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# Efficacy of Techniques Used in the Medical Diagnosis and Treatment of Glioblastoma

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## ABSTRACT

Upon diagnosis, patients are presented with various treatment options with which to choose from. Oftentimes, however, the patient is oblivious to what exactly is being presented to them. The complexity of the medical field is unrivaled, and patients are often blind to what is being done, especially in oncology. Oncology is regarded as an incredibly complex field with even more complex subgroups. One of society's most perplexing cancers is Glioblastoma, a type of brain cancer in which a growth appears in the brain or spinal cord. Scientists know very little about the disease as it affects an extremely small percentage of the population. However, it is important to be informed about the possible treatment options and specific details of each. The purpose of this research is to inform society of the treatment options for Glioblastoma and how effective they are at curing the disease. This journal elaborates on these complex treatments, ranging from the classic methods of radiation therapy to the intricate methods of brain surgery. Upon reading this paper, one will have a deeper understanding of what it means to undergo cancer treatment, especially for a sickness as dire as Glioblastoma. The paper will explain three techniques used to treat Glioblastoma including how the treatment is performed, under what circumstances it will be performed, and the effectiveness of the technique. These treatments are incredibly elaborate, but by congesting the main cancer treatment techniques into one, organized document, patients can better their understanding of Glioblastoma and its treatment options.

## Introduction

There is an abundance of cancers in existence that pose lethal effects, but one of the world's most puzzling forms is Glioblastoma Multiforme (GBM), a rare type of brain cancer in which a malignant tumor affects the brain or spine. A tumor is the concentration of rapidly replicating cells. Symptoms of Glioblastoma include headache, nausea, drowsiness, blurred vision, personality changes, seizures, etc., caused by the pressure stemming from the increasing size of the tumor, typically located in the frontal and temporal lobes or the spinal cord (See Figure 1).

The risk of Glioblastoma begins to arrive between the ages of 45 and 70; the potential to appear in children and middle-aged individuals is shallow but possible. Radiologists typically use Magnetic Resonance Imaging (MRI)–a technique in which magnetic fields and radio waves are emitted–to penetrate the skin and provide an accurate perception of the human body to locate the tumor. Tumors are typically graded on a scale of 1(I) to 4(IV), the higher the number, the more aggressive, intense, and fast spreading the tumor is, affecting the surrounding tissue. The grade, in many cases, determines the likelihood of recurrence and success of treatments. Glioblastomas are classified as grade IV brain tumors.

Scientists have developed various methods with which to treat Glioblastoma that have proven to be highly effective. However, the efficacy of these techniques is variable, and confounding variables such as age, underlying conditions, etc., are factors that must be considered when determining a patient's optimal route for treatment. The methods of treatment that will be discussed in this journal are radiation, chemotherapy, craniotomy, and clinical trials. Taking any of these routes poses its own tribulations but all techniques have been proven effective in one way or another.

This journal will evaluate, in detail, the efficacies of the potential treatments for Glioblastoma, considering success rates, limitations, etc. The paper details elaborate explanations of each treatment, presenting potential opportunities and obstacles that are posed by each treatment to determine the ideal path. What are the efficacies of techniques used by oncologists in the treatment of Glioblastoma?

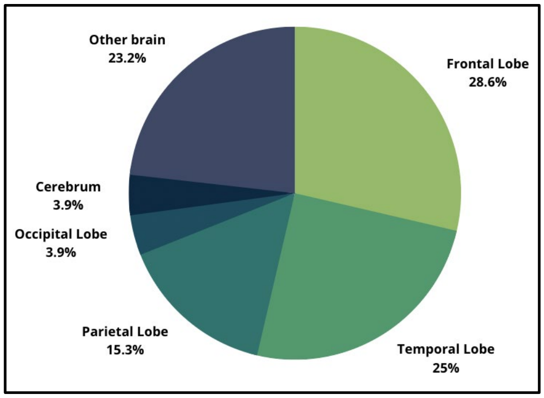


Figure 1. Prevalence of Glioblastoma in the brain

## Diagnosis

Diagnosis of Glioblastoma Multiforme (GBM) can be challenging due to its rarity and difficult positioning in the brain or spine, but modern technology and experienced doctors have made it possible.

The onset of Glioblastoma is often mistaken with symptoms of the common headache: throbbing pain, fatigue, etc. Typically, victims of Glioblastoma seek medical attention once over-the-counter medications such as Acetaminophen (Tylenol), Aspirin, and Ibuprofen (Advil), are ineffective. Signs begin to manifest between the ages of 45-70 and are more common in men (See Figure 2). Typical to many cancers, Glioblastoma is very difficult to detect in its early stages, hence its very high mortality rate.

However, under further examination using MRI (Magnetic Resonance Imaging), oncologists can better diagnose the symptoms. MRI is an imaging technique used by radiologists to provide a viable visual of internal structures. During an MRI, the patient is placed in a large, cylindrical magnet and must remain incredibly still to produce clear images. This imaging technique works on a very molecular level. To begin, a magnetic field is formed by the large magnets of the machine. This force will align the protons of human tissue, coercing them into alignment with the magnetic field. Upon alignment, radio currents are sent, stimulating the protons and knocking them out of equilibrium with the magnetic field. This essentially releases energy that is simultaneously detected by the machine. The machine differentiates the various types of tissue based on the time taken to realign with the magnetic field and the energy released after radio currents have dispersed. Through radio waves and magnetic fields emitted by the machine, specialists are provided with clear images of bodily structures. This technique is widely accepted for its noninvasive nature, specificity, and accuracy in locating tumors (See Figure 3).

Through further development of this technique, which originated in the 1970s, it has proven to be highly effective, successfully diagnosing tumors 93% of the time, a considerable improvement from the medical field's traditional method of biopsies (observing extracted samples of tissue).

Another method of diagnosing a patient with Glioblastoma is performing a liquid biopsy. A biopsy, in general terms, is the extraction of a sample of tissue to determine the extent to which a disease has infiltrated the body. For example, a gastroenterologist will extract a sample of the large intestine while conducting a colonoscopy, to test for colon cancer. A liquid biopsy is a specialized biopsy in which a sample of blood or other liquid is examined to determine its affiliation with the tumor: does the liquid contain tumor cells? Glioblastomas can spread throughout the body, hence their malignancy. Tumor DNA circulates in the blood in an individual with cancer. Therefore, if a blood sample is removed from an individual with cancer, it should contain tumor cells. First blood must be extracted from an area relatively near the glioblastoma. This will provide the highest likelihood of recognizing tumor cells. Next, the small sample of blood will be spun at incredibly high speeds to separate the plasma. A pathologist will examine the plasma to identify if there are any cancerous cells in the sample, by examining the DNA and RNA structure, chromosomes, and any potential mutations to make a diagnosis. This is a much less invasive method of diagnosing Glioblastoma while also providing accurate results.

Diagnosis of Glioblastoma and establishment of its stage of development is vital as it establishes potential treatment options for the patient.

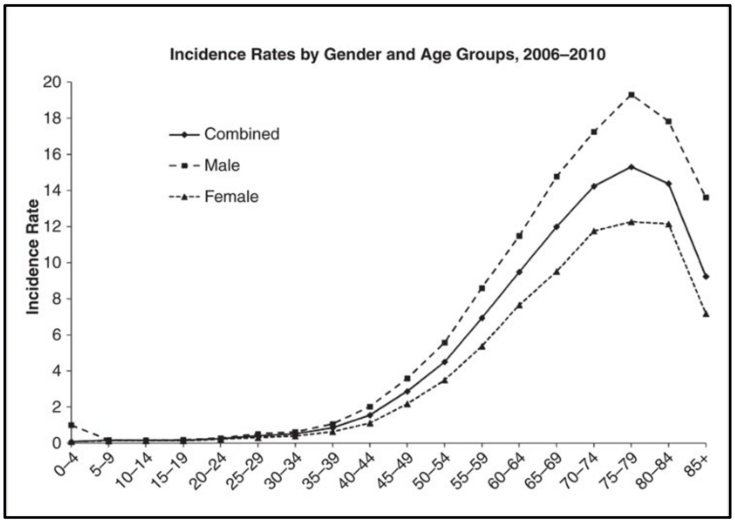


Figure 2. Age of Glioblastoma onset in males and females

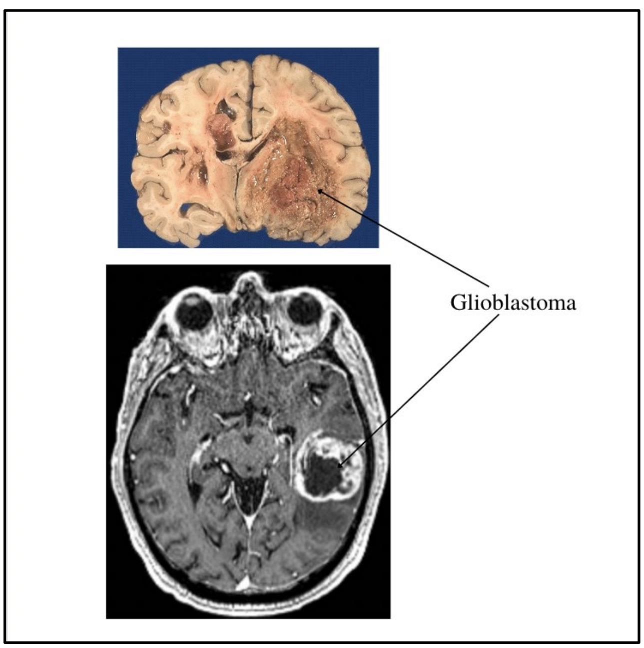


Figure 3. Appearance of the tumor in an MRI scan and a brain sample

## Craniotomy

The most opted method of treatment for Glioblastoma is craniotomy. A craniotomy is an operation in which a portion of the skull–referred to as the "bone flap"–is surgically removed, exposing the brain. This gives surgeons direct access to the tumor. The portion of the skull removed will be reattached once the cancerous mass has been removed.

To begin, a radiologist must locate the tumor using magnetic resonance imaging (MRI). This lays the foundation for the procedure because it determines where the bone flap will be removed. Combined with CT scans, surgeons are provided with a detailed 3D image of the brain and the tumor, which will form a frame of reference for performing the operation. Upon locating the tumor, surgery begins. A team of specialized surgeons known as neurosurgeons will perform the surgery. A neurosurgeon will cut the scalp and remove the bone flap from the patient's skull, revealing the brain.

With the tumor revealed, there are a few methods with which to extract the mass. One is to remove it with a scalpel or other sharp tool by cutting around the Glioblastoma's periphery. Blue light is typically used to differentiate cancerous tissue from healthy tissue. Another method of removing the Glioblastoma is a technique used as ultrasonic aspiration when ultrasonic waves are projected toward the tumor. This breaks down the contents of the tumor by degrading the cell membranes of the tumor cells. Attached to the device is a suction used to clear the surgical field of the cancerous tissue. Once all cancerous tissue is removed from the brain, the bone flap is reattached using brackets and the skin is stitched back together.

In very rare cases, an awake craniotomy is executed. This is when the patient is awake and conscious of all or specific parts of the surgery. This may seem absurd, but considering various factors, it poses a potential solution to an almost fatal situation. An awake craniotomy will only be performed if the location of the tumor is in a very critical location: near vital cortexes such as the sensorimotor cortex. The purpose of the patient's awareness is to assess neurological activity while performing certain tasks. During surgery, the patient may be tasked with lifting their arm or wiggling their toes to locate which part of the brain is responsible for those functions. The process of examining neural activity is known as neurophysiological monitoring (electric currents transmitted when performing tasks are monitored).

In a study conducted at OHSU (Oregon Health & Science University), 69 trial patients underwent an awake craniotomy, referred to as DBS(deep brain stimulation) in the study. After reviewing the results of the study, researchers established that undergoing an awake craniotomy did not benefit the results of the surgery. In fact, craniotomies that were performed while the patient was asleep resulted in much more favorable results. Patients experienced much better communication and speech.

In a study published in the Journal of Neuro-Oncology, Michael Brendan Cloney, Adam M Sonabend, Jonathan Yun, and Jinyan Yang, performed craniotomies on 10 test subjects, 5 with Glioblastoma, 1 with a typical glioma, and 4 with a lower grade brain tumor. With each subject, the doctors examined post-operation symptoms to gauge a numerical value to judge the complication rate. After examining the collected data, it was concluded that in the 5 subjects with Glioblastoma, the craniotomy resulted in an average of 20.06%, less than the remaining 5 procedures' average complication rate of 25.1%. Therefore, performing a craniotomy proved to be a very effective method posing very minimal risks.

Craniotomy is regarded as the most effective method of removing as much of the Glioblastoma as possible. In fact, in a study at Strong Memorial Hospital, 213 craniotomies were conducted. Of those surgeries, 96% of individuals were able to go home within the week of their craniotomy. The other 4% entered rehabilitation centers afterward due to complications. Performing a craniotomy provides the most foolproof method with which to eliminate as much cancerous tissue as possible without altering the biochemical makeup of the patient's body. Cancer treatment such as chemotherapy alters the molecular makeup of cells.

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| Type of Tumor | Subject | Complication Rate |
|---|---|---|
| Glioblastoma | Chang | 24.2% |
| | Talacchi | 23.0% |
| | D'Amico | 21.4% |
| | Tamaka | 18.9% |
| | Hoover | 12.8% |
| Glioma (II-IV) | Fadul | 31.0% |
| ≥3 tumor types | Sawaya | 32.0% |
| | Brell | 27.5% |
| | Moiyadi | 18.0% |
| | Taylor | 17.0% |

Figure 4. Results of the Journal of Neuro-Oncology study regarding complications after a craniotomy

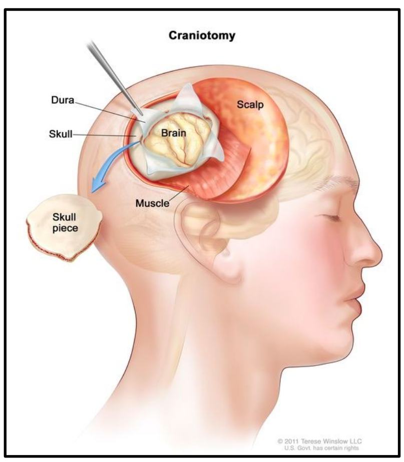


Figure 5. Diagram of a Craniotomy

## Chemotherapy

Chemotherapy is the most common method used in cancer treatment; however, it does not eradicate Glioblastoma from the body. It can, however, shrink the tumor so a craniotomy can be performed.

Chemotherapy is an option for cancer treatment in which the patient partakes in a regimen of doses. These doses of chemo are solutions containing one or more "anti-cancer drugs". These types of drugs, when infused into the patient, will enter the nucleus of cancerous cells, and degrade the DNA. In optimal cases, this will kill the cell. The cell will no longer undergo cytokinesis, continue the cell cycle, and cancer will not prolong in the body. These doses of chemo will come in the form of a pill or a solution of saline. Depending on the cancer, the patient will either be given regular doses of the pill or infusions of the solution. Pills can also be taken at home, but infusions must be done in licensed clinics or hospitals.

Chemo used to treat Glioblastoma consists of drugs known as alkylating agents which are “cytotoxic”, meaning they kill cells. Alkylating agents work by entering the cell, mimicking beneficial molecules that cells allow to diffuse through the membrane. The cell implements the drug into its molecular structure. However, once inside, these drugs demolish the cell’s genetic material: DNA and RNA. Without these vital nucleic acids, the cell has no way of functioning, progressing through the cell cycle, etc.; It simply dies. Not only do they degrade existing genetic material, but they also interfere with DNA and RNA synthesis, restricting the cell from multiplying. A few examples of these drugs are Altretamine ($C_9H_{18}N_6$), Bendamustine ($C_{16}H_{21}Cl_2N_3O_2$), Busulfan ($C_6H_{14}O_6S_2$), Carboplatin ($C_6H_{12}N_2O_4Pt$), Carmustine ($C_5H_9Cl_2N_3O_2$), Chlorambucil ($C_{14}H_{19}Cl_2NO_2$), Cisplatin ($Pt(NH_3)_2Cl_2$), Cyclophosphamide ($C_7H_{15}Cl_2N_2O_2P$), but the drug which was deemed most effective against Glioblastoma, coining the term “gold standard”, is Temozolomide ($C_6H_6N_6O_2$). When the drug[s] enter the bloodstream through the regular doses of chemotherapy, they wreak havoc on the cancerous cells, killing them and constricting their ability to reproduce. Since cancer is the uncontrollable replication of cells, this can be very effective.

When an alkylating agent enters the bloodstream, in this case, Temozolomide, it enters the cell by diffusing through the cell membrane. These agents mimic vital molecules that are required for the cell to function. Through the intake of these agents into the cell, they proceed to the nucleus, where the genetic material of the cell is located. The agent (Temozolomide for Glioblastoma) will replace the alkyl groups in the DNA with hydrogen atoms. This is fatal for the cell because it completely alters the nucleic acid's molecular structure. If the DNA is dysfunctional, the instructions to proceed through the cell cycle and mitote are unavailable. Therefore, the cell will die and its potential for future daughter cells is extinguished. The more of these cancerous cells that die, the less replication occurs, and the cancer slowly begins to disappear.

In a study, 27-59% of individuals who underwent chemotherapy to treat their Glioblastoma were “progression-free” meaning the cancer is not spreading (the drug is effective). Therefore, Chemotherapy is effective at curing Glioblastoma to an extent, but it can be concluded it has its limitations when treating highly invasive and malignant tumors.

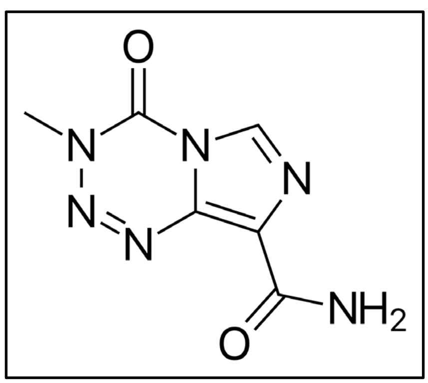


Figure 6. Temozolomide molecular structure

## Radiation

Radiation is the method of treating Glioblastoma that is typically used if the location of the tumor deems it unable to perform a craniotomy. Undergoing radiation is the alternative to surgery, or it is done after surgery to ensure the tumor has disappeared.

Radiation therapy is when x-rays, gamma rays, or photons are directed towards the tumor, killing the cancerous cells. Based on the varying intensities of the waves, the DNA located inside the nucleus of cancerous cells will be destroyed, eliminating the cells' ability to reproduce and the tumor to enlarge. As the tumor shrinks and pressure is released, the symptoms of Glioblastoma will begin to dissipate until the mass has disappeared.

With high-grade brain tumors such as Glioblastoma, there are two types of radiation that a patient can undergo: Intensity-modulated radiation therapy (IMRT) and Stereotactic radiosurgery. Intensity-modulated radiation therapy is a great option for oddly shaped tumors or tumors located near vital organs (the brain). IMRT allows radiation to be directed with extreme precision, preventing the risk of coming in contact with healthy tissue surrounding the tumor. First, 3D images of the tumor are taken to get an accurate representation of size, shape, and location. After having the images examined by specialists, the location of the tumor is inputted into the complex software in the linear accelerator (the device that administers radiation). Once all required tools and information are collected, a radiation therapist uses the device to administer highly specific doses of radiation that are aimed precisely at the tumor using the software to which the information was inputted in to. This mitigates the risk that the radiation will damage perfectly healthy cells. By utilizing this innovative method of treatment, oncologists can better regulate the magnitude of the radiation to eliminate the majority of cancerous cells and decrease the likelihood that healthy cells will be destroyed in the process.

Stereotactic radiosurgery (SRS) is similar to Intensity-modulated radiation therapy in many ways. However, SRS is typically used for smaller, abnormally shaped tumors that require extreme precision. The radiation emitted during Stereotactic radiosurgery is highly concentrated to pinpoint small tumors in the brain and kill the cells. The waves also prevent the nearby, healthy tissue from degrading since they are very precise and more controlled than other forms of radiation. This method of radiation therapy also requires fewer sessions, not because the tumor is relatively smaller, but because the waves are much stronger and more efficient. The extreme precision demonstrated by linear accelerators when performing stereotactic radiosurgery allows for a more efficient recovery with minimal damage to perfectly functional cells.

Radiation has proven itself to be a very effective method of treating cancer. It targets the tumor directly and is a much faster form of treatment than others such as chemotherapy. In contrast to chemotherapy, radiation targets the tumor specifically and doesn't alter cells in the bloodstream.

## Conclusion

After reviewing the benefits and drawbacks of each cancer treatment technique, it is evident that Craniotomy is by far the most foolproof method of successfully removing the cancer from the body due to the direct removal of the tumor from the brain. Aside from surgery, there are minimal risks and patients almost always recover flawlessly. Chemotherapy adds drugs to the bloodstream, but the cancerous cells of glioblastoma are not as prevalent in the blood as other cancers such as leukemia. Radiation is typically used on cancerous masses away from vital organs. Therefore, the most effective way to treat Glioblastoma Multiforme is to perform craniotomy.

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