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Review Article

A Brief Intro to Brain Tumor, Cause, Spread, Surpassing of BBB, Effects on CNS, Diagnosis, Treatment, and Proliferation in Community

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ABSTRACT

Brain tumor is an accumulation of abnormally growing cells in the brain. The authors have covered in detail about formation, types of brain tumors in different tissues of the brain causing severe discomfort for the patient. A brief discussion between brain tumor and leptomeningeal disease is also presented in the article. A combination of surgery, radiation, and chemotherapy treatment improves the prognosis for leptomeningeal disease. Some tumor types are especially sensitive to chemotherapy injected directly into the cerebrospinal fluid, either by lumbar puncture ("spinal tap") or through a surgically implanted device called an Ommaya. Detailed effects of malignancy in brain on central nervous system have been covered in the article. The spread of lump and its expectancy in population have been covered in the research. Authors have also described the effects of lump on the other organs of the body and how lump is spread to other parts and tissues of body. The main part of the research project covers field work describing how myeloma is identified using axial tomography. Article also covers the use of Brachytherapy for the treatment of melanoma. Radiotherapy for treatment of tumors is also expressed in the article.

Keywords: Blood-Brain Barrier (BBB); Leptomeningeal; Colliculi; Radiotherapy; Chemotherapy; Ommaya reservoir

INTRODUCTION

No one is ready to hear a sentence by its physician "it's a brain tumor". Brain tumor is a cluster of abnormal cells that grows out of control in brain. Brain tumors are most lethal type of cancer which is difficult to manage due to inherent suboptimal bioavailability of the chemotherapy agent at tumor site. Leptomeningeal disease is when the cancer cells spread to fluid surrounding the brain cells instead of brain tissues itself. Brain tumors may form within the cells of brain or can be a metastatic tumors the origin of which is in other parts of body and may affect the cells of brain resulting in defects in the functioning of central nervous system. Glioblastoma is although a primary tumor but it's the most lethal of all. Some tumors may be benign meaning that they are not cancerous and just the abnormal outgrowth of the tissues being affected by the lump. While others are malignant tumors that may produce within the brain (primary tumors) or have origin in other body tissues and through their malignancy, affect the brain tissues (secondary tumors). Malignant tumors are cancerous in nature (Figures 1 and 2).

LITERATURE REVIEW

The main point which arises here is that in the presence of a Blood-Brain Barrier (BBB) how does a tumor become cancerous? How do malignant tumors breach the BBB and affect other body organs and how do secondary tumors from their origin affect the brain tissues? Unfortunately, there is no definite answer for that now because Scientists have yet not succeeded to answer this question that answer would also be a response and a treatment to stop and limit the spread of brain tumors to a specific area. But there are some speculations and theories and research works that suggest that tumor progression leads to BTB structural changes including neuronal death, astrocyte end-feet displacement (from primary and metastatic cancer cells), and heterogenous pericyte and astrocyte subpopulation, all of which can reduce the barrier functions of CNS endothelium [1].

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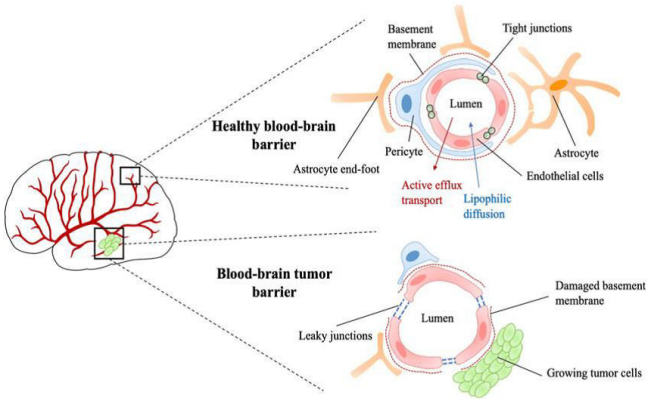

Figure 1: Blood Brain and Blood (BBB) tumor barrier.

Classification of brain tumor

More than 120 types of tumors have been identified with their names based on the part of the brain they are invading.

There are two types of brain tumors depending on their origin.

Primary

- Within brain.
- Cured viva surgery.
- Benign in nature.

Secondary

- To the brain from a different part of the body,
- Usually not curable.
- Cancerous in nature.
- Especially from lungs, breast, skin (Melanoma), colon, kidney, thyroid gland.

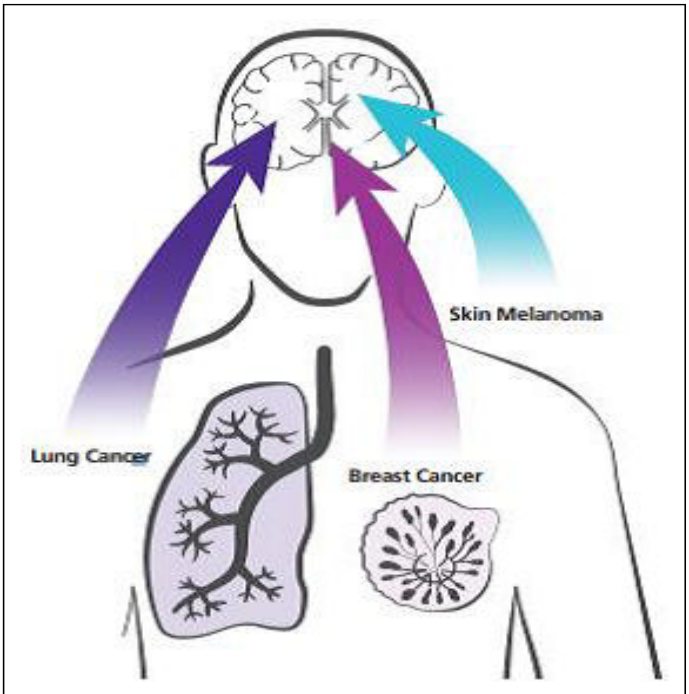

Figure 2: Metastatic brain tumor.

In 2000, the World Health Organization (WHO) revised the classification of neoplasms affecting the central nervous system, based on a century-old premise that each type of tumor originated from one specific cell type [2]. Purely based on histologic features, this classification system relies almost entirely on visual assessment of the microscopic appearance of the tumor specimen, which raises the concern for subjectivity and interobserver variability. Moreover, the classification system does not take into consideration other important factors such as anatomic location and size of the tumor, both of which will determine surgical accessibility and degree of respectability.

Despite its shortcomings, the WHO classification scheme of brain tumors remains the primary basis for guiding therapy and assessing overall prognosis in patients with brain tumors. The classification system also forms the basis for scientific study in brain tumor research, as well as the clinical understanding of tumor biology, clinical response, and patient prognosis. Although most malignant Brain tumors are uniformly fatal, rare but distinct instances do occur in which tumors respond to therapy and cure is achieved. The current WHO classification, however, falls short of predicting the therapeutic response of each tumor within the same histologic grade and cannot provide precise guidance of therapy, especially those targeting specific molecular or genetic pathways of tumor genesis. A need exists for improvement in the brain tumor classification scheme to one that can guide therapy and assess early treatment response and is clinically significant in terms of providing clinical endpoints and outcome measures. It is unlikely that, based on histologic classification alone, the grading of brain tumors will provide meaningful endpoints for therapeutic trials. To that end, surrogate or biological tumor markers derived from neuroimaging hold much promise to fill that role by potentially providing novel information on biological differences between 2 tumors of the same type and grade that respond drastically differently to therapy.

How secondary tumor breaches to brain?

The cancerous cells from their primary site of action broke off and spread to the brain through the bloodstream and lymph system. Diapedesis is a vital part of tumor metastasis whereby tumor cells attach to and cross the endothelium to enter the circulation. Cancer cells affect the small vessels that supply to their primary origin and then through small vessels travel to enter the bloodstream. The lumps travel within the bloodstream till they got stuck at a particular site and then start invading and multiplying developing into secondary tumors. To invade the BBB parenchyma metastatic cells have to transmigrate through the endothelial cell layer of brain capillaries, which forms the morphological basis of the Blood-Brain Barrier (BBB) (Figure 3). Research has shown that the in the brain these tumors traveling along the bloodstream give off to small particles called extracellular vesicles which cross the Blood Brain Barrier (BBB) and make the brain more hospitable to metastatic tumors [3].

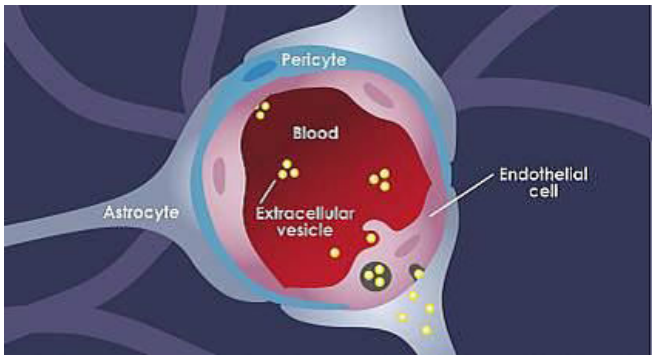

Figure 3: Cancer vesicles breaching Blood Brain Barrier (BBB).

Effects of brain tumor on CNS

A CNS tumor starts as primary cancer originating in the brain, spinal cord, and spinal fluid and then spreads to CNS. As tumors grow it creates functional and structural changes in the surrounding tissues which results in headache, nausea, vomiting, and balance problems. Tumors in cranial nerves lead to hearing loss, balancing problems, weakness of facial muscles, facial numbness or pain, and trouble swallowing. Spinal tumors can compress spinal nerves leading to loss of movement just the location of the tumor. Abnormal gait, loss of sense of position, tingling, numbness, and abnormality in motion are the common sign and symptoms of tumors affecting the spinal cord (Table 1 and Figures 4 and 5).

The brain is divided into three major regions/sections.

- Fore brain (cerebrum, thalamus, hypothalamus)
- Mid brain (colliculi, tegmentum, cerebral peduncles)
- Hind brain (pons, cerebellum, medulla oblongata)

Table 1: Effects of brain tumor on CNS.

Cerebrum	Cerebellum	Brain stem
•Largest part of the brain •Having two parts or hemispheres left and right •Initiate and coordinates movement and control temperature	•Named as little brain •Located below the cerebrum •Important for making postures •Maintain Balance	• Bottom part of brain • Connect brain to spinal cord • Send signals from brain to the rest of the body • Control subconscious • Body function breathing, heart rate, etc.
Parts	**Parts**	**Parts**
•Left and right frontal lobes •Left and right temporal lobes •Left and right parietal lobes •Left and right occipital lobes	•Cerebrocerebellum •Spinocerebellum •Vestibulocerebellum	• Midbrain • Pons • Medulla oblongata

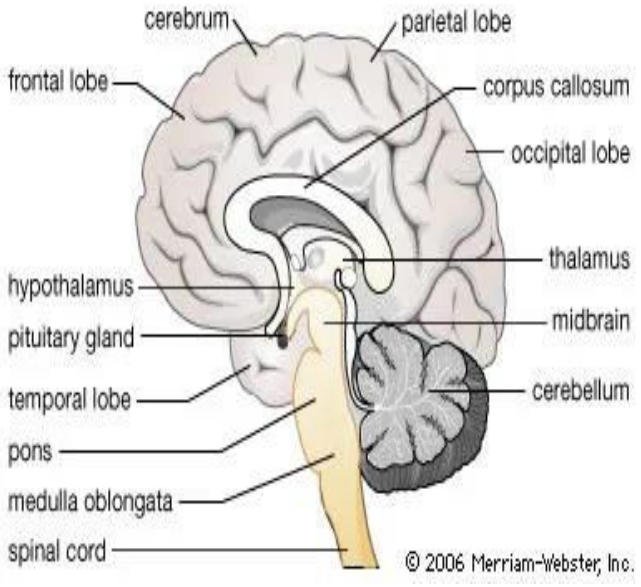

Figure 4: Brain.

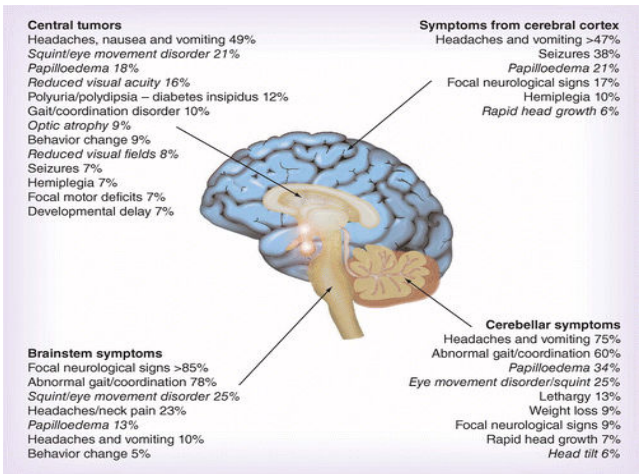

Figure 5: Effects of tumor on CNS.

Brain tumors can develop in any part of the brain or skull, including its protective lining, the underside of the brain (skull base), the brainstem, the sinuses and the nasal cavity, and many other areas. So the area of the brain getting affected by tumors results in malfunctioning and nervous disorders [4].

Methodology

Imaging tests can help find out to doctors whether the tumor is the primary brain tumor or if it is cancer that spread to the brain from elsewhere the brain. This diagnosis is very important because it changes the protocols for imaging as well as the conditions of the treatment. If it is cancer, it should be a PET scan to find out the origin of cancer and whether it is spread from the lungs, breast, colon, thyroid gland, skin, kidney, etc. If it is a primary brain tumor started and limited to a particular area of the brain, then only a CT head scan would be sufficient. Consider these factors when running a diagnostic test.

- Sign and symptoms of patient.
- The type of tumor suspected.
- Age and general health of patient.
- Results of earlier medical tests.

Most brain tumors are diagnosed by an internist or neurologist by just observing the physical condition of a patient having specific symptoms. After observing the symptoms and taking the medical history of the patient the doctors may prescribe the radiologic diagnostic tests. In this article, we will cover the axial tomographic diagnosis of brain tumors [5].

MRI scans

In general, diagnosing a brain tumor starts with referring the patient for a magnetic resonance imaging scan. It is the primary and basic modality for showing brain tumors. It is the best tool that shows the brain tissues more clearly than any other tool of diagnostic imaging. It uses strong magnets to create pictures inside the brain. Once the diagnosis is done, the type of brain tumor can be identified by looking at results from a sample of tissues obtained through biopsy or surgery. The test can last for 15 to 90 minutes. It is a painless procedure with an accuracy of 87%. But if the patient is claustrophobic, use a sedative to relax him/her. Apply sedatives much before the actual scan. This test can't be performed if the patient has any kind of metal implant. Instead, a CT examination is the primary method of detecting Brain tumors.

How brain tumor is detected using MRI? Three types of specialized MRI scans can be performed for accurate diagnosis.

Magnetic Resonance Spectroscopy (MRS): It is a non-invasive technique that is used for measuring biochemical changes in the brain in the presence of a tumor. It creates a graph or spectrum arraying the type and quantity of chemicals in the brain. By comparing the results of a tumor to that of normal brain tissue, it can sometimes help determine the type of tumor (or how quickly it is likely to grow), although a biopsy of the tumor is often still needed to get an accurate diagnosis. MRS can also be used after treatment to help determine if an area that still looks abnormal on another test is a remaining tumor or if it is more likely to be scar tissue (Figure 6).

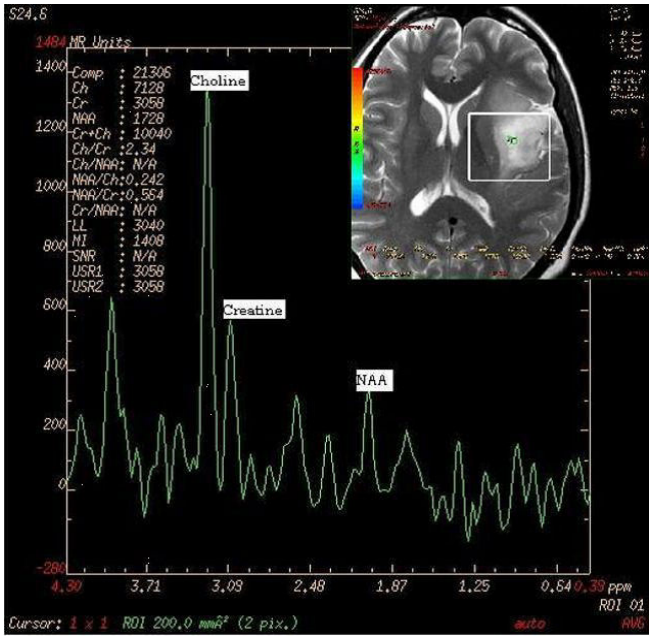

Figure 6: Magnetic Resonance Spectroscopy (MRS) of brain.

Perfusion MRI scans (Perfusion MR): A dye is injected that can be used to look at the blood flow in different types of brain tissues. It produces a high-quality image with high spatial resolution (Figure 7). It can also be used in post-treatment monitoring [6].

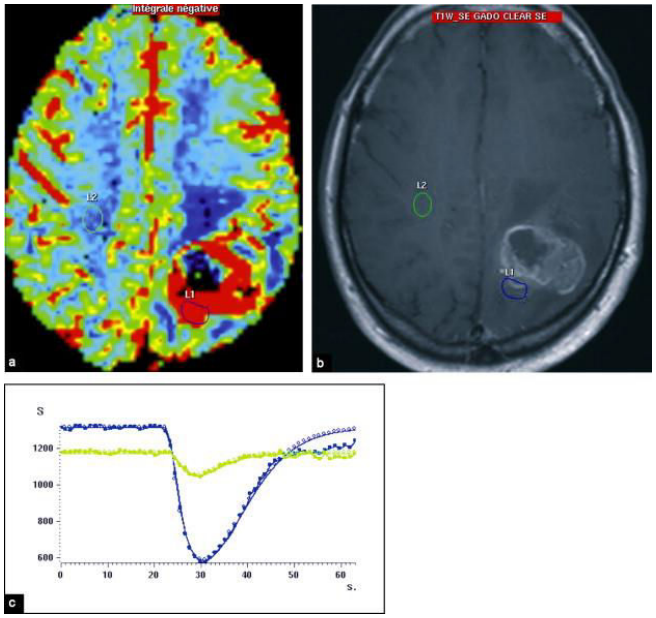

Figure 7: Perfusion MRI scans (Perfusion MR) of brain.

Functional MRI scans (MRF): Before performing the surgery to remove brain tumors and abnormally growing tissues, the surgeon must know the exact location and spread of the brain tumor. This can be assessed by having a functional MRI. It doesn't use any kind of dye. The success of MRF-based brain tumor detection indicates that tumor-related abnormal vascularization and perfusion could result in tumor-specific BOLD signals and lead to tumor component identification (Figure 8).

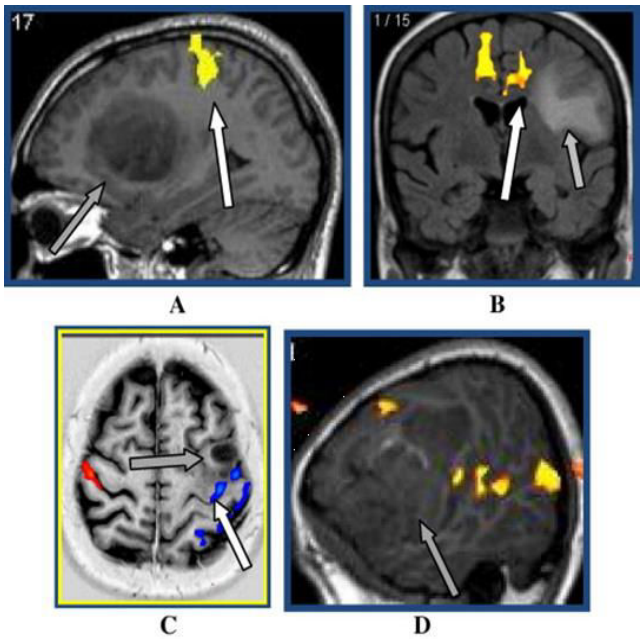

Figure 8: Functional MRI scans (MRF) of brain.

CT scan

CT scan involves a series of computerized-based X-ray images. A Ct Head scan shows detailed, 3-D images of any abnormality or tumor in brain tissues. A CT image can help find bleeding or any enlargement in fluid-filled ventricles accompanied by a change in the bone structure of the head and any kind of suspicion of a tumor affecting brain tissues. CT is used as a replacement for MRI which is the primary and basic modality for diagnosis of brain tumor if the patient has the following problems

- When the tumor is present near the bony structure of the skull cranium or spine.
- When the patient has a pacemaker in their heart and can't undergo MRI.
- CT scan can be performed with or without contrast. But when we are required.
- To perform CT angiogram (or venogram).
- To evaluate an abscess.
- For malignancy.
- Create a clear distinguished image of targeted tissues.
- Known CNS tumor, investigation for potential intracranial metastases.
- An unexpected abnormality on the plain scan.

In these specific conditions, a contrast study can be performed. Contrast can be injected directly into veins or can be given orally in the form of liquid or pills (Figures 9-11) [7].

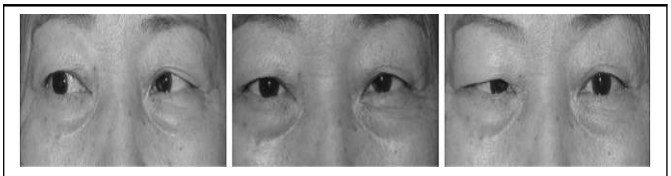

Figure 9: Photograph of the patient upon first examination showing her inability to abduct the left eye beyond the midline.

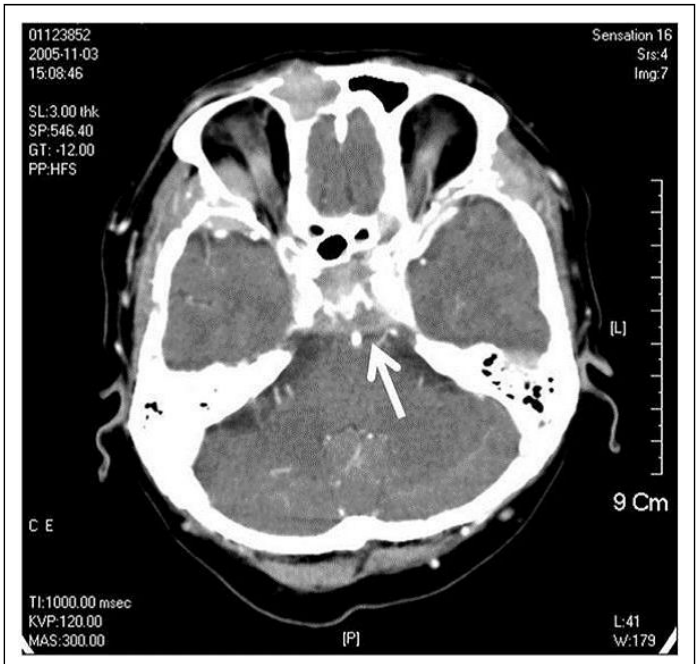

Figure 10: Axial contrast-enhanced CT scans show posterior bulging of the cavernous sinus showing soft tissue mass within the cavernous sinus affecting the sixth cranial nerve.

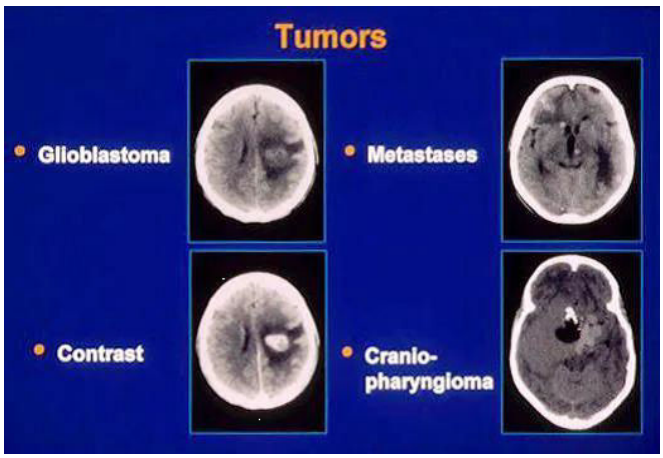

Figure 11: CT tumor with and without contrast.

Positron Emission Tomography (PET) CT scan

A PET scan is used first to find out the tumor when the patient is receiving treatment or tumors restart after being restricted and removed surgically from the body. A PET scan is usually preferred with CT and is known as PET-CT scan. In this procedure, a radioactive substance is injected into the body. The actively dividing cells of the body absorb the radiations emitted by this substance. The amount of radioactivity is too low to be harmful. As the tumor is most likely to be much more active than other cells so it absorbs much more radiation thus appearing much more distinguished than other body parts. A scanner then detects this substance and produces an image of the object (Figures 12 and 13) [8].

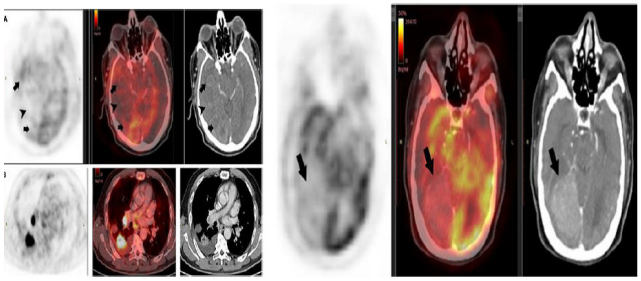

Figure 12: Brain metastasis.

Cerebral angiogram/arteriogram: Series of X-ray-generated images that shows the X-ray based images of the arteries of the brain. X-rays are taken after a special medium called contrast is injected into the main arteries of the patient's head.

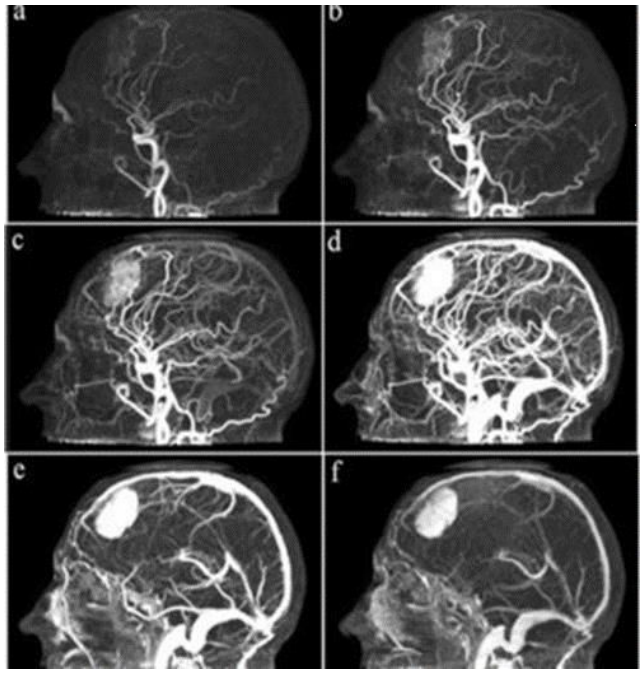

Figure 13: Blood supply of meningiomas.

Lumbar puncture or spinal tap: It is a procedure in which a needle is used to take a sample of cerebrospinal fluid to look for the tumor cells, blood, or tumor markers. Tumor markers or biomarkers are substances found in higher than normal amounts in the blood, urine, spinal fluid, or other body fluid with certain types of tumors. Typically an anesthetic is given before the procedure to numb the patient's lower back.

Myelogram: It is recommended to find out whether has spread to the spinal cord, other parts of the brain, or the spinal fluid. A myelogram uses a dye injected into the CSF that surrounds the spinal cord. The dye shows up on an X-ray and can outline the spinal cord to help the doctor look for a tumor.

Neurological, vision, and hearing tests: These tests help the specialist to judge how the tumor is affecting the functions of the brain. It helps to locate the tumor and so to limit it through follow-up therapy. A vision test detects any kind of damage to the optical nerve as well as to the person's field of vision.

Neurocognitive assessment: This consists of a detailed evaluation of all major components and functions of the brain such as memory, expressive and linguistic behaviors, calculation, dexterity, and overall well-being of the patient.

Evoked potentials: It is used to measure the potential of nerves in the brain. Any disturbance or discontinuity will suggest the tumor. It can often detect acoustic schwannoma, a noncancerous brain tumor. This test can be used as a guide when removing a tumor that is growing around important nerves.

DISCUSSION

Treatment

Treatment involves a multidisciplinary team which is a combination of different medical experts which involves different kinds of treatment. Generally, four strategies are involved in treating a brain tumor.

1. Surgery
2. Radiotherapy
3. Chemotherapy
4. Targeted therapy

The choice of a particular treatment strategy involves consideration of these factors

- Spread of tumor.
- Amount of pressure the tumor is putting on parts of the brain.
- Size and structure of tumor.
- Patient preference and overall health.

Surgery can be a sufficient treatment for a low-grade tumor and is particularly significant if the whole of the lump can be removed successfully. If, however, surgery is not fully successful in removing the tumor, the remaining part can be removed by radiotherapy and chemotherapy. But for a high-grade tumor that has spread to delicate parts of the brain and spinal cord, surgery can be much more harmful than beneficial because it can damage the nerves and thus cause specific disorders related to nerves. For high-grade tumors, treatment starts with surgery which is followed by chemotherapy and radiotherapy.

Radiotherapy is used to slow down or stop the growth of brain tumors. It involves external high-energy beam radiation which is bombarded by a machine onto specific cells affected by cancer. It involves the shrinking of the tumor and reduces the pressure inside the skull and thus symptoms caused by brain tumor improves. If the tumor is deep inside the brain a special type of radiotherapy called stereotactic radiotherapy is used. It also damages the normal surrounding cells. Radiotherapy is not effective for secondary brain tumors. Treatment is given once a day and 3 to 5 days a week (Figure 14) [3].

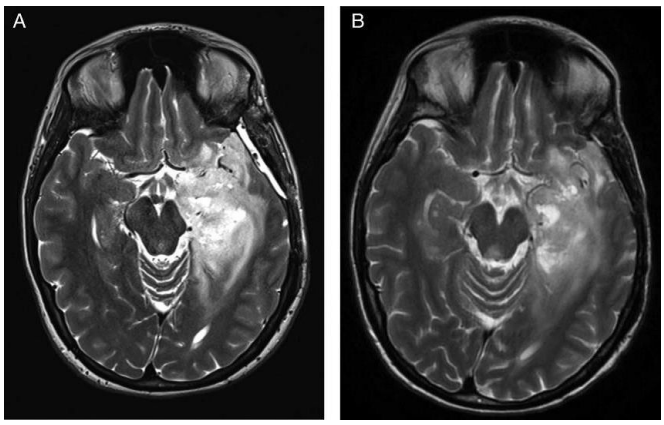

Figure 14: Tumor before and after radiotherapy.

Chemotherapy involves the usage of cytotoxic circulating in the blood to destroy the brain tumor cells. The drugs can be injected through a drip in the blood directly, into the spine (Intrathecal chemotherapy), into the brain, or through oral ways (Tablets and capsules). Chemotherapy is composed of cycles of treatment. Chemotherapy can be challenging because of the presence of the Blood-Brain Barrier (BBB). Common types of chemotherapy drugs for brain tumors include temozolamide, procarbazine, BCNU and CCNU, vincristine, and PCV (a combination of drugs). Common side effects of chemotherapy include feeling sick and a drop in the levels of white blood cells causing an increased risk of infection. You might have chemotherapy:

- After surgery.
- With radiotherapy.
- For a brain tumor that has come back after treatment.

A special mechanism used to deliver drugs during surgery directly to the brain by passing Blood Brain Barrier (BBB) is called Ommaya reservoir. The treatment team places a plastic-made domed-shaped structure pierced under the scalp in the brain. It is called a ventricular access device or Ommaya reservoir. The doctor put a small needle through the device gently and inject chemotherapy straight into cerebrospinal fluid. This bypass BBB and it means that medic can give small doses of chemotherapy in this way (Figure 15).

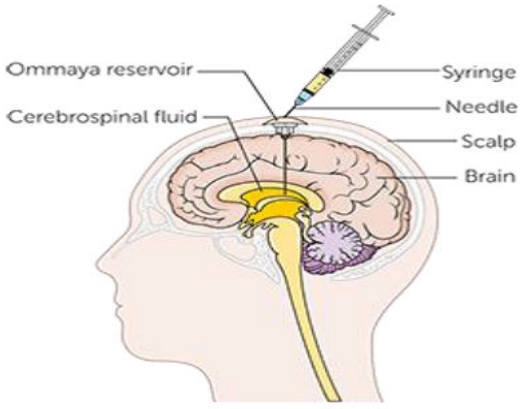

Figure 15: Ommaya reservoir.

The authors visited government based major health facilities in Faisalabad city. They had quite an informative discussion with the oncology department doctors and medicos about the percentage of affected persons with brain tumors here in the city and its neighborhood. The results were quite surprising. A primary brain or spinal cord tumor is a tumor that starts in the brain or spinal cord. This year, an estimated 25,050 adults (14,170 men and 10,880 women) in Pakistan will be diagnosed with primary cancerous tumors of the brain and spinal cord. A person's likelihood of developing this type of tumor in their lifetime is less than 1%. Brain tumors account for 85% to 90% of all primary Central Nervous System (CNS) tumors. Worldwide, an estimated 308,102 people were diagnosed with a primary brain or spinal cord tumor in 2020. About 4,170 children under the age of 15 will also be diagnosed with a brain or CNS tumor this year in the United States. The rest of this guide deals with primary brain tumors in adults. Learn more about brain tumors in children. Brain and other nervous system cancer is the 10th leading cause of death for men and women. It is estimated that 18,280 adults in the United States (10,710 men and 7,570 women) will die from primary cancerous brain and CNS tumors this year. Worldwide, an estimated 251,329 people died from primary cancerous brain and CNS tumors in 2020.

CONCLUSION

The 5-year survival rate tells you what percent of people live at least 5 years after the tumor is found. The 5-year survival rate for people in the United States with a cancerous brain or CNS tumor is almost 36%. The 10-year survival rate is almost 31%. Age is a factor in general survival rates after a cancerous brain or CNS tumor is diagnosed. The 5-year survival rate for people younger than age 15 is about 75%. For people age 15 to 39, the 5-year survival rate nears 72%. The 5-year survival rate for people aged 40 and over is 21%. However, survival rates vary widely and depend on several factors, including the type of brain or spinal cord tumor. Talk with your doctor about what to expect with your diagnosis. It is important to remember that statistics on the survival rates for people with a brain tumor are an estimate. The estimate may not reflect the results of advancements in how a brain tumor has been diagnosed or treated in the last 5 years.

- People need physical, emotional, and nervous backup to fight this disease because once they hear from their doctors that it's brain cancer, they lose all hope of survival.
- It is the hour of need to educate the people and guide them properly about the disease because once they got affected by cancer they had old traditional beliefs that they can't survive so it's of no worth to fight for the lost cause.

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