



Recognized causes of Cancer in dogs and Cats & Advances in Cancer treatment in Pet Animals

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Cancer is a major cause of death in dogs and cats. Forty five percent of dogs greater than ten years of age die of cancer and in 23% it's the cause of death in dogs of any age. This high rate of cancer deaths is often attributed to dogs living longer as a result of vaccination, parasite control, leash laws and better nutrition. The current death rate from cancer in animal is higher than observed in humans but it must be remembered that almost 40% of humans die of heart disease and stroke, a disease group not commonly observed in our pet animal population. Many of our clients don't realize the high death rate from cancer in animal and are shocked when they find out and often ask many questions; why do animals have such a high cancer rate? What causes cancer in pets? How long has my pet had the cancer? The answer to the first question has been better vaccines, leash laws, parasite control etc, How long has my pet had the cancer is often raised out of guilt that they should have found it sooner and only recently could be answered based on scientific evidence. From the time the first cancer cell develops to the time it is first detectable clinically takes twenty five doublings which results in a clinically detectable mass of about 0.5 cm in size. The average doubling time for beast tumors in women is about 169 days which means the tumor has been there but not clinically detectable for about 11 years. The doubling times for some animal tumors have been measured. The shortest time is just 12 hours for some fibrosarcomas (FSA) in cats and the shortest time in dogs is 2.2 days for osteosarcoma (OSA). Others range to 40-60 days. Thus tumor in cats can develop within 2 weeks for example following vaccination and 2 mos. in dogs but may have been as there long as up to three years prior to diagnosis. The point to be made is that tumors in general in animals grow faster than in our human counterpart.

Recognized causes of cancer in dogs and cats: Hormones, herbicides, viruses, drugs, magnetic fields, genetics, pesticides, trauma, radiation, solar radiation, obesity, microchips, vaccines and other causes of chronic inflammation. Few would disagree that the best way to treat cancer is to prevent it. In order to prevent we need to know what causes cancer in dogs and cats. **Obesity** has been shown to be a risk factor in humans for cancer and recent has been established in animals well. Thus the veterinarian should leverage this information with client to help reduce the risk of cancer in their pets. **Genetics** just like in humans also play a significant role in the risk of developing cancer; 60% of Golden retrievers will die of cancer, Golden retrievers and Rottweiller have an increased risk for Osteosarcoma and lymphoma. Some breeds such as Chihuahuas, Dachshunds and Pomeranians have an extremely low risk for developing cancer.

Genetics have also been linked to cancer subtypes. Spitz, Boxers, Golden Retrievers tend to develop T cell lymphomas while European breeds cockers etc. develop B cell lymphomas. Scottish terriers are at increased risk to develop transitional cell carcinomas of the bladder. Giant Schnauzers and standard poodles are at risk of developing multiple nail bed squamous cell carcinomas that in some cases leads to recommending prophylactic removal of all the nails by some veterinarians! **Chemical carcinogens**; Herbicides had been shown to increase the risk of lymphoma, topical insecticides have been shown to increase the risk of bladder cancer, and flea collar have been linked to local squamous cell carcinoma development in cats. **Hormones**; progesterone administration has been shown to increase the risk of mammary cancer in cats and testosterone from either the testes or the adrenal gland stimulate perianal gland tumor growth and is the basis of castration recommendation to control them. Another **drug** that has been linked to transitional cell carcinoma of the bladder in dogs and man is cyclophosphamide (cytoxan) and is why this drug is not used to treat chronic immune mediated disease as much as it once was in either species. **Sun light** is a known cancer inducing agent in humans and dogs and cats. Areas of greatest risk are non-pigmented locations and sparsely haired areas or breeds. So head and neck and belly are frequent locations in dogs and cats. The sun skin protection benefit of a good hair coat has been measured to be between 30-70 SPF! SPF is a measure of sun screen protection most used in humans are usually between SPFs of 15-30. The most common tumor that are induced by UV radiation are squamous cell carcinomas and dermal hemangiosarcomas. **Radiation** is often used to treat cancer but it also can cause cancer and the type of cancer produced depends on the fractionation scheme used in treating the cancer; a coarse high dose fractionation scheme induces sarcomas: fibrosarcomas being most frequently reported at the treatment site, Low dose elections radiation often produce squamous cell carcinomas at the treatment site. The role of **magnetic radiation from powerlines** and tumor risk is still being debated some studies had indicated an increase of lymphoma in people and dogs other studies have not found and increase in risk of developing this cancer. **Asbestos** is a known cause of mesothelioma and lung cancer in humans and it has also been shown to occur at higher rates in animal living with patient associated tumors presumably because they share similar exposure to the agent. **Viral oncogenesis**; Papilloma viruses are known causes of cancer in people and have been to linked to head and neck cancer as well as uterine cancer. Papilloma viruses have be to cause lesion that progress to squamous cell carcinoma in cats and dogs. Retroviruses FeLV is a well-recognized cause of lymphoma in cats and a mutation of the FeLV virus can result in the feline sarcoma virus that produces soft tissue sarcomas in cats, FIV does not in itself produce tumors but rather its immuosuppression which puts cats at increased risk for hematologic tumors such as lymphoma similar to what is observed in immunosuppression people with HIV infections. **Inflammation** and its association with cancer has been the subject of more than 30,000 articles in the last 20 years. Our knowledge of the association between the use of certain vaccines and other injectables and cancer in cats has expanded since the first published association between the use of rabies and leukemia vaccines and sarcoma development was published more than a decade ago. These tumors have been now linked to variety of injectables like leufeneron, long lasting penicillin, rabies, leukemia and certain panluekopenia vaccines. The common thread is an associated injection site inflammatory process caused components within these injectables that are believed to act as promoters in the pathogenesis on this tumor. Inflammation and proliferation at the fracture sites leads to increased risk of sarcoma development. The association of inflammation and the parasite spirocerca lupi in dogs has long

been documented. The association between microchip implantation and inflammation is only recently been recognized.

Cancer causing viruses in dogs and cats:

FELINE LEUKEMIA VIRUS

The incidence of FeLV has dropped 50% in the last twenty years in the North America and Europe largely due to our understanding of the pathogenesis of the disease and the professions use of FeLV testing and vaccination against the disease. Along with the decrease in FeLV infection rate has been a decline in FeLV associated disease and lymphoma. To better understand the FeLV prevention measures and vaccine strategies for the virus one needs to review the pathogenesis of the infection which remains the number one fatal infectious disease of adult cats. FeLV is a retrovirus that incorporates into the genome of the host cell through reverse transcriptase. That fact in itself is important in that although humoral immunity may protect against infection once the virus has invaded and is incorporated in the genome cellular immunity becomes the predominate protective response from the host. So vaccines that stimulate both humoral and cell mediated immunity are likely to be preferred. FeLV positive cats may harbor three subgroups of the virus A, B and or C. Only subgroup A is naturally transmitted between cats the other subgroups that infect cats arise as a result of recombination events or mutations with subgroup A. Thus FeLV vaccines must contain and protect against FeLV subgroup A. The need for vaccines to contain subgroups B or C is questionable if you protect against subgroup A.

FeLV is a RNA enveloped virus this is produce in large amounts infected cats and is present in saliva an tears and milk which serve a source of transmission. However the virus is easily killed by desiccation and disinfectants thus routine cleaning will prevent fomite transmission of the virus. Simple cage cleaning washing your hands after handling infected cats etc are very effective in reducing the spread of the virus within a veterinary hospital, In addition, FeLV testing all blood and tissue donors is recommended.

Testing and removal strategies developed and employed prior to FeLV vaccines development have been shown to be very effective in controlling the spread of FeLV in the cat population. After FeLV was first discovered in the mid-1960s the highest rate of infections was in multiple cat households and catteries. Free roaming cats and single cat households had very low infection rates. In the early 1970s a mandatory test and removal program in the Netherlands was utilized by all cat breeders there. Within four years the infection rate which was 11% in these catteries dropped to less than 2% and no infested cats have been reported since 1984 in these facilities.

FIV : Unlike FeLV does not cause cancer directly but produces marked immunosuppression which results in the failure of the immune system to purge cancer cells especially those of the hematopoietic system. Higher incidence of lymphoma are observed in FIV positive cats. The vaccine for FIV is only marginally effective, interferes with testing for FIV in cats and contain adjuvants their use increases the risk of injection site cancers. The roll of the vaccines in disease reduction in the population is yet to established.

Papillomaviruses

Both DNA- and RNA-containing viruses are known to cause cancer. Papillomaviruses are DNA viruses through the process of integration, activate the expression of normal cellular genes,

leading to overexpression or inactivation of genes, resulting in cellular transformation or uncontrolled growth.

Papillomaviruses are oncogenic, contagious, and infectious and have been described in a number of species of animals. Papillomaviruses are considered species specific, and isolates of humans, cattle, cats and dogs lack serologic cross-reactivity. However, similar species such as the coyote may be infected with dog isolates. Papillomaviruses of the family Papovaviridae are responsible for producing benign, mucocutaneous, canine papillomas and benign often multicentric lesion in cats some of which may progress to carcinoma in situ (Bowens disease).

The canine and feline papillomaviruses are larger than the parvoviruses of dogs and cats but are similar in structure. Electron microscopy has been used to identify the presence of the virus in infected tissues. Like other papillomaviruses, the canine and feline papillomavirus is resistant, acid stable, and relatively thermostable. There is only a limited sequence homology between the DNA sequences of papillomaviruses of different species, but substantial sequence homology exists between isolates derived from any given species.

Pathogenesis Papillomas develop after introduction of papillomavirus through breaks in the epithelium. Different viruses derived from the same species are believed to correlate with the type of clinical disease produced by the virus (i.e., oral isolates vs. cutaneous isolate), although this feature of papillomaviruses is yet to be proven for the dog or the cat, experimentally ocular isolates have produced oral papillomas in the dog. The presence of and location of mature complete viruses on the surface of papillomas are believed to aid in its transmission to adjacent epithelial tissues. In contrast to oncogenic or transforming DNA viruses, papillomaviruses rarely integrate into the cellular genome and remain episomal.

Infections of epithelial cells results in a marked increase in cellular mitosis and hyperplasia of cells with a strand of spongiosum, with subsequent degeneration and hyperkeratinization. Clinical evidence of hyperplasia and hyperkeratinization usually begins 4 to 6 weeks after infection. Canine papillomas in general persist for 4 to 6 months in the mouth and 6 months to 1 year on the skin before undergoing spontaneous regression, and multiple warts generally regress simultaneously. Although antibodies are produced against the papillomavirus, antibody levels do not appear to correlate with either growth or regression of the papilloma, and the mechanism of induction or regression remains unknown. Recently a papilloma virus vaccine has been made available for humans none are currently available for dogs and cats.

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The new advances in the treatment of cancer;

Cancer immunotherapy has until recently been nonspecific with injection of bacterial extracts, and cytokines such as interferon. Recently however a **canary pox vectored melanoma vaccine** has been developed for the treatment and prevent of the spread of this tumor in the dog. New treatment options have moved forward into the new era with the recent approval of the first canine melanoma vaccine for the treatment of oral malignant melanoma. They have chosen to target defined melanoma differentiation antigens of the tyrosinase family.

Tyrosinase is a melanosomal glycoprotein, essential in melanin synthesis. Approximately 400 dogs with previously histologically confirmed spontaneous malignant melanoma were treated with xenogeneic DNA vaccinations. All dogs were clinically staged according to the WHO staging system of stage I (tumor < 2 cm diameter), II (tumors 2-4 cm. diameter, negative nodes), stage III (tumor > 4 cm. and/or positive nodes) or stage IV (distant metastatic disease). Dogs with WHO stage II, III or IV histologically confirmed malignant melanoma were allowed entrance onto the study due to the lack of effective available systemic treatments. The signalments of dogs on this study have been similar to those in previously reported CMM studies. No toxicity was seen in any dogs receiving the aforementioned vaccines with the exception of minimal to mild pain responses at vaccination, one muGP75 dog experienced mild aural depigmentation, and one muTyr dog has experienced moderate foot pad vitiligo. Dogs with stage II-III loco-regionally controlled CMM across the xenogeneic vaccine studies have a Kaplan-Meier (KM) median survival time (MST) of > 2 years (median not yet reached). The KM MST for all stage II-IV dogs treated with huTyr, muGP75 and muTyr are 389, 153 and 224 days, respectively. The KM MST for stage II-IV dogs treated with 50mcg MuTyr, 100/400/800mcg HuGM-CSF or combination MuTyr/HuGM-CSF are 242, 148 and > 900 (median not reached, 6/9 dogs still alive) days, respectively. For dogs on the Phase Ib MuTyr/HuGM-CSF/Combination trial, significant differences in MST were noted across pre-vaccination stage (stage IV MST = 99 days, stage III = 553 days and stage II > 401 days, P < .001). The results from dogs vaccinated with huTyr were published in 2003 (Bergman et al, Clin Cancer Res 2003). The results of these trials demonstrate that xenogeneic DNA vaccination in CMM is: 1) safe, 2) develops specific anti-tyrosinase humoral immune responses, 3) potentially therapeutic with particularly exciting results in stage II/III local-regional controlled disease and dogs receiving MuTyr/HuGM-CSF combination, and 4) an attractive candidate for further evaluation in an adjuvant, minimal residual disease Phase II setting for CMM. From new etiologies to better diagnostics and staging technologies and better treatments clinical veterinary oncology has become of age.

Targeted therapy is one of the newest treats that targets an abnormal function of genes that are driving the cancer. Palladia (Toceranib) is the first to be come to the US market and is a multikinase inhibitor which interferes with a number pathways in addition to Kit in mast cell tumors for which it was designed. Palladia is effective in mast cell tumors and is most effective in the higher grades where the defect in Kit is the greatest. Because it is a multi-kinase agent its spectrum of active hits a wide range of tumor type including anal gland adenocarcinoma, thyroid carcinoma, hemangiosarcoma, mammary carcinoma etc. the first dose regimen was EO but was found be too toxic and has been cut back to MWF and the dose reduced to 2.75 mg/kg. The common side effects are depigmentation of the nose and anorexia and diarrhea. PepsidAC and drug holidays of two to seven days makes it manageable drug.

Metronmic chemotherapy is very popular in the treatment of older humans that can't tolerate tradition chemotherapy and has been proven effective in dogs as well. Instead of targeting the tumor cell it targets the blood vessels that support the tumor. Just as a city needs roads to grow the tumor needs fresh blood vessels to grow, new blood vessel formation often referred to as angiogenesis then is the target. These vessels are very sensitive to cox2 inhibition so things like piroxicam, deramaxx and previcox are effective in addition to low dose alkylator administration. Drugs that interfere with growth cytokines like palladia (toceranib) or tamoxifen are frequently

used in a metronomic combination. As the term implies they are given regularly rather than as in a pulse fashion. Pulse administration is designed to allow normal tissue to repair and recover, in metronomic therapy we don't want repair to take place and give the drugs continuously similar to treating autoimmune disease where we are trying to dampen the immune system.