Article #3

CE Liver Tumors in Cats and Dogs

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ABSTRACT:

Tumors affecting the liver can be either primary or metastatic. Metastatic involvement is more common than primary hepatobiliary tumors. The four categories of primary hepatic tumors in cats and dogs are hepatocellular, bile duct, mesenchymal, and neuroendocrine. In dogs, malignant variants of these tumors are more common, whereas benign neoplasia, particularly cystic bile duct adenoma, is more frequent in cats. Primary hepatic tumors are morphologically classified as massive, nodular, or diffuse. The prognosis is better for massive tumors than for nodular, diffuse, or metastatic liver tumors because surgical resection is possible and can be curative, particularly for hepatocellular carcinoma in dogs and bile duct adenoma and myelolipoma in cats. In contrast, treatment options are limited for cats and dogs with nodular, diffuse, and metastatic liver tumors as surgery is often not possible and other forms of therapy have not been investigated.

Primary hepatic tumors are uncommon and account for 0.6% to 1.5% of all canine tumors and 1.0% to 2.9% of all feline tumors, but they represent up to 6.9% of nonhematopoietic tumors in cats.[1–4] Metastatic disease is more common and occurs two and a half times more frequently than primary liver tumors in dogs, particularly from primary cancer of the spleen, pancreas, and gastrointestinal tract.[1,2] The liver can also be involved in other malignant processes, such as lymphoma, malignant histiocytosis, and systemic mastocytosis.[2,3]

The four basic categories of primary malignant hepatic tumors in cats and dogs are hepatocellular, bile duct, neuroendocrine (or carcinoid), and mesenchymal.[4] Malignant variants are more common in dogs, whereas benign tumors occur more frequently in cats.[2–8] There are three morphologic types of these primary hepatic tumors: massive, nodular, and diffuse (Table 1).[5] Massive liver tumors are defined as large, solitary masses confined to a single liver lobe; nodular tumors are multifocal and involve several liver lobes; and diffuse involvement may represent the final spectrum of neoplastic disease with multifocal or coalescing nodules in all liver lobes or diffuse effacement of the hepatic parenchyma.[4,5] The prognosis for cats and dogs with liver tumors is determined by histology and morphology. The prognosis is good for massive hepatocellular carcinoma (HCC) and for benign tumors because complete surgical resection is possible and their biologic behavior is relatively nonaggressive.[7–11] In contrast, the prognosis is poor for cats with any type of malignant tumor and for dogs with malignant tumors other than massive HCC.[2–14]

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DIAGNOSIS

Presenting Signs and Physical Examination

Hepatobiliary tumors are symptomatic in approximately 50% of cats and 75% of dogs, especially in animals with malignant tumors.[1–21] The most common presenting signs are nonspecific and include inappetence, weight loss, lethargy, vomiting, polydipsia/polyuria, and

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Table 1. Frequency of Morphologic Classifications of Malignant Primary Liver Tumors in Dogs[4–14]

Tumor Type	Massive	Nodular	Diffuse
Hepatocellular carcinoma	53%–84%	16%–25%	0%–19%
Bile duct carcinoma	37%–46%	0%–46%	17%–54%
Neuroendocrine tumor	0%	33%	67%
Sarcoma	36%	64%	0%

ascites.[1–21] Seizures, which are uncommon, may be caused by hepatic encephalopathy, paraneoplastic hypoglycemia, or central nervous system metastasis.[5,9,22] Icterus is more commonly seen in dogs with extrahepatic bile duct carcinomas or diffuse neuroendocrine tumors.[2,5,12] However, these signs rarely assist in differentiating primary and metastatic liver tumors from nonneoplastic hepatic disease.[3] Physical examination findings can be equally unrewarding. A cranial abdominal mass is palpable in up to 75% of cats and dogs with liver tumors, although palpation can be misleading since hepatic enlargement may either be absent in nodular and diffuse forms of liver tumors or missed due to the protected position of the liver in the cranial abdomen deep to the caudal rib cage.[1–21]

Laboratory Tests

Hematologic and serum biochemical abnormalities are usually nonspecific. Leukocytosis, anemia, and thrombocytosis are common in dogs with liver tumors.[1–14] Leukocytosis is probably caused by inflammation and necrosis associated with large liver masses.[9,10] Anemia is usually mild and nonregenerative.[5,11] The cause of anemia is unknown, although hypotheses include the presence of chronic disease, inflammation, red blood cell sequestration, and iron deficiency.[23] Thrombocytosis, defined as a platelet count greater than $500 \times 10^3/\mu l$, is seen in approximately 50% of dogs with massive HCC.[11] Proposed causes of thrombocytosis include anemia, iron deficiency, inflammatory cytokines, and paraneoplastic production of thrombopoietin.[24–26] Anemia and thrombocytopenia can be seen in dogs with primary and metastatic hepatic hemangiosarcoma (HSA).[3] Prolonged coagulation times and clotting factor abnormalities have been identified in dogs with hepatobiliary tumors, although these are rarely clinically relevant.[27]

Liver enzymes are commonly elevated in dogs with hepatobiliary tumors (Table 2). There is no apparent correlation between the degree of hepatic involvement and the magnitude of liver enzyme alterations[4]; however, liver enzyme abnormalities may provide an indication of the type of tumor and may distinguish primary from metastatic liver tumors. Alkaline phosphatase (ALP) and alanine transferase (ALT) are commonly increased in dogs with primary hepatic tumors.[1] In contrast, aspartate aminotransferase (AST) and bilirubin are more consistently elevated in dogs with metastatic liver tumors.[1,28] Furthermore, an AST:ALT ratio less than 1 is consistent with HCC or bile duct carcinoma, whereas a neuroendocrine tumor or sarcoma is more likely when the ratio is greater than 1.[5] In general, however, liver enzyme elevations are not specific for the diagnosis of hepatobiliary diseases.[29] Other changes in serum biochemical profile in dogs with hepatic tumors include hypoglycemia, hypoalbuminemia, hyperglobulinemia, and increased preprandial and postprandial bile acids.[1,2,5,9–14] In contrast to what occurs in dogs, azotemia is often present in cats with hepatobiliary tumors and may be the only biochemical abnormality, although liver enzyme abnormalities, especially in ALT, AST, and total bilirubin, are also common and are significantly higher in cats with malignant tumors.[6–8]

Table 2. Frequency of Hematologic and Serum Biochemical Abnormalities in Cats and Dogs with Hepatobiliary Tumors[4–14]

Parameter	Cats	Dogs
Leukocytosis	NR	54%–73%
Anemia	NR	27%–51%
Hypoalbuminemia	NR	52%–83%
Increased ALP	10%–64%	61%–100%
Increased ALT	10%–78%	44%–75%
Increased AST	15%–78%	56%–100%
Increased GGT	78%	39%
Increased total bilirubin	33%–78%	18%–33%

GGT = γ-glutamyltransferase; *NR* = not reported.

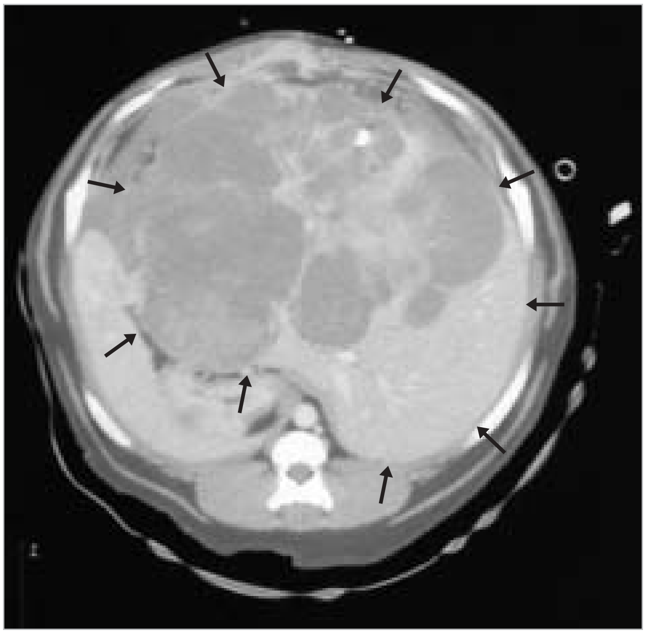

Figure 1. Sagittal CT of a dog with a massive hepatocellular carcinoma. The liver tumor appears large *(arrows)* and unresectable. In this case, however, surgical resection was possible and this dog was still alive 355 days postoperatively.

Figure 2. The massive hepatocellular carcinoma in Figure 1 following surgical resection.

Imaging

Radiography, ultrasonography, and advanced imaging can be used for the diagnosis, staging, and surgical planning of cats and dogs with hepatobiliary tumors. A cranial abdominal mass, with caudal and lateral displacement of the stomach, is frequently seen on abdominal radiographs of cats and dogs with massive liver tumors.[10,11,30] Occasionally, mineralization of the biliary tree is seen in dogs with bile duct carcinoma.[4] Sonographic examination is recommended because these radiographic findings are not specific for the diagnosis of a hepatic mass and do not provide information on the relationship of the hepatic mass with regional anatomic structures.

Abdominal ultrasonography is the preferred method for identifying and characterizing hepatobiliary tumors in cats and dogs.[18,31–35] Sonographic examination is useful in determining the presence of a hepatic mass and for defining the tumor as cystic or solid, and massive, nodular, or diffuse.[18,31–35] If focal, the size and location of the mass, and its relationship with adjacent anatomic structures, such as the gallbladder or caudal vena cava, can be assessed.[18,31–35] Furthermore, tumor vascularization can be determined using Doppler imaging techniques.[4] The ultrasonographic appearance of hepatobiliary tumors varies and does not correlate with histologic tumor type.[18,31–35]

Ultrasound-guided fine-needle aspiration or needle-core biopsy of hepatic masses are useful, minimally-invasive techniques to obtain cellular or tissue samples for diagnostic purposes.[32–35] A coagulation profile is recommended before hepatic biopsy because mild to moderate hemorrhage is the most frequent complication, occurring in approximately 5% of cases.[32–35] A correct diagnosis is obtained in up to 60% of hepatic aspirates and 90% of needle-core biopsies. More invasive techniques, such as laparoscopy and open keyhole approaches, can also be used for the biopsy and staging of cats and dogs with suspected liver tumors. However, for solitary and massive hepatic masses, surgical resection can be performed without a preoperative biopsy since both diagnosis and treatment can be achieved in a single procedure.

Advanced imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), are preferred for the diagnosis and staging of liver tumors in humans.[36] Unlike ultrasonography, imaging appearance will frequently provide an indication of tumor type. Furthermore, CT and MRI are more sensitive for the detection of small hepatic lesions and for determination of the relationship of liver masses with adjacent vascular and soft tissue structures.[36] The use of advanced

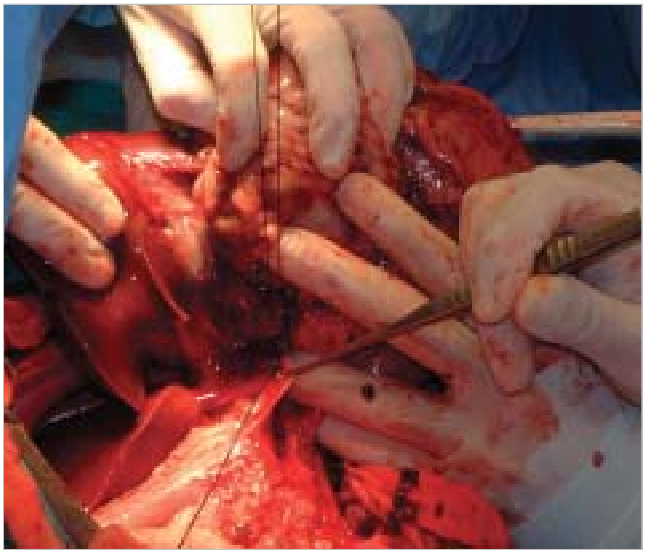

Figure 3. **Liver lobectomy of a massive hepatocellular carcinoma using mattress sutures.**

Figure 4. **Liver lobectomy of a massive hepatocellular carcinoma using a thoracoabdominal surgical stapling device.**

imaging in cats and dogs with hepatobiliary tumors has not been evaluated. Anecdotally, CT has tended to overestimate the frequency of disease in dogs with massive HCC and may inappropriately result in these tumors being deemed unresectable (Figures 1 and 2).

Imaging is also important for the staging of liver tumors in cats and dogs. Local extension and regional metastasis can be assessed with abdominal ultrasonography, CT, MRI, or laparoscopy. The sonographic appearance of nodular hyperplasia and metastatic disease is similar, and biopsy of such lesions is required before excluding animals from curative-intent surgery.[37] Although rare at the time of diagnosis, pulmonary metastases should be evaluated with three-view thoracic radiographs or advanced imaging techniques.

Other Diagnostic Tests

Serum tumor markers, particularly α-fetoprotein, are used for the diagnosis, treatment monitoring, and prognostication of HCC in humans.[36] In 75% of dogs with HCC, serum levels of α-fetoprotein are increased.[38,39] However, α-fetoprotein is also increased in other types of liver tumors, such as lymphoma and bile duct carcinoma, and nonneoplastic hepatic disease.[39,40]

HEPATOCELLULAR TUMORS

Hepatocellular tumors include HCC, hepatocellular adenoma, and hepatoblastoma.[4] Hepatocellular adenoma is usually an incidental finding and rarely causes clinical signs.[2] In cats, hepatocellular adenoma occurs more frequently than HCC, whereas HCC is more common than adenoma in dogs.[2,5,6] Hepatoblastoma is a rare tumor of primordial hepatic stem cells and has only been reported in one dog.[15] HCC is the most common primary liver tumor in dogs, accounting for 50% of cases, and second most common in cats.[2–8] There is a strong correlation between hepatitis viruses B and C, cirrhosis, and HCC in humans.[36] A viral etiology has also been demonstrated in woodchucks, but not in cats or dogs.[6–9] Cirrhosis is also rare in dogs with HCC.[6] In one study, 20% of dogs with HCC had additional tumors diagnosed, although most were benign and endocrine in origin.[5] A breed and sex predisposition has not been confirmed in dogs with HCC, although miniature schnauzers and male dogs are overrepresented in some studies.[5,9,11,30] Morphologically, 53% to 83% of HCCs are massive (Figure 2), 16% to 25% are nodular, and up to 19% are diffuse.[2,5] The left liver lobes, comprising the left lateral and medial lobes and papillary process of the caudate lobe, are involved in over two-thirds of dogs with massive HCC.[5,9–11] Metastasis to regional lymph nodes, peritoneum, and lungs is more common in dogs with nodular and diffuse HCC.[2,5,9] Other metastatic sites include the heart, kidneys, adrenal glands, pancreas, intestines, spleen, and urinary bladder.[2,5,9] The metastatic rate varies from 0% to 37% for dogs with massive HCC and 93% to 100% for dogs with nodular and diffuse HCC.[2,5–11]

Liver lobectomy is recommended for dogs with massive HCC. Surgical techniques for liver lobectomy include finger-fracture, mass ligation, mattress sutures (Figure 3), and surgical stapling (Figure 4).[41] The finger-fracture technique, involving blunt dissection through hepatic parenchyma and individual ligation of bile ducts and vessels, is acceptable for smaller lesions. Mass ligation is not recommended for large dogs or for dogs with tumors involving either the central or right liver divisions or tumors with a wide base.[41] Surgical staplers are preferred for liver lobectomy as operative time is shorter with fewer complications.[41] Advanced imaging and intraoperative ultrasonography may provide information on the relationship of right-sided and central liver tumors with the caudal vena cava before liver lobectomy. Complications following liver lobectomy include hemorrhage, vascular compromise to adjacent liver lobes, transient hypoglycemia, and reduced hepatic function.[4,41]

A study of 40 dogs with massive HCC found that left-sided tumors were common, surgical resection resulted in a median survival time greater than 1,460 days, and the only prognostic factor was tumor location.[11] The prognosis was poorer for right-sided liver tumors, involving either the right lateral lobe or caudate process of the caudate lobe because intraoperative death was more likely due to caudal vena cava trauma during surgical dissection.[11] Poor prognostic factors in human HCC include cirrhosis, tumor volume, number of tumors, vascular invasion, clinical stage, incomplete surgical resection, and increased serum concentration of tumor markers, such as α-fetoprotein.[36] In dogs with massive HCC, local tumor recurrence and metastatic disease are rare, and most deaths are unrelated to HCC.[10,11]

In contrast, the prognosis for dogs with nodular and diffuse HCC is poor. Surgical resection is usually not possible due to involvement of multiple liver lobes. Treatment options for nodular and diffuse HCC in humans include liver transplantation or minimally invasive procedures, such as ablation or embolization, for regional control.[36] Regional ablative techniques include percutaneous injection of ethanol or acetic acid, cryotherapy, microwave coagulation therapy, laser therapy, and radiofrequency ablation.[36] Transarterial chemoembolization is often used in humans with unresectable HCC.[36] Bland embolization and chemoembolization have recently been reported to have moderate success in the palliation of HCC in two dogs.[42] The role of radiation and chemotherapy in the management of HCC is unknown. Radiation therapy is unlikely to be effective because the canine liver cannot tolerate cumulative doses greater than 30 Gy.[4,36] In humans, HCC is considered chemoresistant, with response rates usually less than 20%.[4,36] The poor response to systemic chemotherapy is probably caused by rapid development of drug resistance, either due to the role of hepatocytes in detoxification or expression of P-glycoprotein, a cell-membrane efflux pump associated with multidrug resistance.[4] Chemotherapy has not been investigated in dogs with HCC. Novel treatment options currently being investigated in human medicine include immunotherapy, hormonal therapy with tamoxifen, and antiangiogenic agents.[36]

BILE DUCT TUMORS

There are two types of bile duct tumors in cats and dogs: bile duct adenoma and carcinoma.[2,5–8,12,13,16–20] Bile duct adenomas are common in cats, accounting for more than 50% of all feline hepatobiliary tumors. These are also termed biliary or hepatobiliary cystadenomas due to their frequent cystic appearance.[6–8,16–18] Male cats may be predisposed.[16,18] Bile duct adenomas usually do not cause clinical signs until they reach a large size and compress adjacent organs.[16–18] There is an even distribution between single and multiple lesions, and liver lobectomy is recommended for resectable cases.[6–8,16–18] Malignant transformation has been reported in humans, and anaplastic changes have been noted in some feline adenomas.[6,16] The prognosis is very good following surgical resection, with resolution of clinical signs and no reports of local recurrence or malignant transformation.[8,16,17]

The four categories of primary hepatic tumors in cats and dogs are hepatocellular, bile duct, mesenchymal, and neuroendocrine.

Figure 5. Intraoperative view of a nodular bile duct carcinoma. Complete resection of this tumor was not possible due to multiple liver lobe involvement.

Bile duct carcinoma is the most common malignant hepatobiliary tumor in cats and the second most common in dogs.[2,5–8] In humans, trematode infestation, cholelithiasis, and sclerosing cholangitis are known risk factors for bile duct carcinoma.[4] Trematodes may also be involved in the etiology of bile duct carcinoma in cats and dogs.[8,13] A predilection for Labrador retrievers has been proposed,[13] and a sex predisposition has been reported for female dogs.[5,12,30] In cats, however, this remains undetermined as both males and females are reported to be predisposed. The distribution of morphologic types of bile duct carcinoma is similar to HCC with 37% to 46% massive, up to 54% nodular (Figure 5), and 17% to 54% diffuse.[2,5,12,13] Bile duct carcinoma can be intrahepatic, extrahepatic, or within the gallbladder.[2,5–8,12,13] An equal distribution of intrahepatic and extrahepatic tumors or extrahepatic predominance has been reported in cats with bile duct carcinoma,[6–8] whereas intrahepatic carcinomas are more common in dogs.[5,12,13] In both species, bile duct carcinoma of the gallbladder is rare, accounting for less than 5% of cases.[2,5–8,12,13] Bile duct carcinomas have an aggressive biologic behavior. In cats, diffuse intraperitoneal metastasis and carcinomatosis occurs in 67% to 80% of cases.[6–8] Metastasis is also frequently reported in dogs, with up to 88% of tumors metastasizing to the regional lymph nodes and lungs.[2,5,12,13] Other metastatic sites include the heart, spleen, adrenal glands, pancreas, kidneys, and spinal cord.[12,13] Surgical resection is recommended for cats and dogs with massive bile duct carcinoma. However, survival time has been poor in cats and dogs treated with liver lobectomy as the majority have died within 6 months due to local recurrence and metastatic disease.[8,43] Bile duct carcinomas in cats and dogs are histologically classified as solid or cystic, but this is not prognostic and other prognostic factors have not been identified.[12] In humans with bile duct carcinoma, papillary histology, extrahepatic location, and complete resection are favorable prognostic factors.[44]

NEUROENDOCRINE TUMORS

Neuroendocrine tumors, also known as carcinoids, are rare primary tumors in cats and dogs.[2,5–8] These tumors arise from neuroectodermal cells and are histologically differentiated from carcinomas with the use of silver stains.[3,14] Neuroendocrine hepatobiliary tumors are usually intrahepatic, although extrahepatic tumors have been reported in the gallbladder.[14,19,20] Carcinoids tend to occur at a younger age than other primary hepatobiliary tumors.[5,14] Carcinoids have an aggressive biologic behavior and are usually not amenable to surgical resection because solitary and massive morphology is rare, with 33% of the tumors being nodular and 67% diffuse.[5,14] The efficacy of radiation therapy and chemotherapy is unknown. The prognosis is poor due to metastasis to the regional lymph nodes, peritoneum, and lungs that occurs in 93% of dogs, usually early in the course of disease.[5,14] Other metastatic sites include the heart, spleen, kidneys, adrenal glands, and pancreas.[14]

SARCOMAS

Primary and nonhematopoietic hepatic sarcomas are rare in cats and dogs.[2,5–8,21] The most common primary hepatic sarcomas are leiomyosarcoma, HSA, and fibrosarcoma.[2,5–8,21,45–47] The liver is a common site for metastatic HSA, but only 4% to 6% have a primary hepatic origin in dogs.[46,47] Other sarcomas include rhabdomyosarcoma, liposarcoma, osteosarcoma, and malignant mesenchymoma.[2–8] Benign mesenchymal tumors, such as hemangioma, are rare.[2–8] There are no known breed predispositions, although a male predilection has been reported.[5] Diffuse morphology has not been reported; massive and nodular types account for 36% and 64% of sarcomas, respectively.[5,21] Hepatic sarcomas have an aggressive biologic behavior. Metastatic disease to the spleen and lungs is reported in 86% to 100% of cases.[5,21] Liver lobectomy can be attempted for solitary and massive sarcomas. However, prognosis is poor because metastatic disease is often present at the time of surgery.[5,21] Chemotherapy has not been investigated in the treatment of primary hepatic sarcomas and, similar to other solid sarcomas, response rates are likely to be poor.[48]

OTHER PRIMARY HEPATIC TUMORS

Myelolipoma is a benign hepatobiliary tumor described in cats.[3,4] Histologically, they are composed of well-differentiated adipose tissue intermixed with normal hematopoietic elements.[4] Chronic hypoxia has been proposed as an etiologic factor because myelolipomas have been reported in liver lobes entrapped in diaphragmatic herniae.[4] Myelolipomas can either be single or multifocal. Surgical resection with liver lobectomy is recommended, and the prognosis is excellent with prolonged survival time and no reports of local recurrence.[4]

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ARTICLE #3 CE TEST

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1. The four basic categories of primary hepatobiliary tumors in cats and dogs are
- a. hepatocellular, bile duct, lymphoma, and neuroendocrine.
- b. hepatocellular, bile duct, neuroendocrine, and sarcoma.
- c. hepatocellular, lymphoma, neuroendocrine, and sarcoma.
- d. hepatocellular, bile duct, lymphoma, and mast cell tumor.

2. What are the three morphologic subtypes of liver tumors?
- a. massive, metastatic, and nodular
- b. massive, metastatic, and diffuse
- c. metastatic, nodular, and diffuse
- d. massive, nodular, and diffuse

3. Metastatic tumors are how many times more common than primary liver tumors in dogs?
- a. 2
- b. 2.5
- c. 3
- d. 4

4. The most common primary sites of tumors metastasizing to the liver in dogs are the
- a. spleen, pancreas, and gastrointestinal tract.
- b. spleen, pancreas, and prostate.
- c. spleen, gastrointestinal tract, and kidneys.
- d. spleen, kidneys, and prostate.

5. The liver enzymes most commonly increased in dogs with primary hepatic tumors are
- a. ALP and ALT.
- b. ALP and AST.
- c. ALT and AST.
- d. AST and bilirubin.

6. The preferred imaging technique for characterizing liver tumors in cats and dogs currently is
- a. abdominal radiography.
- b. abdominal ultrasonography.
- c. CT.
- d. MRI.

7. The most common hepatocellular tumor in dogs is
- a. hepatocellular adenoma.
- b. hepatoblastoma.
- c. hepatocellular carcinoma.
- d. bile duct carcinoma.

8. The recommended treatment option for massive hepatocellular carcinoma in dogs is
- a. surgical liver lobectomy.
- b. embolization.
- c. chemotherapy.
- d. radiation therapy.

9. What is the prognosis for long-term survival in dogs with appropriately treated massive hepatocellular carcinoma?
- a. poor
- b. guarded
- c. good
- d. dismal

10. The most common primary hepatobiliary tumor in cats is
- a. hepatocellular carcinoma.
- b. bile duct carcinoma.
- c. osteosarcoma.
- d. bile duct adenoma.

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ARTICLE #1
Surgical Hemostasis—*J. B. Erne, F. A. Mann*
1. d 2. c 3. b 4. d 5. a
6. b 7. d 8. c 9. d 10. d

ARTICLE #2
Transmission Times and Prevention of Tick-Borne Diseases in Dogs—*L. Kidd, E. B. Breitschwerdt*
1. b 2. d 3. d 4. a 5. d
6. b 7. c 8. c 9. d 10. a

ARTICLE #3
Canine Elbow Dysplasia: Anatomy and Pathogenesis—*C. T. Trostel, R. M. McLaughlin, R. R. Pool*
1. d 2. c 3. e 4. d 5. e
6. e 7. a 8. a 9. b 10. e

ARTICLE #4
Canine Elbow Dysplasia: Incidence, Diagnosis, Treatment, and Prognosis—*C. T. Trostel, R. M. McLaughlin, R. R. Pool*
1. d 2. c 3. e 4. b 5. e
6. e 7. d 8. d 9. e 10. b

ARTICLE #5
Frostbite in Birds: Pathophysiology and Treatment—*J. F. X. Wellehan*
1. b 2. c 3. a 4. c 5. d
6. b 7. a 8. c 9. d 10. b

ARTICLE #6
Polymethylmethacrylate Beads for Treating Orthopedic Infections—*A. I. Sayegh, R. M. Moore*
1. b 2. c 3. a 4. a 5. d
6. c 7. d 8. b 9. a 10. d