

*Studying cancer in dogs as a path towards a world  
where we no longer fear cancer*

## **An update on canine hemangiosarcoma**

(HSA Part I)

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### **What is hemangiosarcoma?**

Hemangiosarcoma is a type of cancer that arises from cells that form blood vessels, and it is one of the most aggressive cancers seen in dogs. It is estimated that more than 50,000 companion dogs develop this disease in the U.S. each year. Hemangiosarcoma occurs primarily in the spleen, followed by the heart, skin, and liver. It spreads beyond the initial site where it forms, and by the time the tumor is diagnosed, cancer cells are likely localized in other parts of the body. Unfortunately, this disease is invariably fatal. More than 50% of dogs with this disease will die within four to six months, and almost 90% will die within a year. Surgery and chemotherapy can prolong life for dogs with hemangiosarcoma, but currently there is no cure. The frequent occurrence of this disease, along with its insidious nature and grim prognosis, has made it a research priority for our group at the Animal Cancer Care and Research Program of the University of Minnesota.

### **Why does hemangiosarcoma occur?**

It appears that there is something peculiar about how the cells that form hemangiosarcomas behave in dogs, and it is possible that heritable traits might contribute to the overall risk of this disease. Specifically, hemangiosarcoma is more common in dogs than it is in other animals or humans. Although dogs of any age and breed are susceptible, hemangiosarcoma occurs more commonly in dogs older than 6 years, and more than half of the affected dogs are older than 10 years. The risk for developing hemangiosarcoma also seems to be higher in certain breeds such as Golden Retrievers, German Shepherds, Portuguese Water Dogs, Bernese Mountain Dogs, Flat Coated Retrievers, Boxers, and Skye Terriers, among others. However, nothing we know to date supports the existence of a “hemangiosarcoma gene(s)” that could be managed by selective breeding or other genetic strategies. And even though certain mutations have been identified that predispose laboratory mice to hemangiosarcoma, there is no evidence that mutations of the same genes contribute in a meaningful way to heritable risk of hemangiosarcoma in dogs.

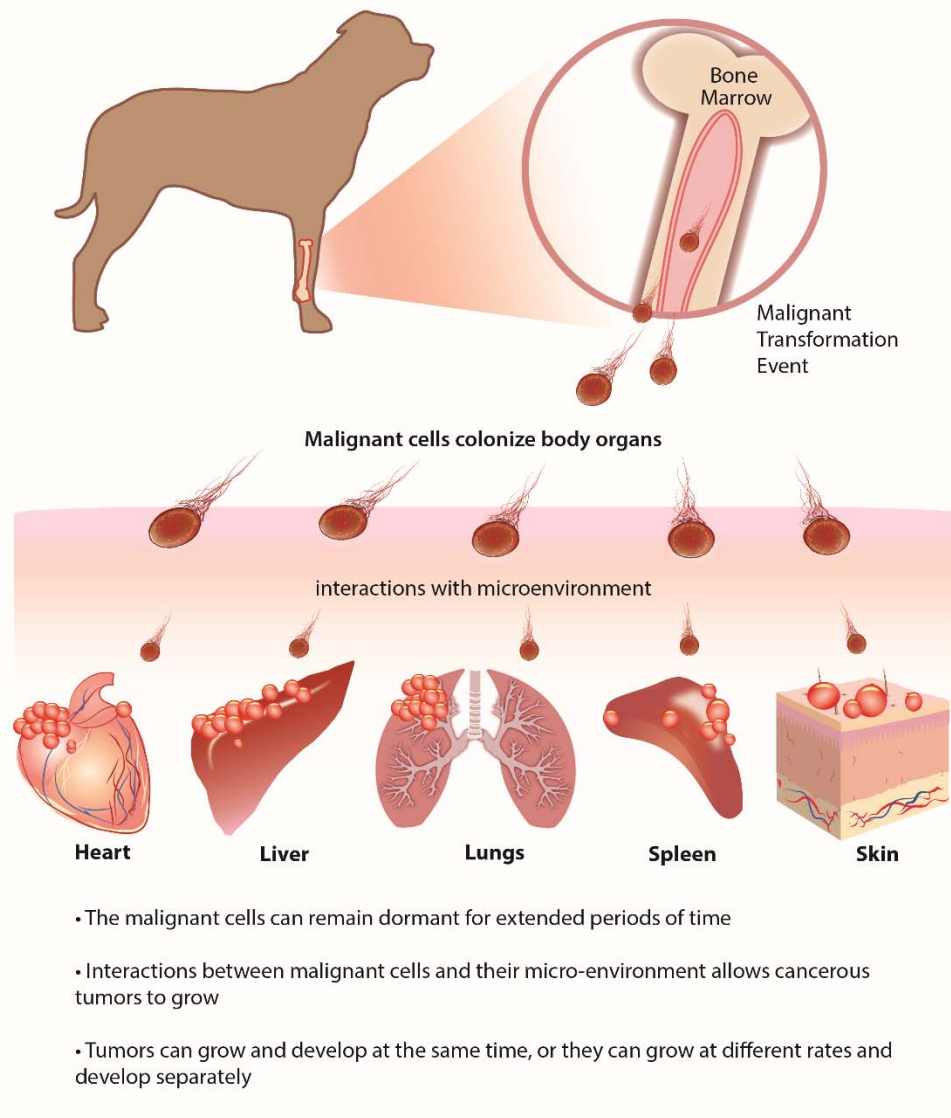
Similarly, there is no evidence that hemangiosarcoma can be prevented by altering lifestyle behaviors, eliminating exposure to toys or other factors in the environment, special diets, etc. In fact, the number of breeds that appear to be at high risk has continued to increase over the past four decades, almost certainly because of greater awareness and recognition of the disease. Indeed, there is no evidence to suggest dogs from any breed, or even mixed breed dogs, are “protected.” Moreover, whatever heritable contribution to risk exists in each breed could be continually evolving due to the influence of popular sires over time. In addition, changes in overall breed popularity could also appear to influence overall risk of hemangiosarcoma as the number of dogs of those particular breeds fluctuates up or down.

We do not completely understand why hemangiosarcoma happens. The cancer appears to start from bone marrow cells that travel throughout the body to aid the formation of new blood vessels. These cells can set up residence in multiple tissues, modify the local environments to sustain their survival needs, and lie dormant for long periods of time (Figure 1). Thus, removal of the spleen to prevent cancer formation is not recommended because, in the absence of a spleen, the malignant cells are probably still able to form tumors in other organs.

### **What does hemangiosarcoma look like?**

Hemangiosarcoma is a cancer that does not cause pain or discomfort. It can develop slowly without interfering with normal body functions and without obvious clinical signs. Tumor cells retain the capability to reside in — and possibly form — blood vessels, but unlike normal blood vessels, the tumor cells inhabit malformed vessels where blood tends to pool and clot. Eventually, these clots obstruct the vessels and prevent fresh blood and nutrients from reaching the tumor cells, in turn causing some of them to die. Because of this cell death, ruptures in the tumor are created and blood escapes through these ruptures into the abdomen, heart sac, chest, or into the space under the skin, depending on the location of the tumor. While substantial blood loss can lead to signs of anemia — such as pale gums, weakness, and lethargy — the signs may be subtle and resolve as dogs reabsorb the blood components and make new blood cells, which is one reason why hemangiosarcoma almost always goes undiagnosed until the late stages of disease. By the time the cancer is diagnosed, it is almost certainly present in other sites, even though metastases may not be visible. Nonetheless, the eventual outcome for most patients is rupture of a tumor, with acute, severe blood loss, collapse, shock, and possibly death.

## Formation and Spread of Canine Hemangiosarcoma



### Figure 1. Formation and Spread of Hemangiosarcoma Tumors in Dogs.

Hemangiosarcoma appears to arise from bone marrow cells that aid in the formation of blood vessels. A transformation event can occur inside the bone marrow, or outside the bone marrow as these cells travel throughout the body to reach sites where new blood vessels are being made. As they circulate, the transformed cells can set up residence in multiple organs like the heart, liver, lungs, spleen, and skin. The cells can lie dormant for long periods of time in each of these sites, until a critical event takes place that leads to the formation of a tumor. One or more tumors can grow simultaneously, creating the patterns of metastasis seen in dogs with hemangiosarcoma. However, it also is possible for tumors to spread by cells moving from one site to another after the initial tumor forms.

## **How is hemangiosarcoma diagnosed in dogs?**

The first step to diagnose hemangiosarcoma in dogs showing clinical signs is a complete and thorough physical exam, which may identify a mass. If there is any reason to suspect hemangiosarcoma, the next step is to conduct imaging tests, such as ultrasound or radiographs (x-rays). If the presence of a mass is confirmed, a biopsy — where a sample of the affected tissue or the entire mass is removed and the material is examined by a pathologist — is needed to definitively diagnose hemangiosarcoma. While biopsies are very effective to diagnose the tumors once they are large enough to be visible, there are no readily available, reliable tests to detect hemangiosarcoma in earlier stages of the disease — although a blood test is being developed specifically for this purpose as part of the Shine On study at the University of Minnesota, with support from the Golden Retriever Foundation, the Portuguese Water Dog Foundation, and the American Boxer Club Charitable Foundation. It is unclear if adding imaging tests to routine well health exams is helpful to diagnose developing tumors. Careful analysis of blood samples by an experienced pathologist may hint at the presence of bleeding episodes and blood vessel abnormalities that are suggestive of hemangiosarcoma. However, this method is neither sensitive (identify true positives) nor specific (identify true negatives) to confirm a hemangiosarcoma diagnosis.

If a diagnosis of hemangiosarcoma is suspected or confirmed through a biopsy, the next step is to determine whether the tumor has spread to other areas (a process called, “staging”). This routinely includes basic blood and urine tests, chest x-rays, and ultrasound examination of the abdomen and potentially the heart. These tests are relatively sensitive; in other words, if a tumor is found at a distant site, metastasis is confirmed. For example, ultrasound of the heart is able to identify the presence of a tumor in the heart 65-90% of the time. However, artifacts can obscure the interpretation of these tests. Advanced imaging modalities, such as computed tomography (CT) and positron emission tomography scans (PET-CT), are being used more commonly, and appear to be more sensitive than conventional x-rays and ultrasound.

## **How is canine hemangiosarcoma treated?**

As stated earlier, hemangiosarcoma in dogs is almost always fatal. Therefore, the principal goal of treatment is not necessarily to achieve a cure, but rather to slow down or delay the spread of the disease and to prevent or delay the occurrence of life-threatening bleeding episodes. This is why surgery to remove any visible tumor mass may be recommended for hemangiosarcoma patients whose condition is otherwise stable even if there is widespread metastasis.

Without treatment, most dogs diagnosed with hemangiosarcoma will die within one to two weeks, although some can survive for several months. For dogs treated with surgery for hemangiosarcoma of the spleen, the median survival time (the length of time when half of dogs receiving this treatment would remain alive) is one to three months. Adding chemotherapy to the treatment — using protocols that include the drug doxorubicin given repeatedly at two to three-week intervals, or possibly a combination of multiple drugs given daily — increases the median survival time to four to six months, making the combination of surgery and chemotherapy the preferred and most effective treatment available for this disease. Hemangiosarcoma cells in most dogs inevitably develop resistance to chemotherapy, so only 10-15% of dogs diagnosed with hemangiosarcoma of the spleen will be alive one year or longer after their diagnosis. Studies performed in the last two decades using new combinations of old drugs, immunotherapy, and new drugs, have shown no benefit to improve survival for dogs with hemangiosarcoma of the spleen as compared to conventional surgery and chemotherapy. Survival time estimates for tumors located in other organs have more uncertainty, but generally the prognosis for tumors that involve the heart, liver, and other internal organs is worse than for tumors of the spleen, and the prognosis for tumors that are localized to the skin is better than for tumors of the spleen.

Alternative and complementary approaches continue to gain popularity in the search for a cure for hemangiosarcoma, but any publicity attributing curative power to a drug after an anecdotal response should be viewed with extreme caution. As noted above, some dogs with hemangiosarcoma will live a year or longer without any evidence of disease. In rare instances dogs will live for several years without disease recurrence. This is almost certainly due to the behavior of the tumors themselves. Hemangiosarcomas are different from other cancers in that some will show extremely slow disease progression regardless of the therapy used. Because of this, we strongly recommend options and treatment recommendations based on objective data and not on anecdotal information that creates false hope and unrealistic expectations both by the pet owners and their veterinarians.

### **Looking to the future**

Hemangiosarcoma is a devastating disease. While there is no cure, our research is showing promising results in the areas of treatments and early detection. This promise gives us hope that we are indeed closer to creating a world where we no longer fear cancer.

In the second part of this series, we will introduce how eBAT, a new and exciting drug created at the University of Minnesota, is being developed and tested to treat and potentially prevent hemangiosarcoma and other incurable cancers.

## **Hemangiosarcoma Basics**

- Hemangiosarcoma in dogs originates from cells in the bone marrow that help in the formation of blood vessels.
- Hemangiosarcoma cells travel throughout the body, increasing the risk that the disease will exist in multiple locations.
- There appears to be some risk for hemangiosarcoma associated with “being a dog,” and the risk seems to be compounded in several breeds, suggesting that heritable traits contribute to the disease. However, our current state of knowledge indicates that this disease is not amenable to genetic management, for example, through breeding strategies.
- There are no known methods for effective prevention of hemangiosarcoma. Altering lifestyle behaviors, eliminating exposure to toys or other factors in the environment, and/or feeding special diets have no effect on the risk of developing this disease.
- Hemangiosarcoma is almost always a fatal disease although its progression can be unpredictable. Most dogs with hemangiosarcoma will show rapid disease progression after diagnosis but in rare cases dogs can live with this disease for months or even years.
- The major goal of treatment is to prevent or delay a terminal bleeding episode. The most effective treatment for hemangiosarcoma includes surgery to remove visible masses, to the extent that it can be done safely, followed by chemotherapy.

## **About the authors**

Dr. Borgatti is Associate Professor of Oncology at the University of Minnesota Veterinary Medical Center. She graduated cum laude from the University of Torino, Italy (1996). After three years in general practice, she received a scholarship to pursue specialized training in oncology at North Carolina State University, where she subsequently remained as a Research Associate, Oncology Intern, and Clinical Instructor in Oncology. She completed a Residency in Comparative Oncology at Purdue University where she also received a Master of Sciences Degree in 2006. Dr. Borgatti became a Diplomate of the American College of Veterinary Internal Medicine (Oncology) in 2006 and a Diplomate of the European College of Veterinary Internal Medicine in 2007. She worked at a specialty referral hospital in North Carolina for two years before joining the faculty at the University of Minnesota in 2008. She is also a Member of the Masonic Cancer Center at the University of Minnesota and Director of the Oncology residency program.

Ms. Fahrenkrug is the former Associate Director of the Comparative Oncology Program and Senior Development Officer at the University of Minnesota College of Veterinary Medicine. She is a graduate of Saint Cloud State University and completed her master's degree at Hamline University in 2005. Ms. Fahrenkrug worked in the medical device industry before joining the University of Minnesota in 2008. She currently serves as Chief Strategy Officer for Half Moon Bay Biotechnology, a company focused on diminishing the impact of cancer on our society.

Dr. Modiano graduated from the Veterinary Medical Scientist Training Program (VMD/PhD) at the University of Pennsylvania in 1991. He completed a residency in Veterinary Clinical Pathology at Colorado State University in 1993 and postdoctoral research at the National Jewish Medical Center in 1995. He was on the faculties of Texas A&M University and the University of Colorado before joining the College of Veterinary Medicine and the Masonic Cancer Center of the University of Minnesota in 2007 as the Alvin and June Perlman Endowed Chair of Animal Oncology and Director of the Animal Cancer Care and Research Program.

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