



Cancer in Dogs The 28th Annual Canine Symposium

The 28th Annual Canine Symposium was held January 31, 1998 at VHUP. The event was organized with the help of the School's Mari Lowe Center for Comparative Oncology and featured a series of presentations on Cancer in Dogs.



Mari Lowe Center for Comparative Oncology

The words cancer and growth are brutally intertwined. But they are also connected in several positive ways, said Dr. Narayan G. Avadhani, professor of biochemistry at the School. In recent years, cancer has met tremendous growth in research, knowledge, technology and treatment modalities. Dr. Avadhani presented Penn's Mari Lowe Center for Comparative Oncology, which conducts extensive cancer research and clinical programs.

Cancer is a genetic disease, Dr. Avadhani explained. Yet cancer is inherited in only

five percent of cases. The rest spontaneously arise following a primary DNA lesion that occurs during the life of an individual. "It is this 95 percent of the population that's going to be extremely important for understanding cancer in both humans and animals.

"Animals are exposed to the same environment and some of the same putative causal factors that we are," he said.

With these issues in mind, the Center, which is supported primarily through individual and foundation contributions, has created a state-of-the-art clinical oncology service at VHUP and today trains veterinary oncologists, conducts multidisciplinary research and supports outside cancer research. Since its establishment four years ago, said Dr. Avadhani, who heads the Center, the number of canine cancer patients at VHUP has more than doubled to some 1,500 cases annually.

J.C.



Cancer Terminology and Symptoms

What exactly is cancer? The language used to discuss cancer and its treatment is composed of many words that are not part of everyday conversation. Dr. Kim Cronin introduced some of the basic terminology that veterinary cancer specialists use and also discussed the early warning signs of cancer to help the symposium audience prepare for the lectures that would follow.

The early warning signs of cancer in small animals are similar to the seven warning signs of cancer in people used by the American Cancer Society. The signs range from: an abnormal swelling that persists or continues to grow, a sore that does not heal, weight loss, bleeding or a discharge from any body opening, reluctance to exercise, a loss of stamina or difficulty breathing, urinating or defecating. Even subtle changes, such as sleeping more, not playing as much and lack of desire to interact may indicate the need for a veterinary evaluation to determine if additional tests are necessary.

The term neoplasia means new growth and is used interchangeably with cancer. It takes about a billion cells, or thirty doublings, before we can actually see a tumor. When rapidly dividing cancer cells invade normal tissue the cancer becomes malignant. Malignant cancers can metastasize -- spread to other parts of the body. During metastasis the cancer cells move through the blood stream or lymphatic

vessels and may settle in tissues distant from their origin. The location where the tumor grew before metastasizing is called the primary site. Benign tumors are not usually invasive and do not metastasize.

The lungs and lymph nodes are the most common sites for tumor metastasis, however, there are many types of cancer that selectively spread to other parts of the body. The way a tumor grows and spreads is called its biologic behavior. The biologic behavior of a tumor determines what tests will be performed, how the animal will be treated therapeutically and what the probable outcome will be.

There are many unique terms used to describe the procedures involved in the clinical workup of an animal with cancer. An aspiration is when a needle attached to a syringe is inserted into the tumor and the plunger on the syringe is drawn back to suction a few cells from the mass for microscopic analysis. Cytology refers to the examination of the cells collected by aspirate. A biopsy involves the surgical removal of a small piece of tissue and examining it under the microscope. Grading of tumors is accomplished by characterizing the tumor cells using the microscope. Tumors are assigned into high, intermediate and low grades based on microscopic evaluation. High grade tumors tend to be very aggressive, they spread early and are difficult to treat. Low grade tumors are exactly the opposite. Staging is the evaluation of the extent of the tumor and the prognosis is the expected outcome for that tumor. A protocol is the overall treatment plan, the drugs used, how often as well as the number of times repeated. Finally, when the bone marrow is no longer able to produce normal cells the patient loses the ability to fight infection and sepsis results. Sepsis is an overwhelming systemic infection. Recognizing the early warning signs of cancer may lead to early detection and significantly increases the likelihood of successful treatment.

M.R.



Cancer Detection through Imaging Studies

Imaging techniques are indispensable in the management of cancer in domestic animals. Dr. Jeffrey A. Wortman, associate professor of radiology at the School, discussed the applications of various imaging modalities in diagnosing cancers, assessing prognoses, planning treatments and monitoring disease response.

Diagnostic imaging techniques, such as radiography -- or "x-rays," are used for

cancer screening, detection, staging and surveillance. Screening tests are employed to detect cancer in a population prior to the onset of clinical signs; unlike in people, in whom screening tests like routine mammography are often performed, these tests are infrequently done in animals. Imaging studies are routinely used to detect the presence of neoplasia in clinically-affected animals. These studies have variable sensitivities and specificities for diagnosing different tumor types; additional tests like tissue biopsy are often added to augment imaging studies.

Imaging tests also serve in staging of cancers. Once the diagnosis is confirmed by histopathology, such imaging diagnostics as thoracic radiography can then be used to detect tumor metastasis from primary sites, such as bone; these "mets" show up as radiopaque (white) nodules. This information is important in affixing prognosis and planning treatments like surgery, radiation therapy and chemotherapy. "If the cancer has spread," said Dr. Wortman, "this indicates that it's aggressive and will be more difficult to treat and cure."

Follow-up imaging studies can then be incorporated into disease surveillance to chronicle disease regression, progression, relapse, and treatment complications.

The imaging methods that are particularly efficacious in veterinary oncology include radiography +/- contrast (i.e. iodinated agents) ultrasound, x-ray computed tomography (CT), magnetic resonance imaging (MRI) and nuclear scintigraphy (scans). The choice of imaging study, Dr. Wortman explained, "depends on many things, like the patient history and (tentative) diagnosis, which will give us some idea of the nature of the cancer and its biological behavior." The choice also depends on what information is being sought, availability and quality of the imaging technology and expertise of the veterinarian interpreting the study.

Ultrasonography, an imaging technique in which deep structures of the body are visualized by recording the reflections of sound waves directed into the tissues, enables one to view masses that may or may not be externally palpable. It can also be used to safely direct biopsy instruments to internal sites so tissue samples can be obtained for pathology. Likewise, a CT scan or an MRI may elucidate a brain tumor that would not be apparent on skull radiographs. The availability of imaging modalities in veterinary medicine is variable. Radiography, including contrast techniques, is ubiquitous throughout private veterinary practice, said Dr. Wortman, and ultrasound is steadily becoming more accessible. But more sophisticated studies, like CT and MRI, are less accessible to animal patients.

Whatever imaging test(s) one selects to screen for, diagnose, stage or monitor cancer, Dr. Wortman advised, one should maximize the fitness of the test by using proper technique. In radiography this includes correct body positioning and film

exposure, and use of contrast agents where appropriate.

"You need to be aware of the limitations of a specific test and try to expand on the test in order to accurately make the diagnosis."

J.C.



Breed Related Cancers

Many cancers have been found to have a breed predilection. Dr. Michael H. Goldschmidt, professor of pathology at the School and head of the Surgical Pathology Service of the Laboratory of Pathology and Toxicology, showed examples of specific cancers in the dog and the breeds most commonly affected.

Dr. Goldschmidt cited a study conducted in the 1960's in the USA that estimated tumor incidence at about 1,100 cases per 100,000 dogs per year. The Laboratory of Pathology had developed an extensive computerized database of canine cases; in the decade preceding 1995 over 130,000 cases in dogs were submitted to the Surgical Pathology Service for diagnosis. Most tumors in these dogs were from the skin, oral cavity, mammary gland and male genitalia. Because of the large size of the database it was often possible to calculate the breed risk for commonly diagnosed tumors.

An example of this was mammary tumors. Benign mammary tumors, seen clinically as well encapsulated masses of varying size and consistency on palpation, were found to have a higher predilection for small breeds of dogs such as the miniature poodle, Yorkshire terrier, Chihuahua and Maltese. Malignant mammary tumors, seen clinically as invasive, inflamed, ulcerated masses with lymphatic invasion in some cases, had a higher predilection in the English setter, Chihuahua, miniature poodle and Afghan hound. Many breeds at decreased risk for developing mammary tumors, such as the golden retriever, Rottweiler and boxer were at high risk for developing soft tissue and mesenchymal tumors.

The incidence and types of tumors are breed related and probably controlled by a single or multiple genes. An example given was the German shepherd which is predisposed to developing nodular dermatofibrosis, a syndrome that is comprised of a three tumor; multiple dermal fibromas (multiple firm masses in the skin), renal cystadenocarcinomas (malignant cystic epithelial tumors throughout the kidneys), and in females uterine leiomyomas (benign tumors of the smooth muscle).

Dr. Goldschmidt also illustrated the increased and decreased breed risks associated with two specific skin tumors, including infundibular keratinizing acanthoma, to which the Norwegian elkhound is highly predisposed with a relative risk of 29, and trichoblastoma, to which the Kerry blue terrier is predisposed with a relative risk of 12.

Other specific tumors with high breed risks were also discussed. These included:

- Trichoepithelioma: basset hound
- Pilomatrixoma: Kerry blue terrier
- Ceruminous adenoma: cocker spaniel
- Anal sac gland carcinoma: English cocker spaniel
- Subungual squamous cell carcinoma: giant schnauzer and Gordon setter
- Subungual malignant melanoma: Scottish terrier
- Melanocytoma: Vizsla and miniature schnauzer
- Liposarcoma: Shetland sheepdog
- Mast cell tumor: boxer and pug
- Cutaneous plasmacytoma: cocker spaniel

Dr. Goldschmidt concluded that by selecting for the specific external features of a dog, its phenotype, we are selecting specific genes, which make that breed more or less susceptible to developing a specific cancer.

J.C.



Cancer Treatment Options

When it comes to treating cancer, quantity and quality should go hand-in-hand. Dr. Karin Sorenmo, assistant professor of oncology at the School, said that cancer therapy is best governed by attempts to prolong life within the realm of maintaining reasonable quality of existence. "We try to maintain the highest degree of function and take as few risks for serious complications as possible" when planning cancer treatment protocols, she said.

Several factors influence cancer treatment decisions. Most important are the tumor type, biological behavior and staging. Malignant tumors are characterized by local invasion +/- distant metastasis. Highly malignant (high grade) tumors often have metastasized by the time the patient's cancer is diagnosed. For high-grade tumors, aggressive treatment combining surgery and chemotherapy is often warranted even if metastases are not yet detectable radiographically. The goal then is not typically

to cure, but rather to prolong survival by slowing disease progression and to provide palliation. On the other hand, tumors that are locally invasive but less likely to spread offer better prognoses and are often treated effectively with surgery and/or radiation therapy.

The patient's overall health status plays a major role in therapy choices. Concurrent diseases should be attended to and the patient evaluated for its ability to tolerate cancer treatment. Life expectancy should be taken into consideration as well; for a slow-growing tumor in an older dog, for example, the treatment drawbacks may outpace the potential benefits.

Owner factors also impact medical decisions because treating cancer requires the owner's money, commitment and emotional resilience.

The three principal cancer treatment modalities are surgery, radiation therapy and chemotherapy. Surgery has two functions in cancer management: to obtain tissue biopsies for definitive diagnosis and to excise lesions completely. Biopsy provides information about the mitotic index and vascularity of the tumor, both of which are increased in rapidly-growing masses. Local lymph nodes can also be biopsied to detect evidence of tumor spreading.

Tumor excision is performed for both curative and -- in the case of painful tumors like osteosarcomas -- palliative reasons. Tumors are resected with wide margins; the objective is to obtain "clean" or cancer-free borders, thereby minimizing the likelihood of local recurrence. Once the lesion is excised, the borders are examined histologically for the presence of neoplastic cells.

Radiation therapy is a suitable alternative to radical surgery for tumors in certain locations, such as the head or legs. Radiation is also important for adjunctive treatment of tumors that are not completely resectable, as well as for locally-invasive tumors like nasal carcinomas, for which surgery alone is usually not curative. As an adjunct to surgery, radiation therapy is effective in sterilizing the borders. If the borders are clean, the main concern then becomes distant metastasis.

Chemotherapy is often combined with surgery or radiation therapy to treat high-grade tumors that are likely to metastasize. In addition, it's the treatment of choice for multicentric cancers like leukemia or lymphosarcoma. Chemotherapy strikes rapidly-dividing cells, which, in addition to cancer cells, include normal cells of the bone marrow, oral mucosa and G.I. tract. Many owners fear potential chemotherapy side effects. However, those seen in people, such as hair loss and nausea, are not typically experienced by dogs. Because most breeds do not have continuously-growing hair, the hair follicular cells are not affected by

chemotherapy. More importantly, the objective for most canine cancer patients is to prolong life rather than establish a cure. Therefore, lower doses and fewer drug combinations are used.

"If we treat aggressively and cause serious complications in these normal tissues, all the while knowing we are not going to cure the animal," Dr. Sorenmo explained, "then we probably haven't done that animal a favor."

Veterinarians administer the same chemotherapy drugs used in human oncology. The drugs are given orally, intravenously or subcutaneously. Extensive owner cooperation is necessary in complying with strict and sometimes rigorous treatment schedules. But the returns can be well worth the effort. Dr. Sorenmo pointed out that chemotherapy extends the average lymphosarcoma survival time from just two months (untreated) to a year; ten to 15 percent of these cases never relapse. For osteosarcoma, following surgery with chemotherapy doubles the survival time over amputation alone.

In designing a cancer treatment protocol utilizing any or all of the aforementioned options, one must first define the treatment goal based on a realistic prognosis. This determines acceptable levels of owner resources spent and patient discomfort tolerated. Dr. Sorenmo cautioned: "The treatment should not be worse than the disease itself."

J.C.



Quality of Life Issues for Canine Cancer Patients

"Quality of life concerns are important to veterinarians who want their patients to feel good, they are important to pet owners because pets are often considered family members, and quality of life is certainly important to our patients" explained Dr. Lillian Duda, lecturer in radiation oncology.

Once a diagnosis of cancer is made, the decision to pursue treatment hinges on the determination of the quality of life that can be expected for the animal from that point onward. The veterinarian can help the pet owner feel comfortable talking about the many issues involved, and they must work together toward a common goal. It is something that should also be discussed between family members and friends because the matter is both personal and emotionally charged.

The main goal in cancer treatment is to secure a high quality of life for as long as possible. A pet may be kept alive in the hospital using supportive measures such as oxygen and intravenous fluids, but, it may not be acceptable to do so if there is no hope of improving the pet enough that it can go home. Quality of life issues are more easily overlooked and more difficult to assess than quantity of life issues. There must be a balance between both. The veterinarian can help by remaining objective and providing information about the cancer and the effects of treatments on the animal. However, the veterinarian depends on the owner to report how their pet is feeling and behaving.

The side effects of cancer therapy are numerous and vary greatly between patients. In general, it is not acceptable to expect the animal to suffer side effects from the treatment without a good chance of a better life. The Animal Medical Center in New York City has developed a scale to assess the overall quality of life for dogs undergoing cancer treatment. They measure the dog's ability to carry out normal daily activities using five parameters. Eating is one of the parameters that is measured. As their quality of life begins to decrease, dogs will often show changes in their eating habits or may have a general loss of appetite, some other parameters are alertness, body conditions, and activity level. This scoring method makes the difficult task of assessing the dog's condition more objective and provides useful medical information. Studies have shown that individuals scoring closer to normal tend to do better overall.

Quality of life means something different to each pet owner. People are asked to come up with and write down their personal minimum level of acceptable quality of life for their pet before it receives treatment. This is done to help them anticipate, and thereby prepare for some of the important decisions they may need to make. If the unanimous goal is to prolong a quality life and to minimize suffering then euthanasia is sometimes the only option remaining. Euthanasia is a humane and responsible decision -- a final therapy allowing the pet to be released from pain and suffering.

M.R.



Nutritional Needs of Canine Cancer Patients

Animals with serious chronic illness are often malnourished. One of the primary reasons this occurs is because their appetites are impaired by the illness and

oftentimes the only food they accept -- table food -- is nutritionally inadequate. This may not be critical for short periods of time, but, when treatments extend for weeks or even months there can be serious effects on the animal's health related to malnourishment. "I like to tell people it is their job to find something their dog will eat adequate amounts of consistently and I can build a balanced diet around it," said Dr. Kathryn Michel, assistant professor of nutrition. Cancer not only affects the patient's quality of life, but, can also impair their ability to tolerate cancer treatments. Meeting the unique needs of patients undergoing cancer therapy is augmented by providing adequate nutrition, however, dietary therapy in this context is considered supportive rather than primary care.

Dr. Michel reviewed the six basic classes of nutrients. "I know that we don't normally think of water as a nutrient but really it is the most essential nutrient there is. An animal will die of dehydration in a much shorter time than it will die from starvation." After water, the body must have nutrients that provide energy such as carbohydrates, fats and protein. Protein not only supplies calories, it is also the source of amino acids which the body uses to make new proteins. Micronutrients are also derived from the minerals and vitamins in the diet. A dog with cancer will require water, adequate calories, protein, minerals and vitamins, however, cancer causes changes in normal metabolism that are not overcome by supplying calories and nutrients. At this time the specific nutritional requirements for dogs with cancer have not been established.

Cancer therapies that reduce the chances of deleterious side effects are always sought, but, they are not always completely successful. Some patients may have nausea, vomiting or diarrhea as a result of their treatment. If an animal associates side effects such as nausea with the act of eating they may stop eating for that reason. This phenomenon is termed a learned food aversion and presents quite a challenge when we try to feed these animals. An important part of nursing a dog or cat through an illness is coaxed feeding. It is very important not to push food on an animal that does not want to eat. It is best to wait until the pet is comfortable and not stressed before presenting food. Do not attempt feeding right after changing bandages or giving medications. It may be best to feed them cold food directly from the refrigerator, as it will not have much taste or aroma. Drugs may be used to reduce nausea as a short term approach if the dogs are having gastrointestinal side effects. Appetite stimulants are most useful in convalescent animals to "jump-start" their appetites, but, really have very limited application. They are not intended for long term use. If the dog shows some interest in food try feeding novel food items or offer food in a different setting or at different times. You can also divide the day's food up into a number of small meals instead of one or two large ones.

Some patients may benefit from nutritional support. These patients often show

signs of malnourishment and have not responded well to coaxed feeding. It may be necessary to feed these dogs using a nasoesophageal or esophageal tube. In critical patients intravenous feeding is given to help animals through a short time period until the chemotherapy takes effect. This is not complete nutritional support, nor is it meant to be used as life support. It is providing adequate nutritional care for a limited time to cancer patients who are unable to nourish themselves during the treatment of their disease.

M.R.



Canine Osteosarcoma

Osteosarcoma is the most common primary bone tumor in dogs, accounting for some 85 percent of canine bone tumors. VHUP clinical specialists Drs. Kim Cronin and Amy Kapatkin explained the disease process of -- and treatments for -- osteosarcoma.

The average osteosarcoma patient is seven or eight years of age, although dogs as young as six months old have been diagnosed with this cancer. It typically strikes large- and giant-breed dogs like great Danes, golden retrievers and German shepherds. Associated with high amounts of stress on weight-bearing limbs, osteosarcoma is almost 500 times as likely to affect dogs over 35 kg than dogs weighing less than 10 kg.

Osteosarcomas tend to anchor themselves in areas of increased bone remodeling, said Dr. Cronin, lecturer in oncology. "Every time you have cell damage or increased turnover, the DNA is more likely to make a mistake when coding for new cells, which can lead to tumor formation." So naturally, previous fractures and chronic bone infections are predisposing factors. These tumors are more likely to occur in the limbs, particularly the forelimbs, which bear most of the body weight; other bones, such as the ribs and skull, can also be affected.

Osteosarcoma is both locally invasive and metastatic. It infiltrates the bone and weakens it. It then spreads throughout the body. The chief presenting signs for osteosarcoma are lameness and pain (which may be intermittent), limb swellings and pathologic fractures at the tumor site.

Because osteosarcoma shares common clinical signs with other conditions like degenerative joint disease (arthritis), infectious diseases and other tumors of the bone (i.e. fibrosarcoma, chondrosarcoma, hemangiosarcoma and synovial cell

tumor), a thorough physical exam, radiographs and biopsy are used to make the final diagnosis. Chest radiographs should be performed in dogs diagnosed with osteosarcoma. According to Dr. Cronin, over 90 percent of afflicted dogs have pulmonary metastasis at the time of diagnosis, although lung nodules may not yet be visible radiographically.

Because of its high metastatic potential, osteosarcoma carries a guarded prognosis. Most patients eventually die of metastasis to the lungs or other organs. The average survival time from the date of diagnosis is 8-12 months. Only 20 percent of patients are alive two years after diagnosis. Without treatment, most patients succumb to the disease within a couple of months.

Treatment is aimed at removing neoplastic sites and preventing further seeding. If the tumor is on a leg, amputation is the usual course. "We must be very aggressive in our initial approach so we don't get regrowth," said Dr. Kapatkin, assistant professor of orthopedics and neurosurgery. The leg is typically disarticulated at the coxofemoral (hip) or scapulohumeral (shoulder) joint. "Amputation is very cosmetic and most of our patients can ambulate well on three legs and are incredibly happy," said Dr. Kapatkin.

Limb sparing is the other surgical approach. Here, the tumor is resected en bloc with 3-5 cm margins, and the gap is filled with bone graft or donor bone. Potential complications include infection, implant failure and tumor recurrence. However, the survival rate is the same for limb-sparing as for amputation.

Surgery can be performed also to excise metastases. Prolonged survival rates have been achieved in cases where three or fewer nodules were present and survival until metastasis was diagnosed radiographically was 300+ days, Dr. Kapatkin said.

Radiation therapy can be potent in destroying neoplastic cells at the primary tumor site and chemotherapy may be employed to prevent or delay metastasis. Several drugs -- including carboplatin, cisplatin and doxorubicin, are part of the osteosarcoma chemotherapy protocol, which is typically initiated 10-14 days after surgery. Immunotherapy, which activates the immune system to combat cancer cells, is part of newer treatment protocols.

J.C.



Canine Brain Tumors

Brain tumors in dogs are not infrequent. Nor are they untreatable. Drs. Charles Vite and Amy Kapatkin clarified the key issues revolving around brain tumors in dogs and their surgical biopsy.

According to Dr. Vite, post-doctoral fellow in neurology at VHUP, brain tumors are a common cause of neurological dysfunction in dogs over five years of age. Primary brain tumors arise from neuroepithelial (i.e. astrocytoma, oligodendrocytoma, choroid plexus neoplasm and ependymal tumors) and meningeal tissue (meningioma). Brain tumors can also arise secondarily from surrounding tissues like the nasal cavity or bone (i.e. nasal carcinoma, chondroma and osteosarcoma), or originate from hematogenous metastasis from tumors elsewhere in the body (i.e. malignant melanoma, hemangiosarcoma and lymphosarcoma).

Clinical signs of a brain tumor depend on the location of the mass. Tumors of the cerebrum and thalamus may result in seizures and depression; tumors of the cerebellum and brain stem typically result in incoordination and cranial nerve deficits. "The clinical signs tell us what part of the brain is affected," said Dr. Vite.

A thorough neurological exam should be performed. Once the location of the lesion is determined based on the neurologic signs, the lesion is then characterized as either neoplastic, inflammatory, cerebrovascular or degenerative. Because nothing is pathognomonic for a brain tumor except biopsy results, one must compile a list of differential diagnoses that can account for the clinical signs. The factors that go into ranking these differential diagnoses are patient signalment (age, breed and sex), chronicity and progression of signs, evidence of focal or multifocal neurologic disease, and presence of other systemic disease.

For example, said Dr. Vite, the differential diagnoses for a six-year-old golden retriever presenting with a sudden onset of generalized seizures include: intracranial tumor, encephalitis, metabolic disease and idiopathic epilepsy. Add to this the dog's history of increasing mental dullness, and idiopathic epilepsy moves further down on the list. Throw in the fact that the dog is blind in the right eye and has right-sided postural deficits and the clinical picture is now most closely referable to either a brain tumor or encephalitis.

A cerebrospinal fluid (CSF) tap, titers to known organisms capable of causing encephalitis, and magnetic resonance imaging (MRI) of the brain can aid in distinguishing between these two possible causes. However, Dr. Vite added, definitive diagnosis of a brain tumor requires biopsy of the mass.

Once a brain tumor is tentatively diagnosed, surgical feasibility is then determined.

Surgical success depends on the type of tumor present and its location, said Dr. Kapatkin, assistant professor of orthopedics and neurosurgery. Most meningiomas are treatable with surgery and adjunctive therapy, increasing a patient's lifespan; pituitary tumors, on the other hand, are not easily treated. The cerebrum is the best location to have a tumor, she added. "We can remove a whole half of the cerebrum and you probably wouldn't notice a big difference in your pet."

The three main surgical approaches are the lateral, transfrontal and suboccipital entries. The lateral -- or parietal -- approach involves making a curved incision and elevating the muscles over the parietal bone. A hole is then drilled in the bone and the cerebrum is accessed. In the transfrontal approach, the frontal sinus is penetrated and the frontal bone is removed using a bone saw. The tumor is removed from the prefrontal area and the bone is replaced. The suboccipital approach, used to enter the cerebellum or brainstem, involves a midline incision made at the caudal aspect of the skull. Care must be taken to avoid potentially lethal laceration of the sinuses in this region. A fourth approach, the ventral approach, is made through the oral cavity. Used mainly to access pituitary microadenomas, this approach carries high risk of infection. Treatment of pituitary tumors may incorporate radiation as a substitute for -- or adjunct to -- surgery.

In addition to sophisticated surgical techniques, Dr. Kapatkin credits advanced post-operative care with the high success rate for brain surgery. Intensive care, including fluids and ventilator therapy, is provided after surgery to prevent or rapidly respond to potential complications, such as seizures, surges in intracranial pressure, and intracranial hemorrhage. Fortunately, most patients suffer no complications. In fact, she said, "Seventy-five percent of patients we do brain surgery on literally eat dinner the same day of their surgery."

J.C.



Mammary Cancer

Tumors of the canine mammary gland are common. They comprise 52% of all tumors in the intact female dog and occur most often between 10 and 11 years of age. The breeds most highly represented are spaniels, terriers, German shepherds as well as toy and miniature poodles. Mammary gland tumors are often associated with early estrogen exposure. "The risk for tumor development is associated with estrogen exposure during the first few years of life and that has a significant importance when it comes to preventing these tumors" said Dr. Karin Sorenmo, assistant professor of oncology. When a dog is spayed before the first estrus, she

has a 0.5% chance of developing breast cancer later in life. If she is spayed before the second estrus there is an 8% chance of developing breast cancer, and spaying after the third estrus -- or any estrus thereafter -- increases the likelihood of mammary cancer to 26%. In dogs that were spayed in addition to having the tumor removed the median survival was 659 days. Whereas, dogs that were left intact after their treatment surgery had a median survival of only 198 days.

The relationship between estrogen and mammary cancer in canines is also important because there are similarities with estrogen and breast cancer in women. Women with breast cancer are usually middle aged to older -- the same age distribution seen in dogs. The most common types of tumors in dogs are the same as those found in women. Canine estrogen positive tumors respond to hormonal therapy by removing the ovaries. Estrogen positive tumors in women respond to Tamoxifen which is an anti-estrogen. Both dogs with mammary gland tumors and women with breast cancer can be treated very effectively if the tumors are small and there is no evidence of metastasis. And both canine and human patients with large primary tumors or metastatic tumors are at high risk for dying from the disease. "I think that dogs can provide some very interesting and valuable models for this disease in women" said Dr. Sorenmo.

It has been reported that about half of the dogs with mammary gland tumors will actually have multiple masses. The caudal glands are affected more frequently. Mammary tumors can feel firm, soft or thickened and vary widely in size. They may be ulcerated, inflamed or edematous and one cannot determine if they are malignant or benign from these signs. "The good thing is that even though this is a very common type of tumor in the intact female dog, half are likely to be benign." To obtain a diagnosis, a wide-margin excisional is performed if the surgical margins are clean this is also the treatment of choice for the primary tumor. However, it is necessary to first evaluate the patient's general health through blood analysis and to look for possible systemic spread of the cancer with chest radiographs. If there is lymph node involvement then the risk for developing distant metastasis in the lungs is much higher.

Once the tumor type has been determined from the biopsy, and the extent of disease has been determined by one work-up, it is possible to suggest an outcome as well as an appropriate treatment. Several good retrospective studies indicate that survival rates are higher for dogs with small tumors. Tumors that are made up of well differentiated cells are likely to have a better prognosis than tumors that are anaplastic and have a high mitotic index. Invasive tumors can be more likely to metastasize than encapsulated ones. In general, tumors that have metastasized, have a much poorer prognosis.

The best treatment option is surgical resection. If the tumor is small it can be

effectively treated with a lumpectomy or a mastectomy. A large tumor or tumors in multiple glands require a broad approach -- regional or radical mastectomy -- in order to remove all the malignant tissues at the primary site. It is thought that the progression of these tumors is dependent upon the presence of estrogen and an ovariectomy -- removal of the ovaries -- makes it less likely that the tumor will continue to grow. Chemotherapy is indicated in dogs that have multiple negative prognostic factors and lymph node metastasis. More work needs to be undertaken in this area because there are no controlled studies to document the effectiveness of adjuvant chemotherapy after surgery in dogs with high risk mammary gland tumors.

The owner has a significant role in preventing canine mammary gland tumors through early detection. All tumors start out small and often appear insidiously. Therefore, it is important for the owner to either examine their dog's glands or provide for regular veterinary check ups. There is one retrospective study from the University of Pennsylvania that found 95% of dogs with mammary gland tumors were likely to be overweight during their first year of life. By feeding a balanced diet, spaying early and providing regular examination of the mammary glands, the pet owner may significantly reduce the chances of tumor development. All tumors should be removed and biopsied because early treatment is crucial for a good outcome. Do not watch and wait.

M.R.



From the Laboratory Bench to the Patient's Bedside

New research in angiogenesis -- or neovascularization -- and its regulation has led to the discovery that inhibitors of this process are potent and promising anti-tumor drugs. "While this work is in its early stages we are very hopeful that we can make a contribution to this growing field" said Dr. Andrei Tikhonenko, assistant professor of pathology.

In the normal adult body there is very little angiogenesis apart from wound healing and menstrual cycling. When angiogenesis occurs, a new blood vessel sprouts from the pre-existing one. The membrane surrounding the original vessel dissociates and the endothelial cells migrate and undergo self proliferation. Cancer biologists and doctors have known for years that almost all malignant tumors are heavily vascularized. The tumor is penetrated by a tightly knit network of small blood

capillaries which supply blood and feed the tumor with oxygen and nutrients. If angiogenesis can be controlled then it may be possible to cut off the blood supply to the tumor and prevent its growth. This concept is attractive because tumor cells are capable of rapidly accumulating mutation and becoming resistant to chemotherapy and other therapies.

Within the last three to four years some of the molecules which are responsible for endothelial cell growth were identified. Most cells in the body -- including tumor cells -- secrete both inhibitors and activators of angiogenesis. However, normal tissues secrete more repressors than activators while tumor cells secrete either more activators or less repressors and turn the angiogenic "switch" on. Some of the molecules that have been identified are: Vascular Endothelial Growth Factor -- the most potent activator of angiogenesis -- as well as some inhibitors such as Thrombospondin I. There are other even more potent inhibitors such as some members of the Interleukin family and Angiostatin, and the most recent addition to the list is a protein called Endostatin.

In a recent study published in Nature magazine, a purified form of Endostatin -- a very potent inhibitor of angiogenesis -- was used. Tumors treated with Endostatin regressed very rapidly. The tumor cells remained, but, in the absence of blood vasculature they did not grow and slowly regressed. When the therapy was discontinued the tumor cells regrouped and formed another tumor. If Endostatin therapy was given again, the tumor regressed again but grew back as soon as therapy was stopped. Surprisingly, after twelve to fourteen cycles the ability of the tumor to grow back was lost. Still, the problem is that Endostatin therapy is too costly for prolonged use.

One type of tumor may be more sensitive to Endostatin -- tumors of the endothelial cells themselves. In canines this tumor is often known as hemangiosarcoma. Hemangiosarcoma is a very malignant tumor and is capable of metastasis and dissemination. This tumor is often fatal for the dog. It most commonly affects the spleen or the right atrium of the heart, particularly in German shepherds. Hemangiosarcomas are comprised of chaotically arranged endothelial cells and may not respond to all of the inhibitors of angiogenesis in the same way that normal endothelial cells do. "We are poised to test the numerous inhibitors of angiogenesis and measure their ability to inhibit the growth and viability of hemangiosarcoma cells," explained Dr. Tikhonenko.

M.R.