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Decoding the puzzle: A multidisciplinary systematic review of adult brainstem glioma

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Highlights

- A thorough examination of the different therapeutic modalities currently used in adult brainstem glioma management, including surgery, radiation therapy, and chemotherapy.
- Analysis of the latest clinical trials and studies investigating novel treatments, immunotherapy, and targeted therapies that have shown potential promise in improving patient outcomes.
- A discussion on the challenges and limitations faced in treating adult brainstem gliomas, along with the identification of areas requiring further research and development.
- Insights into patient prognosis and factors influencing treatment response, aiding clinicians in making informed decisions.

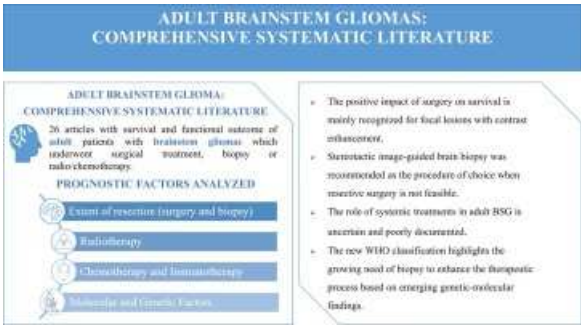
ABSTRACT

Adult brainstem gliomas (BSGs) are a group of rare central nervous system tumors with varying prognoses and controversial standard treatment strategies. To provide an overview of current trends, a systematic review using the PRISMA guidelines, Class of evidence (CE) and strength of recommendation (SR), was conducted. The review identified 27 studies. Surgery was found to have a positive impact on survival, particularly for focal lesions with CE II SR C. Stereotactic image-guided biopsy was recommended when resective surgery was not feasible with CE II and SR B. The role of systemic treatments remains unclear. Eight studies provided

molecular biology data.

This review gathers crucial literature on diagnosis and management of adult BSGs. It provides evidence-based guidance with updated recommendations for diagnosing and treating, taking into account recent molecular and genetic advancements. The importance of brain biopsy is emphasized to optimize treatment using emerging genetic-molecular findings and explore potential targeted therapies.

Graphical abstract



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Introduction

Brainstem gliomas (BSGs) account for approximately 20% of primary tumors of the central nervous system in pediatric patients; however, in adults, they are rare, and represent less than 2% of all neoplasms occurring at this site (Grimm and Chamberlain, 2013, Smith et al., 1998, Reyes-Botero et al., 2014, Theeler et al., 2015, Ramos et al., 2013).

Gliomas occurring in the brainstem are heterogeneous in both adults and pediatric patients and include tumors showing either a diffuse or circumscribed growth pattern.

Adult brainstem tumors are most frequently found in the pons (60%-63%), with occurrences also in the medulla oblongata (25%) and the midbrain (12%-15%). In up to 80% of cases, a combination of these brainstem regions is affected. Brainstem gliomas in adults typically have been subdivided based on clinical and radiographic characteristics into diffuse intrinsic, low-grade brainstem gliomas; focal, malignant brainstem gliomas; focal, tectal gliomas; and exophytically growing tumors (Eisele and Reardon (2016), Guillamo 2001). Despite similarities in clinical presentation and radiographic appearance, the prognosis varies widely between adult and pediatric brainstem gliomas (BSGs). These differences may reflect distinct histological and molecular features between age groups, regardless of the radiological tumor appearance, including lesion site and contrast enhancement. Given the challenging location and potential diagnostic uncertainty, the importance of surgical biopsy and pathologic confirmation cannot be overstated in guiding subsequent management decisions (Eisele and Reardon (2016)).

The only circumscribed glioma reported to occur in the brainstem is pilocytic astrocytoma (Yang et al., (2022)), which is classified as grade 1 by the World Health Organization (WHO) (Louis et al., 2021) (Table 1). All the three types of so-called “adult-type” diffuse gliomas were reported in the brainstem of adult patients. Among these, glioblastoma (GBM) *IDH*-wildtype (classified as grade 4 by the WHO), is the most frequently occurring in the brainstem (Zhou et al., 2021), whereas *IDH*-mutant astrocytomas (grade 2, 3, or 4) are less common, and oligodendroglioma *IDH*-mutant and 1p/19q codeleted (grade 2 or 3) are exceptional at this site

(Zhou et al., 2021, Hodges et al., 2015). Among the so-called "pediatric-type" low-grade diffuse gliomas, angiocentric glioma (WHO grade 1), diffuse astrocytoma *MYB*- or *MYBL1*-altered (WHO grade 1), and MAPK pathway-altered diffuse gliomas (which are currently considered as low-grade tumors) may rarely occur in the brainstem of children (Chan et al., 2017, Ryall et al., 2020), but epidemiological data in adults are currently lacking. With regard to pediatric-type high-grade diffuse gliomas, diffuse midline glioma *H3* K27-altered, which is classified WHO grade 4 owing to its dismal prognosis (Kesari et al., 2008, Guillamo et al., 2001, Reithmeier et al., 2014), can also occur in the brainstem of adults (Zhou et al., 2021, Eschbacher et al., 2021, Manjunath et al., 2021). Nonetheless, epidemiological data are scarce owing to the recent description of this tumor type. Finally, diffuse pediatric-type high-grade glioma *IDH*- and *H3*-wildtype, classified as grade 4, has been identified in the brainstem in children (Korshunov et al., 2017), whereas epidemiological data in adults are not available.

Since the majority of BSGs in adults are high-grade, they are commonly regarded as aggressive and fatal diseases (Eisele and Reardon (2016)). Defining adequate treatment options for adult BSGs is extremely challenging, mainly because of their rarity and absence of prospective clinical trials. As a result, current therapeutic options for are limited.

Despite significant advancements in surgery and radiotherapy, the prognosis remains extremely poor, with a median overall survival (OS) of 24.1 months and 5-year OS rate of only 11.8% (Babu et al., 2014, Maxwell et al., 2018). Adult BSG prognosis is influenced by a wide range of factors, including clinical, radiological, surgical, and molecular factors. According to several studies, the presence of contrast enhancement or necrosis on magnetic resonance imaging (MRI) scans, as well as an infiltrative growth pattern, are strongly associated with poor prognosis and low survival rates (Kesari et al., 2008, Guillamo et al., 2001, Reithmeier et al., 2014). Additionally, older age has been linked to worse clinical outcomes, which may be attributed to a higher incidence of high-grade lesions (HGG) (WHO grade 3 and 4) in elderly patients than in younger patients.

The optimal management of adult BSG is debated and poorly defined (Babu et al., 2014, Faulkner et al., 2021, Leibetseder et al., 2022). Before the advent of MRI, BSGs were considered malignant and unresectable. In recent decades, with the advancement of neuroradiological, anesthesiological, neurophysiological and neurosurgical techniques, a growing number of investigations has demonstrated that focal lesions may benefit from surgical resection with favorable clinical outcomes. Considering the difficulty in planning prospective clinical trials, the role and the optimal schedule of both radiotherapy and chemotherapy in the treatment of adult BSGs remain unclear.

The purpose of this review was to provide an updated overview of treatments for adult BSGs, emphasizing the importance of interdisciplinary management. This study considers the primary pathological features and novel molecular stratification of BSGs and their prognostic value. Moreover, the roles of surgery, or radiotherapy and emerging targeted therapies in terms of safety and impact on OS have described. To ensure a rigorous and comprehensive analysis, we conducted a thorough systematic multidisciplinary review to summarize the results according to the class of evidence (CE) and the strength of recommendation (SR).

Section snippets

Study Design

The aim of this systematic review was to describe the current multidisciplinary approach in adult BSG diagnosis and management, and to report the evidence and limitations of each treatment. The methods used were pre-specified and are presented in accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). Both prospective and retrospective

clinical studies were considered. This study followed a pre-specified protocol…

Study selection process

Using a combination of keywords, MeSH and Emtree hierarchical terms, the investigators found 480 potentially relevant articles, that were saved in a unique Pubmed (.nbib) file, which was then imported into Endnote to identify possible duplicates. After the removal of duplicates and papers published before 1977, 48 studies were deleted. The remaining 432 studies were screened by title, and subsequently by abstract, leading to the exclusion of 225 more studies (Cohen's k coefficient =0.91). An…

Discussion

Currently available therapeutic options for adult BSGs include surgery, radiotherapy (RT), chemotherapy, and biological treatments such as antiangiogenic treatments and targeted therapies. However, due to the rarity of these tumors, there is no established standard approach for their treatment, leading to ongoing debate. Despite the absence of effective therapeutic regimens established by clinical studies, radiotherapy, with or without concurrent chemotherapy, is frequently utilized as a…

Conclusion

With the rapid progress in the fields of molecular classification, epigenetics, and cancer therapeutics, it is highly probable that significant advancements will be made in this area within the next decade. This progress will enable the development of evidence-based management protocols for adult BSG. Currently, we carefully select patients who can safely undergo biopsy or resection for the purpose of symptom management, molecular testing for prognosis, and enrollment in therapeutic studies…

Ethical Approval

The IRB approval was waived given that the study is a systematic review with de-identified patient data.…

CRediT author contribution statement

TI: Conceptualization, Methodology, Validation, Data curation, Writing—original draft preparation, Writing—review and editing, Visualization, Supervision. N.M.: Data curation, Software, Writing—original draft preparation, Writing—review and editing, Visualization. GL: Writing—original draft preparation, Writing—review and editing, Visualization. JB: Writing—original draft preparation, Writing—review and editing, Visualization. AR: Writing—original draft preparation, Writing—review and editing,…

Uncited references

(Brat et al., 2021, Chang et al., 2021, Chen et al., 2020, Greenberger et al., 1977)…

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper…

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.…

Consent for publication

No individual patient data were collected, so patient consent was not required.…

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