytoma in the CPA and perform a systematic review of the literature for all cases of exophytic grade 4 astrocytomas of any molecular subtype in this region. Given the anatomic complexity of the cranial base, the primary focus of this study was to evaluate treatment strategies, including the use and feasibility of emerging operative adjuncts, for high-grade CPA astrocytomas. Further, in light of recent advancements in our understanding of glioma biology, we also sought to assess the reliability of molecular genetics reporting in the literature and to highlight the concomitant importance of accurate, integrated diagnoses on disease course, particularly for malignant tumors arising in challenging anatomic locations.

Materials and Methods

A retrospective review of electronic medical records of our case study was performed in accordance with institutional guidelines. A systematic literature review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was then performed to identify all adult cases of WHO grade 4 astrocytoma in which the primary tumor component was in the CPA (Fig. 1). Search terms used in multiple databases included the following: (“glioblastoma” OR “glioblastoma multiforme” OR “GBM” OR “high grade glioma” OR “high grade astrocytoma” OR “gliosarcoma”) AND (“cerebellopontine angle” OR “cerebellopontine fissure” OR “cerebellopontine cistern” OR “CPA”). The search period spanned January 1, 1960 to December 1, 2022. Exclusion criteria included age less than 18 years, posterior fossa tumors without a predominant extra-axial component, insufficient data, and studies published in a non-English language. Intrinsic brainstem gliomas with minimal exophytic growth were excluded as these tumors are not subject to the same radiographic mimicry of CPA pathology or consideration for surgical treatment.

Data abstraction included study year, demographics, clinical presentation, radiographic characteristics, molecular profile, treatment regimen, and outcome.

Results

Illustrative Case

Clinical Presentation

A 58-year-old white man presented with progressive suboccipital headaches, disequilibrium, and gait disturbance over 4 months. Magnetic resonance imaging (MRI) demonstrated a large heterogeneously enhancing, right extra-axial CPA mass with brainstem compression and Meckel’s cave extension (Fig. 2A–C). The T1-isointense lesion displayed heterogeneous T2 signal suggestive of cystic degeneration. No intra-axial component was readily identified. Based on radiographic appearance and location, differential diagnosis initially favored trigeminal schwannoma.

Operative Course

The patient underwent a right retrosigmoid craniotomy for tumor resection. Significant adherence to cranial nerves (CNs), cerebellum, and brainstem was encountered. Intraoperative biopsy was inconclusive; therefore, the tumor was internally debulked to prioritize brainstem decompression and additional tissue collection before closing. Postoperatively, the patient developed a House–Brackmann grade 2 right facial weakness and 50% subjective ipsilateral hearing loss.

Permanent histopathologic analysis confirmed diagnosis of grade 4 astrocytoma necessitating further cytoreduction. Using the previous craniotomy, careful tumor resection proceeded from the CN VII/VIII complex to the basilar artery beyond midline. A thin rim of residual tumor was left on the ventral pons and trigeminal nerve root entry zone to avoid injury.

Histopathology

Immunohistochemistry was positive for OLIG2, GFAP, IDH-1 R132H variant, retained ATRX, and an elevated Ki-67 index (Fig. 3). Methylguanine-DNA-methyltransferase (MGMT) hypermethylation was present. All additional markers were negative, and no additional genetic variants including
1p/19q co-deletion and H3K27 were evident. The IDH-1 mutation was confirmed with next-generation sequencing. Integrated molecular diagnosis was consistent with WHO grade 4 astrocytoma, IDH-1 mutant.

Postoperative Course
The patient developed mild ipsilateral V1 hypesthesia and CN VI palsy, without exacerbation of previous deficits. Immediate postoperative MRI demonstrated greater than 80% resection of the enhancing mass (►Fig. 2D–F). He was discharged home on postoperative day 5 and subsequently completed chemoradiation using intensity-modulated radiation therapy (IMRT) and 12 cycles of TMZ. The patient’s cranial neuropathies gradually resolved. At 40 months, he remains alive without tumor progression (►Fig. 2G–I).

Systematic Review
Eighteen articles published from 1997 to 2021 met the criteria for analysis. A total of 21 patients were identified with an exophytic grade 4 CPA astrocytoma, the characteristics of which are summarized in ►Table 1.1,8-12,18-29

Patient Demographics and Clinical Presentation
The mean age at presentation was 49.70 ± 19.2 years. Twelve patients were males (57.1%) and 9 patients were females (42.9%). Symptom duration ranged from 1 to 36 months prior to presentation with a mean of 6.5 ± 8.8 months. The most common symptoms were gait ataxia, headache, and CN V, VII, and VIII palsies. Six cases with primary tumors reported diagnostic presumption of benign CPA pathology as a contributor to delayed time to surgery and diagnosis.22-24,27,28

Tumor Characteristics
Nineteen patients were diagnosed with glioblastoma (GBM) based on histopathology (90.4%).8-12,18-28 The remaining two cases were consistent with gliosarcoma (18.6%).1,29 Seventeen cases were primary tumors (81.0%);1,9-11,18-21,23,24,26-29 while 4 cases had a history of GBM in a remote intracranial area (19.0%): 2 ipsilateral frontal, 1 contralateral temporal, and 1 thoracic spine.8,12,25 Only five cases offered molecular profiling and were IDH-1 wild type (23.8%), thus confirming an integrated diagnosis of GBM.9,10,18,19,23 Thirteen patients exhibited exophytic tumors with intra-axial origins postulated.
Fig. 2  Neuroimaging of the representative case study. Preoperative magnetic resonance imaging (MRI) demonstrating a $5.2 \times 4.9 \times 2.9$ cm right cerebellopontine angle (CPA) tumor with pontine displacement and Meckel’s cave extension (blue arrow). Notable characteristics include (A) central T2 hypointensity with a cystic periphery (yellow arrow) and (B,C) heterogeneous contrast enhancement. Postoperative MRI 24 hours after subtotal tumor resection demonstrating (D) minimal brainstem and cerebellar edema with (E,F) nodular enhancement adjacent to the ventral pons and tentorium (red arrows). Postoperative MRI at 36 months revealing (G) stable cerebellar encephalomalacia and cystic change within the dorsal pons and (H,I) decreased enhancement in the right prepontine cistern and ventral pons (green arrows).
as either the pons (n = 4; 19.0%),\textsuperscript{12,21,22} or the cerebellum (n = 5; 23.8%),\textsuperscript{18–20,25,27} or were reportedly indistinguishable (n = 4; 19.0%).\textsuperscript{1,10,11,29} The remaining eight tumors arose from the CN root entry zones (38.1%).\textsuperscript{8,9,12,23,24,26,28}

Surgical Resection
Eighteen patients (85.7%) underwent surgical intervention,\textsuperscript{1,8–11,18–24,26–29} with 15 subtotal resections (71.4%),\textsuperscript{1,8,10,18–24,26–28} and 3 stereotactic biopsies (14.3%).\textsuperscript{9,11,12} No study reported gross total resection (GTR). The retrosigmoid craniotomy was the most common surgical approach. No article discussed use of intraoperative adjuncts for cytoreduction nor consideration of treatment strategies beyond chemoradiation.

Medical Therapy
Fourteen patients underwent the Stupp chemoradiation protocol (66.7%),\textsuperscript{1,8–12,18,19,23,25,27} while 2 patients underwent radiation only (9.5%).\textsuperscript{20,21} One patient died prior to further management (9.5%).\textsuperscript{24} and three patients refused intervention after diagnosis (14.3%).\textsuperscript{26,28,29} For recurrence, two patients underwent additional chemotherapy (9.5%).\textsuperscript{12,25} and one patient had radiosurgery with intrathecal bevacizumab.\textsuperscript{8} Use of locoregional chemoradiation was reported in only one patient who received carmustine wafers during surgery.\textsuperscript{18} No patient received TTF.

Follow-Up and Outcomes
Fourteen patients had reported follow-up (66.7%) with a mean time of 7.78 ± 6.60 months.\textsuperscript{1,9–11,18–20,23,24,26–29} Five patients were deceased (23.8%) with mean OS of 6.35 ± 6.67 months.\textsuperscript{18,24,26–28} Four patients were alive at the 1-year follow-up (19.0%),\textsuperscript{11,12,18,19,27} while only one patient was alive at 2 years (4.7%).\textsuperscript{19} Progression-free survival (PFS) was largely unknown. Kaplan–Meier estimates of the median OS and the 1-year survival rate for patients with primary tumors were 15 months and 61.9%, respectively (\textsuperscript{Fig. 4}).

Discussion
Infratentorial high-grade astrocytomas presenting as a predominant exophytic CPA mass are exceedingly rare, with only 21 cases reported in the literature. Given the scarcity of this entity, malignant lateral skull base astrocytomas represent both a significant diagnostic and therapeutic challenge. Overlapping radiographic features with benign CPA pathology potentially delay diagnosis, while safe, maximal tumor resection is inherently limited by traversing eloquent neurovasculature and a narrow working corridor bounded by the petrous apex, clivus, and brainstem. These anatomic borders and contents further limit diversification of treatment strategies beyond the standard of care in this region.

First, the preoperative diagnosis in our case was not straightforward. Radiographic features initially favored a large trigeminal schwannoma with cystic necrosis or malignant nerve sheath tumor extending into Meckel’s cave. The radiographic mimicry of nerve sheath tumors was also reported in one-third of literature cases without metastatic disease.\textsuperscript{22–24,27,28,30} Despite prompt resection, this case could have been easily presumed to be a benign tumor, thereby delaying treatment and worsening prognosis. Likewise, the mean time from symptom onset to diagnosis exceeded 6 months in the literature, with authors citing similar presumptions. In contrast, supratentorial primary brain tumors and high-grade tumors are usually diagnosed
<table>
<thead>
<tr>
<th>Study</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Presenting symptoms</th>
<th>Symptom duration (mo)</th>
<th>MRI characteristics</th>
<th>Neoplasm origin</th>
<th>Histopathologic diagnosis</th>
<th>Integrated molecular diagnosis</th>
<th>EOR</th>
<th>Chemo-therapy</th>
<th>Radiation therapy</th>
<th>OS/follow-up</th>
<th>Outcome</th>
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<tr>
<td>Swaroop and Whittle</td>
<td>22</td>
<td>M</td>
<td>CN VI–IX palsies, ataxia</td>
<td>12</td>
<td>NR</td>
<td>Pons</td>
<td>GBM</td>
<td>Unk</td>
<td>STR</td>
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<td>None</td>
<td>NR</td>
<td>NR</td>
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<td>Yamamoto et al</td>
<td>61</td>
<td>F</td>
<td>Gait ataxia, upward gaze palsies, nystagmus</td>
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<td>Heterogeneous enhancement; extension into the perimesencephalic cisterns</td>
<td>Cerebellum</td>
<td>GBM</td>
<td>Unk</td>
<td>STR</td>
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<td>Yes</td>
<td>12 mo</td>
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<tr>
<td>Wu et al</td>
<td>60</td>
<td>M</td>
<td>CN VI-VIII palsies, dysarthria, dysphagia, gait ataxia</td>
<td>2</td>
<td>Heterogeneous ring enhancement, extension into the IAC (3.6 x 3.3 x 3.3 cm)</td>
<td>CN VIII REZ</td>
<td>GBM</td>
<td>Unk</td>
<td>STR</td>
<td>None</td>
<td>None</td>
<td>2 mo</td>
<td>Deceased</td>
</tr>
<tr>
<td>Salkunke et al</td>
<td>59</td>
<td>M</td>
<td>Hearing loss, dysmetria, hemiparesis, HA, emesis</td>
<td>3</td>
<td>Heterogeneous enhancement, extension into the pons</td>
<td>Pons</td>
<td>GBM</td>
<td>Unk</td>
<td>STR</td>
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<td>Yes</td>
<td>NR</td>
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<td>Taraszewska et al</td>
<td>29</td>
<td>F</td>
<td>HA, nystagmus, ataxia, hemiparesis</td>
<td>NR</td>
<td>Bilateral enhancing CPA masses (2.7 x 1.6 x 3.5 cm; 2.6 x 1.9 x 2.0 cm)</td>
<td>CN VIII REZ</td>
<td>GBM</td>
<td>Unk</td>
<td>STR</td>
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<td>None</td>
<td>1 wk</td>
<td>Deceased</td>
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<td>Matsuda et al</td>
<td>69</td>
<td>M</td>
<td>TN</td>
<td>NR</td>
<td>Heterogeneous enhancement, intratumoral hemorrhage</td>
<td>Cerebellum</td>
<td>GBM</td>
<td>GBM (IDH1 WT)</td>
<td>STR</td>
<td>Yes: TMZ</td>
<td>Yes</td>
<td>24 mo</td>
<td>Alive with progression</td>
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<tr>
<td>Varghese et al</td>
<td>22</td>
<td>M</td>
<td>Emesis, ataxia</td>
<td>1</td>
<td>Heterogeneous enhancement, centered within left cerebellar peduncle</td>
<td>Cerebellum</td>
<td>Metastatic GBM (thoracic spine)</td>
<td>Unk</td>
<td>None</td>
<td>Yes: TMZ</td>
<td>Yes</td>
<td>NR</td>
<td>Alive</td>
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<tr>
<td>Breshears et al</td>
<td>67</td>
<td>M</td>
<td>CN V palsy</td>
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<td>Peripheral enhancement, cystic, extension into the CN V root entry zone (1.7 x 1.1 x 0.7 cm)</td>
<td>CN V REZ</td>
<td>GBM</td>
<td>GBM (IDH1 WT)</td>
<td>Biopsy</td>
<td>Yes: TMZ</td>
<td>Yes</td>
<td>5.75 mo</td>
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<td>Mabray et al</td>
<td>67</td>
<td>M</td>
<td>CN V palsy</td>
<td>2</td>
<td>Heterogeneous peripheral enhancement, cystic mass, extension into the CN V root entry zone</td>
<td>Pons</td>
<td>GBM</td>
<td>Unk</td>
<td>Biopsy</td>
<td>Yes</td>
<td>Yes</td>
<td>12 mo</td>
<td>Alive</td>
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<tr>
<td>53 F</td>
<td>Asymptomatic</td>
<td>15</td>
<td>CN V REZ</td>
<td>Metastatic GBM (R frontal)</td>
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<td>Yes</td>
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<tr>
<td>22 M</td>
<td>AMS</td>
<td>18</td>
<td>Cystic mass, extension into the CN V root entry zone</td>
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<td>Metastatic GBM (R frontal)</td>
<td>Unk</td>
<td>None</td>
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<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Alive with progression</td>
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<tr>
<td>24 F</td>
<td>CN V and VI palsies</td>
<td>NR</td>
<td>Heterogeneous peripheral enhancement, extension into the R CN V root entry zone</td>
<td>Pons</td>
<td>GBM</td>
<td>Unk</td>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>Alive with progression</td>
<td></td>
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<tr>
<td>71 F</td>
<td>Tininitus, CN VIII palsies, HA, emesis, nystagmus, hemiparesis, dysmetria, ataxia</td>
<td>4</td>
<td>Homogeneous enhancement, extension into the IAC, intratumoral hemorrhage (3.6 x 4.1 cm)</td>
<td>Pons/cerebellum</td>
<td>Gliosarcoma</td>
<td>Gliosarcoma (IDH1 WT)</td>
<td>STR (70%)</td>
<td>Yes: TMZ</td>
<td>Yes</td>
<td>6 mo</td>
<td>Alive</td>
<td></td>
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<tr>
<td>71 F</td>
<td>Gait ataxia</td>
<td>3</td>
<td>Homogeneous enhancement (2.7 x 2.2 cm)</td>
<td>Pons/cerebellum</td>
<td>GBM</td>
<td>Unk</td>
<td>Biopsy</td>
<td>Yes: TMZ</td>
<td>Yes</td>
<td>12 mo</td>
<td>Alive</td>
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<td>Study</td>
<td>Age (y)</td>
<td>Sex</td>
<td>Presenting symptoms</td>
<td>Symptom duration (mo)</td>
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<td>Neoplasm origin</td>
<td>Histopathologic diagnosis</td>
<td>Integrated molecular diagnosis</td>
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<td>Chemo-therapy</td>
<td>Radiation therapy</td>
<td>OS/follow-up</td>
<td>Outcome</td>
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<td>Panigrahi et al</td>
<td>52</td>
<td>F</td>
<td>CN VI and VIII palsies dysmetria, gait ataxia</td>
<td>2</td>
<td>Homogeneous enhancement (2.4 x 2.1 x 2.4 cm)</td>
<td>Cerebellum</td>
<td>GBM</td>
<td>Unk.</td>
<td>STR</td>
<td>None</td>
<td>Yes</td>
<td>4 mo</td>
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<tr>
<td>Takami et al</td>
<td>55</td>
<td>M</td>
<td>Vertigo, CN VII palsy</td>
<td>4</td>
<td>Centered within the IAC with 8-mm CPA extension, necrosis</td>
<td>CN VIII REZ</td>
<td>GBM (IDH1 WT)</td>
<td>STR (99%)</td>
<td>Yes: TMZ</td>
<td>Yes</td>
<td>Yes</td>
<td>5 mo</td>
<td>Alive</td>
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<tr>
<td>Yoon et al</td>
<td>78</td>
<td>M</td>
<td>Dizziness, gait ataxia</td>
<td>3</td>
<td>Heterogeneous enhancement, dural tail, intratumoral hemorrhage (5.6 x 4.8 x 3.2 cm)</td>
<td>Pons/cerebellum</td>
<td>Gliosarcoma</td>
<td>STR</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>9 mo</td>
<td>Alive</td>
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<tr>
<td>Marinello et al</td>
<td>49</td>
<td>F</td>
<td>HA, dizziness, CN VIII palsy, TN, gait ataxia</td>
<td>0.5</td>
<td>Homogeneous enhancement</td>
<td>Cerebellum</td>
<td>GBM (IDH1 WT)</td>
<td>STR</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>15 mo</td>
<td>Deceased</td>
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<tr>
<td>Yang et al</td>
<td>55</td>
<td>M</td>
<td>CN VII–XII palsies, gait ataxia, nystagmus</td>
<td>3</td>
<td>Heterogeneous ring enhancement, en-hanging CN VIII root, intratumoral hemorrhage</td>
<td>CN VIII REZ</td>
<td>GBM (IDH1 WT, MGMT-met)</td>
<td>STR</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>2.5 mo</td>
<td>Deceased</td>
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<tr>
<td>Bajwa et al</td>
<td>24</td>
<td>F</td>
<td>HA, emesis, dizziness, dysmetria, CN VII palsy</td>
<td>6</td>
<td>Heterogeneous enhancement (3.4 x 2.3 x 3.2 cm)</td>
<td>CN VII REZ</td>
<td>GBM (thoracic spine)</td>
<td>Unk.</td>
<td>STR</td>
<td>Yes: TMZ, fotemustine, camustine wafers</td>
<td>Yes</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Kiyofuji et al</td>
<td>45</td>
<td>M</td>
<td>Gait ataxia, CN VII-X palsies</td>
<td>36</td>
<td>Heterogeneous enhancement, internal calcifications (5.5 cm)</td>
<td>Pons/cerebellum</td>
<td>GBM (IDH1 WT, MGMT-met)</td>
<td>STR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>1 wk</td>
<td>Alive</td>
</tr>
<tr>
<td>This study</td>
<td>58</td>
<td>M</td>
<td>Vertigo, gait ataxia</td>
<td>4</td>
<td>Heterogeneous enhancement, extension into Meckel's cave (5.2 x 4.9 x 2.9 cm)</td>
<td>Pons/cerebellum</td>
<td>GBM (Grade 4 astrocytoma (IDH1 mutant, MGMT-met))</td>
<td>STR (80%)</td>
<td>Yes: TMZ</td>
<td>Yes</td>
<td>Yes</td>
<td>36 mo</td>
<td>Alive</td>
</tr>
</tbody>
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Abbreviations: CN, cranial nerve; EOR, extent of resection; F, female; HA, headache; IAC, internal acoustic canal; IDH, isocitrate dehydrogenase; M, male; met, methylated; MGMT, methylguanine-DNA-methyltransferase; mo, months; MRI, magnetic resonance imaging; NR, not reported; OS, overall survival; R, right; REZ, root entry zone; STR, subtotal resection; TMZ, temozolomide; TN, trigeminal neuralgia; Unk., Unknown; WHO, World Health Organization; WT, wild type.
within 39 and 26 days, respectively.\textsuperscript{31} Consideration of high-grade astrocytomas as a potential diagnosis in the CPA is vital to obtaining urgent histopathologic diagnosis and swiftly implementing adjuvant treatment.

Despite subtotal resection, our patient responded well to chemoradiation and remains alive at 40 months without tumor progression, likely due to a favorable genetic profile including IDH-1 R132H mutation, CDKN2A retention, and MGMT hypermethylation.\textsuperscript{5,32,33} Despite discovery of IDH mutations in 2009,\textsuperscript{34} and the standardization and emphasis of integrating diagnosis with molecular profiling in 2016 and 2021,\textsuperscript{4} this review uncovered sparse molecular genetics reporting for CPA astrocytomas. In all, 68.4\% of cases published after 2019 lacked genetic analysis,\textsuperscript{8,11,12,20–22,24,29} while over half of studies published after 2016 failed to mention IDH or MGMT testing at all.\textsuperscript{8,9,11,20} As a result, only 26.3\% of CPA GBMs diagnosed by histopathology had a corresponding integrated diagnosis with confirmed IDH wild-type profile.\textsuperscript{1,9,10,18,19,23} and only one case reported survival of up to 2 years.\textsuperscript{12} While our case study ultimately represents a different disease entity, it is important to remember that anatomic tumor location drives the ability to achieve maximal treatment, which is an integral step for optimizing survival. Further, insufficient reporting of molecular profiles in this cohort ultimately restricts our understanding of the complex relationship between anatomic location and molecular genetics on prognosis and outcome and emphasizes the critical utility of investigating molecular profiles for malignant tumors with rare growth patterns.

The retrosigmoid approach, used the most in this cohort, provides adequate visualization and access for GTR of many benign CPA lesions, yet the malignant features of high-grade astrocytomas render this feat challenging. Infiltration of adjacent skull base foramina and brainstem parenchyma causes marked adherence to eloquent structures and poor margins for safe resection, as seen in our case.\textsuperscript{35} Due to the significant survival benefit associated with maximal resection beyond enhancing tumors, adjuncts to surgery are needed to address residual macroscopic and microscopic disease, yet their utility is elusive.\textsuperscript{30,36,37} 5-aminolevulinic acid (5-ALA), for example, improves the extent of resection through intraoperative fluorescence of malignant tumor, but its use requires preoperative anticipation of glial pathology. Since glioma was not a suspected pathology in the preoperative setting in our case, similar to at least a third of the literature cases, nor has 5-ALA shown benefit for other neoplasms, its use was not considered.\textsuperscript{38} Intraoperative MRI and neuroendoscopy may contribute toward improved resection in this highly eloquent region; however, their usefulness is debated and subject to availability of resource.\textsuperscript{39} Surgical adjuncts like intraoperative ultrasound have limited value within the CPA due to the incompatibility of its geometric configuration with the anatomic corridor.

Possible treatment adjuncts with growing use in supratentorial tumors include TTF, laser interstitial thermal therapy (LITT), and high-intensity focused ultrasound (HIFU), which have not been specifically explored for use in the lateral skull base. Optune is a Food and Drug Administration (FDA) approved device that utilizes electric TTF to cause apoptosis and has demonstrated superior rates of PFS and OS compared with chemoradiation alone.\textsuperscript{40} However, the device’s standard array placement limits field coverage to the posterior fossa, and an alternative configuration has yet to be clinically validated.\textsuperscript{41} LITT may treat GBM recurrence via minimally invasive thermal ablation in areas difficult to access with open surgery, yet concerns regarding increased morbidity of thermal ablation in the posterior fossa and poor local control rates in brainstem gliomas preclude its use.\textsuperscript{42–44} Further, no study to date has specifically examined its safety or feasibility for CPA lesions.\textsuperscript{43} Finally, HIFU uses ultrasonic waves to disrupt the blood–brain barrier to improve chemotherapy delivery, boost immunogenicity, and induce thermal ablation, but similar mechanistic challenges in the CPA are likely given the broad-based configuration of the...
piezoelectric transducer. Ultimately, our patient, like those in the literature, was not a candidate for any of these ancillary therapies.

Even with advances in adjuvant therapies unrestricted by anatomic location, like immunotherapy and locoregional chemoradiation, therapeutic progress over the past decade remains limited. Only one study reported the use of locoregional carmustine wafers in the resection cavity to bridge treatment to radiation. Despite an increase in OS by 2 to 4 months, carmustine wafers have a toxic side effect profile that deters its mainstay use. A recent FDA-approved implantable radiation source called GammaTile, comprising bioresorbable collagen and cesium-131, offers a similar therapeutic strategy; however, its safety and efficacy in the posterior fossa has yet to be specifically evaluated. Intrathecal bevacizumab was utilized once in this review for tumor recurrence; however, no association with improved survival is evident. Clinical trials for various targeted therapies and immunotherapies like checkpoint inhibitors represent another frontier for investigation with eventual options dependent on individual tumor biology and effective drug delivery.

While the utility of systemic chemoradiation is certainly less restricted by anatomic tumor location, gaps in knowledge persist regarding optimization of current radiotherapy strategies for grade 4 astrocytoma arising in the CPA. Present strategies derive primarily from our understanding of supratentorial astrocytomas where fractionated external beam radiotherapy using photons remains a cornerstone of treatment to radiation. Despite the Stupp protocol and one of few adjuncts to radiation using photons remains a cornerstone of treatment to radiation. Despite the Stupp protocol and one of few adjuncts to radiation intensity, treatment time, and dosimetry have yielded advanced planning techniques meant to provide safer delivery near eloquent tissue such as IMRT, which was employed in our case study, volumetric-modulated arc therapy (VMAT), and hypofractionated protocols in elderly patients, respectively. These techniques are particularly useful for posterior fossa astrocytomas where adverse effects incur greater morbidity and have demonstrated similar survival outcomes with more acceptable toxicity profiles. The use of protons, however, further reduces normal tissue radiation exposure due to steeper dose gradients, lower tissue side scatter due to the relatively larger masses of charged particles, and more uniform dose delivery. While proton beam radiation may result in greater incidence of radiation necrosis, a recent retrospective study suggested improvement in survival compared with conventional radiation for high-grade astrocytoma. Moreover, when treating benign tumors in the CPA, improved rates of hearing preservation were evident with utilization of protons. Current randomized control trials are underway to elucidate the benefits of particle therapy using protons, neutrons, or carbon ions in grade 4 astrocytomas, which may prove beneficial in eloquent locations like the CPA.

Finally, stereotactic radiosurgery (SRS) represents a treatment modality commonly utilized for benign CPA tumors yet reserved only as salvage therapy for treatment of locally recurrent high-grade astrocytomas. An optimal SRS technique and regimen remains investigational for high-grade astrocytomas despite anatomic location, and may still prove of limited use in the posterior fossa due to its increased toxicity and rates of radiation necrosis as compared with the conventional radiotherapy. The addition of concomitant systemic therapy like TMZ to radiosensitize the tumor or bevacizumab to reduce risk of radionecrosis upfront is further being explored for each radiotherapy technique and remains inconclusive, although one patient in the literature did undergo SRS with bevacizumab for tumor recurrence. While novel treatment adjuncts like TTF require significant design modifications to overcome the anatomic restrictions of the CPA, adjustments to existing chemoradiation techniques and the development of targeted therapies represent the most viable pathway forward for improving treatment of high-grade astrocytomas in this challenging location.

Limitations

The limitations of our systematic review include its retrospective design and inconsistent data reporting. Although our review demonstrates significant mortality rates within the first year, we could not provide a reliable estimate of survival due to limited follow-up. Notably, many of the studies lacked information regarding molecular tumor profiles. The small number of published cases also restricts our interpretation of clinical outcomes for this rare entity. Larger cohort studies are necessary to fully understand the intricacies of this malignant disease when involving the skull base.

Conclusions

WHO grade 4 astrocytomas with large exophytic growth into the cerebellopontine cistern are exceedingly rare but should remain a pertinent differential diagnosis in patients with subacute CPA syndrome. The understanding of biologic tumor behavior and oncologic outcomes in this area as compared with supratentorial and intrinsic infratentorial astrocytomas remains unclear and underreported. Due to the intrinsically narrow anatomic corridor with an abundance of eloquent structures, surgery and therapeutic adjuncts remain highly limited and merit further investigation.

Consent to Participate

Informed consent was obtained from all individual participants included in the study.

Consent to Publish

Images contained within this manuscript are restricted to radiographic or histological information without individual data.

Ethical Approval

This is a retrospective study. The Inova Institutional Review Board has confirmed that no ethical approval is required.
Author Contributions
All the authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by D.D.D., A.D.G., L.A.M., and J.V.D. The first draft of the manuscript was written by D.D.D. and A.D.G., and all the authors commented on previous versions of the manuscript. All the authors read and approved the final manuscript.

Conflict of Interest
None declared.

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