Liver tumors: diagnosis and treatment

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Introduction

Primary liver neoplasms are infrequent in the dog and cat, with an estimated prevalence in necropsy studies of 0.6-2.6% in canines and 1.5-2.3% in felines. In the dog liver metastases are much more frequent than primary hepatic tumors, and affect 30.6-36.8% of all animals with non-hepatic neoplasms, the spleen, pancreas and gastro-intestinal tract being the most common primary tumor locations implicated in such metastases. In cats it is estimated that 20% of all liver tumors are metastases of primary malignancies located in the pancreas, gastrointestinal tract or kidneys (1,2,3,4,5).

Primary liver neoplasms are usually classified according to their cellular origin and macroscopic appearance. With respect to their cellular origin, these tumors may be hepatobiliary, hematopoietic, sarcomas, or metastases of other tumors *(Table 1)*. In relation to their morphological presentation, they can be classified as lobular, multiple nodular or diffuse *(Table 2)*. The combination of histopatho-logical and morphological classification has consequences for the prognosis and treatment strategy in these animals; a clinician must therefore always address these factors in order to take correct management decisions. In dogs, malignant tumors are more common than benign lesions. In cats, biliary neoplasms are the most common presentation, particularly intrahepatic forms (6,7).

▶ KEY POINTS

➜ Primary hepatobiliary neoplasms are rare in the dog and cat, and tend to affect older animals which present with non-specific or gastrointestinal clinical signs.

➜ The clinico-morphological presentation of the disease, its cellular origin and its nature (benign or malignant) usually determine the therapeutic options and prognosis.

➜ The clinical approach to such cases involves multiple laboratory tests including urine and coagulation analysis, survey radiographs and abdominal ultrasound, as well as liver cytology or biopsy.

➜ Surgery only offers a good prognosis in the case of lobar presentations or benign neoplasms. Chemotherapy is usually ineffective for primary liver tumors.

➜ Most animals with malignant lesions tend to have metastases or diffuse disease presentations at the time of diagnosis, with a correspondingly poor prognosis.

Table 1.

Classification of liver neoplasms according to cellular origin.

Primary	• **Hepatobiliary neoplasm:** - Hepatocellular carcinoma - Biliary carcinoma (cholangiocarcinoma, biliary adenocarcinoma) - Hepatocellular adenoma (hepatoma) - Biliary duct adenoma (cystoadenoma) - Carcinoid tumor (neuroectodermal neoplasm) • **Hematopoietic neoplasm:** - Lymphoma - Leukemia • **Sarcomas:** - Hemangiosarcoma - Sarcoma - Leiomyosarcoma - Rhabdomyosarcoma - Osteosarcoma - Chondrosarcoma
Metastatic	• **Gastrointestinal tract** • **Spleen** • **Pancreas** • **Kidneys** • **Mammary tissue** • **Prostate**

◉ Clinical presentation and clinical signs

Most animals with liver neoplasia present with non-specific clinical signs such as anorexia and weight loss; it is estimated that these may be noted in 75% of canine and 50% of feline cases. Less frequent signs may include vomiting or diarrhea, although in cats vomiting can be common. Approximately 50% of the animals may present as polydipsic/polyuric, whilst others may show pale mucosal membranes or acute weakness due to anemia and hypovolemic shock secondary to tumor rupture. However, up to 25% of all animals show no clinical signs, and evidence of the presence of a liver tumor is only established upon identifying an increase in liver enzymes (7,8).

The most common findings on physical examination are a mass in the cephalad portion of the abdomen and abdominal bloating (30% of cases) or jaundice (18% of cases). In cases of metastasis, jaundice is very infrequent. Other less commonly described manifestations are neurological signs due to hepatic encephalopathy, or paraneoplastic syndromes such as hypoglycemia or skin alterations. There have been reports of myasthenia gravis associated with biliary carcinoma (7).

◉ Clinical approach and staging

The clinical approach to an animal with a suspected liver neoplasm should include basic information such as a complete blood count, blood biochemistry, coagulation tests, urinalysis, thoracic and abdominal radiographs, abdominal ultrasound *(Figures 1)*, and fine-needle aspiration biopsy of the liver where possible.

Laboratory test findings

Table 3 shows the most frequent hematological and biochemical alterations in animals with liver neoplasms. Leukocytosis associated with liver neoplasia is a result of inflammation and necrosis of large tumors. Anemia tends to be moderate and non-regenerative, and is thought to be due to chronic illness, inflammation or iron deficiency. Thrombocytosis can be seen in 50% of animals with hepatocellular carcinoma, and is attributable

Table 2.

Definition and percentage incidence of the morphological presentation of different liver tumors in the dog.

Morphological presentation	Definition	Incidence in hepatocellular carcinoma	Incidence in biliary carcinoma	Incidence in sarcoma	Incidence in carcinoid tumor
Lobular or massive	Nodule or large mass in a single liver lobe	53-84%	37-46%	36%	0%
Multiple nodular	Several nodules throughout the liver parenchyma, or several affected liver lobes	16-25%	0-21%	64%	33%
Diffuse or infiltrating	Multiple coalescent nodules in all the lobes, or diffuse disappearance of the liver parenchyma	0-19%	17-54%	67%	0%

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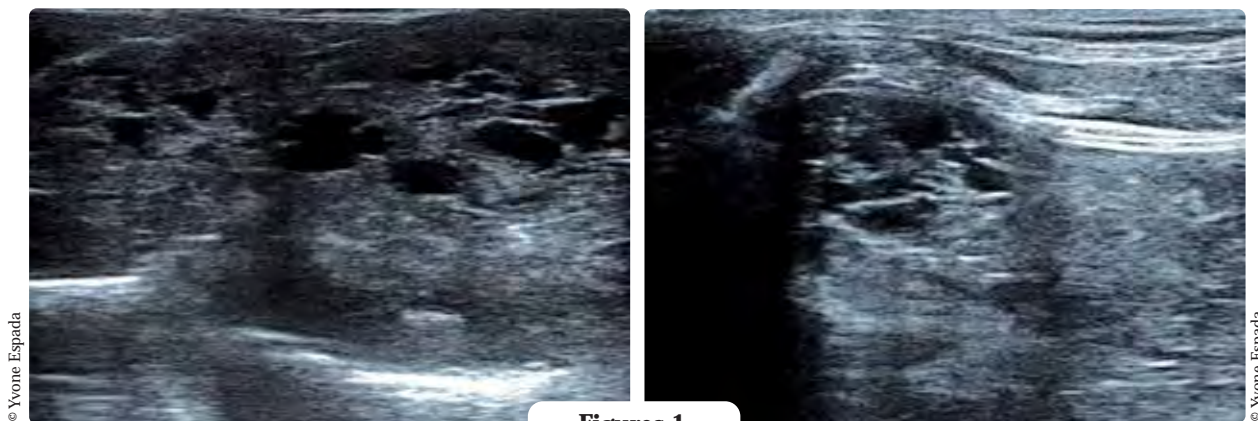
Figures 1.

Ultrasound appearance of biliary adenoma in two cats.

to a paraneoplastic syndrome characterized by thrombopoietin production, iron deficiency or anemia.

Liver enzyme elevation is a frequent, but not universal, finding in animals with liver neoplasms, and the degree of enzyme elevation does not correlate with the degree of liver involvement or the severity of the disease. According to one study (9), animals with primary liver tumors tend to show a more marked increase in ALT and ALP than animals with metastasis, while the latter tend to show a greater increase in bilirubin and AST. It also has been suggested that an AST/ALT ratio of < 1 is more compatible with carcinoma, while a ratio of > 1 is more indicative of sarcoma or carcinoid tumor. Other reported biochemical changes include hypoglycemia, hypo- or hyper-albumine-mia and increased bile acids. Hypoglycemia as a paraneoplastic syndrome associated with hepato-cellular carcinoma is attributed to the secretion of insulin-like growth factor II (IGF-II). Unlike dogs, cats usually present with a high incidence of nitrogenated compound elevation (9,10).

Coagulation factor changes are more commonly associated with hemangiosarcoma, although in end-stage liver neoplasia or in decompensated animals it is possible to observe coagulation factor deficiency or disseminated intravascular coagulation. Consequently a coagulation study is recommended before deciding on any invasive procedure in these animals (8).

Alpha-fetoprotein has been evaluated in the dog, and is seen to be increased in 75% of animals with hepatocellular carcinoma and in 55% of those with biliary carcinomas. However, the use of this tumor marker is limited by the fact that it is also increased in cases of hepatic lymphoma and other liver neoplasms/diseases, and only very significant increases in alpha-fetoprotein may be taken to indicate hepatocellular carcinoma.

Radiography

Abdominal radiographies may reveal the presence of a mass in the cephalad abdominal space, although this depends on the size of the neoplasm or metastases. Other reported findings are dorsal displacement of the stomach, hepatomegaly, loss of abdominal contrast (due to the presence of free fluid) and, occasionally, biliary tract calcification. Thoracic radiography can be useful and should be

Table 3.

Hematological and biochemical changes observed in dogs and cats with liver neoplasms.

Parameter	Change	Incidence in dog	Incidence in cat
Hematocrit	decrease	27-50%	?
Leukocytes	increase	54-73%	?
Platelets	increase	50% (in hepato-cellular carcinoma)	?
ALP	increase	61-100%	10-64%
ALT	increase	44-75%	10-78%
GGT	increase	39%	78%
Total bilirubin	increase	18-33%	33-78%
Bile acids	increase	50-75%	67%
Albumin	decrease	52-83%	?
Albumin	increase	occasionally	?
Glucose	decrease	occasionally	?

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Figure 2a.

Ultrasound view of a 10-year-old mixed-breed dog with a large hyperechogenic mass in the liver.

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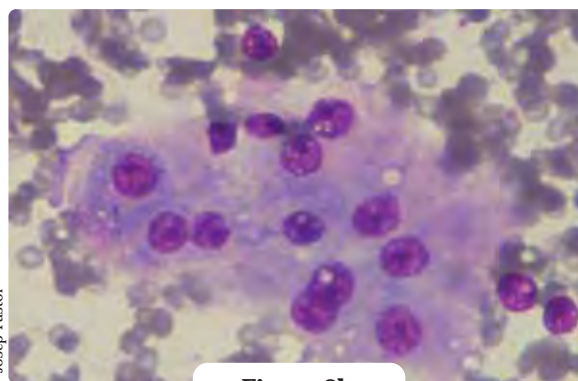
Figure 2b.

Ultrasound-guided cytology revealed abundant normal-appearing liver cells suggestive of nodular hyperplasia.

included as part of the staging procedure of animals with a view to evidencing metastatic disease (11).

Abdominal ultrasound

Ultrasound examination in veterinary practice commonly demonstrates changes within an animal's liver which may take a variety of forms. Most liver ultrasound changes are not pathognomic of a given disease process, and the final diagnosis is established on the basis of the clinical and blood test findings, and the cytological or histopathological results *(Figure 2)*. The basic ultrasound patterns are described in *Table 4*. Ultrasound is also very useful for evaluating the rest of the abdomen in animals with suspected liver neoplasia, particularly for tumors of the liver parenchyma and lymph nodes, and for the staging of such tumors (11-15).

Table 4.

Basic ultrasound patterns in liver neoplasia.

Diffuse or multifocal	• Diffuse or multifocal liver neoplasms tend to present with hepatomegaly, but this depends on the degree of infiltration. Liver carcinomas can be diffuse or affect multiple lobes, with variable ultrasound characteristics depending on the presence of necrosis, inflammation, hemorrhage or cavitation. In these malignant tumors it is common to observe a mixed echogenicity pattern. Lymphoma can affect the liver without detectable ultrasound changes, or cause diffuse hypoechogenicity, hyperechogenicity or mixed echogenicity with or without hypoechoic nodules. Consequently, if lymphoma is suspected, even if the liver ultrasound findings appear normal, fine-needle aspiration cytology is recommended. Histiocytic neoplasms are more often associated with multiple nodules and hypoechoic masses, though diffuse liver hypoechogenicity has also been described. Mast cell infiltration of the liver tends to produce diffuse hyperechogenicity.
Nodular patterns	• Benign nodular hyperplasia is common, particularly in dogs, and accounts for many of the focal liver lesions identified on ultrasound exploration. It been estimated that 25-36% of all nodular masses detected in the liver are nodular hyperplasias. • Benign liver adenomas or hepatomas can manifest as a focal mass of variable size and of normally hyperechoic characteristics. • Primary liver neoplasms such as hepatocellular carcinoma can present as focal or multifocal masses, though less often so than in the case of metastases. Focal hypoechoic lesions with a hyperechoic center or core (known as target or bull's-eye lesions) are usually associated with metastases, though some benign processes such as nodular hyperplasia can generate similar patterns.
Biliary obstruction	• Ultrasound has become an important tool for evaluating biliary obstruction in icteric dogs and cats. Primary tumors of the liver, biliary tract, duodenum or pancreas have been shown to be capable of causing biliary obstruction.

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Figure 3.

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Macroscopic appearance of diffuse hepatocellular carcinoma during exploratory laparotomy in a dog.

Figure 4.

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Macroscopic appearance of intrahepatic biliary carcinoma during exploratory laparotomy in a dog.

Liver cytology and biopsy

Liver cytology is useful for the initial evaluation of hepatomegaly and normally allows differentiation between primary tumors, metastatic disease and focal infection. However, cytology is unable to distinguish between benign focal inflammatory disease and progressive chronic disease, and cannot establish the extent of a lesion. Likewise, a definitive diagnosis of regenerative nodular hyperplasia cannot be established, and the technique is unable to differentiate a benign inflammatory reaction from the cell changes associated with other pathologies that cause liver damage.

Contraindications to ultrasound-guided cytology include the following:

• Coagulation abnormalities: if one or more coagulation test parameters are altered, it is advisable to administer vitamin K1 via the subcutaneous route 12 hours before cytology.
• Cavitary masses: the ultrasound detection of a large cavitary lesion in an elderly dog usually contraindicates cytology, particularly in male German shepherds or golden retrievers, due to the high probability that such lesions correspond to hemangiosarcoma.

One of the inconveniences of liver cytology is that it cannot correctly distinguish between liver adenoma and a regenerative nodule, and histological differentiation is moreover often problematic. For example, some hepatocellular carcinomas may be composed of apparently normal hepatocytes, while others present obvious features of malignancy. As a result, in many cases it proves necessary to resort to ultrasound-guided biopsy, laparoscopy or exploratory laparotomy. However, cytology can determine the presence of lymphoma, mastocytoma or histiocytic sarcoma, and contribute to the initial classification of the cellular type of the neoplasm *(Table 1)*. While the concordance between the cytological and histopathological findings is generally good the reported rate varies from 14-86% (12-15).

◎ Treatment and prognosis

The treatment to be provided and the prognosis of the animals with primary liver neoplasms depend on the cellular origin of the tumor, its benign or malignant nature, and the morphological presentation. The clinician should decide if surgery or palliative care is the treatment of choice for individual patients. Palliative treatment is the option for animals that are not surgical candidates and consists of pain management and general liver failure treatment recommendations. The success of newer options such as metronomic therapy or the use of antiangiogenics or tyrosin kinase inhibitors in the treatment of these patients is as yet unproven.

Hepatocellular carcinomas

No clear breed predisposition is observed with canine liver neoplasms, although poodles, fox terriers and Labrador retrievers may have a greater incidence of hepatocellular carcinoma *(Figure 3)*. The macroscopic presentation is clinically very important, since 100% of the diffuse forms show metastasis at the time of diagnosis, *versus* 40% of the isolated presentations. Metastatic spread

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Figure 5.

Multiple liver nodules in a dog with splenic hemangiosarcoma. Biopsy confirmed their metastatic nature.

usually affects the regional lymph nodes, lungs and peritoneum. The treatment of choice is surgical resection where possible; however surgical complications are reported in over 28% of cases, with a mortality rate of almost 12%. The right and caudad lobes of the liver pose the greatest surgical challenge, due to the proximity of the caudal vena cava. If the neoplasm is lobular and without metastases, the prognosis is good. However, this is rare, since most animals have metastases at the time of diagnosis; early diagnosis of this tumor would be ideal, but the nonspecific clinical presentation makes this difficult. Without surgery, the average life expectancy is 270 days and prognosis is generally poor. No effective chemotherapy options have been described, though mitoxantrone has been reported to be helpful in some cases. The most common situation is a lack of treatment response due to p-glycoprotein expression in the liver cells. In cats, hepatocellular carcinoma is less frequent, and less data is available (16-19).

Hepatocellular adenomas
These tumors are also known as hepatomas and are more common in cats than in dogs. In the latter it is sometimes very difficult to distinguish adenoma from reactive nodular hyperplasia, and biopsy is needed to clarify the diagnosis. The prognosis is usually good, but it is advisable to resect the lesions if they cause problems; they can grow very large and spontaneous rupture is frequent.

Bile duct carcinoma/adenocarcinoma/ cholangiocarcinoma
These are the most common liver malignancies in cats, and the second most common liver malignancy

in dogs *(Figure 4)*. Tumor behavior is very aggressive in both species, and metastases are present at the time of diagnosis in 60-88% of cases. Biliary carcinomas usually metastasize to the regional lymph nodes, lungs and peritoneum, but also to the kidneys, heart, adrenal glands, eye or bone. These tumors are usually classified as either intrahepatic or extra-hepatic bile duct lesions – intrahepatic tumors being more common in dogs, and extra-hepatic neoplasms in cats. Three morphological forms or presentations have been described (lobular, multifocal and diffuse); in general, only the lobular form should be subjected to surgical removal, and only if there is no evidence of metastasis. In the other presentations the prognosis is very poor, and surgery is usually not feasible. Even if removal is possible, the prognosis remains poor, since most animals die within 6 months of surgery. No effective chemotherapeutic options have been described in application to these malignancies (20).

Bile duct adenomas
Also known as biliary cystoadenomas, biliary adenomas or cholangiocellular adenomas, these tumors are infrequent in the dog, but are the most common lesions in cats, where males appear to be more frequently affected than females. In cats, 50% of these lesions are isolated or lobular, and 50% are multifocal. The prognosis is usually good, since these lesions constitute incidental findings, but they tend to grow until their associated mass effect or compressive action upon other organs gives rise to clinical symptoms – in which case surgical resection is usually required (21).

Other neoplasms
Neuroendocrine (carcinoid) tumors are infrequent in the dog and cat. They tend to present as diffuse lesions, but should not be mistaken for metastasis or tumors of other origins. They have also been described in the gallbladder, and can show partial response to cholecystectomy. However, the prognosis is generally poor, and metastatic disease is considered to be present in 90% of the cases at the time of diagnosis (7).

Primary liver sarcomas are again infrequent in the dog and cat. Leiomyosarcoma is the most common canine presentation, although there have also

been reports of hemangiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma and histiocytic sarcomas. In cats, hemangiosarcoma is the most common primary sarcoma. These are usually very aggressive tumors, metastasizing in 86-100% of cases or spreading diffusely within the liver. The response to chemotherapy is similar to that seen in other sarcomas. As an example, histiocytic sarcomas respond partially to lomustine (CCNU), with a mean duration of remission of 85 days and a survival of 172 days (22).

There have also been descriptions of benign neoplasms such as fibroma and hemangioma, but these are much less frequent. On the other hand, metastases *(Figure 5)* must always be considered as a possibility when a hepatic tumor is diagnosed.

◉ Conclusion

Primary hepatobiliary neoplasms are infrequent in the dog and cat, and tend to affect elderly animals with nonspecific or gastrointestinal clinical manifestations. The clinico-morphological present-ation of the disease, its cellular origin and benign or malignant nature usually determine the therapeutic options and prognosis. Definitive diagnosis and accurate classification require complete laboratory testing, radiography and ultrasound, as well as liver cytology or biopsy. Surgical resection of a hepatobiliary tumor offers a good prognosis in only a few cases and should only be undertaken after due consideration of all the factors. ◉

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