Hemangiosarcomas (HSAs, hemangioendotheliomas, angiosarcomas) are malignant neoplasms that originate from the circulating endothelial precursors. They occur predominantly in older dogs (8 to 10 years of age) and in males; German Shepherd Dogs and Golden Retrievers are at high risk for this neoplasm.

The spleen, right atrium, subcutis, and retroperitoneal space are common sites of involvement at the time of presentation; in Greyhounds, most HSAs originate in a muscle in the rear limb. Approximately 50% of the tumors originate in the spleen, 25% in the right atrium, 13% in subcutaneous tissue, 5% in the liver, 5% in the liver-spleen-right atrium, and 1% to 2% simultaneously in other organs (i.e., kidney, urinary bladder, bone, tongue, prostate). The latter are referred to as multiple tumor, undeterminable primary. In general, the biologic behavior of this neoplasm is highly aggressive, with most anatomic forms of the tumor infiltrating and metastasizing early in the disease. The exceptions are primary dermal and conjunctival or third eyelid HSAs, which have a low metastatic potential.

Clinical and Clinicopathologic Features
The owners’ complaints and the clinical signs at presentation are usually related to the site of origin of the primary tumor; to the presence or absence of metastatic lesions; and to the development of spontaneous tumor rupture, coagulopathies, or cardiac arrhythmias. More than half of the dogs with HSA are evaluated because of acute collapse after spontaneous rupture of the primary tumor or a metastatic lesion. Some episodes of collapse may stem from ventricular arrhythmias, which are relatively common in dogs with splenic or cardiac HSA. In addition, dogs with splenic HSA often are seen because of abdominal distention secondary to tumor growth or hemoabdomen.

Dogs with cardiac HSA usually are presented for evaluation of right-sided congestive heart failure (caused by cardiac tamponade) or cardiac arrhythmias (see the chapters on cardiovascular system disorders for additional information). Dogs with cutaneous or subcutaneous neoplasms are usually evaluated because of a lump, that may be surrounded by hemorrhage. Greyhounds with intramuscular HSA typically present with a swollen and bruised rear limb; the tumor is frequently in the biceps femoris or quadriceps.

Two common problems in dogs with HSA, regardless of the primary location or stage, are anemia and spontaneous bleeding. The anemia is usually the result of intracavitary bleeding, microangiopathic hemolysis (MAHA), or both, whereas the spontaneous bleeding is usually
caused by disseminated intravascular coagulation (DIC) or thrombocytopenia secondary to MAHA (see later discussion). HSA is so highly associated with clinical DIC that at our hospital dogs with DIC of acute onset but without an obvious primary cause are evaluated for HSA first.

Hemangiosarcomas are usually associated with a wide variety of hematologic and hemostatic abnormalities. Hematologic abnormalities in dogs with HSA have been well characterized and include anemia; thrombocytopenia; the presence of nucleated red blood cells (RBCs), RBC fragments (schistocytes), and acanthocytes in the blood smear; and leukocytosis with neutrophilia, a left shift, and monocytosis. In addition, hemostatic abnormalities are also common in dogs with HSAs. However, these hematologic abnormalities are location dependent; for example, in our clinic anemia, thrombocytopenia, schistocytosis, and acanthocytosis are significantly more common in dogs with splenic, right atrial, or visceral HSA than in dogs with subcutaneous or dermal HSA.

Most dogs with HSA (83%) evaluated at our clinic are anemic; more than one half had RBC fragmentation and acanthocytosis. The pretreatment hemostasis profiles are normal in <20% of the dogs; most dogs (75%) have thrombocytopenia. Approximately one half of the hemostasis profiles meet three or more criteria for diagnosis of DIC. Approximately 25% of these dogs die as a result of their hemostatic abnormalities.

Diagnosis
Hemangiosarcomas can be diagnosed cytologically on the basis of the appearance of fine-needle aspirates (FNA) or impression smears. The neoplastic cells are similar to those in other sarcomas in that they are spindle-shaped or polyhedral; however, they are quite large (40-50µm); have large nuclei with a lacy chromatin pattern and one or more nucleoli; and a bluish gray, usually vacuolated cytoplasm. Nucleated RBCs and acanthocytes/schistocytes are frequently present in FNAs of HSAs, independently of the primary site. Although HSA cells are relatively easy to identify in tissue aspirates or impression smears, they are extremely difficult to identify in HSA-associated effusions. The probability of establishing a cytologic diagnosis of HSA after evaluating effusions is less than 25%. An additional problem with effusions is that they frequently contain reactive mesothelial cells that may resemble neoplastic cells, leading to a false-positive diagnosis of HSA.

In general, a presumptive clinical or cytologic diagnosis of HSA should be confirmed histopathologically, if feasible. Because of the large size of some splenic HSAs, however, multiple samples (from different morphologic areas) should be submitted in appropriate fixative. Histochemically, HSA cells are positive for von Willebrand factor antigen in approximately 90% of the cases; CD31 is a relatively new marker of endothelial origin positive in most HSAs.

Metastatic sites can be detected radiographically, ultrasonographically, or on computed tomography (CT). Our routine staging system for dogs with HSA includes a complete blood count
(CBC), serum biochemistry profile, hemostasis screen, urinalysis, thoracic radiographs, abdominal ultrasonography, and echocardiography. The latter is used to identify cardiac masses and determine the baseline fractional shortening before instituting doxorubicin-containing chemotherapy (see the section on treatment and prognosis).

Thoracic radiographs in dogs with metastatic HSA are typically characterized by the presence of interstitial or alveolar infiltrates, as opposed to the common “cannonball” metastatic lesions seen with other tumors. The radiographic pattern may be due to true metastases or to DIC and intrapulmonary bleeding, or adult respiratory distress syndrome (ARDS).

Ultrasonography constitutes a reliable way to evaluate dogs with suspected or confirmed HSA for intraabdominal disease. Neoplastic lesions appear as nodules with variable echogenicity, ranging from anechoic to hyperechoic. Hepatic metastatic lesions can often be identified using this imaging technique. However, the clinician should bear in mind that what appear to be metastatic nodules in the liver of a dog with a splenic mass may represent regenerative hyperplasia rather than true metastatic lesions. Contrast ultrasonography appears to enhance the operator’s ability to detect hepatic metastatic nodules from HAS, but it is not easily available.

**Treatment and Prognosis**

Historically, the mainstay of treatment for dogs with HSA has been surgery, although the results have been poor. Survival times vary with the location and stage of the tumor, but in general (with the exception of dermal and conjunctival or third eyelid HSAs), they are quite short (approximately 20 to 60 days, with a 1-year survival rate of 10%). Results of treatment combining surgery and postoperative adjuvant chemotherapy with doxorubicin; doxorubicin and cyclophosphamide (AC protocol); and vincristine, doxorubicin, and cyclophosphamide (VAC protocol) are better than with surgery alone. Median survival times range from 140 to 202 days.

Clinical stage has been considered a negative prognostic factor for survival. In a recent study, we hypothesized that the median survival time (MST) of dogs with metastatic (stage III) HSA treated with a VAC chemotherapy protocol protocol (see box on cancer chemotherapy protocols at the end of this chapter) would not be different than those with stage I/II HSA. Sixty-seven dogs with HSA in different anatomical locations were evaluated retrospectively. All dogs received the VAC protocol, as adjuvant to surgery (n=50), neoadjuvant (n=3), or as the sole treatment modality (n=14). There was no significant difference between the MST of dogs with stage III (n=25; 195 days) and stage I/II (n=42; 189 days) HAS. For dogs presenting with splenic HSA alone, there was no significant difference between the MST of dogs with stage III (195 days; range 17-742) and stage I/II (133 days; range 23-415) disease. The overall response rate (CR and PR) was 86%. No unacceptable toxicities were observed. Dogs with stage III HSA treated with the VAC protocol have a similar prognosis to dogs with stage I/II HSA; therefore, dogs with HSA and evidence of metastases at the time of diagnosis should not be denied treatment.
Although similar results were reported for dogs treated either with doxorubicin and cyclophosphamide or with doxorubicin alone, in my experience, the prognosis for dogs with HSA is better if a three-drug combination, instead of a two-drug combination or monochemotherapy, is used. In our clinic we have rarely been able to administer more than 3 or 4 doses of single agent doxorubicin in dogs with HSA because they have already relapsed.

In summary, HSAs are usually diagnosed on the basis of historical, physical examination, and clinicopathologic findings, in conjunction with ultrasonographic and radiographic changes. A morphologic diagnosis can usually be made on the basis of cytologic findings, but histopathology may be necessary. Although surgery is the preferred treatment, survival times in such animals are extremely short (except in dogs with dermal or conjunctival/third eyelid HSA). Postoperative adjuvant chemotherapy using doxorubicin-containing protocols prolongs survival in dogs with this malignancy.
**VAC protocol (21-day cycle)**

- Vincristine: 0.75 mg/m² IV on days 8 and 15
- Doxorubicin: 30 mg/m² IV (or 1 mg/kg if <10 kg) on day 1
- Cyclophosphamide: 200-300 mg/m² PO on day 10
- Sulfa-trimethoprim: 15 mg/kg PO q12h