

Glial Tumors

(astrocytomas, oligodendrogliomas)

and

the Phase I Clinical Trial of M032 in Canine patients with Glial Brain Tumors



INTRODUCTION

Any tumor that comes from the supportive tissue within the brain is termed a *glioma*. There are several types and several grades of each type.

Several glial cell tumors are described and are often graded on a scale of I to IV, with the lower grades being less aggressive. They may also be classified as low-grade (slow growth), medium-grade (moderate growth), or high-grade (rapid growth). Other descriptions can include cell types (astrocytoma, oligodendroglioma) and the most severe is termed “glioblastoma multiforme” or GBM. In veterinary patients, some believe the Grade III Oligodendroglioma is comparable to the GBM in humans. Nonetheless, any type of glial cell tumor is a serious disease and the opportunities for treatment are often limited.

INCIDENCE

According to the UCD College of Veterinary Medicine web-site, glial tumors (specifically astrocytomas and oligodendrogliomas) are the second most common group of canine brain tumors. Although the incidence of different grades of astrocytic tumors varies quite considerably between humans and dogs, the tumors themselves appear to be very similar at many levels.

Astrocytomas and oligodendrogliomas appear to have a similar rate of occurrence in dogs (incidence varies somewhat between studies). Brachycephalic dogs (Boxers, English Bulldogs, French Bulldogs, Boston terriers) have a higher incidence of glial tumors, particularly oligodendrogliomas. The majority of tumors

occur in animals > 6 years of age, however young animals (<3years) can be affected, and glial tumors can occur in animals as young as 6 months of age. The rate in males and females is approximately the same.

Both oligodendrogliomas and astrocytomas occur most frequently in the cerebral cortex.

Oligodendrogliomas occur most commonly in the frontal/temporal lobes, while the lower grade astrocytomas appear to have a predilection for the temporal/parietal lobes. Similar to their human tumor counterparts, canine high grade oligodendrogliomas and astrocytomas commonly invade into the ventricular system.¹

CAUSE

There is no known prevention of brain tumors and the causes of most are unknown. However, we do know that certain genes on specific chromosomes can predispose to the development of glial cell tumors in certain breeds of dogs.

CLINICAL SIGNS

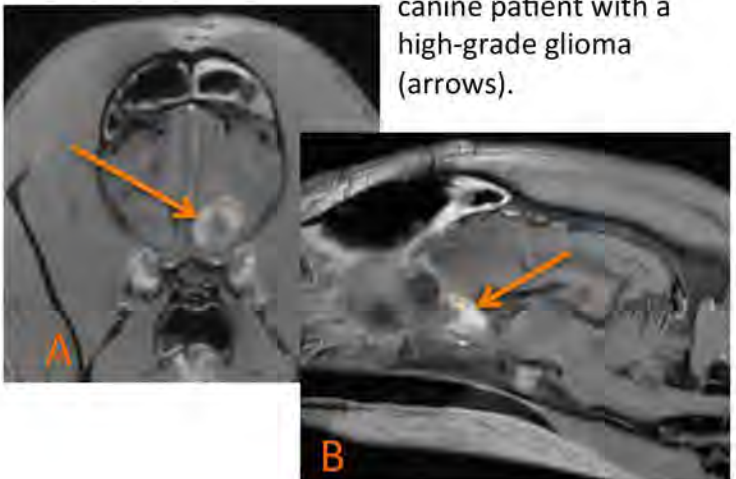
Specific clinical signs can vary, often depending on the location of the tumor and the effects it has on that portion of the brain. Many times with tumors in the frontal lobe of the canine brain, the very first indication of a problem is when the patient experiences a seizure. In other locations, the tumor can be manifested by abnormalities the veterinary neurologist / neurosurgeon notices on a neurologic examination. Because of the variability and the fact that many of these tumors can be quite large before clinical signs are noted, the first indications of a neurologic problem in the brain should alert the owner to seek a consultation and determine if advanced imaging (MRI) is indicated.

1 <http://www.vetmed.ucdavis.edu/vsr/Neurology/Disorders/Brain%20Tumor%20Info.html>

DIAGNOSIS

To obtain an accurate diagnosis, the veterinary neurologist will begin with a neurological examination followed by an MRI. The scan may be done with a contrast dye that makes the border and details of the tumor more visible. If it is a tumor, the scan will help your doctor determine the size, location and probable type of tumor. An MRS (magnetic resonance spectroscopy) scan is another part of the diagnosis and measures chemical and mineral levels in a tumor. Those measurements may help distinguish a brain tumor from other medical problems, such as infection (parasite, bacterial and fungus), an immune-mediated disorder, or a stroke. On MRI with contrast, high grade gliomas show brightly (this is called enhancement); low grade gliomas frequently do not enhance with contrast, or slightly enhance. However, only the examination of a patient's tumor tissue under a microscope and molecular analysis can confirm an exact diagnosis.

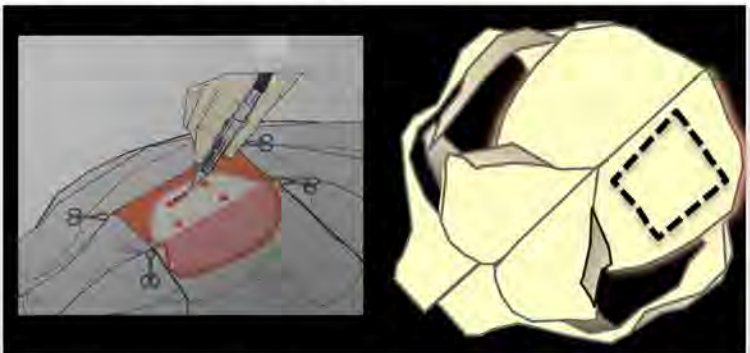
Images (A, transverse; B, Sagittal) from an MRI of canine patient with a high-grade glioma (arrows).



TREATMENT

Surgery

Generally, the first step in treatment of Grade III glial tumors is surgery. With today's modern techniques, surgery can be safely performed in most patients, depending on tumor location. The goals of surgery are 1) to obtain tumor tissue for confirming the diagnosis and planning treatment; 2) remove as much tumor as safely possible to reduce signs caused by the tumor; and 3) to prepare the patient for additional forms of therapy. Partial tumor removal may be performed to reduce the swelling in the brain and reduce seizure activity. Complete removal of all visible tumor is optimal, but cannot always be performed safely and, even with this, microscopic elements of the tumor (tumor cells) will almost always remain. This is why additional or adjunctive therapy is needed. Surgery to remove a brain tumor is performed by making an opening in the skull over the tumor site – this is known as a craniotomy or craniectomy. Next, specialized neurosurgery equipment and instrumentation are used to locate and expose the tumor site. Care is taken to remove mostly only the tumor tissue and great care is taken to avoid important normal structures and large blood vessels. Tissue from the tumor is removed and submitted for additional tests that may include histopathology, special stains, histochemistry, and possible genetic testing.



*** Illustrations of a surgical approach to perform a craniectomy in the dog ***

Adjunctive Therapy

While many therapies have been tried, none have been universally successful, but some have been helpful in maintaining quality of life from several months to a few years. And while researchers and clinicians in both the human and veterinary neurosurgery and oncology fields have worked hard through laboratory trials and clinical trials to find more effective treatments, these tumors have proven especially hard to conquer.

Radiation therapy is often used following surgery. With more modern equipment, this form of therapy has few side effect in dogs.

Chemotherapy has only recently been shown to have any effect on these tumors and some of these therapies have minimal side effects, but can be quite expensive, especially in larger dogs.

Researchers are also developing new ways to deliver drugs or biologic agents to the tumor site. One such way is placement of a special catheter near the tumor site after surgical removal and using a special container or reservoir to slowly deliver the product to the brain tissue. This should pose no additional danger to the patient, but is helpful in the placement of the drug or agent directly into the remaining tumor area.

CANINE IMMUNOTHERAPEUTICS PHASE I CLINICAL TRIAL

Immuno therapy is considered the cutting edge of cancer treatments. Our project utilizes this by several means including inducing the tumor to attract cells that can kill it and reducing the tumor's ability to acquire adequate blood supply.

What is a Phase I Study?

Doctors do phase I clinical trials to learn if a new drug, treatment, or combination of treatments is safe for patients.

In a phase I clinical trial, doctors collect information on:

- The dose or treatment
- When and how often to administer the medication
- Any side effects or problems
- How the body responds to the treatment. For example, how it affects the cancer or cancer side effects.

If you join a phase I clinical trial, your pet could be one of the first to get a promising new drug or treatment.

Phase I clinical trials last several months to a year. They usually have 10 to 30 participants. The treatment might help the cancer, and the clinical trial information can help other patients in the future.

Our Study

Our study is funded by the National Institutes of Health (NIH) and therefore went through rigorous review before being accepted and before being awarded the grant to conduct the study. This study is a multicenter study and is centralized by the Neurosurgery Department at the University of Alabama at Birmingham (UAB). Veterinary participants are Mississippi State University, Auburn University, Tuskegee University, and the University of Georgia. And, in actuality, this therapy as a clinical trial was initiated first in humans, and has thus far been safe and effective. Again, this is on the cutting edge of therapy in both humans and canines.

How Does the Therapy Work?

After removal of the tumor and a day of recovery, a very modified virus that has been shown to only infect glioma tumor cells will be slowly delivered

through a specialized device called a “Rickham Reservoir” that was implanted just under the skin at the time of surgery. This reservoir is connected to a tube or catheter that delivers the virus to the tumor site. Here the virus is designed to invade the remaining tumor cells and deliver genes that will kill the tumor.

Is This Safe for My Dog? Is It Safe For Me?

A lot of effort has gone into developing this virus through extensive modifications and extensive safety testing – enough so that the NIH and FDA have approved its use in animals, including humans! Consequently there have never been shown any risks associated with this. We do, however, take sensible precautions nonetheless. For two weeks after receiving this modified virus, we are requiring the patients to avoid close contact such as licking the face with pregnant women, infants and toddlers, and individuals with decreased immunity. Again, we have no evidence of a potential problem with the spread of the virus, but in a Phase I study, this is always included in the precautions.

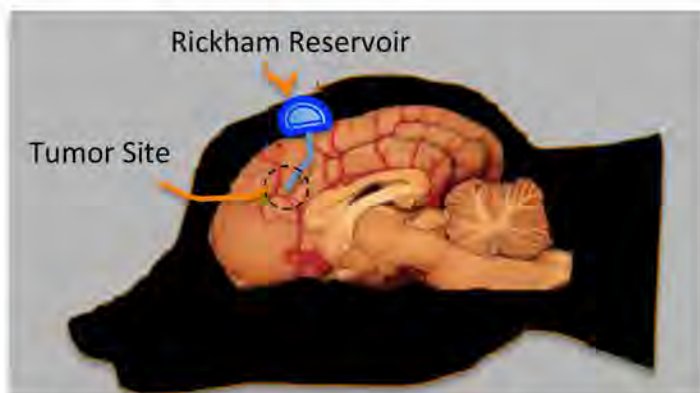


Illustration of the placement of the Rickham reservoir and the attached catheter leading to the tumor site.

Who Is Eligible?

Canine patients that have a clinical and MRI findings consistent with a diagnosis of a malignant (grade III) brain tumor are eligible. They must be at least 6 months of age and are generally healthy with no co-morbidities that are likely to prove fatal within the next 6 to 12 months.

What Are the Scheduled Components of the Treatment?

Patients admitted to the study will have the images reviewed and the surgery planned within 2 days of admission. Surgery will be performed by a board-certified veterinary neurologist / neurosurgeon with extensive training and experience in performing the procedure. Surgical treatment in this will not vary from what has been routinely performed for canine brain tumors. At the end of the procedure the reservoir and catheters will be placed and a CT scan will be made to insure proper placement of the devices. On the following day, with mild sedation, the virus will be injected into the reservoir. We will also take blood samples at that time and your dog will be receiving levetiracetam orally as an anticonvulsant throughout the study. Our canine brain tumor patients are always kept in the ICU so they receive 24/7 monitoring throughout their hospitalization. Blood samples will also be taken during hospitalization, and at 2 weeks, 4 weeks, 3 months, 6 months, 9 months, and 12 months after the surgery. Follow-up MRIs will be made at 28 days, 3 months, and 6 months after surgery. ***ALL OF THE TREATMENTS AND FOLLOW-UP EVALUATIONS WILL BE COVERED BY THE STUDY.***

Participation is entirely voluntary and patients can be withdrawn from the study at any time with the understanding the participant owner will become responsible for all expenses up that time if they withdraw from the study.

Our goal, throughout the study, is to provide quality care for your pet and none of the components of the surgery other than the reservoir and catheter placement differs from our usual protocol for canine brain tumor patients.

We certainly hope this therapy will provide the best option for treatment of this dreaded disease and, in addition, will provide very valuable information for both canine and human patient glioma therapy in the future. With all procedures there are risks, but every precaution will be taken and your pet's quality of life is the number one priority of all members of our neurosurgery team, the ICU staff and the anesthesia staff.

And while we hope we can provide an answer for this disease, we know that all treatments are not 100% effective for all individuals. In that light, when the time comes when this disease or some other disease progresses in your pet and there is not quality of life, sadly, death by natural causes or euthanasia will happen at some point. Because of the extreme importance of learning all we can about the effectiveness of this therapy, we must ask for a post-mortem examination of your pet. By enrolling into this study, you will sign papers that allow us to perform this procedure at whatever time this unfortunate event occurs. We know that is hard to think about at this time, but its critical importance to your pet and future canine and human patients makes this necessary. We are happy to answer any questions about this when the time is appropriate.

