Differentiation of Hepatocellular Carcinoma from Intrahepatic Cholangiocarcinoma as the Cause of Biliary Obstruction: Value of Dynamic CT During the Hepatic Arterial Phase

June-Sik Cho, M.D., Dae-Hong Kim, M.D., Kyung-Sook Shin, M.D., Jin-Keun Kwak, M.D.

Purpose: To evaluate the usefulness of dynamic CT during the hepatic arterial phase with rapid IV injection of contrast material in distinguishing hepatocellular carcinoma (HCC) from intrahepatic cholangiocarcinoma (ICAC) as the cause of biliary obstruction.

Materials and Methods: We retrospectively reviewed two-phase dynamic incremental CT or helical CT findings in 22 patients with intrahepatic duct obstruction secondary to pathologically proven HCCs (n = 12) or ICACs (n = 10). Two-phase CT scans were obtained 20 - 45 seconds (hepatic arterial phase) or 2 minutes (equilibrium phase) after the initiation of a bolus injection of contrast material (5mL/sec, 150mL). The enhancement patterns of tumors, as seen on two-phase images, were classified as hypo-, iso-, or hyperattenuated, relative to surrounding liver parenchyma. Two-phase images were compared and correlated with pathologic findings.

Results: During the hepatic arterial phase, diffuse high-enhancement was seen in nine HCCs (75%) and partial enhancement in three (25%); five (50%) of the ten ICACs were hypodense and five (50%) were hypodense with peripheral enhancement. During the equilibrium phase, however, all HCCs were hypodense and capsular enhancement was seen in four cases (33.3%). All ICACs were hypodense with mild peripheral or central heterogeneous enhancement. Contrast enhancement patterns of HCCs during the hepatic arterial phase were significantly different (p < .0001) from those of ICACs.

Conclusion: Our results suggest that dynamic CT during the hepatic arterial phase, with rapid IV injection of contrast material, is useful for the differentiation of HCC from ICAC as the cause of biliary obstruction.

Index words: Liver neoplasms, CT, Bile ducts, stenosis or obstruction, Computed tomography (CT), contrast enhancement.

If conventional contrast-enhanced CT is used, hepatocellular carcinoma (HCC) can be confused with intrahepatic cholangiocarcinoma (ICAC) with or without bile duct invasion. Despite remarkable recent improvements in the diagnostic tools involved, HCC with intrahepatic duct dilatation is, therefore, often still incorrectly diagnosed as ICAC(1, 2). It has been reported, however, that if contrast-enhanced dynamic CT or dynamic MR imaging is used, contrast enhancement patterns of HCCs and ICACs are significantly different(3 - 8). If dynamic CT with rapid IV injection of contrast material is performed during the hepatic arterial phase, it is therefore possible to differentiate HCC with bile duct obstruction from ICAC.

Conventional CT or MRI findings of HCCs with bile duct involvement have recently been reported(2, 9), but to our knowledge, description of the differential contrast-enhanced dynamic CT findings of ICAC and
HCC with intrahepatic duct obstruction have not been published. The purpose of this study was to determine the usefulness of dynamic CT during the hepatic arterial phase, with rapid IV injection of contrast material, in distinguishing HCC from ICAC as the cause of intrahepatic biliary obstruction.

**Materials and Methods**

Between October 1992 and February 1997, liver sonography was performed for the purpose of screening patients with clinically suspected hepatic tumors. In order to characterize these lesions, two-phase incremental or helical CT was performed; in 12 patients with pathologically proven HCCs, intrahepatic duct obstruction was diagnosed on the basis of cholangiographic, sonographic, and CT findings. As a comparison group for evaluating the differences as seen on two-phase dynamic CT between ICAC and HCC, we selected 18 patients with pathologically proven ICACs; they had undergone two-phase dynamic CT scans of the liver due to hepatic tumors. Of the 18, ten who were diagnosed by cholangiography, sonography, and CT as suffering from ICAC with intrahepatic duct obstruction were included in this study. The remaining eight, who had ICACs without biliary obstruction, were excluded.

Eight of the 12 patients with HCCs were men and four were women, their mean age was 59 (range, 42–73) years. Among the ten patients with ICACs, eight were men and two were women; their mean age was 65 (range, 46–86) years.

Pathologic proof of HCC or ICAC was obtained by sonography-guided percutaneous core biopsy using an 18-20-gauge cutting needle. Bile duct obstruction secondary to HCCs was confirmed by a cholangiogram (percutaneous transhepatic cholangiography in five patients, or endoscopic retrograde cholangiography in four) and in the remaining three, bile duct obstruction was diagnosed on the basis of sonographic and CT findings.

To evaluate the enhancement patterns of lesions, all 22 patients received a uniphase IV injection of contrast material. A total of 150mL of non-ionic contrast medium (iodine 300mg/mL, Iopromide; Schering, Berlin, Germany) was administered with a power injector at a rate of 5mL/second for 30 seconds. For IV injection of contrast material into the antecubital vein, an 18-20-gauge sheath needle was used. The higher bolus injection of nonionic contrast material was well tolerated by all patients and there were no side effects.

In six patients, two-phase dynamic incremental CT scanning of the liver was performed with a Xpeed scanner (Toshiba Medical System, Tokyo, Japan) at 120 kVp and 150 mAs, while in 16 patients, two-phase helical CT scanning of the liver was performed with a HiSpeed advantage scanner (General Electric Medical System, Milwaukee, USA) at 120 kVp and 250–280 mAs. Hepatic arterial phase images were obtained 20–45 seconds after the initiation of IV injection of a bolus of contrast material. For hepatic arterial phase imaging with incremental CT, the lesion was localized by precontrast CT scanning of the liver. When lesions were isodense on precontrast CT scans, sonographic findings were used to localized the lesion. Hepatic arterial phase scanning with incremental CT was performed with a 2.7-second scanning time and a 1.6-second interscan delay, and contiguous 5- or 10-mm collimation. Five contiguous scans with a single 25-second breath-hold were obtained at the lesion site of the liver as seen on precontrast CT or sonogram.

Hepatic arterial phase scanning with helical CT was

<table>
<thead>
<tr>
<th>Table 1. Contrast Enhancement Patterns of Hepatocellular Carcinomas with Bile Duct Invasion (n=12) and Intrahepatic Cholangiocarcinoms (n=10) on Two-Phase Dynamic CT.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Contrast Enhancement Patterns</strong></td>
</tr>
<tr>
<td><strong>HCCs (n=12)</strong></td>
</tr>
<tr>
<td><strong>ICAC (n=10)</strong></td>
</tr>
<tr>
<td>Arterial phase</td>
</tr>
<tr>
<td>Hyperattenuation</td>
</tr>
<tr>
<td>Diffuse</td>
</tr>
<tr>
<td>Partial</td>
</tr>
<tr>
<td>Peripheral</td>
</tr>
<tr>
<td>Hypoattenuation</td>
</tr>
<tr>
<td>Equilibrium phase</td>
</tr>
<tr>
<td>Hypoattenuation</td>
</tr>
<tr>
<td>Hypoattenuation with capsular enhancement</td>
</tr>
<tr>
<td>Hypoattenuation with mild peripheral enhancement</td>
</tr>
<tr>
<td>Hypoattenuation with mild heterogeneous enhancement</td>
</tr>
</tbody>
</table>

HCC: hepatocellular carcinoma, ICAC: intrahepatic cholangiocarcinoma, n: number of patient
performed with a 1-second scan, 1:1 pitch, 7-mm collimation, and 7-mm reconstruction. For the entire liver, 25 continuous scans with a single 25-second breath-fold were obtained. Equilibrium phase scanning was performed 2–4 minutes after the initiation of IV injection of a bolus of contrast material. For equilibrium phase imaging, 20 contiguous scans from the diaphragmatic dome to the inferior pole of the kidney were obtained with 10-mm collimation and 10-mm interval.

HCCs were solitary in eight patients and satellite nodules were present in four. ICACs were solitary in eight patients and satellite nodules were present in two. In cases with multiple satellite nodules, the number and size of satellite lesions were not recorded because of lack of pathologic confirmation of these lesions.

Contrast enhancement of HCCs and ICACs was classified as hypo-, iso-, or hyperattenuated, relative to enhancement of surrounding liver parenchyma as seen on two-phase images. Each lesion was separately evaluated for homogeneity or heterogeneity of enhancement, patterns of contrast enhancement(diffuse, partial or peripheral), tumor margin(well- or ill-defined), and the presence or absence of late capsular enhancement. Capsular enhancement regarded as lesion showed thin membrane-like enhancement. Two-phase dynamic CT images in 12 patients with HCCs and ten with ICACs were retrospectively reviewed by two radiologists(C.J.S., K.D.H.), who reached a consensus.

Two-phase CT findings were compared and correlated with histopathologic findings and clinical manifestations including the level of serum α-fetoprotein and total bilirubin. Liver cirrhosis and portal vein thrombosis were diagnosed on the basis of images obtained by sonography, CT, and clinical manifestations.

Fisher's exact test was used to test for differences in enhancement patterns between HCCs and ICACs; a p value of <.05 was considered statistically significant.

Results

The maximum diameter of 12 HCCs ranged from 3 to 13(mean, 7.1) cm. Nine of these HCCs were in the right hepatic lobe and three were in the left lobe; seven were

![Fig. 1. A 63-year-old woman with hepatocellular carcinoma.](image-url)
ill-defined and five were well-defined. The enhancement patterns of HCCs, as seen on two-phase images, are shown in Table 1. During the hepatic arterial phase, HCCs were hyperdense, with a moderate to marked degree of diffuse enhancement (Fig. 1A) in nine (75%) and partial enhancement in three (25%). In four patients (33.3%), multiple satellite nodules were also highly enhanced (Fig. 2A). During the equilibrium phase, however, all HCCs (Figs. 1B, 2B) became hypodense and satellite nodules were poorly identified.

Incomplete or complete capsular enhancement (Fig. 1B) was seen in four cases (33.3%). Focal dilatation of intrahepatic ducts around the tumors, or the diffuse dilatation of both intrahepatic ducts was associated in all 12 patients with HCCs. In four HCCs, intraluminal tumor extension (Fig. 2C) into the extrahepatic duct occurred; three of the four showed high enhancement of intraluminal tumor (Fig. 1C) during the hepatic arterial phase, similar to that of primary tumor.

The sizes of ten ICACs ranged from 5 to 10 (mean, 6.9) cm in maximum diameter. Five of the ten were in the right hepatic lobe and the others were in the left lobe. Five were relatively well-defined and five were ill-defined. The enhancement patterns of ICACs on two-phase images are shown in Table 1. During the hepatic arterial phase, five ICACs (50%) were hypodense (Fig. 3A) and five (50%) were hypodense with peripheral enhancement (Fig. 4A). During the equilibrium phase, however, all ICACs were hypodense with mild peripheral or central heterogeneous enhancement (Figs. 3B, 4B). No ICACs showed capsular enhancement. Focal or diffuse dilatation of the intrahepatic ducts was seen in all ICACs. Diffuse, mild dilatation of peripheral intrahepatic ducts was seen in three cases (30%) and c-
orchiasis was confirmed in the stool examination (Fig. 4). During the equilibrium phase, it was difficult to differentiate HCCs with intrahepatic duct dilatation from ICACs; during the hepatic arterial phase, however, enhancement patterns of HCCs with intrahepatic duct obstruction were significantly different (p < 0.0001) from those of ICACs. Additional findings were liver cirrhosis in ten patients with HCCs and in one with ICAC. Portal vein thrombosis was found in six patients with HCCs and in one with ICAC.

Discussion

Obstructive jaundice has been regarded as an uncommon complication of HCC, with an incidence of 2–8% in patients with HCCs (1, 2, 10–13). HCC-induced biliary obstruction can be caused by direct tumor invasion of intrahepatic ducts, pedunculated tumor extension into the extrahepatic bile ducts, blood clots or necrotic fragments from the tumor, and metastatic lymph node compression of the major ducts in the porta hepatitis (11–13). The prognosis of patients with obstructive jaundice due to HCC seems to be poor, since most tumors with major bile duct invasion are large and infiltrative. In order to effectively plan management strategies, the identification of specific causes of obstructive jaundice is important (2).

On CT scans, intrahepatic duct dilatation secondary

![Fig. 3. A 57-year-old man with intrahepatic cholangiocarcinoma.](image)

A. CT scan during the hepatic arterial phase shows a hypodense mass (arrow) in the medial segment of the left hepatic lobe.

B. CT scan during the equilibrium phase shows a well-defined hypodense mass (arrow) with mild heterogeneous enhancement and moderate dilatation of both intrahepatic ducts.

![Fig. 4. A 56-year-old man with intrahepatic cholangiocarcinoma and clonorchiasis.](image)

A. CT scan during hepatic phase with peripheral enhancement (arrowheads) in the left hepatic lobe and marked dilatation of the left intrahepatic ducts due to hilar extension of tumor.

B. CT scan during the equilibrium phase shows an ill-defined hypodense mass with mild peripheral enhancement (arrowheads). Note mild, diffuse dilatation of the right intrahepatic ducts and clonorchiasis was confirmed in the stool examination.
to HCC is suggested when intrahepatic duct dilatation is associated with marked elevation of serum α-fetoprotein level and a well-delineated, encapsulated intrahepatic mass(1, 2). Since, however, the enhancement patterns of both tumors are similar and intrahepatic duct dilatation is a common CT feature of ICAC, infiltrative HCC with bile duct invasion may be difficult to differentiate from ICAC on conventional contrast-enhanced CT scans.

HCCs are hypervascular tumors which are supplied by hepatic arteries(3—5). They become maximally hyperdense during the hepatic arterial phase of dynamic CT and rapidly less dense during the portal venous phase, and then gradually become hypodense during the delayed phase(3—6). Dynamic CT during the hepatic arterial phase, with rapid bolus injection of contrast material and early initiation of scanning, has therefore been used for the detection and characterization of HCCs(5, 6). To characterize hepatic tumors, we performed two-phase dynamic incremental or helical CT during the hepatic arterial and equilibrium phases, with rapid IV injection of contrast material. During the hepatic arterial phase, nine of the 12 HCCs (75%) showed diffuse high-enhancement before adequate enhancement of surrounding liver parenchyma, and three (25%) were partially enhanced. In addition, multiple, enhanced, small satellite nodules were readily detectable in four cases. During the equilibrium phase, however, all HCCs showed hypoattenuation relative to liver parenchyma, and because the lesions became isodense or slightly hypodense, multiple satellite nodules were poorly depicted. The enhancement patterns of HCCs with biliary obstruction, as seen on two-phase dynamic CT scans, were similar to those of HCCs without biliary obstruction.

ICACs contain abundant stroma and fibrous tissue; on contrast-enhanced CT scans, this tumor therefore appears as an irregular mass with low attenuation, mild contrast enhancement at the periphery during the early phase, and delayed or prolonged, homogeneous enhancement due to extensive interstitial space during the delayed phase(3, 6, 14—16). This enhancement of ICACs during the delayed phase, which is obtained 10—20 minutes after contrast administration, is due to slow wash-in and wash-out of contrast material in fibrous tissue(3, 16). Dynamic studies of ICAC using CT or MR have reported that this tumor shows characteristic early peripheral enhancement followed by progressive central fill-in of contrast material and pooling within the tumor on late images(7, 8). In our series, most ICACs were poorly enhanced during the hepatic arterial phase and peripheral enhancement was seen in five cases (50%). During this phase, enhancement patterns of HCCs were, therefore, significantly different from those of ICACs. During the equilibrium phase, all ICACs were hypodense with mild peripheral or central heterogeneous enhancement, and no capsular enhancement was seen. Because delayed-phase images were not obtained for more than ten minutes, we did not observe prolonged or delayed enhancement, a characteristic finding of ICAC. During the equilibrium phase, eight HCCs (66.7%), which showed ill-defined hypodense infiltrating masses without capsular enhancement, were therefore difficult to differentiate from ICACs. However, four HCCs (33.3%) showed complete or incomplete capsular enhancement, and this helped distinguish HCCs from ICACs.

Although we have encountered a small number of HCCs with biliary obstruction, the frequency of capsular enhancement was similar to that of HCCs without such obstruction. Soyer et al.(2), however, reported that encapsulation was absent in all ten HCCs with intrahepatic duct dilatation and suggested that a lack of encapsulation in patients with HCCs might favor bile duct involvement. This difference between their results and ours might be explained by the fact that the frequency of HCC encapsulation among Asian populations is significantly higher than among non-Asians(17, 18).

On conventional contrast-enhanced CT, intraluminal filling defects of the bile duct due to blood clots and/or necrotic tumor tissue are difficult to differentiate from pedunculated HCC(10). Intrabiliary mass enhancement, however, as seen on contrast-enhanced CT scans, indicates extension of HCC rather than a blood clot(9). In our series, intraluminal tumor extension into the bile duct, as confirmed by cholangiography, was seen in four patients with HCCs. In three of these cases, the tumor was highly enhanced during the hepatic arterial phase, resembling an enhanced primary tumor. We believe that for the diagnosis of intrabiliary extension of HCC, such a finding is useful.

Our study has certain limitations; two-phase dynamic CT findings were evaluated in which intrahepatic duct dilatation was secondary to HCCs or ICACs—a relatively small number of cases. In our series, all 12 HCCs showed a mild to marked degree of diffuse or partial hyperattenuation during the hepatic arterial phase. Other studies, however, have reported that during the arterial phase, HCCs can be poorly enhanced, the degree of enhancement depending on associated fatty metamorphosis and arterioporal shunt, the degree of cell differentiation, and tumor size(19, 20). We therefore believe that this difference between our report
and others is due to our restricted number of cases. Another limitation was that we obtained equilibrium phase instead of the delayed phase images; the latter are accepted as being ideal for the characterization of cholangiocarcinoma.

In our study, capsular enhancement of HCCs during the equilibrium phase was helpful in differentiating these from ICACs, but it was difficult to differentiate unencapsulated infiltrative HCCs from ICACs. During the hepatic arterial phase, however, most HCCs were highly enhanced and most ICACs were poorly enhanced except in cases with peripheral enhancement. Contrast enhancement patterns of HCCs during the hepatic arterial phase were significantly different from those of ICACs. In addition, hepatic arterial-phase images helped detect small satellite nodules and intrabiliary tumor extension of HCCs. In conclusion, our results suggest that dynamic CT during the hepatic arterial phase is useful for the differentiation of HCC from ICAC as the cause of biliary obstruction.

References
3. Baron RL. Understanding and optimizing use of contrast material for CT of the liver. AJR 1994; 163: 323-331
담관폐쇄의 원인으로 간세포암과 간내 담관암의 감별에 있어
간동맥기 역동적 CT의 유용성!

목 적 : 담관폐쇄의 원인으로 간내 담관암으로부터 간세포암을 구별하는데 있어 조영제를 급속 정맥 주입하면서 시행하는 간동맥기 역동적 CT의 유용성을 평가하고자 하였다.

대상 및 방법 : 간내 담관폐쇄를 동반하였으며 병리조직적으로 확진된 12예의 간세포암과 10예의 간내 담관암 환자를 대상으로 이중시기 역동적 CT 혹은 나선식 CT소견을 후향적으로 분석하였다. 150mL의 조영제를 초당 5mL의 속도로 주입하면서 조영제 주입시작후 20-45초에 간동맥기 영상을 얻고 2분에 조직평형기 영상을 얻는 이중시기 역동적 CT 혹은 나선식 CT를 시행하였다. 종양의 조영증강 양상은 주위 간실질과 비교하여 저, 동등, 고음영으로 분류하여 이중시기 영상을 비교하였다.

결 과 : 간동맥기에서 12예의 간세포암은 모두 고음영을 보였으며, 이중 9예(75%)는 전반적인 현저한 조영증강, 3예(25%)는 부분적인 조영증강을 보였다. 반면에 10예의 간내 담관암은 모두 저음영을 보였고, 이중 5예(50%)는 종양 주변부의 조영증강을 보였다. 조직평형기에서 간세포암은 12예 모두 저음영을 보였고, 이중 4예(33.3%)는 피막의 조영증강을 보였다. 반면에 간내 담관암의 경우 10예 모두 저음영을 보였고 병변의 주변부 혹은 중심부에서 약하고 불균일한 조영증강을 보였다. 간동맥기에서 간세포암의 조영증강 양상은 간내 담관암과 유의성 있는 차이를 보였다(p<.0001).

결 론 : 조영제를 급속 정맥 주입하면서 시행하는 간동맥기 역동적 CT는 담관폐쇄의 원인으로 간내 담관암으로부터 간세포암을 감별하는데 있어 유용한 방법으로 생각된다.