PAPER

# Lack of associations between ultrasonographic appearance of parenchymal lesions of the canine liver and histological diagnosis

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**Objective:** To assess if there are any ultrasonographic features that may enable tentative diagnosis of hepatic parenchymal disease.

**Methods:** Records of 371 dogs that had abdominal ultrasonography and abnormal liver on biopsy or necropsy were reviewed.

**Results:** Histological diagnoses were hepatitis (n=77), nodular hyperplasia (n=47), vacuolar change (n=45), fibrosis (n=32), primary hepatic carcinoma (n=30), lymphoma (n=28), metastatic neoplasia (n=27), necrosis (n=21), lipidosis (n=17), haemangiosarcoma (n=13), round cell tumour (n=9), hepatocellular adenoma (n=8), degenerative change (n=6), steroid hepatopathy (n=7) and extramedullary haematopoiesis (n=4). The most prevalent ultrasonographic features were multifocal lesions (63% livers with haemangiosarcoma and 43% livers with hepatocellular carcinoma), diffuse lesions (71% livers with steroid hepatopathy, 44% livers with fibrosis and 40% livers with vacuolar hepatopathy), hyperechoic lesions (71% livers with steroid hepatopathy, 41% livers with lipidosis and 38% livers with fibrosis), heterogeneous lesions (62% livers with haemangiosarcoma), hepatomegaly (43% livers with steroid hepatopathy) and peritoneal fluid (62% livers with haemangiosarcoma). Target lesions were associated with malignancy in 67% instances. Marked variability in ultrasonographic appearance of lesions was observed for all diagnoses, and no statistically significant associations between ultrasonographic appearance and diagnosis were found.

**Clinical Significance:** Histological examination remains essential for diagnosis of canine hepatic disease.

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## INTRODUCTION

Ultrasonography is an established method for examining the canine liver, which enables assessment of its echogenicity, echotexture, size and shape as a means of detecting lesions affecting the hepatic parenchyma (Stowater and others 1990, Voros and others 1991, Biller and others 1992, Biller and Blackwelder 1998, Schwarz and others 1998, Peppler and others 2005, Schwartz and others 2006). Although certain ultrasonographic signs have been associated with specific hepatic diseases (Whiteley and others 1989, Cuccovillo and Lamb 2002, Nyman and others 2004), ultrasonography is generally considered unsuitable as a method for diagnosis because of the large degree of overlap in the ultrasonographic signs that can occur with different hepatic diseases (Lamb 1991, Feeney and others 2008). Therefore, diagnosis of hepatic parenchymal lesions found by ultrasonography

relies on cytological or histological examination of cells obtained by fine needle aspiration or biopsy, respectively. This statement appears to be widely accepted; however, investigators continue to make attempts to identify ultrasonographic signs that could be used to correctly predict the cellular diagnosis (Guillot and others 2009). The aim of this study was to utilise case records of a relatively large number of dogs that had hepatic ultrasonography and subsequent histological diagnosis to assess if there are any ultrasonographic features that may enable tentative diagnosis when histology is pending or when managing patients in which liver biopsy is considered inappropriate (for example because of coagulopathy).

## MATERIALS AND METHODS

Hospital records for the period 1999 to 2009 were searched for dogs that had abdominal ultrasonography and subsequent liver biopsy and/or necropsy within 7 days. A list of all dogs that had abdominal ultrasonography and biopsy of the liver and/or necropsy was generated using data from the computerised billing records. Ultrasound and histopathology reports for these animals were then reviewed.

On the basis of ultrasound reports, the parenchyma of the liver was categorised as normal or abnormal and the appearance of parenchymal lesions categorised by distribution (focal, multifocal or diffuse), echogenicity (hyperechoic, hypoechoic, heteroechoic or isoechoic compared to adjacent hepatic parenchyma), presence of target lesions (focal lesions with concentric appearance), presence of a suspected cavitary lesion (focal lesion with a central hypoechoic or anechoic zone), cyst (rounded, thin-walled structure with anechoic contents and far enhancement), calcified material (focal markedly hyperechoic foci with or without an acoustic shadow), subjective liver size, presence of peritoneal fluid and – in patients with peritoneal fluid – presence of abnormal surface contour. The histological diagnosis originally assigned by the attending pathologist was recorded. Cases were excluded when liver histology was normal, inconclusive or non-diagnostic, when patient records were incomplete or when a specific diagnosis occurred in less than four dogs. Dogs with congenital portosystemic shunts were also excluded. In instances where both liver biopsy and necropsy results were available, the necropsy results were used preferentially.

Ultrasonography before September 1999 was performed using a 7·5-MHz mechanical sector transducer (Apogee CX, ATL UK Ltd). For the remainder of the study period, a 2- to 6-MHz curvilinear, a 5- to 8·5-MHz curvilinear, a 5- to 8-MHz vector array transducer or a 5- to 14-MHz linear transducer were used (Sequoia, Siemens Medical Solutions). All examinations were performed by a board-certified radiologist or a radiology resident working under their direct observation. Dogs were scanned in right and/or left lateral recumbency and were usually manually restrained, although some patients were sedated to facilitate scanning. For biopsy, dogs were either sedated heavily or anaesthetised. Several patients had biopsies performed under ultrasound guidance several days after their initial scan; cases in which the ultrasonographic appearance of the liver changed between the first scan and the biopsy were excluded.

Hepatic biopsies were obtained ante mortem using 14, 16 or 18G spring-loaded needles (Quick-core, Cook or Monopty, Bard Inc) (de Rycke and others 1999) under ultrasound guidance or at exploratory laparotomy or surgically using a direct excisional technique (Rothuizen and Twedt 2009). Histology and necropsy were performed by board-certified pathologists.

Summary tables of the frequency data were prepared. In order to look for associations between ultrasonographic appearance and histological diagnosis, data were tested using multivariable classification tree methodology (R v2.10.1, The R foundation for Statistical Computing) (Hosmer and Lemeshow 2000).

## RESULTS

A total of 371 dogs with 15 different hepatic diagnoses satisfied the inclusion criteria (Table 1). On the basis of the 206 dogs for which exact method of biopsy was recorded, 41% biopsies were obtained under ultrasound guidance and 59% by direct visualisation at surgery or necropsy. Hepatic metastases included 12 carcinomas of various types, 7 haemangiosarcoma, 3 adenocarcinoma and 1 case each of phaeochromocytoma, leiomyosarcoma, fibrosarcoma and an undifferentiated mesenchymal tumour. Sensitivity of ultrasonography ranged from 86% for steroid hepatopathy to 48% for hepatitis.

Ultrasonographic features of lesions affecting the hepatic parenchyma are summarised in Table 2. The most prevalent ultrasonographic features were multifocal lesions (observed in 63% livers with haemangiosarcoma and 43% livers with hepatocellular carcinoma), diffuse lesions (in 71% livers with steroid hepatopathy, 44% livers with fibrosis and 40% livers with vacuolar hepatopathy), hyperechoic lesions (in 71% livers with steroid hepatopathy, 41% livers with lipidosis and 38% livers with fibrosis), heterogeneous lesions (in 62% livers with haemangiosarcoma), signs of hepatomegaly (in 43% livers with steroid hepatopathy) and peritoneal fluid (in 62% livers with haemangiosarcoma). Target lesions were associated with malignancy in 67% instances.

**Table 1. Summary of hepatic diagnoses in 371 dogs**

| Histological diagnosis | n (%) | Sensitivity* (%) |
|---|---|---|
| Hepatitis | 77 (21) | 37/77 (48) |
| Nodular hyperplasia | 47 (13) | 33/47 (70) |
| Vacuolar hepatopathy | 45 (12) | 30/45 (67) |
| Fibrosis | 32 (9) | 22/32 (69) |
| Hepatocellular carcinoma | 30 (8) | 24/30 (80) |
| Lymphoma | 28 (8) | 19/28 (68) |
| Metastasis | 27 (7) | 15/27 (56) |
| Necrosis | 21 (6) | 13/21 (62) |
| Lipidosis | 17 (5) | 13/17 (76) |
| Haemangiosarcoma | 13 (4) | 11/13 (85) |
| Round cell neoplasia | 9 (2) | 4/9 (44) |
| Hepatocellular adenoma | 8 (2) | 6/8 (75) |
| Steroid hepatopathy | 7 (2) | 6/7 (86) |
| Degeneration | 6 (2) | 4/6 (67) |
| Extramedullary haematopoiesis | 4 (1) | 3/4 (75) |

*Proportion of affected dogs in which the liver appeared abnormal ultrasonographically

**Table 2. Summary of ultrasonographic features of lesions affecting the liver in 371 dogs with hepatic disease**

| | | Lesion distribution | | | Lesion echogenicity | | | | | | Hepatic volume | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Diagnosis | n | Focal | Multifocal | Diffuse | Hyperechoic | Hypoechoic | Isoechoic | Heterechoic | Target lesions | Cavitary lesion | Calcified | Reduced | Increased | Ascites | Abnormal surface contour |
| Hepatitis | 77 | 6 | 9 | 17 | 8 | 13 | 2 | 10 | 2 | 2 | 0 | 2 | 9 | 16 | 1 |
| Nodular hyperplasia | 47 | 4 | 11 | 13 | 8 | 12 | 0 | 9 | 2 | 3 | 0 | 5 | 7 | 17 | 5 |
| Vacuolar hepatopathy | 45 | 0 | 7 | 18 | 10 | 5 | 5 | 8 | 0 | 1 | 1 | 2 | 8 | 10 | 0 |
| Fibrosis | 32 | 1 | 3 | 14 | 12 | 1 | 0 | 8 | 1 | 1 | 0 | 1 | 5 | 8 | 1 |
| Hepatocellular carcinoma | 30 | 6 | 13 | 3 | 2 | 6 | 0 | 11 | 4 | 1 | 0 | 0 | 4 | 6 | 2 |
| Lymphoma | 28 | 2 | 6 | 5 | 7 | 5 | 1 | 4 | 1 | 1 | 0 | 2 | 5 | 5 | 1 |
| Metastasis | 27 | 2 | 9 | 3 | 5 | 3 | 0 | 7 | 4 | 1 | 1 | 1 | 1 | 2 | 0 |
| Necrosis | 21 | 3 | 4 | 5 | 5 | 3 | 2 | 2 | 0 | 0 | 1 | 1 | 4 | 7 | 2 |
| Lipidosis | 17 | 1 | 2 | 9 | 7 | 1 | 1 | 3 | 1 | 0 | 0 | 1 | 4 | 1 | 0 |
| Haemangiosarcoma | 13 | 0 | 7 | 1 | 1 | 0 | 0 | 8 | 1 | 1 | 0 | 1 | 4 | 8 | 1 |
| Round cell neoplasia | 9 | 0 | 3 | 0 | 0 | 1 | 0 | 1 | 2 | 0 | 0 | 0 | 2 | 0 | 0 |
| Hepatocellular adenoma | 8 | 2 | 2 | 1 | 3 | 0 | 1 | 2 | 0 | 0 | 0 | 1 | 2 | 1 | 1 |
| Steroid hepatopathy | 7 | 0 | 1 | 5 | 5 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 2 | 0 |
| Degeneration | 6 | 1 | 0 | 2 | 2 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 2 | 0 | 0 |
| Extramedullary haematopoiesis | 4 | 0 | 1 | 2 | 2 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 0 |

**Table 3. The most prevalent combinations of ultrasonographic signs associated with hepatic diagnoses**

| Histological diagnosis | Ultrasonographic appearance of hepatic parenchymal lesions | Prevalence (%) |
|---|---|---|
| Hepatitis | Multifocal, hypoechoic | 8/77 (10) |
| | Diffuse, heteroechoic | 8/77 (10) |
| Nodular hyperplasia | Multifocal, hypoechoic | 7/47 (15) |
| Vacuolar hepatopathy | Diffuse, hyperechoic | 8/45 (18) |
| Fibrosis | Diffuse, hyperechoic | 8/32 (25) |
| Hepatocellular carcinoma | Multifocal, heteroechoic | 5/30 (17) |
| Lymphoma | Multifocal, hypoechoic | 4/28 (14) |
| Metastasis | Multifocal, hyperechoic | 4/27 (15) |
| Necrosis | Diffuse, hyperechoic | 4/21 (19) |
| Lipidosis | Diffuse, hyperechoic | 7/17 (41) |
| Haemangiosarcoma | Multifocal, heteroechoic | 7/13 (54) |
| Steroid hepatopathy | Diffuse, hyperechoic | 5/7 (71) |
| Degeneration | Diffuse, hyperechoic | 2/6 (33) |

The most prevalent combinations of ultrasonographic features of lesions observed for the various hepatic diagnoses are summarised in Table 3. Of these, the most prevalent combinations were diffusely hyperechoic parenchyma (observed in 71% livers with steroid hepatopathy and 41% livers with lipidosis) and multifocal heteroechoic lesions (in 54% livers with haemangiosarcoma). The most prevalent combination of ultrasonographic features for all neoplasms combined was multifocal heteroechoic lesions (in 16% affected livers).

Analysis of the data using multivariable methodology failed to find significant associations because of insufficient power for this number of diagnoses, despite the relatively large sample size. Merging groups with different diagnosis (e.g. all the dogs with neoplasia) also failed to find significant associations. As a result, no statistically significant associations between ultrasonographic appearance and diagnosis were found.

## DISCUSSION

Previous studies have found that ultrasonography has low sensitivity for hepatic parenchymal lesions (Lamb and others 1991, Voros and others 1991, Sato and Solano 2004, Crabtree and others 2010, Book and others 2011, Marolf and others 2012). In this series, for example, the sensitivity of ultrasonography for hepatic metastasis was 56% and for hepatitis was 48%. Such low sensitivity means that hepatic disease cannot be ruled out ultrasonographically; hence, if significant hepatic disease is suspected clinically, biopsy should be considered equally important in animals with and without ultrasonographic signs of hepatic disease. The values reported here are likely to overestimate sensitivity because dogs with ultrasonographic lesions were more likely to be biopsied than those without. Estimates of sensitivity of ultrasonography will be affected by multiple factors that cannot be rigorously controlled in practice, such as the quality of the ultrasound system, quality of skin-transducer contact, thickness of skin and subcutaneous fat and motion blur. Debatably, ultrasound is a useful clinical tool for animals with suspected hepatic parenchymal disease primarily because it enables minimally

invasive hepatic biopsy, not because it can be used as a basis for diagnosis. This position is in marked contrast to that which pertains to dogs (and cats) with suspected congenital portosystemic shunts, for which ultrasonography is an accurate diagnostic test (Lamb 1996, d'Anjou and others 2004).

Marked variability in ultrasonographic appearance of lesions was observed for all diagnoses, and no statistically significant associations between ultrasonographic appearance and diagnosis were found. Despite this result, certain conditions had a relatively high prevalence of ultrasonographic signs. For example, a diffuse, hyperechoic appearance of the liver was observed in 71% livers with steroid hepatopathy. This reflects the increase in ultrasonic backscatter that occurs in dogs treated with corticosteroids (O'Brien and others 1996). Less marked trends for diffuse lesions were observed for hepatic lipidosis and fibrosis. Detection of a diffuse hepatic lesion by ultrasonography can be difficult because recognition of any change in echogenicity relies on subjective comparison of the liver with adjacent structures, such as the spleen or abdominal fat (Lamb 1991, Biller and others 1992). Reliability of this assessment will be undermined by variations in conformation of the patient, transducer frequency, ultrasound machine settings and observers. Specifically, the difficulty of recognising a diffuse increase in hepatic echogenicity is emphasised by the occurrence of focal fatty sparing, which appears as a hypoechoic lesion within an apparently normal liver, when it is actually relatively normal liver surrounded by steatosis (Karcaaltincaba and Akhan 2007).

Ultrasonographic diagnosis of focal liver lesions is problematic because of the wide range of conditions that may appear ultrasonographically as focal or multifocal. Although hepatocellular carcinoma was the most frequent diagnosis in dogs with focal or multifocal lesions in this series, hepatitis and nodular hyperplasia also occurred frequently. An early report suggested that hepatocellular carcinoma appeared consistently as a focal hyperechoic mass (Whiteley and others 1989); however, these findings are contradicted by this study and by previous studies in which carcinomas were associated with a range of appearances including multifocal, hypoechoic and heterogeneous (Vörös and others 1991, Newell and others 1998, Guillot and others 2009).

Although it is generally accepted that there are no ultrasonographic findings that can be used as a basis for specific hepatic diagnosis, a recent report found significant associations between several ultrasonographic findings or combinations of findings with certain conditions. For example, presence of hepatic mass lesion larger than 3 cm in diameter was considered predictive of neoplasia, whereas presence of hepatic nodules smaller than 3 cm in diameter was considered predictive of vacuolar hepatopathy (Guillot and others 2009). In this study, target lesions, which have been previously considered a sign of malignancy (Cuccovillo and Lamb 2002), were associated with malignant hepatic lesions in 67% instances.

The presence of ascites has also previously been reported to be suggestive of abdominal neoplasia in both dogs (Guillot and others 2009) and cats (Newell and others 1998, Wright and others 1999). In this study, 62% of dogs with haemangiosarcoma had peritoneal fluid; however, most dogs with peritoneal fluid had non-neoplastic diagnoses. Presence of peritoneal fluid facilitated detection of abnormal hepatic surface contour in dogs with various diagnoses.

In a clinical setting, it is essential that the ultrasonographer collects and attempts to relate findings affecting multiple abdominal structures to support a tentative diagnosis, and it is a limitation of this study that the appearance of the other abdominal structures was not taken into account. Further evaluation of other organs may have affected the likelihood of certain diagnoses, for example lymphoma may be more likely in the presence of enlarged abdominal lymph nodes. In a previous study that used classification tree analysis to create a diagnostic algorithm for ultrasound findings of the liver of cats, it was found that the appearance of the spleen and abdominal lymph nodes carried more weight than the appearance of the liver (Newell and others 1998). Another recent study of 229 dogs and 104 cats used both hepatic parenchymal ultrasonographic criteria and selected extrahepatic criteria to search for associations that would enable differential diagnosis of seven categories of diffuse hepatic diseases (Feeney and others 2008); however, none were found. For the purposes of this study, we concentrated on the appearance of the liver because we were interested specifically in possible correlations between ultrasonographic features and histological diagnoses. This approach excluded the possibility of finding significant associations with other abdominal lesions; however, this study compares favourably in having a larger number of patients than previous studies. Despite having a relatively large number of subjects, multivariable analysis of the results failed because of insufficient statistical power to test for associations with a large number of hepatic diagnoses. For the same reason, an analysis to test associations between combinations of findings (distribution, echogenicity, liver size etc) and diagnosis, which is what ultrasonographers attempt to do in a clinical setting, was not possible.

Other limitations of this study include variability associated with use of multiple observers (both for ultrasonography and pathology), lack of rigorous spatial registration of ultrasonographic lesions and the biopsy sites and sampling error associated with collection of tissue for histology. The net effect of these limitations is a degree of uncertainty that the histological reports truly represent the tissue observed to be abnormal ultrasonographically. Diagnosis for the purposes of this study was based on the predominant histological lesion, with each dog classified as a single diagnosis despite the frequent occurrence of multiple histological features, such as nodular hyperplasia and fibrosis. Classification by single diagnosis was considered a necessary constraint for the purposes of descriptive and analytical statistics; however, it obscures a potentially confounding effect whereby a lesion considered minor or secondary on the basis of histological appearance could perturb the acoustic properties of the liver more than a concurrent lesion considered to be primary.

Diagnosis in this study was based on histological examination of liver tissue collected by either ultrasound-guided or surgical biopsy or necropsy. Accepting these different methods allows inclusion of a larger number of patients; however, it introduces variability because results of histology based on ultrasound-guided needle biopsy do not always agree with results from

samples taken at surgery or necropsy (Cole and others 2002, Wang and others 2004). Lack of agreement between hepatic cytology and corresponding histology is also observed frequently, for example because inflammation may not be evident in cytological specimens from animals with hepatitis (Roth 2001, Wang and others 2004). The fundamental reason for these discrepancies is the sampling error associated with small tissue samples collected by needle core biopsy compared with those obtained by a wedge biopsy taken at surgery or necropsy. For this reason, we did not include patients that had cytological examination alone and we gave precedence to the biopsies obtained at surgery or necropsy in all patients that had them. Despite this limitation, ultrasound-guided tissue core biopsy of the liver is considered preferable to fine needle aspiration alone, especially for inflammatory diseases (Weiss and others 2001), regardless of the greater cost and the higher risk of complications (de Rycke and others 1999, Weiss and Moritz 2002, Wang and others 2004, Rothuizen and Twedt 2009).

Use of ultrasound contrast media as a means to distinguish the various causes of hepatic nodules has been studied extensively in humans (Strobel and others 2000, Bryant and others 2004, Cosgrove and Blomley 2004). In dogs, malignant hepatic nodules had early wash-in and early wash-out of bubbles compared to surrounding parenchyma (O'Brien and others 2004), consistently appeared hypoechoic compared to surrounding parenchyma (O'Brien and others 2004) and were associated with tortuous feeding arteries (Rossi and others 2008, Taeymans and Penninck 2011). Such studies demonstrated that contrast ultrasonography helps to characterise hepatic lesions, but it remains to be seen if this technique will ever be considered accurate enough to replace biopsy.

While ultrasonography is frequently used to look for signs of liver disease in dogs, it is an insensitive test and tentative diagnoses should not be performed based on ultrasonographic findings alone because of the marked overlap in appearance of different hepatic conditions. Histological examination remains essential for diagnosis of canine hepatic disease.

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## Conflict of interest

None of the authors of this article has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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