Canine Hemangiosarcoma
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Dr. Lynda Beaver received her DVM from Ontario Veterinary College in 1989. After working as a general practitioner for a number of years, she decided to specialize in the field of veterinary oncology. She spent four years as an oncology technician at the University of Wisconsin-Madison prior to completing a small animal medicine and surgery internship at the University of Illinois. She then concluded an Oncology internship at Southern Arizona Veterinary Specialty and Emergency Center in Tucson, Arizona.

Dr. Beaver finished a three-year medical oncology residency at Arizona Veterinary Specialist in 2008, and became board-certified in medical oncology in 2010.

Hemangiosarcoma (HSA) is a malignant cancer that arises from endothelial cells, and can develop in any organ with a blood supply. HSA represents about 5% of all noncutaneous primary malignant neoplasms and 2 to 3% of all skin tumors in dogs. The etiology of HSA is not completely understood, but there is evidence that dysregulation of molecular pathways governing angiogenesis may be important in the pathogenesis. German Shepherds, Golden Retrievers, Labrador Retrievers, and Schnauzers appear to be overrepresented, suggesting an inherited or familial predisposition in these breeds.

The most common primary sites are the spleen (28% -50%), right atrium and auricle (3% – 50%), and the skin or subcutaneous tissue (13%). Tumors in all but dermal locations are generally associated with aggressive metastasis and short survival times; in general, the deeper the tumor, the greater the likelihood of metastasis. Metastasis is typically hematogenous or through transabdominal implantation following splenic rupture, and the liver, omentum, and lung are the most common sites. Unfortunately, even with aggressive treatment, many dogs with hemangiosarcoma lose to their disease within the first year. The following is a summary of the most common types of hemangiosarcoma seen in practice:

Cutaneous (dermal) hemangiosarcoma:

Cutaneous HSAs are found most frequently in dogs with minimal pigmentation and thin hair coats (e.g. Whippets, Beagles, white Bulldogs, and Italian Greyhounds), and appear to be associated with ultraviolet light exposure. True dermal hemangiosarcomas, without any evidence of subdermal infiltration, represent the one form of this disease that does not, at least initially, follow an aggressive course. These lesions typically appear as slightly raised, red or purple masses...continued on page 2
that resemble blood blisters, and may be found in combination with benign hemangiomas, which usually appear as small, flat, red skin lesions. Many dogs develop multiple lesions, typically involving the ventrum and limbs.

Cutaneous (dermal) Hemangiosarcoma

Surgical excision of these masses has typically been considered the treatment of choice, although they also respond very nicely to laser ablation, which allows many lesions to be treated fast and efficiently, with a quick recovery. Small, flat lesions can also be treated very effectively with cryotherapy. In one study, the median survival time for dogs with cutaneous (dermal) hemangiosarcomas treated with surgery was 26 months. In my experience, many of these dogs can be managed for years, but most will develop new lesions on a regular basis, and will need intermittent surgery and/or cryotherapy to keep the disease under control. It is important to monitor these patients diligently and address new lesions before they have a chance to become more invasive. Eventually, some of these patients may go on to develop a more aggressive form of the disease.

Subcutaneous and intramuscular hemangiosarcoma:

Subcutaneous and intramuscular hemangiosarcomas often present as large, ill-defined, subcutaneous masses. Lameness may be present, especially with intramuscular tumors that involve the limbs. Cytology of these masses is often unrewarding, owing to the very vascular nature of these tumors. Fine-needle aspirate of these masses often results in a very bloody sample, which is not diagnostic, but may raise the index of suspicion for HSA. A biopsy is usually needed to confirm a diagnosis, however there is significant risk of hemorrhage, and baseline labwork, including a platelet count and ideally a coagulation profile, should be done first.

Large, ulcerated, subcutaneous hemangiosarcoma

Most studies have shown that subcutaneous and intramuscular hemangiosarcomas behave aggressively, with similar survival times to those of visceral hemangiosarcomas. Surgery is the treatment of choice for these tumors, however, complete surgical excision is often difficult due to the size and invasiveness of these tumors. Prior to surgery, staging, including chest x-rays and an abdominal ultrasound, should be done to rule out metastatic disease. In addition, a CT scan may be beneficial in some patients to help plan surgery. Unfortunately, the long-term prognosis for these patients is guarded in most cases, based on the inability to obtain adequate local tumor control, and the high incidence of metastatic disease. Median survival times with surgery alone in 1 study were approximately 6 months for subcutaneous HSA’s and about 10 months for intramuscular HSA’s (these numbers were not statistically
significant). Given the high metastatic rate of these tumors, adjuvant chemotherapy should be recommended, and doxorubicin-based protocols are generally regarded as the most effective chemotherapy option against hemangiosarcoma, and have been associated with improved survival times. With chemotherapy, median survival times have ranged from 211 days to 425 days, although one study showed a median survival time of over 3 years for dogs with subcutaneous HSA that had adequate local tumor control (i.e. complete surgical excision +/- radiation therapy) plus doxorubicin-based chemotherapy. In this study, dogs with intramuscular tumors had a median survival time of only 9 months, indicating more aggressive behavior, although this has not been confirmed in all studies. Negative prognostic factors in dogs with subcutaneous or intramuscular HSA’s include size (> 4 cm), lack of adequate local tumor control, and the presence of metastatic disease at the time of diagnosis. The role of radiation therapy for incompletely resected HSA’s remains to be determined, however, in situations where tumors cannot be resected, or owners elect not to pursue aggressive surgery, palliative radiation protocols can shrink tumors significantly, and improve quality of life, for an average of 2 to 4 months. Palliative radiation protocols involve fewer treatments (usually 5 doses), and minimal side effects, and have at least a partial response in about 75% of dogs. Chemotherapy can also be used in the face of gross disease, either palliatively, or to down stage tumors prior to surgery. In 1 study of dogs with non-resectable subcutaneous HSA, approximately 40% of dogs had some response to doxorubicin-based chemotherapy, although responses were short lived.

**Visceral Hemangiosarcoma:**

The spleen is the most common visceral site of HSA, but other possible sites of origin include the right atrium and auricle, kidney, liver, and prostate. Splenic masses are a relatively common finding in canine patients, and the double two-thirds rule (2/3 of splenic masses are malignant, and 2/3 of these are HSA) is often referenced, although one study found that approximately 70% of dogs with splenic masses presenting with nontraumatic hemoabdomen had HSA. Other potential differentials would include hematoma, hemangioma, and other sarcomas. Many dogs with splenic HSA present for acute onset of weakness and collapse secondary to hemorrhage from the mass. This may be preceded by milder, intermittent, episodes of transient weakness which resolve spontaneously over 12 to 36 hours as a result of less severe episodes of bleeding that are subsequently reabsorbed. Otherwise, dogs may present with vague signs of lethargy, inappetance, and weight loss and an abdominal mass is palpated during exam. Labwork from these patients often reveals an anemia, usually characterized by the presence of schistocytes (associated with microangiopathic hemolysis from the abnormal tumor vasculature). Thrombocytopenia is also commonly noted, and many dogs have abnormalities in the coagulation profile, with up to 50% meeting the criteria for DIC. Classic abdominal ultrasound findings include a cavitated splenic mass(es) and ascites, and abdominocentesis will reveal serosanguineous or hemorrhagic effusion.
that does not clot. Cytology of these masses is rarely diagnostic due to hemodilution, and biopsy is not recommended due to the risk of hemorrhage and potential for seeding of the peritoneum. During abdominal ultrasound, other abdominal organs should be evaluated carefully for evidence of metastatic disease. Chest x-rays and an ultrasound of the heart should also be done prior to surgery, to rule out the presence of pulmonary metastasis and a concurrent right atrial mass respectively; up to 25% of dogs with splenic tumors will also have a mass in the heart. If there is no evidence of metastatic disease at the time of diagnosis, splenectomy is the treatment of choice; however, with surgery alone survival times are short, ranging from 19 to 86 days, as most dogs develop metastatic disease very quickly. Chemotherapy helps to delay the onset of metastatic disease, and adjuvant chemotherapy with a doxorubicin-based protocol extends the median survival time to between 141 and 179 days, but unfortunately less than 10% of patients survive to 1 year. Stage of disease has been shown to be prognostic in patients with HSA – dogs with stage 1 disease (i.e. unruptured splenic mass) have a better prognosis than dogs in which the spleen has ruptured. Dogs with gross metastatic disease at the time of diagnosis (i.e. stage 3) carry a worse prognosis, and surgery is largely palliative. One study did evaluate the use of an aggressive doxorubicin-based protocol (doxorubicin, dacarbazine, and vincristine) in dogs with advanced stage disease. In this study, there was an overall response rate (complete plus partial responses) of 47%, however, this protocol was associated with significant toxicity, and the median survival time was still only 125 days. Dogs with cardiac hemangiosarcoma usually present with signs related to the presence of pericardial effusion. The mass can be visualized in the majority of patients via an echocardiogram. A pericardectomy can be performed as a palliative treatment, or in combination with attempted removal of the mass. In one study of dogs undergoing surgery plus or minus chemotherapy, median survival times ranged from 4 to 7 months, and were similar to those of splenic hemangiosarcoma.

Primary renal HSA occurs less commonly, but appears to carry a slightly better prognosis. One study showed that dogs with renal hemangiosarcomas had a lower risk of distant metastasis and hemoperitoneum and the time of diagnosis (vs splenic HSA) and a median survival time of 278 days when dogs were treated with surgery (nephrectomy) +/- adjuvant chemotherapy.

**Antiangiogenic Protocols:**

Angiogenesis is the formation of new blood vessels from existing microvessels. Without the ability to form new blood vessels, tumors cannot grow to be more than about 2 mm in diameter. Angiogenesis is also an essential component of metastasis, providing the principal route by which tumor cells leave the primary tumor site and enter the circulation. Low dose chemotherapy (metronomic chemotherapy) protocols are a relatively new concept in veterinary oncology, and focus to prevent angiogenesis, and therefore tumor progression and metastatic disease. Such protocols may also stimulate an immune response as they selectively deplete regulatory T-cells, which are present in increased numbers.
in cancer patients and are normally involved in preventing anti-tumor immune responses. Current metronomic protocols generally combine agents which directly and indirectly inhibit angiogenesis and typically include cytotoxic chemotherapy drugs, non-steroidal anti-inflammatory drugs (NSAIDs) and molecularly targeted therapies. Such protocols are particularly attractive for the treatment of HSA, because the neoplastic cells are believed to arise from transformed endothelial cells, and therefore may retain their susceptibility to antiangiogenic agents and HSA is a highly vascular tumor, and therefore may respond to inhibitors of normal endothelial cells. Several chemotherapy drugs (including cyclophosphamide and etoposide) directly damage endothelial cells in vitro and in vivo and cytotoxicity can be seen with traditional chemotherapy dosing schedules (i.e. higher doses less often). However, the treatment breaks required when using these types of protocols allow the tumor vascular endothelial cells to recover and resume growth during these breaks, leading to only transient disruption of the blood supply to the tumor. Studies have shown that lower drug doses given on a more frequent basis better target angiogenesis, and are also associated with less myelosuppression and GI toxicity. When cyclophosphamide was given in a continuous, low dose schedule, significant antiangiogenic activity persisted throughout the treatment period and was associated with control of tumor growth. There is also evidence that inhibitors of COX enzymes, such as non-steroidal anti-inflammatory medications, may have both direct and indirect anti-angiogenic effects. As such, metronomic chemotherapy protocols often combine a non-steroidal anti-inflammatory medication, with low-dose cyclophosphamide chemotherapy, in an attempt to delay tumor progression through the inhibition of angiogenesis. In one study that evaluated the use of a low-dose chemotherapy protocol in dogs with splenic hemangiosarcoma following splenectomy, the median survival time was 178 days, indicating that it was at least as effective as conventional doxorubicin-based chemotherapy. Toceranib (Palladia), a tyrosine kinase inhibitor that is licensed for use in the treatment of canine mast cell tumors, also exhibits antiangiogenic activity through inhibition of the receptor tyrosine kinases vascular endothelial growth factor receptor and platelet derived growth factor receptor. This drug is currently being investigated in several studies for its potential benefit in the treatment of non-mast cell disease through its antiangiogenic properties.

**Summary:**

Unfortunately, in most cases, other than cutaneous tumors confined to the dermis, hemangiosarcoma is a very aggressive disease, both locally and with regard to its ability to spread to distant sites, with many patients losing to this disease within the first year of diagnosis. Surgery plus doxorubicin-based chemotherapy are considered standard of care, but better treatment options are needed in order to extend survival times.

Kayla, another cancer survivor

Antiangiogenic protocols, either alone, or in addition to standard chemotherapy protocols, may provide us with a way to extend survival times in these patients, although further research is needed to better define their role.
AVS CORE VALUES

INNOVATION
We will strive to discover and share knowledge that will continuously improve the veterinary profession.

EXCELLENCE
At Arizona Veterinary Specialists, our standard is excellence in all that we do and the way in which we do it.

COMPASSION
The spirit of all our relationships will be driven by compassion.

PATIENT CARE
We are committed to providing compassionate, ethical, and quality care to our patients. We treat them as if they are members of our own families.

INTEGRITY
We will conduct ourselves in a manner that will instill confidence and trust in all of our interactions.

Our mission is to enhance the quality of our patients' lives, to strengthen the human-animal bond, and to provide a safe and stimulating work environment for all of our team members.

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Questions or comments?
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Arizona Veterinary Dental Specialists Gilbert, PLLC

**Dentistry**
- Periodontics
- Dental digital radiography
- Endodontics
- Nasal disease treatment
- Oral disease treatment
- Oral surgery
- Orthodontics
- Restoration

Eye Care for Animals, dba Ophthalmology

- Biomicroscopy
- Indirect ophthalmoscopy
- Electroretinography
- Ultrasonography
- Applanation tonometry
- Fluorescein angiography
- Glaucoma treatment
- Cataract surgery
- Corneal reconstructive surgery
- Treatment of eyelid abnormalities

Desert Veterinary Medical Specialists, dba Internal Medicine

- Endoscopy
  - Bronchoscopy
  - Bronchoalveolar lavage
  - Colonoscopy
  - Cystoscopy
  - Foreign body retrieval
  - Gastroduodenoscopy
  - PEG tube placement
  - Rhinoscopy
- Endocrine disorders
- Emergency consultations
- Blood and plasma transfusions
- Gastrointestinal diseases
- Genitourinary disorders
- Hepatic diseases
- Infectious diseases
- Intensive care treatment
- Immune-mediated diseases
- Nutrition consultations
- Oxygen therapy
- Pancreatic diseases
- Pulmonary diseases
- Renal disease
- Respiratory diseases
- Second opinion examinations
- Ultrasoundography
- Tracheal and urethral stenting

Southwest Veterinary Oncology, PLLC

**Radiation Oncology**
- Linear accelerator radiation therapy
- I-131 radioactive iodine treatment

**Medical Oncology**
- Chemotherapy
- Immunotherapy
- Cryotherapy
- Oncologic surgery
- Clinical trials

Eye Care for Animals, dba Ophthalmology

- Biomicroscopy
- Indirect ophthalmoscopy
- Electroretinography
- Ultrasonography
- Applanation tonometry
- Fluorescein angiography
- Glaucoma treatment
- Cataract surgery
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- Respiratory diseases
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- Ultrasoundography
- Tracheal and urethral stenting

Dermatology for Animals, PC

**Dermatology**
- Allergy testing (skin testing) and immunotherapy
- CO₂ laser for ablation of skin tumors
- Testing for food allergies and hypoallergenic diets
- Ear disease diagnosis and treatment
- Bacterial and fungal skin disease diagnosis and treatment
- Cytological smears and microbiologic examinations
- Ectoparasite identification and treatment
- Immune-mediated and hormonal skin disease diagnosis and treatment
- Treatments of nail and nail bed disorders
- Skin biopsy sampling and histopathology interpretation

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Southwest Veterinary Surgical Service, PC

Surgery
- Abdominal surgery
- Airway surgery
- Angular limb deformity surgery
- Arthroscopy
- CT Scans
- External skeletal fixation
- Fracture repair
- Neurologic surgery
- Oncologic surgery
- Oral surgery, such as maxillofacial surgery and oral fractures
- Orthopedic surgery
- Otologic surgery
- Perineal surgery
- Reconstructive surgery
- Ring fixators
- Soft Tissue surgery
- Thoracic surgery
- Tibial Plateau Leveling Osteotomy (TPLO)
- Triple Pelvic Osteotomy (TPO)
- Total Hip Replacement (THR) both cemented and cementless procedures available
- Tracheal Stenting
- Tibial Tuberosity Advancement (TTA)

Anesthesia and Pain Management
- Anesthetic management of high risk and critical care patients
- Extensive anesthesia monitoring
  - Blood pressure, both direct and indirect
  - Pulse oximetry
  - Electrocardiogram
  - Capnography
  - Body temperature
  - Ventilator therapy
- Pain patches
- Chronic pain management consultations

Emergency Animal Clinic, PLC

Emergency and Critical Care
- In house diagnostic tests
- STAT laboratory blood tests
- Complete Blood Count (CBC)
- Serum biochemical analysis
- Blood gas analysis
- Urinalysis
- Blood lactate measurement
- Coagulation testing
- Ethylene glycol (Antifreeze) testing
- Parvovirus testing
- Digital x-rays
- Radiologist interpretation optional
- Scanning ultrasound
- Electrocardiogram (EKG)
- Blood pressure
- Gastrointestinal endoscopy
- Specialized Therapies
- Intravascular volume expansion/shock therapy
- Blood component therapy
- Rattlesnake antivenom therapy
- Oxygen
- Short and long term ventilator therapy
- Anesthetic ventilator
- Pain medication delivery via constant rate infusion
- Nutritional support
- Feeding tube placement
- Peritoneal dialysis
- Continuous suction for chest and other drains
- Central and peripheral IV catheter placement
- Cardiopulmonary Cerebral Resuscitation (CPCR) with advanced life support
- Electrical defibrillation, cardioversion and emergency transthoracic pacing
- Anesthesia for high-risk critical patients
- Soft tissue emergency surgical procedures performed by our emergency veterinarians (included, but not limited to):
- Wound repair
- Emergency tracheostomy
- Chest tube placement
- Abdominal surgeries
- Gastric Dilatation Volvulus (GDV) or bloat surgery
- GI foreign body removal
- C-section
- Splenectomy
- Bladder stone removal
- Intensive monitoring
- Electrocardiogram (EKG)
- Blood pressure (direct arterial and indirect)
- Urinary catheter placement and measurement of urine output
- Pulse oximetry (Oxygen saturation)
- Capnography (End Tidal CO2)
- Central venous pressure
- Arterial and venous blood gas measurement
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  (Practice Limited to Dermatology)
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