Massive hepatocellular carcinoma in dogs: 48 cases (1992–2002)

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Objective—To determine clinical signs, diagnostic findings, outcome, and prognostic factors in dogs treated surgically for massive hepatocellular carcinoma (HCC) and compare survival times of surgically and conservatively treated dogs.

Design—Retrospective study.

Animals—48 dogs.

Procedure—Medical records were examined for clinical signs, diagnostic and surgical findings, and postoperative outcome. Dogs were allocated into surgery and nonsurgery groups depending on whether curative-intent liver lobectomy was performed. Data from the surgical and nonsurgical groups were analyzed to identify prognostic factors and determine and compare rates of tumor control and survival time.

Results—42 dogs were treated surgically, and 6 were managed conservatively. In the surgery group, intraoperative mortality rate was 4.8% with no local recurrence, metastatic rate was 4.8%, and median survival time was > 1,460 days (range, 1 to 1,460 days). High alanine aminotransferase and aspartate aminotransferase activities were associated with poor prognosis. Median survival time for the nonsurgery group was 270 days (range, 0 to 415 days), which was significantly less than that of surgically treated dogs.

Conclusions and Clinical Relevance—Liver lobectomy is recommended for dogs with massive HCC because tumor-related mortality rate was 15.4 times higher in dogs in the nonsurgery group, compared with the surgery group. Tumor control was excellent after surgical resection with no local recurrence and a low metastatic rate. Prognostic factors were identified, but their clinical relevance was uncertain because only 9.5% of dogs in the surgery group died as a result of their disease. (*J Am Vet Med Assoc* 2004;225:1225–1230)

Primary liver tumors are uncommonly reported in dogs, comprising 0.6% to 1.3% of all canine neoplasms.[1] **Hepatocellular carcinoma (HCC)** is the most common, although other malignant liver tumors include bile duct carcinoma, carcinoids, and sarcomas.[2,3] Three gross morphologic subtypes of HCC have been described: massive, nodular, and diffuse.[1] Nodular and diffuse HCC, which account for 29% and 10% of all HCCs, respectively, involve multiple liver lobes and are usually not amenable to surgical resection.[1] In contrast, massive HCC, defined as a large tumor affecting a single liver lobe, represents 61% of all canine HCCs and is potentially resectable.[1,4] In humans, HCC is frequently associated with chronic liver diseases, such as cirrhosis and infection with hepatitis viruses B and C, and 5-year survival rates after surgery are < 50%.[5] However, similar associations have not been identified in dogs because hepatitis B virus has not been detected in dogs and cirrhosis has been diagnosed in only 7% of dogs with HCC.[1,6] Furthermore, the clinical outcome after liver lobectomy appears better in dogs, with a mean survival time > 300 days and no disease-related deaths.[4] The purpose of this retrospective study was to determine clinical signs, diagnostic findings, outcome, and prognostic factors in dogs treated surgically for massive HCC and compare survival times of surgically and conservatively treated dogs. We hypothesized that dogs with massive HCC would have a substantial survival benefit after liver lobectomy and that survival time would be prolonged with a low rate of local recurrence and distant metastasis.

Criteria for Selection of Cases

The medical and histopathology records at Colorado State University Veterinary Teaching Hospital were reviewed for dogs with liver tumors from January 1992 to June 2002. Dogs were included if massive HCC was confirmed by use of exploratory laparoscopic or open surgery and histopathologic confirmation. Criteria for exclusion included nodular and diffuse HCC, and non-HCC primary and metastatic liver tumors.

Procedures

The records of each dog were reviewed, and information was recorded on signalment, clinical signs at initial evaluation, physical examination findings, preoperative diagnostic tests, surgical findings, adjunctive treatment, and postoperative outcome. Body condition was recorded as underweight only when specifically stated in the records, and no interpretation was made between body weight and breed. Preoperative diagnostic tests included hematologic analysis, serum biochemical testing, postprandial bile acid assays, coagulation profile, blood typing, urinalysis, abdominal imaging with radiography, ultrasonography and **computed tomography (CT)**, cytologic examination of

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samples obtained via ultrasound-guided liver aspiration, and 3-view thoracic radiography.

Hematologic abnormalities were defined with anemia as PCV < 40%, microcytosis as **mean corpuscular volume (MCV)** < 62 fL, thrombocytosis as platelet count > 500 × 10^3 cells/µL, and leukocytosis as WBC count > 15 × 10^3 cells/µL. The upper reference limits for serum **alkaline phosphatase (ALP)**, **alanine aminotransferase (ALT)**, **aspartate aminotransferase (AST)**, and **γ-glutamyltransferase (GGT)** activities were defined as 141, 120, 40, and 6 U/L, respectively, whereas hypercholesterolemia was defined as cholesterol concentration > 300 mg/dL. The following ratios of liver enzymes were calculated: ALP:ALT, ALP:AST, ALP:GGT, ALT:AST, ALT:GGT, and AST:GGT. The number and combination of liver enzymes with high activities were recorded for each dog. Urinalysis abnormalities were also defined with hyposthenuria as urine specific gravity < 1.030, hematuria as > 5 RBCs/hpf or a positive reading on dipstick evaluation, and proteinuria as a positive reading on dipstick evaluation.

Surgical biopsy or liver lobectomy was performed in all dogs. The surgery report was reviewed for liver lobe involvement, size of the tumor, evidence of local extension and metastatic disease, resection technique, and intraoperative complications such as blood loss and death. The liver lobe affected by the tumor was recorded as either left, central, or right.[7] Left-sided tumors involved the left lateral lobe, left medial lobe, or papillary process of the caudate lobe. Central tumors originated in either the right medial or quadrate liver lobes. Right-sided tumors affected either the right lateral lobe or caudate process of the caudate lobe. Tumor size was determined from the surgery report. If only 2 dimensions were recorded, cubic size was estimated by multiplying these 2 dimensions by their mean value. Histologic specimens were reviewed by a single pathologist (BEP). The degree of differentiation was recorded as well, moderately, or poorly differentiated on the basis of mitotic rate, degree of nuclear pleomorphism, and resemblance to normal hepatocellular tissue. The surgical margins were not inked, but completeness of excision was evaluated by examining tissue specimens from the cut edge of the resected liver lobe.

Postoperative outcome was determined from case records and telephone contact with the referring veterinarian and owners. Survival time was calculated from the time of surgery (biopsy or excision) to death or termination of the study period. The cause of death was recorded as either related or unrelated to HCC and its treatment. For those dogs that survived the surgical procedure, death was designated as tumor-related if there was evidence of a hepatic mass or pulmonary metastases on physical examination or diagnostic imaging at the time of death or euthanasia.

Statistical analyses—Actuarial Kaplan-Meier survival analysis with log rank was used to compare survival after biopsy only (nonsurgery group) or surgical resection of massive HCC (surgery group). Cox proportional hazards regression analysis was used to calculate the hazard ratio and 95% confidence interval for surgery variables while adjusting for potential confounders and to determine whether the effect of surgery was dependent on the presence or absence of other risk factors. Likelihood ratio tests were used to determine whether these results were associated with survival, and confidence intervals were calculated to determine whether these variables were significant. Cox proportional hazards regression analysis was also used to identify prognostic factors for survival in the surgery and nonsurgery groups by use of signalment, clinical signs, diagnostic and surgical findings, and histopathology results. The Cox model assumes proportionality of effects across time. This assumption was automatically verified by use of the statistical package[a] used for analyses and by comparing parallelism in log cumulative hazard plots. χ^2 And Fisher exact tests were used to assess the relationship of thrombocytosis with anemia, leukocytosis, and tumor size; hematuria with anemia and coagulopathy; and proteinuria with hematuria, hypoproteinemia, and hypoalbuminemia. Computer software packages[a,b] were used to perform the statistical analyses. For all comparisons, a value of $P < 0.05$ was considered significant.

Results

Massive HCC was histologically confirmed in 48 dogs after either exploratory celiotomy or laparoscopy. Forty-two dogs were treated with partial or total liver lobectomy, and 6 dogs received incisional biopsy only. The median ages for dogs in the surgery and nonsurgery groups were 11 years (range, 6 to 17 years) and 12 years (range, 8 to 21 years), respectively, and these were not significantly ($P = 1.0$) different. Nineteen dogs were female and 23 were male in the surgery group, and in the nonsurgery group, there were 4 females and 2 males. There were no significant ($P = 0.42$) differences in sex distribution between groups. A variety of breeds were represented. In the surgery group, there were 5 each of Golden Retriever and mixed breed; 3 each of Australian Cattle Dog, Chow Chow, Miniature Schnauzer, Shar Pei, and Siberian Husky; 3 each of Keeshund and Labrador Retriever; and 1 each of Airedale, Alaskan Malamute, Australian Shepherd, Bassett Hound, Beagle, Border Collie, Bulldog, Chesapeake Bay Retriever, English Springer Spaniel, Hungarian Puli, Samoyed, Shih Tzu, and Spitz. The nonsurgery group included 2 mixed-breed dogs and 1 each of Golden Retriever, Labrador Retriever, Jack Russell Terrier, and Australian Terrier. The median body weight of dogs in the surgery group was 21.6 kg (47.5 lb; range, 6.8 to 40.5 kg [15 to 89 lb]), and the median body weight of dogs in the nonsurgery group was 29.1 kg (64 lb; range, 6.8 to 34.5 kg [15 to 76 lb]). There was no significant ($P = 0.97$) difference in the body weights of dogs in the surgery and nonsurgery groups.

Surgically treated dogs—Seventy-one percent of dogs in the surgery group had clinical signs of HCC. Of these 30 dogs, 14 (46.7%) had weight loss and 13 (43.3%) had inappetence and lethargy. Other clinical signs at initial evaluation included vomiting (n = 7), polyuria (9), polydipsia (6), and seizures (2). Median duration of clinical signs prior to evaluation was 68 days (range, 12 hours to 365 days).

An abdominal mass was palpable in 19 dogs during physical examination (45%). Signs of abdominal pain were detected in 7 dogs, and ascites was detected

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in 2 dogs. Body condition was specifically stated for 17 dogs, and 11 of these were considered underweight. Icterus was not detected in any dog. Other findings included cardiac murmur (n = 1), laryngeal paralysis (1), and other tumors (ulnar osteosarcoma [1], mammary adenoma [1], and perianal adenoma [1]).

Hematology was performed in 41 dogs, although platelet count and MCV were available in 39 dogs (**Table 1**). Anemia was detected in 22 (53.7%) dogs, and PCV ranged from 35% to 39% in 13 of these dogs. Thrombocytosis was diagnosed in 18 (46.2%) dogs, microcytosis in 12 (30.8%) dogs, and leukocytosis in 11 (26.8%) dogs.

Serum biochemical analyses were performed in 42 dogs, and total protein, albumin, ALP, and ALT were evaluated in all dogs (**Table 2**). Serum AST activity and cholesterol concentration were evaluated in 41 dogs, and GGT was evaluated in 39 dogs. Serum ALP activity was high in 40 (95.2%) dogs, ALT activity was high in 37 (88.1%) dogs, AST activity was high in 27 (65.9%) dogs, and GGT activity was high in 21 (53.8%) dogs. Activity of a single liver enzyme was high in 4 (9.5%) dogs, activities of 2 liver enzymes were high in 7 (16.7%) dogs, activities of 3 liver enzymes were high in 15 dogs (35.7%), and activities of all 4 liver enzymes were high in 16 (38.1%) dogs. The following combinations of liver enzymes with high activities were identified: ALP only (n = 3 dogs), ALT only (1), ALP-ALT (5), ALP-GGT (1), ALT-AST (1), ALP-ALT-AST (9), ALP-ALT-GGT (5), ALP-AST-GGT (1), and ALP-ALT-AST-GGT (16). The median ratio for ALP:ALT was 9.0, ALP:AST was 12.4, ALP:GGT was 86.0, ALT:AST was 4.8, ALT:GGT was 32.5, and AST:GGT was 8.6. Other abnormalities included hypercholesterolemia in 13 (31.0%) dogs, hypoproteinemia in 2 (4.8%) dogs, hypoalbuminemia in 3 (7.1%) dogs, and hypoglycemia in 2 dogs.

Other blood tests included prothrombin time (n = 28), activated partial thromboplastin time (29), blood typing (26), and serum bile acids (8). Coagulation profile was abnormal in 6 dogs, with prothrombin time prolonged in 3 dogs and activated partial thromboplastin time prolonged in 5 dogs. Postprandial bile acids concentration was high in all 8 dogs.

Urinalysis was performed in 19 dogs. Hyposthenuria was diagnosed in 16 dogs, macroscopic or microscopic hematuria in 16 dogs, and proteinuria in 12 dogs. Hematuria was not significantly associated with either anemia ($P = 0.61$) or prolonged coagulation profiles ($P = 1.00$). Proteinuria was not significantly ($P = 0.89$) associated with hematuria. *P* values for hypoproteinemia and hypoalbuminemia could not be calculated because neither was detected in dogs with proteinuria.

Table 1—Hematologic and coagulation test results in dogs treated with surgery or conservatively for massive hepatocellular carcinoma (HCC).

	Surgery					No surgery					
Parameter	No. of dogs	Mean	Median	Range	Abnormal (%)	No. of dogs	Mean	Median	Range	Abnormal (%)	*P* value
Leukocytes ($\times 10^3$ cells/µL)	41	12.1	10.4	5.9–41.0	26.8	6	11.0	11.7	7.2–13.8	0	1.00
PCV (%)	41	38.0	40.0	14–54	53.7	6	36.3	39.0	26–42	83.3	0.53
MCV (fl)	39	55.0	64.0	48–76	30.8	6	62.7	62.0	58–67	16.7	0.41
Platelets ($\times 10^3$ cells/µL)	39	403.5	485	51–1,426	46.2	6	507.5	709	218–949	50.0	0.63
PT (s)	28	4.8	9.1	7.5–12.3	10.7	5	9.1	9.0	8.4–10.3	20.0	1.00
APTT (s)	29	8.2	13.0	7.4–19.6	17.2	4	8.1	13.4	9.3–15.1	0	1.00

MCV = Mean corpuscular volume. PT = Prothrombin time. APTT = Activated partial thromboplastin time.

Table 2—Serum biochemical results and liver enzyme activity ratios for dogs with massive HCC.

	Surgery					No surgery					
Parameter	No. of dogs	Mean	Median	Range	Abnormal (%)	No. of dogs	Mean	Median	Range	Abnormal (%)	*P* value
Protein (g/dL)	42	6.4	6.8	3.5–8.1	4.8	6	6.6	6.4	5.8–8.0	0	1.00
Albumin (g/dL)	42	3.4	3.6	1.7–5.2	7.1	6	3.3	3.2	2.3–4.4	16.7	1.00
ALP (IU/L)	42	1,932.7	1,117.0	59–17,470	95.2	6	1,453.5	235.0	33–6,650	50.0	0.98
ALT (IU/L)	42	1,083.0	347.0	4–20,534	88.1	6	525.0	615.0	74–949	66.7	0.009*
AST (IU/L)	41	554.5	64.0	19–7,898	65.9	6	114.3	124.0	43–147	100	0.028*
GGT (IU/L)	39	14.6	9.0	0–152	53.8	5	95.8	11.0	9–424	100	0.86
ALP:ALT	42	7.9	9.0	0.1–88.8	NA	6	1.9	1.1	0.1–7.4	NA	0.25
ALP:AST	40	26.7	12.4	0.1–124.9	NA	6	12.3	5.5	0.2–54.5	NA	0.028*
ALP:GGT	38	256.5	86.0	17.1–4,023	NA	5	20.6	15.7	6.7–47.5	NA	0.48
ALT:AST	40	5.0	4.8	0.02–18.4	NA	6	5.4	7.0	0.6–12.5	NA	0.028*
ALT:GGT	38	96.0	32.5	0.6–1,173	31.0	5	20.9	8.8	2.1–59.7	NA	0.57
AST:GGT	38	37.2	8.6	0.3–570.2	100	5	65.8	4.8	0.3–12.7	NA	0.73
Cholesterol (mg/dL)	42	265.5	276.0	88–500	NA	6	310.5	295.0	118–625	33.3	1.00
Bile acids (mg/dL)	8	11.4	27.8	17.1–63.5	NA	2	44.1	59.1	29.0–59.1	100	NA

*Significant ($P < 0.05$) difference between groups.
ALP = Alkaline phosphatase. ALT = Alanine aminotransferase. AST = Aspartate aminotransferase. GGT = γ-glutamyltransferase. NA = Not assessed.

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Abdominal radiographs were taken in 9 dogs, an abdominal ultrasound was performed in 31 dogs, and 3-view thoracic radiographs were obtained in 34 dogs. Pulmonary metastasis was not detected in any dog. A cranial abdominal mass, displacing the stomach caudally and laterally, was identified in all 9 dogs that were radiographed. A hepatic mass was detected in 29 (93.5%) dogs during abdominal ultrasonography. An ultrasound-guided aspirate of the hepatic mass was performed in 17 of these dogs and was consistent with either HCC or carcinoma in 12 dogs. Abdominal CT imaging was performed in 1 dog and subjectively overestimated the volume of disease because tumor size was known from open abdominal surgery performed 30 days previously in that dog.

A single large liver tumor was detected during exploratory celiotomy in all 42 dogs (**Figure 1**). The side of liver involvement was recorded in 41 dogs; the left liver lobe was affected in 28 (68.3%) dogs, the central liver lobe was affected in 8 (19.5%) dogs, and the right liver lobe was affected in 5 (12.2%) dogs. One dog had a torsion in the neoplastic left lateral liver lobe. The median volume of the liver tumors was 1,320 cm^3. Two dogs exsanguinated intraoperatively as a result of trauma to the caudal vena cava during attempted resection of a right-sided liver tumor. Liver lobectomy was performed in the remaining 40 dogs with either suture material (n = 9) or a thoracoabdominal stapling device (31). Intraoperative complications were reported in 12 (28.6%) dogs, including major hemorrhage (n = 3), moderate hemorrhage (1), mild hemorrhage (6), and resection of the left lateral liver lobe because of vascular compromise following left medial liver lobectomy (2).

Histopathologic features of the liver tumors were consistent with HCC in all 42 dogs. The degree of differentiation of HCC was recorded in 37 dogs, with well-differentiated HCC in 29 dogs, moderately differentiated HCC in 7 dogs, and poorly differentiated HCC in 1 dog. Surgical margins were assessed in all dogs, and incomplete resection was detected in 4 dogs.

In the surgery group, the **median survival time (MST)** was not reached and was > 1,460 days (range, 1 to 1,460 days; mean, 409 days). In comparison, the MST for dogs in the nonsurgery group was 270 days (range, 0 to 415 days; mean, 162 days). Dogs in the surgery group had significantly ($P < 0.001$) longer MST than dogs in the nonsurgery group with a hazard ratio of 15.4 (95% confidence interval, 3.25 to 72.3). In the surgery group, 18 dogs were still alive at the conclusion of the study period (range, 62 to 1,015 days) and 24 dogs had died (range, 1 to 1,460 days; **Figure 2**). Follow-up information for these dogs was based on physical examination (n = 42), hematologic and serum biochemical results (37), ultrasonography (18), thoracic radiographs (16), and either laparoscopy or exploratory celiotomy (4). These tests were performed during the period between surgery and telephone interviews with the owner and referring veterinarian but were not necessarily performed at either consistent time intervals or, if the dog had died, at the time of euthanasia. Of the 5 dogs in which postoperative blood tests were not performed, 3 dogs died during the perioperative period (2 dogs died from exsanguination intraoperatively, and 1 dog died 2 days postoperatively) and 1 dog was lost to follow-up. Of the 12 dogs in which postoperative imaging was not performed, 5 dogs died during the perioperative period (2 dogs died from exsanguination intraoperatively, and 3 dogs died within 5 days of surgery) and 1 dog died 22 days postoperatively. Four deaths were tumor related, including 2 intraoperative deaths (4.8%) and 1 case each of regional (hepatic) and distant (lungs) metastasis (4.8%). All 6 dogs in the nonsurgery group had died, 5 because of progressive tumor growth.

In the surgery group, factors significantly associated with poor prognosis included high serum activity of ALT

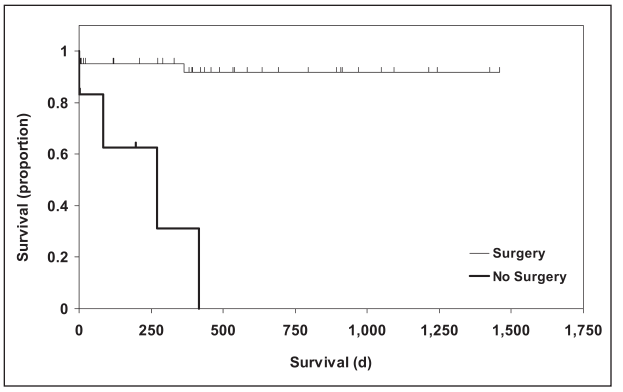

Figure 2—Kaplan-Meier survival curve for dogs with massive HCC treated surgically (via liver lobectomy) or nonsurgically.

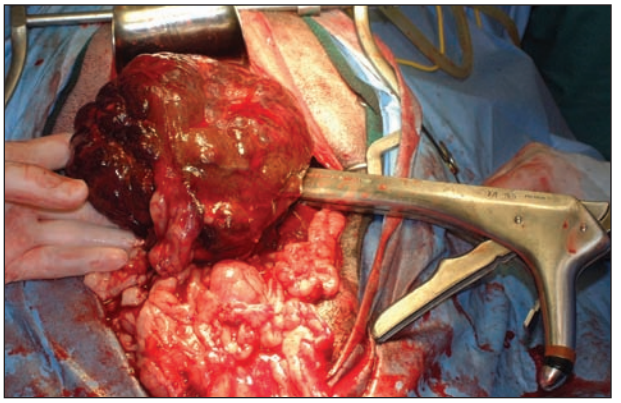

Figure 1—Photograph of the intraoperative appearance of a massive hepatocellular carcinoma (HCC) in a dog.

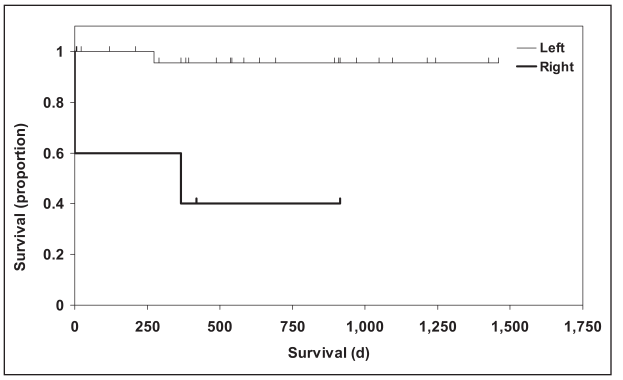

Figure 3—Kaplan-Meier survival curve for the side of liver tumor involvement (right vs left) in dogs treated with liver lobectomy for massive HCC.

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($P = 0.01$) and AST ($P = 0.03$), increased ALP:AST ($P = 0.03$) and ALT:AST ($P = 0.03$) ratios, and right-sided liver tumors ($P = 0.003$). There was no significant association between survival and either tumor size ($P = 0.08$) or completeness of surgical resection ($P = 0.11$). The influence of the degree of histologic differentiation on survival could not be calculated because all dogs with well and poorly differentiated tumors were censored from analysis because none had disease-related events. The MST for dogs with massive HCC involving the left liver lobes was > 1,460 days (range, 6 to 1,460 days), > 795 days for central liver lobes (range, 2 to 795 days), and 365 days for right-sided liver lobes (range, 1 to 913 days). Liver lobectomy for left-sided massive HCC was associated with significantly better MST than right-sided HCC (**Figure 3**). However, when the 2 intraoperative deaths were excluded from analysis and only dogs that survived surgery were compared, there was no significant ($P = 0.181$) difference between left- and right-sided tumors with an adjusted MST of > 913 days for right-sided HCC.

Discussion

The results of this retrospective study supported our hypothesis that dogs with massive HCC are amenable to surgical resection with prolonged survival times and low rates of local recurrence and distant metastasis. Local recurrence was not reported despite histologic evidence of incomplete resection in 4 dogs. In a previous study,[4] local recurrence was detected in 1 of 18 dogs after liver lobectomy. Patnaik et al[1] reported a rate of 36.6% for distant metastasis in dogs with massive HCC; however, the metastatic rate in our study was only 4.8% (1 dog each with liver or pulmonary metastasis). The low reported rate of local recurrence and distant metastasis may provide a true indication of the biological behavior of massive HCC in dogs; however, because our retrospective study was limited by inconsistent follow-up evaluations, we cannot exclude the possibility that these tumors have a more aggressive, albeit slowly progressive, course of disease. Conversely, regional metastasis was presumptively diagnosed in 1 dog on the basis of ultrasonographic findings but was not confirmed cytologically. This may have been misdiagnosed because 2 other dogs in our study had ultrasonographic evidence of multiple hepatic lesions that were subsequently diagnosed as nodular hyperplasia via histologic assessment of laparoscopic biopsy specimens. Furthermore, the diagnosis of pulmonary metastasis in 1 dog was based on thoracic radiographs and not confirmed by either necropsy or histopathology.

Anemia was a common hematologic abnormality in the dogs reported here. Anemia was nonregenerative, and in > 60% of dogs, the severity of anemia was considered mild with PCV from 35% to 39%. In contrast to previous studies,[1,4] leukocytosis was infrequently diagnosed. Thrombocytosis was detected in almost 50% of dogs and has not previously been reported in canine HCC.[1,4] Thrombocytosis is associated with a variety of human malignancies, including carcinomas of the lung, stomach, colon, and female reproductive system, but not HCC.[8-12] The causative factors involved in tumor-related thrombocytosis are poorly understood, although anemia, inflammatory cytokines, and chronic iron deficiency are implicated.[13,14] In the present study, a significant association between thrombocytosis and anemia, inflammation, or tumor size was not found. The possibility that thrombocytosis may represent a paraneoplastic syndrome in dogs with massive HCC is presently being investigated.

Serum activities of liver enzymes are typically high in dogs with massive HCC. In accordance with previous studies, activities of ALP and ALT were most frequently increased, although activities of more than 1 liver enzyme were high in 90% of dogs.[1,4] High serum activities of ALT and AST were identified as indicators of poor prognosis in dogs with massive HCC. Alanine aminotransferase is a liver-specific cytosolic enzyme, whereas AST is nonspecific and has both cytosolic and mitochondrial liver isoenzymes.[15] Increases in AST parallel increases in ALT, and both are associated with leakage as a result of altered membrane permeability. The degree of change in AST and ALT is proportional to the extent of hepatocellular injury.[15] In dogs with massive HCC, high activities may be caused by aggressive biological behavior, such as fast growth rate or large tumor size. Interestingly, postprandial serum bile acids concentrations were increased in all 8 dogs tested, and this may be indicative of hepatic dysfunction. Potential causes of hepatic dysfunction in these dogs include reactive changes in the remaining liver parenchyma secondary to the tumor, compression of the biliary tree by massive HCC, or the release of cytokines from neoplastic cells affecting bile acid metabolism. However, none of these causes could be validated because grossly normal liver was not biopsied and postoperative serum bile acids concentrations were not evaluated to ascertain whether these abnormalities resolved after hepatic lobectomy. Other serum biochemical abnormalities commonly associated with hepatic disease, such as hypoalbuminemia, hypocholesterolemia, and coagulopathy, were infrequently diagnosed in dogs with massive HCC.

A hepatic mass was detected in most of the dogs evaluated via ultrasonography. The ultrasonographic appearance of massive HCC was not uniform, ranging from hypoechoic to hyperechoic, but was not isoechoic with adjacent normal hepatic parenchyma. In humans, the echogenicity of HCC changes from hypoechoic when the tumor is small to hyperechoic when the tumor is large.[22] In contrast to radiography, ultrasonography provided further information on the size of the hepatic mass and side of liver involvement. However, because of the large size of these masses, it was often difficult to differentiate impingement and invasion of adjacent anatomic structures and determine the proximity of vital vascular structures, such as the caudal vena cava. Advanced imaging modalities, such as CT and magnetic resonance imaging, are routinely used in humans for the detection of hepatic masses because they are more sensitive for tumors > 2 cm in diameter and provide better information on the relationship of the hepatic mass with other anatomic structures.[16,17]

On the basis of results of the present study, a large intra-abdominal mass, with or without a definitive diagnosis, warrants exploratory surgery for further staging and determination of resectability. Left-sided liver lobes

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were involved in 68.3% of dogs, with central and right-sided liver lobes less frequently affected. The predilection of massive HCC for left liver lobes has been reported.[1,4] Lesions in other liver lobes were not detected, which contrasts with a pathologic study in which secondary lesions were diagnosed in 80% of dogs with massive HCC.[1] Curative-intent liver lobectomy was attempted in all dogs in the surgery group and performed with either suture material or stapling equipment.

The surgical complication rate was 28.6% with an operative mortality rate of 4.8%. Complications included marked hemorrhage as a result of caudal vena cava trauma in 3 dogs during dissection of right-sided liver tumors, mild to moderate hemorrhage after liver lobectomy in 7 dogs, and vascular compromise to the left lateral liver lobe after left medial liver lobectomy in 2 dogs. Two of the 3 dogs with iatrogenic caval trauma died from exsanguination. Except for major hemorrhage, all complications were easily managed without compromising intraoperative or postoperative performance.

The MST for dogs in the surgery group was not reached and was > 1,460 days. In contrast, the MST for dogs in the nonsurgery group was 270 days, which was significantly less than that of dogs treated by liver lobectomy. Furthermore, disease-related deaths were 15.4 times more frequent in dogs managed conservatively, compared with dogs managed surgically.

In our study, factors associated with a poor prognosis included high ALT and AST serum activities and tumor location. Dogs with left-sided tumors lived significantly longer than dogs with right-sided tumors. The high intraoperative mortality rate associated with resection of right-sided liver tumors (40%) is the most likely explanation for these findings because there were no significant differences in survival time when intraoperative deaths were excluded from analysis. The use of advanced imaging modalities to delineate the relationship between the liver mass and caudal vena cava warrants further investigation, especially if a right-sided liver tumor is suspected on the basis of radiographic or ultrasonographic examination because the caudal vena cava is intimately associated with the right liver and, particularly, caudate liver lobe.[18] Factors associated with a poor prognosis in humans with HCC include male sex, hypoalbuminemia, high serum activity of AST, large tumor size, multiple tumors, vascular invasion, satellite lesions, and poorly differentiated tumors.[19-21] In the present study, multiple tumors were not identified and the presence and degree of vascular invasion were not assessed. Furthermore, there were no associations between survival and other variables, such as sex, serum albumin concentration, tumor size, completeness of surgical resection, or the degree of tumor differentiation.

The present study had a number of limitations. Because it was a retrospective study, treatment and follow-up protocols were not standardized. However, dogs with massive HCC in the surgery group received a standard treatment (ie, liver lobectomy), and postoperative management was not targeted for antineoplastic effects. Follow-up recommendations included serum biochemical analyses, 3-view thoracic radiographs, and abdominal ultrasound examination every 3 months for the first 12 months and then every 6 months thereafter. However, these tests were not performed at consistent time intervals and not necessarily at the time of euthanasia or death. As a result, the incidence of tumor recurrence and metastasis may have been underestimated. If the biological behavior of massive HCC was actually more aggressive than suggested by the results of the present study, survival time would not be as impressive and the ability to detect a significant effect of tumor characteristics, such as tumor size, degree of differentiation, and completeness of surgical resection, on survival may have been improved.

[a]Statview, SAS Institute Inc, Cary, NC.
[b]Solo Power Analysis, BMDP Statistical Software, Los Angeles, Calif.

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