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Review Article

NOVEL STRATEGIES IN GLIOBLASTOMA MANAGEMENT: AN OUTLOOK

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ABSTRACT

Glioma or brain tumors are one of the leading causes of death. The World Health Organization (WHO) lists 126 types of central nervous system tumors. Although the cause of brain tumors are unknown, each year approximately 1,90,000 people in the United States and 10,000 people in Canada will be diagnosed with a primary or metastatic brain tumor. Brain tumors are the number two cause of death in men age 45 and younger. Only 31 percent of males and 30 percent of females survive five years following the diagnosis of a primary or malignant brain tumor. Childhood brain tumors are the leading cause of cancer death in people age 20 and younger. Although as many as 69 percent of children with brain tumors will survive, they are often left with long-term side effects. Enhancing the quality of life of people with brain tumors requires access to quality specialty care, clinical trials, follow-up care and rehabilitative services.

Key words: *CNS disorders, Neuro-behavioural dysfunctions, Neuro-degenerative disorders.*

INTRODUCTION

A brain tumor is a collection of damaged cells that multiply out of control within the brain. Also called a neoplasm, growth, mass or lesion, a brain tumor is classified as either primary or secondary (metastatic), and can be benign or malignant. Primary brain tumors develop and generally remain in the brain. Secondary brain tumors, or metastatic brain tumors, are cancers that develop elsewhere in the body and spread to the brain. The most common cancers that spread to the brain are lung and breast cancers. Malignant brain tumors grow rapidly and invade other cells. Benign brain tumors generally do not grow rapidly. However, even benign tumors can be life-threatening. The adult body normally forms new cells only when they are needed to replace old or damaged ones. Infants and children form new cells to complete their development in addition to those needed for repair. A tumor develops if normal or abnormal cells multiply when they are not needed (Gail Segal)[1]. A brain tumor is a mass of unnecessary cells growing in the brain. There are two basic kinds of brain tumors i.e. primary brain tumors and metastatic brain tumors. Primary brain tumors start, and tend to stay, in the brain. Metastatic brain tumors begin as cancer elsewhere in the body and spreads to the brain. When doctors describe brain tumors, they often use the words “benign” or “malignant.” Those descriptions refer to the degree of malignancy or aggressiveness of a brain tumor. It is not always easy to classify a brain tumor as “benign” or “malignant” as many factors other than the pathological features contribute to the outcome.

Brain Tumor Grades and Types

Primary Brain Tumors: American Brain Tumor Association[14] found that a tumor that starts in the brain is a primary brain tumor. Glioblastoma multiform, astrocytoma, medullo blastoma, and ependymoma are examples of primary brain tumors. Primary brain tumors can be grouped into benign tumors and malignant tumors.

Benign Brain Tumors: A benign brain tumor consists of very slow growing cells, usually has distinct borders, and rarely spreads. When viewed under a microscope, the cells have an almost normal appearance. Surgery alone might be an effective treatment for this type of tumor. A brain tumor composed of benign cells, but located in a vital area, can be considered to be life-threatening although the tumor and its cells would not be classified as malignant.

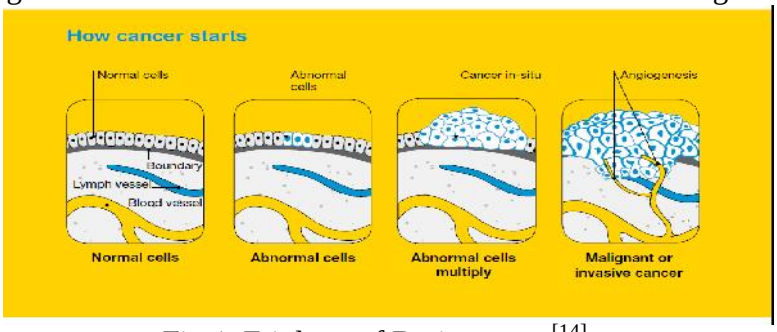

Fig:1 Etiology of Brain tumor [14]

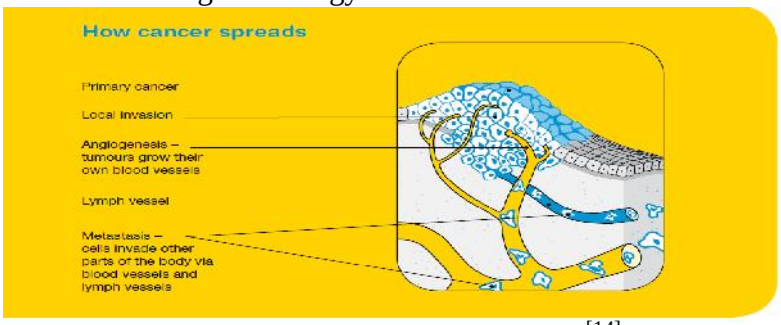

Fig 2: Proliferation of Tumor cells [14]

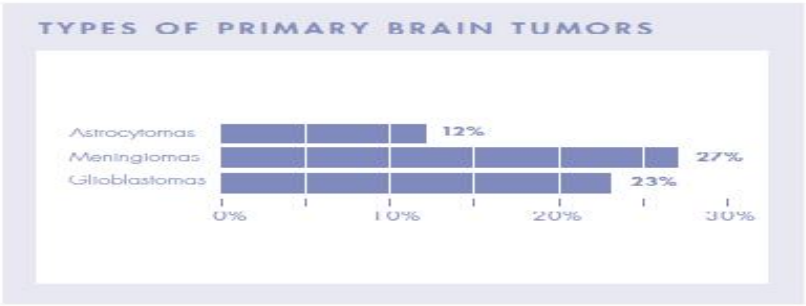

Fig 3: Types of Brain tumor [8]

Malignant Brain Tumors: A malignant brain tumor is usually rapid growing, invasive, and life-threatening. Malignant brain tumors are often called brain cancer. However, since primary brain tumors rarely spread outside the brain and spinal cord, they do not exactly fit the general definition of cancer. Malignant brain tumors that are cancerous can spread within the brain and spine. They rarely spread to other parts of the body. They lack distinct borders due to their tendency to send “roots” into nearby normal tissue. They can also shed cells that travel to distant

parts of the brain and spine by way of the cerebrospinal fluid. Some malignant tumors, however, do remain localized to a region of the brain or spinal cord.

Metastatic brain tumors: Metastatic Brain Tumors: Cancer cells that begin growing elsewhere in the body and then travel to the brain form metastatic brain tumors. For example, cancers of the lung, breast, colon and skin (melanoma) frequently spread to the brain via the blood-stream or a magnetic-like attraction to other organs of the body. All metastatic brain tumors are, by definition, malignant. Metastatic brain tumors begin as cancer elsewhere in the body and spreads to the brain. For example, cancers of the lung, breast, colon and skin (melanoma) frequently spread to the brain via the bloodstream or a magnetic-like attraction to other organs of the body. All metastatic brain tumors are, by definition, malignant. The most malignant tumors are given a grade of IV. They reproduce rapidly, can have a bizarre appearance when viewed under the microscope, and easily grow into surrounding normal brain tissue. These tumors form new blood vessels so they can maintain their rapid growth. They also have areas of dead cells in their center. The glioblastoma multiforme is the most common example of a grade IV tumor.

WHO (World Health Organization) Grading System and National Cancer Institute[3] found the following classification:

GRADE I TUMOR

- Slow growing cells
- Almost normal appearance under a microscope
- Least malignant
- Usually associated with long-term survival

GRADE II TUMOR

- Relatively slow growing cells
- Slightly abnormal appearance under a microscope
- Can invade adjacent normal tissue
- Can recur as a higher grade tumor

GRADE III TUMOR

- Actively reproducing abnormal cells
- Abnormal appearance under a microscope
- Infiltrate adjacent normal brain tissue
- Tumor tends to recur, often at higher grade

GRADE IV TUMOR

- Abnormal cells which reproduce rapidly
- Very abnormal appearance under a microscope
- Form new blood vessels to maintain rapid growth
- Areas of dead cells in center

Etiology of Brain Tumor.

American Brain Tumor Association[13]found that causes and risk factors can be environmental, such as being exposed to poisonous substances in the home or at work, eating or not eating certain foods, or whether or not we exercise/smoke cigarettes/drink alcohol. They can be genetic, such as being born with a mutation/susceptibility that one inherits from parents. Or, these genetic mutations/susceptibilities may accumulate over time, as one grows older.

Environmental Factors: Many studies have examined a wide spectrum of environmental factors as a cause for brain tumors. Of the long list of factors studied, only exposure to ionizing radiation has consistently been shown to put one at increased risk for developing a brain tumor. Some studies have shown a history of allergies as an adult, a mother eating fruits and vegetables during

pregnancy, eating fruits and vegetables as a child, and having chicken pox as a child puts one at a decreased risk of development of brain tumors. However, environmental exposures can be difficult to accurately measure leading to inconsistent results across studies. Therefore, inconsistent results have been found, in both adults and children, for a long list of environmental factors. These factors include: vinyl chloride exposure, working in synthetic rubber manufacturing or petroleum refining/ production, history of head trauma, epilepsy, seizures or convulsions, cured food consumption (nitrites), viruses and common infections, cigarette smoking, alcohol consumption, cell phone use (in the US and in Europe), residential power line exposure, exposure to air pollution, smoking when pregnant, second hand smoke exposure, agricultural worker exposures, industrial formaldehyde exposure and use of common drugs (for example, birth control pills, sleeping pills, headache medication, over-the-counter pain medication, antihistamines). More studies need to be performed before we can say whether or not these are true risk factors for developing a brain tumor.

Genetic Factors: Anything that refers to our genes can be called "genetic". However, only 5–10% of all cancer is actually inherited from one generation to another in a family (i.e. "heredity"). Hence, there are very few families where multiple people in that family would have a brain tumor. There are a few rare, hereditary genetic syndromes that involve brain tumors. In those syndromes, a mutation in a specific gene is passed from grandparent, to parent, to child. These syndromes, along with the inherited gene, are: NF1 (NF1 gene), NF2 (NF2 gene), Turcots (APC gene), Gorlins (PTCH gene), tuberous sclerosis (TSC1 and TSC2 genes) and Li-Fraumeni syndrome (TP53 gene). The vast majority of genetic risk factors are not inherited at birth but actually accumulate over time as we age. Genes are the operating instructions for the entire body. While most of our genes go about their jobs as expected, a small number may become inactive or begin functioning abnormally. The end result of an abnormal gene can be as simple as two different colored eyes or as complex as the onset of a disease.

There are many different types of genes thought to be working incorrectly in brain tumors:

- Tumor suppressor genes make proteins that stop tumor growth in normal cells. The most well-defined tumor suppressor gene is TP53, which is believed to play a role in causing a low-grade brain tumor to develop into a high-grade brain tumor.
- Oncogenes make proteins that cause cells to grow in an out-of-control manner.
- Growth factors play a role in making sure that cells grow normally. EGFR is a growth factor that has been well studied in brain tumors and has been shown to be in very high quantities in high-grade brain tumors, causing these tumors to grow abnormally fast.
- Cyclin-dependent kinase inhibitors play a role in making sure that the cell goes through its growth cycle normally.
- DNA repair genes make proteins that control accurate repair of damaged DNA. ERCC1 is a DNA repair gene that has been shown to be associated with oligo dendrogliomas but not with GBMs.
- Carcinogen metabolizing genes make proteins that break down toxic chemicals in the body that could cause damage to one's DNA, like the chemicals in cigarette smoke and/or alcohol.
- Immune response genes make proteins that control how one's immune system responds to viruses and infections.

Radiotherapy

People who have had radiation to the head, usually to treat another type of cancer, may be at an increased risk of developing a tumor. This may affect people who had radiotherapy for childhood leukemia.

Cell Phone

Although public interest in the topic remains high, to date little evidence exists to suggest an association between cell phone use and the risk of meningioma 47 Multiple studies have been performed in United States, 40,65 European, and Israeli populations including the Interphone case–control study of cell phones and brain tumor risk. 10,28,30,31,42,44,46, 55,100 none of these studies found a significant association between cell phone use and meningioma risk. However, inconsistent findings have been reported for an increased risk of acoustic neuroma, 27–29 some types of high-grade gliomas 10,29 and long-term cell phone usage. Follow-up time in the majority of these studies is relatively short and measurements of cell phone exposure vary between studies, therefore further long-term study of cell phone exposure may be warranted.

OBJECTIVE OF THE STUDY:

The main objective of the present work is as follows:

1. To gain all the background information about the brain tumors, their causes, signs and symptoms, mortality rate trends etc.
2. To know the newer .techniques and advancements in the field of drug delivery system.
3. To know the side effects of the drugs used in the treatment.
4. To check the combination therapy of drugs (if any available) for the best possible results.

LITERATURE REVIEW:

Signs and Symptoms depending upon location of the Brain Tumor: Cedars-Sinai[4] found that specific symptoms vary, depending on which structures and tissues are affected. Because some brain tumors grow slowly or may be located at a distance from critical structures, they may not cause symptoms or be detected until they have become fairly large.

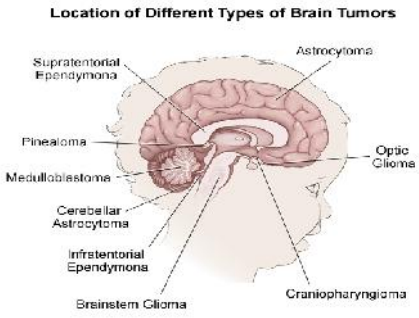

Fig 4: Types of Brain Tumors [3]

Increased intracranial pressure (ICP) - caused by extra tissue or fluid in the brain. Pressure may increase because one or more of the ventricles that drain cerebrospinal fluid (CSF, the fluid that surrounds the brain and spinal cord) has been blocked, causing the fluid to be trapped in the brain. Increased ICP can cause the following:

- Headache
- Vomiting (usually in the morning)
- Nausea
- Personality changes
- Irritability
- Drowsiness
- Depression

- Decreased cardiac and respiratory function and eventually coma if not treated

Symptoms of Brain Tumor in the spinal cord may include:

- Tingling or numbness in hands, feet, arms or legs
- Loss of sexual function
- Loss of bladder or bowel control
- Headache

Symptoms of brain tumors in the cerebrum (front of brain) may include:

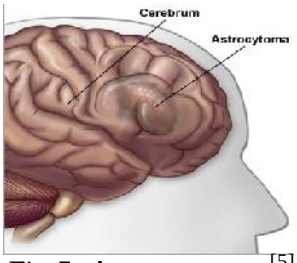

Fig 5: Astrocytomas [5]

- Seizures
- Visual changes
- Slurred speech
- Paralysis or weakness on half of the body or face
- Increased intracranial pressure (ICP)
- Drowsiness and/or confusion
- Personality changes/impaired judgement
- Short-term memory loss
- GIT disturbances
- Communication problems

Symptoms of brain tumors in the brainstem (middle of brain) may include:

- Seizures
- Endocrine problems (diabetes and/or hormone regulation)
- Visual changes or double vision
- Headaches
- Paralysis of nerves/muscles of the face, or half of the body
- Respiratory changes
- Increased intracranial pressure (ICP)
- Clumsy, uncoordinated walk
- Hearing loss
- Personality changes

Symptoms of brain tumors in the cerebellum (back of brain) may include:

- Increased intracranial pressure (ICP)
- Vomiting (usually occurs in the morning without nausea)
- Headache
- Uncoordinated muscle movements
- Problems walking (ataxia)

Incidence and Mortality Rate Trends

Brain tumors are much more common among adults than among children. However, if a child is diagnosed with a brain tumor, it is more likely to be malignant. Adults are more likely to be diagnosed with a non-malignant tumor. Malignant brain tumors were seen in 65.2 percent of brain tumor diagnoses in children, as compared to 33.7 percent in adults. Incidence rates for tumors of neuroepithelial tissue, a common type of brain tumor that is malignant in 94.9 percent of cases, were highest among men. Glioblastoma, a subtype of neuroepithelial tissue tumors, occurred 1.6 times more often in men than in women. Meningioma, a non-malignant brain tumor, was the most frequently diagnosed type of brain tumor. Meningiomas were diagnosed over twice as often in women when compared to men and more often in blacks than whites. Death rates for malignant brain tumors were stable from 1999 through 2007 in children (up to age 19) but declined significantly in adults (over age 20) at a rate of 1.2 percent each year. Death rates for benign brain tumors declined significantly in adults by 2.3 percent each year and by 2.5 percent each year in children (up to age 10).

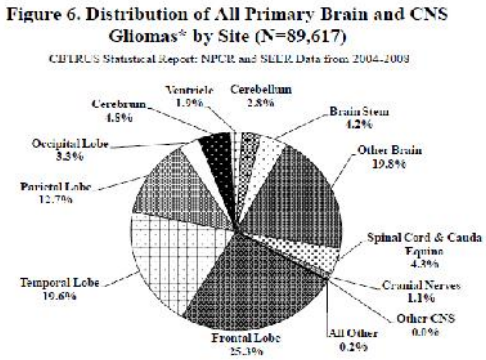

Fig 6: Distribution of Brain Tumors in CNS [7]

- Brain tumors are slightly more common in men than in women.
- Brain tumors, although can develop at any age but the risk increases with age.
- People who've been exposed to radiation to their head, such as children who had radiotherapy to the head for leukemia, are at a slightly higher risk of developing a brain tumor.

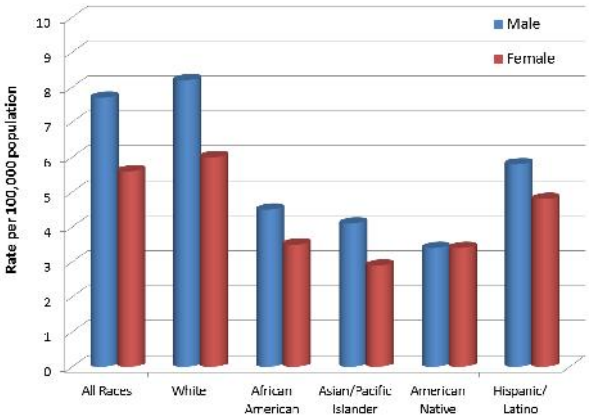

Fig 7: Mortality rate trends of Brain Tumor [8]

Whites had the highest incidence rates of brain tumors (malignant and non-malignant combined) at 19.0 per 100,000, followed by Hispanics at 17.8 per 100,000, and blacks at 17.7 per 100,000. American Indian/Alaska Natives had lower incidence rates of brain and other nervous system tumors at 15.3 per 100,000, and Asian and Pacific Islanders had the lowest rates at 13.5 per 100,000. Glioblastoma was the most common type of neuroepithelial brain cancer, with whites having the highest incidence rates, followed by Hispanics, blacks, and American Indian/Alaska Natives. Asian and Pacific Islanders had roughly one-half the rate of these tumors when compared to whites.

Epidemiology of brain tumors in childhood

Rachel and susan[6] found that malignant brain tumors are the leading cause of cancer death among children and the second most common type of pediatric cancer. Despite several decades of epidemiologic investigation, the etiology of childhood brain tumors (CBT) is still largely unknown. A few genetic syndromes and ionizing radiation are established risk factors. Many environmental exposures and infectious agents have been suspected of playing a role in the development of CBT.

Black Peter M claren[2] studied that most brain tumors are cancers that have spread from their original site in a breast or lung, for example. But each year, about 23,000 adults in the United States are diagnosed with a primary brain tumor, a cancer that begins in the brain. In this booklet, we'll talk about the new ways that doctors are finding to treat these tumors, giving hope to patients and their families. About 60 percent of primary brain tumors are glioblastomas, the most common and fastest-growing form of brain cancer. Researchers have studied many possible causes, such as cell phone use, exposure to certain viruses, exposure to electromagnetic fields near high-tension wires, brain injuries, diet, the chemicals in plastic, and radiation treatment. Still, none has been shown to cause brain cancer. The symptoms of brain tumors vary. Sometimes a tumor causes a general symptom such as a headache. This is due to the pressure that a tumor can place on the brain. In other cases, a tumor causes more specific symptoms related to its location. For example, a tumor found in the part of the brain that controls movement may cause muscle weakness.

Diagnosis of Brain Tumors

Brain tumors may be diagnosed and evaluated using one or more of several different types of procedures:

- MRI - Magnetic Resonance Imaging
- CT - Computerized Tomography
- PET - Positron Emission Tomography
- Biopsy

MRI, CT, and PET scanning are all ways to take pictures of the inside of the body. They are all painless, and do not require surgery.

- *MRI - Magnetic Resonance Imaging: MRIs use an extremely strong magnet to produce images. With contrast-enhanced MRI, the patient is first injected with a dye that makes normal and tumor tissue display differently. If your loved one requires an MRI, be sure to tell your doctor of any history of allergies or drug reactions. Because the MRI uses a magnet, no metal can be brought into the room while the MRI is taking place. Patients who have pacemakers and/or metal implants cannot have an MRI.*

- *CT - Computerized Tomography: James Rubenstein[15] studied that a CT scan may be used for patients who cannot undergo MRI because they have pacemakers, metal implants, allergies or claustrophobia. CT scan machines take multiple x-rays of small areas of the brain from different angles. The computer then combines the scans to make a detailed, three-dimensional image.*
- PET - Positron Emission Tomography Scan: James Rubenstein[15] studied that PET scans are sometimes used in addition to MRI or CT to evaluate brain tumors. After receiving treatment for a brain tumor, PET scans can also be used to detect new tumor growth and scar tissue or any necrosis. The contrast agent for PET is a radioactive sugar. The PET scan reads which parts of the brain consume more of the sugar (tumors) and which parts consume hardly any at all (scar tissue; necrosis).
- Biopsy: MRI, CT, and PET scanning are all ways to take pictures of the inside of the body. They are all painless, and do not require surgery. Under certain circumstances, however, a doctor may need to take a biopsy. That is, a small piece of the tumor tissue is surgically removed to be studied. This can be done as part of surgery or as part of a special procedure. There are three types of biopsies:

• Needle biopsy: A narrow, hollow needle is inserted through a hole in the skull and into the tumor.
• Stereotactic or computer-directed needle biopsy: A computer provides detailed information about the location of the tumor, based on a CT or MRI scan.
• Closed biopsy: A computer helps to physically guide removal of the tumor sample.

- *Angiogram*: Dye injected into the bloodstream makes blood vessels in the brain show up on an x-ray. If a tumor is present, the x-ray may show the tumor or blood vessels that are feeding into the tumor.
- *Spinal tap*: Your doctor may remove a sample of cerebrospinal fluid (the fluid that fills the spaces in and around the brain and spinal cord). This procedure is performed with local anesthesia. The doctor uses a long, thin needle to remove fluid from the lower part of the spinal column. A spinal tap takes about 30 minutes. You must lie flat for several hours afterward to keep from getting a headache. A laboratory checks the fluid for cancer cells or other signs of problems.
- *Neurologic exam*: Your doctor checks your vision, hearing, alertness, muscle strength, coordination, and reflexes. Your doctor also examines your eyes to look for swelling caused by a tumor pressing on the nerve that connects the eye and the brain.
- *Computer Aided Detection of Brain Tumor in Magnetic Resonance Images:* Abhishek Raj[10] found that Brain tumor is an abnormal mass of tissue with uncoordinated growth inside the skull which may invade and damage nerves and other healthy tissues. Non-homogeneities of the brain tissues result in inaccurate detection of tumor boundaries with the existing methods for contrast enhancement and segmentation of magnetic resonance images (MRI).This paper presents an improved framework for computer aided detection of brain tumor.

MANAGEMENT OF BRAIN TUMOR:

As with most cancers, there are four main treatments for brain cancer that can be used alone or in combination: surgery, radiation, chemotherapy, and targeted treatments. By removing or shrinking brain tumors, doctors relieve the pressure on the brain these tumors can cause. Treatment also reduces other symptoms such as seizures, headaches, or difficulty with balance.

Surgery

Jeffrey Bruce[9] et al studied that many brain tumors are surgically removed using a procedure called a craniotomy. In this procedure, the surgeon opens the skull and removes as much of the tumor as possible. Recent advances have improved the safety of craniotomy. For example, special computers hooked up to MRI monitors allow surgeons to view a "map" of different parts of the brain. The map helps them find and remove tumors more easily and safely. interrupting the flow of spinal fluid. Spinal fluid, which protects and nourishes the brain, needs to circulate throughout the brain. If the fluid is blocked, the surgeon may insert a shunt, or plastic tube, that enables the fluid to be redirected to a different area of the brain.

Chemotherapy

R.Srinivasan[8] et al studied that chemotherapy is a cancer treatment that uses drugs to stop the growth of cancer cells, either by killing the cells or by stopping the cells from dividing. When chemotherapy is taken by mouth or injected into a vein or muscle, the drugs enter the bloodstream and can reach cancer cells throughout the body (systemic chemotherapy). When chemotherapy is placed directly into the spinal column, an organ, or a body cavity such as the abdomen, the drugs mainly affect cancer cells in those areas (regional chemotherapy). A dissolving wafer may be used to deliver an anticancer drug directly into the brain tumor site after the tumor has been removed by surgery. The way the chemotherapy is given depends on the type and stage of the cancer being treated. Carrie and timothy[18] studied that metastatic brain tumors are the most common cerebral tumors, occurring with a higher incidence than all primary brain tumors combined. On autopsy, 25% of patients with systemic cancer are found to have intracranial metastases.

Nanotechnology in the Treatment of Brain Tumors: Potential innovations and applications: Thomas Merewether[16] studied that as brain tumors present specific challenges in terms of treatment, alternative and more effective possibilities are under relentless research. Nanotechnology provides a plethora of opportunities to improve and expand on such treatments, and throughout this paper we shall postulate as to the possible further uses of nanotechnology in the treatment of brain tumors. Specifically, we will predict additional ways in which two current treatments under development could be improved and enhanced, via the inclusion of nanoparticles, in order to treat brain tumors; incorporating a selection of our own ideas regarding nanotechnological application.

Radiation Therapy or Radiotherapy

Los Angeles caregiver resource center[7] found that patients with more than one tumor, or with one tumor that is not readily accessible, are typically treated with radiation therapy. Radiation Therapy is the uses of painless x-rays directed to damage or destroy tumor cells. Radiation may be used after surgery to prevent the tumor from coming back or to destroy tumor tissue that could not be completely removed. Different types of radiotherapy are described below. Stereotactic Radiosurgery is a more targeted form of radiation therapy, and is not actually surgery at all. It is called "radiosurgery" because it is so precise and focused. Because this form of radiation targets the tumor more precisely, it is less likely to hurt healthy tissue. Stereotactic radiosurgery only treats tumors that can be detected on MRI or CT scans. Whole Brain Radiation Therapy (WBRT) delivers an even dose of radiation to the entire brain. The advantages of whole brain radiotherapy are that it can treat large and small tumors, many tumors at the same time, and tumors deep in the brain that cannot be removed through surgery. Side effects of whole brain radiotherapy may include nausea, vomiting, headache, fever, and temporary worsening of neurological symptoms such as memory loss and difficulty thinking. Brachytherapy also called

interstitial radiation therapy, is another form of targeted radiation for patients with tumors that are not responsive to other types of treatment.

Targeted Treatments

Jeffrey Bruce[9] et.al studied that unlike chemotherapy, targeted treatments block specific cell mechanisms that are thought to be important for cancer cell growth. Targeted treatments are meant to spare healthy tissues and cause less severe side effects. One type of targeted treatment used to treat glioblastoma is bevacizumab (Avastin). Bevacizumab helps block the development of blood vessels. This is an important part of treating brain tumors, because this type of cancer develops very strong networks of blood vessels that feed tumor growth. Recently, the U. S. Food and Drug Administration approved bevacizumab for treating people with glioblastoma tumors that continue growing after standard treatment. Bevacizumab is also approved for the treatment of some types of colon, rectal, breast, and lung cancers.

New Treatments on the Horizon

Jeffrey Bruce[9] et al studied that in addition to the treatment advances discussed above, there are also a number of other promising leads in the research on brain tumors

New ways to deliver chemotherapy: When anti-cancer drugs are given in pill form or through a vein, they have to travel throughout the body before getting to the brain. As the drugs travel, they can cause side effects such as nausea. Researchers are developing chemotherapy that can be delivered directly into the brain tumor itself. For example, Gliadel is a little wafer containing an anti-cancer drug called carmustine. After removing tumors with traditional surgery, surgeons can leave these wafers in the brain, where they slowly dissolve and release the drug. Another new technique is called convection-enhanced delivery of chemotherapy. Doctors put one to four tiny tubes into a brain tumor and connect the tubes to a pump that delivers large doses of chemotherapy directly into the brain.

Radiation sensitizers: These are drugs that get into the cells of a brain tumor and make them more likely to be treated successfully by radiation. As a result, doctors can use lower doses of radiation, reducing treatment side effects.

Gene therapy: Researchers are trying to pinpoint specific genes that cause brain tumor growth. Once the genes are identified, researchers hope to find ways to “turn them off,” so they won’t promote cancer growth. For example, one large study recently identified a gene called IDH1, which is often involved in the growth of glioblastoma tumors.

Oka H *et.al*[23] describe the clinicopathological features of 25 brainstem gliomas (BSGs). Twenty BSGs located in the pons and were all in children. Four BSGs located in the medulla oblongata were in 2 children and 2 adults. One (in a child) was located in the midbrain. Radiological findings on MR images were low-intensity on T1 weighted images and high-intensity on T2 weighted images. Mean survival when pontine glioma was treated by radiotherapy and/or use of temozolomide was 14 months, although 4 patients (3 cervicomedullary types and one focal type arising from midbrain) are alive. Follow up was from 5 months to 6 years. Histopathological features of 10 cases of the diffuse type were: 4 grade II astrocytomas, 4 grade III astrocytomas, and 2 glioblastomas. MIB-1 index was from 0.8 to 38 %. P53 was positive for 80 % of 15 tumors and there were no negative results. MGMT was positive in 60 % of 15 tumors and negative in 12.4 %. IDH1 was negative in 61.6 %. There was no positive result for IDH1 in this study. Thus, our histopathological results were indicative of high p53 immunoreactivity and no IDH1 immunoreactivity related to secondary malignant change.

Takeuchi H. Et.al.[24] studied that there have been some recent reports about glioblastoma with oligodendroglial (OG) components and malignant glioma with primitive neuroectodermal tumor

(PNET)-like components. We investigated whether the presence and extent of OG components and PNET-like components influenced the prognosis in patients with glioblastoma. Eighty-six patients with glioblastoma were divided into an OG group (28 %), which revealed areas with a honeycomb appearance, and a non-OG group (72 %) without a honeycomb appearance. Patients with glioblastoma were also divided into a PNET group (27 %), which revealed areas with PNET-like features defined as neoplastic cells with high N/C ratios and hyperchromatic oval-carrot-shaped nuclei, and lacked the typical honeycomb appearance, and a non-PNET group (73 %) without PNET features. There were no significant differences in overall survival among the OG, the non-OG, the PNET, and the non-PNET groups. Two patients who survived longer than 36 months had both OG and PNET components with 1p or 19q loss of heterozygosity. Perinuclear halo, which is a characteristic feature of oligodendrogliomas, is an artifact of tissue fixation. Therefore, we should not readily use the term glioblastoma with OG components. PNET-like components, which are considered rare in malignant gliomas, may be frequently identified in glioblastomas.

Helage S et.al[25] studied that Cerebral Aspergillosis is a rare pathology of poor prognosis in spite of the use of adapted antifungal treatments. This infection of the central nervous system is generally the complication of an invasive aspergillosis with hematogenic scattering from pulmonary focal spots. It can arise in immune component patients treated with prolonged corticotherapy or chemo-radiotherapy for cancer. A case of lethal cerebral aspergillosis in a patient with an infiltrative glioma treated with corticotherapy and radiotherapy is reported. Clinico-pathological aspects and therapeutic approach are described.

Drug Treatment of Malignant gliomas:

Carrie and timothy[27] studied that malignant gliomas are the most common and typically the most aggressive primary tumor seen in the CNS. Glial tumors are composed of astrocytomas, oligo dendrogliomas, anaplastic oligoastrocytomas (AO), ependymomas, and glioblastoma multiforme (GBM), and account for over 60% of primary brain tumors. Despite significant evaluation with laboratory and clinical research, the benefit of chemotherapy in this deadly tumor type, particularly in GBM, has long been debated. Yet recently there has been confirmative data that has provided much-needed results to support the use of adjuvant chemotherapy in glioblastoma multiforme.

- *PCV (Procarbazine, CCNU, Vincristine):* PCV has a long history in the management of malignant gliomas. Until recently, this chemotherapy regimen was thought to be superior to BCNU in treating patients with anaplastic astrocytomas and anaplastic AOs in the adjuvant setting. The PCV regimen is based on a 6-week cycle where procarbazine is given at a dosage of 60 mg/m2/day daily from day 8 to 21, CCNU 110 mg/m2 on day 1, and vincristine 1.4 mg/m2 intravenous push on day 14 and day 29, typically, with a maximum of six courses of PCV. Potential side effects include myelosuppression, nausea, vomiting, peripheral neuropathy secondary to vincristine, and pulmonary fibrosis secondary to CCNU.
- *Temozolomide:* Temozolomide is the first oral chemotherapy agent to be approved by the US Food and Drug Administration for use in the treatment of malignant gliomasin the past 20 years. Temozolomide was approved in 1999 for use in patients with anaplastic astrocytomas who have failed prior treatment with a nitrosourea and procarbazine, yet is clinically being used in both the adjuvant and recurrent setting for patients with both grade 3 and 4 malignant gliomas. Temozolomide, a methylating agent, is an oral chemotherapeutic agent that is commonly administered according to one of the following regimens. The most common regimen used is given at a dose of 150 to 200 mg/m2 daily for 5 days, followed by a 23-day

rest. Temozolomide can be administered for up to 24 months if there is no evidence of tumor progression during this interval. The alternate regimen that has been evaluated in the setting of concurrent radiation therapy is low-dose temozolomide at 75 mg/m2 daily during radiation therapy, followed by a 4-week rest, and then the earlier mentioned 150 to 200 mg/m2 regimen is resumed 4 weeks after the cessation of radiotherapy.

- *Nitrosoureas:* The nitrosoureas have the longest history of use and have traditionally been considered the most active chemotherapeutic agents for the treatment of malignant gliomas. The two most common nitrosoureas used in the management of malignant gliomas are carmustine (BCNU) and CCNU. Nitrosoureas are lipid-soluble agents that are able to cross the BBB with greater ease than other agents. BCNU has mainly been evaluated as single-agent therapy, while most data with CCNU is in combination therapy, and will be discussed in greater detail in the next section. Nitrosoureas have been studied and are used in both adjuvant and recurrent disease. BCNU is given at a dosage of 150 to 200/m2 intravenously every 6 to 8 weeks, depending on if the patient has been pretreated.
- *Irinotecan:* Irinotecan is a semi-synthetic analogue of camptothecin, an alkaloid extract from the Chinese tree camptotheca acuminata. Irinotecan shows antitumor activity by interacting with topoisomerase I, resulting in DNA double-strand breaks. Irinotecan is administered intravenously and there are various treatment schedules, with the most common regimen in malignant gliomas being 300 to 350 mg/m2 intravenously every 3 weeks. Additionally, it was shown that enzyme-inducing anticonvulsants affect the metabolism of the irinotecan, and therefore larger dosages are required in this patient population to obtain efficacy.37 Irinotecan has been evaluated in the recurrent setting and has shown activity in a subset of patients with recurrent malignant gliomas. In phase II studies, partial responses of 14% to 15% were shown, along with stable disease ranging from 14% to 55%.37,38 Unfortunately, similar to other chemotherapy options, these responses have not proven to be durable, as seen with a median time to tumor progression as short as 6 weeks. Optimizing radiotherapy of brain tumours by a combination of temozolomide & lonidamine:

S. Prabhakara[26] studied that Temozolomide (TMZ), a second generation alkylating drug, an effective cytotoxicagent as well as radiosensitizer for malignant brain tumours, has side effects like myelosuppression. Lonidamine (LND) increases the effectiveness of several experimental multiple chemotherapy protocols, without increasing bone marrow toxicities and is effective in brain tumour patients. The objective of the present studies was to investigate whether combining clinically relevant doses of LND and TMZ could increase the proliferation and radiation response of malignant human brain tumour cells *in vitro*. Continuous presence of TMZ or LND for two days significantly inhibited cell proliferation in a concentration dependent manner. The frequencies of non viable cells increased significantly only at higher concentrations of LND. Combination of 20 μM TMZ with 100 μM LND had additive effects on proliferation response, without affecting cell viability. Short-term drug treatments without irradiation did not induce micronuclei formation. Cell proliferation and viability were also not affected. However, post-irradiation presence of either of these drugs for 4 h significantly reduced the proliferation response, 24 and 48 h after treatments. It was further inhibited by the combination treatment. On the contrary, radiation induced micronuclei formation was enhanced by either of the drugs; which was significantly increased by the combined treatment, 24h as well as 48h after irradiation. No effects on cell viability were observed, immediately after these treatments as well as at later time points.

Nagendra[28] studied that drug delivery research focuses on several innovative methods, including nanoparticles microparticles as carriers of anticancer agents, PEG technology, encapsulating anticancer drugs in liposomes, and monoclonal antibodies for the delivery of anticancer payloads. For instance, significant differences were found between normal human brain and brain tumour capillaries, including differential expression of calcium-activated potassium (KCa) and ATP-sensitive potassium (KATP) channels. Recent progress in the molecular targeting of tumor-specific antigens with specific agents, however, can be exploited by identifying additional novel targets for modulating BBB/BTB permeability. Future studies will seek to determine whether there are significant differences in the expression levels (induced or suppressed) of certain genes and proteins between normal and brain tumor capillary ECs. Increasing evidence suggests that vascular endothelial cells from cerebral blood vessels over express ion channels, and these channels play an important role in modulating endothelial cell functions including regulating BBB permeability. Major transport routes across the BBB to brain parenchyma are via pinocytotic vesicles and endothelial tight junctions. BTB transport, however, is altered due to rearrangement of the neurovascular unit by the tumor microenvironment. It has been shown by transmission electron microscopy that potassium channel agonists induce the accelerated formation of transport vesicles in both brain tumor capillary endothelium and tumor cells by the activation of their respective potassium channels. Therefore, vesicular transport, rather than the opening of endothelial tight junctions, seems to be largely responsible for enhanced drug delivery across the BTB. A direct relationship was found between an increase in the number of brain tumor capillary endothelial vesicles and increased BTB permeability. Most significantly, it was observed that brain tumor capillary ECs form far more vesicles than normal brain capillary ECs without altering the endothelial tight junctions in response to vasomodulators, such as NS-1619 and minoxidil sulfate.

Jing Huo et.al.[29] studied that this preliminary study explores novel methods using diffusion weighted (DW) MR images as a biomarker to detect early GBM brain tumor response to treatment. Apparent diffusion coefficient (ADC) map, calculated from DW-MR images, can provide unique information of tumor response at cellular level. In this study, we investigate whether changes in ADC histograms between two scans, taken 5-7 weeks apart before and after treatment, could predict treatment effectiveness before lesion size changes are observed on later scans. The contribution of our work is to exploit quantitative pattern classification techniques for the prediction. For both pre- and post-treatment scans, we first compute the histogram from the ADC values covered within the tumor. Then we apply supervised learning on features extracted from the histogram for classification. We evaluated our approach with pool data of 86 patients with GBM under chemotherapy while 40 responded and 46 did not respond based on tumor size reduction. We compared Fisher's linear discriminant analysis, Ada Boost and random forests classifier using leave one out cross validation(LOOCV), resulting in the best accuracy of 67.44%.

Yoshiyuki Itoh et.al.[30] found that retrospectively analyzed patients with brain metastasis from lung cancer to evaluate treatment modalities for metastatic brain tumors and to devise criteria for individualized treatment plans. Between October, 1986 and December, 1994, 90 patients were selected for this study. The majority (67.8%) received wholebrain radiotherapy (WBRT) alone. WBRT following surgical removal was carried out on 14 patients (15.5%). The median dose of radiation therapy was 43.3 Gy for WBRT. The results were as follows: (1) PS (1 and 2 vs. 3 and 4), which showed a significant difference ($p<0.0001$) in survival by both univariate analysis and multivariate analysis, (2) brain metastasis alone or concurrent metastases to other sites

(p=0.0001) by univariate analysis, (3) the primary lesion controlled or uncontrolled (p=0.0006) by univariate analysis, (4) solitary brain metastasis or multiple brain metastases (p=0.0145) by univariate analysis. Patients were classified into 3 groups, A (PS1, 2, the primary lesion controlled, no distant metastasis and solitary brain metastasis), B (others except for groups A and C), and C (PS 3,4) based on 4 significant factors. Although the possibility of individualized treatment was suggested, based on 4 factors associated with the patient's condition and disease progression before treatment for brain metastasis, further evaluation by randomized clinical trials is needed.

Yong-Eun Lee Koo et.al.[31] studied that the ability to deliver effective concentrations of contrast or therapeutic agents selectively to tumors is a key factor for the efficacy of cancer detection and therapy. The utilization of the nanoparticle as a potential vector for brain or other site-specific delivery has the following advantages, due to its excellent engineerability and non-toxicity:

1. The loading/releasing of active agents (drugs/contrast agents) can be controlled. The drugs are loaded into nanoparticles by encapsulation, adsorption or covalent linkage. The loaded amount is controllable by changing the size of the nanoparticles or the number of linkers inside and on the surface of the nanoparticles. Each nanoparticle can carry a large amount of molecular therapeutic and/or contrast agents. Release of the agents may occur by desorption, diffusion through the NP matrix, or polymer wall, and/or NP erosion, which can all be controlled by the type of the nanoparticle's polymer matrix, i.e., having it become swollen or degradable in the tumor environment.
2. Specific molecular-targeting factors can be attached for localized binding to and/or uptake by the tumor cells, as well as for passage through the blood– brain barrier when appropriate. It should be noted that the selective delivery of nanoparticles to tumor is sometimes achieved due to the "leaky" tumor vasculature, which is known as the enhanced permeability and retention (EPR) effect. This and tumor-specific targeting moieties on the surface turn the nanoparticles into very efficient delivery vectors for tumors. Moreover, the use of targeted nanoparticles can achieve the delivery of large amounts of therapeutic or imaging agents per targeting biorecognition event, which is a major clinical advantage over simple immune targeted drugs.
3. A hydrophilic coating can be given to the nanoparticle to provide reduced uptake by the RES, resulting in both increased delivery of the nanoparticles to tumor sites and reduced toxicity to other body tissues.
4. The nanoparticle matrix provides protection, for the active agents, from enzymatic or environmental degradation.
5. The nanoparticles can alleviate the problem posed by the MDR of cancer cells against many drugs; done by masking the drugs entrapped within the nanoparticles. This feature may enhance the delivery of drugs that are normally excluded from tumors.

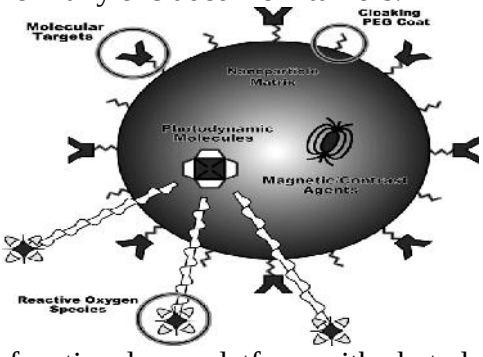

Fig 09: Multi-functional nanoplatform with photodynamic dye.[32]

Alonso MM et.al.[32] found that brain tumor stem cells (BTSCs) were isolated from surgical human malignant gliomas. This cancer cell population has been identified as the root for tumor initiation and resistance to therapies. Thus, it is imperative to develop new therapies that can eradicate this subpopulation to improve the prognosis of patients with brain tumors. Our group previously reported the antiglioma effect of the tumor-selective oncolytic adenovirus Delta-24-RGD that is now being tested in a phase I clinical trial for patients with malignant gliomas. We also showed that Delta-24-RGD infects, replicates in, and induces cell death in BTSCs. Interestingly, we observed that adenoviral-infected cells undergo autophagy and that autophagy-related cytoplasmic vacuolization might be part of the lysis process. Here, we summarize the materials and methods used in our study as follows: establishment of neurosphere cultures from surgical samples of human glioblastoma multiformes; assessment of stem cell markers; examination of adenoviral receptors in BTSCs; evaluation of the cytotoxicity induced by oncolytic adenoviruses; and assessment of autophagy in oncolytic adenovirus-infected BTSCs in vitro, and finally we describe a method to detect upregulation of the autophagy-related protein Atg5 in tumors treated with Delta- 24-RGD.

Meic H. Schmidt et.al.[33] studied that Photodynamic therapy (PDT) is a novel local treatment for recurrent brain tumors. The cytotoxic photodynamic effect on tumor cells depends on the interaction of localized photosensitizer, light and oxygen. Experimental and clinical studies indicate selective accumulation of photosensitizing drugs in brain tumors. In clinical practice the most common photosensitizer administered for brain tumor is hematoporphyrin derivative (HPD) and Photofrin porfimer sodium. Both of these photosensitizers are an inhomogeneous mixture of molecules that have two significant absorption peaks at 390 and 630 nm. Light penetration into brain and tumor tissue increases with longer wavelength light. Thus, because of the infiltrative nature of many brain tumors and in particular malignant gliomas, 630 nm laser light is frequently used as a light energy source. Light delivery to the tumor tissue can be accomplished via fiber optics that are directly inserted into the tumor or with an inflatable balloon adapter that is placed into the resection cavity. Until recently both these methods depended on costly laser technology. However, based on preliminary animal studies newer broad-spectrum high energy light-emitting diode (LED) technology might be useful in the treatment of brain tumors. Clinical studies in patients with newly diagnosed and recurrent brain tumors demonstrate that PDT has acceptable toxicity and can result in significant tumor responses. The most significant systemic side effect is temporary skin toxicity which can b avoided with light exposure precautions. Neurotoxicity, including brain stem hemorrhage, necrosis, and edema of brain tissue leading to focal clinical neurologic deficits has been demonstrated in animal studies and clinical studies. Because of these potential toxicities patients with a tumor in close proximity to eloquent brain are frequently excluded from clinical studies. The goal of this study was to evaluate the toxicity of PDT and LEDs on brain tissue in patients with recurrent brain tumors near eloquent regions.

Bodo E Lippitz[34] studied that Gamma Knife radiosurgery is highly effective even for brain metastases that are otherwise resistant to conventional fractionated externalbeam radiation therapy. Gamma Knife treatment is carried out in one session (one day) under local anaesthesia and causes low physical stress to the patient. The necessary precision requires a stereotactic magnetic resonance imaging (MRI) study before radiosurgery and a mstereotactic frame fixation during treatment. Generally, prescription doses of 18–22Gy are applied in Gamma Knife treatment of cerebral metastases. Doses are expressed as ‘minimum’ or ‘prescription doses’, reflecting the dose applied to the tumour periphery. This very often corresponds to the 50% isodose, resulting in an inhomogenous dose distribution within the tumour, with a maximum

dose ranging between 36 and 50Gy. It has been shown that this lack of dose homogeneity is irrelevant for the outcome. It is crucial to understand how Gamma Knife radiosurgery compares with microsurgery in the local control of metastases and prognosis. Three retrospective studies suggest that the two techniques are equivalent in terms of local control of the treated brain tumour.10–12 A recent prospective randomised study compared the efficacy of radiosurgery of brain metastases with the combined effect of open microsurgery plus WBRT.13 The minimally invasive approach with Gamma Knife radiosurgery provided equally good results to the invasive combination of open tumour resection and conventional radiotherapy with regard to survival, neurological death rates and freedom from local recurrence. Radiosurgery was associated with a shorter hospital stay, less frequent and shorter-duration steroid application and lower frequency of toxicities. Improved scores for role functioning and quality of life were seen six weeks after radiosurgery.13 Therefore, the therapeutic effect of Gamma Knife radiosurgery can be considered as equivalent to that of standard surgical approaches.

CONCLUDATORY COMMENS:

Quality of life is an important area of clinical neuro-oncology that is increasingly relevant as survivorship increases and as patients experience potential morbidities associated with new therapies. This review of quality-of-life studies in the brain tumor population aims to summarize what is currently known about quality of life in patients with both low-grade and high-grade tumors and suggest how we may use this knowledge to direct future research. To date, reports on quality of life have been primarily qualitative and focused on specific symptoms such as fatigue, sleep disorders, and cognitive dysfunction, as well as some symptom clusters. However, the increasing interest in exploring quality of life as a primary end point for cancer therapy has established a need for prospective, controlled studies to assess baseline and serial quality-of-life parameters in brain tumor patients in order to plan and evaluate appropriate and timely interventions for their symptoms. The use of nanotechnology for therapy has grown exponentially over the last two decades. By comparison, the growth of nanotechnology in the imaging and treatment of brain cancer has only begun but has already shown great promise. In this review, we have briefly provided the reader with an overview of targeted NP design (inorganic or organic synthesis, functionalization and loading of drug payloads), as well as the exciting frontier of theranostics.

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