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Late Phase Images in Whole Liver Double Phase CT during Hepatic Arteriography in the Diagnosis of Well-differentiated Hepatocellular Carcinomas

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Summary. **Early phase images by double phase CT during hepatic arteriography (CTHA-1) and CT during arterial portography (CTAP) are useful for detecting and characterizing, well-differentiated hepatocellular carcinomas (HCCs). Still, the development of even more accurate diagnostic methods is desired. We therefore evaluated late phase images of double phase CTHA (CTHA-2) for the detection and characterization of HCCs. We analyzed the findings of CTHA-2 in 20 well-differentiated HCC nodules. Fourteen nodules were well-differentiated HCCs, 1 was well-differentiated HCC with adenomatous hyperplasia, and 5 were mixed with well- and moderately (or poorly) differentiated HCCs (wd+mpd-HCC). A combination of CTHA-1 and CTAP could not reveal 2 of 5 were wd+mpd-HCC nodules; however CTHA-2 suggested dedifferentiation of the nodules. In conclusion, CTHA-2 clearly demonstrated the dedifferentiation of well-differentiated HCCs.**

Key words—low-grade dysplastic nodules, high-grade dysplastic nodules, wd-HCCs, early phase of CTHA, late phase of CTHA, CTAP.

INTRODUCTION

With recent developments in diagnostic imaging, the number of detectable well-differentiated hepatocellular carcinomas (wd-HCCs) has been increasing[1,2]. The practical value of computed tomography (CT) during arterial portography (CTAP) and computed tomography during hepatic arteriography (CTHA) has been widely recognized[3]. The combined use of the two methods improves the estimation of the grade of HCC nodule malignancy[4,5]. However, CTHA performed immediately after commencing the injection of contrast materials (early phase CTHA; CTHA-1) cannot differentiate some wd-HCCs from moderately or poorly differentiated HCCs (mpd-HCC)[4,5].

The use of double phase CTHA (with two instances of image acquisition; (CTHA-1) and about 50 s after injection of contrast materials (late phase CTHA; CTHA-2)) has recently been introduced to the clinic. The advantage of this method is its ability to differentiate between hypervascular HCC and hypervascular pseudolesions[6,7]. However, little literature exists on the value of double phase CTHA for the diagnosis of well-differentiated HCCs. In this study, we evaluated double phase CTHA, especially the usefulness of CTHA-2 in the diagnosis of well-differentiated HCCs.

MATERIALS AND METHODS

Patients

We reviewed the findings of CTAP and CTHA in 17 patients who were diagnosed by surgical resection or

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Abbreviations—AH, adenomatous hyperplasia; CT, computed tomography; CTAP, CT during arterial portography; CTHA, CT during hepatic arteriography; HCC, hepatocellular carcinoma; HGDN, high-grade dysplastic nodules; LGDN, low-grade dysplastic nodules.

tumor biopsy as having wd-HCCs between June 1997 and June 2002 at Niigata University Hospital, Japan. The 17 patients, 13 men and 4 women, had an average age of 64.3 years, with a range of 48–76. Twelve patients had liver cirrhosis, and 5 had chronic hepatitis. Three patients had 2 nodules, and the remaining 14 had a single HCC nodule. Their diameters ranged from 7–30 mm (mean 15 mm) in the 20 nodules: 6–10 mm in 4 nodules, 11–15 mm in 8 nodules, 16–20 mm in 6, 21–29 mm in 1, and 30 mm in 1. Fifteen nodules were located in the right lobe and 5 were in the left lobe.

Histological diagnosis

The histological diagnosis was confirmed on 20 wd-HCC nodules in 17 of the cases, including 5 nodules in 4 surgically resected specimens and 15 in 13 biopsied specimens. Of the 20 nodules, 1 nodule was a mixed type of adenomatous hyperplasic (AH) and wd-HCC (AH+wd-HCC), and 14 nodules were wd-HCC. Five nodules were each of a mixed type of wd-HCC and wd+mpd-HCC.

CTHA and CTAP

We carried out CTHA and CTAP in the CT room after insertion of a catheter in the angiography room. The contrast medium iopromide (Proscope, Tanabe Pharmaceuticals, Tokyo, Japan) was used at a concentration of 140 mg I/ml. In CTHA, the total dose of the contrast medium was 60 ml and the injection rate was 2 ml/s when the tip of the catheter was inserted into the common or proper hepatic artery; 1/2 or 1/3 of the total dose and injection rate was used when the left or right hepatic artery was catheterized. The CTHA-1 (early phase) and CTHA-2 (late phase) scanning was begun 10 s and 50 s after the start of the injection, respectively. In CTAP, a catheter tip was inserted into a superior mesenteric artery, 100 ml of the contrast medium was injected with the rate of 2 ml/s, and the scanning was begun 40 s after the start of injection.

We used a single detector CT scanner (Lemage Supreme, General Electric-Yokogawa Medical Systems, Tokyo, Japan), or a multi-detector array CT scanner (Light Speed Qxi, General Electric-Yokogawa Medical Systems, Tokyo, Japan). Using the former scanner, the beam width was 5 mm, the pitch was 1.4, and image reconstruction was performed with a 5 mm thickness and at 5 mm intervals. Using the latter CT scanner, the detector width was 2.5 mm×4, the pitch was 3, and image reconstruction was performed with a 2.5 mm thickness and intervals.

RESULTS

CTHA and CTAP

Table 1 shows the CTHA and CTAP findings of each nodule, and Table 2 summarizes the association between CTHA findings and histology. CTHA-1 detected 17 lesions, whereas CTHA-2 revealed 18.

Four nodules showed a ringed high density on CTHA-2. Two of them displayed high density on CTHA-1, and were wd+mpd-HCCs. The remaining 2 showed low density on CTHA-1; 1 was wd+mpd-HCC confirmed with resection (Fig. 1), and 1 a wd-HCC nodule confirmed by biopsy. Two wd+mpd-HCCs confirmed with resection had fibrous capsules.

Two nodules showed low density with a hyperdense spot on both CTHA-1 and CTHA-2. In one of the nodules, the hypervascular part was of a moderately differentiated HCC, and the hypovascular part was of wd-HCC. In the other nodule, the hypervascular part was of wd-HCC, and the hypovascular part was of adenomatous hyperplasia. Ten nodules showed low density on both CTHA-1 and CTHA-2, and were all of wd-HCC. Two nodules showed iso density on CTHA-1 and low density on CTHA-2. One of the two nodules was wd-HCC (by tumor biopsy), and the other was wd+mpd-HCC (by surgical resection), which did not have a fibrous capsule (Fig. 2). One nodule showed iso density on both CTHA-1 and CTHA-2, and was of wd-HCC. Another nodule showed low density on CTHA-1 and iso density on CTHA-2, and was wd-HCC (Table 2).

In summary, on CTHA-2, 3 of 4 nodules with a ringed high density, 1 of 12 nodules with low density, and none of 2 nodules with iso density were wd+mpd-HCCs.

CTAP revealed 12 (60%) of 20 lesions. (Table 1).

Sensitivity of CTHA and CTAP

The sensitivity of HCC was thus 85% (17/20) on CTHA-1, 90% (18/20) with combined use of CTHA-1 and CTAP, and 95% (19/20) when CTHA-2 was added to CTHA-1 and CTAP (Table 3).

DISCUSSION

Hepatocellular nodules in chronic liver diseases show multistep dedifferentiation[8]. Initially, a nodule becomes a large regenerative nodule, and it changes into AH[9] (both are classified as low-grade dysplastic nodules (LGDN) by the International Working Party

Table 1. Association between CTHA, CTAP and histological findings in each nodule

No	Size (mm)	CTHA-1	CTHA-2	CTAP	Histology	
1	15	High	Ring	Low	well-poor HCC	(fc+)
2	20	High	Ring	Low	well HCC	(bp)
3	7	Low	Ring	Low	well-mode HCC	(fc+)
4	15	Low	Ring	Low	well HCC	(bp)
5	12	Iso	Iso	Iso	well HCC	(bp)
6	10	Iso	Low	Iso	well-mode HCC	(fc−)
7	13	Iso	Low	Low	well HCC	(bp)
8	15	Low/High	Low/High	Iso/Low	well-mode HCC	(bp)
9	23	Low/High	Low/High	Iso/Low	AH-well HCC	(bp)
10	29	Low	Low	Iso	well HCC	(fc−)
11	16	Low	Low	Iso	well HCC	(bp)
12	15	Low	Low	Iso	well HCC	(bp)
13	30	Low	Low	Iso	well HCC	(bp)
14	10	Low	Low	Iso	well HCC	(fc−)
15	18	Low	Low	Low	well HCC	(bp)
16	12	Low	Low	Low	well HCC	(bp)
17	12	Low	Low	Low	well HCC	(bp)
18	10	Low	Low	Low	well HCC	(bp)
19	20	Low	Low	Low	well HCC	(bp)
20	16	Low	Iso	High	well HCC	(bp)

AH, adenomatous hyperplasia; well HCC, well-differentiated hepatocellular carcinoma; mode HCC, moderately differentiated hepatocellular carcinoma; poor HCC, poorly differentiated hepatocellular carcinoma; low, low density; iso, iso density; high, high density; ring, iso or low density with ringed high density; (fc+), resected fibrous capsule present; (fc−), resected fibrous capsule absent; (bp), biopsy.

Table 2. Association between CTHA and histological findings in each nodule

Histology	No. of nodules							
	CTHA-1	High	Low	Iso	Vascular spot in hypovascular	Low	Iso	Low
	CTHA-2	Ring	Ring	Low		Low	Iso	Iso
AH-well HCC					1			
Well HCC			1	1		10	1	1
Well-mode HCC		1	1	1	1			
Well-poor HCC		1						
Total		2	2	2	2	10	1	1

AH, adenomatous hyperplasia; well HCC, well-differentiated hepatocellular carcinoma; mode HCC, moderately differentiated hepatocellular carcinoma; poor HCC, poorly differentiated hepatocellular carcinoma; low, low density; iso, iso density; high, high density; ring, iso or low density with ringed high density.

of the World Congress of Gastroenterology). Then they transform into an atypical adenomatous hyperplasia, early wd-HCC (both are classified as high-grade dysplastic nodules (HGDN)), wd-HCC, and finally mpd-HCC[5,9−12].

Blood supply changes accompany the dedifferentiation of these hepatocellular nodules. Initially, the hepatic arterial and portal venous flow is

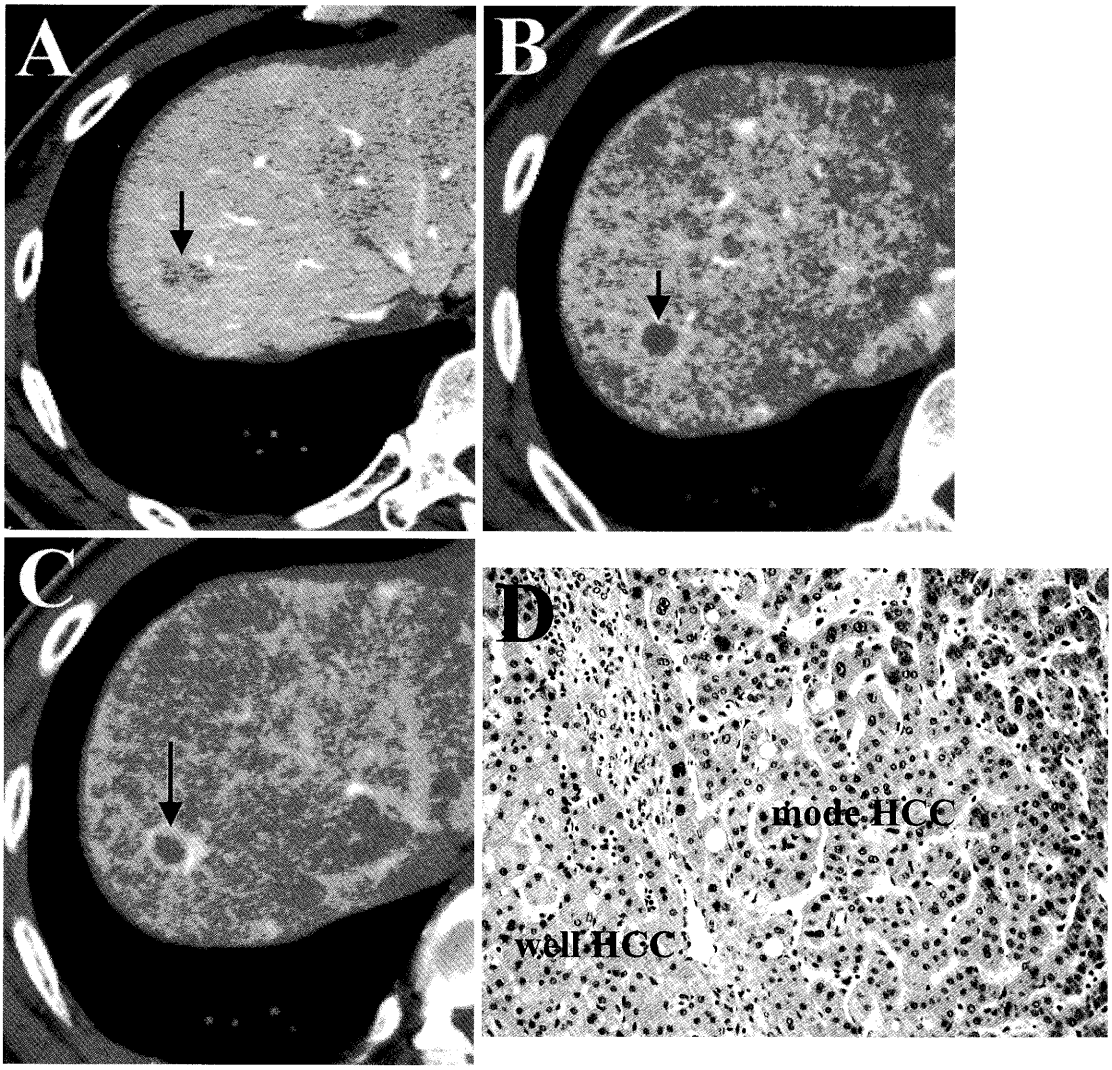

Fig. 1. Well and moderately differentiated hepatocellular carcinoma (wd+mpd-HCC) in S8 of the liver in a 48-year-old male with chronic liver disease. **A.** On CT during arterial portography (CTAP), the tumor is visualized as low density (perfusion defect) (*arrow*). **B.** Early phase of CT during hepatic arteriography (CTHA-1): the tumor shows low density (*arrow*). [According to the findings of CTAP and CTHA-1, the tumor was diagnosed as well-differentiated HCC (wd-HCC)]. **C.** In contrast, the late phase of CT during hepatic arteriography (CTHA-2) shows a ringed high density (*arrow*), which suggests the moderately or poorly differentiated HCC. **D.** Light microscopic view (×160) of the resected specimen of the tumor with hematoxylin-eosin staining reveals well to moderately differentiated HCC.

Table 3. Sensitivity of CTHA and CTAP for 20 nodules

	Total (%)
CTHA-1	17 (85)
CTHA-1+CTAP	18 (90)
CTHA-1+CTAP+CTHA-2	19 (95)

the same as the flow of non-tumorous liver tissue. Secondly, arterial flow decreases, while portal venous inflow remains basically at the original level. Then both arterial and portal venous flows are decreased. Finally, arterial inflow with tumor-associated new arteries increases rapidly. Because these changes in blood supply can be visualized with CTHA-1 and CTAP, these methods are reported to be useful for the evaluation of the differentiation of hepatocellular lesions[4,5,13–17].

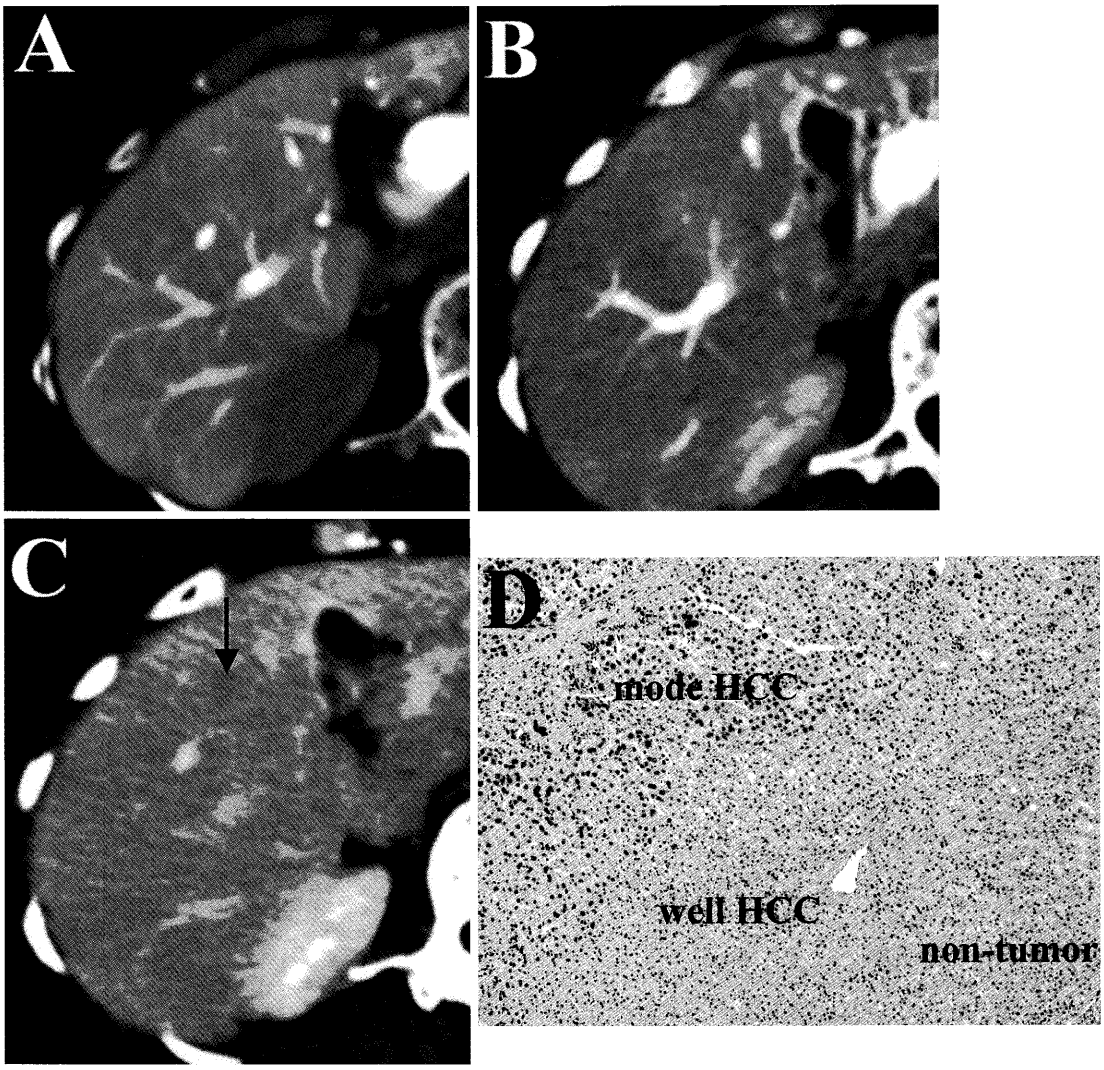

Fig. 2. Well and moderately differentiated hepatocellular carcinoma (wd+mpd-HCC) in S5 of the liver in a 64-year-old female with chronic liver disease. **A.** On CT during arterial portography (CTAP), the tumor is visualized as iso density (i.e. invisible). **B.** Early phase of CT during hepatic arteriography (CTHA-1): the tumor shows iso density (invisible). **C.** Late phase of CT during hepatic arteriography (CTHA-2) shows low density (*arrow*). **D.** Light microscopic view (×80) of the resected specimen of the tumor with hematoxylin-eosin staining reveals well to moderately differentiated HCC. These tumor cells had replaced hepatocytes on the border of the tumor.

However, on CTHA-1 and CTAP, there are overlaps in findings among LGDN, HGDN, wd-HCCs and mpd-HCCs. Therefore, an estimation of differentiation based on blood supply is not completely reliable[4,11].

Recently, the blood drainage flow of hepatocellular nodules has been investigated. The drainage veins of encapsulated HCCs are mainly the portal veins (and partly the hepatic veins). On the other hand, the blood drainage pathways of non-encapsulated HCCs run from the tumor sinusoid, via the surrounding hepatic sinusoid, to hepatic venules[15]. Most mpd-HCCs have capsules, whereas most wd-HCC nodules are non-encapsulated[18]. Therefore, in mpd-HCCs, the drainage vessel is predominantly the portal vein, and in wd-HCCs, the drainage vessel is mainly the hepatic vein.

On single level cine CTHA, hypervascular HCC showed a corona-shaped hyperdense area surrounding the nodule after the inflow of contrast material into the nodule, and Ueda et al. demonstrated that this hyperdense area is the result of portal venous

drainage[16]. These observations are consistent with ringed high density on CTHA-2[6,19]. Ringed high density visualized on CTHA shows portal venous drainage, which is predominantly seen in mpd-HCC. Therefore, CTHA-2 is useful for evaluating the blood drainage flow of hepatocellular nodules.

In this study, 4 of 20 nodules with wd-HCC showed a ringed high density on CTHA, and 3 of the 4 had a component of mpd-HCC. Two nodules, which showed high density on CTHA-1 and low density on CTAP, revealed moderately or poorly differentiated components, confirming blood supply studies. However, the remaining 2 nodules showed low density both on CTHA-1 and CTAP, which are visualized mainly in wd-HCC[5]. One of the 2 nodules was moderately differentiated HCC with a fibrous capsule on the resected specimen (Fig. 1, Table 1 and 2). The other nodule was diagnosed as wd-HCC by biopsy, but this nodule showed increased arterial blood flow on dynamic CT and MRI. The reason for this discrepancy may be the result of an error in the histologic sampling biopsy[5]. The ringed high density on CTHA-2 showed the drainage vessel to be the portal vein, and revealed poorer differentiation, even though the blood supply studies (CTHA-1 and CTAP) suggested a well-differentiated nature (Fig. 1).

Two nodules showed low density with a hyperdense spot on CTHA-2. The hypervascular part represented a histologically less differentiated part, thereby showing these nodules to represent well-differentiated hepatocellular lesions with focal dedifferentiation. However, CTHA-1 revealed the same findings as CTHA-2, and CTHA-2 added no information for tumor differentiation.

Twelve nodules showed low density on CTHA-2. Ten of them were also low density on CTHA-1, and all of these nodules were wd-HCC. Therefore, CTHA-2 showed no additional information for the differentiation of these 10 nodules. However, the remaining 2 nodules were iso density on CTHA-1. One of these 2 was wd+mpd-HCC (Fig. 2) and the other was wd-HCC. The findings of these nodules (iso density on CTHA-1 and low density on CTHA-2) may represent a transition period from wd-HCCs to moderately or poorly differentiated HCC. Wd-HCC is predominantly hypodense both on CTHA-1 and CTHA-2, whereas the moderately or poorly differentiated HCC is usually hyperdense on CTHA-1 and shows a ringed high density on CTHA-2[20]. Wd+mpd-HCC is isodense on CTAP. This tumor had no capsule, and there were hepatocytes on the border of the tumor. The contrast medium from the portal vein might enter via non-tumoral or tumor sinusoids[21].

CTHA-2 could not detect 2 nodules. One of them was iso density, and the other nodule was low density on CTHA-1, and both were recognized as wd-HCC. Both nodules showed a normal or increased portal blood supply on CTAP. The findings from the latter nodule may have been caused by a decrease in the normal hepatic arterial blood flow and stagnation of blood flow within tumor blood sinusoids prior to the formation of tumor-associated arterial vessels[13,22].

In summary, the addition of CTHA-2 to CTHA-1 and CTAP provides information regarding the blood drainage of the hepatocellular nodules.

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