Computed Tomography during Arteriography and Arterial Portography in Small Hepatocellular Carcinoma and Dysplastic Nodule: A Prospective Study

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We studied the relationship between the findings of computed tomography during arteriography (CTA) and computed tomography during arterial portography (CTAP), and pathologic findings of 81 small nodular lesions (3 cm or less in diameter) in resected liver specimens. The 81 lesions consisted of 8 dysplastic nodule (DN) lesions, 23 well-differentiated hepatocellular carcinomas (early HCCs) and 50 moderately or poorly differentiated HCCs (advanced HCCs). We also performed standard computed tomography (CT), digital subtraction angiography (DSA), magnetic resonance imaging (MRI), and ultrasonography, and compared sensitivities with CTA, CTAP, or combination of CTA and CTAP with other imaging methods. Forty-four of the 50 advanced HCCs, 12 of the 23 early HCCs, and none of 8 DNs hyperattenuated with CTA and hypoattenuated with CTAP. The sensitivity for the early HCCs was significantly higher for CTA and CTAP in combination as compared with DSA or standard CT. The sensitivity for the advanced HCCs was significantly higher for CTA and CTAP in combination than with DSA. The sequential changes of the blood supply from the portal vein to the hepatic artery during the development of the HCCs were observed. Although CTA and CTAP in combination were useful for the distinction of advanced HCC from early HCC or DN, CTA and CTAP used in combination were not superior to CTA alone in the detection of such lesions.

Key words: Hepatocellular carcinoma — Angio CT — CT during arteriography — CT during arterial portography — Adenomatous hyperplasia

Hepatocellular carcinoma (HCC) is one of the common malignant liver tumors in Japan.1) With progress in imaging techniques, such as ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI), the number of small hepatic nodules detected in patients with chronic liver disease has increased.2–4) The presence of small additional HCCs undetectable before liver resection is a critical problem.5) These small nodules detectable in the liver include dysplastic nodule (DN, adenomatous hyperplasia),6) which is thought to be a premalignant lesion,7–10) and HCC. The typical form of HCC, moderately or poorly differentiated HCC, appears as a hypervascular lesion on a conventional angiogram and is principally supplied by the hepatic artery.2–4) Well-differentiated HCCs and DNs exhibit various patterns on hepatic angiograms, depending on the supply of blood from the portal vein.2–4, 11, 12) In the diagnosis of small nodules, it is important to realize the differences in their blood supply. Recently, the usefulness of computed tomography during arterial portography (CTAP) in the detection of small hepatic tumors has been reported.8–10) The role of computed tomography during arteriography (CTA) has also been reported.4, 11, 12–19) However, there have been few reports about results from CTA and CTAP in combination, or comparison of the sensitivity of the methods with other imaging methods, or studies of the sequential changes in blood supply during the various stages of hepatocarcinogenesis as evaluated by these methods. We have performed a prospective study using various imaging methods including CTA and CTAP, and compared the CTA and CTAP findings with the pathologic findings of the tumors. We also studied the effectiveness of using CTA and CTAP in combination to detect and differentially diagnose small hepatic nodules.

MATERIALS AND METHODS

Patients During the period between June 1994 and November 1997, 54 patients with small hepatic nodules (3 cm or less in diameter) underwent both CTA and CTAP before hepatic resection or needle biopsy, at our department. The 54 patients had a total of 81 lesions. The ages of the 54 patients (49 men and 5 women) ranged from 36 to 76 years with a median age of 60. Thirty-six of the 54 patients had liver cirrhosis. The results of hepatitis B surface antigen test were positive in 8 patients and an ELISA test using a second- or third-generation antibody to hepatitis C virus yielded positive results in 44 patients. Pathologic examination of operative or needle specimens indi-
cated that 8 nodules were DN (DN group), 23 nodules were well-differentiated HCC (early HCC group), 50 nodules were moderately or poorly differentiated HCC (advanced HCC group). The pathologic diagnosis was made based on the General Rules for the Clinical and Pathological Study of Primary Liver Cancer in Japan, with some modifications. A DN was defined as a nodular lesion of hepatocytes at least 1 mm in diameter with dysplasia but without definite histologic criteria of malignancy.

**Diagnostic imaging** For US, an SSD-2000 unit (Aloka Co., Ltd., Tokyo) and a 5.0-MHz transducer were used. Standard CT images were obtained with a X-Vigor (Toshiba, Tokyo). The liver was scanned in 10-mm thick sections for 2.0 s with 10 mm gaps between sections. MRI (Toshiba, Tokyo) and a 5.0-MHz transducer were used. Gradient Echo images were obtained for the T1 weighted (GE, SIGNA-HORIZON, Milwaukee, WI, or SIEMENS MAGNETOM, VISION, Erlangen, Germany). Gradient Echo images were obtained for the T1 weighted image with a repetition time (TR) of 130–160 ms and an echo time (TE) of 4–5 ms. The flip angle was set at 90 degrees. For the T2 weighted image, First Spin Echo images were of TR 3000–4000 ms, and TE 80–100 ms. The section thickness was 8 mm with gaps of 2 mm. Angiograms were evaluated by digital subtraction angiography (DSA). DSA was performed by a DSA apparatus (DHF-1510CX, Hitachi Medical Corp., Tokyo) with a 0.6-mm focal spot, and a 12-inch diameter image intensifier on a 1024×1024 matrix. DSA with a selective catheterization distal to the common hepatic artery was performed using 15 to 25 ml of a contrast medium [Iopamiron, Schering (300 mg/ml)], at an injection rate of 3.0 to 8.0 ml/s. The CTA and CTAP scans were obtained using a commercially available unit (CT-W 2000, Hitachi Medical Corp.) for 5-mm thick sections. A catheter was placed in the common hepatic artery for the CTA and in the superior mesenteric artery for the CTAP. A total of 60 ml of iopamidol [Iopamiron (300 mg/ml)] diluted with saline (1:2 ratio) was used for the CTA; 90 ml of the same agent at the same dilution ratio was used for the CTAP. The contrast agents were administered with a power injector. CT scanning was begun 7 s after the start of the injection of contrast material for CTA and 30 s after injection for CTAP at a speed of 2 and 3 ml/s, respectively. The findings from the images were evaluated by at least two radiologists for CTA, CTAP, standard CT (unenhanced, enhanced, and dynamic CT combined), DSA, and MRI, and by at least two surgeons for US. The sensitivity of detecting hepatic nodules were calculated for CTA, CTAP, CTA and CTAP in combination, standard CT, DSA, preoperative US, and intraoperative US. The χ² or Fisher’s exact test and Bonferroni’s method were used for statistical analysis.

This study was in accordance with the Helsinki Declaration and the guidelines of the ethical committee of our institution. Informed consent was obtained from each patient.

### RESULTS

A comparison of the CTA and CTAP findings with the histologic findings of the nodules is shown in Table I. With CTA, 44 of the 50 advanced HCCs, 12 of the 23 early HCCs, and none of the 8 DNs were shown as hyperattenuating masses. Seven of the 23 early HCCs and 2 of the 8 DNs were shown as hypooattenuating masses. Four of the 23 early HCCs and 6 of the 8 DNs were shown as isoattenuating masses. With CTAP, 45 of the 50 advanced HCCs and 14 of the 23 early HCCs were shown as hypooattenuating masses. Nine early HCCs and all 8 DNs were shown as isoattenuating masses. Six of the 8 DNs, 4 of the 23 early HCCs, and 5 of 50 advanced HCCs were not detected by either CTA or CTAP since these nodules were shown as isoattenuating masses. With CTA and CTAP in combination, 44 of the 50 advanced HCCs, 12 of the 23 early HCCs and none of the 8 DNs were shown as hyperattenuating with CTA, and hypooattenuating with CTAP (Fig. 1). These imaging findings have been reported to be a typical pattern of overt HCCs. Eleven of the 23 early HCCs and 8 DNs were not shown as having typical HCC patterns (Fig. 2). The proportion of the nodules shown as having the typical HCC pattern was significantly higher in the advanced HCC group than in the early HCC group or the DN group (P=0.0021, P<0.0001, respectively). The proportion was also significantly higher in the early HCC group than in the DN group (P=0.0116). As the nodule became less differentiated, an increasing proportion of nodules appeared as having the typical HCC pattern, indicating a progressive change in the blood supply from the portal vein to the hepatic artery during the various stages of hepatocarcinogenesis. In 7 early HCCs shown as hypooattenuating with CTA, pathologic examinations showed that fatty changes, which are often found in the early stage of HCC, were observed in 6 of the 7 nodules, and another nodule consisted of clear cells.

| Table I. Comparison of CTA and CTAP Imaging Findings with Pathologic Findings of Nodules |
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| **Pathologic findings (No. of nodules)** | **DN** | **Early HCC** | **Advanced HCC** |
| **CTA*** | **CTAP*** | **hyper** | **hypo** | **iso** | **hypo** | **iso** | **hypo** | **iso** |
| hyper | hypo | 0 | 12 | 44 |
| iso | hypo | 0 | 0 | 1 |
| iso | iso | 6 | 4 | 5 |
| hypo | hypo | 0 | 2 | 0 |
| hypo | iso | 2 | 5 | 0 |
| Total | 8 | 23 | 50 |

**DN,** dysplastic nodule; **early HCC,** well-differentiated HCC; **advanced HCC,** moderately and poorly differentiated HCC; **hypo,** hypooattenuating; **iso,** isoattenuating; **hyper,** hyperattenuating.
Sensitivity with CTA was 25% for DNs, 83% for early HCCs, and 88% for advanced HCCs (Table II). Sensitivity with CTAP was 0% for DNs, 61% for early HCCs, and 90% for advanced HCCs. With CTA and CTAP in combination, the sensitivity was 25% for DNs, 83% for early HCCs, and 90% for advanced HCCs. Thus, CTA and CTAP used in combination were not superior to CTA alone. Of 32 nodules of 1 cm or less in diameter, 15 nodules (6 DNs, 4 early HCCs, and 5 advanced HCCs) were not detected with CTA and CTAP in combination, whereas all nodules of diameter more than 1 cm were detected.

For the detection of advanced HCCs, the sensitivity was significantly higher with CTA and CTAP utilized in combination than with DSA (angiography, \( P = 0.0395 \)) and the sensitivity tended to be higher with CTA and CTAP in combination than with standard CT \( (P = 0.0664) \). For the detection of early HCCs, the sensitivity was significantly higher with CTA and CTAP in combination than with DSA or with standard CT \( (P = 0.0067, P = 0.0195, \text{respectively}) \). Two advanced HCCs, one early HCC, and 2 DNs were detected only by CTA or CTA and CTAP in combination before surgery. Of the 8 DNs, 3 were detected by intraoperative US, 2 were detected by the CTA, and 1 was detected by preoperative US, whereas none of 8 DNs was detected with CTAP.

**DISCUSSION**

Normal hepatic tissues are surrounded by sinusoids with 70% of the blood supply derived from the portal vein. In contrast, nearly 100% of the blood supply is derived from the hepatic artery in advanced HCCs. Most HCCs are considered to develop in multistep fashion.\(^7\)\(^-\)\(^10\),\(^22\) Chronic active hepatitis leads to liver cirrhosis, which produces DNs, and finally HCCs appearing within the nodule of DN. Sequential changes of blood supply from the portal vein to the hepatic artery and sinusoidal structure have been observed during the development of DNs into HCCs.\(^11\),\(^19\) Our previous study of immunohistochemistry...
and angiography revealed that DNs are supplied by the portal system and maintain sinusoidal structures. \(^{23}\) However, early HCCs are supplied by a combination of the portal and arterial vessels. Advanced HCCs develop a capillary network that is supplied by branches of the hepatic artery. Similar findings were also observed in hepatocarcinogenesis in rats. \(^{24}\) In this study, all DNs and 9 of the 23 early HCCs were shown as isoattenuating with CTAP, indicating that DNs and some well-differentiated HCCs have sinusoids resembling normal sinusoids. Seven of the 23 early HCCs were hypointensating with CTA and fatty change or clear cells were found in the 7 nodules, which indicated that the development of the capillaries was immature in the nodules. \(^{17}\) With CTA and CTAP in combination, 44 of the 50 advanced HCCs, 12 of the 23 early HCCs, and none of 8 DNs were shown as having a typical HCC pattern. The sequential change in blood supply from the portal vein to the hepatic artery during the development of HCC was reconfirmed in this study.

The usefulness of CTAP for detection of small HCCs has been reported. \(^{3,11,13–19}\) However, there have been few reports about the usefulness of CTA and CTAP in combination. In this study, although the difference was not statistically significant, CTA was shown to be more sensitive than CTAP for the detection of DNs and early HCCs. With CTA and CTAP in combination, 15 of 32 nodules of 1 cm or less in diameter could not be detected, without regard to the differentiation of the nodules. The sensitivity of either CTA, or CTAP for such small nodules was not satisfactory in other studies. \(^{14,15,17}\) The use of wide section thickness, respiratory movement, and partial-volume averaging may be the cause of some false-negative results. Several studies have reported a higher sensitivity with CTAP compared with MRI, standard CT, angiography, or some combination of them. \(^{3,13,14}\) In our study, the sensitivity for early HCC was significantly higher for CTA and CTAP utilized in combination than in DSA or standard CT. The sensitivity for advanced HCC was significantly higher for CTA and CTAP in combination than with DSA and tended to be higher for CTA and CTAP than with standard CT. Two advanced HCCs, one early HCC, and 2 DNs were detected only by CTA or CT and CTAP in combination before surgery. CTA and CTAP used in combination were not superior to CTA alone. Some imaging methods, including MRI and CTAP, may be unnecessary for the detection of such lesions.

Degree of differentiation in HCCs has been reported as a significant risk factor in the recurrence of HCC after resection; the incidence of recurrence was significantly higher in moderately or poorly differentiated HCCs than in well-differentiated HCCs. \(^{25,26}\) Metastasis has not been reported in the case of well-differentiated HCCs or from HCCs of Edmondson-Steiner grade I. \(^7,21\) On the other hands, portal invasion, a risk factor for recurrence, \(^{25,26}\) is often found in patients with advanced HCCs. \(^{27}\) It seems important to be able to differentiate advanced HCCs from well-differentiated HCCs. In this study, the proportion of nodules with the typical HCC pattern was significantly higher in advanced HCCs than in early HCCs or in DNs. With CTA and CTAP used in combination, it is possible to differentiate advanced HCCs from early HCCs or DNs in some patients, which is useful in developing a strategy to treat HCC and to estimate the outcome after operation.

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