OPEN ACCESS

Saudi Journal of Medicine

Abbreviated Key Title: Saudi J Med
ISSN 2518-3389 (Print) |ISSN 2518-3397 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Original Research Article

Diagnosis and Treatment of Pediatric Gliosarcoma: A Systematic Review of Published Case Reports

Anas S. Alyazidi[1*]

[1]Undergraduate Student, Faculty of Medicine, King Abdulaziz University, Jeddah, KSA

DOI: 10.36348/sjm.2021.v06i08.006 | **Received:** 16.07.2021 | **Accepted:** 21.08.2021 | **Published:** 27.08.2021

***Corresponding Author:** Anas S. Alyazidi

Abstract

Introduction: Gliosarcomas are a rare histopathologic variant of glioblastoma, which is the most common and aggressive malignant primary brain tumor in humans according to the World Health Organization's classification of central nervous system tumors. The survival period of gliosarcomas ranges from 4 to 18.5 months. The genetic profile might include p53 mutations, PTEN mutations, homozygous p16 deletion, and more. Symptoms' may include migraines, convulsions and others. ***Methods:*** A systematic literature review was conducted through June 2021 using the following keyword "gliosarcoma." Then, an offline search was performed in the references of the relevant previous reviews to ensure the comprehensive inclusion of all relevant reports using the Mendeley citation tool. All case reports that addressing patients of 18 years old and younger, both male and female were included. ***Results:*** The literature yielded a total number of 1398 unique articles filtered into 10 articles (12 case reports) that included various forms of diagnostic procedure including MRI, CT scan, and other techniques. Treatments were mainly focusing on surgical intervention, chemoradiotherapy alongside other medications. ***Discussion:*** Gliosarcoma is considered a difficult challenge for physicians. A combination of poor prognosis and indefinitive management procedures and treatment options; makes the disease difficult to address. In general, the increasing number of treatment courses did not guarantee an increase in survival. Even with complicated treatment many had a low survival rate. What complicated many cases are the fact that even with an initial positive outcomes there were still a deterioration in the patients' conditions often leading to their death.

Keywords: gliosarcoma, glioblastoma, craniotomy, chemotherapy, radiotherapy, nervous system, review.

INTRODUCTION

Gliosarcomas are a rare histopathologic variation of glioblastoma, the most frequent and severe primary brain tumor in humans [1]. Gliosarcomas are aggressive tumors with a biphasic growth pattern composed of glial and sarcomatous components [2]. It is a grade IV tumor that is malignant and rapidly growing, according to the World Health Organization's (WHO) classification of central nervous system (CNS) tumors. Gliosarcomas are thought to account for 2% of all glioblastomas. Gliosarcomas, like conventional glioblastoma, have a poor prognosis with a survival rate ranging from 4 to 18.5 months, and would almost never be more than 40 months. The median survival time for intraventricular gliosarcomas is fewer than 8 months [3]. It is further classified as primary, which can be identified during the first surgery or biopsy without a prior diagnosis of glioblastoma, and secondary, which can be detected following radiation treatment on a pre-existing glioma. Many genetic abnormalities are the underlying cause of the disease. Some might have p53 mutations, PTEN mutations, and homozygous p16 deletion although it was unusual for some gliosarcoma patients to have amplification or overexpression of the EGF receptor in their genetic profile; this means that gliosarcomas had a genetic profile comparable to that of new (de novo) glioblastomas, except for the absence of EGF receptor (EGFR) amplification/overexpression. Histologically, the tumor varies in size and appearance from case to case. Tumor tissue aggregate sizes can range from 1.5 cm to 12 cm, with a mean and median size of 6 cm and 5 cm, respectively. depicts a histologic study from the literature, which was acquired from 11 cases and revealed relatively diverse descriptions for each tumor [4]. Gliosarcomas can spread to other places via cerebrospinal fluid, however they seldom move outside the CNS to other organs. Symptoms may include migraines, convulsions, cognitive deterioration, and mobility and balance issues [5]. In a study included a total number of 16,388 patients with gliosarcomas or glioblastoma, gliosarcomas were responsible for 353

cases, or 2.2 percent of the population [6]. Based on data from published case reports, this systematic review will address diagnosis and treatment strategies.

METHODOLOGY

Study design and methods

A systematic literature review of all published literature was conducted. We searched PubMed, The New England Journal of Medicine (NEJM), The Lancet, and The Journal of the American Medical Association (JAMA) through June 2021 using the following keyword "gliosarcoma." Then, an offline search was performed in the references of the relevant previous reviews to ensure the comprehensive inclusion of all relevant reports using the Mendeley citation tool.

ELIGIBILITY CRITERIA

Included studies were selected according to the following criteria:

- Case reports studies
- Studies on patients with gliosarcoma
- Case reports for pediatric patients
- Articles relevant to diagnosis and treatment

Case reports with the following conditions were excluded

- Patients with other diseases that mimic gliosarcoma
- Case reports with no diagnostic or therapeutic options
- Studies other than case reports (i.e. case series and prospective cohorts)

Subject population

Case reports that addressed patients of 18 years old and younger, both male and female.

RESULTS AND DISCUSSION

Our literature search yielded 1398 unique citations. Following titles and abstract screening, 20 articles were assessed for full-text screening. Finally, 10 articles reporting a total of 13 cases, but only 12 were included in this systematic review, with one excluded as it does not meet our inclusion eligibility criteria. The PRISMA flow diagram of the study selection process is shown in **Figure 1**.

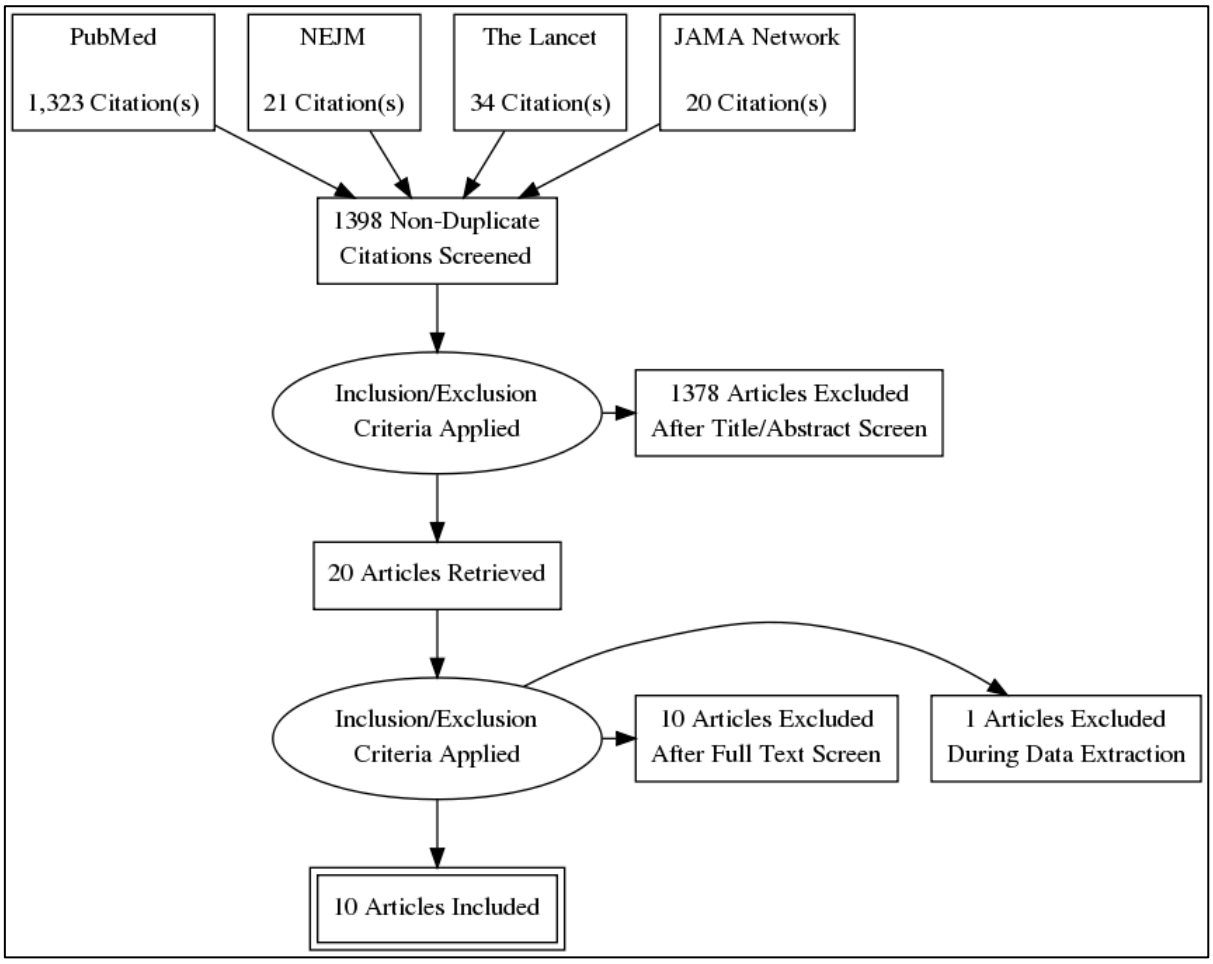

Fig-1: PRISMA flow diagram

Seven patients were male while five were females. The mean age of patients was 11.5 years old, ranging from 4-18 years old.

Seven patients were male while five were females. The mean age of patients was 11.5 years old, ranging from 4-18 years old. The first clinical case in the literature reported by *(Jeng & Reynolds,* [7] concerning a pediatric gliosarcoma invading the surrounding orbit of a 12-year-old male patient who presented with a headache. Many other findings were provided in this presentation that revealed gliosarcoma and glioblastoma (a precursor to secondary gliosarcoma) patients with headache. A glioblastoma multiforme was discovered and was excised and treated with both radiation and chemotherapy. The tumor returned as gliosarcoma seven months after treatment. Despite treatment, the tumor continued to grow and finally penetrated the right orbit. Thereafter, the patient experienced proptosis, or a blind, painful eye. In another clinical case with a similar presentation, *Sugita et al.,* [8] reported two cases of 52-year-old and 18-year-old patients with two weeks of headaches. The case of the 52-year-old patient was excluded for not meeting the eligibility criteria. In the second case, an MRI scan was requested, which indicated enhanced T1-low to iso, T2-iso to high-intensity lesions in the pineal gland region. On histological examination, the tumor displayed uniform growth of small spindle cells with disordered fascicles and cellular atypia. Desmin expression was detected immunohistochemically, and the majority of spindle tumor cells tested positive. GFAP was found on glial tumor cells. In addition, all tumor cells expressed CD133, Musashi1, and SOX-2. The patient was diagnosed with gliosarcomas in his pineal gland region based on the discussed microscopic appearances and immunohistochemistry findings. These results also indicated that pluripotential cancer stem cells differentiated into glial and muscle cell lines at tumor growth. *Ravisankar et al.,* [9] reported that an 11-year-old male patient presented to the outpatient department with a case of primary gliosarcoma with fibrosarcomatous differentiation. For the past two months, the patient had intermittent headache and vomiting. The findings on the computed tomography scan (CT Scan) revealed a meningioma, with a contrast-enhancing isodense space-occupying lesion with areas of calcification in the right temporoparietal cortex with surrounding edema, which was suggestive of a meningioma. Further investigation was carried out using magnetic resonance imaging (MRI), which revealed that the lesion was T1 hypointense and T2 hyperintense, with irregular enhancement on contrast. A portion of the lesion was sent for squash cytology during a craniotomy operation. The smear had a cellular appearance with discohesive sheets and clusters of pleomorphic oval to polygonal cells with extensive eosinophilic cytoplasm, cytoplasmic vacuolation, and prominent nuclear atypia on a necrosis and hemorrhage background. It was suggested that the tumor was an unusual teratoid/rhabdoid tumor. A histopathologic examination revealed many irregular gray-white soft tissue fragments with an irregular and nodular exterior surface after the space-occupying tumor was removed. Variegated cut surface with gray tan parts, glistening spots, cystic areas, and hemorrhagic areas. Few calcified areas were also seen. Areas stained with hematoxylin and eosin (H&E) revealed a highly cellular neoplasm constituted primarily of spindle-shaped cells with pleomorphic oval to elongated hyperchromatic nuclei. With frequent mitosis, cells were organized in a "herringbone" pattern. Gliosarcoma with leiomyosarcomatous differentiation and teratoma with malignant transformation were among the differential diagnosis. Vimentin immunostaining revealed cytoplasmic positivity in 70% of the cells. In 30% of the cells, smooth muscle actin displayed weak localized positive. S100, epithelial membrane antigen, myogenin, and glial fibrillary acidic protein immunostaining were all negative. The final diagnosis was gliosarcoma with fibrosarcomatous differentiation. The patient moves on to therapy, by undergoing concurrent chemoradiation with temozolomide. He is currently on his second maintenance cycle, with a minor improvement in his symptoms. *Neelima et al.,* [10] described a case with comparable symptoms, involving an 11-year-old male boy who had intermittent headache and vomiting for one month. An early bilateral papilledema was discovered during neurologic examinations. An MRI of the brain revealed a large, round, well-defined mass lesion in the left thalamic region. A high-grade glioma of the thalamus was diagnosed prior to surgery. A yellowish necrotic suckable tumor emerging from the posterolateral surface of the thalamus and expanding too many locations was discovered intraoperatively. Histopathological examination revealed an oligoastrocytoma with prominent nuclear atypia, mitotic signs, pseudopalisading necrosis, and vascular endothelial growth. The sarcomatous component of the case figures had reticulin fibers, whereas the glial component was devoid of reticulin fibers, indicating a diagnosis of gliosarcoma along with immunohistochemistry and reticulin stain findings. *Melo et al.,* [11] reported a 4-year-old male child who was rushed to the hospital with rapidly worsening headache, generalized seizures, and left hemiparesis, primarily in the face and arm. A CT scan was used to conduct the investigation, which revealed a mass tumor in the right temporal lobe with irregular contrast enhancement. A radical excision of the neoplasia was performed as part of the medical treatment. The histological results in the case indicated gliosarcoma. Treatment continued, and adjuvant chemoradiotherapy was indicated but not followed by the patient's guardians due to the family's poor socioeconomic status. Three months later, the child was brought back with deterioration in consciousness and seizures that were still going on. The patient died three months after the second neurosurgical intervention, with a three-month overall survival rate. According to the authors'

discussion, the main cause of death is the family's socioeconomic constraints on adjuvant therapy, despite the fact that infantile gliosarcoma sometimes responds to adjuvant chemoradiotherapy. *Burzynski et al.,* [12] presented the final male case included in the literature, which focused on long-term survival (>13 years) in a child with recurrent diffuse pontine gliosarcoma. The patient was a 9-year-old male. In December 1999, the patient presented to their clinic with a 5-year history of brain tumor. His health was strong until the end of 1994, when he began to deteriorate, with recurring bouts of vomiting necessitating many local hospital stays. He had a series of grand mal seizures in March 1995 and was later diagnosed with a massive right temporal brain tumor. In a craniotomy treatment, 80% of the tumor was excised. Multiple difficulties and management approaches were implemented until February 1999, when he experienced tremendous growth and his tumor tripled in size. Pathologic findings included an initial diagnosis of high-grade glioma in another 70% of the tumor that was removed. After submitting the tumor to a consulting neuropathologist, the final diagnosis of gliosarcoma was made. Radiation therapy was administered, and the patient was given high-doses of cyclophosphamide and thiotepa over time, followed by stem cell rescue. He was able to decrease the recurrent tumor, but a month later, magnetic resonance imaging (MRI) revealed considerable growth. On September 5, 1999, he began taking temozolomide (TMZ), but his condition advanced. During treatment, the patient experienced the expected side effects of chemotherapy and radiotherapy. He had severe neutropenia, thrombocytopenia, and anemia, as well as intermittent temperature spikes (which could indicate septicemia), and was routinely treated with antibiotics and pentamidine prophylaxis against Pneumocystis pneumonia. He seemed tired, drowsy, and complained of generalized weakness. His recent clinical history was corroborated by his physical examination. He also had substantial adiadochokinesis and trouble with finger-to-nose and heel-to-shin tests on the right side, which he could not accomplish on the left; investigations were also performed. Antineoplaston A10 and AS2-1 were used in the treatment (ANP). Medications that were deemed necessary for the patient's wellbeing and did not interfere with the treatment evaluation were administered at the discretion of the investigator. Throughout his lengthy course of therapy, the patient continued to take the dexamethasone that had been prescribed to him prior to arriving to the clinic. Seizure medications such as phenytoin, divalproex sodium, lamotrigine, and levetiracetam were all used to control seizures. Various antibiotics were used to treat occasional infections. MRI and positron emission tomography (PET) scans were used to assess progression. Although strong doses of chemotherapy and stem cell rescue reduced the main tumor size initially, it was quickly followed by a huge growth. For the first four years, the patient was successfully managed. His brain tumor then turned into a very malignant gliosarcoma, which progressed rapidly. As previously stated, the patient had a variety of treatments. *Chikkannaiah et al.,* [13] reported the first female case in this literature regarding a de novo gliosarcoma case occurring in the posterior fossa of an 11-year-old female patient. For one month, the patient had presented to the neurosurgical outpatient clinic with headaches, vomiting, and swaying when walking. There was no history of fever or seizures, nor were there any contributing family histories. During the inspection, she was cognizant, alert, and reacted to commands. There was bilateral appendicular ataxia. Bilateral papilledema was discovered during a fundoscopy. A brain MRI revealed irregularly enhanced lesions in the cerebellar vermis that extended bilaterally. Following that, a clinical diagnosis of cerebellar tuberculoma was considered. She had a subtotal occipital craniotomy as well as a large complete decompression. The lesion was solid and had reached the surface of the cerebellum at the time of operation. The tumor was in numerous pieces, was white, and glistened with patches of bleeding and necrosis. The tumor was microscopically cellular, with tightly packed clusters of tumor cells displaying a biphasic pattern, as well as glial and sarcomatous areas. The tumor lacked epithelial membrane antigen (EMA) and synaptophysin, ruling out anaplastic ependymoma, meningioma, or glioneuronal tumor. Given the aforementioned characteristics and additional facts, the diagnosis of de novo pediatric gliosarcoma was made. *Granados et al.,* [14] reported a case of a 5-year-old female who was transferred with a history of 2 weeks of severe headache that woke her up during the night, associated with several episodes of vomiting, double vision, left gaze deviation, and gait disturbances. She was alert with physical examinations. CT scan showed a mass lesion in the pineal gland region. An MRI also revealed a mass lesion. A germinal cell tumor was suspected, followed by a pineal parenchymal or glial cell tumor. An endoscopic biopsy was performed. Histopathologic findings revealed a high-grade glial cell lesion, and immunohistochemistry confirmed grade 4 gliosarcoma. Her clinical condition was improved as a result of the surgical procedure by craniotomy. Following an investigation, no metastases were discovered. Chemotherapy was started, coupled with temozolomide adjuvant therapy and radiation. Neurologic symptoms such as nystagmus, hemiparesis, gait instability, tremor, and myoclonic type seizures continued two months later. Brain CT and MRI tests revealed no improvement, and their findings were factored into the treatment plan. Surgical resection was thus ruled out. Because of the poor therapeutic response and prognosis, the oncology team opted to cease chemotherapy with concurrent radiotherapy and begin palliative symptom care. *Salvati et al.,* [15] reported 3 cases of two females and a male. The first case included a 15-year-old female patient who presented with a 10-day history of circadian headache associated with morning vomiting, often not

preceded by nausea. A few days before her admittance, she had a 10-minute loss of consciousness followed by bewilderment. A lesion with high-grade glioma features was discovered during neurological and MRI testing. A surgical operation was performed, and the total eradication of the lesion was verified microscopically. Histopathological investigation revealed a glioblastoma-like tumor with an extensive sarcomatous component with spindle-cell components, either organized in bundles or without a distinct architectural arrangement. Her parents refused the suggested neoadjuvant procedures, which included chemotherapy and radiotherapy. She had been living normally for four months before experiencing a few of episodes resembling widespread comitial seizures. After two days, her consciousness began to deteriorate. Aside from support therapy with steroids (betamethasone), antiepileptic medication (phenobarbital), and stomach protection (ranitidine), no specific medical treatment was offered. There were no additional radiological investigations, and the patient died one month following the onset of these new symptoms. A 13-year-old female suffered from severe headaches and a decrease in psychomotor speed in the second occurrence. CT and MRI tests, as well as emergency surgery, were all conducted. Finally, histological investigation revealed a common population with glioblastoma traits and a modest "sarcoma-like" component. The patient is in good health nine months following surgery and shows no evidence of recurrence. The third case was a 16-year-old male patient who had previously been irradiated for a scalp angioma. He began experiencing recurring paresthesia-like episodes on one side of his body two months before admission. These attacks lasted a few minutes and happened several times a day. A brain MRI combined with a spectroscopic and functional examination was performed. The findings indicated a benign meningeal lesion with elevated NAA/Cho ratios. Surgery was performed, the postoperative recovery was uncomplicated, and the patient was discharged in good general and neurological health. Integrated therapy combining structural radiation with the multi-leaf approach and chemotherapy with temozolomide. This was followed by 12 cycles of temozolomide treatment. A two-year follow-up revealed no evidence of illness progression. *Malde et al.*, [16] reported a rare case of a female patient presented with gliosarcoma after eight years of treating medulloblastoma. She first presented with 2 weeks of intermittent headache, vomiting, instability when walking, dimness of vision, and poor hearing on the left side. She was diagnosed with medulloblastoma when she was 13 years old. The researchers considered the possibility of a radiation-induced tumor and present evidence to support this hypothesis. After the resection of the second tumor in the brain, gliosarcoma was verified. The investigation made use of CT imaging of the brain, which revealed many abnormalities, as well as histological and immunohistochemical findings. She had a suboccipital craniotomy and got postoperative craniospinal radiation. She also had monthly cycles of vincristine and lomustine adjuvant treatment. There was no sign of the disease on CT imaging follow-up.

CONCLUSION

In summary, gliosarcoma is considered a difficult challenge for doctors and physicians. The combination of poor prognosis and indefinitive management procedures as well as for treatment options; makes the disease difficult to address. Based on practical case reports which were included in this review the diagnostic methods were mainly clustering on the use of CT and MRI scans. Findings upon using MRI usually revealed a mass – in some cases round – lesions and tumors. CT and MRI scans were constantly used as successful investigation methods to determine if the patient has the tumor cells. In some cases CT scan managed to reveal associated abnormalities that some contributed to reduce the survival rate. Histological and immunohistochemical test were occasionally requested and their findings contributed to the establishment of the diagnosis. However, treatment options included different procedure some of which were surgical intervention, radiation and chemical therapy, and certain drugs and medications which were primarily to control associated symptoms which included seizures, fever, cognitive problems and other complications. Although the treatment might become or even lengthy; occasionally it managed to control the patient but the majority had a poor prognosis. Alongside this struggle, socioeconomic restriction might become a barrier that further complicates the cases. Although Infantile gliosarcoma sometimes responds to adjuvant chemoradiotherapy in one case included in the literature, the patient's guardians did not follow-up to the indicated adjuvant chemoradiotherapy due to their poor socioeconomic status, upon follow-up with the physician the child was brought back with a decline in his health which led to its death three months after the second neurosurgical intervention leading to the establishment of a three-month overall survival rate. Regardless of these added complications, chemoradiation was combined temozolomide and showed a minor symptomatic development. High-doses of cyclophosphamide and thiotepa were also given but showed a restrictive improvement that was later halted and tumor continued to grow. In some lengthy course dexamethasone were also prescribed before the patient's arrival to the clinic. Supportive drugs were used depending on each case independently. In general, the increasing number of treatment course did not guarantee the survival of patients nor a better prognosis and an increasing survival rate. Even with complicated treatment many had a low survival rate. What complicated many cases is the fact that even with an initial positive outcomes there were still a deterioration in the patients' conditions often leading to their death. From my point of view, I believe that spreading more knowledge and summarizing actual cases as such mentioned in this research help to better understand the

overall management plans of the disease and assist in limiting other practices that limit treatment options mainly referring to social practices especially by patients' guardians.

ETHICAL APPROVAL

This article is based on previously conducted research and does not involve any new studies of human or animal subjects performed by any of the authors; as such ethics approval and consent to participate were not required.

ACKNOWLEDGMENT

The author would like to express his special thanks of gratitude to Hani A. Alturkistani, PhD from the Department of Anatomy, Faculty of Medicine at King Abdulaziz University, for his critical revision of the manuscript as well as for the valuable commentaries and advices which were carried out throughout the making of this work.

Funding

This research received no specific grants or funds

Conflict of Interest

The authors report no conflicts of interest in this work.

REFERENCES

1. Wang, Z., Peet, N. P., Zhang, P., Jiang, Y., & Rong, L. (2021). Current development of glioblastoma therapeutic agents. *Molecular Cancer Therapeutics*.
2. Frandsen, S., Broholm, H., Larsen, V. A., Grunnet, K., Møller, S., Poulsen, H. S., & Michaelsen, S. R. (2019). Clinical characteristics of gliosarcoma and outcomes from standardized treatment relative to conventional glioblastoma. *Frontiers in oncology*, *9*, 1425.
3. Huo, Z., Di Yang, J. S., Li, Y., Wu, H., Meng, Y., Zhang, S., ... & Liang, Z. (2014). Primary gliosarcoma with long-survival: report of two cases and review of literature. *International journal of clinical and experimental pathology*, *7*(9), 6323.
4. Din, N. U., Ishtiaq, H., Rahim, S., Abdul-Ghafar, J., & Ahmad, Z. (2021). Gliosarcoma in patients under 20 years of age. A clinicopathologic study of 11 cases and detailed review of the literature. *BMC pediatrics*, *21*(1), 1-10.
5. https://www.cancer.gov/rare-brain-spine-tumor/tumors/gliosarcoma
6. Kozak, K. R., Mahadevan, A., & Moody, J. S. (2009). Adult gliosarcoma: epidemiology, natural history, and factors associated with outcome. *Neuro-oncology*, *11*(2), 183-191.
7. Jeng, F., & Reynolds, A. (2020). Retrobulbar chlorpromazine injection in a child with gliosarcoma invasion into the orbits. *BMJ Case Reports CP*, *13*(6), e233394.
8. Sugita, Y., Terasaki, M., Tanigawa, K., Ohshima, K., Morioka, M., Higaki, K., ... & Nakashima, S. (2016). Gliosarcomas arising from the pineal gland region: uncommon localization and rare tumors. *Neuropathology*, *36*(1), 56-63.
9. Ravisankar, S., Chander, R. V., & Devadoss, P. K. (2012). Pediatric gliosarcoma with fibrosarcomatous differentiation: report of a rare case. *Indian Journal of Pathology and Microbiology*, *55*(4), 521.
10. Neelima, R., Abraham, M., Kapilamoorthy, T. R., Hingwala, D. R., & Radhakrishnan, V. V. (2012). Pediatric gliosarcoma of thalamus. *Neurology India*, *60*(6), 674.
11. Melo, J. R. T., Souza, A. L. P. B. D., Reis, R. C., & Almeida, M. A. C. D. (2008). Infantile gliosarcoma. *Arquivos de neuro-psiquiatria*, *66*, 88-89.
12. Burzynski, S. R., Janicki, T. J., Burzynski, G. S., & Marszalek, A. (2014). Long-term survival (> 13 years) in a child with recurrent diffuse pontine gliosarcoma: a case report. *Journal of Pediatric Hematology/Oncology*, *36*(7), e433.
13. Chikkannaiah, P., Bharath, R. D., Sampath, S., & Santosh, V. (2012). De novo gliosarcoma occurring in the posterior fossa of a 11-year-old girl. *Clinical neuropathology*, *31*(5), 389-391.
14. Granados, A. M., Ospina, C., & Paredes, S. (2018). Pineal gliosarcoma in a 5-year-old girl. *Radiology case reports*, *13*(1), 244-247.
15. Salvati, M., Lenzi, J., Brogna, C., Frati, A., Piccirilli, M., Giangaspero, F., & Raco, A. (2006). Childhood's gliosarcomas: pathological and therapeutical considerations on three cases and critical review of the literature. *Child's Nervous System*, *22*(10), 1301-1306.
16. Malde, R., Jalali, R., Muzumdar, D., Shet, T., & Kurkure, P. (2004). Gliosarcoma occurring 8 years after treatment for a medulloblastoma. *Child's Nervous System*, *20*(4), 243-246.