The purpose of this study was to determine whether triphasic multi-detector row computed tomography (MDCT) can substitute digital subtraction angiography (DSA) for the preoperative detection of hypervascular hepatocellular carcinoma (HCC).

Forty-three patients with nodular HCC underwent first triphasic MDCT examination: pre-contrast, hepatic arterial, portovenous, and delayed phase. Within 4 weeks, they underwent digital hepatic angiography with an intra-arterial chemotherapy with iodized oil and Pharmorubicin. Lipiodol computed tomography (CT) was performed in 4 weeks after infusion. A follow-up MDCT examination was performed between 3 to 6 months after lipiodol CT. Serial CT scans were reviewed and compared with DSA images to detect hepatic nodules.

MDCT and DSA had the same sensitivity in detecting nodules >20 mm in diameter. For the nodules 10-20 mm, MDCT detected 56 (sensitivity = 94.6%), DSA detected 49 (sensitivity = 89.5%, p = 0.003). For the nodules <10 mm, MDCT identified 72 (sensitivity = 94.7%), DSA detected 60, sensitivity was 78.9% (p = 0.001).

Because of superior lesion detectability of MDCT as compared with DSA, MDCT may substitute DSA in the preoperative examination for hypervascular HCC.

Key words: Computed tomography, Digital Subtraction Angiography (DSA), Hepatocellular carcinoma (HCC)

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide and is frequently found in patients with alcohol abuse, viral hepatitis, or metabolic liver disease. Surgical resection and liver transplantation offer the best curative options and achieve high rates of complete responses, especially in patients with small HCCs and good residual liver function [2].

Liver resection is a treatment alternative for small, noninvasive HCC in patients with cirrhosis [2]. Because of many factors, such as multicentric tumors, intrahepatic metastases, early vascular invasion, coexisting advanced liver cirrhosis, and comorbidities, many patients are not suitable candidates for curative resection [3]. Liver transplantation seems to be the treatment of choice for monofocal HCC <5 cm in diameter and for select cases of plurifocal HCC [4]. As a consequence, proper evaluation of patients for intrahepatic metastases or daughter nodules is essential to determine the appropriate treatment [5]. The main difficulty is in the detection of small tumors, including plurifocal lesions and intrahepatic metastasis. Failure to detect these lesions may lead to inappropriate surgical intervention.

Most HCCs are hypervascular. They are strongly enhanced during the hepatic arterial phase of imaging, and they become isoattenuated or hypoat-
Detection of hypervascular HCC with MDCT and DSA

tenuated in the portovenous phase. These are sensitive and specific features for the diagnosis of HCCs. Hepatic angiography and computed tomography (CT) have become standard methods for the clinical diagnosis of HCC [6-11]. Lipiodol CT, in which scans are acquired after an injection of iodized oil, is reported to be the most sensitive preoperative imaging modality for the detection of HCCs, especially intrahepatic metastatic nodules [12, 13].

The multidetector-row CT (MDCT) is a technologic advance that allows for the simultaneous acquisition of several images during a single rotation of the X-ray tube. If a CT scanner with a 16-detector array is used, an entire hepatic acquisition can be accomplished within 4–8 seconds [14]. However, no consensus has been reached whether MDCT obviates digital subtraction angiography (DSA), which is relatively invasive.

The purpose of this study was to determine whether triphasic MDCT can substitute DSA for the preoperative detection of hypervascular and nodular HCC.

PATIENTS AND METHODS

Patients

Between January 2003 and October 2004, we enrolled 43 patients with nodular HCC who were referred to our department for transarterial chemoembolization. Diagnostic criteria were based on pathologic findings in samples obtained from percutaneous needle biopsy or on serum alpha-fetoprotein levels >200 ng/ml plus positive findings of two different image modalities. Patients provided written informed consent to undergo the imaging studies.

Patients first underwent triphasic hepatic MDCT examination. They then received a DSA examination and intra-arterial chemoembolization with infusion of iodized oil and Pharmorubicin (Pharmacia & Upjohn) within 4 weeks. Lipiodol CT was performed in about 4 weeks after the infusion. Follow-up MDCT examination was performed between 3 to 6 months after lipiodol CT. The interval of our study was limited between the first MDCT and the follow-up MDCT after lipiodol CT which was shorter than 8 months. The serial CT scans were reviewed and compared with the DSA images for the detection of hepatic nodules.

MDCT Procedure

MDCT images of the liver were obtained with a CT scanner (Lightspeed Ultra 16, GE Medical Systems, Milwaukee, WI) by using the following parameters: gantry rotation times of 0.6 second for nonenhanced study and for the hepatic arterial and portovenous phases, with 0.8 second for the delayed phase; a 5-mm section thickness; 27.5-mm/second table speed; 120 kVp; and 160–440 mA. No oral contrast material was given before the examination.

The patients underwent nonenhanced and triphasic helical CT scanning. First, patients were imaged with a MDCT scanner in a craniocaudal direction beginning at dome of the liver. Then, nonionic contrast medium (Optiray 350, Tyco Healthcare, Mansfield, MA) was administered at a total dose of 100 to 120 mL with an injection rate of 3 mL/seconds through an antecubital vein. For triphasic acquisitions, scanning was started with a 10 second scan delay for the hepatic arterial phase after the attenuation value of the aorta reached 120 HU. Fifteen seconds after the end point of the hepatic arterial phase, the scans for the portovenous phase were acquired. Delayed-phase images were acquired 80 seconds after the end of the acquisition of portovenous phase. Whole-liver scanning was completed in 4 to 8 seconds with the patients holding their breath.

DSA Procedure

DSA images were obtained with two digital angiographic systems (Integris Allura; Philips, Best, the Netherlands; Advantx LCA/DLX, GE Medical Systems). By using local anesthesia, 40 to 50 mL of the nonionic contrast medium (Optiray 350, Tyco Healthcare) was injected at a rate of 4 to 5 mL/second for celiac and superior mesenteric arteriography. Afterward, the bilateral lobar arteriographies followed by focal segmental or subsegmental arteriographies were obtained with injection of contrast medium at the rate of 1 to 3 mL/second for total 3 to 12 mL of nonionic contrast medium according to the size of vessel. Variants were excluded. After angiography was performed, 3 to 18 mL of iodized oil mixed with 3 to 9 mg Pharmorubicin (Pharmacia & Upjohn) according to the tumor size was infused through the 4F catheter under fluoroscopic guidance. CT examination of the liver was performed within 4 weeks after the intra-arterial injection of iodized oil was administered to evaluate areas of lipiodol retention.

Image Analysis

Two attending radiologists interpreted the images obtained with each radiological method in conference. If there was discrepancy between the two radiologists,
Detection of hypervascular HCC with MDCT and DSA

A third radiologist joined to reach consensus. Tumors detected on MDCT, lipiodol CT, and DSA were labeled and recorded. A true lesion was defined as the presence of persistent retention of lipiodol or lesion enlargement on serial images. A pseudolesion was defined as a lesion with no interval change in its size, shape, or enhancement pattern on serial images or as one with no lipiodol retention on lipiodol CT.

Statistical Analysis

Statistical software (SAS version 8.1; SAS Institute Inc., Cary, NC) was used for data analysis. To compare the various techniques, a chi-squared test was performed, and p values <0.05 were considered to indicate a statistically significant difference.

RESULTS

Figures 1 and 2 showed two cases of HCC nodules identified on triphasic MDCT but not by DSA. A hepatocellular carcinoma nodule identified by triphasic MDCT but not by DSA. a. MDCT scan during the arterial phase shows a hypervascular tumor in S2/3 (arrowhead); b. The lesion is not detected by DSA of left hepatic artery; c. Follow-up lipiodol CT showed lipiodol retention and enlargement of the lesion.

Table 1. The comparison of tumor number between multidetector row helical computed tomography(MDCT) and digital subtraction angiography (DSA) among HCC patients (n = 43)

<table>
<thead>
<tr>
<th>Tumor size (mm)</th>
<th>MDCT number</th>
<th>DSA number</th>
<th>P value for ( \chi^2 )-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>79</td>
<td>60</td>
<td>0.001</td>
</tr>
<tr>
<td>10-20</td>
<td>56</td>
<td>49</td>
<td>0.003</td>
</tr>
<tr>
<td>≥20</td>
<td>45</td>
<td>45</td>
<td>0.018</td>
</tr>
<tr>
<td>Total</td>
<td>180</td>
<td>154</td>
<td></td>
</tr>
</tbody>
</table>

Figures 2. Hepatocellular carcinoma nodule identified by MDCT, but not by DSA. a. Enhancing recurrent tumor measuring 0.5cm in diameter (arrowhead) were depicted as hyperattenuating lesions during the arterial phase by MDCT; b. The lesion was not detected by DSA; c. The lesion was deposited by follow-up MDCT (arrowhead).
For nodules >20 mm, MDCT and DSA both depicted 45 nodules, with a mean of 1.05 nodules per patient. For nodules measuring 10 to 20 mm, MDCT depicted 56, or seven nodules more than the DSA did. Four of these seven nodules were proved to be true lesions, and three were false lesions. The sensitivity of MDCT for this group of nodules was 94.6% compared with 83.1% for DSA ($p = 0.03$). For nodules <10 mm, MDCT depicted 79 nodules, or 19 more than the DSA did. Thirteen of these 19 nodules were true lesions, and six were false lesions. When the serial images were reviewed, MDCT failed to demonstrate four nodules, whereas DSA missed 15. The sensitivity of MDCT for this group of nodules was 94.7% compared with 78.9% for DSA ($p = 0.01$).

**DISCUSSION**

The principle for imaging HCC take advantages of two pathologic events: the substitution of arterial vessels for portal vessels and the gradual disappearance of the reticuloendothelial system [15].

MDCT focuses on the first pathologic alteration, which is new arterial vascularization that contributes to early enhancement. Several studies were conducted to evaluate the role of multiphasic scanning with MDCT to detect small, hypervascular HCCs. Fast, thin-section (6-mm) MDCT improved the detection of hypervascular small HCC [16-20]. Seong et al. stated that the sensitivity for detecting hepatocellular tumors was 91.03% with a specificity of 95.3% [21].

Lipiodol CT makes use of the second pathologic phenomenon, i.e., gradual disappearance of the reticuloendothelial system. Kupffer cells but not neoplastic nodules eliminate the iodized oil retained in the hepatic parenchyma within 3 to 4 weeks. Therefore, retained lipiodol can easily be detected by performing a second CT scan 3 to 4 weeks after an injection. However, false-positive results occur when lipiodol persists in nonneoplastic areas of the liver because of angiomas, alterations in the reticuloendothelial system, or changes at the site of previous liver biopsy [22]. False-negative results can occur if lipiodol does not reach the neoplastic foci and/or if tracer is eliminated from the foci. Several studies focused on the sensitivity of lipiodol CT in the detection of HCC. Researchers compared pathologic specimens obtained from biopsy, partial resection, or liver transplantation and reported sensitivities ranging from 40% to 90% [23-28].

We performed a second MDCT examination between 3 to 6 months after lipiodol CT. Therefore, the diagnostic standard was based not only on single MDCT or lipiodol CT studies but also on a comparison of interval changes on serial images. Although we know of no published discussions about the accuracy of lesion detection on serial imaging, the accuracy of this approach might reasonably be higher than of single MDCT or lipiodol CT examinations. In addition, our DSA measurements were taken as part of routine preoperative examination before liver surgery for HCC. Sensitivities of DSA were 87.5% for nodules sized 10 to 20 mm and 78.9% for nodules <10 mm. The sensitivity of MDCT was 94.6% for nodules of 10 to 20 mm and 94.7% for nodules <10 mm; these were significantly superior to the sensitivities of DSA. In addition, MDCT depicted 56 nodules sized 10 to 20 mm, or seven nodules more than DSA. Among the seven nodules, three were false lesions, which had nodular morphology. These false lesions showed enhancement in the early arterial phase and isodensation to hypoattenuation in the portovenous phase; these findings are identical to those of typical small, hypervascular HCCs. Such lesions can be small arteriportal shunts or small HCCs that were treated and that atrophied without lipiodol retention. We could ascertain the nature of these lesions without pathologic proof.

As for the preoperative diagnosis of HCC, the sensitivity of the modality is a major concern. Our study showed that MDCT significantly improved the detection of lesions compared with DSA. Moreover, MDCT is a noninvasive examination.

The present study had several limitations. First, hypovascular and infiltrative HCCs could not be identified by using the modalities studied and must be excluded. Second, specificity was not confirmed, but a combination of the clinical courses, the laboratory values, and the imaging appearances may be sufficient for a presumptive diagnosis of hypervascular HCC nodules. Third, not all HCC nodules included in our study had pathologic proof. Finally, the accuracy of serial imaging follow-up, which was limited to about 8 months overall, could not be ascertained; and slow-growing lesions might have been missed. Longer follow-up period may be necessary.

In conclusion, MDCT may obviate DSA in the preoperative examination for HCC because of superior lesion detectability with MDCT compared with DSA.

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多層次電腦斷層掃瞄對於高血管性肝細胞腫瘤患者的術前評估之角色：與數位減影血管攝影之比較

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本研究的目的是為確定多層次電腦斷層掃描是否可以取代具侵入性的數位減影血管攝影作為高血管性肝細胞癌的標準術前診斷。

總共43位臨床證實肝細胞癌的病人進行三相的多層次電腦斷層掃瞄。掃瞄總共包共顯影前（pre-contrast）、肝臟動脈相（hepatic arterial phase）、肝門靜脈相（portovenous phase）和延遲相（delay phase）。掃瞄完畢後一個月之內所有病人皆接受數位減影血管攝影以及經肝動脈化學栓塞療法並注射碘化油滴。病人在血管攝影之後約一個月進行一次，且在碘化油滴多層次電腦斷層掃描後3到6個月後再進行第二次多層次電腦斷層掃瞄。病人的所有系列影像均被重新檢視，且以多層次電腦斷層掃瞄與數位減影血管攝影所得之影像進行比較。

對於大於20mm的肝細胞腫瘤，多層次電腦斷層掃瞄和數位減影血管攝影的敏感度相同。對於10-20mm的肝細胞腫瘤，多層次電腦斷層掃瞄的檢測敏感度（sensitivity）為94.6％，而數位減影血管攝影的敏感度為83.1％。對於10mm以下的肝細胞腫瘤，多層次電腦斷層掃瞄之敏感度為94.7％，而數位減影血管攝影之敏感度為78.9％。

由於對於肝細胞腫瘤診斷能力之較為優越性，多層次電腦斷層掃瞄可以取代數位減影血管攝影作為肝細胞癌的標準術前診斷。

關鍵詞：電腦斷層攝影，數位減影血管攝影，肝細胞癌