Review Article

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Posterior fossa ependymomas in children and adolescents - the state of the art

Marcos Devanir Silva da Costa[1], Carolina Torres Soares[1], Patricia Alessandra Dastoli[1], Jardel Mendonça Nicácio[1], Frederico Adolfo Benevides Silva[1], Maria Teresa de Seixas Alves[3], Michael Jenwei Chen[4], Andrea Maria Cappellano[5], Nasjla Saba Silva[5], Sergio Cavalheiro[1]

[1] Departamento de Neurocirurgia, Universidade Federal de São Paulo (Federal University of São Paulo), São Paulo - SP, Brazil

[2] Departamento de Radiologia, Instituto de Oncologia Pediátrica (IOP/GRAACC) (Pediatric Oncology Institute), São Paulo - SP, Brazil

[3] Departamento de Patologia, Universidade Federal de São Paulo (Federal University of São Paulo), São Paulo - SP, Brazil

[4] Departamento de Radioterapia, Instituto de Oncologia Pediátrica (IOP/GRAACC) (Pediatric Oncology Institute), São Paulo - SP, Brazil

[5]Departamento de Neuro-oncologia, Instituto de Oncologia Pediátrica (IOP/GRAACC) (Pediatric Oncology Institute), São Paulo - SP, Brazil

✉ Carolina Torres Soares, MD

e-mail: csoares@unifesp.br

Available at:
http://www.archpedneurosurg.com.br/

Introduction: Central nervous system tumors in pediatric patients represent the most frequent solid tumor type in this age group, especially ependymomas, which comprise 5% of childhood intracranial tumors and occur mainly in the posterior fossa.

Methods: The MEDLINE and ClinicalTrials databases were searched for studies on posterior fossa ependymomas, 64 studies met the search criteria.

Results: Symptoms include ataxia, vertigo, headache, vomiting, cranial nerve palsies, or papilledema resulting from intracranial hypertension due to obstruction of CSF circulation. Imaging examination often reveals posterior fossa ependymomas in the fourth ventricle or cerebellopontine angle; they may extend through the foramina of Luschka, Magendie, and/or magnum. These tumors cause a significant mass effect, displacing rather than invading the hidbrain, and may involve vessels or cranial nerves, making surgical resection difficult. Various radiological features have been studied to distinguish between ependymomas and other histological types, as well as between ependymoma subtypes.

The 2021 WHO classification of central nervous system tumors classifies ependymomas by location. Three types occur in the posterior fossa: subependymomas, PF-A, and PF-B. These are differentiated by the degree of DNA methylation and CpG islands, which can be assessed by immunohistochemical analysis with H3K27me3.

Conclusion: The consensus on the treatment of PF ependymomas in children advocates the maximum possible surgical resection, followed by radiotherapy in patients >1 year. Chemotherapy remains controversial. Recent studies suggest molecular subgroups as an independent prognostic factor in posterior fossa ependymomas. The therapeutic challenge of ependymomas requires new treatment options, based on new technologies and molecular discoveries.

Keywords: ependymomas, posterior fossa tumor, pediatric neurosurgery, neuro-oncology

INTRODUCTION

Central nervous system tumors in pediatric patients represent the most frequent type of solid tumors in this age group and constitute a major challenge, being the leading cause of death by neoplasm in children. Among these tumors, ependymomas stand out, accounting for 5% of childhood intracranial tumors, with two thirds of intracranial ependymomas occuring in children under 5 years of age and in the posterior fossa (1-3). Given the magnitude and importance of this neoplasm, this study aimed to review the most important topics in the current knowledge of posterior fossa ependymomas in children.

MATERIALS AND METHODS

An extensive review of the literature on posterior fossa ependymomas was performed with no date limit. The MEDLINE database was accessed using PubMed Central at the National Institutes of Health National Library of Medicine (NIH/NLM), (http://www.ncbi.nlm.nih.gov/pubmed/). The search terms included “Ependymoma,” “Cranial Fossa, posterior,” “Pediatrics,” and "Management." Articles published at any time in the English language were analyzed. The ClinicalTrials database was also searched for ongoing clinical trials, and 17 studies were found related to the terms "Ependymoma" and "Pediatrics."

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RESULTS

A total of 96 articles were found, and 57 that matched the search criteria were selected. Among the clinical trials, 7 studies were selected that matched the search criteria.

DISCUSSION

Clinical presentation

A child with ataxia, vertigo, headache, vomiting, cranial nerve palsies, or papilledema should be suspected of having an intracranial neoplasm and investigated by imaging. The signs and symptoms usually result from intracranial hypertension due to the tumor obstructing the CSF circulation. Another clinical manifestation is torticollis caused by tumor growth through the foramen magnum (3-6). Although the signs and symptoms seem very clear, in a sizeable portion of patients these symptoms initially go unnoticed and the child is not diagnosed until the tumor has obliterated the CSF outflow through the fourth ventricle and the patient has intracranial hypertension secondary to obstructive hydrocephalus. Continued medical education, promotion, and dissemination of warning signs are important actions to encourage early diagnosis.

Imaging and radiogenomic findings

On imaging examination, posterior fossa ependymomas often present in the fourth ventricle or in the cerebellopontine angle, and may extend through the foramen of Luschka, foramen of Magendie, and/or foramen magnum. On skull computed tomography (CT), iso- or hyperdense tissue is observed (Figure 1), with calcifications in 50% of cases (Figure 1) or hemorrhages and heterogeneous post-contrast enhancement (Figure 2). On skull magnetic resonance imaging (MRI), ependymomas present homogeneously hypoattenuating on T1 (Figures 3 and 4), hyperattenuating on T2 (Figure 5), and heterogeneous on contrast enhancement (Figure 6, 7 and 8), and may also show hemorrhage, necrosis, and calcification spots in this radiologic method (Figure 9). The use of the diffusion sequence allows distinguishing between low-grade gliomas versus ependymomas/medulloblastomas (Figure 10) because ependymomas/medulloblastomas present high cellularity and are diffusion-resistant on DWI-ADC weighting. Medulloblastomas present a more marked diffusion restriction than ependymomas, which is another useful feature in differentiating these two tumors (2,7).

In this imaging investigation, it is essential to assess the extent of tumor growth. In general, posterior fossa ependymomas cause a significant mass effect, displacing rather than invading the hindbrain. Also, their lateral extension through Luschka's foramen may involve vital structures such as cranial vessels or nerves (Figure 10), making surgical resection difficult, which is uncommon in cases of medulloblastomas and astrocytomas.

Another point related to examination images is the classification of ependymomas into two molecular subgroups, PF-A and PF-B. Thus, it is noteworthy that recent studies have shown a significant difference between posterior fossa ependymoma subgroups based on image texture on MRI scans. Zhang et al. proposed an artificial intelligence strategy capable of identifying radiological phenotypes on MRI and differentiating subgroups. This study stratified patients into high (HAP) or low risk (LFP), with a statistically relevant difference in survival, and the machine learning was considered efficient with an AUC of 0.86. The authors also explore the possibility that tumors that infringe on the fourth ventricle or foramen of Luschka or exhibit radial involvement of the hindbrain could be more aggressive tumors; on the other hand, less aggressive tumors would present a more longitudinal growth and respect the anatomical limits of the fourth ventricle (8). Cui et al. performed a similar study with DWI diffusion sequences, separating patients into high or low risk, with differences in disease-free survival (9).

Da Costa et al. also showed that the involvement profile of the posterior fossa ependymoma in the hindbrain can provide important information regarding disease-free survival and the capacity for total resection, since tumors more restricted to the fourth ventricle would have a higher disease-free survival than those that exit through the foramen of Luschka and those that totally involve the hindbrain, i.e., demonstrate radial growth (10).

Histopathological classification

Named after their origin, ependymomas derive from the cells lining the ventricles and the medullary canal -- ependymocytes -- which, in turn, result from differentiation of radial glial cells. Histologically, this neoplasm shows uniform cellularity, with formation of ependymal rosettes, tubules, and perivascular pseudorosettes.

Traditionally, neoplasms are divided according to their histopathological characteristics, which allows a better understanding of the evolution of each group and thus more effective interventions. However, for ependymomas, the histological gradation between subependymoma (grade I), myxopapillary (grade I), classic (grade II), and anaplastic (grade III) has little advantage for the treatment and prognosis of patients, since the interpretation of the slides is a subjective evaluation and depends on the experience of the pathologist in charge, presenting great variability among the individual decisions of several pathologists on the same sample (11).

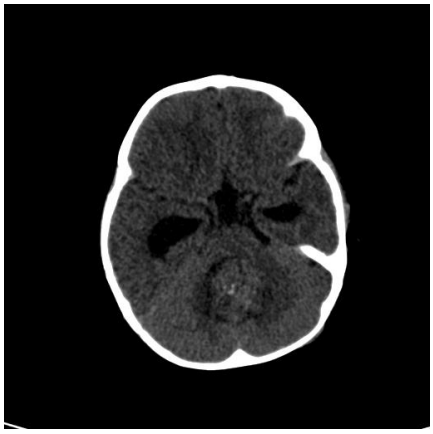

Figure 1- Axial brain CT slice showing tumor in fourth ventricle with calcifications.

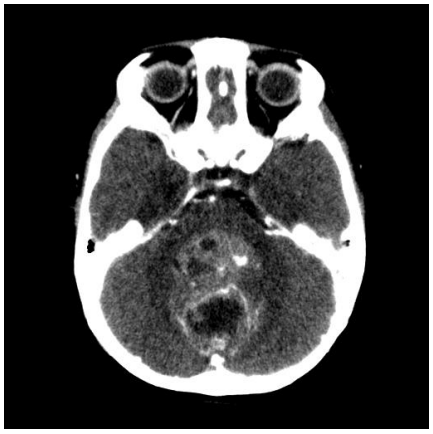

Figure 2- Axial brain CT slice showing tumor in fourth ventricle with heterogenous enhancement.

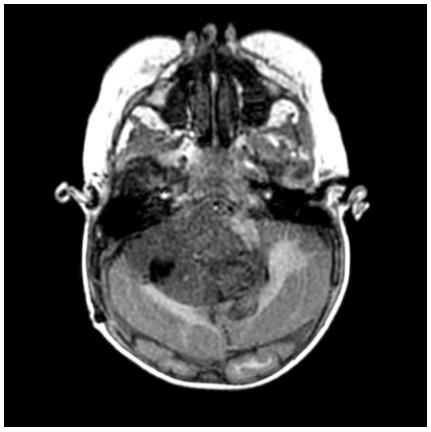

Figure 3- Axial brain MRI T1-weighted slice showing hypoattenuating tumor in fourth ventricle and exiting through the Luschka foramen in the right side, displacing the hindbrain.

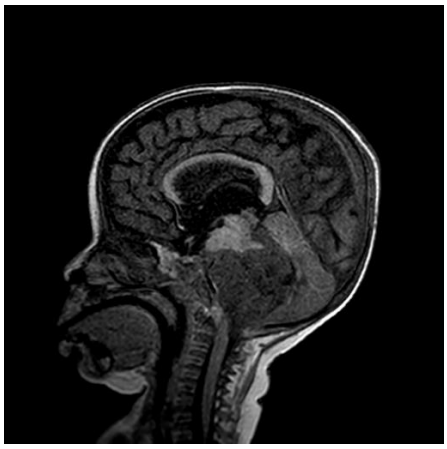

Figure 4- Sagittal brain MRI T1-weighted slice showing hypoattenuating tumor in fourth ventricle, exiting the Luschka foramen in the right side.

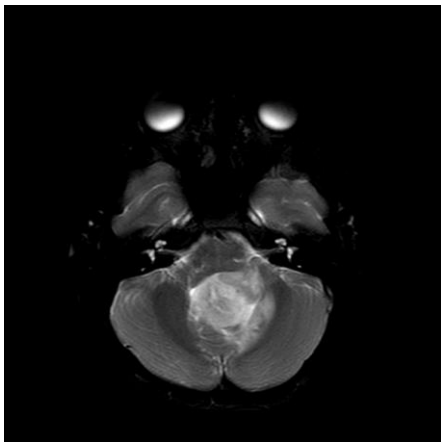

Figure 5- Axial brain MRI T2-weighted slice showing hyperattenuating tumor in fourth ventricle.

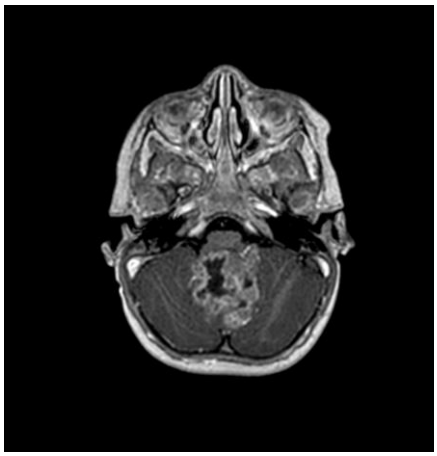

Figure 6- Axial brain MRI post-contrast slice showing heterogeneous enhancement of the tumor.

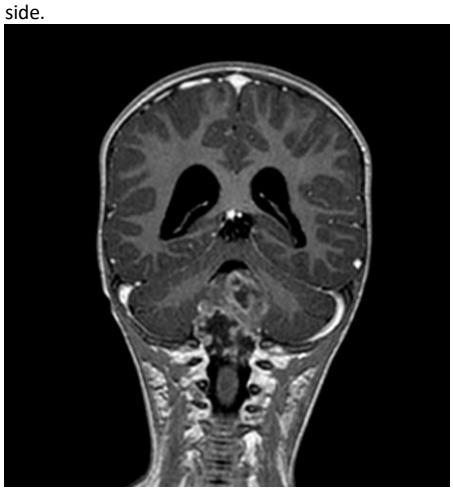

Figure 7- Coronal MRI post-contrast slice showing heterogeneous enhancement of the tumor

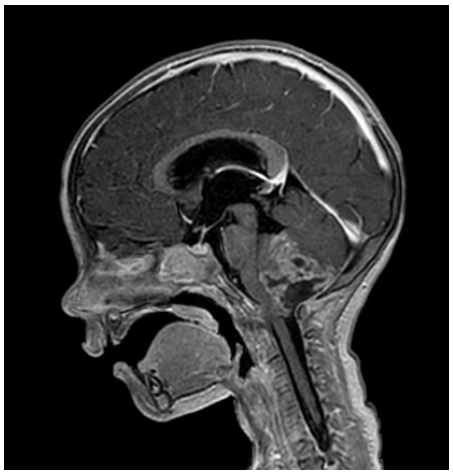

Figure 8- Sagittal MRI post-contrast slice showing heterogeneous enhancement of the tumor, and existing through the Magendie foramen.

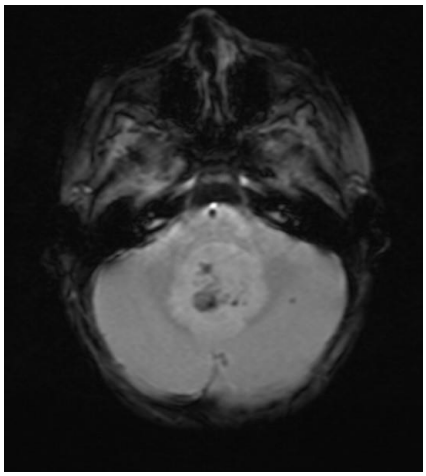

Figure 9- Axial MRI slice showing tumor in fourth ventricle through the Luschka foramen with calcifications.

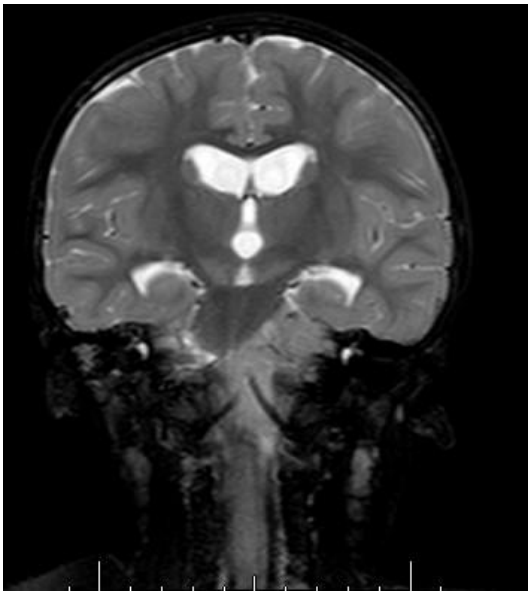

Figure 10- Coronal MRI T2- weighted slice showing arterial involvement by the tumor.

In view of technological advances, the most recent classification of the World Health Organization (WHO) for central nervous system tumors emphasized the importance of new molecular techniques for the identification and grouping of tumors, together with histological gradation and topography, thus seeking greater diagnostic accuracy and greater predictability of disease evolution (12).

In the new WHO classification of central nervous system tumors (2021) (13,14) ependymomas are divided into supratentorial (ST), spinal cord (SP), and posterior fossa (PF) tumors. In the posterior fossa, three groups can be found: subependymomas (SE), PF-A, and PF-B. These are differentiated by the degree of DNA methylation and CpG islands, which can be evaluated by immunohistochemical analysis with H3K27me3 (15-17). Notably, the PF-A and PF-B subgroups are still molecularly heterogeneous, pointing to a future distinction into additional subgroups according to the expression of specific gene families (18-20).

The PF-A subgroup represents 90% of posterior fossa tumors and occurs mainly in young patients, with a median age of 3 years, a slight prevalence of males, and has a worse prognosis, with lower overall and disease-free survival (19-22). In molecular studies, hypermethylation of CpG islands and global hypomethylation of DNA are observed and on immunohistochemical analysis with H3K27me3 (Figure 11), and a global reduction of this histone confirms the diagnosis. Other chromosomal mutations identified for PF-A tumors include gain of segment 1q or loss of segment 6q, both with a negative effect on prognosis (19-21,23).

The PF-B subgroup, on the other hand, occurs more commonly in patients with a median age around 30 years, and may affect adolescents, with a slight prevalence of females and a better prognosis compared with the A

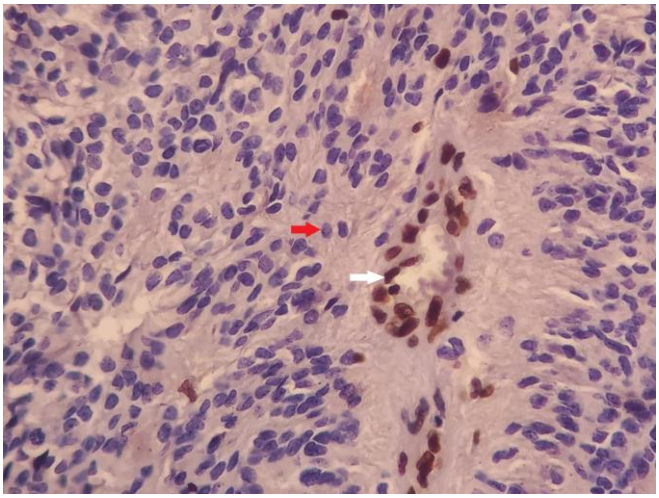

Figure 11- Immunohistochemical reaction of a PFA case, with H3K27me3 loss of expression, where internal control, brownish nuclei from endothelium (white arrow), and global reduction of this histone from tumor cells (red arrow).

subgroup (19-22,24). On immunohistochemistry with H3K27me3, PF-B shows a retention of at least 80% (Figure 12). Among the chromosomal variations related to this group are monosomy 6, loss of segment 22q, trisomy 18, monosomy 10, monosomy 17, trisomy 5, and trisomy 8 (19,20,25). (See Table 1 for a comparison between the subgroups)

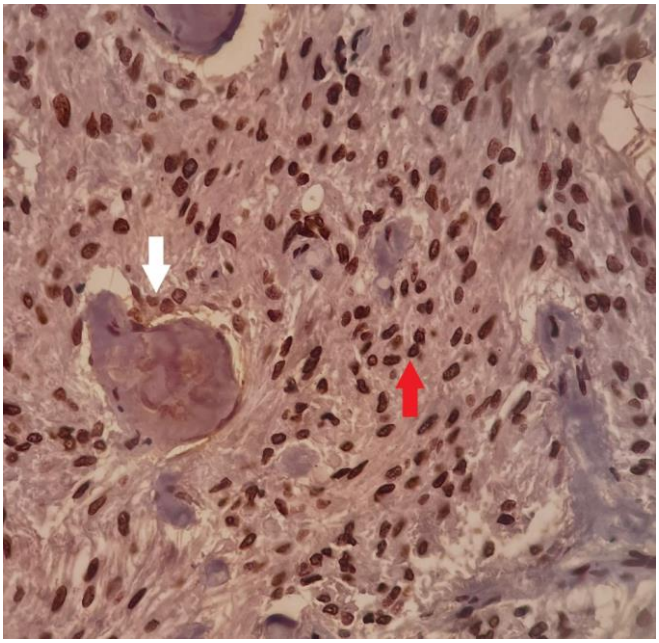

Figure 12- Immunohistochemical reaction of a PFB case, with H3K27me3 maintained expression, where internal control, brownish nuclei from endothelium (white arrow), and tumor cells (red arrow).

Subependymomas (SS) may originate in several sites of the CNS, but mostly affect the adult population, present a low degree of nuclear atypia, and have an extremely favorable prognosis, even when submitted to subtotal resection (6,26,27).

Table 1- Table comparing PFA and PFB main characteristics

	PFA	PFB
Median age	3 years	30 years
Sex Prevalence (M:F)	Male (1.8:1)	Female (0.7:1)
Profile H3K27me3	Loss of expression >80%	Expression maintenance
Common mutations	Gain 1q | Loss 6q	Monosomy 6, 10 or 17 | 22q loss | Trisomy 5, 8 or 18
5-year OS	68%	100%
5-year PFS	33%	73%

Although useful, the use of molecular characterization still faces challenges for its wide integration considering its cost and complexity, especially the DNA methylation method. The use of immunohistochemistry with H3K27me3, on the other hand, has a great potential for routine use, as it is more accessible.

Although the classification of central nervous system tumors has made great strides, it still has room for improvement.

Treatments and Outcomes

The current consensus on the treatment of posterior fossa ependymomas in pediatric patients advocates the maximum possible surgical resection, followed by radiotherapy in patients older than 1 year. The benefit of chemotherapy, as there is no survival gain (10,28,29).

Historically, for patients who achieve safe total resection, overall survival ranges from 61-90%, while disease-free survival ranges from 38-82%. In patients with subtotal resection, overall survival ranges from 22-52% and disease-free survival ranges from 0-41%. (3,30-33). Recurrence occurs at the primary site in 80% of cases and most commonly within the first two years of follow-up. The therapeutic strategy for recurrence is the same: surgery and re-irradiation (3,34-37). Re-irradiation has been shown to change the disease history in recurrent pediatric ependymomas, so that the population treated with new radiation therapy during recurrence has an overall 3-year survival rate of 81%, compared with 7% for those treated with other strategies (36). In addition, re-irradiation (RT2) combined with neuroaxis irradiation (CSI) in patients with local recurrence has been found to affect 5-year disease-free survival (100% for RT2+CSI versus 10% for focal RT2) (37).

The evidence of the benefits of complete resection has motivated research into new ways to achieve maximum excision of ependymomas. Thus, second-look surgeries were cited as early as 1997 as favorable and even today have proven to be safe and beneficial, without additional morbidity and mortality, and with an increase in the extent of resection (38-40).

A study by Merchant et al. showed the benefits of radical surgery associated with high-dose conformal radiotherapy even for younger patients, between 1-3 years of age, with an overall survival of 81% and a disease-free survival of 69%. Radiotherapy should extend 1cm beyond the tumor bed, with a total dose between 54-59.4Gy (3,28,41).

Shah et al. analyzed the impact of adjuvant radiotherapy for pediatric ependymomas and showed that the time to initiation of therapy after surgery, the total dose, and the age of the patients did not alter overall survival, and delay could be accepted in case of clinical complications(42). This reinforces the importance of radiotherapy in the treatment of ependymomas, but does not mean cases without clinical complications can tolerate delays in starting radiotherapy.

More recent studies point to molecular subgroups as an independent prognostic factor for patients with posterior fossa ependymomas (24,40,43). Ramaswamy et al. (43), for example, found the PF-A subgroup to be the most significant prognostic factor for both overall survival and disease-free survival, imposing a 4-fold higher risk of shorter overall survival (HR 4.3 95% CI 1.88 to 9.87), while incomplete resection imposes a 2-fold higher risk of shorter overall survival (HR 2.13 95% CI 1.60 to 2.82). First-line adjuvant radiotherapy, on the other hand, showed protection of overall survival (HR 0.52 95% CI 0.38 to 0.72). This analysis also observed a low recurrence rate in part of the PFB subgroup, indicating a possible trend towards surgery-only treatment in low-risk patients.

Also in the molecular era, Zapotocky et al. showed an increase in the overall survival of patients with posterior fossa ependymomas in recent decades, probably due to the increased experience of surgeons and advances in safety to achieve maximum safe resection and the introduction of adjuvant radiotherapy from 1 year of age. However, serial assessments with the Full Scale Intelligence Quotient in patients undergoing adjuvant radiotherapy, excluding those undergoing re-irradiation or neuroaxial RT, showed neurocognitive impairment as sequelae associated with radiotherapy treatment, with a mean decline of 1.33 IQ points per year (44).

In comparing surgical positioning strategies for posterior fossa tumors, Orliaguet et al. found that the sitting position was less associated with perioperative complications (45). Comparing openings in the posterior fossa, Gnanalingham et al. found that craniectomies were associated with increased CSF fistulas, infections, pseudomeningocele, revision of the operative wound, and postoperative hospital stay, compared with craniotomies (46).

Many access routes have been described and modified over time. Currently, studies indicate that the choice of technique should account for the location and infiltration of the tumor, the experience of the surgeon, and expected possible complications. No statistical difference has been observed between techniques when comparing the degree of resection (47-49). Among postoperative complications, speech alteration is the most common in surgery for

posterior fossa tumors. A recent multicenter study sought factors associated with the development of postoperative mutism or speech impairment in children undergoing resection of infratentorial tumors and found that the telelovelar access increased the risk (OR 1.7 95% CI 1.03-2.9), unlike the transvermian access (50). In addition, the duration of surgery, age, tumor location, and histology also affect this risk; in this regard, ependymomas showed no increased risk of postoperative mutism (50).

The use of chemotherapeutic agents has been the subject of several clinical trials; however, Evans et al., Timmermann et al., and Massimino et al. dide not identify a survival benefit of adjuvant chemotherapy for pediatric intracranial ependymomas (40,51,52). Recently, in the final result of the SIOP I trial, Ritzmann et al. showed that tumor remnants after incomplete resection respond to chemotherapy with vincristine, etoposide, and cyclophosphamide in 65% of cases (53). This study, however, did not measure the impact on survival and was designed for intracranial ependymomas, making no distinction among responses according to location. Da Costa et al. also evaluated the use of chemotherapy and found no difference between the group that used chemotherapy and the group that did not, showing no benefit (10).

Perspectives

Faced with the constant therapeutic challenge of ependymomas, new treatment options have been studied, based mainly on new technologies and aligned with molecular discoveries.

For the development of targeted therapies, Michealraj et al. investigated the regulation of metabolism in PFA-group tumor cells, finding epigenetic changes that necessitated a hypoxic microenvironment and low basal level of H3K27me3 through the action of intermediary products of metabolism, which can be harnessed as therapeutic targets (54).

In addition, Taylor et al. showed that ependymomas most likely originate from radial glial stem cells, explaining the uniqueness of this tumor in terms of its location in the central nervous system and further identifying possible targets for enhancing therapeutic response, such as the ABC membrane transport system (55).

In addition, the use of target therapy with CSF-infused CAR T-cells has shown good results in animal models for metastatic posterior fossa ependymomas (56). In vitro tests with ependymoma cultures revealed the great antitumor potential of a protein called Amblyomin-X extracted from the saliva of Amblyomma cajennense ticks (57).

Finally, some pilot studies are being conducted to evaluate the safety and applicability of different drugs, anti-tumor therapies, vaccines, and even electric fields (Optune) for the treatment of ependymomas or recurrent ependymomas (58-64).

CONCLUSION

Posterior fossa ependymomas are challenging tumors in pediatric neuro-oncology because they are relatively frequent, and younger children more commonly have the PFA subtype which has a worse prognosis. The pediatric neurosurgeon plays a key role in the treatment of these patients because total resection changes the overall and disease-free survival of these children; every technical effort should be made to increase the extent of resection with maximum functional safety. Radiotherapy also plays an important role, but chemotherapy has a restricted indication, due to the lack of efficacy evidenced in the most current studies.

ACKNOWLEDGMENTS

DISCLOSURES

Ethical approval

This study was performed in line with the principles of the Declaration of Helsinki.

Consent to participate

The patients gave consent to use their information and images for research purposes. *Consent for publication*

The patient gave consent to use his information and images for publication.

Conflict of interest

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

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CONTRIBUTIONS

-**Marcos Devanir Silva da Costa**: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing
-**Carolina Torres Soares**: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing
-**Patricia Alessandra Dastoli**: Writing – review & editing

-**Jardel Mendonça Nicácio:** Writing – review & editing
-**Frederico Adolfo Benevides Silva**: Writing – review & editing
-**Maria Teresa de Seixas Alves**: Writing – review & editing
-**Michael Jenwei Chen**: Writing – review & editing
-**Andrea Maria Cappellano:** Review & editing
-**Nasjla Saba Silva:** Review & editing
-**Sergio Cavalheiro:** Supervision, Review & editing

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