Posterior Fossa Intra-Axial Tumors in Adults

Rachel Grossman and Zvi Ram

Key words
- Brain tumors
- Ependymomas
- Gliomas
- Lymphomas
- Medulloblastomas
- Outcome
- Pilocytic astrocytomas
- Posterior fossa

Abbreviations and Acronyms
CNS: Central nervous system
GTR: Gross total resection
OS: Overall survival
PA: Pilocytic astrocytoma
Shh: Sonic hedgehog
SRS: Subtotal resection
VHL: Von Hippel-Lindau
Wnt: Wingless
WHO: World Health Organization

INTRODUCTION
The posterior fossa is the site of many types of tumors, and brain metastases are the most common adult malignancies in this region. Other brain tumors, such as ependymomas, medulloblastomas, and juvenile pilocytic astrocytomas (PAs), mostly occur during childhood and are relatively rare in adults. The prognostic factors and therapeutic management of adult patients with these tumors are controversial because of their rarity, their heterogeneity, and the lack of sufficient data in the literature.

EPENDYOMAS
Ependymoma, a relatively rare tumor in adults, accounts for only 2%–5% of all intracranial tumors, but it is the fourth most common brain tumor in children. About 30% of pediatric ependymomas are diagnosed in children <3 years old. Ependymomas arise from ependymal cells and mostly occur in the posterior fossa. They are classified as subependymomas (World Health Organization [WHO] grade I), ependymomas (WHO grade II), and anaplastic ependymomas (WHO grade III). Posterior fossa ependymomas comprise 50% of ependymomas in adults. Despite the histologic similarity of ependymomas, they are very heterogeneous tumors. Transcriptional profiling of 2 large independent cohorts of patients with ependymomas revealed the existence of 2 demographically, transcriptionally, genetically, and clinically distinct groups of posterior fossa ependymomas. Group A patients were younger; had laterally located tumors with a balanced genome; and were much more likely to exhibit recurrence, metastasis at recurrence, and death compared with group B patients. Loss of chromosome 22 was 1 of the most frequent genomic alterations, occurring often in group B posterior fossa ependymomas and rarely in group A tumors with upregulation of the LAMA2 gene in group A and NELL2 in group B. Moreover, group A included other biomarkers known to be associated with poor outcome, such as chitinase 3-like 1, tenascin-C, vascular endothelial growth factor, epithelial growth factor receptor, Erb-B2 receptor tyrosine kinase 4, baculoviral inhibitor of apoptosis repeat-containing 5, and S100 calcium-binding protein A6.

BACKGROUND: The posterior fossa is the site of many types of tumors, and brain metastases are the most common malignancies in that location among adults. Other brain tumors, such as ependymomas, medulloblastomas, and juvenile pilocytic astrocytomas, mostly occur during childhood and are relatively rare in adults. Most primary malignant brain tumors, such as gliomas and lymphomas, tend to be located in the supratentorial compartment.

METHODS: This review summarizes prognostic factors, therapeutic management, and molecular data of intra-axial posterior fossa tumors in adults, including ependymomas, medulloblastomas, and pilocytic astrocytomas.

RESULTS: The literature on intra-axial posterior fossa tumors in adults relies mainly on limited retrospective clinical studies, and such studies employ a wide range of treatment approaches that are usually based on therapies developed specifically for children or for supratentorial brain tumors.

CONCLUSIONS: The clinical course and surgical outcome of adult patients with intra-axial brain tumors in the posterior fossa are summarized in this review. The prognostic factors and therapeutic management of patients with these tumors are controversial because of their rarity, their heterogeneity, and the lack of sufficient data in the literature.
remained to be defined. The lack of validated significant prognostic factors can probably be explained by the small number of patients included in reported series, the heterogeneity of the patient population in terms of age (adults and children) and anatomic location (supratentorial, infratentorial, and spinal), and the very long treatment periods. The treatment paradigm for WHO II posterior fossa ependymomas in adults continues to be controversial, and there are essentially no standard clinical guidelines for treatment. The largest, relatively homogeneous clinical series of WHO grade II supratentorial and infratentorial brain ependymomas in adults comprised 114 patients from 32 French neurosurgical centers who underwent surgery during the period 1990–2004.6 Most ependymomas (80.7%) were located in the posterior fossa. Multivariate analysis revealed that overall survival (OS) was associated with the preoperative Karnofsky performance scale score and extent of surgical resection.

These findings are in line with other clinical series of adults with posterior fossa ependymomas.2,7,8 Reni et al.4 conducted a multicenter study of 70 adult patients with ependymomas and reported longer survival in younger patients and in patients with an infratentorial tumor location. Mirzadeh et al.7 retrospectively summarized the functional recovery of 45 adult patients with posterior fossa ependymomas. The authors reported that 75.6% of the patients had returned to their preoperative functional status at 1 year. Several variables, such as large tumor volume (>30 cm³), cystic changes on preoperative magnetic resonance imaging, hyperintense T2-weighted magnetic resonance imaging signal surrounding the resection cavity, and need for cerebrospinal fluid diversion, were identified as being associated with worse functional and neurologic outcomes.

The specific molecular subtype is unknown during surgery but may be important for planning postoperative adjuvant therapy. Because group B tumors are much less likely to recur, group B patients can be treated less aggressively than group A patients. Radiation therapy for ependymomas has been a matter of debate for decades. In a French neurosurgical cohort, radiotherapy was not associated with enhanced survival among the study population as a whole,7 but rather only for a subgroup that underwent subtotal resection (STR). The same trend was reported by Guyotat et al.2 in a multicenter retrospective study of 106 patients with infratentorial ependymomas. Patients who underwent gross total resection (GTR) followed by radiation therapy had no progression-free survival or OS benefit, but there was a significant survival benefit in a subgroup of patients who were operated for STR and received postoperative radiation therapy compared with patients who did not receive adjuvant treatment. However, several retrospective studies based on large and uniform cohorts of patients with infratentorial ependymomas showed better disease control for patients after GTR and radiotherapy compared with GTR alone.6,7 Overall, the existing literature supports a role for a maximal extent of surgery and the preoperative performance status on determining prognosis in low-grade ependymomas in adults. The role of adjuvant radiation therapy is still unclear, but it seems to have a favorable impact on OS and progression-free survival in incompletely resected WHO grade II ependymomas.7 Prospective clinical trials are warranted to assess the actual impact of postoperative radiation therapy in this population.

### PA

PAs are classified by WHO as grade I astrocytic tumors.10 They represent 40% of brain tumors in children but are rarely found in adults, for whom the annual incidence is 4.8 per 1 million.11 PAs in adults tend to be located in the supratentorial compartment and to have an unfavorable prognosis. The most common genomic abnormalities found in sporadic PAs are BRAF fusion genes,12 which appear mostly in cerebellar

### Table 1. Clinical, Histopathologic, and Molecular Summary of Posterior Fossa Tumors in Adults

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Incidence</th>
<th>Prognostic Factors</th>
<th>Histopathology</th>
<th>Molecular Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ependymomas</td>
<td>2%–5%</td>
<td>KPS, EOR</td>
<td>WHO I, subependymoma; WHO II, ependymoma;</td>
<td>Group A: younger, laterally located tumors, worse</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>WHO III, anaplastic ependymoma</td>
<td>prognosis; upregulation of LAMC2;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>upregulation of NELL2</td>
</tr>
<tr>
<td>PAs</td>
<td>3%</td>
<td>KPS, EOR</td>
<td>PA; anaplastic PA</td>
<td>BRAF mutation (&gt;70%)</td>
</tr>
<tr>
<td>Medulloblastomas</td>
<td>1%–3%</td>
<td>EOR</td>
<td>WHO IV, classic, nodular desmoplastic, large cell/</td>
<td>Wnt: rare in adults; CNOT11 gene mutation; better</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>anaplastic</td>
<td>prognosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Shh: mainly in adults; intermediate prognosis;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PTHC1 mutation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Group 3: worst prognosis; MYC mutation/amplification</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Group 4: intermediate prognosis; mostly in adults;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MYCN and CDK6 amplification</td>
</tr>
<tr>
<td>Cerebellar hemangioblastomas</td>
<td>10%</td>
<td>—</td>
<td>WHO I</td>
<td>VHL gene mutation</td>
</tr>
<tr>
<td>Gliomas</td>
<td>4.4%</td>
<td>Age, KPS, EOR</td>
<td>WHO II, low-grade glioma; WHO III, anaplastic</td>
<td>IDH mutation; loss of expression mutations of ATRX;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>astrocytoma; WHO IV, glioastoma</td>
<td>EGFR amplification; TERT mutation; PTEN mutation</td>
</tr>
</tbody>
</table>

KPS, Karnofsky performance scale; EOR, extent of resection; WHO, World Health Organization; PA, pilocytic astrocytoma; Wnt, Wingless; Shh, Sonic hedgehog.
PAs and are less frequent in PAs at other sites. Data on the long-term outcome of patients with PAs in the posterior fossa are limited. Although some studies suggest that adult patients with PA have a benign course after initial surgical resection, other studies suggest the opposite. Ellis et al. reported a cohort of 20 adult patients with PA for whom there was a 30% recurrence rate. Among their patients, 3 out of 4 who were operated for tumor recurrence showed a malignant transformation of their tumor. These results are similar to the findings reported by Stüer et al., who summarized the clinical course of 44 adult patients with PA who were operated on in a single institution. The authors also reported 30% tumor recurrence or disease progression. Specifically, 12 patients had cerebellar PAs, and 7 had brainstem PAs; GTR was achieved in 66% of the cerebellar PAs, whereas only 33% of the brainstem PAs could be completely removed. Adjuvant radiotherapy (54–58 Gy) was given in all cases of primary or secondary anaplastic PA, and 4 patients received concomitant chemotherapy consisting of a combination of procarbazine, lomustine, and vincristine. One patient who received concomitant chemotherapy was also treated with temozolomide. Performance status before and after surgery, as measured by the Karnofsky performance scale, was strongly associated with enhanced OS. Complete surgical resection seems to be curative in all patients with PAs that are WHO grade I. Of 19 patients reported by Stüer et al. who underwent GTR, there was no tumor recurrence in 18 patients over a median follow-up period of 55 months; 1 patient in whom a WHO grade III anaplastic PA was diagnosed experienced tumor recurrence. A series by Wade et al. included 10 patients who underwent surgery for tumor resection; 8 patients underwent GTR, and 2 patients underwent STR. After a follow-up period of up to 334 months, only patients who underwent STR had tumor recurrence. The recurrence rate was not correlated to the tumor proliferation index, as assessed by Ki-67.

There are limited data and no randomized studies to guide treatment policy for PA, especially regarding postsurgical management. Patients are usually either observed expectantly or offered upfront adjuvant treatment. The use of BRAF inhibitors can hypothetically be a treatment option for PA; the benefit of this treatment has yet to be analyzed in large clinical studies. It is acceptable to observe patients after GTR, reserving radiation therapy for salvage. In a series of 30 adults with PA, 13 patients were found to have infratentorial tumors. Radiation therapy was given to 4 patients after STR and 1 patient after GTR. The authors concluded that postoperative radiation therapy had no effect on OS.

**MEDULLOBLASTOMAS**

Medulloblastoma is 1 of the most common brain tumors in children, accounting for up to 30% of all pediatric central nervous system (CNS) tumors. They are rare in adults, accounting for 1%–3% of all adult primary brain tumors. For that reason, most of the literature on medulloblastomas in adults relies on retrospective analyses over several decades and include a wide range of treatment protocols that are usually based on therapies developed for children. It has become clear more recently that medulloblastomas in adults have distinct molecular, radiologic, and clinical properties. In contrast to pediatric medulloblastomas, which tend to be located in the vermis, tumors in adults tend to involve the cerebellar hemispheres. Another difference from pediatric tumors is the greater prevalence of late recurrence. Riffaud et al. reported a recurrence rate of 41% with a median time to recurrence of 4.2 years (range, 0.7–18 years). In a phase II prospective study, Brandes et al. reported that the risk for recurrence in adults with medulloblastomas increased markedly after 7 years of follow-up in low-risk patients. These results suggest that adults with medulloblastomas have an ongoing lifetime risk for tumor recurrence and cannot be considered cured, even after several years of remission.

More recent advances in molecular biology have allowed the identification of 4 distinct molecular subgroups. Two well-characterized subgroups of medulloblastoma with peculiar pathways are known as Wingless (Wnt) and Sonic hedgehog (Shh), and the remaining 2 subgroups are known as groups 3 and 4. Each subgroup has different cytogenetic, mutational, and gene expression signatures; demographics; histology; and prognosis. 1) Wnt is the least common subgroup, has a better prognosis, and accounts for 10% of all medulloblastomas (15% in adults). Typically, Wnt medulloblastomas occur in children >3 years old and are rarely found in adults. The most common genetic alteration of Wnt medulloblastomas, present in 90% of the cases, is CTNNB1 gene mutation, which leads to enhanced activation of MYC and MYCN oncogenes and subsequent increase in cellular proliferation. Other frequently altered genes are DDX3X (50%), SMARCA4 (26%), MLL2 (12%), and TP53 (12%) and loss of chromosome 6q and 17p. 2) The Shh subgroup, consisting of 30% of all patients with medulloblastoma, mainly comprises adults (60%) and infants. The prognosis is intermediate for both age groups. The most commonly found genetic mutations in Shh subgroup are PTC1 (28%) and SUFU. Other frequently mutated genes are TP53 (13%), MLL2 (13%), MYCN (8%), LDB1 (7%), and GLI2 (5%). 3) Group 3 has the worst prognosis, with a high tendency to metastasize, and is very rare in adults and more common in children and infants. The most common genetic alteration in this subgroup is proto-oncogene MYC mutation/amplification and an elevated genomic instability with frequent chromosome 13p gains, 10q and 5q loss, and the presence of isochromosome 17. 4) Group 4 is the largest subgroup, accounting for 35% of all medulloblastomas with intermediate prognosis. These medulloblastomas mostly occur in adults (20%–25% of all adult medulloblastomas) and children (35%). Group 4 is characterized by MYCN and CDK6 amplifications.

The initial treatment paradigm for adults with newly diagnosed medulloblastomas includes maximal safe resection followed by postoperative radiotherapy and possibly adjuvant chemotherapy. Growing evidence correlates patient outcome with extent of tumor resection. Postoperative radiation therapy of 36–40 Gy to the spinal axis followed by a boost of 54–58 Gy to the posterior fossa is given in most cases. This treatment is associated with a 5-year OS rate of 58%–84%. In contrast to medulloblastoma in childhood, the role of chemotherapy in adults is not well defined, and chemotherapy is usually given to high-risk patients. Moreover, there is no consensus regarding the specific regimen to be used.
Treatment of patients with disease recurrence is challenging, and there is no clear protocol at the present time. Although no randomized controlled studies have assessed the role of reoperation, retrospective clinical series suggest that, when feasible, patients should undergo repeat resection of the recurrent tumor followed by radiation therapy, high-dose chemotherapy, and stem cell transplantation.14

CEREBELLAR HEMANGIOBLASTOMA
Hemangioblastomas are benign vascular tumors, classified as WHO grade I tumors, that are composed of stromal cells and abundant capillaries.38 Hemangioblastomas can be found in any part of the CNS, but they are most frequently located in the posterior fossa.36 These tumors constitute 2% of all brain tumors and represent 10% of all posterior fossa tumors in adults. Approximately 25% of hemangioblastomas are associated with von Hippel-Lindau disease (VHL), an autosomal dominant inherited disease characterized by the development of hemangioblastomas of the CNS and retina, clear cell renal carcinoma, pheochromocytoma, pancreatic tumors, and endolymphatic sac tumors. The rest of the hemangioblastomas occur sporadically. The histologic appearance of sporadic hemangioblastomas or VHL-associated hemangioblastomas is identical. Previous clinical studies tended to mix sporadic hemangioblastomas with VHL-associated hemangioblastomas. Sporadic hemangioblastomas are solitary in most cases and usually occur in adults, whereas hemangioblastomas in patients with VHL tend to be multiple, evolve rapidly, and occur in younger patients (mean age of 29 years). Several clinical series estimated that multiple hemangioblastomas develop in 60%—90% of patients with VHL;57,59 also, systemic manifestation of VHL carries a major deleterious impact on the quality of life of the patients.59

The radiologic appearance of a hemangioblastoma is classified into 4 types: without associated cysts, with intratumoral associated cysts, with associated peritumoral cysts, and with both peritumoral and intratumoral cysts.40 Peritumoral cysts tend to be associated with a more symptomatic clinical course depending on the rate of cyst growth and volume. The mechanism of peritumoral cyst formation is different from the mechanism associated with intratumoral cyst formation. Specifically, an intratumoral cyst results from tumor necrosis, whereas a peritumoral cyst is the result of surrounding interstitial pressure, increased tumor vascular permeability, and tumor surrounding edema.56,60

In general, resection of hemangioblastomas in patients with VHL is indicated when the lesion causes symptoms. The treatment for sporadic and VHL-associated CNS hemangioblastomas is resection. Because of their abundant vascularity, surgical resection of hemangioblastomas may result in significant intraoperative blood loss, and preoperative vascular embolization has been rarely reported.41 Resection of symptomatic hemangioblastomas improves or stabilizes the patient’s symptoms and overall outcome. The recurrence rate after removal of sporadic or VHL-associated hemangioblastomas is 20%—33%.42 Analysis of 40 CNS hemangioblastomas in 20 patients with VHL treated with radiosurgery showed no progression in 33% of the patients 6 years after treatment; however, this was similar to the natural history of untreated patients with hemangioblastomas.35 Tumor removal leads to resolution of the peritumoral cysts, and removal of the cyst wall is not required in every case. Resection of the tumor causes the cyst to collapse. However, it is important to carefully inspect the cyst wall intraoperatively to detect small tumor foci. Overall, the treatment paradigm of symptomatic hemangioblastomas is surgical resection and the avoidance of unnecessary therapies, especially for tumors that may not progress.

GLIOMAS
Gliomas constitute the most common primary tumor in the brain. However, they are most frequently located supratentorially. A few clinical series with limited numbers of patients (mostly with infratentorial gliomas) have been reported.55,66 Although glioblastoma, a WHO grade IV glioma, is the most common primary brain tumor, cerebellar glioblastomas are rare and constitute only 0.4%—3.4% of all intracranial glioblastomas. The largest clinical series of patients with cerebellar glioblastomas used clinical data from the population-based Surveillance, Epidemiology and End Results national database during the years 1973—2009.63 Attempts have been made to identify factors associated with survival in this patient population and compare them factors associated with survival in patients with supratentorial glioblastomas. It seemed that cerebellar glioblastomas tended to occur in younger patients, had smaller tumor size, and had a shorter OS (median survival of 8 months). Moreover, the cerebellar location of a glioblastoma independently predicted poor survival compared with other locations.64 In another single-center clinical series of 45 adults with cerebellar glioblastomas, the authors found that preoperative tumor volume, extent of tumor resection, brainstem invasion, and further postoperative neuro-oncologic treatment all were significantly associated with enhanced survival.44 Tsung et al.45 conducted a retrospective review of 21 patients with cerebellar glioblastoma and noted that this distinct patient population tended to be young (mean age of 39 years at diagnosis) and that postoperative chemotherapy was associated with extended survival. The extent of resection had no impact on either OS or progression-free survival. This finding may reflect the small cohort of patients who presented with a mixture of true cerebellar gliomas with tumors with brainstem involvement and even with tumors that caused leptomeningeal spread. Strauss et al.46 reported a unique subpopulation of 16 patients with a diagnosis of supratentorial glioma who developed late noncontiguous infratentorial extension of their tumors. In that report, another 2 patients had concurrent disease in the posterior fossa at the time of diagnosis of their primary supratentorial tumor. All 18 patients had hyperintense lesions on fluid attenuated inversion recovery magnetic resonance imaging, which were observed as being adjacent or around the fourth ventricle causing a mass effect and displacement of the ventricle. Of 18 patients, 12 had high-grade gliomas, and 6 had low-grade gliomas. Biopsies were not performed in most of the posterior fossa tumors, and it is unknown whether malignant transformation had occurred. Overall, it was unclear whether this progression represented secondary expansion of the primary disease (multifocal) or if there actually had been multiple primary tumors (multicentric). However, it was clear that secondary posterior fossa involvement was associated with a poor prognosis.
OTHER POSTERIOR FOSSA TUMORS

Intracranial Dermoid Cysts

Intracranial dermoid cysts are congenital lesions that account for approximately 0.3% of all intracranial lesions and occur most commonly in the posterior fossa. These cysts are encapsulated by stratified squamous epithelium and contain dermal derivatives, such as hair follicles, sebaceous glands, and sweat glands. These lesions typically grow slowly, with most not becoming symptomatic until the third decade of life. Growth of these cysts occurs as a result of the accumulation of desquamated cell debris from their capsule. These cysts are most commonly located in the midline, and often the cyst’s capsule is tightly attached to the surrounding parenchyma, nerves, or vasculature and is difficult to remove. They can manifest with CNS infection and cause elevated intracranial pressure and hydrocephalus. GTR, when safely feasible, is the mainstay of treatment to prevent further episodes of infection.

Epidermoid Cysts

Epidermoid cysts are benign, slow-growing congenital neoplasms of the CNS that contain waxy keratinous material that originated from retained ectodermal remnants. These cysts account for approximately 0.5%–1% of all intracranial tumors and develop from aberrant ectodermal embryonic tissue in the neural groove in the first month of embryonal development. Epidermoid cysts are most commonly located in the cerebellum, pontine angle, and parasellar region. In a retrospective analysis of 50 cases of posterior fossa epidermoid cysts surgically treated over a decade, the most common presenting symptoms were trigeminal neuralgia, hearing loss, gait ataxia, and increased intracranial pressure. The recurrence rate was much higher among patients who underwent STR compared with GTR.

CONCLUSIONS

This review summarizes the current data on intra-axial tumors in the posterior fossa in adults to help familiarize readers with these rare pathologies. The clinical course, prognostic factors, and therapeutic management of this relatively rare and heterogeneous group of patients are still debated. More data on the clinical course of this unique group of patients need to be obtained.

REFERENCES


Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Accepted March 2015, accepted 22 December 2015 Citation: World Neurourol. (2016) 88:140-145. http://dx.doi.org/10.1016/j.wneu.2015.12.086 Journal homepage: www.WORLDNEUROSURGERY.org Available online: www.sciencedirect.com 1878-8750/ - see front matter © 2016 Elsevier Inc. All rights reserved.