PILOCYTIC ASTROCYTOMAS IN ADULTS: A REVIEW

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ABSTRACT
This review aims to bring existing studies on pilocytic astrocytoma (PA) in adults, seeking a better understanding of tumor behavior in these patients. This study was conducted with the search for published studies available on NCBI, PubMed, MEDLINE, Scielo and Google Scholar, following the criteria of having useful information to understand pilocytic astrocytomas in adults or including important factors for comparison with the childhood tumor subtype. The points that are known so far about PAs in adults have been characterized. There is a decrease in survival of these patients depending on the location, especially over 60 years old and one of the factors that causes this is anaplasia, that may lead to malignant transformation of the tumor. Headache, visual disturbances, vertigo motor difficulties are some of the most common symptoms in these individuals and the preferential treatment is the total resection of the tumor. The patient's age group may be related to the aggressiveness of the tumor, and it is possible to infer that research in this area is still of quite importance and necessary for a deeper understanding of the development and behavior of pilocytic astrocytoma in adult patients.

Keywords: Astrocytoma; Incidence; Pathology; Recurrence.

ASTROCITOMAS PILOCÍTICOS EM ADULTOS: UMA REVISÃO

RESUMO
Esta revisão tem como objetivo trazer estudos existentes sobre o astrocitoma pilocítico (AP) em adultos, buscando uma melhor compreensão do comportamento tumoral nestes pacientes. Este estudo foi realizado a partir da busca de estudos publicados disponíveis no NCBI, PubMed, MEDLINE, Scielo e Google Acadêmico, seguindo o critério de ter informações úteis para compreender os astrocitomas pilocíticos em adultos ou incluir fatores importantes para comparação com o subtipo de tumor infantil. Foram caracterizados os pontos conhecidos até o momento sobre APs em adultos. Há uma diminuição da sobrevida desses pacientes dependendo da localização, principalmente acima de 60 anos e um dos fatores que causa isso é a anaplasia, que pode levar à transformação maligna do tumor. Cefaléia, distúrbios visuais, dificuldades motoras vertiginosas são alguns dos sintomas mais comuns nesses indivíduos e o tratamento preferencial é a ressecção total do tumor. A faixa etária do paciente pode estar relacionada à agressividade do tumor, e é possível inferir que pesquisas nessa área ainda são bastante importantes e necessárias para uma compreensão mais profunda do desenvolvimento e comportamento do astrocitoma pilocítico em pacientes adultos.

Palavras-chave: Astrocitoma; Incidência; Patologia; Recorrência.

INTRODUCTION

Pilocytic astrocytomas (PA) are the most common primary central nervous system tumors found in children and adolescents, accounting for approximately 15% of all brain tumors (1) and 8,3% of all tumors in the adolescent age group (2). Histologically they are

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classified as grade I by the World Health Organization (WHO), considered benign tumors and often has an indolent behavior with an excellent prognosis of overall survival rates of more than 20 years (1,3). These tumors are most found during the first two decades of life, reaching peak incidence between 0 and 9 years (4), and diagnosis in patients over 50 years old is rare (5,6).

Increasing age is directly related to decreased survival in patients with pilocytic astrocytoma (7), as the tumor tends to be more aggressive in adults (8,9). These individuals also usually have higher rates of tumor recurrence (10). Due to its rare presence in adults, there are few studies referring to development of PA in adults, and although favorable prognoses have already been found (5,6,11), there are reports that the tumor is associated with a worse prognosis and higher mortality in these individuals than in children (12-14).

Pediatric and adult brain tumors differ both in incidence rates and in factors such as histology, molecular pathology, location, and outcome (15). Therefore, this review aims to bring existing studies on pilocytic astrocytoma in the adult age group, seeking a better understanding of tumor behavior in these patients.

METHODS

For this research, no time limit was established. The following keywords were used: adult pilocytic astrocytoma AND pathology, histology, diagnostic, treatment, mutation, fusion, molecular. The selected studies met the following criteria: having useful information to understand pilocytic astrocytomas in adults or including important factors for comparison with the childhood tumor subtype, available in NCBI, PubMed, MEDLINE, Scielo and Google Scholar.

RESULTS

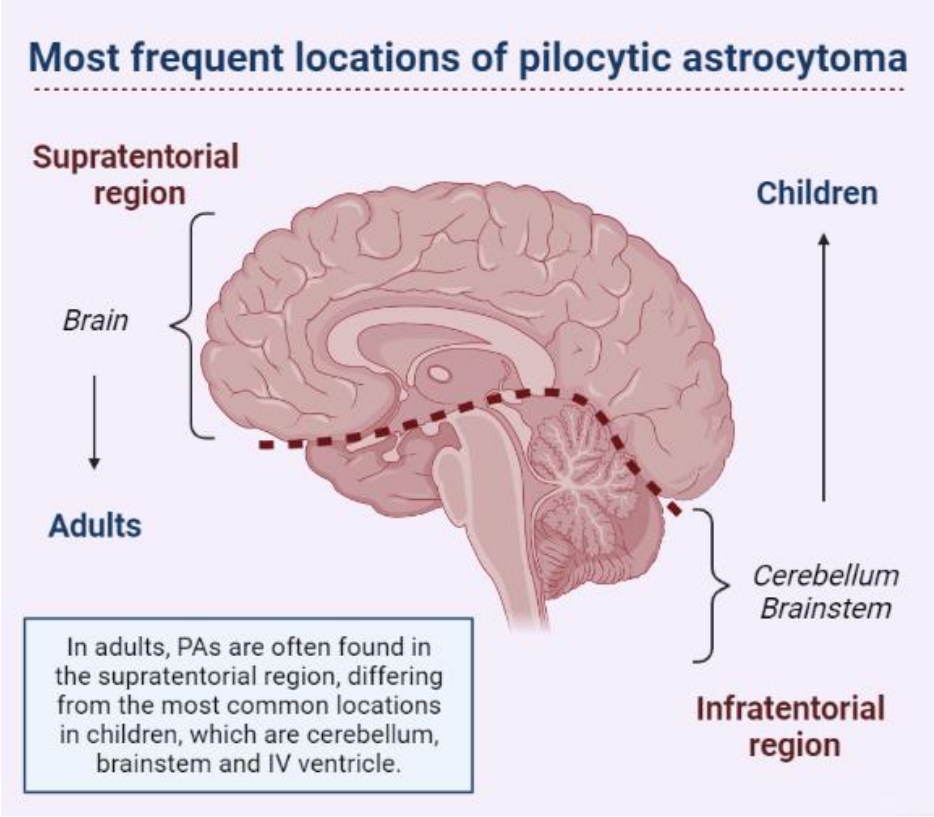
Tumor incidence and location

Pilocytic astrocytoma accounts for less than 2% of adult gliomas (4) and has an incidence of less than 0.1 per 100,000 people in individuals over 45 years old, compared with 0.8 per 100,000 children (14). Adult PAs have a mean age at diagnosis of 32 years, with a slight predominance of females (6). In general, they can develop in different places on the neuroaxis. The classic tumor in children develops in the cerebellum, whereas in adults it is more common in the supratentorial region (16,17), as shown in Figure 1. This fact has already

been associated with increased recurrence rates and lower disease-free survival in these patients (18).

It is not known if adult PAs appear asymptomatically early in life and therefore go undetected in childhood, or if they develop during adulthood. The methylation patterns analyzed by Voronina et al. (2021) indicate differences between adult and pediatric PAs according to their location and origin. Adult pilocytic astrocytomas that developed in childhood and are called “old tumors” are found in the infratentorial region, more specifically in the cerebellum. These data suggest that these tumors potentially develop from early precursor cells. Adult PAs that develop around the time they are diagnosed, in turn, are more often found in the supratentorial region. This finding corroborates the fact reported in the literature that supratentorial and infratentorial PAs occurs with different frequencies in children and adults and are linked to distinct genetic alterations and gene expression signatures (19). Analyzing the location of the tumor is essential to understand its origin and the patient's prognosis.

Figure 1 (made by the authors) - Most frequent locations of pilocytic astrocytoma



Prognostic Factors and Diagnostic

Clinical factors such as older age and higher BMI were associated with a worse prognosis in adult patients with PA. Elevated BMI has previously been reported as a prognostic factor in several types of cancer and, in the context of brain tumors, it was associated with a worse survival (10).

There are some radiological findings that characterize pilocytic astrocytomas in general. Magnetic resonance imaging (MRI) usually demonstrates the classic appearance of a cystic lesion with a solid nodule. On T1 weighted, the tumor appears hypo to isointense in relation to brain tissue, and hyperintense on T2. Factors such as the presence of an exophytic component and solid composition in the imaging exam may increase the likelihood of tumor recurrence or progression (20).

Atypical imaging features have been described in adult pilocytic astrocytomas, as well as neoplasms with mixed cystic and solid areas and variable degrees of contrast enhancement (12). Although MRI is the preferred technique for diagnosing these tumors, misinterpretations can often occur in which PAs are characterized as other tumor types. In infratentorial lesions, astrocytomas have already been confused with hemangioblastomas or ependymomas, while in the supratentorial region, low-grade glioma was the most frequently diagnosed, followed by gangliogliomas and neurocytomas (13).

Computed tomography (CT) can be used to assess tumor density, calcifications, and bleeding (21). New and advanced neuroimaging techniques such as cerebral perfusion scintigraphy and magnetic resonance spectroscopy have become increasingly recognized as auxiliary methods in the differential diagnosis of low-grade or high-grade gliomas. The importance of these methods has been described especially in cases of anaplastic pilocytic astrocytomas, usually found in older patients compared to conventional PA, but present in younger patients than those with anaplastic astrocytoma (22).

Histology and Clinical Manifestations

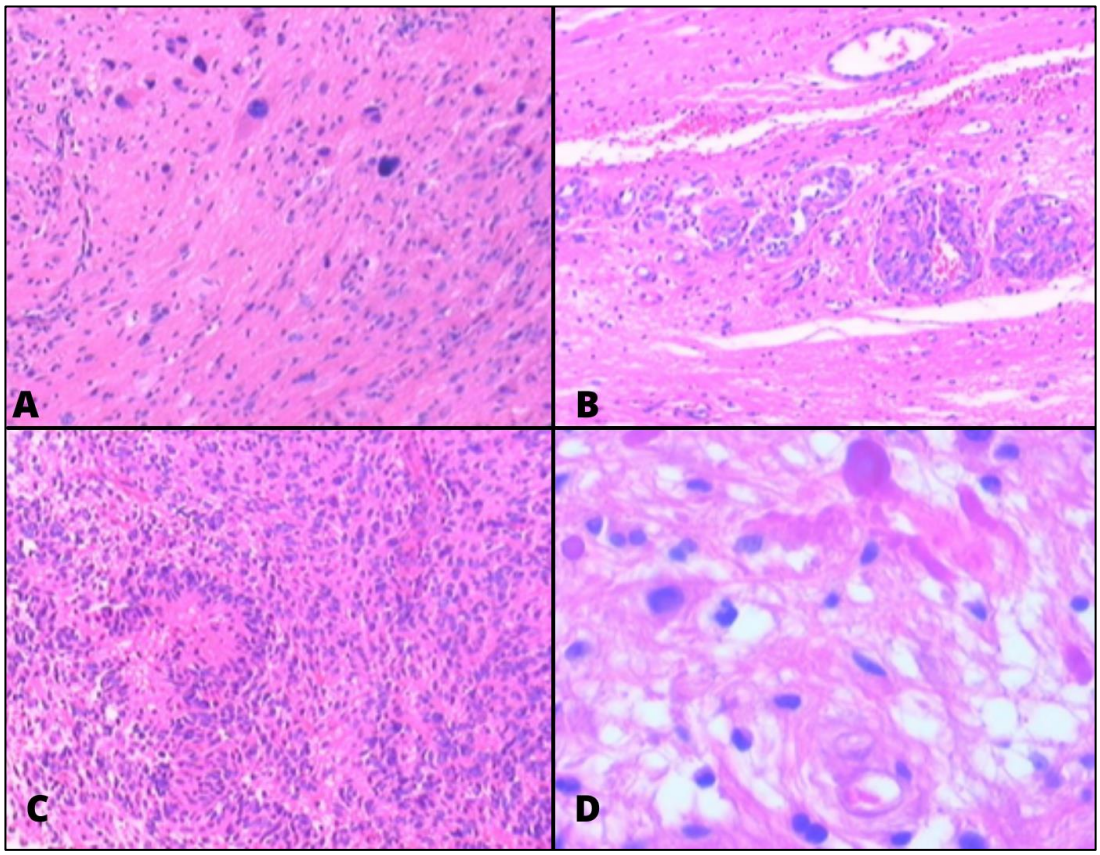
In general, PAs behave as grade I and are characterized microscopically by a biphasic pattern, with compact bipolar cells and areas with microcysts, hyalinized vessels and occasional granular bodies. Both in children and in adults, Rosenthal fibers are often present, elongated, and homogeneous structures formed within the cytoplasmic extensions of astrocytes. The reactive astrocytes show strong staining of glial fibrillary acidic protein (GFAP) present in the cytoskeleton of these cells (23).

Degenerative changes such as ischemic necrosis can be observed, and sometimes calcifications are present. Rare mitosis, hyperchromatic and pleomorphic nuclei, glomeruloid vascular proliferation, and leptomeningeal infiltration are factors that can be observed in the diagnosis of pilocytic astrocytoma; however, they are not necessarily indicators of malignancy and may be confused with microscopic characteristics present in other astrocytic tumors (23).

Malignant transformations have been reported during the clinical course of pilocytic astrocytoma, in which the diagnosis changes due to the appearance of anaplastic histological alterations (10,24), such as mitosis, necrosis and increased cellularity. These tumors with signs of histopathological malignancy are designated with various terminologies, such as atypical PA/ malignant/ with anaplasia/ with anaplastic features/ or anaplastic pilocytic astrocytoma (21). Anaplasia is rarely observed in PAs, but it occurs more frequently in older patients (25), causing more aggressive tumor behavior and worse prognosis for these individuals. Median overall survival of 13 months has been reported in cases like these (14,26).

Histological features of an adult anaplastic astrocytoma include more than 4 mitoses per 10 high potency fields, hypercellularity, histological atypia with or without necrosis, and non-infiltrative lesion (21,26,27). Some histological features that can be observed in anaplastic astrocytomas are shown in Figure 2.

Figure 2 - Histological features of anaplastic astrocytoma



Images analyzed by our research group. Fibrilar area with cytologic atypia, HE, 20x (A); Microvascular hyperplasia, HE, 10x (B); Hypercellularity with "pseudopalisading" necrosis and mitosis, HE, 10x (C); Fibrilar region with Rosenthal fibers, HE, 40x (D).

Some authors describe the diagnosis of a hemorrhagic PA as an uncommon finding in adult pilocytic astrocytomas (28-30). Hemorrhage associated with low-grade tumors is rarely found and may be related to abnormal vasculature present in the tumor, in addition to local metabolic factors. However, the risk of a hemorrhagic transformation appears to be equal between pediatric and adult populations (30).

The most common symptoms in children and adults are nausea, vomiting and headaches. Motor deficits may be present, depending on the location of the tumor (31), and in adult patients the presence of seizures, hydrocephalus and hemorrhage has been reported (6). In a study with 46 patients older than 18 years, the majority (65.2%) presented headache initially, followed by visual disturbances (34.8%), symptoms of high intracranial pressure (28.3%), vertigo (28, 3%), motor difficulties (19.6%), sensory symptoms (17.4%), psychiatric symptoms (13.3%), seizures (8.7%), ataxia (8.7%) and speech disorders (4.3%) (10).

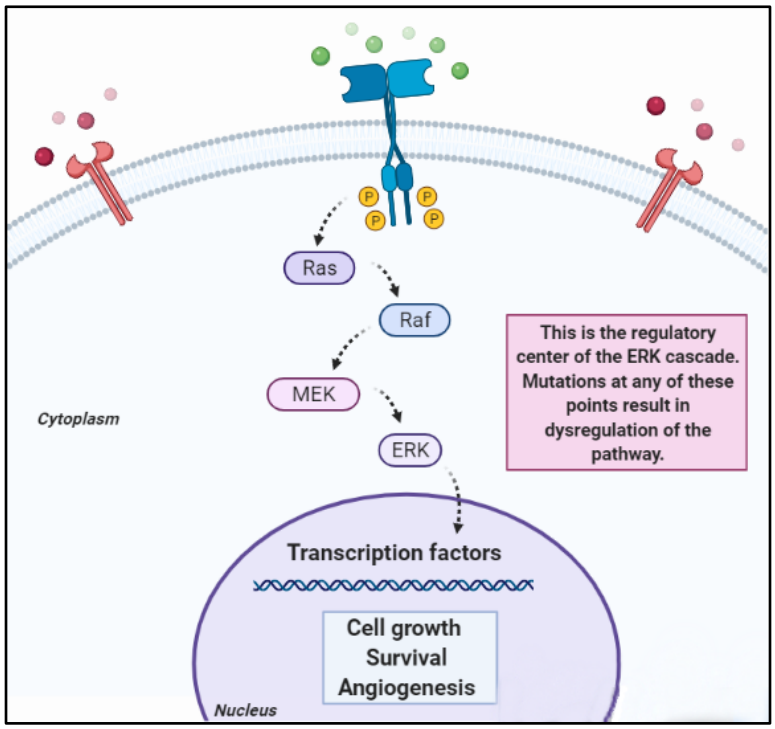
The neurological and cognitive functions of patients analyzed by Brown et al. (2015) remained stable during clinical follow-up (32).

Molecular Characteristics

Unlike other glioma subtypes, there are no fully known molecular patterns in adult PAs yet, but there are markers that have been associated with tumor development and can help to identify high-risk patients, so that they can be guided to the best type of treatment (18). Although there is evidence for a distinct spectrum of molecular changes, there is still no clear consensus regarding age-scale differences (33,19).

It is known that the molecular origin of pilocytic astrocytoma is related to the activation of the RAS/RAF/MAPK pathway (Figure 3), in which two molecular alterations are frequently found: the fusion of the *BRAF-KIAA1549* gene and the *BRAF V600E* mutation (34), in addition to other alterations including genes such as *NF1*, *KRAS*, *FGFR1*, *PTPN11*, *NTRK*, *RAF1* and *SRGAP* (35,36). The relationship between specific changes in MAPK and tumor aggressiveness still needs to be further studied.

Figure 3 (made by the authors): Phosphorylation of RAS-RAF-MEK ERK, one of the MAPK pathways.



The *BRAF-KIAA1549* fusion occurs as a result of duplication of 7q34 chromosome region and is more commonly found in the pediatric age group than in adults (23). Hasselblatt et al. (2011) report that they found it in 79% of cases from 0 to 10 years old, 51% at ages 11 to 20, 42% at 21 to 30, 30% at 31 to 40 and 7% in individuals with over 40 years old (37). This fact may be associated with decreased survival with increasing age, since the presence of fusion in pediatric astrocytomas is related to a better prognosis (38).

Activating mutations of the *BRAF* oncogene are called somatic and cause the substitution of the amino acid valine for glutamic acid at codon 600 of the derived protein, giving rise to the *BRAF V600E* (39). These changes are found in about 75% of cases of PAs and have been associated with extracerebellar locations (7,40). The combination of *BRAF V600E* analysis and *BRAF* gene fusion is a proven good diagnostic tool. In general, the frequency of both markers is lower in adult patients (37,17).

On the other hand, epigenetic mechanisms have been studied in the molecular oncogenesis of pilocytic astrocytomas, such as the hypermethylation mentioned by Junk et al. (2019) that can occur in the *MGMT* gene promoter (*METHYLGUANINE-DNA METHYLTRANSFERASE*, OMIM #156569) and thus be related to responsiveness of the tumor (18).

Treatment and Survival

The preferred treatment for all patients with pilocytic astrocytoma is total surgical removal of the tumor with as little neurological damage as possible (41), and for adult individuals this has been the only method that demonstrates a benefit in terms of survival (12). A higher recurrence rate was observed in cases of adults treated with subtotal resection (38.9%) than in those completely resected (4%), confirming that patients who undergo total resection are less likely to relapse than those treated by any other surgical or non-surgical technique (10). However, the tumor location often makes surgery unviable, as in cases where the PA affects the optic pathway or presents an aggressive behavior in the hypothalamus region (42). In these situations, it is possible to use additional therapies, such as radiotherapy (RT) and chemotherapy.

There is controversy regarding the use of radiotherapy, as vasculopathies, secondary neoplasms and neurocognitive deficits are associated with the radiation involved (16). Ishkanian et al. (2011) describe good results with RT, in which the 5-year progression free-survival (PFS) rate for patients who were kept under postoperative observation was 42%,

compared with 91% in the group of those who received radiation after surgery. At 10 years, the PFS rate was 17% versus 60%, respectively (43). Khalafallah et al. (2020) report that adult patients who received RT after subtotal tumor removal had a significantly higher risk of death compared to those who did not (44). Therefore, due to severe side effects, its use is usually restricted to treatment in cases of optical, diencephalic and brainstem lesions (16,45). In general, RT is considered a treatment option for recurrent cases of tumor progression that are not stabilized with chemotherapy and when there is no possibility of further surgery, in adults or children (23). Some doctors recommend its use after total or subtotal resection only for patients considered to be high risk (14).

Chemotherapy usually consists of temozolomide, which is responsible for penetrating the blood-brain barrier and is often used to treat malignant gliomas. The use of carboplatin and vincristine has been reported as well (17). Parsons et al. (2020) describe in their findings that younger patients are more likely to receive chemotherapy than older individuals (45). Therefore, adjuvant RT and chemotherapy are generally reserved for high-grade astrocytomas and should only be considered for low-grade tumors in specific settings (46).

Surgery and radiotherapy remain the mainstays of treatment for CNS tumors, with adjuvant chemotherapy when indicated. Even though these are the most used treatment options, they can be responsible for acute and chronic morbidities. For this reason, the use of immunotherapy has been growing with good results in the treatment of brain tumors. This type of treatment involves the modulation of immune activity and has been shown to be effective in combating different types of cancer. It can be a good solution for cases in which it is not possible to perform total tumor resection, as healthy tissue is preserved while only the tumor site is kept as a target. There are several mechanisms by which immunotherapy can act, including direct antitumor activity, checkpoint blockade, vaccination, oncolytic viruses, or microenvironment repolarization. For adult patients with glioma this is an emerging field that can rapidly assess effectiveness and side effects and may provide hope for a population of patients seeking to recover their quality of life (47). As pilocytic astrocytomas are known to express higher levels of transcription and expression of vascular endothelial growth factor (VEGF), immunotherapy agents such as bevacizumab have also been used in inoperable cases and have shown promising results in adult population (48). It has already been described in a study with favorable clinical and radiographic responses, as it is a monoclonal antibody aimed at decreasing the permeability of the vasculature (49).

The survival of patients with PA significantly decreases with increasing age (7). The overall ten-year survival rate for patients over 40 years old is estimated at 76% (4), while for the pediatric age group this rate can reach 95% (15). A five-year survival rate of 63% has been reported for ages over 60 years old (6). Recurrence rates in adults are significant and cases of PA with increased proliferative activity can be found. The difference in outcome between adults and children with PA may be precisely in the aggressiveness profile of the tumor in different age groups, and thus, tumor-related death is not uncommon (10,5,12).

The main characteristics that differentiate pediatric PAs from adults, according to the literature, are shown in Table 1 below:

Table 1 - Main differences between pediatric and adult pilocytic astrocytomas

Features	**Children**	**Adults**
Incidence	25% of pediatric brain tumors	1.5 percent of adult brain tumors
Location	Cerebellar (70%) Brainstem and optical pathway (10–20%) Spinal cord (2–5%)	Supratentorial (35-45%) Cerebellar (35-40%) Brainstem and optical pathway (5–10%) Spinal cord (2–5%)
Most common symptoms	Headache, convulsion	Headache, visual disturbances, dizziness
Molecular changes	*BRAF*: 70%	*BRAF*: 20%
Preferential treatment	Total resection	Total resection
Recurrence rate	2-5%	42%
Estimated survival	95%	63% over 60 years old

Source: (5,11,13,41,10)

Discussion and Conclusion

Pilocytic astrocytomas usually develop during childhood and adolescence. However, they can also be found in adult individuals and, depending on the location, the prognosis of these cases can be poor (4,13,14). There are not many studies on the behavior of PAs in these patients, but it is known that there is a decrease in survival with increasing age (38), especially over 60 years old (6).

It is not known if the molecular changes that initiate tumor development in this age group are the same as those that occur in pediatric age. On the other hand, there are important

markers that helps to define the diagnosis (18,19). Among the alterations in the MAPK pathway, the fusion of the *BRAF-KIAA1549* gene and the *BRAF V600E* mutation (34) stand out, both less present in older patients.

After the diagnosis of pilocytic astrocytoma, the preferential treatment for each case must be chosen, analyzing the tumor location and the clinical characteristics of the patient. The preferred treatment is total surgical removal of the tumor and for adult individuals this has been the method with the greatest benefits in terms of survival (43,12). However, some cases cannot be submitted to the total removal of the tumor, and for this reason, subtotal resection is chosen, often accompanied by adjuvant therapies such as radiotherapy, chemotherapy or immunotherapy (16,14,47). There is controversy regarding the use of RT and, in general, it is considered a treatment option for recurrent cases or for patients considered to be at high risk.

The survival of patients with PA significantly decreases with increasing age (7) depending on location, and for this reason many studies on the tumoral behavior of PA in adults are still needed. However, a survival rate of 63% has been reported in individuals over 60 years of age (6) and recurrence rates in these individuals are significant (10,5,12).

From the data found in this literature review, it is possible to infer that research in this area is still of quite importance and necessary for a deeper understanding of the development and behavior of pilocytic astrocytoma in adult patients. The information we have so far contributes to the attention of the scientific community to focus even more on understanding the subject and seeking the best treatment for patients with pilocytic astrocytoma.

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REFERENCES

1. Ostrom QT, Gittleman H, Liao P, Vecchione-Koval T, Wolinsky Y, Kruchko C, et al. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2010-2014. *Neuro Oncol*. 2017;19 (suppl_5): 1-88. https://doi.org/10.1093/neuonc/nox158.

2. Ostrom QT, Patil N, Cioffi G, Waite K, Kruchko C, Barnholtz-Sloan JS. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2013–2017. *Neuro Oncol*. 2020;22(suppl_1): iv1–iv96. https://doi.org/10.1093/neuonc/noaa200.

3. Ding C, Tihan T. Recent Progress in the Pathology and Genetics of Pilocytic and Pilomyxoid Astrocytomas. *Balkan Med J*. 2019;36(1):3-11. https://doi.org/10.4274/balkanmedj.2018.1001.

4. Ostrom QT, Gittleman H, Truitt G, Boscia A, Kruchko C, Barnholtz-Sloan JS. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2011-2015. *Neuro Oncol*. 2018;20(suppl_4):iv1-iv86. https://doi.org/10.1093/neuonc/noy131.

5. Boschetti G, Santos AJ, Fermon KP, Honório GLF, Batistella G, Kusma SZ, et al. Adult Pilocytic Astrocytomas: A Brazilian Series. *World Neurosurg*. 2020;133:e115-e120. https://doi.org/10.1016/j.wneu.2019.08.146.

6. Bond KM, Hughes JD, Porter AL, Orina J, Fang S, Parney IF. Adult Pilocytic Astrocytoma: An Institutional Series and Systematic Literature Review for Extent of Resection and Recurrence. *World Neurosurg*. 2018;110:276-283. https://doi.org/10.1016/j.wneu.2017.11.102.

7. Lapointe S, Perry A, Butowski NA. Primary brain tumours in adults. *Lancet*. 2018;392(10145):432-446. https://doi.org/10.1016/S0140-6736(18)30990-5 .

8. Park JH, Jung N, Kang SJ, Kim HS, Kim E, Lee HJ, et al. Survival and Prognosis of Patients with Pilocytic Astrocytoma: A Single-Center Study. *Brain tumor research and treatment.* 2019;7(2):92-97. https://doi.org/10.14791/btrt.2019.7.e36.

9. Ryu HH, Jung TY, Lee GJ, Lee KH, Jung SH, Jung S, et al. Differences in the clinical courses of pediatric and adult pilocytic astrocytomas with progression: a single-institution study. *Childs Nerv Syst*. 2015;31:2063–2069. https://doi.org/10.1007/s00381-015-2887-z.

10. Mair MJ, Wöhrer A, Furtner J, Simonovska A, Kiesel B, Oberndorfer S, et al. Clinical characteristics and prognostic factors of adult patients with pilocytic astrocytoma. *J Neurooncol*. 2020;148(1):187-198. https://doi.org/10.1007/s11060-020-03513-9.

11. Bell D, Chitnavis BP, Al-Sarraj S, Connor S, Sharr MM, Gullan RW. Pilocytic astrocytoma of the adult--clinical features, radiological features and management. *British Journal of Neurosurgery*. 2004;18(6):613–616. https://doi.org/10.1080/02688690400022896.

12. Stüer C, Vilz B, Majores M, Becker A, Schramm J, Simon M. Frequent recurrence and progression in pilocytic astrocytoma in adults. *Cancer*. 2007;110(12):2799-808. https://doi.org/10.1002/cncr.23148.

13. Lee KJ, Marchan E, Peterson J, Harrell AC, Quinones-Hinojosa A, Brown PD, et al. Management and Survival of Adult Patients with Pilocytic Astrocytoma in the National Cancer Database. *World Neurosurg*. 2018;112:e881-e887. https://doi.org/10.1016/j.wneu.2018.01.208.

14. Johnson DR, Brown PD, Galanis E, Hammack JE. Pilocytic astrocytoma survival in adults: analysis of the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute. *J Neurooncol*. 2012;108:187-193. https://doi.org/10.1007/s11060-012-0829-0.

15. Greuter L, Guzman R, Soleman J. Typical Pediatric Brain Tumors Occurring in Adults-Differences in Management and Outcome. Biomedicines. 2021;9(4):356. https://doi.org/10.3390/biomedicines9040356.

16. Burkhard C, Di Patre PL, Schüler D, Schüler G, Yaşargil MG, Yonekawa Y, et al. A population-based study of the incidence and survival rates in patients with pilocytic astrocytoma. *J Neurosurg*. 2003;98(6):1170-4. https://doi.org/10.3171/jns.2003.98.6.1170.

17. Theeler BJ, Ellezam B, Sadighi ZS, Mehta V, Tran MD, Adesina AM, et al. Adult Pilocytic Astrocytomas: Clinical Features and Molecular Analysis. *Neuro-Oncology*. 2014;16:841–847. https://doi.org/10.1093/neuonc/not246.

18. Jungk C, Reinhardt A, Warta R, Capper D, Deimling AV, Herold-Mende C, et al. Extent of Resection, MGMT Promoter Methylation Status and Tumor Location Independently Predict Progression-Free Survival in Adult Sporadic Pilocytic Astrocytoma. *Cancers (Basel)*. 2019;11(8):1072. https://doi.org/10.3390/cancers11081072.

19. Voronina N, Aichmüller C, Kolb T, Korshunov A, Ryzhova M, Barnholtz-Sloan J, et al. The age of adult pilocytic astrocytoma cells. *Oncogene*. 2021;40:2830–2841. https://doi.org/10.1038/s41388-021-01738-0.

20. Villanueva KG, Rea ND, Krieger MD. Novel Surgical and Radiologic Risk Factors for Progression or Recurrence of Pediatric Pilocytic Astrocytoma. *Pediatric Neurosurgery*. 2019;54(6):375-385. https://doi.org/10.1159/000503110.

21. Gareton A, Tauziède-Espariat A, Dangouloff-Ros V, Roux A, Saffroy R, Castel D, et al. The histomolecular criteria established for adult anaplastic pilocytic astrocytoma are not applicable to the pediatric population. *Acta Neuropathol*. 2020;139(2):287-303. https://doi.org/10.1007/s00401-019-02088-8.

22. Fiechter M, Hewer E, Knecht U, Wiest R, Beck J, Raabe A, et al. Adult anaplastic pilocytic astrocytoma - a diagnostic challenge? A case series and literature review. *Clin Neurol Neurosurg*. 2016;147:98-104. https://doi.org/10.1016/j.clineuro.2016.06.005.

23. Salles D, Laviola G, Malinverni ACM, Stávale JN. Pilocytic Astrocytoma: A Review of General, Clinical, and Molecular Characteristics. *J Child Neurol*. 2020;35(12):852-858. https://doi.org/10.1177/0883073820937225.

24. Tanaka T, Teshigawara A, Takei J, Tochigi S, Hasegawa Y, Murayama Y, et al. Rapid Recurrence and Anaplastic Transformation of a Pilocytic Astrocytoma in an Elderly Patient: Case Report and Review of the Literature. *World Neurosurg*. 2020;142:441-449. https://doi.org/10.1016/j.wneu.2020.06.173.

25. González – Vargas PM, Félix LC, Thenier-Villa JL, Núñez AD, Zaragoza AL, Alonso CC. Anaplastic Pilocytic Astrocytoma in adults: A comprehensive literature review based on 2 clinical cases. *Interdisciplinary Neurosurgery*. 2021;25:101141. https://doi.org/10.1016/j.inat.2021.101141.

26. Rodriguez FJ, Scheithauer BW, Burger PC, Jenkins S, Giannini C. Anaplasia in Pilocytic Astrocytoma Predicts Aggressive Behavior. *Am. J. Surg. Pathol*. 2010;340:147–160. https://doi.org/10.1097/PAS.0b013e3181c75238.

27. Sugita Y, Nakashima S, Ohshima K, Terasaki M, Morioka M. Anaplastic astrocytomas with abundant Rosenthal fibers in elderly patients: a diagnostic pitfall of high-grade gliomas. *Neuropathology*. 2013;33(5):533–540. https://doi.org/10.1111/neup.12025.

28. Sun S, Zhou H, Ding ZZ, Shi H. Cerebellar pilocytic astrocytomas with spontaneous intratumoral hemorrhage in the elderly: A case report and review of the literature. *Medicine (Baltimore)*. 2018;97(31):e11329. https://doi.org/10.1097/MD.0000000000011329.

29. Prasad GL, Nandeesh BN, Menon GR. Hemorrhagic presentation of intracranial pilocytic astrocytomas: literature review. *Neurosurgical Review*. 2019;42(1):97-106. https://doi.org/10.1007/s10143-017-0915-z.

30. Cortez GM, Monteiro A, Ludwig B, Hanel R. Reappraisal of haemorrhagic suprasellar pilocytic astrocytoma during adulthood. *BMJ Case Reports*. 2020;13(10):e235662. https://doi.org/10.1136/bcr-2020-235662.

31. Kristiansen I, Strinnholm M, Strömberg B, Frisk P. Clinical characteristics, long-term complications and health-related quality of life (HRQoL) in children and young adults treated for low-grade astrocytoma in the posterior fossa in childhood. *J Neurooncol*. 2019;142:203–210. https://doi.org/10.1007/s11060-018-03085-9.

32. Brown PD, Anderson SK, Carrero XW, O'Neill BP, Giannini C, Galanis E, et al. Adult patients with supratentorial pilocytic astrocytoma: long-term follow-up of prospective multicenter clinical trial NCCTG-867251 (alliance). *Neuro-Oncol Pract.* 2015;2(4):199-204. https://doi.org/10.1093/nop/npv031.

33. Brokinkel B, Peetz-Dienhart S, Ligges S, Brentrup A, Stummer W, Paulus W, et al. A comparative analysis of MAPK pathway hallmark alterations in pilocytic astrocytomas: age-related and mutually exclusive. [corrected]. *Neuropathol Appl Neurobiol*. 2015;41:258–61. https://doi.org/10.1111/nan.12145.

34. Sadighi Z, Slopis J. Pilocytic astrocytoma: a disease with evolving molecular heterogeneity. *J Child Neurol*. 2013;28(5):625-32. https://doi.org/10.1177/0883073813476141.

35. Chen YH, Gutmann DH. The molecular and cell biology of pediatric low-grade gliomas. *Oncogene*. 2014;33:2019-2026. https://doi.org/10.1038/onc.2013.148.

36. Tomic TT, Olausson J, Wilzen A, Sabel M, Truvé K, Sjögren H, et al. A new GTF2I-BRAF fusion mediating MAPK pathway activation in pilocytic astrocytoma. *PLoS One*. 2017;12(4):e0175638. https://doi.org/10.1371/journal.pone.0175638.

37. Hasselblatt M, Riesmeier B, Lechtape B, Brentrup A, Stummer W, Albert FK, et al. BRAF-KIAA1549 fusion transcripts are less frequent in pilocytic astrocytomas diagnosed in adults: BRAF-KIAA1549 fusion transcripts in pilocytic astrocytoma. *Neuropathol. Appl. Neurobiol*. 2011;37(7):803–806. https://doi.org/10.1111/j.1365-2990.2011.01193.x.

38. Gregory TA, Chumbley LB, Henson JW, Theeler BJ. Adult pilocytic astrocytoma in the molecular era: a comprehensive review. *CNS Oncol*. 2021;10(1):CNS68. https://doi.org/10.2217/cns-2020-0027.

39. Drobysheva A, Klesse LJ, Bowers DC, Rajaram V, Rakheja D, Timmons CF, et al. Targeted MAPK Pathway Inhibitors in Patients With Disseminated Pilocytic Astrocytomas. *Journal of the National Comprehensive Cancer Network*. 2017;15(8):978–982. https://doi.org/10.6004/jnccn.2017.0139.

40. Schindler G, Capper D, Meyer J, Janzarik W, Omran H, Herold-Mende C, et al. Analysis of BRAF V600E mutation in 1,320 nervous system tumors reveals high mutation frequencies in pleomorphic xanthoastrocytoma, ganglioglioma and extra-cerebellar pilocytic astrocytoma. *Acta Neuropathol*. 2011;121(3):397-405. https://doi.org/10.1007/s00401-011-0802-6.

41. Nelson AJ, Zakaria R, Jenkinson MD, Brodbelt AR. Extent of resection predicts risk of progression in adult pilocytic astrocytoma. *British Journal of Neurosurgery*. 2019;33(3):343-347. https://doi.org/10.1080/02688697.2018.1549315.

42. Wan MJ, Ullrich NJ, Manley PE, Kieran MW, Goumnerova LC, Heidary G. Long-term visual outcomes of optic pathway gliomas in pediatric patients without neurofibromatosis type 1. *J Neurooncol*. 2016;129(1):173-8. https://doi.org/10.1007/s11060-016-2163-4.

43. Ishkanian A, Laperriere NJ, Xu W, Millar BA, Payne D, Mason W, et al. Upfront observation versus radiation for adult pilocytic astrocytoma. *Cancer*. 2011;117(17):4070-4079. https://doi.org/10.1002/cncr.25988.

44. Khalafallah AM, Jimenez AE, Shah PP, Brem H, Mukherjee D. Effect of radiation therapy on overall survival following subtotal resection of adult pilocytic astrocytoma. *J Clin Neurosci*. 2020;81:340-345. https://doi.org/10.1016/j.jocn.2020.10.020.

45. Parsons MW, Whipple NS, Poppe MM, Mendez JS, Cannon DM, Burt LM. The use and efficacy of chemotherapy and radiotherapy in children and adults with pilocytic astrocytoma. *Journal of Neuro-oncology*. 2021;151(2):93-101. https://doi.org/10.1007/s11060-020-03653-y.

46. Lavrador JP, Oliveira E, Pimentel J, Livraghi S. Adult pilocytic astrocytoma of conus medullaris: clinical considerations and review of the literature. *CNS Oncology*. 2017;6(2):107–110. https://doi.org/10.2217/cns-2016-0030.

47. Lieberman NAP, Vitanza NA, Crane CA. Immunotherapy for brain tumors: understanding early successes and limitations. *Expert Rev Neurother*. 2018;18(3):251-259. https://doi.org/10.1080/14737175.2018.1425617.

48. Wasilewski A, Mohile N. Durable response to bevacizumab in adults with recurrent pilocytic astrocytoma. *CNS Oncol*. 2018;7(3):CNS26. https://doi.org/10.2217/cns-2017-0039.

49. Carabenciov ID, Bhargav AG, Uhm JH, Ruff MW. Bevacizumab Use in Refractory Adult Pilocytic Astrocytoma: A Single-Center Case Series. *Neurologist*. 2019;24(3):87-89. https://doi.org/10.1097/NRL.0000000000000227.