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Value of Hepatic Arterial Phase CT Versus Lipiodol Ultrafluid CT in the Detection of Hepatocellular Carcinoma

Stefano Colagrande, Rossana Fargnoli, Francesca Dal Pozzo, Alessandra Bindi, Luigi Rega, and Natale Villari

Objective: To evaluate the role of hepatic arterial phase (HAP) spiral computed tomography (CT), as compared with iodized oil (Lipiodol ultrafluid [LUF]) CT for revealing nodular hepatocellular carcinomas (HCC).

Methods: Twenty-four cirrhotic patients underwent two-phase HCT examination: HAP 25 seconds and portal phase 70 seconds after injection of 1.5 mL/Kg contrast medium. All patients also underwent hepatic angiography and intraarterial infusion of iodized oil; LUF CT was performed 3–4 weeks after infusion. HCT images were compared with LUF CT images for detection of hepatic nodules.

Results: We found no significant difference between the sensitivity of HAP CT and LUF CT for nodules >10 mm, while HAP CT was more sensitive than LUF CT in revealing nodules <10 mm (47 vs. 27, $p < 0.001$).

Conclusions: HCT should be considered as the first method for the detection of HCC, whereas LUF CT should be used only for therapy.

Key Words: Hepatocellular carcinoma—Spiral CT—Lipiodol CT—Liver neoplasms—Diagnosis.

In developed countries, hepatocellular carcinoma (HCC) is an uncommon disease, accounting for about 1–2% of all malignancies. However its prevalence is remarkably high in patients with cirrhosis of the liver, since 10% of patients dying from cirrhosis have HCC at autopsy (1). The development of HCC in cirrhosis is a multistage process, where a regenerative nodule of liver cirrhosis progresses to overt/advanced HCC through adenomatous hyperplasia, atypical adenomatous hyperplasia, and early HCC (2). Progression to HCC is associated with major changes in the vascular pattern, resulting in an increase in arterial and a reciprocal decrease in portal blood supply to the nodule. In addition, reticuloendothelial cells are usually absent in HCC (3). All these characteristics are of major importance for the early detection of HCC in cirrhosis by imaging techniques. Indeed, hepatic angiography and Lipiodol (Guerbet S.A., Aulnay sous Bois, France) ultrafluid (LUF) angiography and computed tomography are considered the gold standard

for the diagnosis of HCC in cirrhosis (4). All these techniques, however, are invasive and expensive, and are therefore not used for initial screening. At present, screening for HCC in patients with cirrhosis of the liver is based on measurement of alphafetoprotein (AFP) and ultrasound (US) examination every 3–12 (average 6) months (4–6). However such a program has a sensitivity of 55–84% for HCC nodules of <3 cm in diameter and of approximately 60% for nodules of 1 cm (7). A similar sensitivity has been reported for conventional computed tomography (CT), which allows visualization of liver enhancement prevalently during the portal phase perfusion of contrast medium.

Spiral CT is a technique that allows the scanning of the upper abdomen in a very short time (<25 seconds). With this technique, it is possible to scan the entire liver parenchyma in a single breath hold, during the hepatic arterial phase (HAP) after the administration of contrast material. In addition, this method requires lower amounts of contrast medium than conventional CT (80–150 versus 150–200 mL) and may therefore be better tolerated by the patient. Previous studies showed that HAP spiral CT is highly sensitive and superior to conventional CT and US in the detection of HCC of <1 cm (8–11).

The present study was performed to evaluate the role of HAP CT, as compared with LUF CT, in the diagnosis of HCC in patients with cirrhosis and US evidence of liver nodules.

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MATERIALS AND METHODS

This investigation was performed in 24 patients with hepatitis C virus (HCV)-related cirrhosis (22 men, 45–83 years old; mean age, 66.8 years) who underwent spiral CT of the liver and LUF CT between March 1996 and December 1998. Patients were enrolled because of US detection of at least one hepatic nodule (20 patients), or high serum AFP with negative US findings (4 patients). Among the 20 patients with US evidence of hepatic nodule(s), 8 also had a rise in AFP. These patients belonged to a larger series of 219 patients with cirrhosis of the liver submitted to screening for HCC by US examination and AFP determination. One hundred eighty-two patients were not enrolled in the study due to negative US findings and normal AFP levels. Of the 37 patients suitable for the study who had undergone spiral CT, 13 were not included because they had either nondiagnostic LUF CT, due to the presence of vascular abnormalities (2 patients), or did not have LUF CT (11 patients) because of advanced (Child class C) cirrhosis (3 patients), presence of liver masses with a diameter >5 cm (3 patients), or refusal to have this procedure (5 patients). US examination was performed by an EsaOte-Ansaldo AU 590 asynchronous scanner (Italy) equipped with wide-angle convex probes of 3.5 MHz.

Spiral CT was performed using a Somatom Plus (Siemens, Erlangen, Germany) scanner. Helical scans were obtained cephalocaudally with section thickness of 8 mm, pitch of 1, matrix 512 × 512, at 170 or 220 mAs, according to the patient's body habitus, and at 120 kV. The entire liver parenchyma was scanned within one breath hold of 20–25 seconds. Three acquisitions were obtained for each patient: one before and two after the i.v. administration of 1.5 mL/kg body wt of nonionic iodinated contrast material (Ultravist 370, Schering, Berlin) at the rate of 3–4 mL/s. The first enhanced CT scan started 25 seconds after the beginning of injection of contrast material (HAP), the second enhanced CT scan was initiated 70 seconds after the bolus (portal venous phase [PVP]). Each examination was completed in approximately 5–6 minutes.

Hepatic angiography with intraarterial injection of lipiodol was obtained with a digital angiographic system (Philips D.V.I., Eindhoven, The Netherlands). After local anesthesia was begun, a catheter was inserted into the aortic artery via the femoral or left brachial artery. Approximately 30 mL of nonionic iodinated contrast medium (Ultravist 150, Schering, Berlin) was injected at the rate of 10–15 mL/s into the abdominal aortic artery using a Pigtail 4 Fr (Cordis Europa N.V., Roden, The Netherlands) to identify all arteries afferent to the liver. Thereafter selective celiac and superior mesenteric angiography was performed. Finally 10–15 mL of Lipiodol was injected into the hepatic artery beyond the origin of the gastroduodenal artery using Terumo Cobra or Cordis Sim 1 catheters.

When areas of angiographic enhancement not completely filled with Lipiodol were detected, a new injection

was performed using greater amounts of Lipiodol. To detect retention of Lipiodol by malignant nodules, a CT scan was performed again 3–4 weeks later.

The number and size of nodules in the HAP and PVP of CT scans, as well as in LUF CT, were evaluated in a blinded fashion by the primary radiologist and two other radiologists, who read the images independently and were unaware of either the clinical characteristics of the patients or the results of the other diagnostic studies. In case of disagreement among the readers with regard to the number of visualized nodules, the lowest value was chosen.

Diagnosis of HCC was confirmed by liver biopsy in all 20 patients who had evidence of at least one liver nodule at US examination. All patients included in the study were clinically followed-up every 3–6 months. Furthermore spiral CT was repeated again 9–12 months later in all patients showing different results at spiral CT and LUF CT examination.

Each nodule was assigned, based on its diameter, to one of the following groups: <10 mm, 10–20 mm, or >20 mm. To compare the various techniques, statistical analysis was conducted separately within each of the three levels of nodule diameter. The Chi-squared test (with Yates' correction for 2 × 2 tables) was used for this purpose. The significance level was set at $p = 0.05$; no corrections were introduced for the presence of multiple simultaneous comparisons.

RESULTS

Cumulative and individual data obtained at US, spiral CT, and LUF CT in the 24 patients included in the study are shown in Tables 1 and 2 and in Fig. 1.

LUF CT detected one or more hepatic nodules in 22 of 24 patients studied, including 2 of 4 patients with high AFP levels but negative US examination. In particular, 8 patients showed one nodule, 4 patients had 2 nodules, 6 patients had 3 nodules, and 4 patients had 4 or more nodules for a total of 65 nodules. In the remaining two patients with negative US examination, LUF CT did not identify any nodules, while HAP CT detected five nodules.

Spiral CT identified 92 hepatic nodules. All of these nodules were observed at HAP CT, while PVP CT detected only 39 nodules (Table 1).

None of the 33 nodules detected by US were missed

TABLE 1. Correlation between tumor size and detectability of hepatocellular carcinoma nodules with each imaging technique (24 patients, 98 nodules)

	CT			
	US	HAP	PVP	Lipiodol
Group 1 <10 mm	2	47	11	27
Group 2 10–20 mm	5	19	4	13
Group 3 >20 mm	26	26	24	25
Total	33	92	39	65

US, ultrasound; HAP, hepatic arterial phase; PVP, portal phase.

TABLE 2. Comparison of detectability of hepatocellular carcinoma nodules between lipiodol computed tomography and hepatic arterial phase computed tomography

Group	CT		
	Lipiodol	Lipiodol-HAP	HAP
<10 mm	5	22	25
10–20 mm	1	12	7
>20 mm	0	25	1
Total	6	59	33

HAP, hepatic arterial phase.

using either LUF CT or HAP spiral CT. When data obtained with LUF CT were compared with those of spiral CT, 59 nodules were detected by both techniques, 6 were detected using only LUF CT, and 33 were detected using only HAP spiral CT (Table 2) (Fig. 1).

The three imaging techniques used in this study (US, spiral CT, and LUF CT) had the same sensitivity in detecting nodules >2 cm (Table 1), since the 26 nodules >2 cm were detected with US as well as with HAP spiral CT (24 at PVP), while LUF CT identified 25 nodules. Spiral CT and LUF CT were also comparable in cases of nodules with a diameter of 10–20 mm. In fact 19 of these nodules were seen at HAP spiral CT (4 at PVP), and 13 at LUF CT ($p =$ not significant). In contrast, US detected only five nodules of this size ($p < 0.001$ versus spiral CT and $p < 0.05$ versus LUF CT). In the case of nodules with diameter of <10 mm, HAP CT identified 47 nodules, LUF CT showed 27 (HAP versus LUF CT: $p < 0.001$), PVP showed 11 ($p < 0.01$ versus LUF CT and $p < 0.001$ versus HAP), and US showed 2 nodules ($p < 0.001$ versus both LUF CT and HAP) (Tables 1 and 2).

Among the 24 patients included in the study, 10 showed the same lesions at both LUF CT and spiral CT. In two patients with multifocal HCC, LUF CT detected six nodules not seen with spiral CT. In one of these two patients, data from LUF CT revealed a more advanced stage of HCC according to Choi's classification (12). On the other hand, 11 patients, including one with multifocal HCC, showed the same nodules with LUF CT and 28 more areas of enhancement with HAP spiral CT. All of the 28 nodules had a diameter of <10 mm and were undetectable with the other imaging techniques used in this study. If all areas of enhancement mentioned above were HCC, six patients would be classified with a more serious advanced stage of HCC (12).

Finally, two patients showed five nodules (three with a diameter of <10 mm and two with a diameter of 10–20 mm) with HAP spiral CT, and none with LUF CT.

Among the 13 patients with hepatic nodules detected only by HAP spiral CT, 4 died within 6 months. The remaining patients underwent at least another examination by spiral CT. Four patients, who received treatment for LUF CT-detected nodules (with percutaneous ethanol injection [PEI] and/or intraarterial injection of iodized oil mixed with doxorubicin hydrochloride plus percutaneous ethanol injection), showed no appreciable changes in the areas of enhancement seen at the first spiral CT; five

other patients had a larger increment in the size and number of such enhanced areas (Fig. 2). Two of these patients, who had no nodules with the first LUF CT, underwent a second LUF CT that identified the previously undetected nodules seen as enhanced areas with HAP spiral CT (Fig. 3).

DISCUSSION

The limits of serial AFP measurements and repeated US in the screening for HCC are well known. Some authors (1,13) think that these procedures have no substantial impact on the overall survival of cirrhotic patients with HCC. In addition, the high rate of early recurrence of HCC after PEI or surgery in patients with a single nodule at US denotes the low sensitivity of US in the staging of originally multiple HCC (14).

This led to the introduction of new imaging techniques for detection and staging of HCC, which takes advantage of two basic events in the evolution of the regenerative nodule of liver cirrhosis to early HCC: 1) the disappearance of portal vessels, which are substituted with arterial vessels; and 2) a progressive disappearance of the reticuloendothelial system (RES).

The latter phenomenon is exploited by LUF CT: LUF that reaches the hepatic parenchyma via the hepatic artery is eliminated within 3–4 weeks by Kupffer cells, but not by neoplastic nodules, which can be easily detected by performing a second CT scan 3–4 weeks later. Unfortunately this technique gives both false positive and false negative results. False positive results are due to the persistence of Lipiodol in nonneoplastic areas of the cirrhotic liver due to an altered RES, within angiomas, or at the site of a previous liver biopsy (15). False negative

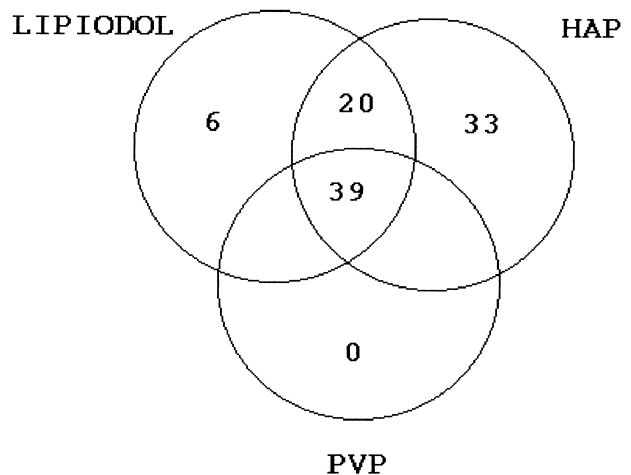


FIG. 1. The relationship between enhancement areas detected at spiral CT, in the hepatic arterial phase (HAP) and the portal venous phase (PVP), respectively, and Lipiodol ultrafluid (LUF) CT. All 39 lesions found at the PVP were also detected with both HAP and LUF CT. Furthermore, 59 enhancement areas not observed at PVP were found at either HAP ($n = 33$) or LUF CT ($n = 6$), or with both techniques ($n = 20$).

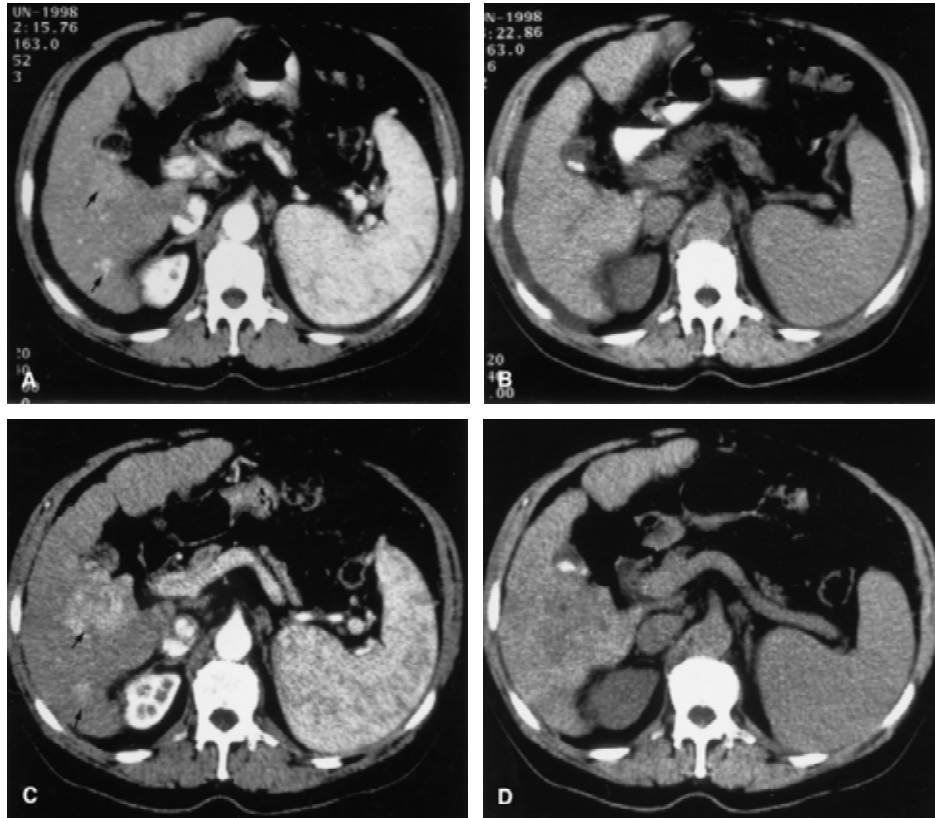


FIG. 2. Hepatocellular carcinoma. **A:** CT scan obtained during the arterial phase shows two smaller nodules (<10 mm) (arrows) in the right lobe, segments V–VI. **B:** CT scan obtained 3–4 weeks after transcatheter arterial chemoembolization with iodized oil shows no iodized oil accumulation in the nodules. **C:** Same case, after 1 year, shows at hepatic arterial phase CT a greater increment in the size of the nodules (arrows). **D:** Lipiodol ultrafluid CT shows no definitive mass.

results are due to the presence of neoplastic foci not reached by Lipiodol and/or tracer eliminated from the foci. Because false negative results are more frequent in the case of small neoplastic nodules (usually <2 cm), Yoshimatsu (16) attributed this phenomenon to a greater degree of differentiation of these small HCC nodules, with persistence of some reticuloendothelial cells, less-developed arterial vascularization, or both.

Spiral CT is focused on the other main characteristic of HCC, which is the development of new arterial vascularization, probably an earlier phenomenon than the disappearance of the RES. The results of this and previous studies (8–10) clearly indicate that spiral CT has a remarkably greater sensitivity than US and conventional CT (which allows prevalent imaging of the liver during the PVP) in detecting HCC nodules, especially when they are small (<1 cm). The advantage of the spiral CT scan is mainly due to the possibility of imaging the liver in the arterial phase, as demonstrated by the comparison between HAP and PVP. In this study, HAP spiral CT was found to have the same sensitivity as LUF CT, because it identified 59 out of the 65 nodules seen with LUF CT. However, spiral CT is more simple and easier to use, and is faster, noninvasive, and less expensive.

In the current investigation, HAP spiral CT showed the presence of 33 enhancement areas not detectable by

LUF CT, 25 of which were <1 cm (Table 2). Unfortunately, US or CT-guided biopsy of these nodules was not feasible, since they were only evident at HAP spiral CT, and the neoplastic nature of these nodules could not be confirmed by pathologic analysis. On the other hand, US or CT-guided needle biopsy is less sensitive than imaging in the detection of this kind of malignancy (75% of needle biopsy versus 97% of imaging) (17), as needle sampling involves only a small part of the lesion, and this may not include the area of neoplastic degeneration.

Although the possibility that some of the enhancement areas observed at the HAP of spiral CT may be false positive, several lines of evidence support, in our opinion, the contention that most of the above enhancement areas are small HCC foci:

1. Five patients showed progression of their disease. In two of them, the nodules seen as enhancement area at spiral CT but not detected by LUF CT were evident when a second LUF CT was done 1 year later (Figs. 2 and 3). These five patients had a greater increment in the size and number of the enhancement areas at the second spiral CT.
2. All these enhancement areas had the same appearance as those confirmed by LUF CT. On the other hand, their characteristics were quite different from those of

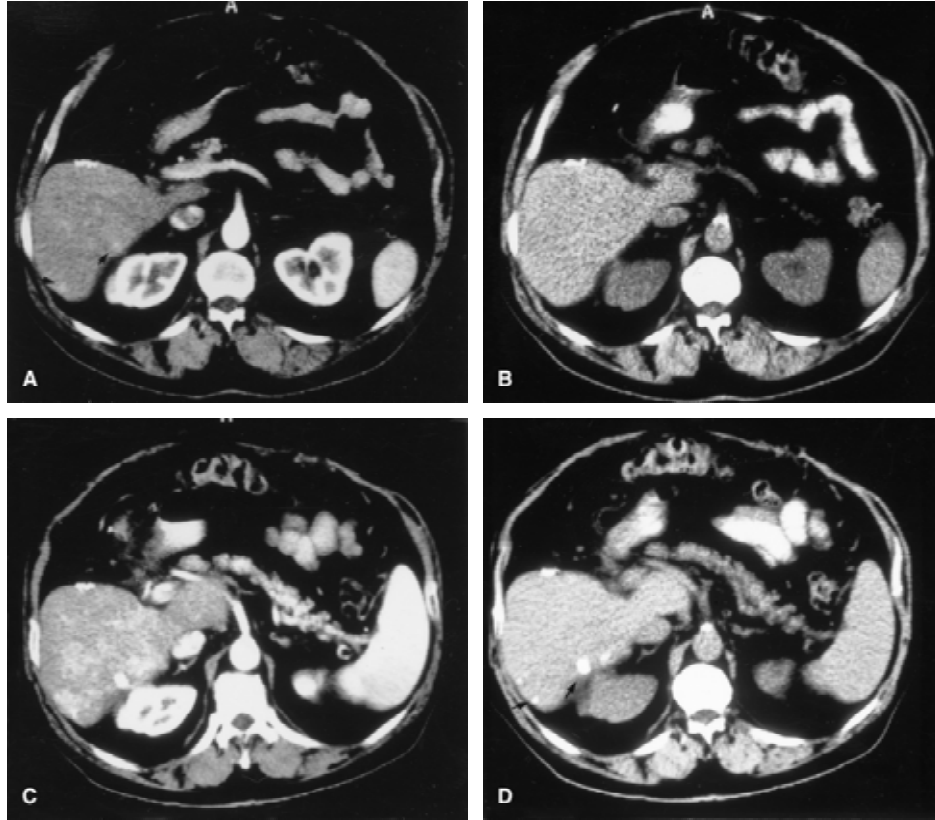


FIG. 3. Hepatocellular carcinoma patient. Hepatic arterial phase (HAP) CT (**A**) shows two smaller nodules (<10 mm) (arrows) in the right lobe, which are not visible with Lipiodol ultrafluid CT (**B**). **C:** After 8 months, a greater increment in the size and number of nodules is seen. **D:** Lipiodol ultrafluid CT shows good demonstration of the masses (arrows) also detected with HAP CT.

angiomas or other vascular abnormalities, such as the highest percentage of THAD (transient hepatic attenuation differences) (18,19).

3. No patient in this study had any nodular lesion at US examination before the detection of HCC.
4. Even if an enhancement area observed at HAP CT is due to a nodule of adenomatous hyperplasia (20), only 4% of dysplastic areas show such a characteristic, which precludes malignant transformation (21). Indeed in patients with cirrhosis of the liver only 2% of enhancement areas are not HCC and are instead benign lesions, including THAD, hemangioma, hepatic peliosis, fibrosis, splenic lobules, and lesions of a cryptogenic nature (19).
5. Data comparing LUF CT with pathologic examination of the explanted liver showed that this technique has a sensitivity of 70–75% in detecting HCC nodules. The 25–30% of neoplastic nodules missed by LUF CT could include the nodules seen only by spiral CT (15).

Of course, HAP spiral CT could miss some HCC nodules; unfortunately, the incidence of false negatives with this technique is currently unknown. In this investigation, 6 of 98 (6.1%) lesions found were detected at LUF CT and were not at HAP CT (Table 2) (Fig. 1). However this figure is not representative of the real percentage of

false negatives of HAP CT, since the accuracy of LUF CT in the diagnosis of HCC nodules is far from 100% (15,16).

Further studies based on accurate follow-up of patients with HCC or a pathologic correlation with livers studied at surgery or autopsy are needed to clarify the nature of hepatic nodules detected by spiral CT.

CONCLUSION

The results of the current investigation clearly indicate that HAP spiral CT is a highly sensitive technique in the detection of HCC foci, especially when the foci are <1 cm in size. In particular, it is superior to conventional CT and US and comparable with LUF CT, with the advantage of lower invasiveness and cost. Spiral CT should therefore be considered the first choice for the diagnosis and staging of HCC in patients with cirrhosis of the liver, whereas LUF CT should be used only for therapy.

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