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Brain cancer: current concepts, diagnosis and prognosis

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Abstract: *Primary brain tumors occur in around 25,000 people a year, and 13,000 deaths in the United States. The incidence of CNS tumors in the United States, Israel, and the Nordic countries is relatively high; Japan and Asian countries have a lower incidence. Less developed countries have lower incidence of tumors due to undiagnosed tumor related deaths. Exposure to vinyl chloride or ionizing radiation is associated with brain tumors. Research studies have not shown link between cell phone or mobile radiation and brain cancer. WHO has classified mobile radiation on IARC, scale into Group B-possibly carcinogenic.Primary and secondary brain tumors present with similar symptoms, depending on the location of location, size, and rate of growth of tumor. Headaches as a result of intracranial pressure can be early symptoms of brain cancer. Other symptoms are tumor site specific that include, poor reasoning, memory, interpretation, loss of vision, poor balance, swallowing and heartbeat, and change in behavior. Diagnosis by computed tomography,magneticresonance, and tissuebiopsy. Treatment depending on neoplasm type, location and may be combined to give the best chances of survival. Surgery, radiation therapy and chemotherapy are the treatment of choice. Published research advocate that "lemongrass (Cymobopogon citratus) has compounds that present anti-cancer.Lemongrass also effective against cervical cancer and other types of cancer cells.*

Keywords: *Braintumor, Clinical presentation. Treatment and outcome*

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I. Introduction

Brain cancer or Brain tumor occurs when abnormal cells form within the brain[1].There are two main types of tumors: malignant or cancerous tumors and benign tumors[1].Cancerous tumors can be divided into primary tumor that starts within the brain, and secondary tumors that have spread from somewhere else, known as brain metastasis tumors[2].Primary brain tumors occur in around 250,000 people a year globally, making up less than 2% of cancers3].In children younger than 15,brain tumors are second only to acute lymphoblastic leukaemia as the most common form pf cance[4]r.Krishnatereya and associates in a series of 231 primary malignant brain tumors(PMBT) concluded that PMBT occur at 20-60 years of age, with male to female ratio of 2.3:1[5].In Australia the average lifetime economic cost of a case of brain cancer is $1,9 million,the greatest of any type of cance[6]r.The cause of most brain tumors is unknownUncommon risk factors include inherited neurofibromatosis,exposure to vinyl chloride,Epstein-Barr virus, and ionizing radiation[1]The evidence of mobile phones is not clear[3]. The most common types of primary tumors in adults are meningiomas (usually benign)and astrocytomas such as glioblastoma[2]..In children, the most common type is a malignant medulloblastoma[3].Symptoms vary depending on the part of the brain involved, headaches, seizures, problem with vision, vomiting, mental changes[2,1]. The headache is classically worse in the morning and goes away with vomiting[1].Diagnosis by computed tomography, magnetic resonance,and tissue biopsy[1,2].Treatment, surgery, radiation therapy and chemotherapy[2]. The manuscript reviews the clinical presentation, treatment and outcome of brain tumor.

II. Prevalence

Figures for incidence of cancers of the brain show a significant difference between more-less developed countries(the less developed countries have lower incidence of tumors of the brain)[7].This could be undiagnosed tumor-related deaths(patients in extremely poor situations do not get diagnosed, simply because they do not have access to the modern diagnostic facilities required to diagnose a brain tumor) and by deaths caused by other poorly-related causes that pre-empt life before tumors develop or tumor become life threatening. Nevertheless studies suggest that certain forms of primary brain tumors are more prevalent among certain groups of the population. The incidence of low-grade astrocytoma has not been shown to vary significantly with nationality. However, examining the incidence of malignant central nervous system (CNS)

tumors has shown some variation with national origin. Since high grade lesions arise low-grade tumors, these trends are worth mentioning. Specifically, the incidence of CNS tumors in the United States,Israel,and the Nordic countries is relatively high, while Japan and Asian Countries have a lower incidence. These differences probably reflect some biological differences as well as differences in pathologic diagnosis reporting[8].Worldwide data on incidence of cancer can be found at WHO(World Health Organization) and is chandelled by the International Agency for Research on Cancer(IARC) located in France[9].

For the United States in the year 2005,it was projected that there would be 43,800 new cases of brain tumors[10], which accounted for less than 1 percent of all cancers,2.4 percent of all cancerdeaths.And 20-25 percent ofpediatriccancers[11,12]. It is estimated that in the United States there are 13,000 deaths per year as a result of brain tumors[13]. Brain,other than CNS or intracranial tumors are the ninth most common cancer in UK (around 13,000 people were diagnosed in 2013),and it is the eight common cause of cancer death(around 5,200,people died in 2012[14]..

III. Contributory factor

Epidemiological studies are required to determine contributory or risk factors[5].Aside from exposure to vinyl chloride or ionizing radiation, there are no environmental factors associated with brain tumors.Mutations and deletions of so called tumor suppressor gene, such as P53, are thought to be cause of some forms of brain tumor[15].Inherited conditions, such as Von Hippel-Lidau disease, multiple endocrine neoplasia, and neurofibromatosis type 2 carry a high risk for the development of brain tumors16]. People with celiac disease have slightly increased risk of developing brain tumor [17].

Although studies have not shown any link between cell phone or mobile phone radiation and occurrence of brain tumor[18],the World Health Organization has classified mobile radiation on the IARC,scale into Group B-possibly carcinogenic[19].Discounting claims that current cell phone may cause brain cancer, modern, third generation phones emit on average, about 1% of the energy emitted by GSM(2G) phones that were in use, when epidemiological studies that observed a slight increase in the risk for glioma-a malignant type of brain cancer- among heavy users of wireless and cordless telephones were conducted[3].

IV. Clinical Manifestations

Clinical symptoms of brain tumors are broad. People with brain tumors will experience them no matter if the tumor is benign (not cancerous) or cancerous[20]. Primary and secondary brain tumors present with similar symptoms, depending on the location, size, and rate of growth of tumo[21]r.For example large tumors in the frontal lobe can cause changes in the ability to think. However, a smaller tumor in the area such as Werneke's area (small area responsible for language comprehension) can result in a greater loss of function [22]..

4.1. Presentation with Headaches: Headaches as a result of intracranial pressure can be an early symptoms of brain cancer[23].However, isolated headache without other symptoms is rarer, and other symptoms often occur before headaches become common[23].Certain warning signs for headache exist which make it more likely to be associated with brain cancer[23].These are defined by the American Academy of Neurology: abnormal neurological examination, headache worsened by Valsalvamaneuver,headache causing awakening from sleep, newheadache in older population, progressively worsening headache, atypicalheadachefeatures, or patient who do not fulfil definition of migraine[23].

4.2.Tumor site specific symptoms: The brain is divided into 4 lobes and each lobe or area has its own function[24].The tumor in any of these lobes may affect the area's performance. The location of the tumor is linked to the symptoms experienced but each person may experience something different[25]Frequent symptoms include:

a).Frontal lobe tumors contribute to poor reasoning, inappropriate social behavior, personalitychange, poorplanning, lowerinhibition, and decreased production of speech (Broca's area).

b).Temporal lobe: tumors in this lobe may contribute to poor memory, loss of hearing, difficulty in language comprehension(Wernicke's area).

c).Parietal lobe: Tumors here may result in poor interpretation of language, decreased sense of touch and pain, and poor spatial and visual perception.

d).Occipital: damage in this lobe may result in poor or loss of vision.

e).Cerebellum:Tumors in this area may cause poor balance, muscle movement and posture.

f).Brain stem: Tumor on this can affect blood pressure, swallowing and heartbeat.

4.3. Change in behavior: Despite the personality and behavior changes that occur in people with brain tumors, little research on such changes has been done24]. A person's personality may be altered due to the tumor damaging lobes of the brain. Since the frontal, temporal and parietal lobes[21],,control inhibition, emotions

,mood ,judgement, reasoning, andbehavior, a primary or secondary tumor in this region can cause inappropriate social behavior[27],temper tantrums, laughing, at things which merit no laughter and even psychological symptoms such as depression and anxiety[25]. Personality changes can have damaging effects such as unemployment, unstable relationship, and lack of control[24].

V. Diagnosis

Most of the brain is separated from the blood by the blood brain barrier (BBB), which exerts a restrictive control to which substances are allowed to pass. Therefore, many tracers that reach tumors in the body very easily would reach brain tumor once there is disruption of the BBB. Thus the disruption the BBB, which can detected by MRI and CT, is regarded as the main diagnostic indicator for malignant gliomas, meningioma's, and brain metastases[28].Although there is no specific clinical symptoms or sign for any brain tumors, the presence of combination of symptoms and the lack of corresponding clinical indications of infections or other causes can be an indication to direct diagnostic investigation towards the possibility of an intracranial neoplasm. Brain tumors have similar characteristics and obstacles when it comes to diagnosis and therapy with tumors located elsewhere in the body. However, they create specific issues that follow closely to the properties of the organ they are in[28]

The diagnosis will start by taking a medical history noting medical antecedents, and current symptoms. Clinical laboratory investigations will serve to exclude infections as the cause of the symptoms Examination in this stage may include the eyes, otolaryngological(or ENT) and electrophysiological examinations. The use of electroencephalography (EEG) often plays arole in the diagnosis of brain tumor. Swelling or obstruction of the passage of cerebrospinal fluid (CSF) form the brain may cause (early) signs of increased intracranial pressure which translates clinical into headaches, vomiting or altered state of consciousness, and in children changes in the diameter of the skull and bulging the fontanelles. More complex symptoms such as endocrine dysfunction should alarm doctors not to exclude brain tumors [28].

A bilateral temporal visual field defect(due to compression of the optic chiasm) or dilation of pupil, and the occurrence of either slowly evolving or the sudden onset of focal neurologicsymptoms, such as cognitive and behavioral impairment(including impaired judgment, memoryloss, lack of recognition, spatial orientation disorders),personality or emotional changes, hemiparesis, hypoesthesia, aphasia, ataxia, visual field impairment, impaired sense of smell, impairedhearing, facialparalysis, doublevision, or more severe symptoms such as tremors, paralysis on one side of the bodyhemiplegia, or(epileptic) seizures in patient with a negative history for epilepsy, shouldraise the possibility of brain tumo[28]r.With medical examination, computedtomography, and magnetic resonance imaging facilitates diagnosis[1,2].

5.1. Pathologic diagnosis and tumor classification: Tumors have characteristics that allow determination of malignancy and how they will evolve, and determining these characteristics will allow the medical team to determine the management plan:

(a) Anaplasia or differentiation of cells and their orientation to one another and blood vessels, a characteristic of anaplastic tumor tissue.

(b)Atypia: an indication of abnormality of a cell(which may be indicative for malignancy).Significance of the abnormality is highly dependent on context.

(c)Neoplasia: the (uncontrolled) division of cells. As such, neoplasia is not problematic but its consequences are: the uncontrolled division of cells means the mass of neoplasm increases in size, and in a confined space such as intracranial cavity this quickly becomes problematic because the mass invades the space of the brain pushing it aside, leading to compression of brain tissue and increased intracranial pressure and destruction of brain parenchyma. Increased intracranial pressure (ICP) may be attributable to the direct mass effect of tumor,increased blood volume, or increased cerebrospinal fluid(CSF) volume, which may, in turn have secondary problems.

(d)Necrosis: the(prenature)death of cells, caused by external factors such as infection, toxin or trauma. Necrotic cells send the wrong chemical signals which prevent phagocytes from disposing of the dead cells, leading to buildup of dead tissue, cell debris and toxins at or near the site of necrotic cells[29].

(e)Arterial and venous hypoxia, or the deprivation of adequate oxygen supply to certain areas of the brain, occurs when tumor makes use of blood vessels for its supply of blood and the neoplasm enters into competition for nutrients with the surrounding brain tissue. More generally a neoplasm may cause release of metabolite and products (e.g.,free radicals, altered electrolytes, neurotransmitters),and recruitments of cellular mediators (e.g., cytokines) that disrupt normal parenchymal function[29].

Secondary tumors of the brain are metastatic and have invaded the brain from cancers from cancers originating in other organs. This means that a cancerous neoplasm has developed in other organ elsewhere in the body and that cancer cells have leaked from the primary tumor and then entered the lymphatic system and blood vessels. They then circulate through the bloodstream, and are deposited in the brain. Secondary brain tumors are

more common in the United States there are about 170,000 new cases every year. Secondary tumors are the most common cause of tumors in the intracranial cavity. The skull bone structure can also be subject to a neoplasm that by its very nature reduces the volume of the intracranial cavity, and can damage the brain [30].
World Health Organization (WHO) grading system is commonly used for astrocytoma. Established in 1993 in an effort to eliminate confusion regarding diagnosis, the WHO system established a four tiered histologic grading guideline for astrocytomas that assigns a grade from 1-4, with 1 being least aggressive and 4 being more aggressive. A primary tumor is one that has started in the brain, as opposed to a metastatic tumor, which is something that has spread to the brain from another part of the body [31].The incidence of metastatic tumors are more prevalent than primary by 4:1 [32].Tumors may or may not be symptomatic some tumors are discovered because the patient has symptoms, others show up incidentally on an imaging scan, or at an autopsy. The most common primary brain tumors are :[33].
(i)Gliomas (50.4%),
(ii)Meningioma's (20.8%),
(iii) Pituitary adenomas (15 %),
(iv)Nerve sheath tumors.
These common tumors can also be organized according to tissue of origin [34].:In children:Pilocytic Astrocytoma(PCA)-tissue: Astrocytes,Ependymoma,and Medulloblastoma-tissue,Ependyma ,and Neurons.In addults- Glioblastomsa Multoforme (GMB),Oligodendro glioma, and Meningioma, tissue: Astrocytes, Oligodendrocytes, and Meninges.

VI. Treatment

Given the location of primary solid neoplasms of the brain in most cases a" do- nothing "option is usually not presented. The various types of treatment are available depending on neoplasm type location and may be combined to give the best chances of survival.Survival rates in primary brain tumors depend on the type of tumor,age,functional status of the patient,the extent of surgical tumor removal and other factors specific to each case[35].

6.1.Surgery: complete or partial resection of the tumor with objective of removing as many tumor cells as possible.Many meningiomas,with the exception of some tumors located at the skull base, can be successfully removed surgically. Most pituitary adenomas can be removed surgically, often using a minimally invasive approach through nasal cavity and skull base(trans nasal, trans spheroidal approach).Larger pituitary adenomas require craniotomy(opening skull) for their removal .Radiotherapy, including stereotactic approaches, is reserved for inoperable cases[36].

Several current research studies aim to improve the surgical removal of brain tumors by labeling tumor cells with 5-aminolevulinic acid that causes them to fluoresce. Postoperative radiotherapy and chemotherapy are integral parts of therapeutic standard for malignant tumors. Radiotherapymay also be administered in cases of "low grade "gliomas when significant tumor burden reduction could not be achieved surgically. Multiple metastatic tumors are generally treated with radiotherapy and chemotherapy rather than surgery and the prognosis in such cases is determined by the primary tumor, and is generally poor[37].

6.2. Radiotherapy: The most commonly used treatment for brain tumors; the tumor is irradiated with beta,x-rays or gamma rays. The goal of radiation therapy is to kill tumor cells while leaving normal brain tissue unharmed. In standard external beam radiation therapy treatment of standard dose"fractions" of radiation are applied to the brain. This process is repeated for a total of 10-tp 30 treatment. Radiotherapy is a treatment method that uses computerized calculations to focus radiation at the site of the tumor while minimizing the radiation dose to the surrounding brain. Radiosurgery may be an adjunct to other treatments, or it may represent the primary treatment technique for some tumors. Forms used include stereotaxicradiosurgery, such as Gamma knife,Cyber knife or Novalis Tx radiosurgery [38].

6.3.Chemotherapy: The treatment option for cancer, however, it is not always used to treat brain tumors as the blood-brain barrier can prevent some drugs from reaching the cancerous cells. Patients undergoing chemotherapy are administered drugs designed to kill tumor cells. Although chemotherapy may improve overall survival in patients with most malignant primary brain tumors, it does so in only about 20 percent of patients.UCLA Neuro-0ncology publishes real- time survival data for patients with diagnosis of glioblastoma multiforme.They are only institution in the United States that displays how brain tumor patients are performing on current therapies. They also show a listing of chemotherapy agents used to treat high grade glioma tumors [39].In addition to chemotherapy, a shunt may be used to relieve symptoms caused by intracranial pressure, by reducing the build-up of fluid(hydrocephalus) caused by the blockage of free flow of cerebrospinal fluid[40].

6.4. Complementary and alternative medicine(CAM): A study published in the Journal of *Advanced Pharmaceutical Technology* and the Journal of *Pharmacognosy Communications* in 2013 revels that "lemongrass(*Cymobopogon citratus*)(Serai,Malay) is loaded with key nutrient compounds that present powerful

antibacterial, antifungal,anti-inflammatory and anti-cancer potential. Study also reveals that lemongrass was also effective against cervical cancer (as well as several other types of cancer cells)[41].

VII. Outcome and survival

Outcome or prognosis of brain cancer depends on the type of cancer diagnosed.Medulloblastoma has good prognosis with chemotherapy radiotherapy, and surgical resection while glioblastoma multiform has a median survival of only 12 months even with aggressive chemotherapy and surgery. Brainstem gliomas have the poorest prognosis of any form of brain cancer, with most patients dying within one year, even with therapy that typically consists of radiation to tumor along with corticosteroids. However, one type focal brainstem gliomas in children, seems open to exceptional prognosis and long term survival has frequently been reported [42].

VIII. Conclusion

Brain tumor is divided into primarytumor that starts in the brain and secondary tumor that has spread from other part of the body. The outcome depends on how far the tumor has spread at the time of presentation. Focal brainstem gliomas in children and Medulloblastoma in adults has good prognosis with surgery, chemotherapy and radiotherapy.

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