

## Brain Tumor in Pediatric Glioblastoma: Review Article

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### ABSTRACT

**Introduction:** Glioblastoma (GBM) is a malignant brain tumor that can occur in children and is very aggressive which means it can grow and spread quickly. Approximately 16% of all primary brain and central nervous system neoplasms are glioblastomas. The incidence of glioblastoma in children varies. Glioblastoma *Low-grade* has a higher incidence in children aged 0 to 14 years, which is 1.8/100,000 while *high-grade* glioblastoma is 0.5/100,000 lower than *low-grade glioblastoma*.

**Content:** GBM develops more frequently in children with specific genetic syndromes, such as neurofibromatosis 1 (NF1), Li-Fraumeni syndrome, hereditary nonpolyposis colon cancer, and tuberous sclerosis.

**Conclusion:** In children, central nervous system tumors are the most common, with 3-15% being glioblastomas. In addition, the prognosis is also poor with high morbidity and mortality so to improve the patient's quality of life, effective therapy is needed. Therapy can be in the form of surgery, radiotherapy, or chemotherapy.

**Keywords:** Pediatrics; brain tumors; glioblastoma



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## Introduction

Glioblastoma (GBM) is a malignant brain tumor that can occur in children and is very aggressive which means it can grow and spread quickly. Approximately 16% of all primary brain and central nervous system neoplasms are glioblastomas.<sup>1</sup> Glioblastomas are formed from cells called astrocytes that function as support for nerve cells. Glioblastoma can occur at any age.<sup>2</sup>

GBM develops more frequently in children with specific genetic syndromes, such as neurofibromatosis 1 (NF1), Li-Fraumeni syndrome, hereditary nonpolyposis colon cancer, and tuberous sclerosis.<sup>(1)</sup> However, most cases of GBM have no known cause. However, there were no risk factors that played a major role in causing glioblastoma. Although GBM is a rare tumor with a global incidence of less than 10 per 100,000 people, GBM still has a poor prognosis with a survival rate of 14-15 months after diagnosis. This makes GBM a major public health problem.<sup>2</sup>

GBM accounts for about 50% of all gliomas in all age groups. The incidence ratio of GBM is higher in men compared to women. The incidence of glioblastoma in children varies. Glioblastoma *Low-grade* has a higher incidence in children aged 0 to 14 years, which is 1.8/100,000 while *high-grade* glioblastoma is 0.5/100,000 lower than *low-grade glioblastoma*. where the incidence rate of glial and neuroepithelial tumors is higher in children aged 0-14 years.<sup>3</sup> Glioblastoma usually presents with non-specific symptoms and lasts a short duration of several months. In addition, the prognosis is also poor with high morbidity and mortality to improve the patient's quality of life, effective therapy is needed. Therapy can be in the form of surgery, radiotherapy, or chemotherapy.<sup>6</sup>

## Definition

Glioblastoma (GBM) is a malignant brain tumor that can occur in children and is very aggressive which means it can grow and spread quickly. About 3,540 brains and CNS (central nervous system) tumors are diagnosed in children aged 0-14 years.<sup>3</sup> Approximately 16% of all primary brain and central nervous system neoplasms are glioblastomas.<sup>1</sup> Glioblastomas are formed from cells called astrocytes that function as support for nerve cells. Glioblastoma can occur at any age.<sup>2</sup>

## Epidemiology

GBM accounts for about 3-15% of primary central nervous system (CNS) tumors. in children. It is inseparable that tumors that occur in the CNS are the most common in childhood and 40-50% of these tumors are formed by astrocytomas. Pediatric glioblastoma (p-GBM) has substantial morbidity and mortality, with the median survival reported for p-GBM ranging from 13-73 months with a 5-year survival of less than 20%. The survival rate for p-GBM has a longer life span than GBM in adults.<sup>1</sup>

Glioma is the most common central nervous system (CNS) tumor in children and adolescents with a very broad clinical picture. Pediatric gliomas are mostly benign slow-growing lesions classified as class I or class II tumors of the CNS. These pediatric low-grade gliomas (LGG) are inherently rare with malignant transformation and show good survival under current treatment strategies. However, most gliomas develop in a short time and grow rapidly so that they are classified as high-grade gliomas by WHO i.e. grade III or IV.<sup>4</sup>

CNS tumors are the 2nd most common childhood tumor after leukemia, it is estimated that the overall incidence of primary CNS tumors in childhood is estimated at around 30/1,000,000 people. While astrocytic tumors account for 40–50% of the CNS in children, high-grade gliomas are relatively rare.<sup>5</sup> According to the 2012 Central Brain Tumor Registry of the United States (CBTRUS) data, the incidence of high-grade glioma in pediatrics is approximately 0.85/100,000 cases. Most investigators estimate the incidence of high-grade gliomas in pediatrics to be between 8-12%. The incidence of p-GBM is estimated to be 3–15% at various ages in children and GBM is most commonly reported in the second decade of life.

The location of p-GBM often occurs in the supratentorial brain region, in the spinal cord it occurs in high-grade gliomas, which is about 3%, whereas involvement of the supratentorial compartment occurs in almost 50% of cases. The incidence of involvement of the structures of the thalamus, corpus callosum, hypothalamus has a low incidence. In the infratentorial compartment of the cerebellum, it is about 1-2% with a rare incidence of p-GBM, whereas in high-grade gliomas that occur in the brainstem, it is almost 20% of intrinsic tumors.<sup>5</sup>

Although GBM is a rare tumor with a global incidence of less than 10 per 100,000 people, GBM still has a poor prognosis with a survival rate of 14-15 months after diagnosis. This makes GBM a major public health problem. GBM accounts for about 50% of all gliomas in all age groups.<sup>3</sup> According to *the international classification of childhood cancer (ICCC)*, the incidence of glioblastoma in children varies. Glioblastoma *Low-grade* has a higher incidence in children aged 0 to 14 years, which is around 1.8/100,000 while *high-grade* is 0.5/100,000 lower than *low-grade* glioblastoma, where the incidence rates of glial and neuroepithelial tumors are higher. Higher in children aged 0-14 years and decreases in late adolescents aged 15-19 years, then increases with age. The histologic subtype of glioblastoma with the highest incidence in children is pilocytic astrocytoma. Astrocytoma and Glioblastoma NOS have the highest incidence in children aged 0-9 years with a decreasing incidence until the age of 19 years.<sup>5</sup>

## **Etiology**

Various factors such as genetic and environmental factors have been studied in terms of the etiology of glioblastoma. GBM develops more frequently in children with specific genetic syndromes, such as neurofibromatosis 1 (NF1), Li-Fraumeni syndrome, hereditary nonpolyposis colon cancer, and tuberous

sclerosis. However, most cases of GBM have no known cause. However, there were no risk factors that played a major role in causing glioblastoma.<sup>7</sup> Until recently exposure to high doses of ionizing radiation was the only thing that could indicate an increased risk of developing gliomas. Other environmental exposures to vinyl chloride, pesticides, smoking, petroleum refining, synthetic rubber manufacture, electromagnetic fields, formaldehyde, and nonionizing radiation from cell phones have been linked to the development of gliomas but these factors have not been shown to cause GBM. An increased risk of developing gliomas is seen in certain genetic diseases, such as neurofibromatosis, tuberous sclerosis, Li-Fraumeni syndrome, retinoblastoma, and Turcot syndrome. However, less than 1% of patients with gliomas have the disease in question.<sup>1,3</sup>

To date, exposure to high doses of ionizing radiation is the only confirmed risk factor. Since the 1960s more than 116 cases of GBM have been reported as a result of radiation exposure and it has been estimated that the overall risk of developing GBM after radiotherapy is 2.5%. In addition, it has been reported that relatively low radiation doses used to treat tinea capitis and cutaneous hemangiomas in children or infants have been associated with a relative risk for glioma.<sup>8</sup> The extensive retrospective cohort data also clearly demonstrate an increased risk of glioma in the pediatric population after exposure to therapeutic intracranial radiation, which is dependent on patient age and radiation dose/volume. Glioma is also passed down through genes in families, but the susceptibility gene has not been identified. Rare genetic disorders including neurofibromatosis type 1 and type 2, tuberous sclerosis are have been found to be associated with an increased incidence of gliomas.<sup>3</sup>

## Pathogenesis

Pathogenesis associated with glioblastoma can be seen from the genetic and molecular aspects. Fact, *the World Health Organization (WHO)* has a classification system based on subtypes of glioblastoma based on histological and immunohistochemical similarity to the cell of origin. This grading is also formed based on histological features related to the level of biological aggressiveness such as necrosis, mitotic features and hyperplasia of the vascular endothelium.<sup>11</sup>

The clinical characteristics of glioblastoma can be divided into primary and secondary. Primary glioblastoma presents de novo without clinical evidence, and the precursor lesion is histological. Changes that occur in primary glioblastoma are mutations and amplification of the *epidermal growth factor receptor (EGFR)* gene, overexpression of *mouse double minute (MDM2)*, depletion of P16, and *loss of heterozygosity (LOH)* of chromosome 10q which carries *phosphatase and tensin. homologous (PTEN)* and TERT promoter mutations.<sup>15</sup> Meanwhile, secondary glioblastoma arises due to the slow development of astrocytoma that previously existed. The changes that occur are overexpression of *platelet-derived growth factor A* and *platelet-derived growth factor receptor alpha (PDGFA/PDGFRa)*, retinoblastoma (RB, LOH 19q and

IDH1/2, TP53 and ATRX mutations). These genetic lesions can be grouped into 3 main signaling pathways namely; altered receptor tyrosine kinase/RAS/PI3K, P53 pathway and RB signaling pathway.<sup>12</sup>

The existence of these genetic change affects cell proliferation and tumor growth with a cascade of mutations in each pathway. In addition, genetic changes also affect the occurrence of angiogenesis. In Glioblastoma, genetic abnormalities will cause morphological changes such as infiltration, necrosis with pseudo palisade, and microvascular proliferation. Neoplastic cells secrete procoagulant proteins that are responsible for endothelial injury and intravascular thrombosis.<sup>5</sup> Intravascular thrombosis can cause hypoxia as well as perivascular tumor necrosis with tumor cell pseudo palisade, an adaptation to hypoxic conditions. Pseudo palisade will express *hypoxia-inducible factor-1a* (HIF-1a) in excess, which will have an impact on the migration of glioblastoma cells from damaged blood vessels. In the presence of proangiogenic factor secretory factors, tumor cells further expand into newly formed blood vessels. In addition to the above factors, there is also the role of inflammatory cytokines, chemokines, and *growth factors* that help modulate proliferation, infiltration and angiogenesis, as well as tumor growth.<sup>9</sup> The study stated that in the area around the growth of glioblastoma tumors there were increased levels of IL-6, IL-8, and IL-1B associated with cell proliferation and decreased *survival rate* patient.<sup>13</sup>

### Clinical Manifestations

Symptoms of glioblastoma are non-specific. The duration of symptoms is usually short and lasts for several months.<sup>6</sup> The most common symptoms are headache, nausea and vomiting, and diplopia. Children with glioblastoma usually present with acute neurologic deterioration resulting from intratumoral hemorrhage.<sup>7</sup> Thus, if CNS symptoms are found in pediatric patients, it is necessary to suspect a brain tumor.<sup>8</sup> Infants and young children usually have difficult-to-diagnose symptoms such as failure to thrive, lethargy, nausea and vomiting, and macrocephaly.<sup>6</sup> Patients with GBM have different signs and symptoms produced by three mechanisms, namely:

1. Direct effects, namely brain tissue damage due to necrosis that causes symptoms such as focal nerve deficits and cognitive impairment that lasts for days to weeks. If the tumor is large with a significant mass it can cause gait imbalance and incontinence.<sup>3</sup>
2. Secondary effects, this is related to the increase in intracranial pressure which is the result of a gradual increase in size and edema around the tumor causing intracranial displacement. The most common symptom can be a headache. Headaches usually have unilateral characteristics and do not have a specific pattern.<sup>3</sup> Headaches are often followed by other symptoms such as seizures, nausea and vomiting, blurred vision, changes in mental status, dysarthria and hemiplegia.<sup>7</sup>

3. The location of the tumor, basically the signs and symptoms caused depend on the area of the brain affected by the tumor. For example, patients who have seizure symptoms indicate that the tumor is located in the frontotemporal lobe area.<sup>6</sup> Meanwhile, in patients who come with changes in personality and cognitive function, the tumor is located in the frontal lobe area.<sup>3</sup>

## Management

### Surgery

Maximum surgical resection followed by chemoradiotherapy is still the best treatment for GBM today. Some studies have reaffirmed the utility of maximal tumor removal in both free progression and overall survival in p-GBM.<sup>10,11</sup> Study *Children's Cancer* showed that children with HGG who underwent surgical resection of 90% or more had a progression-free survival of  $35 \pm 7\%$  compared with a 5-year progression-free survival of  $17 \pm 4\%$  in patients who do not.<sup>13</sup> It was also reported in a study that p-GBM single-center experiences suggest that the extent of tumor excision is a strong predictor of progression-free long survival as well as overall survival.<sup>6</sup> The utility of maximal surgical excision has been demonstrated in multiple propensity analyses, having scientific value as well as randomized clinical trials.<sup>10</sup> The degree of resection depends on the location and extent of the tumor.<sup>6</sup> Brainstem locations, midline supratentorial tumors, tumors involving the eloquent area, etc., are often difficult to completely excise without causing significant neurologic deficits. In addition to providing tissue for diagnosis, *debulking* reduces tumor-associated mass effects and potentiates the effects of adjuvant therapy. Different intraoperative imaging techniques allow wider excision of the tumor which in turn translates to better survival outcomes.<sup>15</sup>

These advanced techniques include intraoperative neural navigation, intraoperative ultrasonography, intraoperative MRI, intraoperative cortical mapping, etc. Recent technological advances using microfluidic chips allow rapid analysis of operative specimens for molecular markers such as IDH mutations in a short period of time.<sup>13,15</sup> Therefore, it is now possible to make a molecular diagnosis even intraoperatively. Such advances have the potential to facilitate intraoperative decision-making regarding future radicalism of surgical excision.<sup>6</sup>

#### 1. Preoperative evaluation

Before admission to the operating room, all surgical candidates are required. Most surgical centers worldwide are required to sign an *informed consent*. For 1 month the patient is advised not to smoke and drink alcohol whenever possible. Preoperative evaluation of intracranial tumors should include an assessment of neurologic and general status. Assessing intracranial pressure (ICP) status is the primary goal in evaluating neurologic status. Preoperative steroids can be given to control ICP by reducing peritumoral edema. It is also worth monitoring for endocrine, muscular, skeletal, gastrointestinal, psychiatric and

hematological complications in the patient. Brain relaxation can be achieved by administering hypertonic saline or mannitol to increase the likelihood of intraoperative brain relaxation.<sup>15</sup>

## 2. Intravenous Anesthesia

Barbiturates have four actions in the brain: (i) hypnosis, (ii) depression of cerebral metabolic rate, (iii) reduction of cerebral blood flow, and (iv) anticonvulsant activity. All of these actions can produce significant hypotension.<sup>15</sup>

## 3. Muscle Relaxation

Neuromuscular blocking agents (*NMBAs*) have no direct effect on CMR, ICP, or CBF. *Pancuronium* can increase heart rate and mean arterial pressure (MAP). Succinylcholine may increase ICP in brain tumor patients, secondary to cerebral activation associated with fasciculations and increased muscle spindle activity; However, when administered together with the intravenous agent propofol, ICP can be reduced.<sup>15</sup>

## 4. Extension of Resection

The goal of resection is to remove as much of the tumor as possible to reduce the mass effect and to obtain brain tissue for pathological analysis. Tumor recurrence occurs within a 2 cm margin of the primary site in 90% of cases.<sup>15</sup>

## 5. Fluorescence Guided Surgery

5-ALA is a naturally occurring amino acid biosynthesized from glycine and succinyl-CoA in the mitochondria. After systemic administration, ALA in tumor cells is metabolized to protoporphyrin IX (PpIX), a photosensitizing porphyrin. PpIX levels were highly specific (98%) in the infiltrating tumor area and were highest at 6 hours after administration. 5-ALA is an orally administered product used for high-grade visualization of glioma tissue during surgery, enabling safer and more extensive tumor resection. Under the excitation of blue light (400-410 nm), tumor tissue appears red, whereas normal tissue (including edema) does not show fluorescence.<sup>15</sup>

## 6. Indocyanine Green

Angiography with *indocyanine green* (ICG) was first developed for ophthalmological purposes in 1956 to evaluate the choroidal microcirculation; Other uses are to assess liver function, live blood flow, and cardiac output. Near-infrared ICG video angiography was introduced in the field of neurosurgery to visualize cerebral blood vessels for aneurysm clipping, bypass, and vascular malformations. Superficial avascular areas in HGT have been seen during pre-resection ICG video angiography. neovascular architecture; changes in caliber, morphology, and direction of blood vessels; and hemodynamic patterns can be observed.

The dye does not penetrate the membrane and therefore cannot define tumor boundaries. ICG helps avoid injury by preserving small caliber vessels during brain tumor surgery.<sup>15</sup>

#### 7. Neuronavigation

Systems have been developed for image-guided neurosurgery to aid in the accurate localization of lesions in the brain. Before craniotomy, the patient's head is secured to the head restraint with head pins; this fixation can cause skin shift (*skin shift*) and reduce accuracy which can be corrected using intraoperative imaging systems (CT and/or magnetic resonance imaging, MRI). The most widely used tracking systems use dual infrared cameras that track the position of the probe relative to a fixed frame of reference. Electromagnetic navigation relies on tracking probes in an electromagnetic field, created by a field generator at a fixed location. Using MRI, positional accuracy is within 2-3 mm during surgery. Neural navigation is most useful as an adjunct to other brain mappings techniques such as conscious mapping and electrocorticography in the resection of lesions in motor areas and fluent language. The use of intraoperative MRI can improve resection rates, quality of life, and survival in glioma patients.<sup>15</sup>

#### 8. Postoperative care

The incidence of postoperative complications within 30 days of tumor resection was as follows: stroke (2.1%), myocardial infarction (1.3%), death (2.7%), infection (2.4%) , and the need for revision surgery (6.6%). Assisting early discharge from hospitals for cancer patients accelerates chemotherapy and/or radiotherapy and other treatments, potentially improving patient outcomes by reducing the period time between surgery and the resumption of daily activities. The bladder catheter should be removed on the first postoperative day or as early as possible. Postoperative artificial nutrition is usually not required in patients unless the patient is in a prolonged coma (>7 days).<sup>15</sup>

### **Radiotherapy**

Radiotherapy is a complementary part of the comprehensive management of p-GBM. This is more because the role of chemotherapy is not yet clear in these patients, unlike their adult counterparts. Typically, radiotherapy doses ranging from 50 to 60 Gy are fractionated over 5-6 weeks. Experiments on hypo/hyper fractionation of the total dose did not show better results. It is routinely used in children older than 3 years. The main reason why it should not be used before 3 years of age is that RT can cause adverse neurocognitive complications due to its deleterious effects on the developing brain. In addition, it is believed that tumors in the early years of life are rather slow and less responsive to irradiation.<sup>6</sup>

## Chemotherapy

Many chemotherapy regimens can be used for *LGG*, *HGG*, and recurrent gliomas. Chemotherapy appears to be a less effective modality when examined alone, offering a slight improvement in survival.<sup>8</sup> However, chemotherapy can be used because it has a cumulative effect which, when combined with other management strategies, can provide a dramatic increase in survival up to three times.<sup>18</sup> CCNU (*chloroethyl-cyclohexyl nitrosourea*) and *vincristine* are the main chemotherapeutic agents used with great effect in clinical trials, and PCV (*procarbazine, lomustine, and vincristine*) have also been reported to improve survival in pediatric glioma cases. *Temozolomide* (TMZ) is a standard chemotherapy modality that appears to increase survival by approximately 2 months in adults, but has failed to demonstrate a survival benefit in a pediatric trial. Chemotherapy with stem cell transplantation is a new modality in treating *HGG*, although its advantages have not been established over other treatment modalities.<sup>8</sup>

## Conclusion

(GBM) is a malignant brain tumor that can occur in children and can grow and spread rapidly caused by both genetic and environmental factors. In children, central nervous system tumors are the most common, with 3-15% being glioblastomas. Glioblastoma usually presents with non-specific symptoms and lasts a short duration of several months.

GBM suffered by a young patient with a good clinical condition. The treatment is maximal resection followed by radiotherapy and adjuvant temozolamide given concurrently and after radiotherapy. The target volume and standard dose of radiation is 60 Gy in 30 administration fractions. In addition, the prognosis is also poor with high morbidity and mortality to improve the patient's quality of life, effective therapy is needed. Therapy can be in the form of surgery, radiotherapy, or chemotherapy.

## Conflict of Interest

There is no conflict of interest

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