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The Evaluation of Hepatocellular Carcinoma with Biphasic Contrast enhanced Helical CT Scan

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Abstract

Objective: To evaluate the role of biphasic contrast-enhanced helical CT including Hepatic Arterial Phase (HAP) imaging with Portal Venous Phase (PVP) imaging, in the detection and characterization of hepatocellular carcinomas.

Methods: The study included 40 patients (M=26, F=14) with histopathologically proven HCC. Age range was between 30-85 years (mean=55) by following consecutive patients with cirrhosis in whom Hepatocellular carcinoma was diagnosed or suspected either by raised serum α (alpha)-fetoprotein level or Ultrasound.

Results: Biphasic contrast-enhanced examination revealed a total of 85 lesions in these 40 patients, out of which 13 were unifocal, 12 showed a dominant mass with satellite lesions, 2 showed cluster of contiguous nodules and 13 were multifocal HCCs.

Mean diameter was 3.1 cm, ranging from 0.8 to 14 cm. On HAP imaging 85% were detected. (hyperattenuating = 69, hypoattenuating = 3) while on PVP imaging detectability was only 48% (hyperattenuating=2, hypoattenuating=39). Hence detectability was significantly ($p=0.008$) superior in HAP as compared to PVP imaging. In 7 patients (17%) tumor was visible only on HAP images. Venous invasion was present in 12 patients (30%) while arterio-portal shunting was seen in 5 patients (13%).

Conclusion: Biphasic contrast enhanced helical CT is a useful method in detection and characterization of HCC (JPMA 54:123;2004).

Introduction

The incidence of HCC varies widely, being most common in Southeast Asia sub-Saharan Africa and much less in North America and Western Europe. Various researchers from Pakistan have reported variable figures about prevalence of HCC in cirrhosis, ranging from 3.7% to 16.7%.¹ Some latest studies conducted in cirrhotic patients have reported 10.96% prevalence of HCC in North Western Frontier Province, 9.1% in Lahore and 8.25% in Karachi. This prevalence rate is high when compared to Spain (6.6%) but low when compared with Italy (19.7%) and Japan (39%).²⁻⁴

In Pakistan HCC is the fourth most common hepatic disorder.⁵ In Asia, sonography is reported to have a high sensitivity in the detection of HCC.⁶ Diagnostic accuracy of USG has been reported as 80% in a prospective study of 32 cases of HCC.⁷ However, the reported numbers were based primarily on retrospective evaluations of pathologically proved cases. Reported sensitivities have been much lower in the United States and Europe.

The availability of helical CT has changed the radiologist's approach to imaging. With the availability of faster CT scanners it is now possible to scan through the entire liver twice- once during the hepatic arterial phase (HAP) and then the portal venous phase (PVP) for hypervascular liver tumor detection and lesion characterization.

Patients and Methods

A prospective study was carried out over a period of 20 months (1-4-2000 to 30-11-2001). Initially 87 consecutive patients were included in the study who presented to the department as diagnosed cases or suspected HCC either by USG or raised serum α -fetoprotein level. Forty patients were selected who were biopsy proven HCC and 47 patients were excluded due to inadequate records or not proven HCC on pathologic results.

Out of the 40 patients, 26 were males, with age range between 30 to 85 years (mean 55 years). All these patients had proven HCC on histopathology and complete records, including CT scans, medical history and pathology reports. All 40 patients were diagnosed to have HCC by pathological findings with percutaneous core-needle biopsy ($n=40$) along with abrupt elevation of serum α -fetoprotein level ($n=16$) and definite tumor growth on follow up USG or CT ($n=5$). Thirty five patients had USG before CT examination, while none had MRI or nuclear scanning. In all patients with HCC, biphasic CT findings were compared and correlated with histopathologic findings and characteristic clinical manifestations.

CT Imaging Protocol

Helical CT scanning of the liver was performed with CTi/Pro GE Medical system at 120 kVp and 200-250 mAs. All patients received oral contrast material (1 liter of 2% Gastrografin) 1 hour before CT examination, followed by

I/V injection of 100 ml nonionic contrast medium for detection and enhancement pattern of the lesions. Contrast was administered with power injector at flow rate of 4 ml/sec (injected in 25 seconds). Biphasic Helical CT scans were obtained in HAP obtained after 20 sec. delay and in PVP after 50-60 sec. delay following the injection of I/V contrast material. In the HAP, slice thickness of 5mm with 5mm inter-slice space and pitch used was 1-1.5 depending upon the liver size. The entire liver for HAP was scanned in one breath hold. Later, additional images of PVP were obtained from the dome of diaphragm to the iliac crest with 7mm slice thickness and 7mm space. The hepatic arterial phase and portal venous phase images in 40 patients with 85 HCCs were compared and assessed for detection and enhancement pattern of the tumors. Any associated finding was sought, I.V.C or biliary ductal infiltration and hepatic or para-aortic lymphadenopathy. Arterio-portal shunting, ascites and pleural effusion if present was noted.

Statistical Analysis

Statistical analysis was performed with the help of a statistician. For comparison of detection of lesions in arterial and venous phase, statistical analysis was performed by using Repeated Measures Design. Statistical data analysis was done by using computer programme SPSS (version 8.0). A p-value of less than 0.05 was considered to indicate statistically significant difference. To find out whether size difference of lesions affected the detectability Tukey's HSD (Honest Significance Difference) test for multiple comparisons was used with level of confidence as $\alpha = 5\%$.⁸

Results

Evaluation of enhancement pattern and detectability in 40 patients with 85 HCCs using biphasic helical CT was performed. Of 85 HCCs, 69 (81%) showed moderate to marked hyperattenuation during the hepatic arterial phase. There was total hyperattenuation in 43 and partial hyperattenuation in 26. The remaining 16 HCCs showed isoattenuation in 13 (15%) and hypoattenuation in 3 (3.5%) during the hepatic arterial phase of imaging. Therefore the detectability of HCC in the HAP of helical CT was 85% (hyperattenuating=69, hypoattenuating=3). Detectability was determined by hyperattenuation or hypoattenuation compared to surrounding enhancing liver. Most of the HCCs showed characteristic hyperattenuation in the HAP before adequate enhancement of liver parenchyma. This was true even in HCCs <1 cm in diameter.

The PVP images showed hyperattenuation in 2 (2.3%), isoattenuation in 42 (49%), and hypoattenuation in 41 (48%). The detectability of HCCs in the PVP was 51% (hyperattenuating = 2, hypoattenuating = 41)

Table. Diagnostic accuracy of two phases.

Tumour size (cm)	No. of lesions	Hepatic arterial phase		Portal venous phase	
		Correctly detected	Sensitivity (%)	Correctly detected	Sensitivity (%)
< 3	52	40	77	29	56
3-5	14	14	100	4	29
>5	19	18	95	10	53
Total	85	72	84	43	51

The detectability of HCCs in HAP imaging was significantly ($p = 0.0008$) superior to the PVP, calculated by using Repeated Measures Test. Lesions were then divided into groups of three sizes (<3 cm, 3-5 cm and >5 cm) for comparison. There was significant difference in detection of lesions of different sizes. ($p\text{-value}=0.006$) Honest significance difference (HSD) value calculated by formula:

$HSD = q (a t N-t) \sqrt{MSE/n}$, where, α = selected significance level, T = no. of patients, N = total no. of observations, MSE = within subjects mean square error and n = no. of observation per group.

Note: $q (a t N-t)$ was obtained from studentized range table.

The value was 0.4937.

$$|\chi_1 - \chi_2| = 0.65 > 0.4937$$

$$|\chi_1 - \chi_3| = 0.5125 > 0.4937$$

$$|\chi_2 - \chi_3| = 0.1352 < 0.4937$$

Where, χ_1 = mean of <3 cm sized lesions, χ_2 = mean of 3-5 cm sized lesions, χ_3 = mean of >5 cm sized lesions

Multiple comparisons among the three size groups using the Tukey's HSD Test lead to the conclusion that mean number of lesions with size <3 cm were significantly different from the mean number of lesions having size 3-5 cm and 5 cm or above.

The reason for this difference is explained by the fact that poorly-differentiated HCCs are usually hypervascular and receive a large arterial blood supply since the portal blood supply tends to decrease progressively as the grade of malignancy increases.⁹ In contrast well-differentiated HCCs, as is frequently the case with small HCCs are sometimes hypovascular and as suggested by Ohashi et al.¹⁰ are better detected when liver parenchyma enhances i.e. in PVP.

Of the 85 HCCs, 16 HCCs (19%) did not show the characteristic enhancement pattern in the hepatic arterial

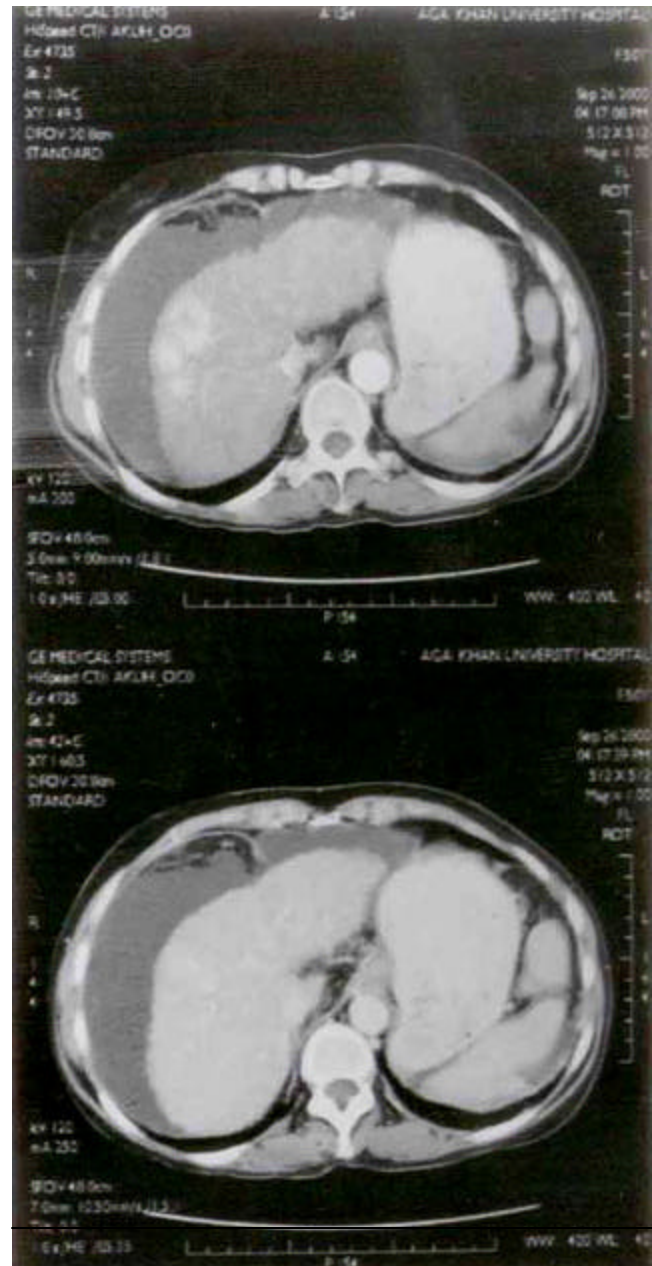
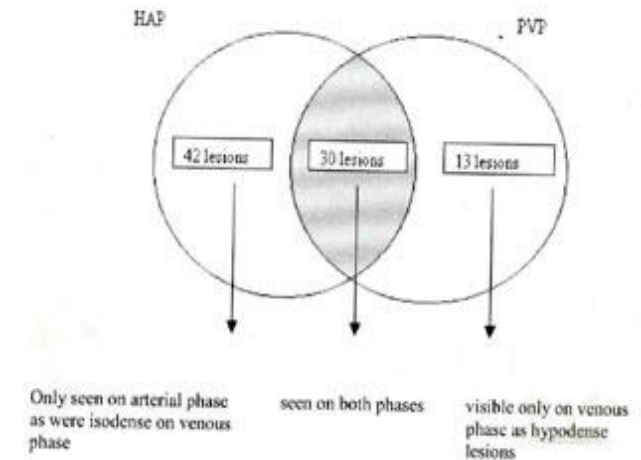
phase of imaging. They were iso or hypodense and were difficult to differentiate from other hepatic tumors including metastases or intrahepatic cholangiocarcinoma. Therefore the detectability of hypervascular HCCs in the hepatic arterial phase according to characteristic enhancement pattern was 79%.

Capsular enhancement although better seen on delayed images was identified in 8 (9%) of 85 tumor on portal venous phase. When the enhancement pattern of HCCs in the hepatic arterial phase was correlated with tumor size, 38 of the 52 HCCs <3 cm in diameter were hyperdense; 30 showed total hyperattenuation and 8 partial hyperattenuation. In cases of 3 to 5cm HCCs, the lesions were hyperdense in 13 of 14 HCCs, 8 showed total hyperattenuation and 5 partial hyperattenuation.

However, in cases of HCCs >5cm, the lesions were hyperdense in 18 of the 19 HCCs; 5 showed total hyperattenuation and 13 mosaic hyperattenuation. The enhancement pattern of HCCs such as total or partial enhancement in the hepatic arterial phase depended on tumor size. Majority of tumors of 3 cm or greater size enhanced confirming them as hypervascular HCCs. These were mostly poorly-differentiated HCCs on histopathology.

Three cases of HCC were complicated with bile duct invasions. Two of these three HCCs were poorly defined, infiltrative lesions that showed heterogenous hyperattenuation during the hepatic arterial phase. However, these two lesions showed hypoattenuation in portal venous phase without capsular enhancement, mimicking intrahepatic cholangiocarcinomas. The lesions were pathologically confirmed as HCCs by percutaneous core needle biopsy.

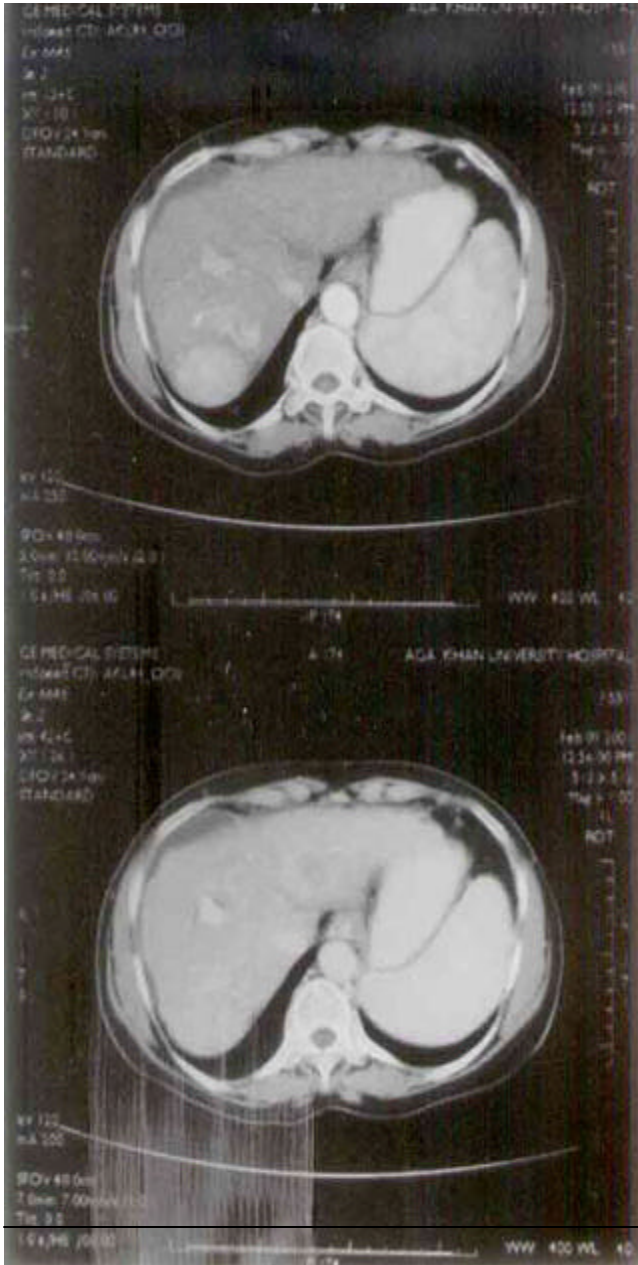
Twenty seven (67%) of the 40 patients with HCCs had associated liver cirrhosis on CT images, and the remaining 13 patients had associated chronic hepatitis or liver cirrhosis on clinical findings and USG images.



Amongst the secondary findings detected by CT, ascites was the most common manifestation of HCC. Varices and lymph node enlargement at the porta hepatis were the other major secondary findings. Venous invasion including the portal vein and hepatic vein was present in (30%) of 40 patients. The frequency of venous invasion was higher in larger HCCs and seen better in portal venous phase. Arterio-portal shunting was better seen in HAP in 5 (12.5%) of 40 patients.

Discussion

It is important to perform CT scans during the hepatic arterial phase for the diagnosis of HCC.^{11,12} The enhancement pattern of HCC during the arterial phase



imaging depends on tumor vascularity, tumor size, presence of peritumoral change in the tumor, and the degree of cirrhosis in the surrounding liver parenchyma.¹³ Factors affecting enhancement patterns of HCC include the volume of contrast material used, length of scan delay after injection of intravenous contrast material and rate of injection of contrast material.^{11,12}

Matsui et al.⁹ reported that early HCC is usually hypovascular and intranodal portal blood flow tends to decrease as the grade of malignancy increases. In addition, the poorly differentiated HCC are usually hypervascular, whereas well-differentiated HCCs are usually hypovascular,

particularly in cases of small-sized tumors.^{10,13,14} The detection of hypervascular HCC in the arterial phase in this study was 85% (72 of 85) confirming the benefit of biphasic contrast-enhanced helical CT to optimally detect HCC, and the results of Baron et al and Ohashi et al.^{10,15}

Portal or hepatic venous invasion is considered to be characteristic for HCC and associated with poor prognosis. The frequency of venous invasion has been reported to vary from 33 to 48%.^{16,17} In our study, portal venous invasion was detected in 30% because images were obtained during the portal venous phase. It was noted that the portal venous phase images were not useful for the detection and characterization of HCC because the lesions showed isoattenuation in 49% (42 of 85 HCC).

CT studies in Asian populations have reported encapsulated HCC in as many as 67% of tumors.^{14,17} In our study only 9% of HCC showed capsular enhancement in the portal venous phase because images were not acquired in delayed phase, which better detects capsular enhancement. Focal nodular hyperplasia, hepatic adenoma and hypervascular metastases enhance during the arterial phase and become isodense to hepatic parenchyma during the portal venous phase.¹⁸ Therefore, HCC must be differentiated from other hypervascular tumors in the arterial phase. Although portal venous invasion and capsular enhancement are features of HCC, CT findings are at times nonspecific and difficult to differentiate other hypervascular tumors from HCC. In our study two of the three HCCs with bile duct invasion were poorly defined, infiltrative lesions that showed heterogeneous hyperattenuation in the hepatic arterial phase without capsular enhancement, mimicking cholangiocarcinomas.

The sensitivities of intraoperative USG, CT arterial portography, and iodized oil CT have been reported to be significantly higher than those of USG, CT or angiography.¹⁴ However these methods being invasive are not commonly used. In our study, however ready depiction of small satellite nodules or intrahepatic metastases of HCC was possible because of adequate enhancement in the hepatic arterial phase.

Since the biphasic helical CT does not have 100% sensitivity for detection of HCC, some lesions are liable to be missed especially the early HCC, as mentioned by Takayasu et al.¹⁹ which results in false-negative findings. Consequently the true sensitivity, specificity and accuracy of biphasic helical CT was also not possible.

In our study HAP images depicted 33% additional HCC in 16 patients (40%) while HAP was the only phase to depict tumors in 7 (18%). The results of our study are comparable to studies by Oliver et al and Baron et al. The only difference was the greater lesion detection in HAP

alone (58%) despite the less number of patients. In western literature it has been reported that the addition of HAP to PVP images depicted 34% additional HCC in approximately one-third of patients while HAP was the only phase to depict tumor in 8-11% of patients.^{15,20} With the advent of multi-detector helical CT, detection and characterization of hepatocellular carcinoma has markedly improved. Multidetector helical CT with its increased spatial and temporal resolution allows multiple perfusion phases of liver to be acquired.^{21,22}

In patients suspected of having hypervascular lesions which include hepatocellular carcinoma and in patients scheduled for liver surgery, a biphasic study should be performed routinely because clinical staging and surgical resectability criteria rely on the accurate accounting of the number and location of tumor nodules.

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