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Boxer Update

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MAST CELL TUMOR

Research of Personalized Medicine
& Checkpoint Immunotherapy

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RESEARCH OF TREATMENTS FOR MAST CELL TUMOR MAY HELP BOXERS

Growing up in a family with a pet Boxer, Joyce Baker Brown fell in love with the breed. Her entire life she has had Boxers and counts herself lucky that her dogs have had few of the health concerns common in the breed. Except for one: Four have died of mast cell tumors (MCT).

Her first Boxer to develop MCT was named “Dewi” (CH Cwmhaf Maestro), who was born in Wales in 2004. The handsome male was the first imported Boxer with natural

ears to earn an American Kennel Club (AKC) Champion title.

“He was a beautiful dog,” says Baker Brown, of Mount Dora, Florida, a member of the American Boxer Charitable Foundation. “When Dewi was 8 years old, he developed mast cell cancer on a leg, but he seemed cured after surgery to remove the lump.”

One morning 14 months later, as Baker Brown and Dewi headed out on their usual walk, she saw a large

A lifetime Boxer owner, Joyce Baker Brown is shown with “Lindi,” left, and “Palmer.” Mast cell tumors hit close to home for her, as she has lost four Boxers to the cancer. Lindi had a mast cell tumor removed six months ago and is doing well.



lump on the dog's leg. "His back leg looked like it had a grapefruit on it," she says. "The cancer was back with a vengeance. This time, it had spread to his heart and lungs."

For unknown reasons, Boxers have an increased risk for MCT, though any breed of dog or mixed breed can develop the cancer. In recent years, significant advances have been made learning about the cancer.

THE MOST COMMON SKIN CANCER IN DOGS

The prognosis for an individual dog with MCT depends on factors such as tumor grade, tumor stage and whether surgery is possible to completely remove the tumor. If MCT is detected early when tumors are small and localized, treatment success is more likely. On the other hand, if the tumor has spread beyond the lymph nodes and is located in areas other than the skin, the prognosis is generally poor.

Evaluating whether spay and neuter surgeries increase the risk of disease, including MCT, investigators at the University of California-Davis studied 12 breeds, of which more than 600 dogs were Boxers. Led by Benjamin Hart, DVM, PhD, Distinguished Professor Emeritus, [the study, which was funded by the AKC Canine Health Foundation](#), found that in Boxers, as well as in other medium and large breeds, early spay and neuter surgeries before 1 year of age were associated with a higher incidence of several common cancers, with MCT among them.

The most common skin cancer in dogs, mast cell tumor is a cancer of a type of white blood cell found throughout the body. Mast cells are an important part of the immune system. They contain histamine, heparin and enzymes that break down proteins and help them do their primary function of defending the body against allergens and

SIGNS OF CANINE MAST CELL CANCER

- **Lesion on or under the skin.** Although mast cell cancer may resemble a rash with multiple bumps, it most often appears as a single lump. Mast cell cancer is called "The Great Pretender" because the lumps can resemble many other skin masses and may range from a small hair-covered bump to large red ulcerated lesions. It may appear to wax and wane in size and sometimes includes bruising and fluid buildup, which is worsened by scratching.
- **Gastrointestinal problems.** Loss of appetite, vomiting or diarrhea may occur. Histamine, a natural inflammatory response secreted by mast cell tumors into the bloodstream, can trigger increased stomach acid and sometimes cause stomach ulcers.
- **Enlarged lymph nodes.** These may appear near the areas of tumor involvement.
- **General signs of cancer.** Weight loss, persistent cough, shortness of breath, bleeding, foul breath, pain, lethargy, and weakness or collapse may be involved.

inflammation. When these cells replicate out of control, they form an aggressive cancer. Besides the skin, MCT can occur in the spleen, liver, gastrointestinal tract, and bone marrow.

When the cancer occurs on the skin, it appears as a red, ulcerated or swollen lump anywhere on the body. As with Dewi, a lump may occur suddenly and grow very quickly, or it may be present for many months with the size of the tumor waxing and waning. When the tumor spreads or metastasizes, the most common sites affected are lymph nodes, spleen and liver.

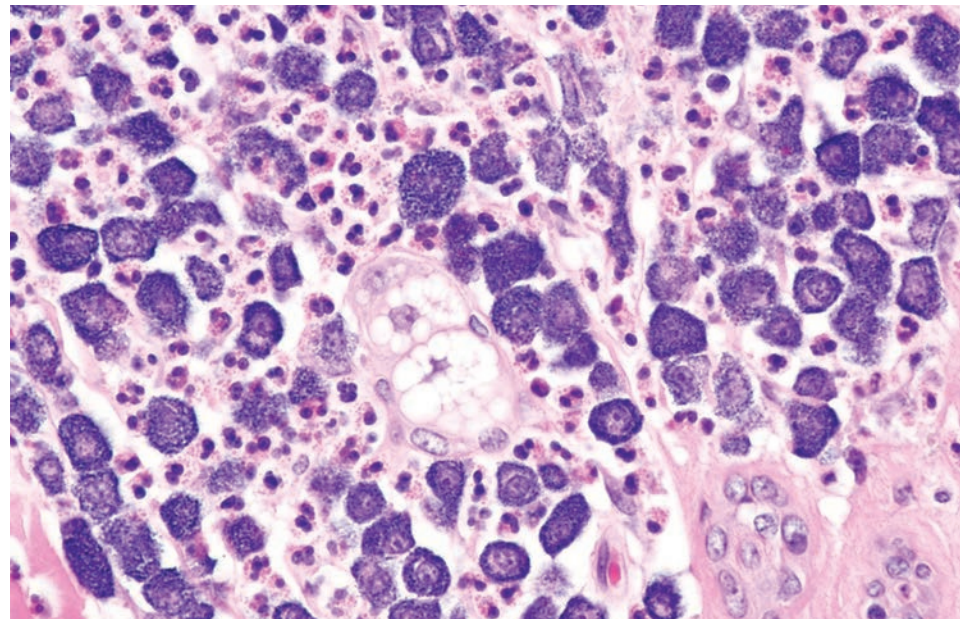
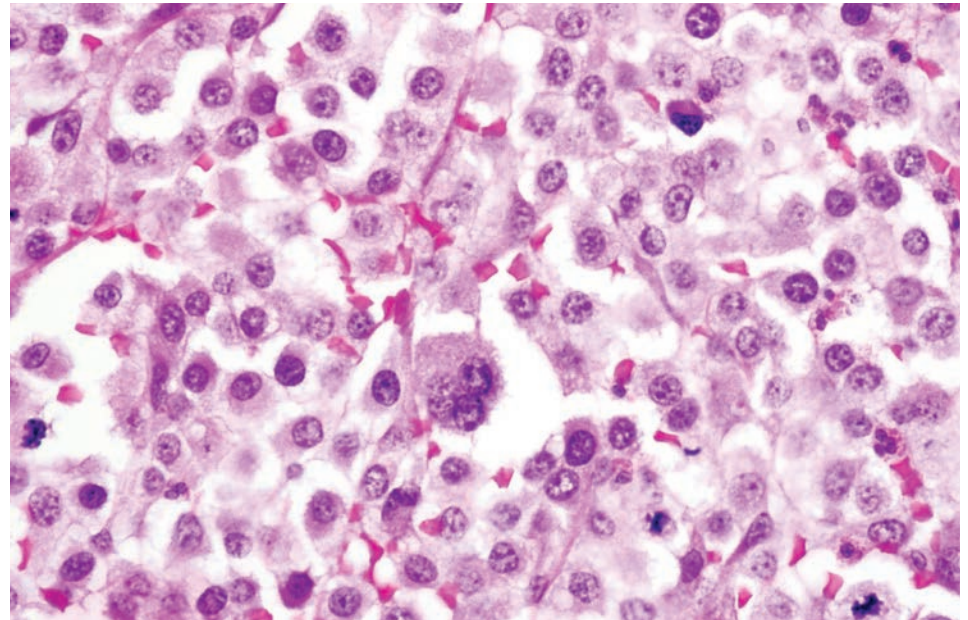
[A two-tier grading system for MCT, developed in 2011 by researchers at Michigan State University](#), has helped to distinguish aggressive tumors from those likely to respond to treatment. Prior to this, a dog's prognosis and therapy were based on a tumor's histologic grade, or the degree of abnormality of cancer cells as seen per microscopic evaluation. The three-tier Patnaik grading system commonly used by veterinary pathologists is more subjective and thus more open to interpretation

variability among pathologists of the same tumor sample. This has caused questionable prognostic value of histologic grading.

The two-tier grading system provides a uniform method for classifying tumors. “The idea of our grading system was to split out dogs with highly aggressive tumors from those with low-grade tumors,” says Matti Kiupel, DVM, PhD, DACVP, professor of anatomic

pathology at Michigan State University. “The goal was to ensure that dogs did not receive unnecessary therapy.

“Our grading system classifies high-grade MCT as those having a significantly shorter time to metastasis or new tumor development with shorter survival time. In our study, the median survival time was less than four months for high-grade MCTs but more than two years for low-grade MCTs.”



The two-tier grading system for MCT developed at Michigan State University separates high-grade aggressive cancers, shown on top, from low-grade tumors, above. [The journal Veterinary Pathology published an article on the two-tier grading system in 2011.](#)

VACCINATION AGAINST CANINE CANCER STUDY UNDERWAY BOXERS ARE AMONG 45 ELIGIBLE BREEDS

A five-year clinical trial, called [the Vaccination Against Canine Cancer Study \(VACCS\)](#), has recently begun to evaluate a new vaccine strategy for the prevention of cancer in dogs. Healthy dogs from 5 ½ to 10 ½ years of age with no history of previous cancer that meet the study criteria are eligible to participate.

Douglas Thamm, VMD, DACVIM (Oncology), the Barbara Cox Anthony Professor of Oncology at Colorado State University, is director of clinical trials for the study. The goal is to enroll 800 dogs representing 45 breeds, including mixed-breed dogs, to test the vaccine, making it the largest clinical trial to date for canine cancer.

“The hope is that the vaccine will act much like vaccines that immunize dogs and people against infectious disease,” Dr. Thamm says. “I’m optimistic about this study and excited to learn whether the vaccine works. Importantly, we’ll have a mountain of data and a golden opportunity to learn about the progressive risk of cancer as dogs age.”

Stephen Albert Johnston, professor and director of the Biodesign Center for Innovations in Medicine at Arizona State University and CEO of Calviri Inc., led the team that developed the vaccine being used in the VACCS trial. The cocktail vaccine targets about 30 abnormal proteins found on the surface of cells of dogs with common cancers, including mast cell tumor, lymphoma, osteosarcoma, and hemangiosarcoma.

Besides potentially providing a new cancer prevention strategy in dogs, the study could help advance a similar approach in treating human cancer. “We should know as soon as two years from now whether the vaccine is having an effect in cancer reduction,” Dr. Johnston says. “If this works — and that’s a big ‘if’ — then we believe it may work in people too.”

The study is supported by a \$6.4 million grant from the Open Philanthropy Project, a nonprofit organization that identifies and funds high-profile humanity focused research, and by Calviri Inc. Those who participate with their dogs will be offered a financial incentive to defray costs associated with the diagnosis and treatment of any cancers their dogs develop, regardless whether they are receiving the vaccine or placebo. All research-related medical care will be covered by the study.

Dogs will be randomly assigned to one of two groups. Half of the dogs will receive the new vaccine and half the placebo vaccine every two weeks for a total of four treatments and then annually. The study will track vaccine reactions, though thus far side effects have not been noted other than moderate local pain or swelling at the injection site. During the study, dogs will live at home. They will be checked two times a year for five years after enrolling.

To qualify for the VACCS trial, dogs must meet the following criteria:

- Owners must live within 150 miles of a clinical trial site: Colorado State University in Fort Collins, University of California-Davis or University of Wisconsin-Madison
- Be between 5 ½ to 10 ½ years of age
- Weigh at least 12 pounds
- Have no history of previous cancer
- Have no significant illness that could result in a life span of less than five years
- Have no history of previous autoimmune disease
- Receive no current treatment with oral or injectable immunosuppressive medications

KIT INHIBITING DRUGS & CHECKPOINT INHIBITORS

Investigations into innovative treatments for MCT include two studies funded by the AKC Canine Health Foundation. A personalized medicine approach to MCTs that are more aggressive because they have a mutation in the *c-kit* gene looked at whether treatment with KIT inhibitors yielded treatment

success. A study of checkpoint molecules, [also supported by the American Boxer Charitable Foundation](#), is progressing this novel cancer immunotherapy in dogs.

“Canine cancer is a devastating disease,” says Dr. Diane Brown, CEO of the AKC Canine Health Foundation, which funds cancer research via its Canine Cancer Research Initiative. “The goal of this research initiative is

Purina and the AKC Canine Health Foundation have worked together since 1997 to support canine health research to benefit all dogs.

to provide funds to support research that will advance understanding of the mechanisms underlying cancer and lead to more effective treatments and educational resources for dog owners and veterinarians.”

Douglas Thamm, VMD, DACVIM (Oncology), the Barbara Cox Anthony Professor of Oncology, led a multi-center study exploring the potential sensitivity of mast cell tumors with *c-kit* gene mutations to KIT-inhibiting drugs. A protein found on the surface of many different types of cells, the KIT protein also may be found in higher than normal amounts or in a changed form on some types of cancer cells, including MCT. [The study was published in 2018 in the *Journal of Veterinary Internal Medicine*.](#)

In the clinical trial, Dr. Thamm and his team compared the effectiveness of toceranib (TOC), a KIT inhibitor sold as Palladia™, and vinblastine (VBL), a chemotherapy drug, in treating dogs with MCT with and without *c-kit* gene mutations. “Our hypothesis was that MCT with *c-kit* mutations would have a superior response to toceranib compared to vinblastine,” Dr. Thamm says.

Sixty dogs received TOC, of which 20 percent had *c-kit* mutations, and 28 dogs were given VBL, with 30 percent having *c-kit* mutations. The overall response rates were 46 percent for dogs receiving TOC and 30 percent for those on VBL.

“Neither the progression free survival time (length of time during and after treatment that a patient lives without getting worse) nor overall survival time (length of time from the start of treatment that a patient is still alive) was significantly different between the treatment groups,” Dr. Thamm says. “As the proportion of dogs with *c-kit* mutations was not different between treatment groups, *c-kit* mutation status did not predict treatment response as we had hoped. Further studies are needed, but this work has helped us to understand the value of these targeted drug therapies.”

Another Colorado State University researcher, Steven Dow, DVM, PhD, DACVIM, professor of immunology and director of the Center for Immune and Regenerative Medicine Clinical Sciences, is soon to complete a study of the effectiveness of OX40 checkpoint molecules as a targeted antibody for canine cancer immunotherapy. In human oncology, clinical trials of antibody therapeutics targeting checkpoint molecules, such as PD-1, have shown remarkable success inducing tumor regression and providing cures against a variety of cancers.

Immune checkpoints regulate the immune system and help to prevent the immune system from attacking cells indiscriminately. Some cancers, however, can protect themselves

CANINE CANCER RESEARCH INITIATIVE

Since 1995, the [AKC Canine Health Foundation](#) has provided funding of over \$12 million to support 207 studies of canine cancer. These investigations have helped scientists learn more about how cancer affects dogs. Discoveries across many types of canine cancer have contributed to earlier diagnoses and more effective treatments and often inform human cancer research via comparative oncology.





from attack by stimulating checkpoint targets. Inhibiting checkpoint molecules are targets for cancer immunotherapy due to their potential for use in multiple types of cancer.

“Checkpoint molecules play a key role in regulating T-cell immunity against cancer,” Dr. Dow explains. “We are developing a second-generation immunotherapy for dogs that follows the first-generation PD-1 antibodies already underway. In this project, the team is characterizing canine OX40 antibodies to determine how they activate effector T cells in dogs. We want to see if they trigger an immune activation in tumor tissues. There’s hope in the near future for completely changing the canine cancer treatment landscape, and that’s happening pretty quickly.”

Meanwhile, Baker Brown’s current Boxer companion is a 6-year-old female named “Lindi” (Hercynia’s Here I Am). Six months ago, Lindi had a MCT removed and thus far is doing well. “I am inspired by all the research of MCT in dogs,” she says. “I definitely feel there is hope coming for Boxer lovers like me whose dogs develop the potentially fatal cancer.” ■

Purina thanks Dr. Joyce Campbell, chair of the American Boxer Club Health and Research Committee and a trustee of the American Boxer Charitable Foundation, for helping us to identify this topic for the *Boxer Update*.

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