Perspective on the Influence of Biopsy on the Survival of Pediatric Patients with Diffuse Brainstem Gliomas: A Literature Review

Perspectiva da influência da biópsia na sobrevida de pacientes pediátricos com Gliomas Difusos do Tronco: Uma revisão de literatura

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Abstract

Introduction Diffuse brainstem gliomas (DBG) represent the most common subtype of pediatric brainstem tumors, characterized by a systematically grim prognosis with a median survival rate of 10% two years post-diagnosis. Unlike other brain tumors, diffuse brainstem gliomas have traditionally relied on cranial magnetic resonance imaging (MRI) as a sufficient diagnostic tool, rendering surgical biopsies deemed unnecessary.

Objectives To conduct a literature review aiming to assess whether the performance of surgical biopsies has influenced the survival outcomes of children with diffuse brainstem gliomas.

Materials and Methods A comprehensive literature review was conducted using electronic databases PubMed, Embase, and LILACS. The search terms included "glioma" or "diffuse glioma" in conjunction with "pediatric" or "childhood," combined with "biopsy" or "stereotactic," and further combined with "brainstem," "pons," "pontine," or "mesencephalon," along with "survival." The searches were limited to studies involving pediatric patients (age <18 years) published between 1980 and 2021.

Results The analysis of the presented data revealed morbidity ranging from 0% to 33.3% and mortality from 0% to 2.2%. Transfrontal access was predominantly favored

Keywords
- brain stem neoplasms
- gliomas
- midline
- diffuse
- childhood
- biopsy

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by most authors, followed by transcerebellar approaches. The rate of inconclusive biopsies varied from 0% to 30%.

Conclusion Given the infiltrative nature of diffuse brainstem gliomas; surgical resection is generally deemed impractical. Radiation therapy remains the standard treatment, providing a marginal survival benefit of ~3 months. There is currently no established chemotherapy protocol for this pathology.

Resumo

Introdução Gliomas difusos do tronco (GDT) são o subtipo de tumor de tronco pediátrico mais comum, com prognóstico sistematicamente sombrio e sobrevida média de 10%, após 2 anos do diagnóstico. Diferentemente dos outros tumores cerebrais, a ressonância magnética de crânio é considerada suficiente para diagnóstico dos gliomas de tronco, fazendo com que a biópsia seja desnecessária.

Objetivos Realizar uma revisão de literatura buscando verificar se a realização de biópsias cirúrgicas impactou de alguma forma na sobrevida das crianças com GDT.

Materiais e Métodos Revisão bibliográfica nas bases de pesquisa de dados eletrônicos PubMed, Embase e LILACS; a partir dos termos: "glioma" ou "glioma difuso," em associação com "pediátrico" ou infância," em combinação com "biópsia" ou "estereotática," em combinação com "tronco cerebral," ou "ponte," ou "pontino," ou "mesencéfalo" em combinação com "sobrevida." As pesquisas foram limitadas a estudos em pacientes pediátricos (idade <18 anos), publicados entre 1980 2021.

Resultados Através da análise dos dados expostos foi possível observar que a morbidade variou de 0 a 33,3% e a mortalidade de 0 a 2,2%. A maioria dos autores preferiu a via de acesso transfrontal, seguida pela transcerebelar. A taxa de biópsias inconclusivas variou de 0 a 30%.

Conclusão Devido às características infiltrativas do tumor, a ressecção cirúrgica é desconsiderada. A radioterapia continua sendo o padrão de tratamento, conferindo benefício de sobrevida de cerca de 3 meses. Não há padrão de quimioterapia definido para essa patologia.

Palavras-chaves
- neoplasias do tronco encefálico
- gliomas
- linha média
- difusos
- infância
- biópsia

Introduction

Diffuse brainstem gliomas (DBGs) are the most common pediatric brainstem tumor subtype, accounting for 75% of tumors in this region in children, according to the CBTRUS published in 2020. It has a consistently poor prognosis and after 2 years of diagnosis, only 10% survive.[1,2] It mainly affects school-age children, with no predilection for sex. It is characterized by a rapid onset of symptoms in previously healthy patients.[3]

These tumors infiltrate both gray and white matter and their cells are often small and monomorphic but can be large and pleomorphic. They usually have astrocytic morphology but may sometimes be oligodendroglial.[4] Corresponds to grade IV glioma, regardless of histological grade.[5] In a recently revised 2021 World Health Organization (WHO) classification for central nervous system (CNS) tumors, most pediatric DBGs have been neuropathologically reclassified into a new tumor entity: diffuse midline glioma, H3-K27-altered.

The molecular profile of this entity is highly heterogeneous, with mutations such as histone H3, activin A receptor, type I (ACVR1), tumor protein p53 (TP53), platelet-derived growth factor receptor A (PDGFRA), phosphatidylinositol 3-kinase α catalytic subunit (PIK3CA) and Myc (MYC).[6] Some combinations of these genes are indicative of the behavior of the disease, for example, overlaps of Tp53 and H3K27M mutations have denoted a more aggressive course, in some series, as well as the loss of ATRX expression, which is an independent predictor of poor prognosis.[5]

Due to the tumor's infiltrative pattern, surgical resection is not considered. Currently, radiotherapy is the standard treatment, providing transient relief of symptoms, and without it, the median survival is 4 months.[2,3] Subsequent tumor progression is the rule and the median overall survival ranges from 8 to 11 months.[3] To date, there is no defined chemotherapy pattern.

Currently, the diagnosis of DBG does not require a biopsy, and is based on the following radiological criteria: a) intrinsic centrally located lesion, involving more than 50% of the axial diameter of the bridge; b) blurring of tumor margins; c) T1 hypointensity; d) T2 hyperintensity; e) irregular or absent contrast uptake; and f) absence of cystic or exophytic components.[7] The conviction of dismissing histopathological study for the diagnosis of DBG was influenced by some studies, among them one by Stroin et al.,[8] who published a

review of 49 children in which CT findings, pathological results, prognosis, and surgical efficacy were correlated. The authors concluded that the biopsy of diffuse lesions of the brainstem leads to a diagnostic yield and prognosis inferior to the radiological findings. Reinforcing the argument against performing biopsies, in 1987, Epstein et al.[9] published a series with 44 patients, in which he concluded that although biopsy can be performed with low morbidity/mortality, there was not enough useful information to justify it. Albright et al.,[10] in 1993, published more on the subject and after a retrospective review stated that performing a biopsy did not change the treatment instituted after the radiological diagnosis of DBG.

Until the end of the 1990s, physicians who cared for children with DBG did not routinely offer biopsy as part of the workup for handling these tumors.[3] This paradigm began to change slowly after some authors challenged this conduct. Among them, it is worth mentioning the work of Samadani et al.[11] (2003), a meta-analysis of 293 brainstem biopsies in adults and children, in which some diagnosis was made in 94% of patients after the first biopsy and in 96% after the second, with a mortality of 0.3% and the presence of persistent neurological deficit of 1%. Hamisch et al.[1] (2017) performed a meta-analysis with a systematic review of 735 pediatric patients with brainstem tumors, demonstrating not only the safety of performing a stereotactic biopsy in these patients but also its importance for identifying future treatments.

The present study aims to analyze the perspective of the influence of biopsy in pediatric DBG patients on the survival of these children.

Materials and Methods

We performed a bibliographic survey in the PubMed, Embase, and LILACS electronic databases; from the terms: "glioma" or "diffuse glioma," in association with "pediatric" or "childhood," in combination with "biopsy" or "stereotactic," in combination with "brainstem," or "bridge," or "pontine," or "midbrain" in combination with "survival." Research was limited to human studies, published in English, from 1980 to 2021. Reference lists of selected publications were also examined to identify additional studies.

Studies were eligible if they reported biopsy data from brainstem tumors (defined as tumors located in the midbrain, pons, or medulla oblongata) in pediatric patients (age <18 years), including details on procedure-related complications (morbidity and mortality).

Studies were excluded if they were descriptions of surgical technique, tumors that were not gliomas or dealt only with therapeutic measures.

Results

The search strategy found 772 results. The screening of titles and abstracts showed that 747 articles did not meet the study's inclusion criteria. Twenty-five complete articles were selected, and after the review, eight studies were eliminated for not meeting the inclusion criteria for the review.

Regarding the selected studies:

A. 2 meta-analyses with systematic review
B. 2 analysis of questionnaires for experts
C. 10 case series
D. 2 review articles

With the aim of better interpreting the results, comparative tables of studies of similar designs were prepared, including the number of patients, surgical access performed, diagnoses obtained, and outcome of the procedures (►**Tables 1** and **2**).

Through the analysis of this data, it was possible to observe that morbidity ranged from 0 to 33.3% and mortality from 0 to 2.2%. Most authors preferred the transfrontal access route, followed by the transcerebellar route. The rate of inconclusive biopsies ranged from 0 to 30%.

Discussion

For most CNS tumors, the first step of the workup includes performing the pathological analysis by performing the biopsy; the next steps are defined based on this result. DBGs are an exception to this pattern due to the correlation between radiological and pathological diagnosis, which provides enough confidence to indicate treatment without the need for confirmation of the lesion.[12]

Table 1 Meta-analysis studies

	Patients	Access	Diagnosis	Outcomes
Hamisch, C[1]	735	60% transfrontal	84.4% glial neoplasms	6.7% morbidity
		40% transcerebellar	7.4% other tumors	0.6% permanent morbidity
			4.5% non-neoplastic diseases	0.6% mortality
			3.5% inconclusive	
Kickingereder, P[2]	1480	64% transfrontal	76.23% glial neoplasms	7.8% morbidity
		36% transcerebellar	11.9% other tumors	1.7% permanent morbidity
			8.61% non-neoplastic diseases	0.9% mortality
			3.16% inconclusive	

Table 2 Case series studies

	Patients	Access	Diagnosis	Outcomes
Ogiwara, H.[17]	7	85% suboccipital	85% glial neoplasms	15% morbidity
		15% retrosigmoid	0% inconclusive	0% permanent morbidity
			0% non-neoplastic diseases	0% mortality
			15% other tumors	
Morais, B.A.[18]	26	9.1% transfrontal	76.9% glial neoplasms	7.6% morbidity
		81.8% transcerebellar	15.4% inconclusive	0% permanent morbidity
		9.1% transoccipital	3.8% non-neoplastic diseases	0% mortality
			3.8% other tumors	
Dellaretti, M.[19]	44	95% transfrontal	88% glial neoplasms	9% morbidity
		4.5% transcerebellar	6.9% inconclusive	9% permanent morbidity
			0% non-neoplastic diseases	0% mortality
			4.5% other tumors	
Quick-Weller, J.[20]	*5*	20% transcerebellar	80% glial neoplasms	0% morbidity
		40% transcerebellar	0% inconclusive	0% permanent morbidity
		40% unspecified	20% non-neoplastic diseases	0% mortality
			0% other tumors	100% unspecified
Albright, A.L.[10]	27	75% suboccipital	100% glial neoplasms	33.3% morbidity
		25% retromastoid	0% inconclusive	33.3% permanent morbidity
			0% non-neoplastic diseases	0% mortality
			0% other tumors	
Manoj, N.[21]	41 (children)	92.7% transfrontal	82.9% glial neoplasms	2.4% morbidity
		7.3% transcerebellar	4.9% inconclusive	2.4% permanent morbidity
			12% non-neoplastic diseases	0% mortality
			2.4% other tumors	
Cage T.A.[12]	9	100% transcerebellar	100% glial neoplasms	11.1% morbidity
			0% inconclusive	0% permanent morbidity
			0% non-neoplastic diseases	0% mortality
			0% other tumors	
Epstein, F.[9]	44	86% suboccipital	93% glial neoplasms	22.7% morbidity
		14% retromastoid	0% inconclusive	22.7% permanent morbidity
			0% non-neoplastic diseases	2.2% mortality
			7% other tumors	
Pérez-Gomes, J. L.[22]	20	100% transcerebellar	90% glial neoplasms	10% morbidity
			10% inconclusive	0% permanent morbidity
			0% non-neoplastic diseases	0% mortality
			0% other tumors	
Pincus, D.W.[23]	10	60% transfrontal	70% glial neoplasms	10% morbidity
		40% transcerebellar	30% inconclusive	10% permanent morbidity
			0% non-neoplastic diseases	0% mortality
			0% other tumors	
Wang, Z.J.[24]	15	100% transcerebellar	100% glial neoplasms	20% morbidity
			0% inconclusive	0% permanent morbidity
			0% non-neoplastic diseases	0% mortality
			0% other tumors	

In recent decades, research has been performed in search of the possibility of offering something more, besides radiotherapy, to these children. However, the targeted therapies offered so far were based on treatments for other pediatric and adult gliomas,[13] which possibly contributed to such poor responses in terms of survival. It is likely that this delay in the advancement of effective therapies is directly related to the low characterization of the individuality of this entity, a result of the choice to spare these patients from performing biopsies.

Fortunately, in the last twenty years, many authors began to challenge this paradigm, and several studies were published demonstrating the low rate of morbidity/mortality in performing biopsies, associated with a high rate of confirmed diagnoses.

Kickingereder et al.,[2] published, in 2013, a systematic review with a meta-analysis of 1480 cases of brainstem tumors, demonstrating that the diagnostic agreement between MR images and histology diverged widely, ranging from 42% to 100%. In addition, a high diagnostic success rate (96.2%) and low complication rates were found (permanent morbidity 1.7%; mortality 0.9%).

Hankinson et al.,[7] in 2011, conducted a survey, in which 86 pediatric neurosurgeons answered questionnaires in which, among other questions, one should classify MR images of brainstem lesions as typical or atypical for DBG. They showed that the agreement was greater than 75% in only 43.8% of the cases shown, which leads us once again to question the safety of the radiological diagnosis.

In the current oncological management, the performance of biopsies comes not only as a diagnostic determinant but also as an essential element for understanding the tumor entity, which allows safely for determining outcomes in relation to survival and offering a substrate for new effective target therapies.

In the recently revised WHO classification (2021) of CNS tumors, the majority of pediatric DBGs were neuropathologically reclassified into a new tumor entity: diffuse midline glioma, H3-K27-altered.[7]

Chen et al.[13] (2020) went further and classified DBGs according to the degree of methylation into four groups: "H3-Pons," "H3-Medulla," "IDH" and "Pilocytic-like Astrocytoma (PA-like), which have characteristics such as overall survival, oncogenic mechanisms, mutational profile, and distinct location. The PA-like group included grade II and III tumors according to the WHO classification, without identifiable IDH and histone H3 mutations, with a more benign clinical course and longer overall survival. The IDH cluster harbored IDH1, ATRX, and Tp53 mutations, being restricted to adult patients. The H3-Medulla group was in the medulla and dorsal medullary point junction. The H3-Pons cluster was present in the pons and cerebellar peduncle, encompassed grade II to IV tumors, and had worse overall survival.

Through works such as those mentioned above, we can glimpse a vision of a not-so-distant future, in which we will have effective targeted therapies in the management of DBGs, based on an understanding of the biology of this entity.

We can cite encouraging works from the discoveries of mutational and epigenetic profiles of these tumors. Among them, the research performed by Balakrishnan et al.,[14] in 2020, in which from the description of the increased expression of BMI1, an epigenetic chromatin modifier that regulates genomic complexes of stem cells and cancer cells, the effect of the H3K27M mutation; the authors were able to demonstrate that inhibition of BMI1 in vivo reduced tumor volume without detectable toxicity.

In 2015, Grasso et al.,[15] performed a multicenter preclinical study, in which the multi-HDAC *Panobinostat* inhibitor was identified, which works by restoring the methylation of H3K27 and normalizes oncogenic gene expression. In 2020, a phase I study of this drug was started, from which we await the results.

Park et al.[16] demonstrated that STAT3, a radioresistance-inducing oncogene present in some cancers such as lung, pancreas, and breast, is upregulated in DBG. This group showed a favorable response from the combination of STAT3 inhibition and radiotherapy, suggesting a potential route of treatment.

The studies cited are just a few examples of the potential offered by the collection of tumor material for analysis. We believe that the more researchers can have access to the materials offered by the biopsy, the closer we will be to the possibility of offering effective treatments to these children.

Conclusion

Biopsy for DBGs is feasible and presents very low complications. There is a tangible prospect of new therapeutic pathways for these children, based on the genetic and epigenetic individualization of these entities, which is only possible from the analysis of tumor tissue. Given the current oncological scenario of precision medicine, there is no possibility of adequately managing DBG patients without offering a biopsy.

Conflict of Interest
None.

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