



## **FOCAL TREATMENTS FOR GLIOBLASTOMA MULTIFORME: A BRIEF REVIEW**

Glioblastoma multiforme (GBM) is the most common of the primary malignant primary brain tumors and is also one of the most difficult tumors to treat effectively. This tumor arises from star-shaped glial (Latin for 'glue') cells called "astrocytes." Astrocytes are cells that normally play an important role in maintaining the blood brain barrier - the filtering mechanism that protects the brain. These tumors begin when, for reasons not completely defined by scientists, a single astrocyte becomes abnormal. If that abnormal astrocyte multiplies, it will produce other such astrocytes, eventually forming an astrocytoma. In practice, there are essentially four grades of astrocytoma. In the World Health Organization classification system, astrocytoma grade IV is the most malignant of the astrocytic tumors. "Astrocytoma grade IV," "glioblastoma multiforme," "glioblastoma," and "GBM" are different names for the same tumor.

Each year, approximately 5 people of every 100,000 living in the United States are diagnosed with a glioblastoma. These tumors represent about 20% of all primary tumors found in the brain. Generally found in people forty through sixty years old, glioblastoma occurs slightly more often in males than females, and usually affects the cerebral hemispheres. It may involve more than one lobe of the brain, or may spread across the hemispheres, creating a so-called "butterfly" appearance on a scan.

GBM is an aggressive tumor that usually regrows within 1-2 centimeters of its site of origin, and almost never spreads to any other organ of the body. Because of this tendency to remain in the same area, it makes sense to concentrate the treatment 'firepower' locally where it is needed the most. To this end, surgical removal of as much tumor as possible can achieve several goals including:

- confirmation of the diagnosis
- relief of symptoms
- removal of potentially treatment-resistant cells before they multiply
- reduction of the number of malignant cells to which the immune system must attempt to respond
- oxygenation of the malignant cells, making them more susceptible to subsequent therapies
- reduction of the amount of harmful by-products released by the malignant cells

Even after the most successful surgery for GBM however, residual microscopic tumor remains. The Neuro-Oncologist chooses an appropriate treatment plan, intended to kill as many additional cells as possible. This plan may include "systemic" treatments - those that circulate through the body to get to the tumor area - or "focal" treatments - those that treat the tumor locally. The body of this paper will review promising focal therapies.

At the operating table, the neurosurgeon is presented with a unique opportunity to make an impact on glioblastoma. Treating the tumor area directly enables the physician to bypass the use of systemic treatments. Focal treatments may bypass the blood brain barrier – this barrier has the ability to limit the effectiveness of some drugs given intravenously, or by mouth. Focal treatment options include placement of chemotherapy wafers, temporary implantation of radiation reservoirs, injection of toxin-tagged monoclonal antibodies, T-cell therapies, or gene therapies. Radiosurgery with the Gamma-Knife, modified linear accelerators, or proton beams are other methods of treating GBM ‘focally,’ although these radiation therapy techniques can be used without surgery when appropriate. We detail some of these therapies below.

**Chemotherapy Wafers:** The term “chemotherapy wafers” usually refers to the use of Gliadel – biodegradable wafers soaked with chemotherapy drug. The active ingredient in these wafers is carmustine, also called BCNU, which is a drug traditionally used to treat glioblastoma. Up to eight dime-sized wafers are laid in the cavity created by surgical removal of the tumor. The wafers then release high concentrations of BCNU locally over a period of two to three weeks. Gliadel does not provide a cure for glioblastoma, however, studies show it is capable of prolonging survival. The side effects associated with this type of chemotherapy delivery system tend to be the same side effects associated with surgery to remove the tumor. Current research focuses on combining Gliadel with other therapies to increase its effectiveness. Treatments such as radiosurgery, temozolomide (Temodar) chemotherapy, and intravenous infusion of O6BG (a compound designed to overcome a major drug resistance factor) seek to intensify the effects of Gliadel.

**Focal radiation therapies:** Standard radiation therapy is a mainstay of treatment for glioblastoma. In select cases, a high-dose “boost” of focally delivered radiation is an attractive option that may enhance control of tumor growth in some patients. Radiating only the active tumor and a small area around it has the advantage of sparing significant amounts of normal brain from the effects of radiation therapy. Commonly used delivery systems include radiosurgery, high-dose temporary implants with iodine or iridium, low-dose permanent implants of iodine, and temporary balloon catheter implants filled with liquid radiation (the GliaSite RTS system). Many studies show a survival advantage in selected groups of patients who received a local boost of radiation to the tumor or tumor area. Limitations to radiation therapy do exist, such as the tendency of GBM to spread into surrounding tissue, the tumor becoming resistant to radiation, and the risk of radiation damage (radiation necrosis).

**Biologic Therapies:** There has been considerable interest in the development of effective biologically-based strategies for focal treatment of GBM. Here, the goal is to treat the tumor on a cellular or molecular level. For example, monoclonal antibodies tagged with a toxin or radiation can be loaded into an implantable reservoir then placed into the cavity created during surgery. In principle, these antibodies are intended to seek and destroy only the ‘foreign’ tumor cells for which they were designed. Another biological treatment uses altered T-cells as an immune therapy. Here, GBM cells obtained at the time of surgery are treated in the laboratory then injected into the patient’s bloodstream. This triggers an immune response in which T-cells, a natural part of the immune system, are released in the blood. These activated anti-tumor T-cells are then harvested and infused back into the cavity created during surgery.

Yet another promising area of research is the use of altered genes. Gene therapy relies on the laboratory creation of genetic material that will somehow discriminate and infect or destroy cancer cells while leaving healthy brain cells functional and unharmed. Usually, this genetic material is inserted into a virus whose purpose is to serve as a delivery system – a “Trojan Horse” approach. Preliminary studies are very encouraging and provide the foundation for amazing new discoveries in this arena.

To summarize, ‘focal’ treatment strategies are a feasible and effective option for those with glioblastoma. Many wonderful and emerging biological agents and chemotherapies are in development – some of these are given by more traditional routes (mouth, vein, artery, or spinal fluid) but are not mentioned in this brief article. Suffice to say that tremendous advancements have taken place in the fight against glioblastoma. The best is yet to come in our relentless search for a cure to this disease.

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