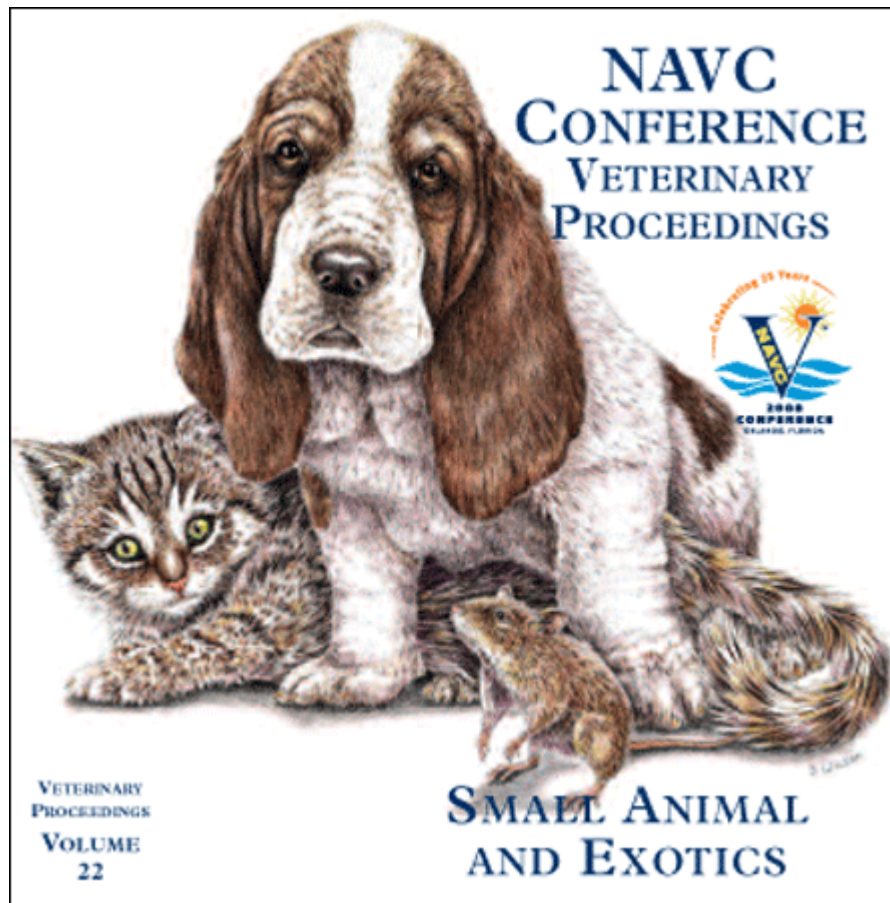


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WHAT'S NEW IN SMALL ANIMAL ONCOLOGY?

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It has been exciting to be a veterinary clinical oncologist the last ten years both in and out of the university. As the ranks of specialists and size of university faculty have expanded the last decade the profession has developed a critical mass and as result the knowledge and experience in the management of cancer in pets has markedly improved. New developments from our knowledge as to the cause of certain types of cancer, new molecular diagnostics, high tech imaging equipment to better stage disease such as computed tomography (CT) and magnetic resonance imaging (MRI), to gene therapy to treat cancer have all contributed to a very exciting time to be a clinical oncologist.

Few would disagree that the best way to treat cancer is to prevent it. 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 such as leufeneron, long-lasting penicillin, and rabies, leukemia, and certain panleukopenia vaccines. The common thread is an associated injection site inflammatory process caused by components within these injectables that are believed to act as promoters in the pathogenesis of this tumor. Industry has responded and provided vector-based vaccines free of adjuvants that virtually eliminate injection site inflammation, which should reduce the risk of vaccine-associated tumors in cats. These revelations have resulted in changes in rabies vaccination policy in many state that have reduce the frequency of rabies vaccine administration and are likely to reduce the incidence of sarcoma in cats. Similarly changes in vaccines guidelines have reduce the frequency and number of other vaccines given to cats.

Advances in tumor diagnostics have brought the profession new diagnostics that now allow earlier diagnosis of lymphoma and transitional cell cancer (TCC) of the bladder. Bladder neoplasms are the most common urinary tract tumors in the dog. Most lower urinary tract tumors are malignant and are transitional cell carcinoma. Lower urinary tract tumors are difficult to diagnose on the basis of results of cytologic examination of the urine sediment, with only 30% to 40% cases having neoplastic cells being observed cytologically. In humans, the bladder tumor antigen (BTA) test has been used in diagnosis of bladder cancer in humans. The use of the veterinary version of this diagnostic test has been recently reevaluated for detection of lower urinary tract malignancies in dogs. The V-BTA test is a latex

agglutination assay for the qualitative detection of bladder tumor analytes in the urine. A recent study evaluated 229 client-owned dogs with 1) TTC of the lower urinary tract, 2) healthy control dogs, 3) unhealthy control dogs with non-TTC urinary tract disease, and 4) unhealthy control dogs without urinary tract disease. Test sensitivities were 88%, 87%, and 85% for all dogs with suspected and confirmed TCC of the urinary bladder, respectively. Test specificities were 84%, 41%, and 86% for healthy control dogs, unhealthy control dogs with non-TCC urinary tract disease, respectively. These results are better than cytology and indicate the test is a good screening test for TTC of the urinary tract in the dog.

Molecular diagnostics that are based on cancers clonality characteristics have been made available to the practitioner. This polymerase chain reaction (PCR)-based technology allows for amplification of antigen binding sites and B and T cells from simple a blood sample or fine needle aspirate that contain DNA. By amplifying the gene products from the sample one can analyze for similarity of the gene products. Gene products that are similar represent clonality as characteristic of cancer while normal tissues produce a diverse population of gene products. The simple tests help diagnosis lymphoma in the dog earlier and helps interrupt equivocal histopathology or cytology finding in canine patients.

New diagnostics using protonomic technology has been developed at the University of Minnesota for looking at the predisposition to injection site sarcomas. Although this technology has now been licensed to a commercial interest it is not yet available to the practitioner.

Better staging of cancer in pet is now available through the wider availability of CT to veterinary practitioners. Recent studies have identified the values of this imaging technology in patients. A recent study of 18 vaccine associated sarcoma found clinical evaluation using calipers for establishing volume underestimated the tumor volume by one half when compared to tumor volumes were established from the CT examination.

Another study compared the use of tradition radiographs and CT in evaluating the thoracic cavity for evidence of spread of the cancer to the lung tissue. The study was carried out in 18 dogs with know pulmonary spread of their cancer. Traditional radiographs detected only 9% of the CT detected pulmonary nodules. The threshold size for the CT in the study was approximately 1 mm while traditional thoracic radiography was 7 to 9 mm. The marked increased sensitivity of thoracic CT or traditional radiography is rapidly making CT the standard of care for detecting pulmonary spread of disease.

Another study establishes the value of fine needle aspiration cytology in evaluation for evidence of regional lymph node spread of neoplasia. When the sensitivity and specificity of physical examination, fine needle aspiration cytology where compared to histopathology of regional lymph nodes in dogs and cats with cancer the sensitivity and specificity of physical examination was only 60% and 72%, respectively, while the sensitivity

and specificity of fine needle aspiration cytology were 100% and 96%, respectively. The good correlation between fine needle aspiration cytology and histological examination of the entire lymph node suggest this technique is reliable and less expensive means of staging veterinary patients with cancer.

The use of serum alkaline phosphatase levels as a prognostic indicator in canine osteosarcoma has been evaluated by three groups. Serum alkaline phosphatase (ALP) levels have been found in one study to be of prognostic significance in a series of 75 dogs with appendicular osteosarcoma. Archived sera were analyzed for total ALP (tALP) and bone ALP (bALP) activities. Dogs with increased (outside normal range) preoperative tALP had a significantly decreased disease-free interval (DFI) (170 days vs. 366 days) and survival time (177 days vs. 495 days) while dogs with increased preoperative bALP had a significantly decreased DFI (147 days vs. 430 days) and survival time (218 days vs. 546 days). In addition, postoperative (40 days) increased bALP was significantly associated with shorter DFI and survival.

On the treatment front new knowledge from a study that looked at the value of L-asparaginase in the management of lymphoma in dogs is likely to change the way we use this drug in the treatment of this disease. The recent study looked at the value of L-asparaginase in the CHOP-based combination protocol for canine lymphoma and found little contribution of the L-asparaginase to remission rate or duration and suggest exclusion of L-asparaginase in combination protocols. The real value of this drug may be in most appreciated when it is reserved for use in rescue treatment protocols or in patients that have failed to obtain a remission after an induction protocols.

The value of radiation therapy in the treatment of mast cell disease was evaluated. 56 dogs were treated with megavoltage radiation for mast cell neoplasia. Total radiation dose ranged from 45 to 57 Gray (Gy), dose per fraction ranged from 3.0 to 4.0 Gy, and radiation treatment time ranged from 14 to 28 days. Median disease free interval (95% CI) was 32.7 (19 to 70) months. Median disease-free interval for dogs older than 7.5 years was 15 (lower limit 7) months as compared with 62 (lower limit 20) for dogs younger than 7.5 years of age ($P = 0.006$). Median disease free interval for dogs with measurable disease was 12 (lower limit 5) months as compared with 54 (32–70) months for dogs with microscopic disease ($P = 0.006$). Radiation treatment time was also significantly related to disease-free interval. Median disease-free interval for dogs treated longer than 22 days was 12 (7–19) months as compared with greater than 50 (lower limit 20) months for dogs treated in 22 or fewer days ($P < 0.001$). More recurrences were observed in dogs treated with 3-per-week fractionation and suggests that tumor proliferation in the interfraction interval may be important. Sex, tumor location, histologic grade, WHO clinical stage, number of radiation fractions, total radiation dose, and dose-per-fraction, as well as the following "yes/no" variables: steroids given, surgery prior to radiation, lymph nodes

irradiated, and development of another mast cell tumor did not appear to influence median disease free interval or survival. Data presented herein support megavoltage radiation as an effective treatment for canine mast cell neoplasia, and suggest that disease-free interval in dogs treated with daily fractions may be longer than that achieved with alternating day fractions.

Complications of chemotherapy treatment are not more epitomized than the extravasation of doxorubicin. The incidence of extravasations of chemotherapeutic agents in human is reported to range from 0.1% to 6% the rate of extravasation in veterinary medicine is unknown. A recent report of the successful use of dexrazone after the extravasation of doxorubicin suggests that this complication of chemotherapy maybe better managed in the future. Dexrasone was administered IV at ten times the dose of doxorubicin given to the patient with not apparent side effects and prevented the severe necrosis often observed after the extravasation of doxorubicin.

The new advances in the treatment of cancer have moved forward into the new era with the recent approval of the first canine melanoma vaccine for the treatment of oral malignant melanoma. Canine patients with advanced disease (WHO stage II, III or IV) have a reported median survival time of 1 to 5 months with standardized therapies. A combination of hypofractionated radiation therapy and chemotherapy have a reported median survival time of one year in stage I oral CMM. Unfortunately, response rates to chemotherapy in humans or dogs with advanced melanoma range from 8% to 28% with little evidence that treatment improves survival Active immunotherapy in the form of vaccines represents one potential therapeutic strategy for melanoma. The advent of DNA vaccination circumvents some of the previously encountered hurdles in vaccine development. One way to induce immunity against a tissue specific differentiation antigen on cancer cells is to vaccinate with xenogeneic antigen or DNA that is homologous to the cancer antigen. It has been shown that vaccination of mice with DNA encoding cancer differentiation antigens is ineffective when self-DNA is used, but tumor immunity can be induced by orthologous DNA from another species. Melanoma differentiation antigens of the tyrosinase family were chosen as targets for this tumor. 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- to 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. 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 50 µg MuTyr, 100/400/800 µg 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) potentially therapeutic with results in stage II/III local-regional controlled disease and dogs receiving MuTyr/HuGM-CSF combination.

From the recognition of new cancer etiologies to better diagnostics, staging technologies and better treatments, clinical veterinary oncology has become of age.

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