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Full Length Research Paper

Detection of hepatocellular carcinoma with multi-slice spiral CT by using double-arterial phase and portal venous phase enhanced scanning: Effect of iodine concentration of contrast material

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The purpose of the study is to evaluate the effect of iodine concentration of contrast material on detection of hepatocellular carcinoma with multi-slice spiral computed tomography (CT) by using double-arterial phase and portal venous phase enhanced scanning. Ninety-four (94) patients with hepatocellular carcinoma (HCC) were examined by hepatic plain CT and contrast-enhanced CT including early arterial phase (EAP), late arterial phase (LAP) and portal venous phase (PVP) scanning. Patients were randomized into two groups to receive Iopamidol 370 mg /ml (47 patients) and 300 mg /ml (47 patients). The images were interpreted by two experienced radiologists together prospectively. The detection sensitivity for tumors of two size categories (≤2 or >2 cm) and iodine concentration groups were calculated and analyzed. A total of 318 lesions were detected with 86 ≤ 2 cm in size and 232 >2 cm. For EAP and LAP, the sensitivity of Iopamidol 370 mg I/ml group was significantly higher than Iopamidol 300 mg I/ml group for tumors ≤ 2 cm and all tumors. For PVP, there were no significant differences between groups. We concluded that high-iodine-concentration contrast material could improve the detection of HCC for EAP and LAP, especially for tumor ≤ 2 cm.

Key words: Contrast agent, administration and dosage, computed tomography (CT), hepatocellular carcinoma (HCC).

INTRODUCTION

With the use of multi-slice spiral CT (MSCT) widely, quadruple-phase CT consisting of early arterial, late arterial, portal venous and delayed phase on detection of hepatocellular carcinoma (HCC) has been recognized (Murakami et al., 2001, 2003, 2005; Pozzi et al., 2006; Schima et al., 2006; Ichikawa et al., 2002; Kajiya et al., 2005; Zhao et al., 2003, 2004). Not only this scanning technique could improve the detection sensitivity of HCC, but also the contrast injection protocol such as contrast material dose, flow rate, iodine concentration of contrast material and timing could impact the detection of HCC (Iannaccone et al., 2005; Breen et al., 2004; Kudo, 2002). The effects of these factors had been studied in helical CT (Heiken et al., 1995; Hänninen et al., 2000; Kormano et al., 1983; Kim et al., 1998; Furuta et al., 2004; Marchianò et al., 2005; Behrendt et al., 2008; Sultana et al., 2003; Herman, 2004), but there were few researches that reported on the effect of iodine concentration of contrast material in which double-arterial phase scanning was used for detection of HCC (Pozzi et al., 2006; Awai et al., 2002; Yagyu et al., 2005). Pozzi et al. (2006) had used high-iodine-concentration contrast agent in MSCT

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Abbreviations: CT, Computed tomography; **HCC,** hepatocellular carcinoma; **EAP,** early arterial phase; **LAP,** late arterial phase; **PVP,** portal venous phase.

Table 1. Demographic and baseline characteristics in two groups.

Parameter	Group A (n = 47)	Group B (n = 47)
Demographic data		
Sex (men/women)	42/5	39/8
Age (years), mean ± SD	51.7 ± 9.8	54.3 ± 10.6
Weight (kg), mean ± SD	60.8 ± 11.7	58.6 ± 13.2
BMI (kg/m^2), mean ± SD	22.3 ± 4.5	20.6 ± 4.1
Baseline liver disease characteristics		
Liver cirrhosis (%)	85.1	89.4
Chronic hepatitis B (%)	48.9	57.4
Chronic hepatitis C (%)	29.8	25.5
Chronic alcoholic hepatitis (%)	21.3	17.0
Iopamidol dose administered (mg)	33744.0 ± 6493.5	32523.0 ± 7326.0
Iopamidol volume administered (ml)*	91.2 ± 17.6	108.4 ± 24.4

Group A = Iopamidol 370 mg I/ml group; Group B = Iopamidol 300 mg I/ml group; BMI = body mass index.
*Significant difference was seen between the groups.

with double-arterial phase to detect HCC, but their results had no control group to be compared with and their conclusion had no statistical analysis to be based on.

The purpose of this article is to evaluate the effect of iodine concentration of contrast material on detection of HCC with MSCT by using double-arterial phase and portal venous phase enhanced scanning with protocols of constant iodine load and constant iodine delivery rate.

MATERIALS AND METHODS

Patients

From September 2007 to July 2008, 126 patients who were suspected to have HCC clinically were assigned randomly to undergo MSCT of the liver with either of the two contrast material injections and scanning protocols. All patients were prospectively and randomly assigned into group A and group B by using a random-number table. Patients with pregnancy, lactation, administration of an iodinated contrast medium within the previous 72 h, history of allergy to Iopamidol, manifest thyrotoxicosis, noncompensated cardiac insufficiency were excluded from this study. All patients gave their informed consents, and this study was approved by our Ethics Committee.

Finally, ninety-four patients (81 men, 13 women, aged between 29 and 91 years, mean age: 53 years) who were diagnosed as HCC (45 confirmed by operation, 18 confirmed by percutaneous biopsy and 31 confirmed by following up for a minimum of six months) were included in this study. All the 94 patients had chronic liver diseases (50 with type B hepatitis, 26 with type C hepatitis and 18 with alcoholic hepatitis) and 82 patients were combined with hepatic cirrhosis.

CT protocol and contrast material infusion

The CT scanner we used was Toshiba Aquilion 16 CT. To keep the total iodine dose and the iodine delivery rate constant for both protocols, patients of group A received Iopamidol (Bracco S.P.A., Italy) 370 mg I/ml (1.5 ml/kg body weight) at a flow rate of 4 ml/s and group B received Iopamidol (Bracco S.P.A., Italy) 300 mg I/ml (1.85 ml/kg body weight) at a flow rate of 4.9 ml/s, by means of a power injector (AD2002-CT, MEDEX, France) with 20-gauge intravenous catheters inserted into an antecubital vein. In the 94 patients, there were 47 patients in group A and 47 patients in group B. Both groups were comparable regarding demographic and baseline liver disease characteristics (Table 1). A saline flush of 40 ml followed the contrast medium injection, using the same injection rate as for the contrast medium. Bolus-tracking technique (Sure Start, Toshiba, Tokyo, Japan) was performed in order to optimize scan delays for early arterial phase (EAP) automatically. The mean injection-to-scan delay for EAP imaging was 23.5 s (range, 18 – 35 s) for group A and 25.5 s (range, 16 – 38 s) for the group B. And the timing of the contrast-enhanced CT scans was uniformly defined: Late arterial phase (LAP) imaging started 15 s after initiation of EAP scanning; portal venous phase (PVP) imaging was initiated 50s after the start of the EAP. In scanning, patients were asked to hold their breath. The CT scanner detector configuration was 16 × 0. 5 mm. The tube voltage applied throughout all CT studies was 120 kVp. The tube current was adjusted according to patient characteristics (mean, 217 mA; range, 105 – 420 mA). In view center, axial images were reconstructed at an effective slice thickness of 2 mm, with a reconstruction interval of 1 mm.

Qualitative analysis

The images were interpreted by two radiologists (with 15 and 6 years experience, respectively, as gastrointestinal radiologist) prospectively together. For each phase, the two readers recorded the details including size, location and the contrast pattern of hepatic lesions. The size of the lesion was defined as the maximal diameter in axial images. The readers assigned one of five confidence levels (Murakami et al., 2001) as follows: 0, no lesion; 1, probably absent; 2, possibly present; 3, probably present; 4, definitely present. If there were disagreements, they discussed or consulted another radiologist (with 9 years experience as a gastrointestinal radiologist) to get into accord. Every recorded lesion was compared with final result. Those lesions among the proved HCC lesions which were assigned a confidence level of 2 or greater were considered as true-positive findings. A lesion which was assigned a confidence level of 0 or 1 but actually was present was considered as a false-negative lesion.

Table 2. Comparison of detection sensitivity of two size categories between groups of different iodine concentrations.

Parameter	Group	HCC (no)	EAP (%)	LAP (%)	PVP (%)
Lesions 2 cm or smaller	A	37	54.1 (20/37)*	83.8 (31/37)*	51.4 (19/37)
	B	49	28.6 (14/49)	55.1 (27/49)	38.8 (19/49)
Lesions larger than 2 cm	A	123	91.1 (112/123)	99.2 (122/123)	99.2 (122/123)
	B	109	88.1 (96/109)	100 (109/109)	99.1 (108/109)
Total	A	160	82.5 (132/160)*	95.6 (153/160)*	88.1 (141/160)
	B	158	69.6 (110/158)	86.1 (136/158)	80.4 (127/158)

Group A = Iopamidol 370 mg I/ml group; Group B = Iopamidol 300 mg I/ml group; HCC, hepatocellular carcinoma; no, number; EAP, early arterial phase; LAP, late arterial phase; PVP, portal venous phase. Data given as percentages. Values in brackets were those used to calculate the percentages. *The value obtained in Group A was significantly higher than that in Group B ($p < 0.05$)

Table 3. Comparison of detection sensitivity and positive predictive values of different phases.

Phases	Lesions 2 cm or smaller		Lesions larger than 2 cm		Total lesions	
	Sensitivity (%)	PPV (%)	Sensitivity (%)	PPV (%)	Sensitivity (%)	PPV (%)
EAP	39.5 (34/86)	51.5 (34/66)	89.7 (208/232)	100 (208/208)	76.1 (242/318)	88.3 (242/274)
LAP	67.4 (58/86)	55.8 (58/104)	99.6 (231/232)	100 (231/231)	90.9 (289/318)	86.3 (289/335)
PVP	44.2 (38/86)	67.9 (38/56)	99.1 (230/232)	100 (230/230)	84.3 (268/318)	93.7 (268/286)
χ^2	15.38	3.55	39.07	-	25.62	9.29
P value	<0.01	>0.05	<0.01	-	<0.01	<0.01

EAP, Early arterial phase; LAP, late arterial phase; PVP, portal venous phase; PPV, positive predictive value. - , we did not compare it because the number was the same. Data given as percentages. Values in brackets were those used to calculate the percentages.

Statistical analysis

Software SPSS 13.0 was used to analyze the results. The detection sensitivity for tumors of two iodine concentration groups for EAP, LAP and PVP was compared with 2 × 2 Chi-square test. Comparison of detection sensitivity and positive predictive values of different phases was tested by R×2 Chi-square test. If p value <0.05, it was considered that there were significant differences.

RESULTS

It was shown that there were 318 HCCs in the 94 patients. Their sizes were from 0.6 to 25.0 cm (mean size 5.2 cm).There were 86 tumors ≤2 cm and 232 tumors >2 cm.

Comparison of detection sensitivity of two size categories (≤2 or >2 cm) between groups of different iodine concentrations (370 mg /ml versus 300 mg /ml) is shown in Table 2. For tumors ≤2 cm, Iopamidol 370 mg /ml group (group A) showed significantly superior sensitivity compared to Iopamidol 300 mg /ml group (group B) for EAP and LAP. For tumors >2 cm, the detection sensitivity had no significant difference between two groups for all phases. Over all of the 318 tumors, the detection sensitivity of Iopamidol 370 mg /ml group (group A) was higher than Iopamidol 300 mg /ml group (group B) for EAP and LAP, but there was no significant difference between two groups for PVP.

The comparison of detection sensitivity and positive predictive values of different phases is shown in Table 3. For tumors ≤2 cm, tumors >2cm and all tumors, the detection sensitivity showed significant differences between phases and the sensitivity of LAP was the highest. For all the tumors, the positive predictive values were 88.3, 86.3, 93.7% for EAP, LAP and PVP, respectively, which showed significant differences between phases and PVP had the highest positive predictive value.

DISCUSSION

During contrast-enhanced CT, detection of HCC depends on several patient dependent factors including cardiac output, body weight, the vascularity of HCC and technology dependent factors, such as the scanning technique and the contrast injection protocol (Iannaccone et al., 2005; Breen et al., 2004; Kudo, 2002). These factors can change the time, concentration and the peak time of contrast agent flowing into tumor. The effects of contrast material dose, flow rate, iodine concentration of contrast material and timing had been studied in helical CT (Heiken et al., 1995; Hänninen et al., 2000; Kormano et al., 1983; Kim et al., 1998; Furuta et al., 2004; Marchianò et al., 2005; Behrendt et al., 2008; Sultana et al., 2003; Herman, 2004), but there were few researches that reported on the effect of iodine concentration of contrast

material in which double-arterial phase scanning was used for detection of HCC (Pozzi et al., 2006; Awai et al., 2002; Yagyu et al., 2005). In 2002, Awai et al. (2002) evaluated the impact of contrast concentration on hypervascular HCC conspicuity with same iodine load per body weight (518 mg/kg) and concluded that the higher concentration may be more efficacious for imaging of HCC during the arterial phase on the basis of contrast materials with higher iodine concentration which could improve tumor-to-liver contrast in the first arterial phase. Yagyu et al. (2005) made a similar research but used a fixed dose of 100 ml and concluded that contrast materials with higher iodine concentration are more effective for depicting hypervascular HCCs on MSCT during the late arterial phase. But there were opposite view points on the effect of iodine concentration of contrast material. In 2008, Behrendt et al. (2008) published one study and the conclusion was that the iodine concentration of contrast media did not significantly influence abdominal contrast enhancement. Awai et al. (2004) even concluded that moderate concentration of contrast material was more effective for depiction of hypervascular HCC than was for high concentration of contrast material. Can high-iodine-concentration contrast material really improve the sensitivity on detection of HCC? Pozzi et al. (2006) used high-iodine-concentration contrast agent in MSCT with double-arterial phase to detect HCC, and got a higher sensitivity than that reported by others. For that reason, they thought that the high-iodine-concentration may improve identification of HCC. But their results had no control group to be compared with and their conclusion had no statistical analysis to be based on. So we compared two contrast materials of different iodine concentration (370 and 300 mg/ml) to evaluate it by comparing the detection sensitivity of two iodine concentration groups, a methodology which was different from previous studies (Heiken et al., 1995; Hänninen et al., 2000; Kormano et al., 1983; Kim et al., 1998; Furuta et al., 2004; Marchianò et al., 2005; Behrendt et al., 2008; Sultana et al., 2003; Herman, 2004; Awai et al., 2002, 2004; Yagyu et al., 2005). Though we thought it is a qualitative method, yet this method could directly show the impact of iodine concentration on detection sensitivity of HCC. For excluding the impact of the dose and flow rate of contrast material, Iopamidol 370 mg/ml (1.5 ml/kg body weight) at a flow rate of 4 ml/s and Iopamidol 300 mg/ml (1.85 ml/kg body weight) at a flow rate of 4.9 ml/s were, respectively, used to keep the total iodine dose (555 mg/kg body weight) and the iodine delivery rate (1.48 versus 1.47 g/s) constant for both protocols. Our results proved that for tumors ≤2 cm and all the tumors, Iopamidol 370 mg/ml group showed significantly superior sensitivity compared to Iopamidol 300 mg /ml group for EAP and LAP. This may be explained by the reason that high-concentration contrast material administered leads to an earlier and more intense arterial enhancement peak, thus improving contrast enhancement of tumor-to- liver, and helping improve diagnostic accuracy for HCC, which had been proved in previous studies (Marchianò et al., 2005; Sultana et al., 2003; Herman, 2004; Yagyu et al., 2005). Although the sensitivity of Iopamidol 370 mg/ml group was higher than that of Iopamidol 300 mg I/ml group for PVP, there was no statistical difference. Our study showed that the detection sensitivity of small HCC nodules was all low for EAP (39.5%), LAP (67.4%) and PVP (44.2%). Therefore, contrast material of higher iodine concentration is recommended for tumors ≤2 cm. But for tumors >2 cm, there was no difference between the two groups. We attributed this to the fact that the tumor is large, so it can be clearly demonstrated and easy to be found. We suggested that if you are sure the tumor is bigger than 2 cm, contrast material of normal iodine concentration is the optimal choice. Otherwise, contrast material of high iodine concentration is recommended.

Since it has been recognized that the double-arterial phase scanning can improve the detection sensitivity of HCC (Murakami et al., 2001, 2003,2005; Pozzi et al., 2006; Schima et al., 2006; Ichikawa et al., 2002; Kajiya et al., 2005; Zhao et al., 2003, 2004), we did not compare it. We analyzed the sensitivity of the three phases, and the LAP was the highest. It was inconsistent with the researches of Foley et al. (2000), who reported that hepatic hypervascular tumors could be identified and evaluated more easily during LAP. We think it is because of the time needed for the contrast-filled arterial blood coming from the hepatic artery to spread within the lesion cavity.

For the tumors of 2 cm or smaller, the positive predictive values of different phases were not all satisfactory (51.5 - 57.5%). Nearly half of the lesions were misdiagnosed. These lesions could be often vascular pseudo lesions due to arterioportal shunting or tiny hemangiomas, but it was sometimes difficult to determine not being an HCC. To HCC bigger than 2 cm, the positive predictive value of different phase were all 100%, therefore, it can be considered that the bigger HCC cannot be left out in double-arterial phase CT scan. To all the tumors, there were significant differences between different phases in positive predictive values and PVP had the highest positive predictive values (93.7%).

There are some limitations to the study. First, double hepatic arterial scans would increase radiation dose. But for improving the detection sensitivity of HCC which had been reported (Murakami et al., 2001, 2003, 2005; Pozzi et al., 2006; Schima et al., 2006; Ichikawa et al., 2002; Kajiya et al., 2005; Zhao et al., 2003, 2004), this method is probably justifiable. Second, it was a parallel group study. The differences between the results of two groups may be attributable to the bias of the patient. However, we analyzed the two different groups separately and evaluated statistical differences between them in terms of demographic data, and baseline liver disease characteristics. And the result showed that there were no

statistical differences in background factors, which made this possibility unlikely. Third, part of the lesions had no pathological confirmation. However, these lesions had confirmatory imaging examinations including CT and followed for a minimum of 6 months by several follow-up methods including ultrasound, contrast-enhanced CT and magnetic resonance imaging (MRI) which constituted good evidence of HCC.

In conclusion, high-iodine-concentration contrast material could improve the detection of HCC for EAP and LAP, and is recommended for tumors ≤2 cm in multiphasic contrast-enhanced MSCT scanning.

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