Pediatric Low Grade and High Grade Gliomas: Diagnosis, Treatment, and Follow Up

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Independent Study and Mentorship

Contents

Abstract

Pediatric low- grade gliomas account for approximately 30-50% of all central nervous system (CNS) tumors. Low-grade gliomas comprise of astrocytic or oligodendrogliomas both of which can differ in clinical progression, however, most low grade gliomas do not go through malignant transformation due to the slow growth of low grade tumor cells. In contrast, optic pathway and brain stem low grade gliomas tend to have minimal potential for gross total resection due to the location of the tumor near underlying healthy tissue. High grade pediatric gliomas are present in 8-12% of all pediatric CNS tumors. Contrary to scientific belief, pediatric high grade gliomas (HGG) distinctly differ from adult HGG. The makeup of the underlying molecular, biological, and histological data differs between the two tumors. However, the detriments caused by both are a result of aggressive malignant lesions in the CNS with very few patients receiving long term survival. Low and high grade gliomas tend to be treated with resection in addition to coupled usage of chemotherapy and radiation therapy in order to achieve the best clinical results. This report analyzes the surgical and nonsurgical treatment options for both high grade and low grade gliomas comprising of low grade astrocytomas, optic pathway gliomas, ependymoma, glioblastoma multiforme, and anaplastic astrocytomas. Prior to creating a treatment plan, clinical trials were assessed to assess the best quality care for each type of tumor.

Keywords: Low-Grade Gliomas, High Grade Gliomas, Astrocytomas, Ependymoma

Introduction

Gliomas are the most common type of tumor in both adults and children. Brain and CNS tumors are impacting around 700,000 Americans and account for the most common type of pediatric cancers with an estimated 28,000 children living with brain tumors in the United States (National Brain Tumor Society, 2015). Gliomas are the abnormal growth of glial cells which are brain cells responsible for insulating and supporting neurons. Specific tumors are categorized by grades based on the division intensity of the cancer cells. Low grade gliomas are categorized as tumors in which tumor cells divide relatively slowly and the progression of the tumor growth is slower than a high grade tumor, which in turn inhibits the tumors from becoming metastatic or spreading to other areas of the CNS. High grade tumors resemble division of tumor cells in an aggressive manner instiageing more vulnerability towards becoming metastatic and malignant. Around 60% of all brain tumors tend to be located in the infratentorial brain which is in the lower part of the brain consisting of both the cerebellum and brainstem. The area of the brain controls mobility and balance due to the brain stem's prominent responsibility in controlling involuntary muscle movements, sensory movements, and passing of information. The supratentorial brain controls thinking, cognition, problem solving, decision making, vocals, etc.High grade gliomas are most prevalent in the supratentorial region when brainstem lesions are not accounted for. Around 35-50% of these tumors occur in the cerebral hemispheres which impact the cognition areas of the brain depending on the amount of pressure enforced on surrounding tissue of the tumor (Fangusaro, J., 2012). Low grade pediatric tumors are the most prevalent in the cerebellum where low grade cerebellar tumors account for 15-25% of all pediatric CNS tumors (Sievert, A. J., & Fisher, M. J., 2009). The majority of pediatric gliomas

are benign, slow growing lesions, rarely going under malignant transformation, and thus being classified as Grade I or II tumors based on the World Health Organization (WHO). However, a portion of pediatric gliomas can be caused by the aggressive division of tumor cells hence being classified as a WHO Grade III or IV tumor. The rapid progression of such tumors can yield lethal results within the span of a few months or a year with many tumors remaining incurable. Despite recent non-surgical and surgical efforts, such tumors seem to be recurrent with often chronic but not necessarily life threatening repercussions. Although malpractice remains common in such complex fields of surgeries, the combined efforts of neurosurgeons, radiation therapists, and oncologists remains to provide quality care to a patient by prolonging the survival rate as much as possible. With unprecedented progress in the last decade or so, new technological advancement are developing to counteract the detriment caused by tumors and the rate of malpractice in neurosurgical fields in which resection of a tumor is not always the most practical approach to treating a tumor.

Diagnosis

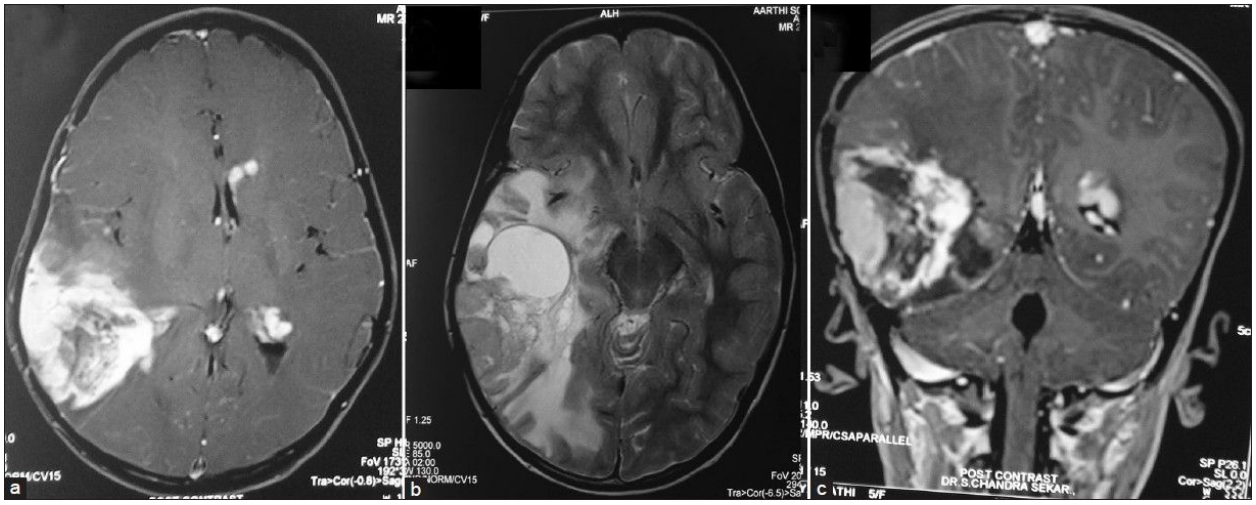
Clinical Diagnosis

Despite clinical diversity in biological character, pediatric gliomas tend to reflect similar visuals in comparison to adult gliomas in visuals on magnetic resonance imaging or computed tomography machines. However similar to most medical diagnoses, pediatric cancer diagnosis begins with a brief clinical diagnosis by a health professional. The doctor analyzed the historic trend in the patient's family history of cancers and tumors as cancer tends to run in familial history. Doctors will conduct a physical and neurological examination to assess the CNS for any abnormalities mental status, mobility, mental coordination, or cognition.

Imaging Techniques

The type of brain tumor is diagnosed through a process of scrutinizing glial cells under a microscope in order to evaluate the type of tumor based on the intensity of cell division, a process known as histology. Pediatric brains are primarily evaluated through the use of a computed tomography machine that takes x-rays of the brain at varied angles to diagnose the tumor. In order to improve the quality of the images, doctors may inject a dye into the patient's vein. A tumor appears to be a mass or a lesion of abnormal tissue growth and when such a mass is found, the doctor may conduct an MRI or a magnetic resonance imaging. A MRI uses a magnet and a chemical called gadolinium which is injected into the vein to illuminate the regions of the brain. The primary purpose of scans are to diagnose the tumor based on preclinical symptoms including headaches and vomiting especially during earlier hours of the day. Due to a prominence of gliomas in the infratentorial region, a common symptom may be a obstruction in

proper mobility including trouble walking and staying awake. If a infant is diagnosed with a glioma, the patient's head may be visibly larger or the first sign may be seizures caused by the tumor. Despite current technological advancements, diagnosing tumors is arduous due to the lack of prevalent symptoms caused by the tumor itself. In most medical cases, the tumor itself does not cause the symptoms, other than seizures, but rather the pressure applied on surrounding tissue can instigate pain or other preclinical symptoms.



(Juliette Siegfried, 2012). *Figure 1 indicating a glioblastoma multiforme with a variegated appearance with white areas, yellow necrotic tissue, hemorrhage regions, and cystic areas. The tumor indicated a WHO Grade IV tumor on a histological scale. Median survival 1 year, 5 year survival <5%.*

Biopsy

The final and most accurate resort for diagnosing brain tumors is in conducting a biopsy. Conducting a biopsy requires the resection of a piece of the tumor in order to visibly scrutinize tumor cells under a microscope to determine the histology of the tumor. Majority of biopsies require the total gross resection of the tumor in order to diagnose the type of tumor based on the

scrutiny or technological machines. In certain circumstances, the tumor may be considered inoperable due to the placement of the tumor in the brain especially in the optic pathway or the brain stem. In such cases, the tumor cannot be resected and tumor diagnosis will primarily be based on MRI or CT scans.

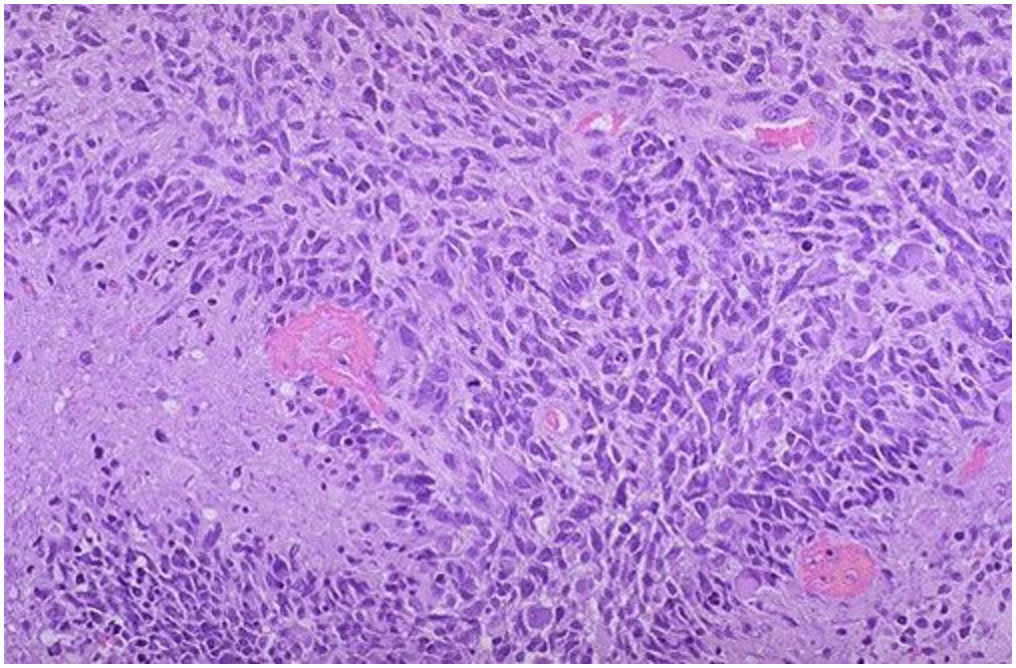


Figure 1.1 indicates a high grade glioblastoma multiforme with intense cell division. Densely packed small cells may indicate a glioblastoma with an oligodendroglioma component indicating a obstruction in the optic pathway.

Treatment

Treatment of brain tumors is ultimately individualized based on the findings of a pediatric oncologist, location of the tumor, the average survival rate, the urgency of the case, and prevalent symptoms of pain or emotional concerns. The primary treatment options for tumors include surgery, radiation therapy, and chemotherapy. Despite individualized treatment plans, the treatment for specific tumors can be assessed based on clinical symptoms, location, size, tolerance to medications, grade of the tumor, and symptoms.

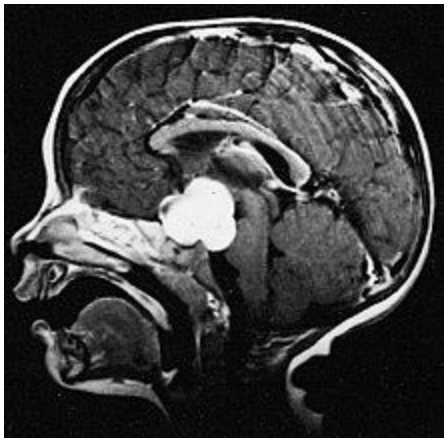
Juvenile Pilocytic Astrocytoma

A Juvenile Pilocytic Astrocytoma is a benign lesion that on most occasions is not metastatic and the tumor cells stay in relatively the same area. The tumors a result of the abnormal growth of glial cells and more specifically astrocytes which are star shaped brain cells responsible for protecting nearby neurons. A JPA is a grade one tumor, indicating that the progression of production of tumor cells is relatively slow in comparison to grade III or grade IV tumors such as glioblastoma multiforme and anaplastic astrocytomas. JPA tend to develop in the infratentorial brain, impacting the cerebrum. Thus, primary symptoms tend to be instability in mobility and inhibitions in movement.

Step 1: Diagnosis

Juvenile Pilocytic Astrocytoma are diagnosed through a combination of CT scans MRI scans to develop a cross-sectional 3-D image of the brain to graph the relative location of the

tumor. For children, constant exposure to radiation can be detrimental and it is the both the doctor's and the parent's responsibility to limit the amount of radiation exposure. The lesion must be checked with a visual field test that test the patient's central vision which assesses how much the patient can see looking straight forward. A neurological exam must also be conducted in order to test for obstruction in mobility of the patient.



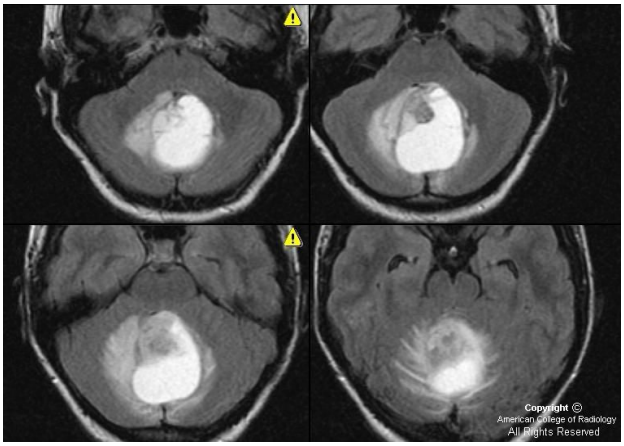


Figure 2.1 and 2.2 show Juvenile Pilocytic Astrocytoma in the hypothalamic region of the brain. Low grade tumors in the infratentorial brain impacting areas of mobility.

Step 2: Treatment

Treatment for JPA are primarily based on the grade of the tumor, the location, size, and degree of malignancy. The tumors pictured above indicate low grade gliomas that can obstruct the optic pathway due to the low placement of the tumor. Tumors are to be treated by total gross resection of the tumor with attempts to remove the most amount of the tumor as possible. The

tumor can be further used for biopsy to address the specific type of tumor and decide on post operative treatment.

JPA tend to be low grade tumors and postoperative steps would be a combination of anticancer drugs and chemotherapy. Chemotherapeutic and therapeutic agents can be used post surgery to kill the remaining tumor tissue without harming surrounding area. Parents must be aware of the biopsy results prior to discussion on the treatment plan and the results of the treatment plan which is ultimately known as informed consent.

Contrary to popular belief, all tumors should not be treated using radiation therapy post surgery, especially in children under the age of five. Often, in the case of radiation therapy, the detriments outweigh the benefits as radiation therapy can inhibit the cognition and thinking skills of the child in the long run. Adjuvant chemotherapy or repeat resection can be used on children that are younger or infants while radiation therapy should be reserved for treatment in older children.

JPA can occur near the optic nerve, thus making them qualified to be treated with proton therapy which is a form of an external beam radiation using protons rather than x-rays. Proton therapy can destroy tumor cells at a low intensity and limits the amount of radiation exposure. Prior to consulting a pediatric oncologist or neurosurgeon, parents are recommended to assess the biopsy of the patient in order to provide the safest treatment option for the patient. Radiation therapy may be minimally invasive, however, the longer terms disadvantages can brings long terms detriments to the patient's ability to communicate and live a healthy life.

Prior to removing the tumor, parents and doctors should hold attention to the growth of the tumor. If a tumor is benign, does not obstruct any nearby vital areas, and does not grow any

further, then surgery may not be needed and would rather cause detriments than advantages. However, if the tumor is applying pressure to surrounding tissues or the brain itself, then consult a physician immediately.

Ependymomas

Pediatric ependymomas are malignant tumors that occur as a result of abnormal growth of ependyma cells which are part of the cerebrospinal fluid that line the ventricles and passageways of the brain and spinal cord. All forms of ependymoma are considered cancer, however, contrary to most malignant tumors, these do not spread to other areas of the body on the majority of medical cases.

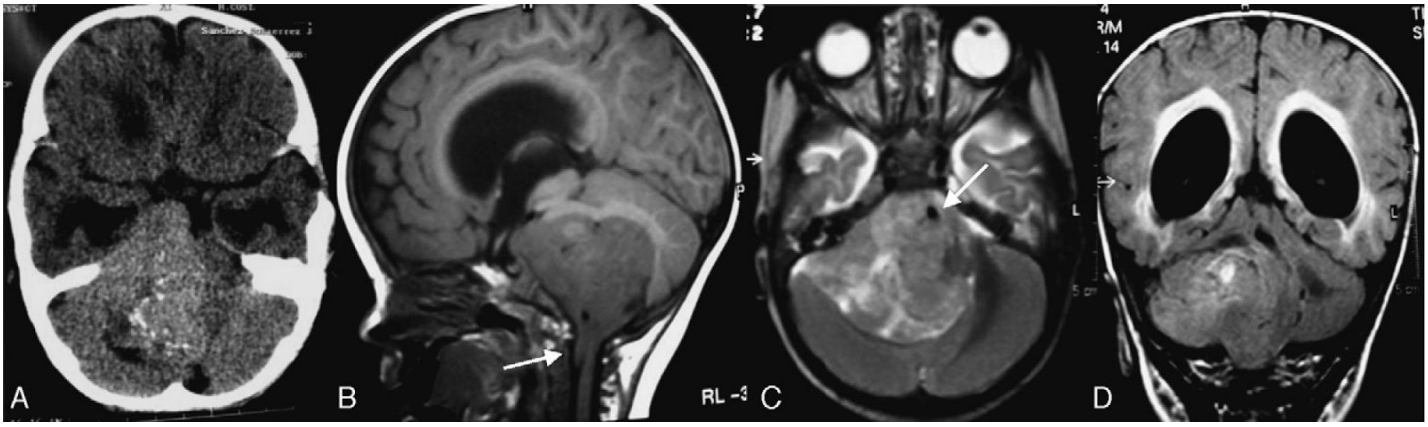


Figure 3.1 Classified as an anaplastic ependymomas which is a grade III brain tumor in the infratentorial of posterior fossa region. (Martínez León, M., Vidal Denis, M., & Weil Lara, B., 2012)

Step 1: Diagnosis

The diagnosis process differs depending on the type of ependymoma including low grade and high grade gliomas. Anaplastic ependymoma are malignant tumor that have a histological

representation of a fast growing tumor in the brain. Ependymoma tend to occur in the fourth ventricle of the brain affecting the cerebellum and the brain stem.

Diagnosis depends on primary evaluations through physical examinations, neurological examinations, MRI and gadolinium, and lumbar puncture. Lumbar puncture is done due to the metastatic nature of these malignant tumors and their ability to spread to other regions in the CNS. The lumbar puncture allows for removing cerebrospinal fluid from the spinal canal in order to assess if there is any resemblance of tumor cells or protein and glucose. A higher concentration of protein and a lower concentration of glucose in the CSF can indicate a tumor.

Ependymomas are the most prevalent in the posterior fossa or infratentorial brain. The tumors are divided into two subcategories including EPN-FPA which is characterized by a largely balance genomic profile with a higher prevalence of the chromosome 1q gain and show biological structure for an increase in expression for genes and proteins which is associated with poor prognosis. In contrast, the EPN-FPB tumors occur in older children and adults both of which show a more favorable prognosis with multiple cytogenetic abnormalities involving chromosomes or chromosomal arms.

Step 2: Biopsy

Diagnostic tests that show results for an ependymoma must evaluated early to minimize detrimental effects. To conduct a biopsy for an ependymoma, part of the skull has to be removed in a process called craniotomy. Using a needle, the doctor will remove part of the brain tissue and a pathologist will examine the tumor cells underneath a microscope to assess how much of the tumor can safely be removed.

Parents must be aware of medical malpractice and ensure that children are not going through surgery if it is not necessary. Misdiagnosis is also a form of medical malpractice and parents should be aware of every biopsy result especially in the cases of malignant brain tumors such as anaplastic ependymomas.

Poor prognosis is the most pertinent for pediatric ependymomas when the tumor is expressing the enzymatic subunit of telomerase, a ribonucleoprotein responsible for elongating chromosome during replication to at the 3' end to ensure the greatest longevity of of chromosomes.

Step 3: Surgery

Based on the degree of malignancy, ependymoma cannot be removed completely from the brain or the spinal canal due to the obstruction they cause to surrounding tissue. Ependymomas can occur in the cerebellum (controls thinking learning, speech, emotions, voluntary movement), cerebellum (movement, balance), Brainstem (breathing, heartbeat, speech), or the spinal cord (sensory feelings and structural support). The amount of tumor that can be resected is primarily based on the location, size, and grade of malignancy. The higher the grade of the tumor, the more urgent clinical care should be. Anaplastic ependymomas tend the be the highest grade for these specific types of tumors. Surgery on ependymoma are, on most occasions, subtotal resections

Step 4: Alternate Treatment Options

3-dimensional conformal radiation therapy (3D-CRT) is a process in which a combination of CT scans and MRI scans can be used to develop a three dimensional model of the tumor and the surrounding tissue to ensure that radiation beams are targeted

specifically at the tumor cells and healthy tissue is not affected. This form of surgery is minimally invasive and a persistent form of surgery in children brains due to the lack of area to surgically remove a tumor. Stereotactic radiosurgery can also be used to prevent ependymomas from becoming recurring tumors. Stereotactic radiosurgery allows for tumor cells to be destroyed with the usage of one radiation beam pointed directly at the tumor and not any surrounding tissue. In children, radiation should always be in low doses unless the tumor is life threatening and the benefits lie in radiation exposure. However on most occasions, radiation therapy can be detrimental due to side effects of nausea, vomiting, headaches, and possible obstruction of surrounding areas.

Glioblastoma Multiforme

Glioblastoma Multiformes (GBMs) are high grade gliomas which are results of the unruly division of supportive cells in the brain known as glial cells. These tumors are aggressive lesions that attack surrounding healthy tissue and can be difficult to treat. Glioblastomas occur in the cerebral regions of the brain which control speech, movement, and sensory feelings. Most GBMs are a result of genetic syndromes and occur the most in children of ages five to nine.

Step 1: Diagnosis

Similar to every other primary brain tumor, tumors can be diagnosed using physical examinations, neurological examinations, and imaging techniques. In addition to the normal MRI and CT scans, magnetic resonance spectroscopy which allows for a distinguishment to be made between normal tissue and tumorous tissue. Positron emission tomographic can indicate the glucose levels because tumors use glucose at a faster rates in comparison to regular tissue which indicates that a brain with a tumor would have lower glucose levels.

After a patient is diagnosed, their individualized treatment plan will be made based on imaging results and in some cases biopsy results as well. Due to the aggressiveness of these types of tumors, however, biopsies cannot always be done.

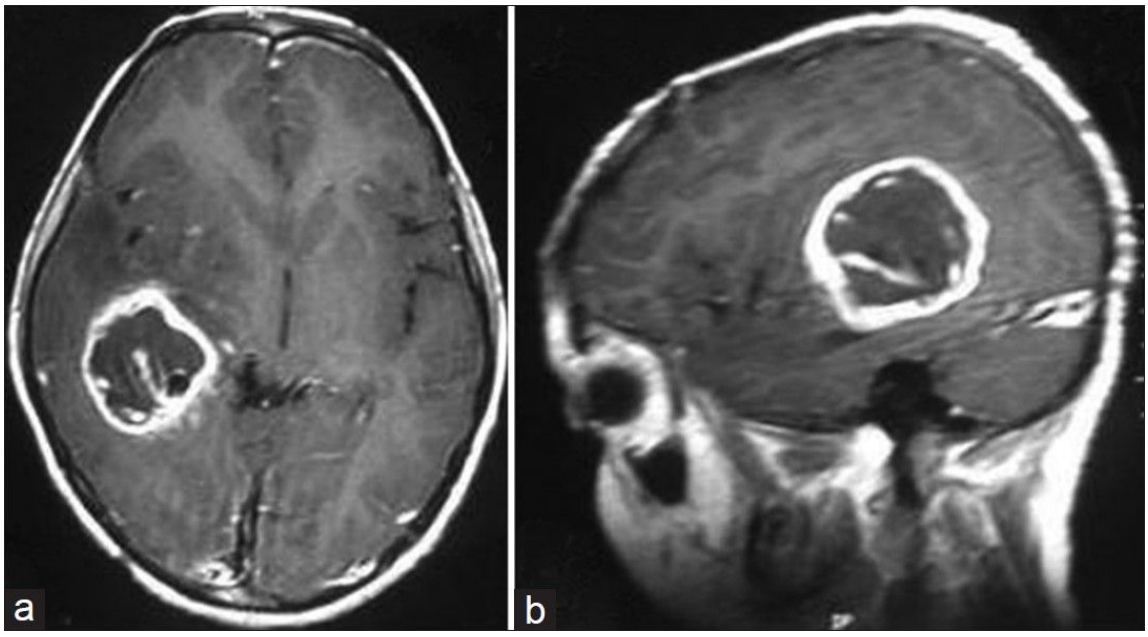


Figure 3.2 (Mahapatra, A., Borkar, S., Lakshmiprasad, G., Subbarao, K., & Sharma, M., 2013). Pediatric Glioblastoma Multiforme. High grade glioma with a high intensity division of tumor cells as seen in the CT scan.

Step 2: Surgery

Surgery techniques are primarily the first step to treat any tumor in which surgeons can use techniques such as intraoperative MRI in which surgeons can visualize a three dimensional model during operations. Due to GBMs being classified as high grade gliomas, they cannot be removed completely surgically due to the impact they have on underlying healthy tissue. The more amount of tumor that can be removed, the greater chance for survival.

Step 3: Radiation Therapy

High energy waves are transmitted through the body through one radiation beam of high intensity or several or low intensity. Radiation therapy allows for the tumor to shrink and the surrounding area to be treated without affecting the healthy tissue. This allows for the increase in chances for survival in the high grade gliomas. Intensity modulated radiation

therapy can be used on GBMs due to technology's ability to give high intensity radiation to the specific tumor and give low intensity exposure to the surrounding healthy tissue.

Step 4: Chemotherapy

Children with GBM cannot necessarily have a better survival rate due to chemotherapy drugs, however, they can inhibit the further growth of the cancer cells or yield in any recurrent tumors. Chemotherapy drugs also come with side effects that doctors should be mindful of when preserving treatments to children below the age of twelve. Chemotherapy drugs, however, do not always work on children due to intensity of drugs and the routine that must be followed which a child may not be able to accustom to as they are still developing.

Follow-Up

In any medical practice, follow-up is vital to the healthy recovery of a patient and to ensure the growth of a pediatric patient under normal circumstances. Neurosurgeons are responsible for following up with a pediatric patients up to their adulthood or teenage years depending on the age of the patient when he or she was diagnosed. Malpractice is often prevalent due to a lack of follow up which results in recurrent tumors in the patient, which can often be overlooked or not noticed at all because a patient may think they are “cured”. An exchange of incorrect information on medical record is a violation of informed consent and can negatively affect the development of a patient, especially in pediatric patients who are constantly in their developing years.

Follow up should be both postoperative and life long for patients with a risk for multiple tumors and especially cancer patients. Post surgery, doctors should be following up with patients on a weekly basis and slowly progress to a monthly basis based on the patients needs. A part of medical practice is to ensure that the patients that leave the office don’t leave from medical practice. In such cases, tumors can come back with greater disadvantages and in a larger abundance which gives more of a reason for follow ups to be conducted. Malpractice often sprouts from the lack of administering postoperative and preoperative conditions which makes it important for both parents and the patients to be aware of the risks and the general treatment plan associated with the tumor they are diagnosed with.

A vital part in medicine is to make sure that the doctor, the patient, and the family of the patient are all aware of the medical treatment plans for the individualized treatment of the patient's tumor. Without doing so, patients risk fatal and life long obstructions in development that could cost a child's future. The purpose of such treatment plans and pamphlets is to ensure that guardians are aware of the circumstances their loved one is going through. Understanding clinical symptoms, biopsies, surgical treatment, and therapeutic management are all vital to the recovery of a patient. The goal of every medical institute is to provide their patients with the best possible care, however, it all starts right in the homes of patients who are willing to understand their treatment.

References

Brain Tumor Misdiagnosis - Cancer Spreading Tumors. *Medical Malpractice Center*. (2018). Medical Malpractice Center. Retrieved from http://malpracticecenter.com/misdiagnosis/brain-tumor/

Brain Tumor: Treatment Options | Cancer.Net. (2012). *Cancer.Net*. Retrieved from https://www.cancer.net/cancer-types/brain-tumor/treatment-options

Childhood Ependymoma Treatment. (2018). *National Cancer Institute*. Retrieved from https://www.cancer.gov/types/brain/patient/child-ependymoma-treatment-pdq

Childhood Astrocytoma Treatment. (2017). *National Cancer Institute*., Retrieved from https://www.cancer.gov/types/brain/patient/child-astrocytoma-treament-pdq

Fangusaro J. Pediatric High Grade Glioma: a Review and Update on Tumor Clinical Characteristics and Biology. *Frontiers in Oncology*. 2012;2:105. doi:10.3389/fonc.2012.00105.

Glioblastoma Multiforme | GBM - Dana-Farber/Boston Children's Cancer and Blood Disorders Center . (2018). *Danafarberbostonchildrens.org*. Retrieved 22 January 2018, from http://www.danafarberbostonchildrens.org/conditions/brain-tumor/glioblastoma-multiforme.aspx

Miller, T. (2016). *All About Pediatric Gliomas (Low and High Grade) | OncoLink*. Retrieved from https://www.oncolink.org/cancers/brain-tumors/all-about-pediatric-gliomas-low-and-high-grade

Sievert AJ, Fisher MJ. Pediatric Low-Grade Gliomas. *Journal of child neurology*. 2009;24(11):1397-1408. doi:10.1177/0883073809342005.