Correlation Between the Blood Supply and Grade of Malignancy of Hepatocellular Nodules Associated with Liver Cirrhosis: Evaluation by CT During Intraarterial Injection of Contrast Medium

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American Journal of Roentgenology 1999;172:969-976.

OBJECTIVE. The purpose of this study is to evaluate the correlation between the intranodular blood supply revealed by CT during intraarterial injection of contrast medium, mainly using helical CT, and the grade of malignancy of hepatocellular nodules associated with liver cirrhosis as classified by the International Working Party of the World Congress of Gastroenterology.

SUBJECTS AND METHODS. We studied 201 histologically proven nodules (101 resected and 100 biopsied nodules), including 47 low-grade dysplastic nodules (low-DNs), 56 high-grade dysplastic nodules (high-DNs), 24 well-differentiated hepatocellular carcinomas (wd-HCCs), and 74 moderately or poorly differentiated HCCs (mp-HCCs), in 139 cirrhotic patients. Findings on CT during arterial portography (n = 201) and CT during hepatic arteriography (n = 74) were reviewed and compared with the histologic diagnosis.

RESULTS. CT findings were classified into four types relative to the surrounding liver: type A (isodense), type B (slightly hypodense), type C (partially hypodense), and type D (markedly hypodense) on CT during arterial portography and type I (isodense), type II (hypodense), type III (partially hyperdense), and type IV (hyperdense) on CT during hepatic arteriography. On CT during arterial portography, the distributions of each type were low-DN (n = 47 [A, n = 36; B, n = 8; C, n = 3]), high-DN (n = 56 [A, n = 18; B, n = 20; C, n = 10; D, n = 8]), wd-HCC (n = 24; [B, n = 4; C, n = 13; D, n = 7]), and mp-HCC (n = 74 [D, n = 74]). On CT during hepatic arteriography, the distributions were low-DN (n = 26 [I, n = 18; II, n = 7; III, n = 1]), high-DN (n = 19 [I, n = 6; II, n = 7; III, n = 4; IV, n = 2]), wd-HCC (n = 15 [I, n = 1; III, n = 8; IV, n = 6]), and mp-HCC (n = 14 [IV, n = 14]). We found a statistically significant correlation between the four types and the grade of malignancy of these nodules.

CONCLUSION. Findings on CT during arterial portography and CT during hepatic arteriography correlated positively with histologic grading when overlap in appearance between dysplastic nodules and HCCs occurred. The concept revealed in this study can apply to diagnoses made on the basis of Doppler sonography, dynamic CT, and MR imaging.

Hepatocellular carcinoma (HCC) is one of the most common malignancies in many parts of the world. Most HCCs develop in cirrhotic livers, especially those caused by hepatitis B or C virus infection. In Japan, more than 90% of the patients with HCC have associated liver cirrhosis due to these infections [1]. Detection of small early-stage HCCs by periodic imaging is possible in patients with these high-risk diseases. However, various kinds of hepatocellular nodules, so-called borderline lesions such as adenomatous hyperplasia, atypical adenomatous hyperplasia, and atypical adenomatous hyperplasia with malignant foci, are also often detected at the same time [2]. The differential diagnosis among these nodules is important clinically for the treatment of cirrhotic patients. However, differentiation among these nodules by sonography, conventional CT, and MR imaging is usually impossible. For this reason, percutaneous biopsy with sonographic guidance is the most accurate diagnostic technique. However, obtaining an exact tissue sample from these small nodules is occasionally difficult. Furthermore, as recently described by Bhattacharya et al. [3] using explant cirrhotic livers, many multicentric small HCCs or borderline lesions are not detected on sonography. Therefore, establishing the differential diagnosis by diagnostic imaging is also important; for this purpose, we previously reported the usefulness of evaluation of the intranodular blood supply on CT during arterial portography and CT during hepatic arteriography [4] and the signal intensity on MR imaging [5] seen in these nodules.

Received July 27, 1998; accepted after revision October 15, 1998.

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AJR 1999;172:969–976

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The histologic concept of these hepatocellular nodules was revised after publication of these reports, and the classification proposed by the Liver Cancer Study Group of Japan [6] is now widely adopted in Japan. Another new classification that could become widely accepted worldwide by pathologists was introduced by the International Working Party of the World Congress of Gastroenterology in 1994 [7]. On the other hand, new CT technology, especially helical CT, has been rapidly developed, and the simultaneous performance of CT during arterial portography and CT during hepatic arteriography within a relatively short time has become possible, with their diagnostic accuracies becoming significantly improved [8, 9].

In this study, we evaluated the differences in the intranodular blood supply revealed by CT during arterial portography and CT during hepatic arteriography, mainly using helical CT, among various kinds of hepatocellular nodules associated with liver cirrhosis histologically diagnosed according to the new classification introduced by the International Working Party of the World Congress of Gastroenterology [7] and discuss their clinical significance.

Subjects and Methods

A total of 201 hepatocellular nodules less than 3 cm in the largest diameter in 139 cirrhotic patients was histologically confirmed and studied at our institution from July 1991 to December 1997 after CT during arterial portography or CT during hepatic arteriography (or both) examinations. In all patients, CT during arterial portography or CT during hepatic arteriography (or both) was performed for the precise evaluation of HCC suspected by sonography, conventional CT, or MR imaging (or all three). One hundred one nodules, including 85 HCCs and 16 dysplastic nodules, were verified by surgical resection; the remaining 100 nodules, including 13 HCCs and 87 dysplastic nodules, were verified by percutaneous biopsy with sonographic guidance using a 21-gauge thin needle. The period between CT during arterial portography or CT during hepatic arteriography (or both) examinations and biopsy or resection was within 1 month. One hundred four men and 35 women were included in the study. The cause of liver cirrhosis was related to hepatitis B virus in 43 patients, hepatitis C virus in 87 patients, both hepatitis B and C viruses in four patients, alcohol in three patients, Budd-Chiari syndrome in one patient, and primary biliary cirrhosis in one patient. Nodules with marked fat deposition showing less than 0 H on CT within the greater part of the nodule were excluded from the study because the precise evaluation of intranodular blood flow on CT during arterial portography or CT during hepatic arteriography and histologic diagnosis by biopsy was occasionally difficult. These nodules were histologically categorized according to the classification proposed by the International Working Party of the World Congress of Gastroenterology [7] by two experienced liver pathologists. According to this classification, these hepatocellular nodules are divided into two categories—namely, dysplastic nodule and HCC. A dysplastic nodule is defined as a nodular lesion of hepatocytes at least 1 mm in diameter with dysplasia but without definite histologic criteria of malignancy and is divided into two subtypes: low-grade dysplastic nodule (low-DN) and high-grade dysplastic nodule (high-DN). In low-DNs, atypia is mild. These nodules are composed of hepatocytes that are minimally abnormal. The nuclear–cytoplasmic ratio is normal or slightly increased. Portal tracts are present. Because separation of large regenerative nodules from low-DNs by biopsy specimen is often impossible, both of them were categorized in the low-DN group in this study. In high-DNs, atypia is at least moderate but insufficient for the diagnosis of malignancy. One or more features may be seen: high nuclear–cytoplasmic ratio, nuclear hyperchromasia, plates more than two cells wide, pseudoglandular formation, and cytoplasmic basophilia. Invasion to stroma or portal tracts is absent. On the other hand, HCC is defined as a malignant neoplasm composed of cells with hepatocellular differentiation. In this study, HCC is classified into two groups: well-differentiated HCC (wd-HCC) and moderately or poorly differentiated HCC (mp-HCC). In wd-HCCs, the lesions reveal irregular, thin trabecular patterns arranged in two or more layers or pseudoglandular patterns (or both). The degree of atypia is almost the same as that of Edmondson-Steiner (Ed.) grade I [10]. In mp-HCCs, the lesions occasionally show a trabecular pattern arranged in several layers, corresponding to the category of Ed.-II or -III of cell atypia.

CT during arterial portography and CT during hepatic arteriography were carried out in the CT room after completion of hepatic angiography using a digital subtraction angiography system in the angiographic room. For hepatic angiography, about 30 ml of iohexol (Omnipaque, 350 mg I/ml; Daiichi, Tokyo, Japan) was used. When both CT during arterial portography and CT during hepatic arteriography were performed, two 4-French catheters were inserted into the ipsilateral common femoral artery by different punctures. In 30 patients, conventional CT during arterial portography was usually performed using a scanner (9800 HiLight; General Electric Medical Systems, Milwaukee, WI) with the following parameters: contiguous 10-mm-thick axial sections, 2-sec imaging time, and 6-sec interscan delay. For conventional CT during arterial portography, 70–100 ml of iohexol (320 mg I/ml) was infused via a catheter in the superior mesenteric artery at a rate of 0.6–0.8 ml/sec according to the scanning time of the entire liver using a power injector (Mark V; Medrad, Pittsburgh, PA) during sequential scanning of the liver with incremental changes in the position of the table. Infusion of contrast material was initiated 20 sec before CT during arterial portography. On the other hand, helical CT during arterial portography was performed in 109 patients using a scanner (HiSpeed Advantage; General Electric Medical Systems) with slip-ring technology with 7-mm slices and 7-mm collimation. The scan duration was 20–25 sec (during a single breath-hold) for a total scanned length of 14–18 cm. Overlapping reconstructions were obtained every 3.5 mm. Helical scanning began 25 sec after beginning the infusion of 60 ml of iohexol (320 mg I/ml) at the speed of 1.5 ml/sec. Helical CT during hepatic arteriography was performed with 3-mm slices, 3-mm collimation, and 1.5-mm reconstruction intervals. For conventional and helical CT arterial portography, 20 μg of prostaglandin E_1 (Prostandin; Ono, Tokyo, Japan) was injected into the superior mesenteric artery immediately before injection of contrast medium. CT during the hepatic arteriography study was divided into two series for scanning the entire liver. CT during hepatic arteriography scanning began 10 sec after initiation of the injection of iohexol (320 mg I/ml) at 1 ml/sec through the 4-French angiographic catheter positioned in the common or proper hepatic artery, and the infusion was continued during scanning. Analysis of the findings on CT during arterial portography in all 201 nodules and CT during hepatic arteriography in 74 nodules was retrospectively performed by consensus of three experienced radiologists without knowledge of the final histologic diagnosis.

Among these nodules, the differences in intranodular portal blood supply evaluated by CT during arterial portography and intranodular arterial supply revealed by CT during hepatic arteriography were analyzed. The correlation between the grade of malignancy of the nodules and CT during arterial portography and CT during hepatic arteriography findings was also evaluated. For statistical analysis, Fisher's exact probability test and Spearman's rank correlation test were used. In addition, the correlation between the findings on CT during arterial portography and CT during hepatic arteriography in each nodule was analyzed.

Results

CT during arterial portography findings were classified into four types relative to the surrounding cirrhotic liver (Fig. 1). In type A, the nodule was not visualized (isodense), indicating almost the same intranodular portal blood supply. In type B, the nodule was revealed as a slightly hypodense area (attenuation in the nodule was higher than that in the intrahepatic inferior vena cava in which no contrast medium flowed in during the scanning) relative to the surrounding liver parenchyma, indicating decreased, but not absent, intranodular portal blood flow. In type C, the nodule was shown as a partially hypodense area (attenuation of this area was lower than that in the intrahepatic inferior vena cava), indicating a partially absent intranodular portal blood supply. In type D, the greater part of the nodule was seen as a markedly hypodense area (attenuation of the entire nodule was more hypodense than that in the inferior vena cava), indicating an absent intranodular portal supply.

CT during hepatic arteriography findings were also categorized into four types relative to the surrounding cirrhotic liver (Fig. 2). In type I,

American Journal of Roentgenology 1999.172:969-976.

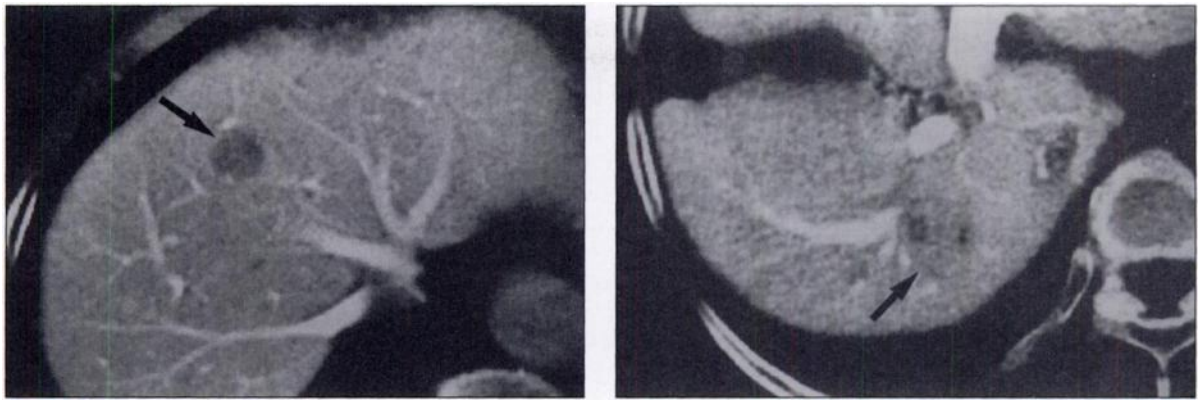
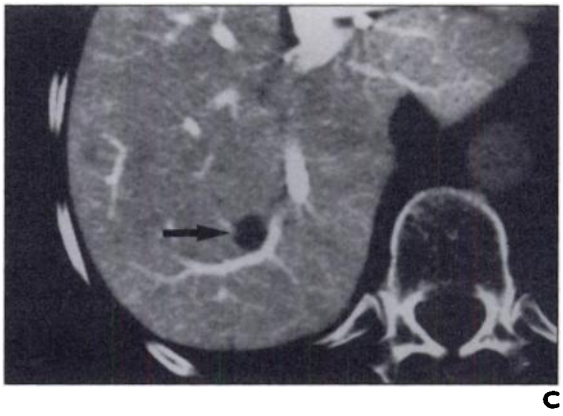
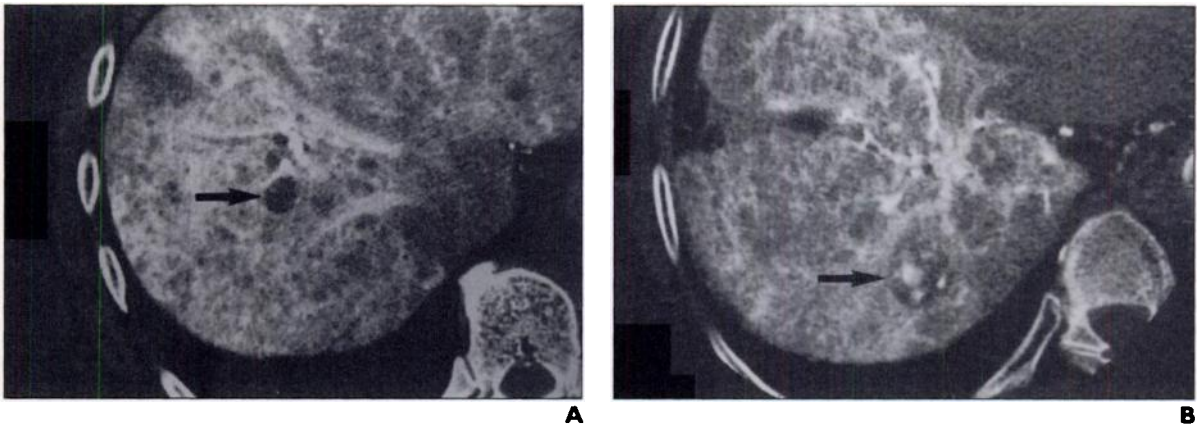


Fig. 1.—Types of findings on CT during arterial portography.
A, Type B nodule in 58-year-old man. Note slightly hypodense nodule (*arrow*).
B, Type C nodule in 66-year-old man. Note partially hypodense nodule (*arrow*).
C, Type D nodule in 62-year-old man. Note markedly hypodense nodule (*arrow*).





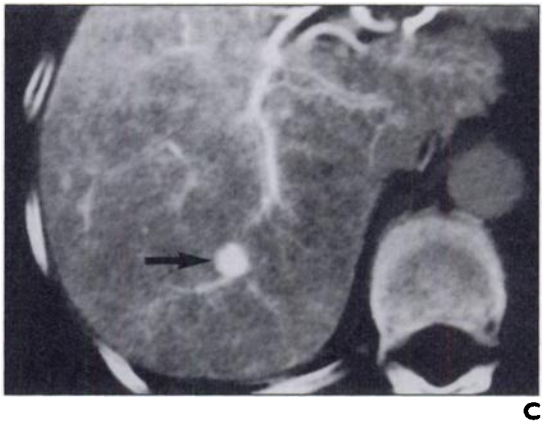


Fig. 2.—Types of findings on CT during hepatic arteriography.
A, Type II nodule in 58-year-old man. Note hypodense nodule (*arrow*).
B, Type III nodule in 66-year-old man. Note partially hyperdense nodule (*arrow*).
C, Type IV nodule in 62-year-old man. Note hyperdense nodule (*arrow*).

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the nodule was not visualized (isodense), indicating almost the same intranodular arterial blood supply. In type II, the nodule was visualized as a hypodense area, indicating decreased intranodular arterial blood supply. In type III, a part of the nodule was hyperdense, indicating a partially increased intranodular arterial blood supply. In type IV, the greater part of the nodule was visualized as a hyperdense area, indicating an increased intranodular arterial blood supply.

Table 1 shows the correlation between the histologic types of the nodules and findings on CT during arterial portography. Thirty-six (76.6%) of 47 low-DNs showed type A (Fig. 3A), and the ratio of type A in low-DNs was higher than that in the other histologic groups. The difference of the ratio of type A between low-DNs and the other histologic groups was statistically significant (Fisher's exact probability test, $p < .05$). The high-DNs had a tendency to show type A or type B (Fig. 4A) without statistical significance compared with those in the other groups. Thirteen (51.2%) of 24 wd-HCCs revealed type C (Fig. 5A), and the ratio of type C in wd-HCCs was higher than that in the other histologic groups with statistical significance ($p < .05$). All 74 mp-HCCs showed type D, and the ratio of type D in mp-HCCs was significantly high compared with that in the other histologic groups ($p < .05$). Table 2 shows the correlation between the histologic types of nodules and the findings on CT during hepatic arteriography. Eighteen (69.2%) of 26 low-DNs showed type I, and seven (26.9%) showed type II (Fig. 3B); however, the ratio of type I in low-DNs was not significantly higher than that in high-DNs. The high-DNs had a tendency to show type I, type II, or type III (Fig. 4B) without statistical significance compared with those in the other groups. Eight (53.3%) of 15 wd-HCCs showed type III (Fig. 5B), and six (40%) showed type IV; however, the ratios were not significantly high compared with those in the other histologic groups. All mp-HCCs showed type IV, and the ratio was significantly high ($p < .05$).

According to these results, findings on CT during arterial portography of types A, B, C, and D were considered to be scored 1, 2, 3, and 4 in order from low to high grade of malignancy of the nodules. The histologic groups were also scored 1, 2, 3, and 4 in order from low to high grade of malignancy. Spearman's rank correlation analysis carried out between them revealed a strong correlation between the types of the intranodular portal blood supply evaluated by CT during arterial portography and the grade of the malignancy of the nodules (ρ, .861; $p < .0001$). The same scoring was used for findings on CT during hepatic arteriography—namely, types I, II, III, and IV were considered to be scored 1, 2, 3, and 4 in order. Spearman's rank correlation analysis between the types of the intranodular arterial blood supply revealed by CT during hepatic arteriography and the grade of malignancy of the nodules also showed a statistically significant correlation (ρ, .820; $p < .0001$).

Table 3 shows the correlation between the types on CT during arterial portography and CT during hepatic arteriography for each of 74 nodules in which both procedures were performed. As shown in Table 3, the nodules visualized as type A on CT during arterial portography had a

TABLE 1 Number and Percentage Distribution of Nodules for Four Types of Findings on CT During Arterial Portography

Histology	*n*	No. (%) of Nodules for Type[a] of Findings on CT During Arterial Portography			
		A	B	C	D
Low-grade dysplastic nodule	47	36 (76.6)[b]	8 (17.0)	3 (6.4)	0 (0.0)
High-grade dysplastic nodule	56	18 (32.1)	20 (35.7)	10 (17.9)	8 (14.3)
Well-differentiated HCC	24	0 (0.0)	4 (16.7)	13 (51.2)[b]	7 (29.2)
Moderately or poorly differentiated HCC	74	0 (0.0)	0 (0.0)	0 (0.0)	74 (100.0)[b]

Note.—*n* = number of nodules, HCC = hepatocellular carcinoma.

[a] Type A = isodense, type B = slightly hypodense, type C = partially hypodense, type D = markedly hypodense.

[b] $p < .05$ (Fisher's exact probability test).

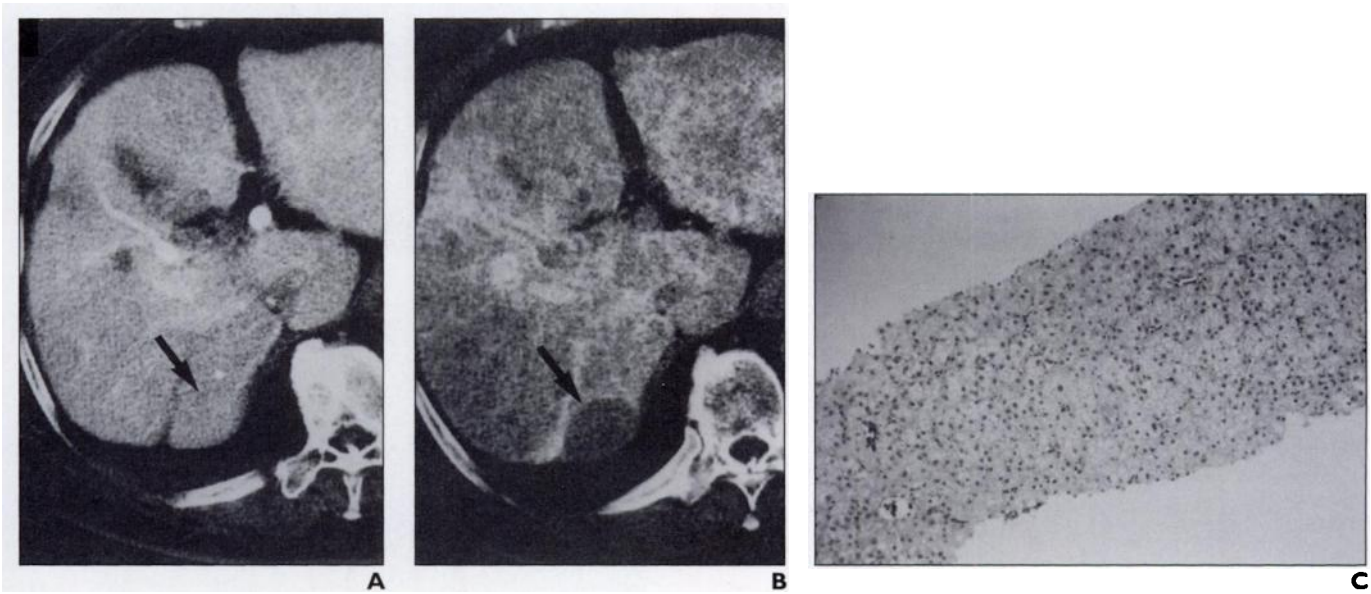
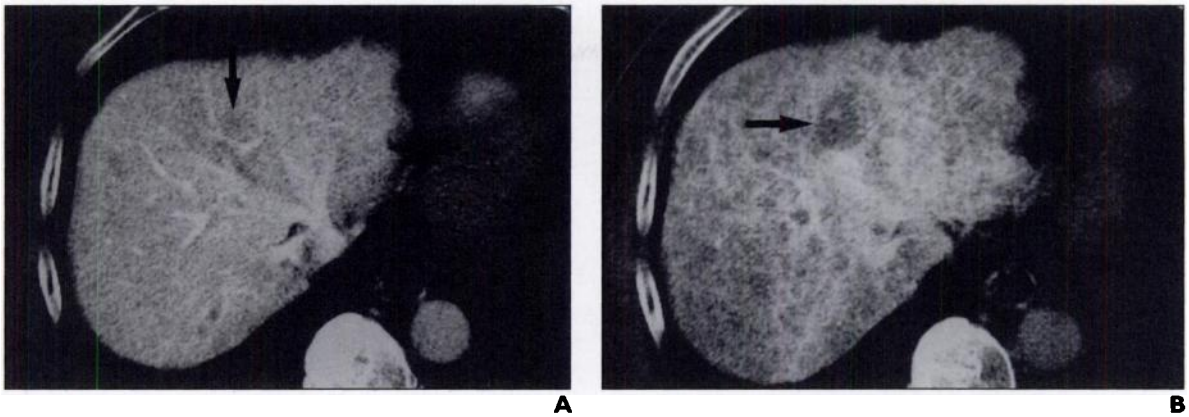
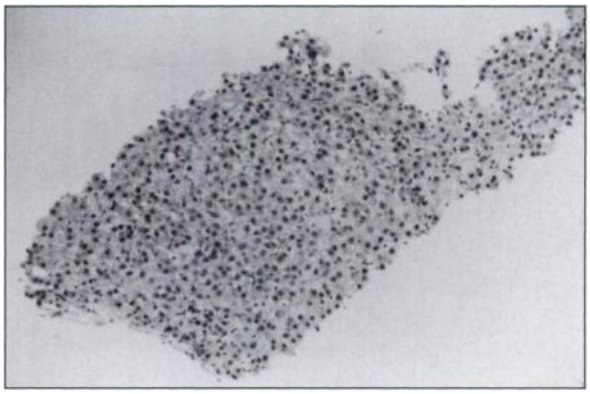


Fig. 3.—Low-grade dysplastic nodule in 53-year-old man.
A, CT during arterial portography fails to reveal nodule (*arrow*).
B, CT during hepatic arteriography shows hypodense nodule (*arrow*).
C, Histologic findings on biopsy specimen reveal low-grade dysplastic nodule. (H and E, ×100)



A B

Fig. 4.—High-grade dysplastic nodule in 62-year-old man.
A, CT during arterial portography shows slightly hypodense nodule (*arrow*).
B, CT during hepatic arteriography reveals hypodense nodule 2.0 cm in diameter (*arrow*).
C, Histologic findings on biopsied specimen reveal high-grade dysplastic nodule. (H and E, ×100)



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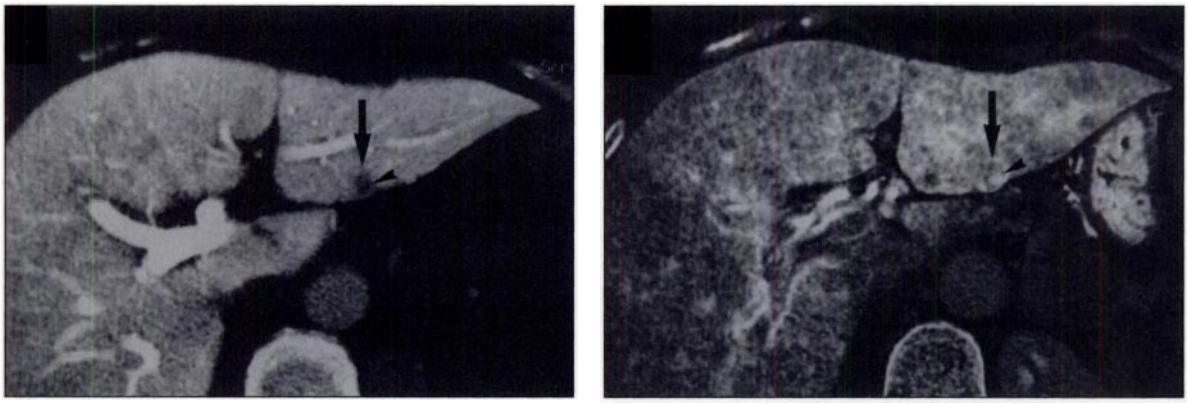
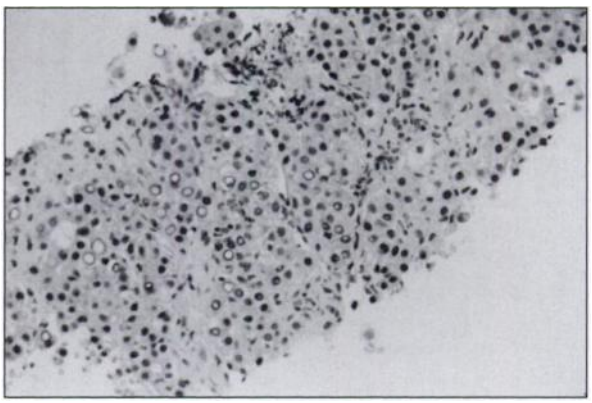


A B



C

Fig. 5.—Well-differentiated hepatocellular carcinoma in 58-year-old woman.
A, CT during arterial portography shows hypodense nodule (*arrow*) with internal more definitely hypodense area (*arrowhead*).
B, CT during hepatic arteriography shows isodense lesion compared with surrounding cirrhotic liver (*arrow*) with internal definite staining focus (*arrowhead*).
C, Histologic findings on biopsied specimen reveal well-differentiated hepatocellular carcinoma. (H and E, ×200)

TABLE 2 Number and Percentage Distribution of Nodules for Four Types of Findings on CT During Hepatic Arteriography

Histology	*n*	No. (%) of Nodules for Type [a] of Findings on CT During Hepatic Arteriography			
		I	II	III	IV
Low-grade dysplastic nodule	26	18 (69.2)	7 (26.9)	1 (3.9)	0 (0.0)
High-grade dysplastic nodule	19	6 (31.6)	7 (36.8)	4 (21.1)	2 (10.5)
Well-differentiated HCC	15	1 (6.7)	0 (0.0)	8 (53.3)	6 (40.0)
Moderately or poorly differentiated HCC	14	0 (0.0)	0 (0.0)	0 (0.0)	14 (100.0) [b]

Note.—*n* = number of nodules, HCC = hepatocellular carcinoma.

[a] Type I = isodense, type II = hypodense, type III = partially hyperdense, type IV = hyperdense.

[b] $p < .05$ (Fisher's exact probability test).

TABLE 3 Correlation Between Findings on CT During Arterial Portography and CT During Hepatic Arteriography in Each Nodule for Which Both Procedures Were Performed

Type [a] of Findings on CT During Hepatic Arteriography	Histology	*n*	No. of Nodules for Type [b] of Findings on CT During Arterial Portography			
			A	B	C	D
I	Low-grade dysplastic nodule	18	15	1	2	0
	High-grade dysplastic nodule	6	3	3	0	0
	Well-differentiated HCC	1	0	0	0	1
II	Low-grade dysplastic nodule	7	7	0	0	0
	High-grade dysplastic nodule	7	5	0	2	0
III	Low-grade dysplastic nodule	1	1	0	0	0
	High-grade dysplastic nodule	4	1	1	2	0
	Well-differentiated HCC	8	0	0	7	1
IV	High-grade dysplastic nodule	2	0	0	0	2
	Well-differentiated HCC	6	0	1	0	5
	Moderately or poorly differentiated HCC	14	0	0	0	14

Note.—*n* = number of nodules, HCC = hepatocellular carcinoma.

[a] Type I = isodense, type II = hypodense, type III = partially hyperdense, type IV = hyperdense.

[b] Type A = isodense, type B = slightly hypodense, type C = partially hypodense, type D = markedly hypodense.

strong tendency to show type I or type II on CT during hepatic arteriography, with type C on CT during arterial portography tending to show type III on CT during hepatic arteriography and type D on CT during arterial portography tending to show type IV on CT during hepatic arteriography.

Discussion

Cirrhotic liver contains various kinds of hepatocellular nodules, including HCC as described. Although the current literature has provided the definitions for these hepatocellular nodules, to our knowledge, no widely accepted nomenclature or diagnostic criteria have been reported. The term "adenomatous hyperplasia" was first used by Edmondson [11] in 1976 and was defined as a sizable and discrete parenchymal nodule that occurred after acute or chronic liver injury. In 1986, Arakawa et al. [12] first described the emergence of malignant hepatocellular lesions in five adenomatous hyperplasias seen in cirrhotic livers and suggested that adenomatous hyperplasia was a preneoplastic lesion of HCC. Since then, other investigators have reported similar cases [13–16], supporting the hypothesis proposed by Arakawa et al. Nakanuma et al. [17], Terada and Nakanuma [18], and Terada et al. [19] classified two types of adenomatous hyperplasia, ordinary adenomatous hyperplasia and atypical adenomatous hyperplasia, according to the degree of hepatocyte atypia seen in these nodules. We used this classification in reporting the imaging findings of adenomatous hyperplasia and overt HCC [4, 5]. However, after these reports were published, the concept of adenomatous hyperplasia and the early stage of wd-HCC was changed according to the understanding of hepatocarcinogenesis in the human cirrhotic liver clarified by accumulated experience in clinical practice [20–23]. To establish a common standard of the histologic diagnosis of these hepatocellular nodules, the classification was proposed in 1992 by the Liver Cancer Study Group of Japan [6]. In this classification, the hepatocellular nodules were divided into adenomatous hyperplasia, atypical adenomatous hyperplasia, early HCC of the well-differentiated type, wd-HCC, and mp-HCCs and was widely used in Japan. However, the concept of early HCC of the well-differentiated type was not well accepted by Western pathologists, and a new classification that was acceptable to pathologists worldwide was introduced in 1994 by the International Working Party of the World Congress of Gastroenterology [7]. According to this new international classification, the low-DN is considered to be consistent with a large regenerative nodule or adenomatous hyperplasia, and the high-DN is considered to be consistent with atypical adenomatous hyperplasia and early HCC of the well-differentiated type used in the classification proposed by the Liver Cancer Study Group of Japan [6].

Because the findings on sonography and conventional CT are almost the same among borderline lesions and early-stage small HCCs, percutaneous biopsy with sonographic guidance is usually performed for definitive diagnosis. However, some important problems exist with this method. First, the pathologic findings of a needle biopsy specimen are not absolutely representative of the entire nodule because of occasional internal heterogeneity. Second, sonographically guided biopsy is impossible for nodules that are invisible on sonography. Third, obtaining a sufficient tissue sample for precise diagnosis from a tiny nodule is not easy. Fourth, the procedure is occasionally time-consuming and rather invasive when tissue from the multicentric coexisting nodules is obtained [3, 19]. Therefore, differential diagnosis among these nodules by imaging is also important clinically. For this purpose, we previously reported that evaluation of the intranodular blood supply using hepatic arteriography and CT during arterial portography was valuable in the differential diagnosis of benign and malignant nodules associated with liver cirrhosis [4]. This concept has become widely accepted and applied in the clinical setting since publication of our report; however, the histologic criteria used in our previous report are insufficient for evaluation of the hepatocellular nodules classified by the recent pathologic concepts, and hepatic arteriography was not as accurate in analyzing the faint arterial blood flow in small nodules. In addition, in a large number of cases, no statistical correlation was proven between the blood sup-

American Journal of Roentgenology 1999.172:969-976.

ply evaluated by imaging diagnosis and grade of malignancy. On the other hand, recent advances in helical CT technique have significantly enhanced the detectability of small nodular lesions in the liver using a thin reconstruction interval during breath-holding and have made both CT during arterial portography and CT during hepatic arteriography possible to perform during routine angiography examination. Therefore, in the present study, we evaluated the correlation between intranodular blood supply revealed by CT during arterial portography and CT during hepatic arteriography, using mainly helical CT, and various kinds of hepatocellular nodules classified by the criteria proposed by the International Working Party [7] in a large number of nodules.

In this study, we found a strong correlation between the intranodular arterial and portal supply evaluated by CT during hepatic arteriography and CT during arterial portography and the grade of malignancy of the hepatocellular nodules—that is, the intranodular portal supply relative to the surrounding liver parenchyma observed by CT during arterial portography was decreased, whereas the intranodular arterial supply revealed by CT during hepatic arteriography was first decreased during the early stage of hepatocarcinogenesis and then increased in accordance with elevation of the grade of malignancy of the nodules. A statistically significant correlation was found between some types of findings on CT during arterial portography or CT during hepatic arteriography and the histologic groups of the nodules. These pairs were as follows: low-DN and type A (almost the same portal supply relative to the surrounding liver), wd-HCC and type C (partially absent portal supply), and mp-HCC and type D (absent portal supply) on CT arterial portography and mp-HCC and type IV (increased arterial supply) on CT during hepatic arteriography ($p < .05$). In addition, there was a tendency without statistical significance that high-DN showed type A or type B on CT during arterial portography, indicating an intermediate portal supply between low-DN and wd-HCC. On CT during hepatic arteriography, there was some tendency that low-DNs showed type I (the same arterial supply); high-DNs showed type I and type II (decreased arterial supply), indicating intermediate arterial supply between the low-DN and wd-HCC; and wd-HCCs showed type III (partially increased arterial supply). Ueda et al. [24] morphometrically examined the vascular supply of adenomatous hyperplasia and HCC and suggested that the portal tracts, including portal vein and hepatic artery, were decreased in accordance with increasing grade of malignancy of the nodules and were almost absent in HCCs. In contrast, abnormal arteries due to tumor angiogenesis occurred in atypical adenomatous hyperplasia during the course of hepatocarcinogenesis and were markedly increased in HCCs. The results obtained in our study correlate well with the histologic findings of Ueda et al., which are useful when estimating the grade of malignancy of the nodules. In our study, the reason that some high-DNs were hypodense or isodense on CT during hepatic arteriography may be that the nodules with decreased portal tracts, including normal hepatic arteries without increased abnormal arteries, were hypodense, and when the increased abnormal arterial supply compensated for the decreased arterial supply through the portal tracts (normally present hepatic artery) in the nodules, they were visualized as isodense. A schematic presentation of this concept regarding the changes of intranodular blood supply in hepatocellular nodules is summarized in Figure 6. Consequently, isodense on CT during hepatic arteriography means two different conditions, one being a large regenerative nodule or low-DN in which almost the same arterial supply through a normal hepatic artery is present and the other being a high-DN in which an increased abnormal arterial supply compensates for a decreased normal arterial supply in the nodule. More than half of wd-HCCs in our study showed a partially absent portal flow on CT during arterial portography, and this rate was significantly high compared with that of the other histologic groups ($p < .05$); most wd-HCCs showed a partially increased or an increased arterial blood supply on CT during hepatic arteriography. This finding suggests that when foci showing absent portal and increased arterial flow indicating mp-HCC foci are revealed in the nodule, the entire nodule is already a wd-HCC in most cases. However, the same type of arterial and portal supply was also seen in some high-DNs and in a few low-DNs. Therefore, we believe that mp-HCC can occur even in these nodules, and a rapid progression of multistep development to HCC may explain this condition.

Although some reports similar to this evaluation had been described by Takayasu et al. [23] and Kudo et al. [25] using CO_2 sonographic angiography, the number of cases in these reports was small, and the histologic definition and terms used were inconsistent. Takayasu et al. analyzed the findings on CT during arterial portography and CT during hepatic arteriography in early HCCs. However, these researchers did not mention the findings of borderline lesions on CT during arterial portography or CT during hepatic arteriography. To our knowledge, our study is the first to use the new classification in a large number of cases, evaluated mainly by an advanced helical CT technique, with confidence of diagnostic accuracy. On the basis of our results, we believe that we can presume the histologic grade of malignancy by evaluation of the blood supply in these nodules using CT during arterial portography and CT during hepatic arteriography. However, because CT during arterial portography and CT during hepatic arteriography are invasive, the findings revealed here should be applied to Doppler sonography, dynamic CT, and dynamic MR imaging. Moreover, the sensitivity in visualizing the arterial blood supply in these small nodules by these techniques is inferior to that of CT during hepatic arteri-

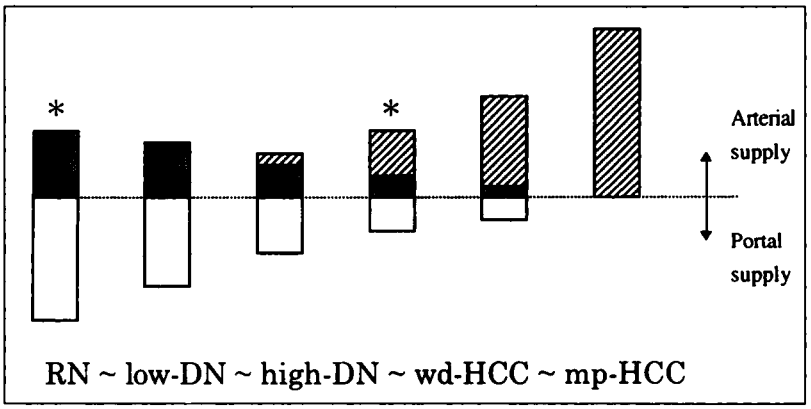


Fig. 6.—Diagram shows changes of intranodular blood supply (shaded bars = hepatic arterial supply, open bars = portal supply, hatched bars = abnormal arterial supply) in hepatocellular nodules associated with liver cirrhosis in accordance with elevation of grade of malignancy of the nodules. RN = regenerative nodule, low-DN = low-grade dysplastic nodule, high-DN = high-grade dysplastic nodule, wd-HCC = well-differentiated hepatocellular carcinoma, mp-HCC = moderately or poorly differentiated hepatocellular carcinoma. Asterisks indicate isodense on CT during hepatic arteriography.

ography, and the precise analysis of intranodular portal supply is almost impossible without CT during arterial portography. Therefore, the efforts to evaluate these nodules noninvasively should be continued. At this time, comprehensive diagnostic imaging, including dynamic CT, dynamic MR imaging, and Doppler sonography, is valuable in clinical practice, and when increased arterial supply is not definite on these examinations, further study by CT during arterial portography and CT during hepatic arteriography is recommended.

In this study, the findings on CT during arterial portography and CT during hepatic arteriography sometimes did not coincide in each nodule with the histologic findings (Tables 1–3). Possible causes of this discrepancy may include histologic heterogeneity in the nodules, possibility of sampling error, and imaging findings modified by the individual physiologic state. However, in a large number of cases, the evaluation proved a statistically significant correlation between the four types of findings on CT during arterial portography and CT during hepatic arteriography and the grade of malignancy of the nodules. Therefore, we believe we were able to overcome these problems.

In this study, prostaglandin E_1 was used as a vasodilator in CT during arterial portography. On the basis of our experience, the frequency of inhomogeneous enhancement of the liver parenchyma due to laminal flow from the unopacified splenic venous blood can be decreased by use of a vasodilator, probably because of increased venous return from the densely opacified superior mesenteric vein and good mixing between blood from the superior mesenteric vein and the splenic vein. Use of a vasodilator might suggest some possibility of modification of intranodular portal flow. This possible difference should be taken into consideration when our results are compared with those obtained on CT during arterial portography without use of a vasodilator.

In conclusion, evaluation of blood supply by CT during intraarterial injection of contrast medium was considered to be valuable to estimate the grade of malignancy of the hepatocellular nodules associated with liver cirrhosis when overlap in the appearance between dysplastic nodules and HCCs occurred and, as a result, to determine the treatment methods of these nodules and of cirrhotic patients. The concept revealed in this study can apply to diagnoses made on the basis of Doppler sonography, dynamic CT, and MR imaging.

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