USE OF OLPM MODEL BASED ON IMAGE FINDINGS FOR SURVIVAL PREDICTION AND BETTER PROGNOSIS OF PATIENTS WITH GLIOBLASTOMA MULTIFORME (BRIANTUMOR)

A Seminar Report

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CERTIFICATE

This is to certify that the seminar report entitled

Glioblastoma Multiforme(GBM) and OLPM model

is a bonafide record of the work done by Mr. Fayik Suhail Roll No. 5783 under our supervision, in partial fulfillment of the requirements for the award of Degree of Bachelor of Engineering in Computer Engineering from SSM College Of Engineering for the year 2019.

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ABSTRACT

CANCER is 2nd most common cause of death after the Ischemic heart disease in the World due to its devastating and health ravaging manifestations and damage that it inflicts upon the human body. It takes away so many lives every day and the numbers are rising each passing year . According to recent report by WHO, more than 18 million people have been diagnosed with cancer in 2018 alone. Cancer is a basically an aberration that begins when a single cell among all the other trillions in a human body begins to grow out of control. The reason for such an obliterating condition are many but spontaneous. Lymphomas, sarcomas, melaomas, glioblastomas etc all begin with that same microscopic accident –Mutation in a single cell.

Till date ,there is no treatment methodolgy that can completely cure CANCER especially in those cases where the cancer has made significant progression. yes,there are treatment methodologies but that only have the capability to ameliorate the potential manifestations of the disease that come with a number of side effects such as radiation therapy, use of chemotherapy agents that leaves a cascading impact on the body. But, never hopeless,Medical researchers have tried every possibility to build up such treatment methologies and therapies that will help patients to achieve sustained remissions and in the way make it possible to completely cure the patient of this malevolent and baleful disease.One such path breaking and revolutionary breakthrough that completely changed the way we treat cancer is CANCER IMMUNOTHERAPY that have got the potential to treat even the deadiest malignancies and almost every type of cancer.

Moving to the Technological front,The use of Radiology and its image guided procedures have brought a paradigm shift in the way we detect,diagnose and treat diseases.The use of X-rays,CT scans,MRI scans and PET scans have become an indispensable part used by medical professtionals for better prognosis of the disease. But these procedures still have their own limitations as they are only restricted to only detecting the location and area of spread of the diseases but this was not sufficient to contain such a deadly disease like cancer.

The use of Artificial Intelligence(AI) and Machine Learning(ML) ushered in another technological revolution while throwing up another promising lifeline to treat such deadly and health ravaging diseases with high degree of precision. Machine Learning remains a young field with many underexplored research opportunities and harnessing such technological tools will certainly give us a great understanding of all the dimesions and aspects of such conditions.

The main objective behind using AI and Machine learning models that along with radiological tools is to harness its potential so as overpower these lethal diseases with a greater force. Scientists have now understood the potential of these technological tools and today they are building up highly complex mathematical models that uses statistical and probabilistic approaches to meticulously prognosticate various parameters that ensures precise survival estimations of the patients suffering from these deadly diseases and also assists medicos to initiate best treatment plans and even know in advance wheather the treatment plans they have initiated are certainly helpful in achieving sustainted remissions or not.

The reason for selecting Glioblastoma(Brain Tumor) as a prime focus in my seminar is quite conspicuous that is worrying trend of how the disease is slowly consuming lives and need to make the people aware to take necessary precautions in advance in order to contain this condition that has become so ubiqituous.The another reason is because of the poor prognosis of Glioblastoma which is one of most common and one of the most aggressive grade IV tumours with its extremely bleak chances of survival.

Although there may be numerous solutions elicited to increase the chances of survival of patients and make better prognosis but one such solution that is surely going to help out the medicos in understanding as well as treating glioblastoma better is a much advanced prediction model that goes by the name of **OLPM(Optimized Linear Prognostic Model)** that has outperformed almost all the previous and recently introduced Machine Learning Models in terms of predicting some significant parameters(morphological and textual descriptors) that it extricates from large amount of datasets(high quality MRI scans) that truly holds better future prospects.

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Chapter 1

INTRODUCTION

Cancer is a disease that begins when cells inside the human body starts to grow out of control. It is basically a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body.There are a number a cancer types that all begin with the same microscopic accident –Mutation in a single cell. I call it "The Emperor Of all Maladies"

It is important is note that not all tumors or lumps are cancerous . Benign tumors are not classified as being cancer because they do not spread to other parts of the body.

There are over 100 different known cancers that affect humans and these are broadly classified on the basis of -into the type of cell they originated into or the body part they arised which include:-

1) *Carcinoma*: Cancers derived from epithelial cells. This group includes many of the most common cancers, particularly in older adults. Nearly all cancers developing in the breast, prostate, lung, pancreas, and colon are carcinomas.
2) *Sarcoma*: Cancers arising from connective tissue (i.e. bone, cartilage, fat, nerve), each of which develop from cells originating in mesenchymal cells outside the bone marrow.
3) Lymphoma and leukemia: These two classes of cancer arise in the blood cells. Leukemia is the most common type of cancer in children accounting for about 30%. However, far more adults develop lymphoma and leukemia.
4) *Germ cell tumor*: Cancers derived from germ or sex cells, most often presenting in the testicle or the ovary (seminoma and dysgerminoma, respectively).
5) *Blastoma*: Cancers derived from immature "precursor" cells or embryonic tissue. Blastomas are more common in children than in older adults etc.

1.1) Potential Manifestations of Cancer-The potential Signs & Symtoms of Cancer include:-

1)Development of a lump in any part of the body

2) abnormal bleeding

3) prolonged cough

4)unexplained weight loss

5)severe headache

6)a change in bowel movements etc

but these symptoms may not necessarily indicate cancer, they can also indicate some other disease as well.

1.2)Potential Causes of cancer- the main causes that becomes the cause of cancer in most of the case involve :-

1)Use of Tobacco and other Tobacco products such as cigarettes.

2)Lack of physical activity and sedentary lifestyle.

3)Obesity and being overweight.

4)Excessive drinking of Alcohol

5)Ionizing radiations and Environmental pollution etc.

Apart from these , bacterial and viral infections are potential factors that cause cancers such as those caused by bacteria and viruses such as Helicobacter pylori, hepatitis B, hepatitisC, Human Papilloma Virus Infection(HPV), Epstein–Barr virus(HerpesVirus) and human immunodeficiency virus (HIV) etc.

1.3)Prophylaxis(Prevention) for Cancer- There are a number of preventive measures that need to be taken for preventing yourself from cancer which include:-

1)No use of Tobacco and Tobaccco related products such as cigarrettes.

2)involving in a lot of physical activity and maintaining a healthy life style.

3)maintaining a healthy body weight(BMI).

4)No use of Alcohol and other alcoholic beverages.

5) Consuming plenty of vegetables, fruits and whole grains.

6) not eating too much processed and red meat.

7) vaccination against certain infectious diseases.

8) avoiding too much exposure to sunlight and other harmful radiations.

1.4) BOTTOMLINE –

1)Cancer can be detected by certain screening tests. It is then typically further investigated by medical imaging such as MRI and PET scans and confirmed by biopsy.

2)After it is detected,it is often treated with some combination of radiation therapy, surgery, chemotherapy and targeted therapy.

The emergence of new forms of therapies have opened new doors in the treatment of cancer and the way it is treated such as – Immunotherapy(Dendritic cell based therapy).

3) In 2015, about 90.5 million people had cancer, About 14.1 million new cases occur a year . It caused about 8.8 million deaths (15.7% of deaths).

According to a recent report by WHO , more than 18 million people are diagnosed with cancer in 2018 alone.

4)Till date there is no treatment methodology that can completely cure the disease especially in those cases where the cancer cells have made significant progression.In most of the cases ,the medico (Oncologist) advices a radiation therapy and systemic chemotherapy but these methods do have a glitch in the sense that they also disrupt other essential cellular and metabolic processes that occur in the human body.

5)The most common types of cancer that are commoly found in males include- lung cancer, prostate cancer, colorectal cancer and stomach cancer. In females, the most common types are breast cancer, colorectal cancer, lung cancer and cervical cancer.

6) In children, acute lymphoblastic leukemia and brain tumors(glioblastoma) are most common, except in Africa where non-Hodgkin lymphoma occurs more often.In 2012, about 165,000 children under 15 years of age were diagnosed with cancer.

7)The financial costs of cancer were estimated at $1.16 trillion USD per year as of 2010.

8)As per the recent data, one of the most common types that humans suffer from is Glioblastoma Multiforme(GBM) , commonly called as glioblastoma or brain tumor – the one with the worst prognosis .

1.5) STATISTICAL DATA ABOUT THE NUMBER OF DEATHS CAUSED BY CANCER-

According to the most recent data available with the National Cancer Institute (NCI), the 10 cancers that killed the most people in the United States between 2003 and 2007 are:

1. Lung and bronchial cancer: 792,495 lives
Lung and bronchial cancer is the top killer cancer in the United States. Smoking and use of tobacco products are the major causes of it, and it strikes most often between the ages of 55 and 65, according to the NCI. There are two major types: non-small cell lung cancer, which is the most common, and small cell lung cancer, which spreads more quickly. More than 157,000 people are expected to die of lung and bronchial cancer in 2010.
2. Colon and rectal cancer:268,783 lives
Colon cancer grows in the tissues of the colon, whereas rectal cancer grows in the last few inches of the large intestine near the anus, according to the National Cancer Institute. Most cases begin as clumps of small, benign cells called polyps that over time become cancerous. Screening is recommended to find the polyps before they become cancerous, according to the Mayo Clinic. Colorectal cancer is expected to kill more than 51,000 people in 2010.

3. Breast cancer: 206,983 lives

Breast cancer is the second most common cancer in women in the United States, after skin cancer, according to the Mayo Clinic. It can also occur in men – there were nearly 2,000 male cases between 2003 and 2008. The cancer usually forms in the ducts that carry milk to the nipple or the glands that produce the milk in women. Nearly 40,000 people are expected to die from breast cancer in 2010, according to the NCI.

4. Pancreatic cancer: 162,878 lives

Pancreatic cancer begins in the tissues of the pancreas, which aids digestion and metabolism regulation. Detection and early intervention are difficult because it often progressives stealthily and rapidly, according to the Mayo Clinic. Pancreatic cancer is expected to claim nearly 37,000 lives in 2010, according to the NCI.

5. Prostate cancer: 144,926 lives

This cancer is the second-leading cause of cancer deaths in men, after lung and bronchial cancer, according to the NCI. Prostate cancer usually starts to grow slowly in the prostate gland, which produces the seminal fluid to transport sperm. Some types remain confined to the gland, and are easier to treat, but others are more aggressive and spread quickly, according to the Mayo Clinic. Prostate cancer is expected to kill about 32,000 men in 2010, according to the NCI.

6. Leukemia: 108,740 lives

There are many types of leukemia, but all affect the blood-forming tissues of the body, such as the bone marrow and the lymphatic system, and result in an overproduction of abnormal white blood cells, according to the NCI. Leukemia types are classified by how fast they progress and which cells they affect; a type called acute myelogenous leukemia killed the most people – 41,714 – between 2003 and 2007. Nearly 22,000 people are expected to die from leukemia in 2010.

7. Non-Hodgkin lymphoma: 104,407 lives

This cancer affects the lymphocytes, a type of white blood cell, and is characterized by larger lymph nodes, fever and weight loss. There are several types of non-Hodgkin lymphoma, and they are categorized by whether the cancer is fast- or slow-growing and which type of lymphocytes are affected, according to the NCI. Non-Hodgkin lymphoma is deadlier than Hodgkin lymphoma, and is expected to kill more than 20,000 people in 2010.

8. Liver and intrahepatic bile duct cancer: 79,773 lives

Liver cancer is one of the most common forms of cancer around the world, but is uncommon in the United States, according to the Mayo Clinic. However, its rates in America are rising. Most liver cancer that occurs in the U.S. begins elsewhere and then spreads to the liver. A closely related cancer is intrahepatic bile duct cancer, which occurs in the duct that carries bile from the liver to the small intestine. Nearly 19,000 Americans are expected to die from liver and intrahepatic bile duct cancer in 2010, according to the NCI.

9. Ovarian cancer: 73,638 lives

Ovarian cancer was the No. 4 cause of cancer death in women between 2003 and 2007, according to the NCI. The median age of women diagnosed with it is 63. The cancer is easier to treat but harder to detect in its early stages, but recent research has brought light to early symptoms that may aid in diagnosis, according to the Mayo Clinic. Those symptoms include abdominal discomfort, urgency to urinate and pelvic pain. Nearly 14,000 women are expected to die of ovarian cancer in 2010, according to the NCI.

10. Esophageal cancer: 66,659 lives

This cancer starts in the cells that line the esophagus (the tube that carries food from the throat to the stomach) and usually occurs in the lower part of the esophagus according to the Mayo Clinic. More men than women died from esophageal cancer between 2003 and 2007, according to the NCI. It is expected to kill 14,500 people in 2010.

1.6) SURVEY OF PATIENTS WITH CANCER IN J&K STATE-

Cancer is the leading cause of death among patients in Jammu and Kashmir (J&K). The objective of this study was to estimate the number of cancer patients receiving treatment at four prospective hospitals in J&K. The data were obtained from the hospital-based records from Government Medical College (GMC) Hospital Jammu, Acharya Shri Chander College of Medical Sciences and Hospital (ASCOMS) Jammu, Sher-iKashmir Institute of Medical Sciences (SKIMS) Srinagar, and Government Medical College (GMC) Hospital, Srinagar, which was scrutinized and analysed.

In this retrospective record review study, the hospital registry entry was regarded suitable for assessing the cancer cases in the J&K.

The data comprised of 6,359 patients who had been diagnosed of various cancer conditions between Jan 2016 and Jan 2017, and obtained treatment from the hospitals. Out of all the cancer patients, men were 4038 (63.5%), and women were 2321 (36.5%). In these hospitals, cancers pertaining to the stomach-1551 (24.4%), lung-1498 (23.6%), esophagus and gastroesophageal (GE) junction-872 (13.7%), colorectal-564 (8.9%), lymphomas-41 (26.5%), skin-191 (3.0%), laryngopharynx-165 (2.6%), acute leukemias-230 (3.6%), prostate-94 (1.5%), brain-154 (2.4%), ovary-258 (4.1%), breast-234 (3.7%), gall bladder-136 (2.1%) were the leading sites in order.

The lung cancer, throat cancer, stomach cancer and lymphoma were found dominant among males, while in females it was cervical cancer, breast cancer, stomach cancer and lung cancer.

The overall incidence of cancer in J&K is on the increase. Cancers of esophagus, stomach and lungs have a high incidence both in men and women in J&K. Future studies on environmental, physiological and genetic factors in relation to these cancers may improve our understanding these malignancies in this state. This will help in the development of better prevention and treatment strategies against these cancers.

1.6.1)Survey findings in four potential Hospitals-

a) **Government Medical College Hospital Jammu (GMC Jammu) -** A total of 1716 cancer patients were observed in GMC Jammu from which the number of male patients was 1125 (65.6%), while as the number of female patients was 591 (34.4%) . In this hospital, stomach-403 (23.5%), lung-398 (23.2%), esophagus and gastroesophageal (GE) junction-216 (12.6%), colorectal-102 (5.9%), lymphomas-98 (5.7%), skin-56 (3.3%), laryngopharynx-43 (2.5%), acute leukemias-79 (4.6%), prostate-21 (1.2%), brain-71 (4.1%), ovary-94 (5.5%), breast-83 (4.8%) and gall bladder-52 (3.0%) were the leading sites of cancer .

b) **Acharya Shri Chander College of Medical Sciences and Hospital Jammu (ASCOMS Jammu)** - Our results showed that a total number of 1040 patients were diagnosed with cancer between Jan 2016 and Jan 2017 in ASCOMS Jammu, out of which male patients included 598 (57.5%) and female patients included 442 (42.5%) .The leading sites of incidence in cancer patients diagnosed in this hospital were stomach-322 (31.0%), lung-243 (23.4%), esophagus and gastroesophageal (GE) junction-176 (16.9%), colorectal-67 (6.4%), lymphomas-45 (4.3%), skin-31 (3.0%), laryngopharynx-22 (2.1%), acute leukemias-23 (2.2%), prostate-09 (0.9%), brain-13 (1.3%), ovary-43 (4.1%), breast-27 (2.6%) and gall bladder-19 (1.8%) .

c) **Sher-i-Kashmir Institute of Medical Sciences Srinagar (SKIMS) Srinagar -** In SKIMS Srinagar, 2513 cancer patients were observed from which the number of male patients was 1635 (65.1%) while female patients were 878 (34.9%) .The leading sites of incidence in cancer patients diagnosed in this hospital were stomach-561 (22.3%), lung-561 (22.3%), esophagus and gastroesophageal (GE) junction-411 (16.4%), colorectal-235 (9.4%), lymphomas-187 (7.4%), skin-78 (3.1%), laryngopharynx-86 (3.4%), acute leukemias-81 (3.2%), prostate-41 (1.6%), brain-58 (2.3%), ovary-91 (3.6%), breast-75 (3.0%) and gall bladder-48 (1.9%) .

d) **Government Medical College Hospital Srinagar (GMC Srinagar) -** In GMC Srinagar, a total of 1090 cancer patients were observed from which the number of male patients was 680 (62.4%) while female patients were 410 (37.6%).In this hospital, stomach-265 (24.4%), lung-296 (27.1%), esophagus and gastroesophageal (GE) junction-69 (6.3%), colorectal-160 (14.7), lymphomas-82 (7.5%), skin-26 (2.4%), laryngopharynx-14 (1.3%), acute leukemias-47 (4.3%), prostate-23 (2.1%), brain-12 (1.1%), ovary-30 (2.8%), breast-49 (4.5%) and gall bladder-17 (1.6%) were the leading sites of cancer.

1.7 SUMMARY

In this section , we defined what is basically ‘cancer’ and its potential manifestations(Signs and Symptoms) and its potential causes and how we can take various precautions in advance in order to prevent ourselves from getting inflicted

such a devastating condition and its unforeseen repercussions. We also highlighted various facts and figures that reflected the seriousness of the disease that takes a heavy toll on human health.

Chapter 2

LITERATURE SURVEY

2.1) GLIOBLASTOMA(Bain Tumor) – Glioblastoma (also called GBM) are malignant GradeIV tumors, where a large portion of tumor cells are reproducing and dividing at any given time. They are nourished by an ample and abnormal tumor vessel blood supply. The tumor is predominantly made up of abnormal astrocytic cells, but also contain a mix of different cell types (including blood vessels) and areas of dead cells (necrosis).

Glioblastomas are infiltrative and invade into nearby regions of the brain. They can also sometimes spread to the opposite side of the brain through connection fibers (corpus callosum). It is exceedingly rare for glioblastomas to spread outside of the brain.

Glioblastomas may arise de novo, meaning they begin as a Grade IV (aggressive) tumors with no evidence of a lower grade precursor. De novo tumors are the most common form of glioblastoma and tend to be more aggressive and tend to affect older patients. Alternatively, secondary glioblastomas may progress from a lower-grade astrocytic tumors (Grade II or Grade III) and evolve into Grade IV tumors over time. In general, these tumors tend to be slower growing initially, but can progressively become aggressive.

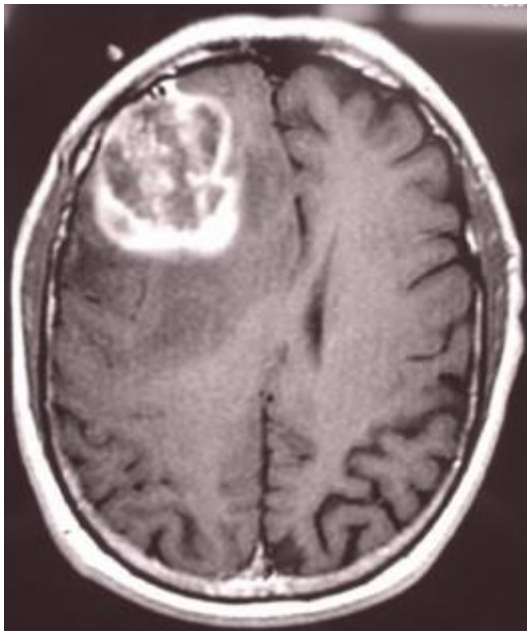
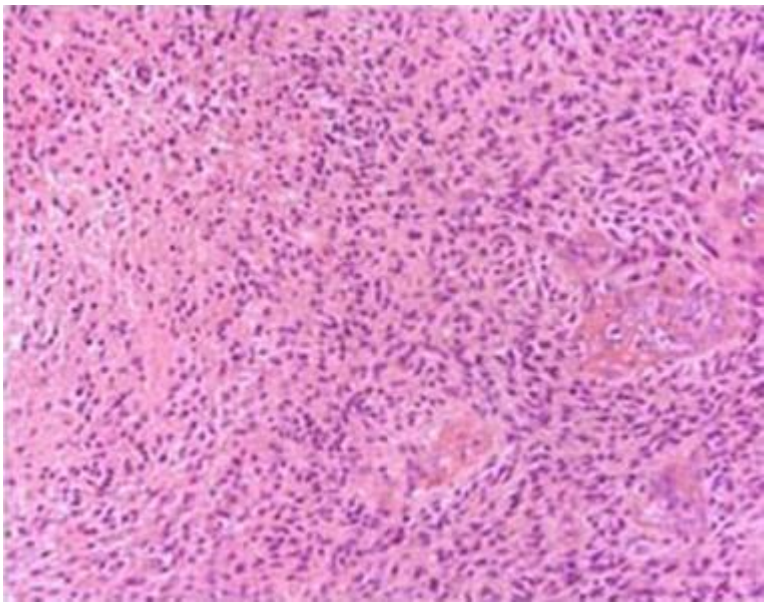


Figure1

MRI scan of a patient with GLIOBLASTOMA(GBM).

Figure2



Histopathologic slide demonstrating a Glioblastoma(GBM).

Glioblastoma multiforme (GBM) (also called **glioblastoma**) is basically a fast-growing glioma that develops from star-shaped glial cells (**astrocytes** and **oligodendrocytes**) that support the health of the nerve cells within the brain.

GBM is often referred to as a **grade IV astrocytoma**. These are the most invasive type of glial tumors, rapidly growing and commonly spreading into nearby brain tissue.

GBMs can arise in the brain **de novo** or evolve from **lower-grade astrocytomas** or o**ligodendrogliomas**. In adults, GBM occurs most often in the cerebral hemispheres, especially in the frontal and temporal lobes of the brain. GBM is a devastating brain cancer that typically results in death in the first 15 months after diagnosis.

There are two subtypes of glioblastoma: 1) glioblastoma, IDH-wild type (90%), frequently defined as primary or de novo predominated in patients over 55 years of age; 2) glioblastoma, IDH mutant (10%) which called secondary with malignant transformation from low grade glioma, common in younger patients under 45 years.

GBMs are **biologically aggressive tumors** that present unique treatment challenges due to the following characteristics-

1)Localization of tumors in the brain.

2)Inherent resistance to conventional therapy.

3)Limited capacity of the brain to repair itself.

4)Migration of malignant cells into adjacent brain tissue.

5)The variably disrupted tumor blood supply which inhibits effective drug delivery.

6)Tumor capillary leakage, resulting in an accumulation of fluid around the tumor; (peritumoral edema) and intracranial hypertension.

7)A limited response to therapy.

8)The resultant neurotoxicity of treatments directed at gliomas.

2.1.1)Prevalence and Incidence-

Glioblastomas represent about 15% of all primary brain tumors. they are slightly more common in men than in women.

The National Cancer Institute estimates that 22,850 adults (12,630 men and 10,280 women) were diagnosed with brain and other nervous system cancer in 2015. It also estimates that in 2015, 15,320 of these diagnoses resulted in death.

GBM has an incidence of two to three per 100,000 adults per year, and accounts for 52 percent of all primary brain tumors. Overall, GBM accounts for about 17 percent of all tumors of the brain (primary and metastatic). These tumors tend to occur in adults between the ages of 45 and 70. Between 2005 and 2009, the median age for death from cancer of the brain and other areas of the central nervous system was age 64.

2.1.2)Symptoms-

Symptoms vary depending on the location of the brain tumor, but may include any of the following-

1)Persistent headaches.

2)Vomiting.

3)Loss of appetite.

4)Changes in mood and personality.

5)Changes in ability to think and learn.

6)New onset of seizures.

7)Speech difficulty of gradual onset.

Patients with glioblastomas develop symptoms rapidly due to mass effect from the tumor itself or from the fluid surrounding the tumor (edema) that causes further brain swelling. For example, common symptoms at diagnosis are related to the increased pressure in the brain (nausea, vomiting, and severe headaches which are typically worse in the morning).

Patients can also present with neurological symptoms which are dependent on the tumor location (for example, weakness or sensory changes of face, arm or leg, balance difficulties and neurocognitive/memory issues).

Other common presentation includes seizures.

2.1.3)Risk Factors-

A very small percentage of glioblastomas are inherited as part of other syndromes such as **Turcot Syndrome**(characterized by the association of colonic polyps and central nervous system tumors. The relative risk of cerebral tumor in patients with familial adenomatous polyposis is considered 92 times more that found in the general population), **Li-Fraumeni syndrome**(a rare disorder that greatly increases the risk of developing several types of cancer, particularly in children and young), and **Neurofibromatosis** type1(a neurocutaneous syndrome that can affect many parts of the body, including the brain, spinal cord, nerves, skin, and other body systems. NF can cause growth of non-cancerous (benign) tumors involving the nerves and brain. It is also called **von-Recklinghausen disease**).

The vast majority of glioblastomas occur randomly, without inherited genetic factors. The only confirmed risk factor is ionizing radiation to the head and neck region.

2.1.4)Diagnosis-

Sophisticated imaging techniques can very accurately pinpoint the location of brain tumors. Diagnostic tools include **computed tomography** (CT or CAT scan) and **magnetic resonance imaging** (MRI).

Intraoperative MRI may also be useful during surgery to guide tissue biopsies and tumor removal. **Magnetic resonance spectroscopy** (MRS) is used to examine the tumor's chemical profile, with **positron emission tomography** (PET scan) helpful in detecting tumor recurrence.

2.1.5)Grading-

After a brain tumor is detected on a CT or MRI scan, a neurosurgeon obtains tumor tissue for a biopsy and the tissue is examined by a neuropathologist.

The analysis of tumor tissue under a microscope is used to assign the tumor a name, grade, and to provide answers to the following questions:

1)From what type of brain cell did the tumor arise? (The name of the tumor is derived from this; for example, astrocytomas arise from astrocytes.)

2)Are there signs of rapid growth in the tumor cells?

3) Are there any specific genetic mutations within the tumor that can help with prognosis and/or provide a target for therapy?

2.1.6)Age Distribution-

The median age at diagnosis for glioblastoma is **64 years** of age, and risk increases with age. IDH mutant glioblastomas develop in patients significantly younger with a median age of 48 years old. Glioblastomas are rare in children.

2.1.7)Treatment Options-

The mainstay of treatment for GBMs is **surgery**, followed by **radiation** and **chemotherapy**. The **primary objective** of **surgery** is to remove as much of the tumor as possible without injuring the surrounding normal brain tissue needed for normal neurological function (such as motor skills, the ability to speak and walk, etc.). However, GBMs are surrounded by a zone of migrating, infiltrating tumor cells that invade surrounding tissues, making it impossible to ever remove the tumor entirely. Surgery provides the ability to reduce the amount of solid tumor tissue within the brain, remove those cells in the center of the tumor that may be resistant to radiation and/or chemotherapy and reduce intracranial pressure. Surgery, by providing a debulking of the tumor, carries the ability to prolong the lives of some patients and to improve the quality of remaining life.

In most cases, surgeons perform a craniotomy, opening the skull to reach the tumor site. This is done frequently with computer-assisted image-guidance and at times using intra-operative mapping techniques to determine the locations of the motor, sensory and speech/language cortex. Intraoperative mapping often involves operating on a patient while they are awake and mapping the anatomy of their language function during the operation. The doctor then decides which portions of the tumor are safe to resect.

After surgery, when the wound is healed, radiation therapy can begin. The goal of radiation therapy is to selectively kill the remaining tumor cells that have infiltrated the surrounding normal brain tissue. In standard external beam radiation therapy, multiple sessions of standard-dose "fractions" of radiation are delivered to the tumor site as well as a margin in order to treat the zone of infiltrating tumor cells. Each treatment induces damage to both healthy and normal tissue.

By the time the next treatment is given, most of the normal cells have repaired the damage, but the tumor tissue has not. This process is repeated for a total of 10 to 30 treatments, usually given once a day, five days a week; depending on the type of tumor. The use of radiation therapy provides most patients with improved outcomes and longer survival rates compared to surgery alone or the best supportive care.

Radiosurgery is a treatment method that uses specialized radiation delivery systems to focus radiation at the site of the tumor while minimizing the radiation dose to the surrounding brain. Radiosurgery may be used in select cases for tumor recurrence, often using additional information derived from MRS or PET scans. It is rarely used in the initial treatment of GBM.

Patients undergoing chemotherapy are administered special drugs designed to kill tumor cells. **Chemotherapy** with the drug **temozolomide** is the current standard of treatment for GBM. The drug is generally administered every day during radiation therapy and then for six to 12 cycles after radiation. Each cycle lasts for 28 days, with **temozolomide** given the first five days of each cycle, followed by 23 days of rest. While the aim of chemotherapy is long-term tumor control, it does so in only about 20 percent of patients. The decision to prescribe other forms of chemotherapy for tumor recurrence is based on a patient's overall health, type of tumor and extent of the cancer. Before considering chemotherapy, patients should discuss it with their oncologists and/or neuro-oncologists.

Because **surgery**, **radiation** and **chemotherapy** are unlikely to result in a prolonged remission of GBM tumors, researchers are always investigating the use of innovative new treatments when the first line therapy has failed. These new treatments are done in clinical trials. A number of these treatments are available on an investigational basis at centers specializing in brain-tumor therapies. These include gene therapy, highly focused radiation therapy, immunotherapy and chemotherapies utilized in conjunction with vaccines. It is important to note that while some of these investigational treatments show promise, the most effective therapies introduced over the past three decades have improved median survival of GBM patients by an average of only three months.

2.1.8)Prognosis-

With standard treatment, median survival for adults with glioblastoma, IDH-wildtype is approximately 11-15 months.

There are factors that can contribute to improved prognosis, such as younger age at diagnosis (less than 50 years), near-complete removal of the tumor in surgery. Important molecular markers are determined after biopsy or surgery, which provide information for diagnosis and prognosis. For patients with IDH mutant glioblastoma, the prognosis is significantly better (median survival of 27 – 31 months) compared to IDH wildtype glioblastoma (median survival 11-13 months) after diagnosis. Another marker, methylation of a gene called MGMT promoter is also an important marker. MGMT is important for the stability of genes in all cells. When it is methylated, it is inactivated. This makes cancer cells more sensitive to certain chemotherapy drugs such as **temozolomide** because the DNA gets so damaged that the tumor cells die.

2.1.9)Bottomline-

Glioblastoma Multiforme(**GBM**) can be difficult to treat since some cells may respond well to certain therapies, while others may not be affected at all. Because of this, the treatment plan for glioblastoma may combine several approaches.

The first step in treating glioblastoma is a surgical procedure to make a diagnosis, to relieve pressure on the brain, and to safely remove as much tumor as possible. Glioblastomas are diffuse and have finger-like tentacles that infiltrate the brain, which makes them very difficult to remove completely. This is particularly true when the tumors are growing near important regions of the brain that control functions such as language and movement/coordination.

Radiation and chemotherapy are used to slow down the growth of residual tumor after surgery and for tumors that cannot be removed with surgery. **Tumor Treating Fields** (**TTFields**) may be also be offered in combination with **chemotherapy**.

The combination of all these methodologies involving- **surgery** followed by **radiation therapy** and **chemotherapy** which essentially becomes the first line of treatment for **glioblastoma** but in case of most **Solid tumors**(**gliomas**),they do not prove much effective as chances of recurrence increases and period is remission lessens.

Furthermore , use of radiation therapy and chemotherapy agents tend to destroy the normal healthy cells which are located in the vicinity of the tumor cells and also disrupt other essential cellular processes.

2.2 RELATED WORK-

2.2.1)CANCER IMMUNOTHERAPY

A number of **Scientists and medical researchers** have tried out methods to **ramp up** the immune response to combat cancer since the later half of the 19th century . Their attempts were at best modest, however , because boosting the Immune System against cancer proved difficult .But the quest for finding methods that will galvanize the immune system into action to unleash a latent power on these suspicious cancer cells without actually harming the normal healthy cells responsible for normal metabolism in the body.

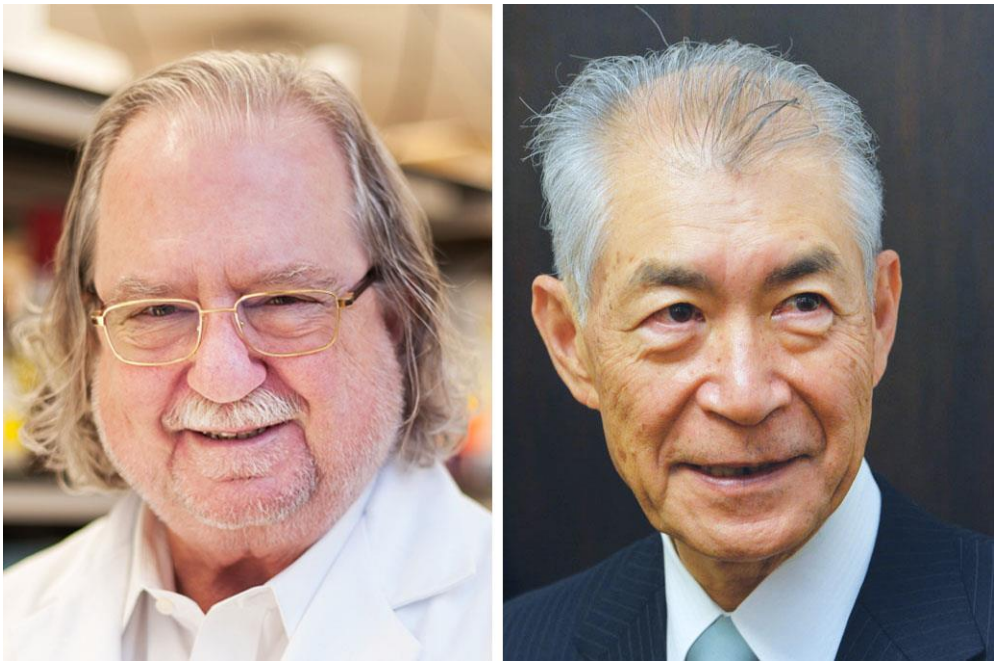
Two **biological stalwarts** and **medical researchers** namely –

James Pattrick Allison of the United States and **Tasuku Honjo** of Japan succeeded in deciphering exactly how cells were interacting so that they could fine-tune methods to control the immune system.Their success has revolutionized cancer treatment.

The **2018 Nobel Prize** in **physiology /Medicine** has been awarded to these stalwarts for their revolutionary and path-breaking discoveries that have led to new medicines that **activate** the **immune system** and drive it to **fight cancers**.

It was awarded to them for their identification of molecules that normally act as a brake on the immune system. That work became the foundation for an entirely novel form of cancer treatment — immune checkpoint therapy (ICT)— which has been credited with saving thousands of lives within the first few years since its approval. for their identification of molecules that normally act as a brake on the immune system. That work became the foundation for an entirely novel form of cancer treatment — immune checkpoint therapy — which has been credited with saving thousands of lives within the first few years since its approval.

Figure 3



James P. Allison (left) **and Tasuku Honjo**(right) awarded the 2018 Nobel Prize in Physiology or Medicine for their development of **cancer immunotherapy**.

These therapies can have the potential to assail even the deadliest malignancies that we have encountered so far.

James.P Allison is the '**chairman**' of the' **Immonology Department**' at **MD Anderson Cancer center** at the **University of Texas** which is in **Houston** ,United States.

His Seminal Report opened new vistas in cancer treatment due to use a novel treatment methodology-**IMMUNOTHERAPY**. Instead of poisoning a tumour or destroying it with radiation therapy or chemotherapy agents, Dr.James P.Allison pioneered ways to unleash the latent power of the immune system to destroy these deadly cancerous cells.

Allison has seen the fatalities of cancer in his very own family .His Mother died of Lymphoma ,one of his uncle died of Melanoma and another uncle died of Lung cancer.Even his elder brother died of deadly prostate cancer.

In the early 1980's,Allison was on the first to identify the T-cell receptor –The part of the T-cell(Thymus cell) that binds to the antigen and functions as the t-cell's ignition switch to launch a scathe on the antigen(which here in this case is the suspicious 'cancer cell').

A few years later,he showed a molecule called CD-28 functions as the T-cell's gas pedal. Then,In 1995,when no one else was thinking there would be such a thing ,he identified the T-cell brakes ,in the process opening up the whole new vistas in the cancer treatment.

Known as "Check-point Blockade", the treatment approach uses **antibodies** to block the action of this braking molecule called as **CTLA-4**(Cytotoxic T-lymphocyte Associated Protien-4) . "By taking the Brakes" off the immune response, the treatment enables a more powerful anti-tumour response.

Allison along with some other researchers have seen that CTLA-4 suppresses the immune responces and that some researchers were hoping to activate more of it in order to treat auto-immune disorders such as **SLE(**Systemic Lupus Erthymatosis), **Vitiligo** or **leukoderma**, **celiac disease**, **diabetes mellitus type 1**, **Graves' disease**, **inflammatory bowel disease**, **multiple sclerosis**, **psoriasis**, **rheumatoid arthritis** etc.

But Allison had a hunch that turning off **CTLA-4** might unleash the Immune System's might against different types of maliganacies.He learned that the protein could put brakes on T-cells,creating what is called a 'Check-point Blockade',it puts a kind of brake on the Immune response.

Eventually, he developed his own specific approach what is called **"Immune Checkpoint therapy(ICT)"** and he clinically demonstrated that it was effective in humans against the usually intractable **skin cancer melanoma** in 2010.

The U.S Food and Drug Administration(FDA) appoved it as a therapy against metastatic melanoma in 2011.

The First drug developed out of this was '**yervoy'**(ipilimumab) which was approved by F.D.A in 2011 for the treatment of metastatic and inoperable advanced melanomas.

All the while that Allison was working on **CTLA-4** 'check-point blockade' protein in the United States, **Tasuku Honjo,** professor in the **department** of i**mmunology** and **genomic medicine** in **Kyoto University** in **Japan** had been studying a similar brake protein in the immune system-**PD1**(**Programmable Cell Death protien**),that reins in **T-cell responces** in a different way.

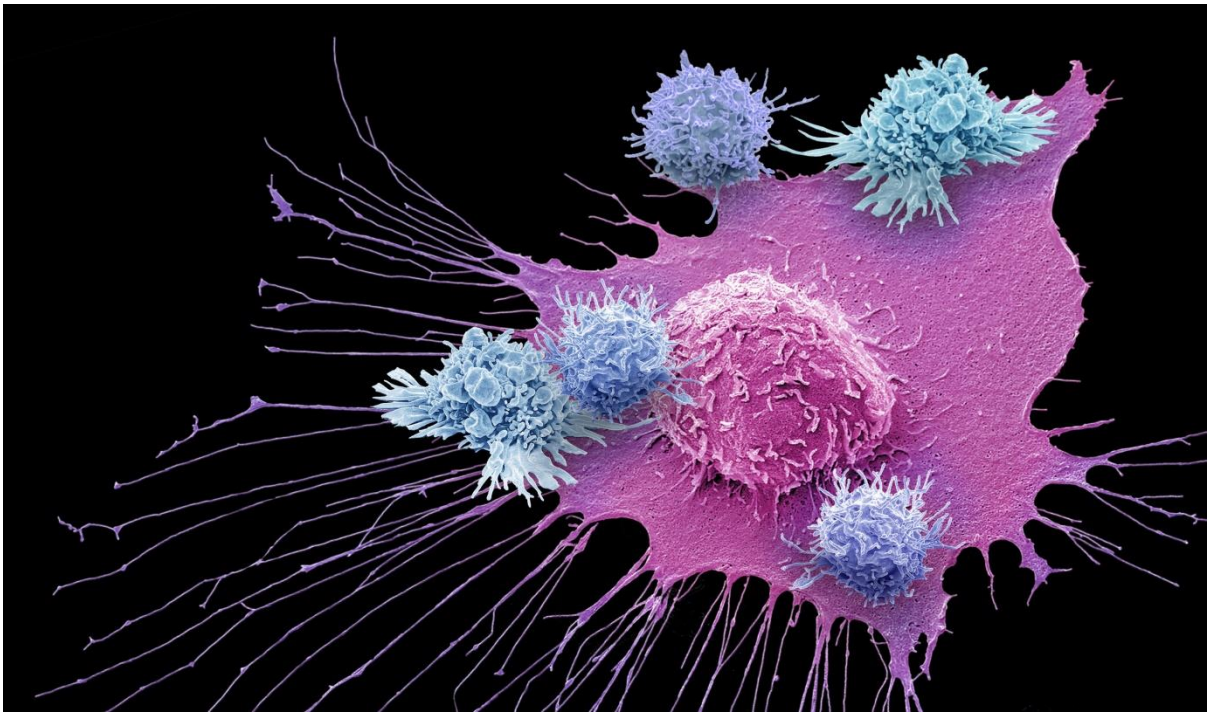
First in the animal experiments and later in the Human clinical trials ,Tasuku Honjo showed that blocking of this braking molecule- PD1 with the help of antibodies could cure several types of cancer.

In 2006, His research was tested in a clinical trial before his newly introduced drug namely **'Opdivo'**(nivolumab) was finally approved in july 2014 in japan and then,subsequently in Europe and United States. This drug is now used against lung cancer and melanoma.

In a particularly impressive demonstration in 2012, the treatment caused long term remission with few side-effects in patients with metastatic cancer that was previously considered untreatable.

It is pertinent to mention that another drug based on Honjo"s research as **'Keytruda'** Was used to treat former United States president 'Jimmy carter' who was diagnosed in 2015 With melanoma that had spread to his brain.

Figure 4



T cells (blue) of the immune system attack a cancer cell (pink) in this color-enhanced **scanning electron micrograph**(**SEM**).

How does cancer immunotherapy work.mp4

Today, immune checkpoint therapies based on PD-1 and CTLA-4, often used together, are in development against many more cancers. As the Nobel Prize foundation noted in its description of the merits of Allison and Honjo's work, immune checkpoint therapy now stands alongside surgery, radiotherapy and chemotherapy: "Their findings have conferred great benefit on mankind; they add a new pillar to the existing cancer treatments."

Immune checkpoint therapy "doesn't work for everyone but lives have been saved, and it has sparked a revolution in thinking about the many other ways in which the immune system can be harnessed or unleashed to fight cancer and other illnesses.

The more that researchers come to understand how the controls on the aggressiveness of the immune system work, including ones that involve other cells and molecules, the more that it may be possible to adjust that aggression as needed. It may be noted that many of the side effects of today's immune checkpoint therapy involve a spillover reaction of inflammation affecting normal tissues. "Currently, we treat those kinds of effects with corticosteroids" and other drugs with their own disadvantages. "But there may be more specific ways to treat those side effects that don't have such global effects on dampening the immune system."

Researchers are racing to expand the use of Immotherapy to benefit more cancer patients .Immunotherapies are a cause of great hope for many patients who are diagnosed with deadly malignancies such as those including melanoma, lymphoma, kidney cancer , lung cancer and bladder cancers.

Currently,Hundreds of clinical trials are underway to achieve sustained remissions and improved Immune responces .But these incredible advances and the promise of cancer cures also come with an eye-popping price tags that reach well past USD1,00,000 per patient which is certainly unaffordable for the people living in third world countries.

Nevertherless,In a nutshell, we can say Unravelling the cellular and molecular basis of treatment resistance should facilitate rational design of new mechanism based studies that can surely make a difference in how we treat cancers but the Foundation lead by Allison and Honjo have certainly helped us to a great extent in conquering the "Emperor Of All Maladies".

It is worthy to note that a kashmiri scientist namely –

'Dr Khalid Shah' who is the **director for Stem Cell Therapeutics and Imaging at Harvard Medical School(HMS)**. His research is based on cancer cells' **Self-Homing ability – the process in which cancer cells can track the cells of their kind that have spread within the same organ or to other parts of body.**

Figure 5

Dr.Khalid Shah (director ,Harvard Stem Cell Cancer Institute)

'This is going to be a game changer & it will surely change the way we will be treating cancers in future said - Dr Khalid Shah'

A US-based Kashmiri scientist is heading a study by team of researchers to treat cancer using "engineered" cancer cells. Under the technique titled "Kill Switch" the scientists are focusing on gene editing cancer cells and employing them to fight the cells of their own kind. "This study is going to be game changer," Dr Khalid Shah, director for Stem Cell Therapeutics and Imaging at Harvard Medical School. The research has gained worldwide attention and could be an answer to the search for widely applicable anti-cancer treatment. Dr Shah said the technique was based on cancer cells' self-homing ability – the process in which cancer cells can track the cells of their kind that have spread within the same organ or to other parts of body. The team is harnessing gene power to overcome drug delivery challenges, helping get therapeutics to tumor sites that may otherwise be difficult to reach. "With our technique, we have shown it is possible to reverse-engineer a patient's own cancer cells and use them to treat cancer," he said. The team developed and tested two techniques to harness the power of cancer cells. The "off the shelf" technique used pre-engineered tumor cells that would need to be matched to a patient's HLA phenotype (essentially, a person's immune fingerprint). The "autologous" approach used CRISPR technology to edit the genome of a patient's cancer cells and insert therapeutic molecules. These cells could then be transferred back into the patient. To test both approaches, the team used mouse models of primary and recurrent brain cancer and breast cancer that has spread to the brain. The team, as per reports in media across world, saw direct migration of engineered cells to the sites of tumors and found evidence that the engineered cells specifically targeted and killed recurrent and metastatic cancer in the mice. The researchers reported that the treatment increased the survival of the mice. Engineered cells were equipped with a "kill switch" that could be activated after treatment – PET imaging

showed that this kill switch worked to eliminate the cells. “We think this has many implications and could be applicable across all cancer cell types,” said Dr Shah who is also vice chair of research in Brigham and Women’s Hospital and faculty at Harvard Medical School and Harvard Stem Cell Institute (HSCI). So far the team has reported promising results in preclinical models across multiple types of cancer cells, establishing a potential roadmap toward clinical translation for treating primary, recurrent and metastatic cancer. The team has successfully developed therapeutic stem cells for cancer, particularly brain tumors. The work on stem cells, Dr Shah feels, holds key for future of therapeutics, particularly the gene edited stem cells. “They have unveiled new possibilities,” Dr Shah said. Calling successful treatment of brain tumors as greatest challenge in oncology, Dr Shah and his team at Harvard Stem Cell Center have been engrossed in demonstrating the promise that stem cells hold to overcome this challenge. “The recognition that different stem cell types, including neural stem cells (NSCs) can integrate appropriately throughout the mammalian brain following transplantation has unveiled exciting chances for their use in neural transplantation,” he said. According to him, the team has demonstrated how different stem cell types, home to sites of cerebral pathology can be armed with therapeutic transgenes, a strategy that can be used to inhibit tumor growth. Dr Shah said the research on gene editing of cancer cells started four years ago at his lab in Harvard. It has been covered by a number of renowned media outlets across the world. Hailing from Srinagar, Dr Shah and his team have pioneered major developments in the stem cell therapy field, successfully developing experimental models to understand basic cancer biology and therapeutic stem cells for cancer, particularly brain tumors. These studies have been published in a number of very high impact journals like Nature Neuroscience, Science, PNAS, Nature Reviews Cancer, JNCI, Stem Cells and Lancet Oncology. An alumni of Burn Hall School, Dr Shah moved to Europe for his higher studies and later joined Harvard Medical School. He has authored two books, Stem Cell Therapeutics for Cancer (Wiley-Blackwell 2013), and Mesenchymal Stem Cells in Cancer Therapy (Elsevier 2014). He has won the Harvard Young Mentor Award and is a recipient of young investigator award from Alliance for cancer gene therapy (ACGT); research fellow award from American Cancer Society (ACS), distinguished research award from Academy of Radiology and Innovation awards from James McDonnell Foundation, American Brain Tumor Association (ABTA) and Goldhirsh foundation. In an effort to translate the exciting therapies developed in his laboratory into clinics, Dr Shah said he has got encouraging response from biotech companies whose main objective is clinical translation of therapeutic cells in cancer patients

2.3 SUMMARY

In this section , we discussed threadbare about some ground breaking researches and experiments that have the potential to change lives and help the cancer patients to lead a normal life. we discussed about various therapies such as IMMUNE

CHECKPOINT THERAPY and gene manipulation technique for cancer cells such as KILL SWITCH that will certainly help both medicos as well as the patients to contain such a devastating condition to a greater extent.

Chapter 3

TECHNOLOGICAL TREATMENT OF DISEASES –

3.1)Radiological Revolution-

Figure 6

HEAD SCAN OF A PATIENT WITH Glioblastoma

One of the biggest advantages of the intermediary world of sciences is the invention as well as the development of some of the most ground-breaking technologies, instruments, and equipment that have led to massive improvements in the world of medicine. Although there are numerous tools or models that have been developed as well as implemented to treat a number of diseases but radiology, it'd be impossible to recognize most contemporary medical fields.

One such field that has been at the fore-front is' Radiology' that uses medical imaging to diagnose and treat diseases within the human body. Variety of imaging techniques such as **X-ray radiography**, **Ultrasound** , **Computed Tomography** (**CT**), **Nuclear Medicine** including **Positron Emission Tomography** (**PET**), and **Magnetic Resonance Imaging** (**MRI)** are used to diagnose or treat diseases. The newly adopted sub-field of **Interventional**

radiology which involves performance of minimally invasive medical procedures with the guidance of imaging technologies to treat a plethora of diseases.

Diagnostic imaging, commonly referred to as radiology, is one of the most revolutionary innovations in the medical world. Radiology has revolutionized how physicians and patients view health and diseases.

Radiology allows medical professionals to peer into the interior of a living human body without having to cut it open. It is the paradigmatically visual discipline of the medical community and as such, extremely important to the growth and development of the field. The benefits of radiology to health and life (in general) cannot be overestimated.

These imaging modalities that followed are inherently digital, and their existence is highly dependent on computing capabilities.These include-**MRI** (Magnetic Resonance Imaging) and **CT** (Computed Tomography). Computers are used to acquire and reconstruct images.

3.2) Use of Artificial Intelligence(AI) and Machine Learning(ML)for better prognosis and Treatment of diseases-

The evolution of medical imaging has led to the development of other technologies to deal with catastrophic diseases such as **Cancer**. Computing made medical imaging easier which increased the number of images produced in the radiology department. The task of managing these large volumes of images can be daunting. As a result, other technologies emerged to deal with this overwhelming number of images.

The newly emerging fields such as **Artificial Intelligence(AI),Machine Learning(ML) , Deep Learning(DL)** etc were introduced in order to make this overwhelmingly complex task of diagnosing and prognosticating these highly complex diseases much better or precise.

The **main** objective of using Artificial Intelligence is to make use of computing methodologies to perform better clinical diagnoses and suggest treatments.

AI has the capability of detecting meaningful relationships in large datasets and has **been** widely **used** in many clinical situations to diagnose, treat, and predict the results.it has got the capability to efficiently diagnose diseases, develop drugs, personalize treatments, and even edit genes.

Artificial intelligence (**AI**) **in healthcare** makes use of complex algorithms and software to estimate human cognition in the analysis of complicated medical data. Specifically, AI is the ability for computer algorithms to approximate conclusions without direct human input.

What distinguishes **AI technology** from traditional technologies in health care is the ability to gain information, process it and give a well-defined output to the end-user. **AI** does this through **machine learning algorithms**. These **algorithms** can recognize patterns in behavior and create its own logic. In order to reduce the margin of error, AI algorithms need to be tested repeatedly.

AI algorithms behave differently from humans in two ways-

1) algorithms are literal that means if you set a goal, the algorithm can't adjust itself and only understand what is has been told explicitly.

2) algorithms are black boxes algorithms can predict extremely precise, but not the cause or the why,

The primary aim of health-related AI applications is to analyze relationships between prevention or treatment techniques and patient outcomes. AI programs have been developed and applied to practices such as diagnosis processes, treatment protocol development, drug development, personalized medicine, and patient monitoring and care.

Analysis of large datasets by machine learning algorithms offers considerable advantages for assimilation and evaluation of large amounts of complex health-care data. However, to effectively use machine learning tools in health care, several limitations must be addressed and key issues considered, such as its clinical implementation and ethics in health-care delivery. Advantages of machine learning include flexibility and scalability compared with traditional biostatistical methods, which makes it deployable for many tasks, such as risk stratification, diagnosis and classification, and survival predictions. Another advantage of machine learning algorithms is the ability to analyse diverse data types (eg, demographic data, laboratory findings, imaging data, and doctors' free-text notes) and incorporate them into predictions for disease risk, diagnosis, prognosis, and appropriate treatments. Despite these advantages, the application of machine learning in health-care delivery also presents unique challenges that require data pre-processing, model training, and refinement of the system with respect to the actual clinical problem. Also crucial are ethical considerations, which include medico-legal implications, doctors' understanding of machine learning tools, and data privacy and security.

3.3) Prognostic model based on imaging findings in Glioblastoma(GBM) -

3.3.1)**Overview** of OLPM model-

Glioblastoma (GBM) is the most common and lethal malignant primary brain tumor with the worst prognosis . The poor prognosis is mainly due to the spatial and

temporal intra-tumor heterogeneity. This genetic heterogeneity reduces the value of invasive biopsy-based genomic analysis, but provides opportunities for medical imaging that depicts the entire tumor in a non-invasive and repeatable way. To explore the correlation between medical images and
underlying genetic characteristics, radiomics has been proposed. Radiomics refers to a process that extracts high-throughput quantitative features from radiographic images and builds predictive models relating image features to genomic patterns and clinical outcomes.

A substantial amount of research has been devoted to understanding different aspects of the disease, specifically the development of different types of biomarkers. Clinical, molecular and imaging parameters have been used to build mathematical models able to classify GBM patients in terms of survival, identify GBM subtypes, predict response to treatment.

Machine learning (ML) techniques have been increasingly used by the radiological research community to construct such models.These methods, when used on sufficiently large data sets, are able to extract hidden information and patterns from data, automatically learning and being able to make predictions about future system behavior.

ML remains a young field with many underexplored research opportunities.The application of ML in radiology, typically being based on large sets of features extracted from medical images, and known as **'radiomics'** has a great potential to increase clinical efficacy. However, together with several interesting applications and discoveries,there have been many studies with serious experimental design flaws. Most pitfalls of ML methods in biomedical research result in common problems such as **'overfitting'**.
In our study, we developed efficient, optimized predictive models using clinical data and high-quality MRI-based morphological information(structural and functional flow information) of GBM patients.
First, we developed a human-built 'Optimized Linear Prognostic Model (OLPM)' on the basis of the researchers' understanding of the predictive value of the variables showing individual prognosis value. We also constructed ML models using some of the best methods available::artificial neural networks (ANN), support vector machines (SVM), and regression trees (RT). Our intention is to compare the OLPM with the previous ML approaches and the best ML-based models recently proposed in the literature to ***construct accurate prognostic estimators*** and to show how a non-rigorous use of ML methods in neuro-oncology can lead to misleading or over-estimated results.

Many studies have built machine-learning (ML)-based prognostic models for glioblastoma (GBM) based on radiological features. We wished to compare the predictive performance of these methods to human knowledge-based approaches. 404 GBM patients were included (311 discovery and 93 validation). 16 morphological and 28 textural descriptors were obtained from pretreatment

volumetric postcontrast T1-weighted magnetic resonance images. Different prognostic ML methods were developed.

An optimized linear prognostic model (OLPM) was also built using the four significant non-correlated parameters with individual prognosis value. OLPM achieved high prognostic value (validation
c-index = 0.817) and outperformed ML models based on either the same parameter set or on the full set of 44 attributes considered. Neural networks with cross-validation-optimized attribute selection
achieved comparable results (validation c-index = 0.825).

ML models using only the four outstanding parameters obtained better results than their counterparts based on all the attributes, which presented overfitting.

In conclusion, OLPM and ML methods studied here provided the most accurate survival predictors for glioblastoma to date, due to a combination of the strength of the methodology, the
quality and volume of the data used and the careful attribute selection. The ML methods studied suffered overfitting and lost prognostic value when the number of parameters was increased.

3.3.2)Terminologies used in OLPM model-

1)p-value-In statistical hypothesis testing, the **p-value** or **probability value** or **significance** is for a given statistical model, the probability that, when the null hypothesis is true. When you perform a hypothesis test in statistics, a **p-value** helps you determine the significance of your results. The **p-value** is a number between 0 and 1 and interpreted in the following way: A small **p-value**(typically ≤ 0.05) indicates strong evidence against the null hypothesis, so you reject the null hypothesis. Most authors refer to **statistically significant** as **P** < 0.05 and **statistically** highly **significant** as **P** < 0.001 (less than one in a thousand chance of being wrong). The **significance** level (alpha) is the probability of type I error(the error we always try to minimize).

2)COX Hazard(risk of death) Ratio- The **hazard ratio** is a comparison between the probability of events in a treatment group, compared to the probability of events in a control group. The **Cox proportional-hazard** is essentially a **survival indicator** commonly used statistical in medical research for investigating the association between the survival time of patients and one or more predictor variables. **hazard ratio** of one means that there is no difference in survival between the two

groups. A **hazard ratio** of greater than one or less than one means that survival was better in one of the groups.

3)C-Index(concordance index)- The **concordance index** (CI), which quantifies the quality of rankings, is the standard performance measure for model assessment in survival analysis. The index of concordance is a "global" index for validating the predictive ability of a survival model. It is the fraction of pairs in your data, where the observation with the higher survival time has the higher probability of survival predicted by your model.

3.3.3) CONSTRUCTION OF OLPM MODEL-The construction of the model is based on the following:-

OBJECTIVES-
We wished to determine whether tumor morphology descriptors obtained from pretreatment magnetic resonance images and clinical variables could predict survival for glioblastoma patients.

METHODS-
A cohort of 404 glioblastoma patients (311 discoveries and 93 validations) was used in the study. Pretreatment volumetric postcontrast T1-weighted magnetic resonance images were segmented to obtain the relevant morphological measures. Kaplan-Meier, Cox proportional hazards, correlations, and Harrell's concordance indexes (c-indexes) were used for the statistical analysis.

CONSTRUCTION-A multivariate Cox regression model was constructed using four outstanding and significant parameters taken from high quality radiological images such as age, CE volume, CE rim width and surface regularity. This model gave c-indexes of 0.735 in the discovery cohort(control group) and 0.744 in the validation cohort(treatment group).
Then, 304 linear predictive models were constructed using some standard procedures.
The equation of the OS(Overall Survival) using the best linear model based on four significant morphological and textual descriptors -age, CE rim width, surface regularity and CE volume is given mathematically as:-

OLPM = 0.030 *age -0.340*CE-rim width -1.100 *Surface Regularity + 0.012* CE volume.

The c-indexes obtained for this model were 0.771 on the discovery cohort, and 0.817 on the validation cohort.

RESULTS- A linear prognostic model based on the outstanding variables (age, contrast-enhanced (CE) rim width, and surface regularity) identified a group of patients with significantly better survival ($p < 0.001$, HR = 2.57) with high accuracy (discovery c-index = 0.74; validation c-index = 0.77). A similar model applied to totally resected patients was also able to predict survival ($p < 0.001$, HR = 3.43) with high predictive value (discovery c-index = 0.81; validation c-index = 0.92). Biopsied patients with better survival were well identified ($p < 0.001$, HR = 7.25) by a model including age and CE volume (c-index = 0.87).

3.3.4)Comparision of prediction values using Conventional Machine Learning Models- The NN(Neural network) constructed using age, CE volume, CE rim width and surface regularity as parameters obtained c-indexes of 0.740 and 0.751 in the discovery and validation cohorts respectively. However, equipped with all the 44 parameters, NN obtained c-indexes of 0.794 and 0.746 respectively.
The optimal attribute combination extracted from the CV process included age, surface regularity, total surface and CE volume. It presented an average c-index along the 20-fold CV (with 50 test patients) of 0.791. This model configuration, trained with the entire discovery cohort and applied with the same threshold on the validation cohort, obtained a c-index of 0.825. The libSVM(Support Vector Machines) method, when restricted to the four morphological parameters, obtained c-indexes of 0.739 and
0.756 in the discovery and validation cohorts respectively. The non-restricted instance of this algorithm achieved c-indexes of 0.752 and 0.700 respectively.
The RFF_SVM(Support Vector Machines) algorithm, when based on the four marginally significant parameters in the Kaplan-Meier analysis, obtained a c-index of 0.747 in the discovery cohort and 0.783 in the validation cohort. The use of all parameters led to c-indexes of 0.801 and 0.766 respectively.
Finally, the RT(Regression Trees) model using age, CE volume, CE rim width and surface regularity as parameters obtained c-indexes of 0.696 and 0.681 in the discovery and validation cohorts respectively. However, equipped with all the
44 parameters, it obtained c-indexes of 0.741 and 0.630 respectively.

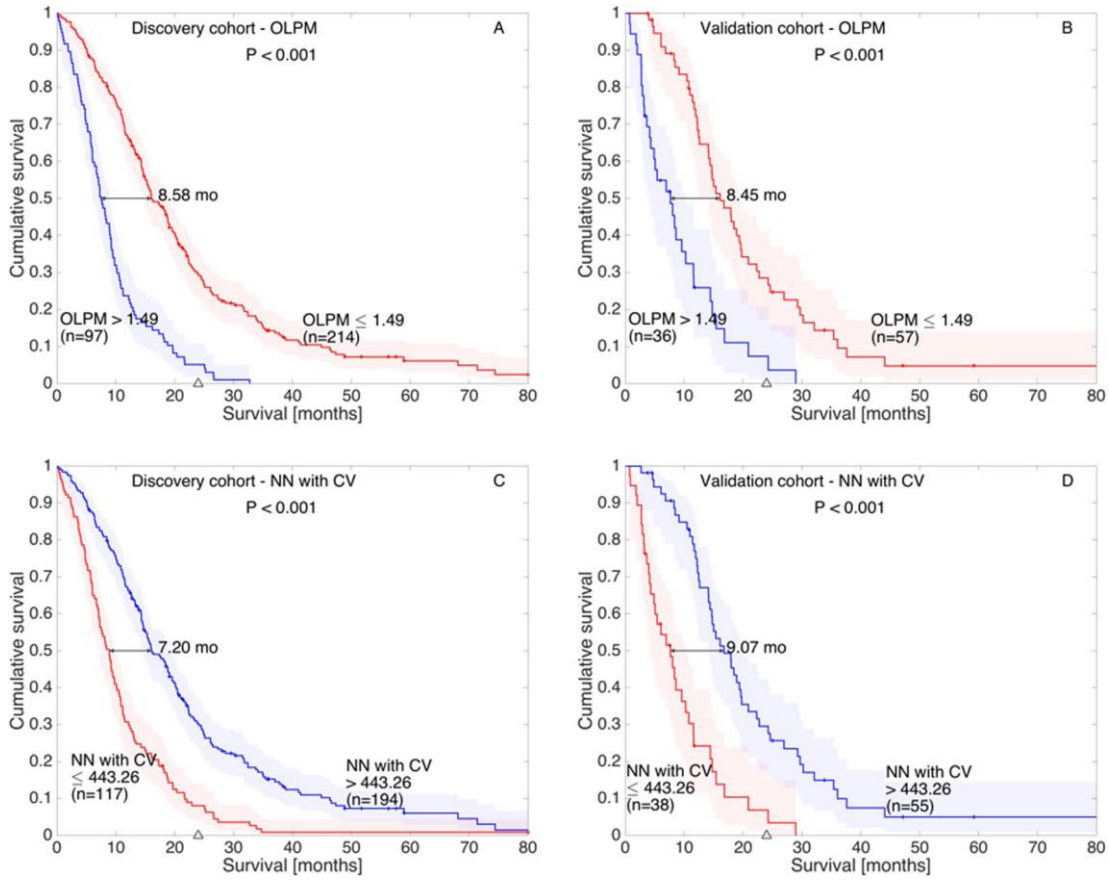


Figure7- Kaplan-Meier curves obtained for the OPML and the best ML method (NN with CV) in the discovery cohorts and Validation cohorts.

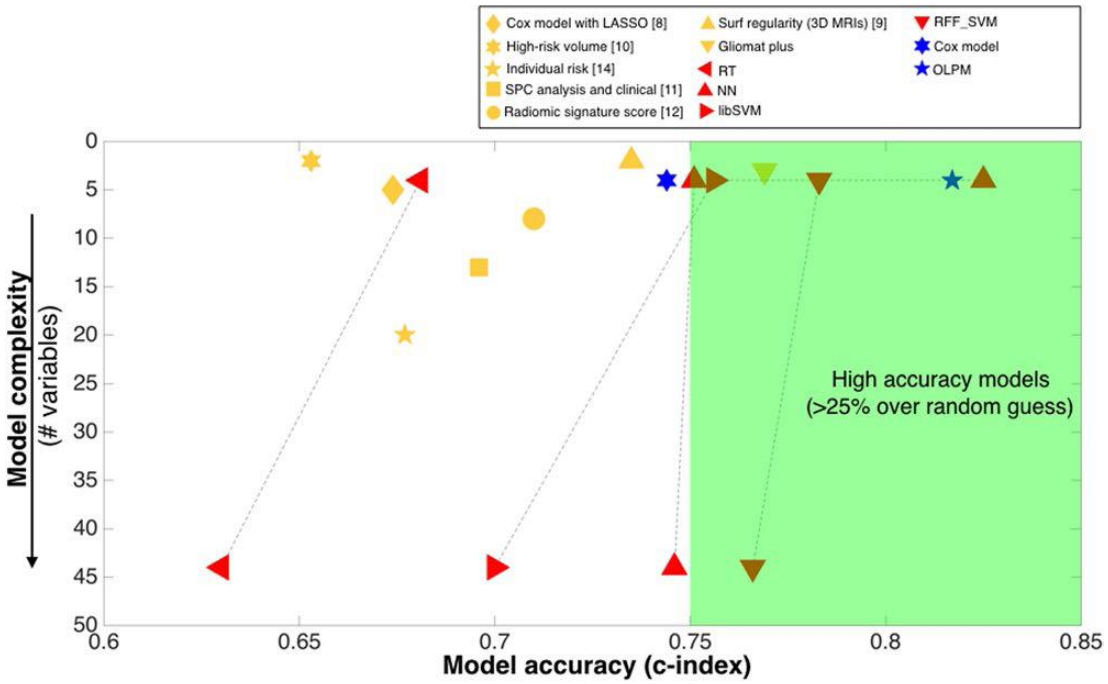
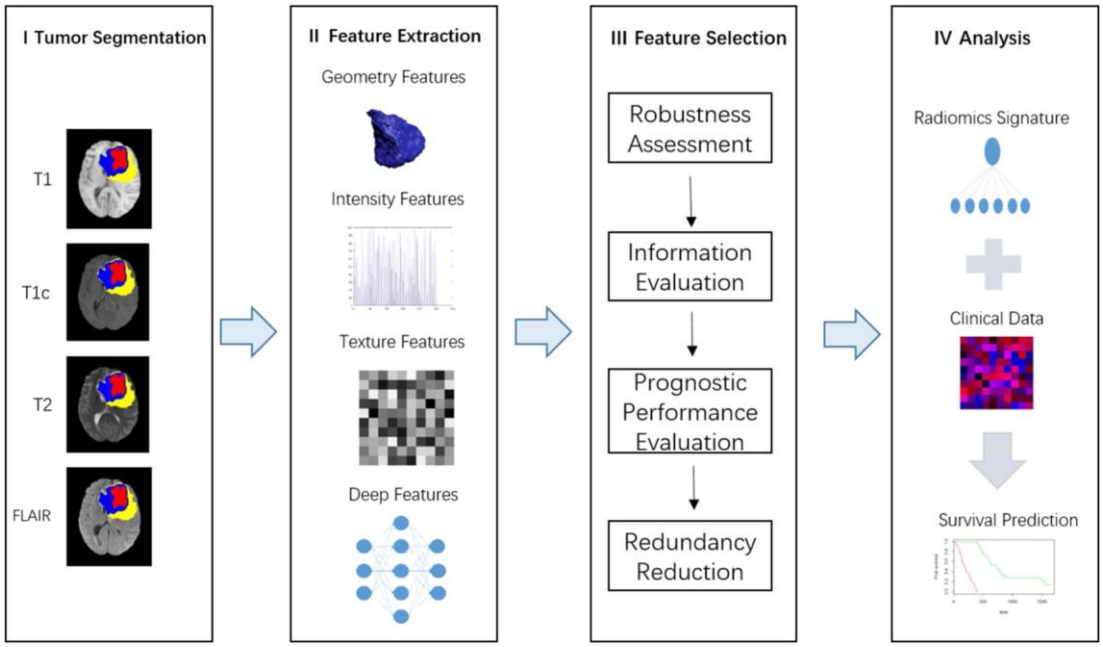


Figure 8- Comparison of the predictive value (c-index) and number of variables for the models developed in this paper versus representative models from the literature. Previous approaches are shown in yellow, with different symbols corresponding to different studies. ML methods described in this paper are shown in red and linear models in blue. Results are given for the best models in each reference and for the validation groups when available.

Figure 9



Workflow of OLPM Model for feature Extraction and survival prediction of patients with Glioblastoma.

3.3.5)CONCLUSION-

Simple linear models based on small sets of meaningful MRI-based pretreatment morphological features and age predicted survival of glioblastoma patients to a high degree of accuracy. The partition of the population using the extent of resection improved the prognostic value of those measures.

3.4) SUMMARY

A combination of two MRI-based morphological features (CE rim width and surface regularity) and patients' age outperformed previous prognosis scores for glioblastoma. Prognosis models for homogeneous surgical procedure groups led to even more accurate survival prediction based on Kaplan-Meier analysis and concordance indexes.

Chapter 4

CONCLUSION AND FUTURE SCOPE-

The use of **Artificial Intelligence** and **Machine Learning** along with its sub types such as **Neural networks** and **Deep Learning** hold promising results due to its meticulous prediction of various parameters and dimensions associated with the problem especially in the field of medical research for helping out in understanding and analyzing the heterogeneity of the disease and ensuring better prognosis of the disease.

Chapter 5

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