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Differential Diagnosis of Hepatic Tumor-like Lesions in Dog by Using Dynamic CT Scanning

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ABSTRACT

Dynamic liver CT scanning is used to observe the hemodynamics of hepatic tumor-like lesions by taking images sequentially after administration of contrast media. In this study in dogs, we compared the hemodynamic patterns of hepatocellular carcinoma (HCC), one of the malignant tumors, and nodular hyperplasia (NH), a benign tumor that is more common in older dogs. Thirty-six dogs with HCC and 40 dogs with NH, which were histopathologically diagnosed at Taniura Animal Hospital, were used as subjects. Dynamic CT scanning was performed and the data of each scanning phase were collected. Dilated blood vessels, septum formation, and capsule formation were noted in the tumors from 25, 17, and 25 animals with HCC, respectively. In the arterial phase, high density and low contrast were noted in 8 and 23 dogs, respectively. Low density was noted in 34 dogs in the equilibrium phase. In contrast, no dilated blood vessels, septum formation, or capsule formation was noted in the dogs with NH. High density, low contrast, and low density were noted in 8, 9, and 23 dogs, respectively, in the arterial phase. In the equilibrium phase, the enhancement level was equal to the surrounding liver tissues in all animals. The CT values of HCC in the plain, the arterial phase, portal venous phase and equilibrium phase after the administration of contrast media, were significantly ($p < 0.05$ to 0.001) lower than those of the surrounding liver tissues. In the arterial phase, the percent incidence of low density was significantly less in HCC than NH, while that of low contrast was significantly greater ($p < 0.001$) in HCC than NH. Dynamic CT scanning identified differences between the hemodynamics and internal structures of HCC and NH in dogs. Dynamic liver CT scanning can therefore be considered a useful technique in the differential diagnosis of hepatic tumor-like lesions in dogs.

Key words: *Dog, Dynamic CT, Hepatocellular carcinoma, Nodular hyperplasia*

Primary hepatocellular carcinoma (HCC), metastatic liver tumor, and hemangioma of the liver are the most common liver tumors in humans. The hemodynamics of HCC is different from that of other tumors because of its tissue type. Human hepatic tumor-like lesions can be diagnosed to some extent by dynamic CT scanning, which takes images for a certain period after administration of contrast media, because they have distinct hemodynamic patterns[23]. There have been some reports suggesting that arterial phase[3,19,20] scanning is essential for the detection of HCC and that portal venous phase[2] scanning is required in order to detect liver metastasis in humans. However, in the veterinary field, dynamic CT scanning has been used infrequently and the staining pattern has not been determined. Furthermore, unlike experimental animals under fixed conditions, animal patients have various body weights/builds. These differences in body weight/build have certain effects on the pharmacokinetic behavior of contrast media, which may make it difficult to take images by dynamic CT scanning. Recently, CT scanning has been used in the veterinary field to detect the presence of intrahepatic micro-nodules, and this has contributed to an increase in the number of surgical resections. However, hemodynamic patterns have not been used to identify the tumor type or to estimate the differentiation level of the tumors. In order to decide the treatment policy, the establishment of qualitative diagnosis is a high priority.

In humans, the dynamic CT scanning technique of variable-speed injection for a fixed time based on body weight ratio may be effective[10]. In this study using dogs, we compared CT imaging of HCC as a malignant tumor and nodular hyperplasia (NH) as a benign tumor, using the dynamic CT scanning technique of variable-speed injection based on body weight ratio[25].

MATERIALS AND METHODS

Animals

Thirty-six dogs with HCC and 40 dogs with NH were used as subjects in this study. These animals were brought to Taniura Animal Hospital between 2004 and 2007 in order to detect hepatic tumor-like lesions by dynamic CT scanning, and they were histopathologically diagnosed as having either HCC or NH.

Before starting the CT scanning, we fully explained to the owners that some of the information obtained by CT scanning would be used for our academic study, and thereafter obtained their informed consent. Furthermore, dynamic CT scanning was performed under general anesthesia in order to protect the dogs from unnecessary stress and injury.

The CT scanning method for dogs

The dogs received general anesthesia for endotracheal intubation and were maintained with controlled ventilation. The animals were monitored using an electrocardiogram (FUKUDA M100; Fukuda ME Kogyo Co., Ltd, Tokyo), a pulse oximeter (NELLCOR ULTRACAP N-6000B; Pryon Corporation, Madison, WI), and a ventilator (Bird Mark 7; Bird Products Corporation, Palm Springs,CA).

A two-slice multidetector-row CT system (Hi Speed NX/IGE; GE Yokogawa Medical Systems, Ltd., Tokyo) was used for X-ray CT examination. The arterial phase, portal venous phase, and equilibrium phase were scanned by dynamic CT using a fixed injection method based on body weight when the dogs were under respiratory arrest by positive-pressure breathing. Nonionic contrast medium containing 300 mg/ml or 350 mg/ml iodine, which was heated in a thermostat bath at 37°C, was injected into the cephalic veins from a contrast delivery system (Auto Enhance A-60; Nemot Kyorindo Co., Ltd., Tokyo) via an 18- to 24-gauge needle. The dosage was 2.0 ml/kg and the injection time was fixed at 15 to 20 s in consideration of the best image reconstruction and slice thickness. A smart preparation technique was used in all cases and a trigger was set according to individual body build. CT scanning was started immediately after contrast media had been delivered through the body. The arterial phase scan was performed for 15 s under respiratory arrest. Respiration was then resumed and continued for 15 s. Subsequently, a portal venous phase scan was performed for 15 s under respiratory arrest. The equilibrium phase scan was performed for 90 s after starting the administration. The CT values were determined using AZE Virtual Place Lexus software and compared by 2D region of interest.

Comparison of CT findings

In order to identify the differential diagnosis criteria for HCC and NH, the CT findings in dogs, including the structure of tumors and the contrast effect, were summarized as follows based on the key diagnosis points of human hepatic tumor-like lesions determined by CT scanning[26] and the General Rules for the Clinical and Pathological Study of Primary Liver Cancer[15].

1. For small (S), middle (M) and large (L) size species of dogs, the affected age, diameter of mass, and incidence of multiple masses were examined and compared between HCC and NH groups.
2. Content/margin of the tumors: Presence or absence of blood vessels, capsules, and septum in the tumors.
3. High density compared with the surrounding hepatic parenchyma: The results from the arterial phase, portal venous phase, and equilibrium phase were compared with those of plain CT, and classified into the following 4 groups: high density, low contrast, isodensity, and low density.

High density was defined as exhibiting a contrast enhancement effect of the whole mass more remarkable than that of the surrounding liver. Low contrast was defined as exhibiting a contrast enhancement effect in a portion of the mass compared with the surrounding liver. Isodensity was defined as an absorbance the same as the surrounding liver. Low density was defined as low absorption in a portion of the mass compared with the surrounding liver and without cystic lesions.

4. Comparison of tumor stain patterns between HCC and NH groups: The CT values of the tumors and the surrounding liver tissues were determined in each phase.

The presence of capsules was confirmed if plain CT and arterial phase scans showed a ring-enhancing low-density lesion in the margin of the tumors or if the portal venous phase and contrast CT scans showed a ring-enhancing high-density lesion. The presence of a septum was confirmed if plain CT and arterial phase scans showed a linear low-density lesion connected by capsules in the tumors or if the portal venous phase and equilibrium phase scans showed a linear high-density lesion in the tumors. If a septum was not observed but the content of a tumor was arranged like a mosaic, it was considered that a septum was

present[29]. Tumor stain was identified as high density, isodensity, or low density compared with the surrounding tissues, but if the density was 20 HU higher than that in plain CT, it was considered as low contrast [16, 24, 27].

Statistical analysis

A χ^2 test was used to compare the incidence of multiple tumors and the incidence of tumor stain between the HCC and NH groups. In addition, an analysis of variance was used to evaluate the difference of affected age and diameter of tumor between the HCC and NH groups, and the difference of CT values in the HCC and NH groups between tumors and the surrounding liver tissues in each phase after the administration of contrast media. The statistical significance of the mean value was obtained using a Student's t-test. $p < 0.05$ was considered to be statistically significant in all statistical tests.

RESULTS

Age, diameter of mass, and multiple masses in dogs with HCC and NH

Table 1 shows the results of affected age, diameter of mass, and incidence of multiple masses in the HCC and NH of the S, M and L size species of dogs. Concerning the age of tumorigenesis, there were no significant differences in the affected ages between the HCC and NH groups in the S, M and L sizes of dogs (Table 1). The diameter of the tumor was significantly ($p < 0.05$ to 0.001) greater in the HCC group compared with the NH group in all sizes of dogs (Table 1). There were no significant differences in the incidence of multiple masses between the HCC and NH groups in S, M and L sizes of dogs (Table 1).

CT findings for HCC

In internal and marginal structures, septum and capsule formation were noted in 17 and 25 dogs, respectively (Table 2). Dilated blood vessels in the tumors were noted in 25 dogs (Table 2).

Table 3 shows tumor stain compared with the surrounding hepatic parenchyma. Plain CT revealed low density in 30 dogs and isodensity in 6 dogs. High density in 8 dogs and low contrast in 23 dogs were noted in the arterial phase, isodensity in 2 dogs and low density in 33 dogs were observed in the portal venous phase; and isodensity in 2 dogs and low density in 34 dogs were observed in the equilibrium phase (Table 3).

Fig. 1 shows the tumor stain pattern in HCC. The CT values, using plain CT, for the arterial phase, portal venous phase, and equilibrium phase after the administration of contrast media were significantly lower in HCC than those of the surrounding liver tissues ($p < 0.05$ to 0.001) (Table 5).

CT findings for NH

Table 2 shows internal and marginal structures. Neither septum nor capsule formation was noted in the dogs. Furthermore, no blood vessels penetrating through the tumors were noted (Table 2).

In tumor stain compared with the surrounding hepatic parenchyma, plain CT revealed low density in 6 dogs and isodensity in 34 dogs (Table 4). High density in 8 dogs, low contrast in 9 dogs, and low density in 23 dogs were noted in the arteri-

Table 1. The affected age, diameter of mass, and incidence of multiple masses in HCC and NH of small (S), middle (M) and large (L) size species of dogs

Variable	Group	S	M	L
Affected age (years)	HCC	12.1 ± 3.0 (14) †	12.6 ± 1.8 (13)	10.7 ± 0.9 (9)
	NH	12.0 ± 2.7 ns (13)	11.5 ± 1.8 ns (20)	10.0 ± 1.4 ns (6)
Diameter of mass (cm)	HCC	5.71 ± 2.30 (14)	6.85 ± 3.78 (13)	7.78 ± 4.52 (9)
	NH	2.46 ± 0.66** (13)	2.45 ± 0.60** (20)	3.33 ± 0.52* (6)
Incidence of multiple masses (%)	HCC	57.1 (8/14) #	61.5 (8/13)	88.9 (8/9)
	NH	38.5 (5/13) ns	45.0 (9/20) ns	66.7 (4/6) ns

† Each value is presented as the mean±SD (n)

No. of dogs with multiple masses / no. of dogs examined in parenthesis

* $p < 0.05$, ** $p < 0.001$ (significantly different from HCC)

ns $p > 0.05$ (not significantly different from HCC)

HCC=hepatocellular carcinoma

NH=nodular hypoerplasia

Table 2. Internal and marginal structures of HCC and NH

Group	Septum	Capsule	Blood vessels
HCC (n = 36)	17 (17/36)	25 (25/36)	25 (25/36)
	53.10 %	78.10 %	78.10 %
NH (n = 40)	0	0	0

HCC=hepatocellular carcinoma
NH=nodular hyperplasia

al phase. Isodensity in 37 dogs, low contrast in 2 dogs, and low density in 1 dog were observed in the portal venous phase. The equilibrium phase scan showed isodensity in all dogs (Table 4).

Fig. 2 shows tumor stain pattern and NH. There were no significant differences in CT values between the internal tumors and the surrounding liver tissues of the plain, arterial phase, portal venous phase, and equilibrium phase in the NH group (Table 6). The results of plain CT scanning revealed that low density was significantly greater and isodensity significantly less in HCC than in HN ($p < 0.001$). Low density was significantly less and low contrast was significantly greater in HCC

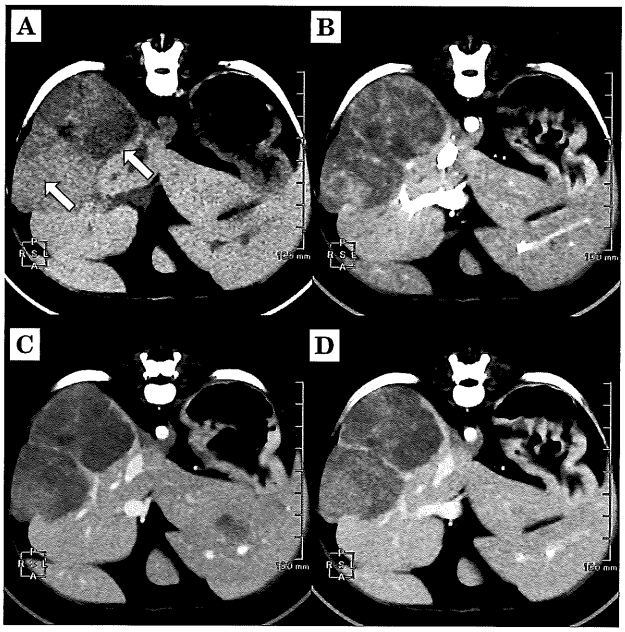

Fig. 1. CT imaging of HCC
The mass (7 × 4 cm) of a case showed low density in the right lobe (arrow). Plain CT (A) showed low density. Contrast effect and blood vessels in the tumor were noted in the arterial phase (B). Low density in the portal venous phase (C) and low density associated with capsule/septum in the equilibrium phase (D) were observed. HCC=hepatocellular carcinoma.

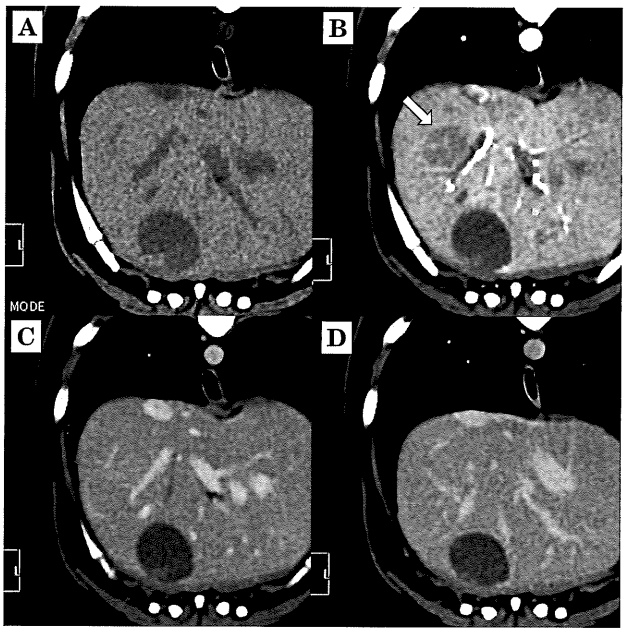

Fig. 2. CT imaging of NH
This is a case that showed a mass at a size of 2.5 cm in the right lobe (arrow). Plain CT (A) showed isodensity, while low-density in the arterial phase (B) and isodensity in the portal venous phase (C) and equilibrium phase (D) were observed. NH=nodular hyperplasia

Table 3. Tumor stain of HCC (n = 36) compared with the surrounding hepatic parenchyma

Stain	Plain CT		Imaging					
			Arterial phase		Portal venous phase		Equilibrium phase	
	No. of cases	%	No. of cases	%	No. of cases	%	No. of cases	%
Low density	30	83.3	4	11.1	33	91.7	34	94.4
Isodensity	6	16.7	1	2.8	2	5.6	2	5.6
Low contrast	0	0	23	63.9	0	0	0	0
High density	0	0	8	22.2	1	2.8	0	0

HCC=hepatocellular carcinoma

Table 4. Tumor stain of NH (n = 40) compared with the surrounding hepatic parenchyma

Stain	Plain CT		Imaging					
			Arterial phase		Portal venous phase		Equilibrium phase	
	No. of cases	%	No. of cases	%	No. of cases	%	No. of cases	%
Low density	6	15.0	23	57.5	1	2.5	0	0
Isodensity	34	85.0	0	0	37	92.5	40	100
Low contrast	0	0	9	22.5	2	5	0	0
High density	0	0	8	20.0	0	0	0	0

NH=nodular hyperplasia

Table 5. CT values of HCC and the surrounding liver tissues in each phase after the administration of contrast media

Site	CT value (Mean ± SD, n = 36)			
	Plain	Arterial phase	Portal venous phase	Equilibrium phase
Surrounding liver tissues	58.1 ± 11.2	106.1 ± 26.4	136.6 ± 23.7	127.7 ± 22.1
Tumor	44.2 ± 11.6***	91.1 ± 35.2 *	109.8 ± 38.9 ***	104.9 ± 34.6 **

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ (significant different to the surrounding liver tissues)
HCC=hepatocellular carcinoma

Table 6. CT values of NH and the surrounding liver tissues in each phase after the administration of contrast media

Site	CT value (Mean ± SD, n = 36)			
	Plain	Arterial phase	Portal venous phase	Equilibrium phase
Surrounding liver tissues	62.7 ± 8.1	111.9 ± 24.8	126.0 ± 21.8	122.9 ± 17.7
Tumor	61.1 ± 10.1 ns	116.1 ± 44.4 ns	130.8 ± 24.3 ns	123.9 ± 17.5 ns

ns $p>0.05$ (not significantly different from the surrounding liver tissues)
NH=nodular hyperplasia

Table 7. Significant difference in the incidence between HCC and NH groups by χ^2 test

	Plain	Arterial phase	Portal venous phase	Equilibrium phase
Low density	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
Isodensity	$p < 0.001$	$p > 0.05$	$p < 0.001$	$p < 0.001$
Low contrast	$p > 0.05$	$p < 0.001$	$p > 0.05$	$p > 0.05$
High density	$p > 0.05$	$p > 0.05$	$p > 0.05$	$p > 0.05$

HCC=hepatocellular carcinoma
NH=nodular hyperplasia

than NH in the arterial phase ($p < 0.001$) (Fig. 2). In the portal venous phase and the equilibrium phase, low density was significantly greater and isodensity was significantly less in HCC than in HN ($p < 0.001$) (Table 7).

DISCUSSION

The incidence of primary liver tumor in dogs is low, accounting for 0.6 to 1.3% of all tumors[12, 22, 23]. HCC is the most common malignant liver tumor[28]. It is well known that in humans there is a strong correlation between HCC and hepatitis B and C viruses and liver cirrhosis[5], whereas some studies have demonstrated that HCC develops in dogs when water containing certain carcinogens, particularly aflatoxin, pyrrolizidine alkaloid, and diethylnitrosamine, is administered experimentally[6, 14]. However, dogs are unlikely to be exposed to these carcinogens under normal circumstances, and no other causes have yet been elucidated[12, 22]. Furthermore, a combination of liver cirrhosis and HCC is rare[22].

In the past, human HCC was diagnosed by autopsy. It mainly presented as a big nodular type tumor with capsules due to liver cirrhosis, which had cancer cells with histologically marked cellular atypia. Recently, multistage carcinogenesis of HCC has been clarified as adenomatous hyperplasia and HCC has been detected in association with liver cirrhosis. In humans, imaging diagnosis plays an important role in the early diagnosis of HCC and the disease stage classification. Some veterinary hospitals apply the diagnostic imaging system to dogs. However, the imaging method has not been fully evaluated. Nevertheless, several pieces of diagnostic equipment have been introduced into veterinary practice, and as a consequence diagnostic imaging will be more commonly used in this field in the near future.

Dynamic CT scanning can identify differences between the liver and HCC, which is useful in distinguishing the diseases[4]. Images of early liver cancer in humans taken by plain CT show isodensity in the arterial phase and low density in the equilibrium phase, or low density in plain CT and in the arterial and equilibrium phases[8, 11, 13, 17].

Iimage of typical advanced HCC taken by plain CT show low density and, transiently, high contrast in the early arterial phase, isodensity in the portal venous phase, and low density in the equilibrium phase.

Qualitative diagnosis may vary depending on the presence or absence of a septum and capsules in the tumor[29]. In humans, lesions with a larger mass exhibit a more developed mosaic structure and capsule formation. Advanced HCC tends to have capsules and/or a septum. HCC with hemorrhagic necrosis is also included in advanced cancer and may be undifferentiated (embryonal) HCC[1].

There have been some reports that dog HCC is likely to be of an undifferentiated type[7, 12]. Given that dog HCC is similar to human HCC, the presence of a septum may suggest that dog HCC is more than moderately well differentiated. This study indicated a high incidence of septums and capsules. However, we did not investigate tumor differentiation in this study because the pathological differentiation of dog HCC is considered to be difficult.

We have experience of a case in which the image definitely showed the HCC pattern although a needle biopsy using ultrasound guidance before surgery indicated NH. The dilemma was eventually solved by histological analysis following tumor resection, which revealed that the tumor was an HCC. Thus, a combined type of HCC and NH may exist in dogs which might make it difficult to obtain an overview of tumor mass by a needle biopsy. Dynamic CT scanning is able to provide an estimate of the tumor differentiation type of such a tumor mass based on the hemodynamic pattern on the CT image. Any examination after the onset of symptoms may, however, be too late. Consequently, early detection is critical. Dilated nutrient vessels penetrating through the tumor are not usually observed in human HCC. However, such vessels were noted in some cases in this study. These blood vessels supply oxygen and nutrition to dog HCCs, which may lead to an increase in tumor size. In fact, the present study demonstrated that the tumor size was significantly greater in HCC compared with NH in small, middle and large species of dogs. These results indicate that HCC increases more rapidly than NH.

The incidence rate of NH in dogs is 15% to 60% and the condition is mainly observed in older dogs. NH usually manifests as a round-shaped benign tumor with a diameter of a few mm to a few cm, and is not clinically serious. Generally, it is detected by chance through biopsy[18]. NH is a non-neoplastic hyperplasia, which is increasingly being detected due to the recent development and prevalence of diagnostic imaging techniques. This disease is sometimes associated with HCC and is removed with HCC by chance during surgery. Differential diagnosis between HCC and NH is essential in order to avoid unnecessary invasion or surgery.

In this study, the NH of all dog subjects had a homogeneous inner structure, unlike HCC, which has a mosaic or heterogeneous pattern. Furthermore, no dilated blood vessels, capsules, or septums were noted in any of the animals. This feature also differentiates NH from HCC. With regard to capsules, the tumor apparently squeezes the surrounding tissues in terms of the histological finding. However, no capsule formation was

observed, which is consistent with the CT imaging[10]. Furthermore, only a few cases showed transient high contrast in the arterial phase and the images in all cases showed isodensity in the equilibrium phase. The majority of NH subjects showed isodensity in the plain CT image and in the equilibrium phase; consequently, plain CT scanning alone is unable to detect it. In addition, the present results demonstrated that the CT values for plain CT and for the arterial phase, portal venous phase, and equilibrium phase after the administration of contrast media were significantly lower in HCC than those of the surrounding liver tissues. In contrast, there were no significant differences in CT values between the NH and the surrounding liver tissues for each phase. These findings indicate that the dynamic CT scanning technique is useful for differential diagnosis between HCC and NH.

In conclusion, dynamic CT scanning can distinguish the hemodynamics and internal structures of HCC and NH in dogs. This technique is therefore useful for differential diagnosis between HCC and NH in dogs.

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