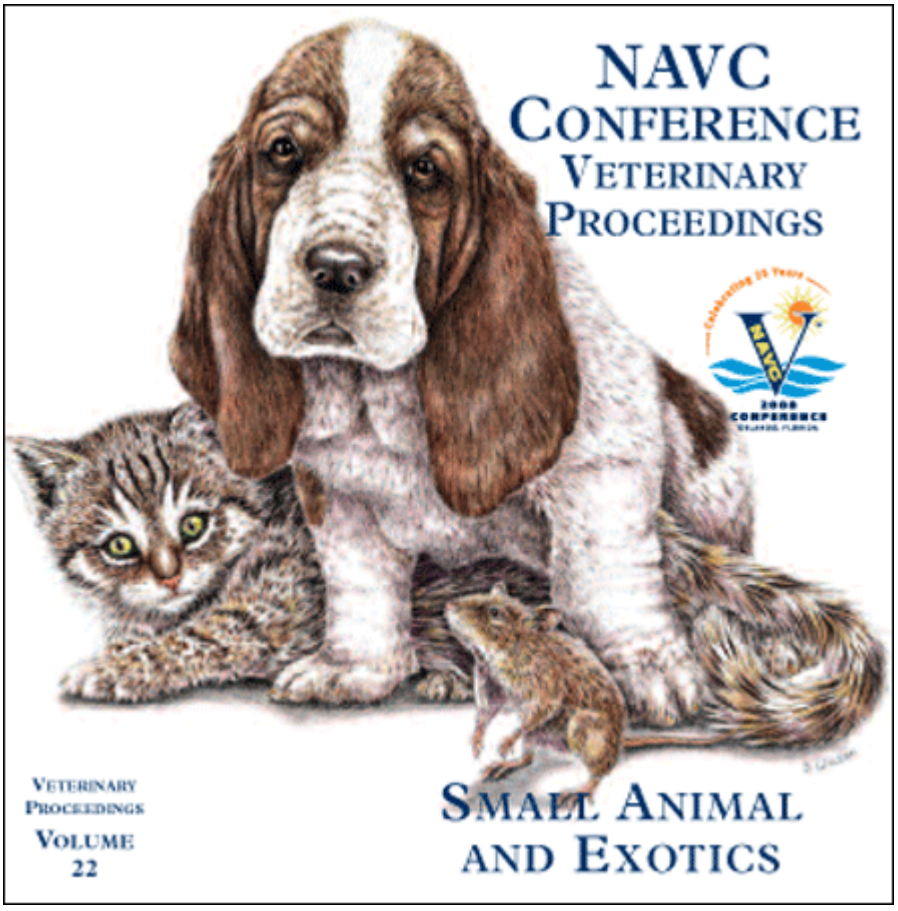
Proceeding of the NAVC
North American Veterinary Conference
Jan. 19-23, 2008, Orlando, Florida



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INTRACRANIAL TUMORS

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Intracranial tumors are well described in dogs and cats. The prevalence of this disorder is reported to be 14.5/100,000 dogs and 3.5/100,000 cats, although other reports indicate an incidence approaching 3% in dogs and slightly in excess of 2% in cats. In both species, meningioma is most common intracranial tumor and astrocytoma is the second most common. Choroid plexus and pituitary tumors are also relatively common and several other types are also reported (Table 1). The entire classification scheme for tumors of neurologic origin seems to be in flux. A number of recent manuscripts have addressed updates and changes to the current World Health Organization (WHO) classification. A variety of neoplasms metastatic to the brain have also been described.

Breeds most commonly identified in one large survey of dogs with primary intracranial tumors in descending order of frequency are mixed-breed dogs, Golden retrievers, Boxers, Labrador retrievers, German Shepherd dogs, Bull Mastiffs, and Rottweilers. The most common breed of cat reported in a different large survey were the domestic short hair followed by the domestic long hair. Affected individuals in both species are typically older (dog mean age 9.4 $\pm$ 3.4 years; cat mean age 11.3 $\pm$ 3.8 years).

Clinical signs are related to the specific intracranial localization, size, and compression of surrounding normal parenchyma, invasiveness, and inflammatory component of the tumor. Intracranial tumors are often slow growing so they are often diagnosed late in the course of the disease. Because growing tumors are confined by the calvaria, compression of adjacent normal brain parenchyma can contribute to clinical signs. Slowly expanding tumors give the brain time to accommodate to increased intracranial pressure and parenchymal compression. During the early stages of disease, clinical signs are often subtle and not dramatic. Later in the course of disease, the clinical signs most often associated with intracranial tumors in dogs are seizures, mentation change, vestibular syndrome, neck pain, vision loss, and occasionally regurgitation. In cats however, the most common sign is mentation change, followed by circling, seizures, ataxia, behavior change, vision loss, pacing and tetraparesis. A host of additional neurologic signs can be present in both species and frequently multiple clinical signs are present in the same individual.

Clinical evaluation of all patients suspected of having intracranial neoplasia should include basic clinical laboratory (complete blood count, chemistry profile, urinalysis), complete ophthalmic examination, neurologic examination, thoracic and abdominal radiographs (to look for metastasis to or from the brain) and some advanced imaging of the brain such as computed tomography (CT) or magnetic resonance (MR) imaging. Because of superior image contrast, MR is the preferred imaging modality for intracranial tumors. T1 and T2 weighted MR images are made during routine scanning and the information they contain is complementary. On T1-weighted images the cerebrospinal fluid (CSF) will appear dark (low signal intensity) and white matter will appear brighter than gray matter because white matter contains less water. The opposite is true on T2-weighted images where CSF appears white and gray matter has a higher signal intensity than does white matter. The signal intensity of the dura is low on both T1 and T2 in part because of its low water content. Tumors of the brain usually have a higher water content than surrounding normal brain so they usually appear hypointense on T1 images and hyperintense with T2 weighting. It is not always possible to distinguish intracranial tumors from other intracranial disorders such as infection with MR.

In one large study of MR images in cats with intracranial tumors found that the overwhelming majority of intracranial tumors in cats were meningiomas. In addition, meningiomas were always extra-axial (outside of the brain parenchyma) and were most often ovoid with marked contrast enhancement and peritumoral edema. Gliomas in this study were always intra-axial with ring enhancement and generally caused more peritumoral edema than other tumors.

Cerebrospinal fluid analysis can be helpful in distinguishing inflammatory from infectious from neoplastic disease. CSF analysis in canine cases of intracranial cancer is usually associated with elevated total protein, elevated white blood count, and a differential cytology characterized by mononuclear, neutrophilic, or mixed cell pleocytosis. However, these are nonspecific findings that are also compatible with other intracranial diagnoses such as granulomatous meningoencephalomyelitis (GME). Some individuals with intracranial tumors have normal CSF. For example, in one study only 39.6% of the cases of dogs with primary intracranial tumors had abnormal CSF.

Biopsy of intracranial tumors is standard of care in human medicine but it is rarely done antemortem in veterinary medicine. Obviously, biopsy is the only means of providing a definitive diagnosis but it is often not attempted because of financial constraints and potential patient morbidity. A number of different biopsy approaches have been described in dogs and cats but the one of most value and lowest morbidity is stereotactic CT-guided brain biopsy.

Loss or mutation of the p53 tumor suppressor gene occurs in about 33% of human astrocytomas, suggesting an early genetic event in tumorogenesis. An important consequence of loss of normal p53 activity is increased genomic instability, which appears to accelerate neoplastic transformation. The EGFR gene is the most frequently amplified oncogene in human astrocytic tumors. Over expression of p53 gene mutations and EGFR have also been identified in dogs with astrocytomas of different sub-types in a similar prevalence to that in man.

Glioblastoma multiforme (GBM) is a WHO grade IV astrocytoma and is the most common intracranial

malignancy in people. The standard of care in humans with glioblastoma multiforme is surgical resection to the extent feasible and adjuvant radiation therapy plus chemotherapy that often involves temozolomide. This tumor type is uncommon in dogs but it has been reported and described in detail.

Treatment to remove the tumor mass and its secondary effects such as edema most commonly includes one or more of the following: surgery, chemotherapy, and radiation therapy. Successful treatment may also require concurrent suppression of seizures with anticonvulsants and the use of substantial doses of corticosteroids to reduce brain swelling. Humans with primary intracranial tumors are often treated with some combination of all three modalities.

An intact blood–brain barrier (BBB) can complicate the use of chemotherapy for intracranial tumors. Drugs given intravenously or orally may or may not reach the tumor. Different strategies exist to overcome the BBB including intra-arterial administration, barrier disruption, new ways of packaging drugs, and inhibiting drug efflux from the tumor. When chemotherapy is given intravascularly there is a common drawback in that the body acts as a sink and even under the best of circumstances, only a small portion of the administered drug reaches the tumor. Because of this, systemic toxicity is usually the dose-limiting factor. Drugs can also be given into the CSF (intrathecal administration) or directly into the tumor where 100% of the administered dose will be delivered to the target site. However, local delivery has variable and unpredictable distribution and concentration within the space into which it is distributed. In addition, local delivery's dose-limiting factor is neurotoxicity. Intravenous chemotherapy for brain tumors in dogs and cats is most commonly used and it primarily involves the use of Lomustine® (60 mg/m^2 orally every 6-8 weeks), Carmustine® (50 mg/m^2 IV over 20 minutes every 6 weeks) and occasionally cytosine arabinoside (600 mg/m^2 IV once a week). Concurrent use of prednisone and anticonvulsants (phenobarbital often plus potassium bromide) is usually required for successful management.

Temozolomide is a relatively new drug that is essentially an oral form of dacarbazine. Temozolomide is usually part of the standard of care of most brain tumors in people, but its use in veterinary medicine is uncommon. Very recently temozolomide use in a different context—rescue therapy for dogs with lymphoma—has been reported and suggests that it is well tolerated at an average dose of about 90 mg/m^2 daily for 5 consecutive days as part of a multi-drug protocol. Temozolomide may be a useful drug in the context of brain tumors in animals, but further investigation is required.

Surgery can be an effective treatment for meningioma if they are superficial enough. Obviously, only experienced neurosurgeons should attempt this but there are many veterinary neurosurgeons that routinely preform partial brain resection. Postoperative management can be intense but the prognosis in many cases is quite favorable. For example, postoperative survival for cats with meningioma is reported to be as long as 72 months assuming they survive the immediate postoperative period.

Radiation therapy for intracranial tumors can also be very rewarding. Radiation protocols vary among veterinary radiation oncologists but doses to the brain of 51 to 54 Gy given in 2.0 or slightly larger fractions are well tolerated. In a very recent report of 46 dogs with brain tumors (dose range 35 to 52.5 Gy) the median survival time calculated for deaths attributed to worsening of neurological signs was 1,174 days while the median survival time of all deaths attributed to disease or treatment consequences was 699 days (23.3 months). The use of computerized treatment planning systems and accurate positioning allows high doses of radiation (80% of total dose) to be limited to the gross tumor volume and the planning treatment volume. These advances allow for better tumor control with fewer side effects (radiation necrosis).

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Table 1. Histologic Classification of Intracranial Tumors in Dogs and Cats

Glial Cell Origin Astrocytoma Oligodendroglioma Oligoastrocytoma	Glial cell tumors are a varied group that pathologists may categorize by different schemes. New subtypes not included in the present WHO classification have been noted in dogs
Choroid Plexus and Ependyma Origin Ependymoma Choroid plexus papilloma Choroid plexus carcinoma	
Neuronal and Mixed Neuronal/Glial Cell Origin Gangliocytoma Ganglioglioma	
Embryonal Origin Olfactory neuroblastoma Medulloblastoma Neuroblastoma Primitive neuroectodermal tumor (PNET)	All embryonal origin tumors have been consolidated by most pathologists to a common term of PNET. PNETs are histologically indistinguishable from cerebellar medulloblastoma, but are found in other locations.
Meningeal Origin Meningioma	
Lymphoreticular Origin T- and B-cell lymphomas Histiocytic sarcoma Reticulosis	Classification of this group is confusing. Mass lesions may be singular or multiple. This group includes inflammatory subtypes that is part of the granulomatous meningoencephalomyelitis (GME) syndrome in dogs.
Pituitary Origin Adenoma Carcinoma	Often are considered to be secondary brain tumors because they affect the brain by means of local extension.
Other All other types are rare to very rare	