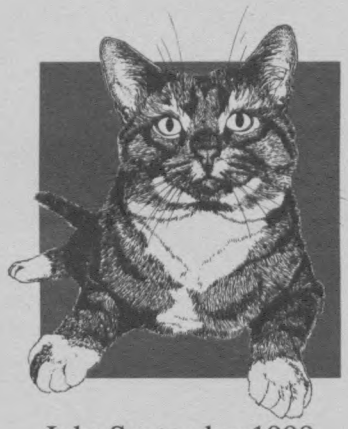


# Feline Health Topics

*for veterinarians*

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# Advanced Neuroimaging


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*Editors Note: This article is an adaptation of Dr. Rodney S. Bagley's presentation at the 1998 American Association of Feline Practitioners and the Academy of Feline Medicine's Fall Meeting.*

Treatment of central nervous system disorders, as with any disease process, requires accurate diagnosis. Historically, specific neurologic diagnoses have often been found only upon postmortem examination. With the development and increasing clinical use of advanced imaging modalities such as computed tomography and magnetic resonance imaging, accurate ante mortem diagnosis of diseases affecting the central nervous system is now possible. As these modalities are more universally recognized and appreciated, improvements in patient management due directly to improvements in understanding of the anatomic and physiologic ramifications of central nervous system disease should result. Access to these modalities for veterinary use, a historical stumbling-block, is increasing as the benefits of this type of imaging are recognized. In this article, computed tomography and magnetic resonance imaging modalities used to aid neuroanatomical diagnosis are reviewed.

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## Computed Tomography (CT)

Computed tomography revolutionized both human and veterinary neurology, and will continue to be an important diagnostic tool in both fields in the future. With CT, information is collected from the relative penetration of a number of X-ray beams projected in a circumferential manner around the head (or other body part). These pieces of information are then arranged by the computer to form a two dimensional image of structures within the cranial cavity or spine. The images can be reformatted in differing planes corresponding to major anatomical planes (i.e. sagittal, transverse, dorsal).

When interpreting information from the advanced imaging modalities, knowledge of cross-sectional anatomy is very helpful. This knowledge aids in correlating information seen with the suspected area of dysfunction based on clinical examination. As it is common to find anatomical abnormalities with advanced imaging that may not result in clinical signs, the use of these imaging techniques is no substitute for an appropriate clinical examination.

When evaluating images of the central nervous system, the most important characteristic to look for is symmetry. For example, a mass on one side of the brain may impinge on the ipsilateral lateral ventricle, causing collapse of that ventricle. A shift of structures from their normal anatomic location due to a space-

occupying mass within the intracranial space is often called *mass effect*.

On a CT image, just as on a radiograph, black colors are associated with tissue of air density. Nervous and other soft tissues appear as varying shades of gray with bone appearing whiter in color. The relative color of the image is dependent on its CT number (a relative representation of tissue density). Tissues are represented on a scale ranging from +1000 to -1000 Housfield units. Tissues of varying densities are shown in Table 1.

**Table 1.** Approximate CT numbers of differing tissues

| Tissue | CT number | Relative color |
|---|---|---|
| Bone | +1000 | White |
| Blood | +100 | |
| Brain Matter | +30 | Gray |
| CSF | +5 | |
| Water | 0 | |
| Fat | -100 | |
| Air | -1000 | Black |

A more finite range of CT numbers within this +1000 to -1000 range can be chosen to highlight certain structures. For example, if bone information is needed, the scale could be adjusted to concentrate more in the higher CT numbers closer to bone density. In this example, this is referred to as a "bone window". The outline of the bone is more easily viewed; however, the contrast between other soft tissues is less distinct.

With CT, tissues seen on the scan can be graded as being *isodense* (same color as brain tissue), *hyperdense* (whiter than brain tissue) and *hypodense* (blacker than brain tissue) on either the pre- or post-contrast scan. Depending upon the quality of the scan, a certain portion of the brain (i.e. gray matter vs. white matter) can be used for comparison. Areas in the brain that are whiter than normal brain parenchyma on the noncontrast scan include mineralization (i.e. mineralized tumor) or hemorrhage. Areas that are blacker than normal brain parenchyma generally contain increased fluid (i.e. edema).

A series of scans are performed before and after intravenous injection of an iodinated contrast material. Abnormalities disrupting the blood-brain-barrier (BBB) may become more apparent with this technique. Loss of integrity of the BBB or increased vascularity may result in an area of increased whiteness after intravenous contrast enhancement. Contrast enhancement is most often seen with tumors, vascular abnormalities, and inflammatory foci.

The major advantage of all of both CT and MR imaging techniques is the ability to non-invasively image structures deep to the surface of the body. Advantages of CT imaging include the ability to image in planes giving a spacial orientation to abnormalities seen. Disadvantages include its use of ionizing radiation (radiation exposure), and its sometimes poor definition of intracranial abnormalities, especially those in the posterior fossa. Spatial resolution, especially for

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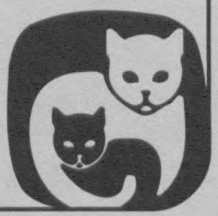

small animals like cats, may not be adequate to determine small (<5 mm) lesions.

**Magnetic resonance (MR) imaging**

The imaging of the brain and other structures with magnetic resonance (MR) is often referred to as magnetic resonance imaging (MRI). Magnetic resonance imaging is a noninvasive procedure that does not employ ionizing radiation. An MR image represents the response of various nuclei to absorb radio frequency energy. Ultrasound and radiographic techniques rely on density of material to produce an image; magnetic resonance relies on the tissue density of hydrogen nuclei. Currently only hydrogen nuclei (which consists of one proton) are used to produce medical magnetic resonance images. The density of the protons is important in determining imaging features, as is the ability of the protons to relax. Various flow phenomena also contribute to signal intensity. All soft tissues can be visualized with MR. Dense bone and air, however, lack signal for imaging due to the inability of the protons to relax in the dense bone matrix, or the relative lack of hydrogen nuclei in air. All other structures are shown as various shades of gray to bright white due to signal intensity variations.

Magnetic resonance relies on a powerful magnetic field in the range of 0.06-2.0 tesla (T). One tesla equals 10,000 gauss. For comparison, the earth's magnetic field equals 0.5 gauss. The high magnetic fields can produce a very strong pull on various metallic objects, and the main danger in magnetic resonance is from inattention to this fact resulting in flying projectiles. Another potential hazard with magnetic resonance can be from interference with implanted stimulating devices such as pacemakers.

After the animal is placed in a strong magnetic field, the tissue protons align with the magnetic field similar to a bar magnetic. Small coils within the unit are turned on to create an excitation field that briefly changes the orientation of the protons. Energy is transferred to these protons when the original alignment is disturbed and when the input is at resonance with the protons in the main magnetic field. The excitation field is then turned off and the protons are free to realign to their original state, giving up the energy they have absorbed. This energy is detected by the small receiving coils acting as antennae. This excitation and detection of the relaxation is repeated several times to obtain sufficient signal to produce an image of the location and nature of the tissue protons in three-dimensional space. The MR image, like CT, is dependent on computer processing of the signals.

Numerous excitation and detection sequences are available. The various sequences provide images of the proton density, and the two basic forms of relaxation, named longitudinal (T1) and transverse (T2). The most commonly used imaging sequence to date has been a spin-echo sequence yielding a proton density and a T2-weighted image followed by a T1-weighted sequence before and following the administration of a paramagnetic contrast agent. The most commonly used contrast agent to date utilizes the paramagnetic material gadolinium (Gd) in the form of Gd-DTPA. This contrast agent acts in a matter similar to the iodinated contrast agents utilized in CT. The main difference is that MR does not visualize the gadolinium but produces an image of the protons that are influenced in their relaxation by the presence of Gd. This material does not pass the intact blood-brain-barrier (BBB), and therefore, the only enhanced areas in the normal brain are those that lack a blood-brain barrier including the pituitary and choroid plexus. Most diseases of the CNS disrupt the BBB resulting in a high signal intensity in the presence of the contrast agent.

Similar to CT, diagnoses utilizing MR are based on mass effect causing displacement of normal structures and the visualization of contrast-enhanced areas. Loss of symmetry, changes in signal intensity, and displacement of normal structures are extremely helpful in arriving at a diagnosis. The improved resolution afforded by MR imaging often allows deterining

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whether lesions are intra- or extra-axial in origin. Extra-axial lesions involve tissue outside the neuronal axis, including meninges, pituitary, and choroid plexus. The location of lesions helps determine potential tissues of origin, and the shape of the mass and visualization of its edges is often useful in describing the degree of malignancy. In general, signal intensity is increased with tumors, especially on the T2-weighted images. Depending on the image sequence, however, tumors may be hypo-intense, iso-intense, or of a heterogeneous intensity as compared to normal surrounding tissue. Extra-axial tumors are often difficult to visualize without contrast enhancement. Meningiomas, especially, are often iso-intense on the proton density, T1-, and T2-weighted images. However, these tumors usually show marked enhancement following the administration of Gd-DTPA.

Because non-neoplastic lesions can mimic the appearance of tumors, biopsy of the abnormal tissue is often required for determination of appropriate therapy. Hydrocephalus is visualized on all imaging sequences, and any obstructions to flow can be readily detected. In addition, MR is extremely useful to visualize edematous changes within the CNS in the absence of contrast enhancement. Magnetic resonance is extremely sensitive at depiction of hemorrhage, and due to the normal degradation of hemoglobin, the age of hemorrhagic occurrence can be estimated. Magnetic resonance provides better detail and more information than CT. Computed tomography, however, is superior in detecting mineralization and bony changes.

Currently, MR must be considered the "gold-standard" for imaging the central nervous system. The anatomic detail and spatial resolution is significantly superior to other modalities. These factors yield an image equal to that visualized at gross dissection thus allowing a rapid familiarity of the diagnostician to these images. Newer pulse sequences have been developed that allow cerebral angiography to be performed without the use of any contrast material. Superior arterial and venous studies can be obtained with this technique. Three-dimensional acquisition is currently possible allowing superior neurosurgical and radiotherapy planning.

Imaging artifacts occur with MR as in all modalities. The main causes of artifacts in images of the CNS are generally motion and deformations in the magnetic field from implanted metallic objects. Since the time required for MR studies is 10 to 60 minutes, general anesthesia must be utilized since MR generates considerable noise that would startle animals. If gas anesthesia is used, a high flow rate, non-rebreathing system allows the standard anesthetic equipment to remain safely outside of the strong magnetic field. With general anesthesia, the lack of patient motion yields excellent animal studies. Rarely do animals have any implanted metallic objects that are magnetic enough to perturb the image field, however micro chips and other steel objects (BB pellets) can create artifacts with MR that affect image quality.

Magnetic resonance is the superior modality today in terms of spacial resolution, soft tissue contrast, the ability to acquire the image in all planes, and the absence of potentially harmful, ionizing radiation. Assuming there are no flying magnetic projectiles, magnetic resonance-guided biopsies can be performed in suitable scanners with specialty instrumentation.

The sophisticated and expensive equipment required for MR is now available in some veterinary teaching institutions and referral centers. Other practices often utilize the facilities of human hospitals and various mobile imaging facilities. ■

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# Vaccine Associated Feline Sarcoma Task Force Update

The Vaccine-Associated Feline Sarcoma Task Force (VAFSTF) met on April 5, 1999 at the American Veterinary Medical Association (AVMA) headquarters to award grants to research proposals scored by independent reviewers. The task force also prepared concise guidelines to assist practitioners in diagnosing and managing vaccine-associated sarcomas.

This year is marked by unprecedented financial support for studies investigating the epidemiology, etiology, and treatment of these rare but aggressive tumors. The task force received its first Platinum level donation of $100,000 from Pfizer Animal Health. As of April 1999, various veterinary organizations, individuals, and vaccine manufacturers contributed over $460,000. The task force wishes to thank the contributors for their generous contributions: (see Table 2 on page 6 for the contributors list).

This support has allowed funding of the following six 1998-1999 projects:

*Epidemiologic Study of Vaccine-Specific Risk and Vaccination Protocols in the Incidence of Vaccine Associated Sarcomas in Cats.* (Principle investigator: P. H. Kass, DVM, PhD). Initially funded for 1998, this study was extended through 1999.

*Molecular Biomarkers of Vaccine-Associated Feline Sarcoma: p53 Mutations and Drug Sensitivity.* (Principle investigator: S. Kanjilal, PhD)

*Papillomavirus, Herpesvirus, and Polyomavirus: Exploring the Etiology of Vaccine-Associated Feline Sarcomas.* (Principle Investigator: M. L. Jackson, DVM, PhD)

*Evaluation of Mutagenicity of Feline Vaccines (excluding rabies) Using the $A_L$ Assay.* (Principle Investigator: S. M. LaRue, DVM, PhD)

*The Utility of Contrast-Enhanced Computed Tomography in the Evaluation and Treatment of Cats with Vaccine-Associated Fibrosarcoma.* (Principle Investigator: M. C. McEntee, DVM, DACVIM, DAVR)

*Towards a Novel Therapy of Vaccine-Associated Feline Sarcomas: Reoviral Oncolysis.* (Principle Investigator: J. A. Ellis, DVM, PhD)

In addition, several applicants were invited to develop preliminary data to submit by September 1, 1999 for a second consideration of their proposals.

Update on 1997-1998 Funded Studies

The Task Force also received reports on the studies that were funded in 1997 and 1998.

*Epidemiologic Study of Vaccine-Specific Risk and Vaccination Protocols in the Incidence of Vaccine Associated Sarcomas in Cats.* (Principle investigator: P. H. Kass, DVM, PhD). Dr. Kass and fellow investigators in a multicenter study are evaluating a number of risk factors, comparing the occurrence in cats with sarcomas to that in cats with basal cell tumors. Veterinary participation in the project has been exemplary; by early May 1999, nearly 2,000 cases and controls have been enrolled in the study.

*Molecular Biomarkers of Vaccine-Associated Feline Sarcomas.* (Principle Investigator: S. Kanjilal, PhD). The researchers at University of Minnesota have established a comprehensive tissue bank of sarcomas, blood, and normal appearing surgical margins. A number of polymorphisms in the p53 gene have been identified, including in morphologically normal tissues adjacent to sarcomas. Preliminary work on identifying signature mutations and correlations to clinical outcomes has been completed.

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**Table 2: Contributors list**

| Source | '97-'98 Donation | | '98-'99 Donation | | Total |
|---|---|---|---|---|---|
| AAHA Foundation | Gold | $50,000 | Gold | $50,000 | $100,000 |
| AVMA | Gold | $50,000 | | | $50,000 |
| AAFP | Silver | $25,000 | | $10,000 | $35,000 |
| CFHC | | $10,000 | | $10,000 | $20,000 |
| OAHF | | | | $5,000 | $5,000 |
| VCS | | $5,000 | | | $5,000 |
| | | | | | |
| Pfizer | Silver | $25,000 | Platinum | $100,000 | $125,000 |
| Fort Dodge | Silver | $25,000 | Silver | $25,000 | $50,000 |
| Intervet | | $10,000 | | $10,000 | $20,000 |
| Merial | | $10,000 | | $10,000 | $20,000 |
| Schering-Plough | | $10,000 | | $10,000 | $20,000 |
| Bayer | | $10,000 | | | $10,000 |
| Synbiotics | | $2,500 | | | $2,500 |
| | | | | | |
| Individuals | | $650 | | | $650 |
| **Total** | | **$233,150** | | **$230,000** | **$463,150** |

(AAFP = American Association of Feline Practitioners; AAHA = American Animal Hospital Association; AVMA = American Veterinary Medical Association; CFHC = Cornell Feline Health Center; OAHF = Ohio Animal Health Foundation; VCS = Veterinary Cancer Society)

*Molecular Analysis of Platelet-Derived Growth Factor (PDGF) and the Cellular Protooncogenes sis, fms, and jun in Feline Vaccine-Associated Sarcomas, and Evaluation of the Role of Local Lymphocytes in Tumorigenesis.* (Principle investigator: M. J. Hendrick, VMD, DACVP). The researchers at University of Pennsylvania have initiated investigation of tumorigenesis by evaluating the role of local lymphocytes. Preliminary data suggest T-lymphocytes tend to infiltrate the sarcomas, while B-lymphocytes do not. The investigators plan to continue their studies by conducting molecular analysis of growth factors and their receptors.

*Growth Factor Expression and Vaccine-Associated Sarcoma Tumorigenicity.* (Principal investigator: E. G. MacEwen, VMD). The researchers at the University of Wisconsin-Madison and MD Anderson Cancer Center have established 14 cell lines from vaccine-associated and non-vaccine-associated feline sarcomas, and initiated evaluations of levels of growth factors HGF, IGF, and PDGF, and the response of cell lines to the growth factors. They have also evaluated the tumorigenic potential of several of the cell lines.

*Comparable Efficacy of Doxorubicin Versus Stealth Liposomal Doxorubicin in Cats with Vaccine-Associated Sarcomas: A Multicenter Randomized Clinical Trial.* (Principle investigator: D. M. Vail, DVM, MS, DACVIM). Vail and colleagues in six sites report that case accrual is ahead of schedule with 74 enrollees at the time of this writing. The stealth form of doxorubicin was found to have a delayed renal toxicity at the dosage of 1.5 mg/kg; studies will continue at the reduced dosage of 1.0 mg/kg.

*Treatment of Feline Vaccine-Associated Sarcomas: Comparison of Tumor Response to Radiation Therapy alone with Radiotherapy Plus an Adjuvant Hemoglobin-Based Oxygen Carrier Radiotherapy Sensitizer, and Follow-up Assessment After Surgery and Chemotherapy.* (Principle Investigator: A. E. Hohenhaus, DVM, DACVIM). This study was funded late in the cycle, and the number of enrolled cases is as yet insufficient to provide meaningful preliminary data.■

The Task Force discussed the diagnosis and treatment of masses with a high index of suspicion for vaccine-associated feline sarcoma, and prepared the following guidelines for practitioners:

**Vaccine Associated Feline Sarcoma Task Force Guidelines: Diagnosis and Treatment of Suspected Sarcomas**

The following recommendations are based on information available as of April 1999 and are subject to revision as new information becomes available.

Diagnosis

1. Record anatomic location, shape, and size (measured by caliper and recorded in three dimensions) of all masses that occur at the site of an injection.

2. Manage a mass that develops at a previous injection site as if it were malignant until proven otherwise. A lesion should be fully assessed and aggressively treated if it meets any one of the following criteria:

    - Persists more than 3 months post-injection
    - Is larger than 2 cm in diameter
    - Is increasing in size after one month post-injection

3. If a mass meets one or more of the above criteria, we recommend that you perform a diagnostic biopsy prior to surgical excision. A tru-cut needle biopsy or incisional wedge biopsy is preferred for diagnosing lesions. Tru-cut biopsy should be done in such a way that subsequent surgical removal can readily include the entire needle tract. Wedge biopsy should be performed so that subsequent surgery can remove all tissue affected by the biopsy. Fine needle aspiration cytology is considered unreliable for the diagnosis of vaccine associated feline sarcomas (VAFS) and is not recommended.

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**Management** - Masses confirmed as malignant should be handled as listed below:

1. Perform routine thoracic radiographs and pre-operative labwork for any malignant mass.
2. When feasible, histologically confirmed VAFSs should be imaged by computerized tomography (CT) or magnetic resonance imaging (MRI). Soft-tissue sarcomas often spread along fascial planes and may be undetectable visually in early stages of tumor growth. Advanced imaging data is very useful in determining the extent of surgery and/or the size of the radiation field that will be needed to maximize the chances for successful treatment.
3. Consult with an oncologist for current treatment options, which may include radiation, chemotherapy, surgery, or other modalities, **prior to** initiating therapy.
4. **Never "shell out" a sarcoma. Incomplete surgical removal of a sarcoma is the most common cause of treatment failure.** Employ oncologic surgical techniques to avoid seeding malignant cells. Remove *at least* a 2-cm margin in all planes, including the deep side. In some instances, this will involve reconstruction of the body wall, removal of bone, or other advanced surgical techniques.
5. Submit the entire excised specimen for histopathology. Mark the excised mass with India ink or suture tags to provide an anatomical reference to facilitate subsequent treatment.
6. Report all histologically confirmed VAFSs to the manufacturer and to U.S. Pharmacopeia at 12601 Twinbrook Parkway, Rockville, MD 20852, 800-487-7776, FAX 301-816-8532, or www.usp.org/prn.

After a sarcoma has been removed:

1. Recheck by physical examination monthly for the first three months, then at least every 3 months for one year.
2. Perform additional diagnostic procedures as appropriate for the abnormalities detected.■

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