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Brain Cancer

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Abstract
Cancer is a significant threat to public health and a leading cause of morbidity across the globe. Of all cancers, brain cancer can be particularly catastrophic as treatment often fails to achieve the desired degree of effectiveness and diagnosis remains associated with a high mortality rate. Africa, as a continent with resource-limited countries, needs to allocate the necessary proper healthcare infrastructure to significantly reduce cancer rates and improve patient survival. A World Health Organization (WHO) Feb 2018 report has recently shown that mortality rate due to brain or central nervous system (CNS) cancer is the highest in the Asian continent. It is of critical importance that cancer be detected earlier so that many of these lives can be saved. As cancer diagnosis is highly invasive, time consuming and expensive, there is an immediate requirement to develop a non-invasive, cost-effective and efficient tools for brain cancer characterization and grade estimation. Brain scans using magnetic resonance imaging (MRI), computed tomography (CT), as well as other imaging modalities, are fast and safer methods for tumor detection. Another objective of this paper is to find the current issues in existing engineering methods and also project a future paradigm. Further, we have highlighted the relationship between brain cancer and other brain disorders like stroke, Alzheimer's, Parkinson's, and Wilson's disease, leukoriaosis, and other neurological disorders in the context of machine learning and the deep learning paradigm.

Keywords: cancer, brain, pathophysiology, imaging, machine learning, extreme learning, deep learning, neurological disorders.

INTRODUCTION:

Brain cancer is one of the most aggressive and difficult-to-treat malignancies. Moreover, in the almost 50 years since the start of the war on cancer, the prospects for people who develop brain cancer have improved much more slowly than those of individuals with other types of cancer. Despite a lack of progress in the clinic, research on this group of conditions is advancing steadily, and treatments with the potential to transform the field are on the horizon. The fatality rate due to brain cancer is the highest in Asia. Brain cancer develops in the brain or spinal cord. The various symptoms of brain cancer include coordination issues, frequent headaches, mood swings, changes in speech, difficulty in concentration, seizures and memory loss. Brain cancer is a form of tumor which stays in the brain or central nervous system.[1] Brain tumors are categorized into various types based on their nature, origin, rate of growth and progression stage. Brain tumors can be either benign or malignant. Benign brain tumor cells rarely invade neighboring healthy cells, have distinct borders and a slow progression rate (e.g., meningiomas, pituitary tumors and astrocytoma's (WHO Grade-I)). Malignant brain tumor cells (e.g., oligodendrogliomas, high-grade astrocytoma's, etc.) readily attack neighboring cells in the brain or spinal cord, have fuzzy borders and

rapid progression rates. Brain tumors can be further classified into two types based on their origin: primary brain tumors and secondary brain tumors. A primary tumor originates directly in the brain. If the tumor emerges in the brain due to cancer existing in some other body organ such as lungs, stomach etc., then it is known as a secondary brain tumor or metastasis. WHO categorizes brain tumors into four grades (I, II, III and IV) as per the rate of growth Brain tumors are also characterized by their progression stages (Stage-0, 1, 2, 3 and 4). Stage-0 refers to cancerous tumor cells which are abnormal, but do not spread to nearby cells. Stages-1, 2 and 3 denote cells which are cancerous and spreading rapidly. Finally in Stage-4 the cancer spreads throughout the body.

Brain cancer diagnosis can be either invasive or non-invasive. Biopsy is the invasive approach where an incision is done to collect a tumor sample for examination. It is considered the gold standard for cancer diagnosis where the pathologists observe various features of cells of the tumor sample under a microscope to confirm malignancy. These imaging modalities help radiologists locate brain disorders, observe disease progression and in surgical planning.[2]

PATHOPHYSIOLOGY OF BRAIN CANCER:

The pathophysiology of brain cancer is discussed here. The reasons of occurrence of brain cancer are given from the perspective of cellular architecture and its functioning within the human body.

Cellular Level Architecture:

The cell is the basic building block of the human body. It also defines the function of each organ within the body such as oxygen flow, blood flow and waste materials management. Each cell has a central control system known as the nucleus which contains 23 pairs of chromosomes consisting of millions of genes. The instructions for these genes are contained within deoxyribonucleic acid (DNA), which is like a blueprint for genes and defines their behavior. The protein of the gene is like a messenger that communicates between the genes themselves. The message conveyed is defined by its 3D structure. Genes control the continuous process of the death of unhealthy or unwanted cells besides reproduction of healthy cells. The main cause of a cancer is uncontrolled growth of cells. A mutation alters this DNA sequence, which is the root cause of malfunctioning of the genes. There are many factors involved in DNA mutations such as environmental, lifestyle, and eating habits.[3]

The genes responsible for cancer are divided into three categories. We introduce and define each category in detail:

- The first category is known as tumor suppressors that controls the cell death cycle (apoptosis). This process has two signaling pathways. In the first pathway, the signal is generated by a cell to kill itself while in the second, the cell receives the death signal from nearby cells. This process of cell death is slowed down by a mutation in one of the pathways. It stops completely if this mutation happens in both pathways, leading to unstoppable cell growth. Some examples of cell suppressor genes are RB1, PTEN, which are responsible for cell death.
- The second category of genes is responsible for the repair of the DNA. Example of DNA repair genes are MGMT and p53 protein. Any malfunctioning in them may trigger cancer.
- The third group known as proto-oncogenes, are in opposition to the function of the tumor suppressor genes and are responsible for the production of the protein fostering the division process and inhibiting the normal cell death. In healthy cells, the cell division cycle is controlled by proto-oncogenes via protein signals which are generated by the cell itself or the connected cells. In this pathway, many

proteins are involved to carry the signal from the cell membrane to nucleus through the cytoplasm. In this process the cell membrane receptor accepts the signal and carries the message to nucleolus through various intermediate factors. Once, the signal reaches to the nucleus, the responsible genes for transcription is activated and performs the cell division task. Mutation alters its functionality which leads to transform this gene into an oncogene. In this situation the gene is unable to switch off the cell division signal and unstoppable growth of the cells may begin.

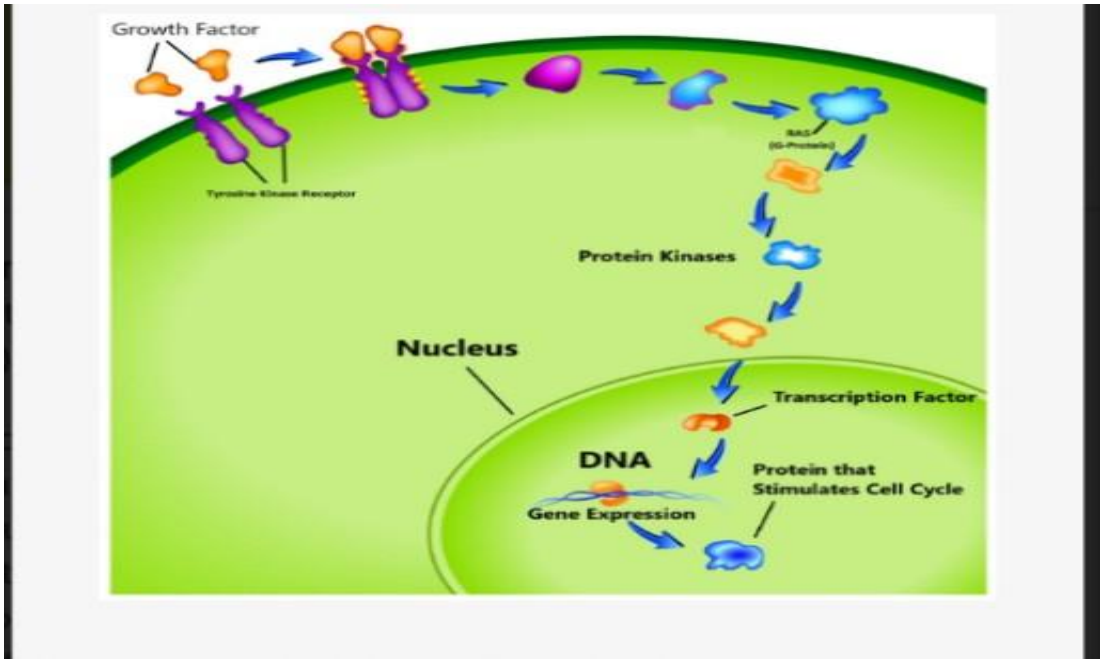

Figure-1: Cell cycle proliferation. (image courtesy: AtheroPoint^{TM}, Roseville, CA, USA).

If cancer starts in the body due to any of the above-mentioned reasons, it is known as a primary tumor which invades other organs directly. If the cancer starts through blood vessels then it known as secondary tumor or metastasis. Even though the secondary tumor is formed, it needs oxygen, nutrients and a blood supply to survive. Many genes exist in the body to detect these needs and start establishing a vascular network for them to satisfy their needs. This process is known as angiogenesis and is another cause of cancer explosion.[4]

Relevancy between Brain Tumor and Genes:

As discussed in the last section, mutations in certain types of genes define the cancer. In various studies, some connection is found between degree of mutation in genes and type of brain tumor, which. Tumor protein-53 (TP53) is involved in DNA repair and initiating apoptosis. Tp53 level is found to be quite abnormal in high-grade gliomas and mutations have been found in more than 80% of tumors. The retinoblastoma (RB1) gene is a tumor suppression gene. RB1 mutation is found in approximately 75% of brain tumors and it is more relevant to glioblastoma. EGFR is a trans-membrane receptor in the receptor tyrosine kinase (RTK) family. Mutation in EGFR will lead to increased cell cycle proliferation and increased tumor cell survival. Mutations in them inhibit enzyme activity. Generally, IDH1 mutation is found less in primary glioblastoma patients (5%), but more in high grade glioblastomas (70–80%)

EPIDEMIOLOGY:

Epidemiological data on brain cancers are lacking in Africa; thus, estimating prevalence and incidence is difficult. Of the total African population, only 11% is covered by cancer registries. Furthermore, cancer registries that meet the Cancer Incidence in Five Continents (CI5) inclusion criteria cover just 1% of the covered population. However, due to the WHO GCO program, international studies, and local hospital research, the prevalence and epidemiology of brain cancer within Africa can now be more accurately estimated.

Based on GCO, in 2020, approximately 9169 novel cases of brain cancer were estimated by SSA, accounting for 3.0% of the overall cases across the globe (WHO, 2020), while around 14.1% of the world population live in the continent (World Bank, 2021). However, in 2016, a Lancet study, based on GBD estimates, reported 12,754 cases of brain cancers (3.9% of the global total) in this region. This same study reported a 13.9% change in brain cancer incidence at age-standardized rates (ASRs) between 1990 and 2016 in these countries. In addition, the African 5-year prevalence was 4.9% in 2020 (WHO, 2020).[5]

Minimal research has been undertaken on the incidence of brain tumors in Africa at a national level. According to a Nigerian study published in 2011, brain cancer accounted for 3.6% of cancer cases in Lagos and Ibadan, coming sixth after breast, cervical, fibroids, liver, and stomach cancer, while the global rate is 1.3% (NCI, 2017). More recently in 2020, the reported incidence of brain tumors in Nigeria was 1798 (WHO, 2020), which means that Nigeria reported over 50% new cases of the average 5-year prevalence (3568) in a single year (WHO, 2020). Moreover, brain cancer was reported as the 13th most common cancer in Nigeria that year, whereas it was only 19th in the world (WHO, 2020).These data discrepancies raise concerns about the credibility of brain cancer reports in Nigeria.

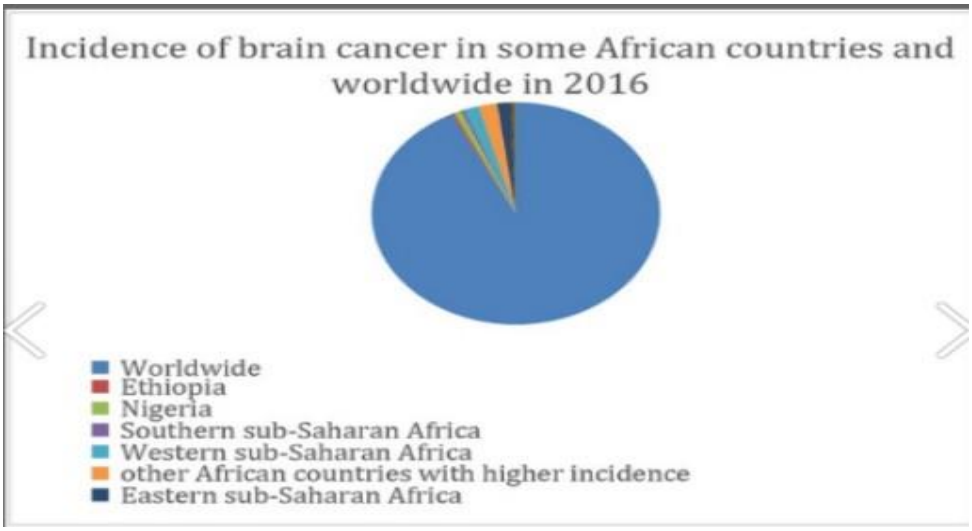

Fig-2: Incidence of brain cancer in some African countries and Worldwide in 2016.

IMAGING MODALITY:

Medical imaging techniques help doctors, medical practitioners and researchers view inside the human body and analyze internal activities without incisions. Cancer diagnosis, grade estimation, treatment response assessment, patient prognosis and surgery planning are the main steps and challenges in cancer treatment. The brain imaging techniques can be categorized into two types: *i.e.*, structural and functional imaging. Structural imaging consists of different measures related to brain structure, tumor location, injuries and other brain disorders. This activity visualization is possible due to metabolic changes in a

certain part of the brain which are reflected in the scans. CT and MRI are used for brain tumor analysis and are able to capture different cross-sections of the body without surgery.[6]

Computed Tomography Imaging:

In a CT scan, an X-ray beam circulates around specific part of the body and a series of images captured from various angles. The computer uses this information to create a series of two- dimensional (2D) cross-sectional image of the organ and combines them to make a three- dimensional (3D) image, which provides a better view of the organs. Positron emission tomography (PET) is a variant of CT where a contrast agent is injected into the body in order to highlight abnormal regions. CT scans are recommended by doctors in many conditions such as hemorrhages, blood clots or cancer. However, CT scans use X- rays which emit ionizing radiation and have the potential to affect living tissues, thereby increasing the risk of cancer. In one study, it is shown that the risk of radiation in CT is 100 times higher than in a normal X-ray diagnosis.

Magnetic Resonance Imaging

MRI is a radiation free and therefore a safer imaging technique than CT and provides finer details of the brain, spinal cord and vascular anatomy due to its good contrast. Axial, sagittal, and coronal are the basic planes of MRI to visualize the brain's anatomy as shown in Figure 2. The most commonly used MRI sequences for brain analysis are Tl-weighted, T2-weighted, and FLAIR. Tl-weighted scan provides gray and white matter contrast. T2-weighted is sensitive to water content and therefore well suited to diseases where the water accumulates inside brain tissues. T1- and T2-weighted images are also used to differentiate cerebrospinal fluid (CSF). The CSF is colorless and found in the brain and spinal cord. It looks dark in T1-weighted imaging and bright on T2-weighted imaging. The third sequence is fluid attenuated inversion recovery (FLAIR) which is similar to T2-weighted image except for its acquisition protocol.[7]

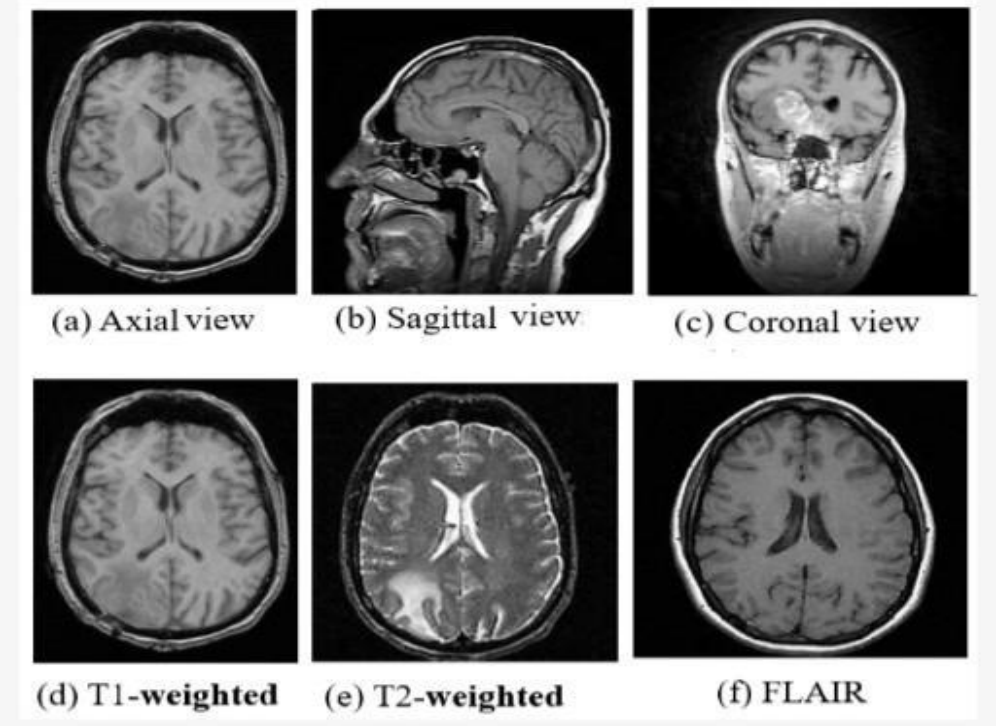

Fig-3: (**a**) Axial view, (**b**) Sagittal view, (**c**) Coronal view and (**d**) T1-weighted, (**e**) T2-weighted and (**f**) FLAIR Images of MRI. (image courtesy: AtheroPoint^{TM}).

Biopsy:
Biopsies are the gold standard for all cancer diagnosis and grade estimation. In a biopsy, the color, shape, and size of the cell nuclei of tumor sample are observed. This brings complexity in manual microscopic biopsy image analysis. The accuracy depends on the experience and expertise of the pathologist and therefore, computer assisted tools can help pathologist in Digital Pathological Image (DPI) analysis and may provide better results than manual approach. Hematoxylin & Eosin (H&E) staining is the most commonly used method for a biopsy sample analysis. Cytopathology is used to know the cell structure, function and their chemistry. Tissue proteins are assessed by using immuno- fluorescence imaging.

MR Spectroscopy:
MRI is able to visualize the anatomical structure of the brain, whereas, Magnetic Resonance spectroscopy (MRS) is able to detect small biochemical changes in the brain. This property is useful for the brain tissue classification in brain tumor, stroke and epilepsy. Here, several metabolites and their products such as amino acids, lactate, lipids, alanine, etc., where, the frequency can be measured in parts per million (ppm). There are unique metabolic signatures associated with each tumor type and their grades, therefore, the neurologist measures the changes between normal and cancerous tissues by the frequency map of ppm of each metabolite. In the authors had proposed a deep learning-based model for brain tumor diagnosis using MRS imaging techniques. The authors proposed three deep models for brain tumor classification into healthy, low- or high-grade tissue types. In another study, the authors proposed a brain tumor grading method using MR spectroscopy. The best performance was achieved by random forest, giving an AUC of 0.91, while a sensitivity of 86.1% was achieved using the LWL-based method.

Types of brain cancer:
1. Primary brain cancer is a condition that tumor cells originate from primary brain tissue. This tumor type is confined only to the brain or spinal cord and never spreads/metastasizes from outside the brain or central nervous system. Primary brain cancer is a rare disease but is super aggressive and has a poor prognosis.
2. Secondary/Metastasized brain cancer is cancer from another part of the body (the original tumor is not brain tissue) that spreads to the brain, e.g., breast cancer metastasizes to the brain or lung cancer with brain metastasis. Secondary brain cancer or "brain metastases" is more common than a primary brain tumor. Treatment and prognosis depend on the primary cancer.[8]

Signs and Symptoms:
Many symptoms of brain cancer are similar to those of less severe conditions. If you experience the symptoms for longer than one week, you should consult a doctor to find the cause and receive timely treatment. The symptoms of brain cancer depend on the size and location of the brain tumor. Brain cancer shares many symptoms with several less serious conditions, especially in the early stages.

Common brain cancer symptoms include:
- a lack of coordination
- a lack of balance
- difficulty walking
- memory lapses

- Speech problems
- abnormal eye movements
- muscle jerking
- Muscle twitching
- unexplained passing out, or syncope
- drowsiness
- seizures: severe (e.g. a convulsion) or mild (a fleeting disturbance of awareness, sensation or jerking muscles)
- weakness or paralysis in part of the body
- general irritability, drowsiness or a change in personality
- disturbed vision, hearing, smell or taste.[9]

Causes of brain cancer:

Some factors that can increase your risk of brain cancer include:

- some brain and spinal cord tumors are more common in people with certain inherited or genetic conditions
- people exposed to very high doses of radiation to the head.

Diagnosis of brain cancer:

CT Scan: A CT (computerized tomography) scan uses x- rays to take multiple pictures of the inside of the body

MRI: MRI (magnetic resonance imaging) scan uses a computer and a powerful magnet cross-sectional picture of your body.

MRS (magnetic resonance spectroscopy): A MRS (magnetic resonance spectroscopy) scan looks for changes in the chemical make-up of the brain and can be done at the same time as an MRI.

PET scan: A PET (positron emission tomography) scan injects a small amount of radioactive solution to show up cancer cells as they absorb the solution faster than normal cells.

SPECT (single proton emission computerized tomography): A single photon emission CT (SPECT) scan takes three-dimensional images of blood flow in the brain and areas with higher blood flow, such as a tum our, will be brighter on the scan.

Lumbar puncture: A lumbar puncture (also known as spinal tap) uses a needle to collect cerebrospinal fluid which will be sent to a laboratory to test for cancer cells.[10]

After a diagnosis of brain cancer:

After finding out you have brain cancer, you may feel shocked, upset, anxious or confused. These are normal responses. A diagnosis of brain cancer affects each person differently. For most it will be a difficult time, however some people manage to continue with their normal daily activities. Your specialist will arrange for a range of health professionals (multidisciplinary team) to plan your treatment. This will be based on several factors including the type, size, location and genetic make-up of the cancer as well as, your age and general health, the types of symptoms you have and your needs and preferences.[11]

Risk factors:

Risk factors that might be related to developing brain cancer include:

- increased age
- a family history of brain cancer
- long-term smoking
- exposure to pesticides, herbicides, and fertilizer
- working with elements that can cause cancer, like lead, plastic, rubber, petroleum, and some textiles.[12]

TREATMENT:

Primary brain cancer is treated differently from secondary brain cancer. Your doctor will determine the appropriate treatment approach, depending on the type, size, and location of the brain cancer, as well as your age and health. The doctor will discuss the pros and cons of the treatments with you.

Brain surgery: It can completely or partially remove the brain tumor, depending on its location. It is the most common treatment.

Chemotherapy: It can shrink the brain tumor and destroy cancerous cells.

Radiation therapy: It can destroy cancerous cells that are beyond removal by brain surgery.

Combination therapy: It treats a patient with chemotherapy and radiation therapy simultaneously.

Targeted/ immunotherapy: It helps restore the immune system's ability to fight brain cancer.

Other medications: It treat symptoms or side effects of brain cancer treatment, i.e., anti-seizure and clinical trial drugs.

Rehabilitation: Such as occupational and physical therapy, to restore your ability to talk, walk, and do daily activities disrupted by brain cancer.

Alternative therapies: Such as eating a balanced diet to boost your immunity and replenish nutrients lost from cancer treatment

Biologic drugs: These drugs boost, direct, or restore your body's natural defenses against your tumor. For example, immunotherapy is a commonly used class of biologic drug that works by increasing your immune system's ability to target and fight cancer.

Other medications: Your doctor may prescribe medications to treat symptoms and side effects caused by your brain tumor and brain cancer treatments.

Clinical trials: In advanced cases of brain cancer that don't respond to treatment, clinical trial therapies and medications may be used. These are treatments that are still in the testing phase. Clinical trails for brain cancer could include an immunotherapy trial and a CAR T cell therapy trial.[13]

Follow-up tests, such as imaging tests to check if brain cancer recure.

Brain tumours may be treated with surgery, radiation therapy, chemotherapy or steroid therapy, or a combination of these treatments.

Some tumours can be removed completely by surgery (craniotomy). Post-operative radiotherapy improves local control and survival. For glioblastomas, temozolomide may be added during or after radiotherapy to further improve outcomes.

If a tumour cannot be removed, the aim of treatment is to slow growth and relieve symptoms by shrinking the tumour and any swelling around it. Treatment options include radiation therapy with or without temozolomide.

Prognosis for brain cancer:

Prognosis means the expected outcome of a disease. An individual's prognosis depends on the type and stage of cancer, as well as their age and general health at the time of diagnosis.

For benign tumors that can be completely removed, cure is likely. For malignant tumours, outcomes depend on how slowly or quickly the tumor develops and responds to treatment.

Prevention:

We cannot prevent all brain cancers, but we can avoid certain risks to lower the chance of developing brain cancer.

- Avoid unnecessary radiation exposure.
- Exercise.
- Quit smoking.

There's no way to prevent brain cancer, but you can reduce your risk by avoiding:

- exposure to pesticides and insecticides
- exposure to carcinogenic chemicals
- unnecessary exposure to radiation.[14]

Conclusion:

Our main focus of the review is to provide state of art in brain cancer area that includes pathophysiology of cancer, imaging modality, WHO guidelines for tumor classification, primary diagnosis methods, and existing computer- assisted algorithms for brain cancer classifications using the machine and deep learning techniques. Finally, we have compared brain tumor with other brain disorders. We have concluded that due to automatic feature extraction capability of DL based methods, recently it is getting more attention and accuracy compared to conventional classification techniques for medical imaging. It is for sure that many lives can be saved if cancer detected and suitable grade estimated through fast and cost- effective diagnosis techniques. Therefore, there is dare need to develop fast, non-invasive and cost-effective diagnosis techniques. Here, DL methods can play a major role for the same. In best of our knowledge, very less work has done for the automatic tumor grading using DL techniques and their full potential, yet to be explored. The incidence of brain cancer is increasing. As the trend of brain cancer in the world is increasing, preventive and protective measures to reduce the risk factors of this cancer are recommended to reduce the incidence of disease.

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