

THE ROLE OF COMPUTED TOMOGRAPHY IN THE DIAGNOSIS OF HEPATOCELLULAR CARCINOMA IN VIRAL HEPATITIS B AND C PATIENTS

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ABSTRACT

BACKGROUND: Hepatocellular carcinoma (HCC) is a major health problem worldwide. It is the fifth most common cancer in the world, and develops in a background of cirrhotic liver. Our objective was to determine the diagnostic accuracy of Tri-phasic MDCT in detection of hepatocellular carcinoma in hepatitis B and C patients, taking histopathology as gold standard. **MATERIAL AND METHODS:** The Cross Sectional study was performed on 183 patients at department of diagnostic radiology and imaging, civil hospital Karachi for a period of eight months from June 2015 to February 2016. Standard MDCT technique is used for evaluation of ultrasound detected hepatic mass in patients with viral hepatitis B or C. Its enhancement pattern on arterial, portal and delayed phase were carefully evaluated and then compared with the histopathology. **RESULTS:** Mean age of the patients was 52.03 ± 13.42 years. Gender distribution shows 128 patients (69.9%) were male while remaining 55 patients (30.1%) were female. Risk factor analysis demonstrated 53 Hepatitis B patients while 130 patients were Hepatitis C positive. True positive cases were 110 and false positive cases were only 2. Positive predictive value was 98.2%, negative predictive value 94.4% with sensitivity 96.5%, specificity 97.1% and accuracy was found to be 96.7%. **CONCLUSION:** The results of this study suggest that CT Imaging proved high Sensitivity and positive predictive values in the detection of hepatocellular carcinoma taking histopathology as gold standard.

Key words: Hepatocellular Carcinoma, HCC, hepatitis B virus, HBV, hepatitis C virus, HCV, histopathology, MDCT, Tri-phasic CT liver

Introduction

Hepatocellular carcinoma is the most common primary liver malignancy. It is an aggressive tumor with high dissemination power. HCC differs from other malignancies in the aspect that it develops in a background of cirrhotic liver parenchyma.¹⁻³ It is among the top three causes of cancer death in the Asia Pacific region because of the high prevalence of its main etiological agents, chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections. HCC is the fourth most common hepatic disease in Pakistan with prevalence of 8-10%.⁴

MDCT plays a pivotal role in the diagnostic work-up of cirrhotic patients, who are at increased risk of developing hepatocellular carcinoma (HCC). Images should be acquired in four phases: non-contrast-enhanced phase, arterial phase, portal venous phase and delayed phase.⁵

The tumor shows characteristic features on CT: arterial hyper enhancement and venous/delayed wash out effect (Fig.1). Increased enhancement of the tumor compared with the surrounding liver parenchyma during the hepatic arterial phase is the cornerstone for the diagnosis of HCC at multiphase MDCT. Tumor washout, i.e. hypo-attenuation relative to the adjacent hepatic parenchyma during the hepatic

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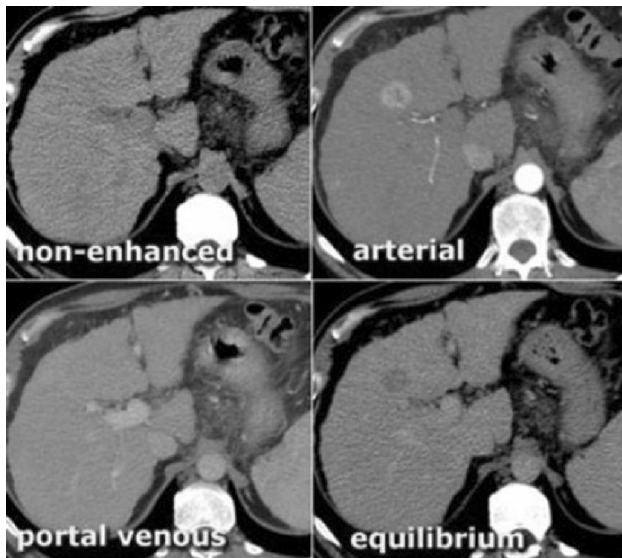


Figure 1: CT appearance of hepatocellular carcinoma

venous or delayed phase, has been recognized as a strong predictor of HCC.^{6,7}

There is paucity of local literature on this topic in Pakistan. After robust literature search, we found only one article in this regard entitled-” the evaluation of hepatocellular carcinoma with biphasic contrast enhanced helical CT scan”, published in year 2004. The aim of our study is to determine the diagnostic accuracy of tri-phasic MDCT in hepatitis B and C patients. Our study will not only indicate the future outcome but also provides the local data which may help us to make strategies for all patients of hepatitis B & C for early detection of HCC.

Material and Methods

Descriptive cross-sectional study with Consecutive non probability sampling technique was conducted for 8 months from June 2015 to February 2016 in the department of radiology, civil hospital Karachi after approval from ethical review committee. All the hepatitis B and C patients of either gender with age range of 26-79years, with ultrasound detected focal liver lesion(s) of size greater than or equal to 2cm, undergoing tri-phasic MDCT scan abdomen were included in this study. By using sajid’s sample size calculator: sensitivity of MDCT= 73.3% (PMID 17885047), specificity 96% (PMID 20920597). Prevalence of HCC 10% d=17% for sensitivity & d =

3% for specificity CI – 95% so the estimated sample size was n =183 patients.

Pregnant women and patients with chronic renal failure and/or serum creatinine greater than 1.5 mg/dl were excluded. Those hepatitis B and C patients were also excluded in which ultrasound of abdomen show no hepatic mass lesion, as Ultrasound is a preliminary requirement for MDCT. Patients in which histopathology sample cannot be obtained because of deranged PT-INR values also met the exclusion criteria. Verbal informed consent was taken for procedure and enrolment for each patient in this study.

MDCT scan was performed with 16 slice- Toshiba Spiral CT Scanner at 120 KVP and 200-250 mAs. All patients received oral contrast material (1 liter of 2% Gastro-graffin) 1 hour before CT examination, followed by I/V injection of 100 ml nonionic contrast medium (ULTRAVIST) for detection and enhancement pattern of the lesions. Contrast was administered with power injector at flow rate of 4 ml/sec. Tri-phasic CT scans were obtained in HAP obtained after 20 sec. delay, in PVP after 60 sec. delay and in delayed venous phase after 3min., following the injection of I/V contrast material. All the relevant features like age, hepatitis B/C risk factor gender, characterization of lesion by CT were recorded on a structured Performa. This was a multi-center study, i.e

Ultrasound guided Tru-Cut liver biopsy was performed by interventional radiologist at SIUT. MDCT diagnosis was compared with the histopathological report.

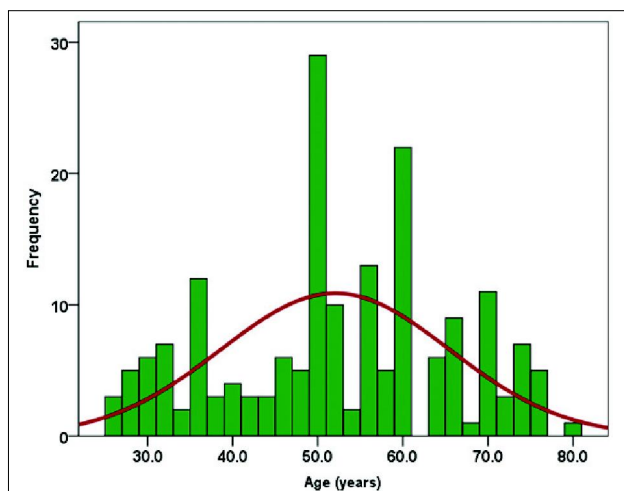
Those patients were labeled as HCC on CT who have hepatic lesion equal to or greater than 2 cm, showing hyper enhancement of tumor as compared to the liver parenchyma at the arterial phase and becoming indistinct or hypo dense compared to the liver parenchyma at the portal venous phase or delayed phase. True Positives (TP) in our study were those Hepatitis B/C patients who have hepatic lesion correctly diagnosed as HCC on MDCT & histopathology. True Negatives (TN) were those hepatic lesions not labeled as HCC on MDCT & histopathology. False Positives (FP) were those hepatic lesions labeled as HCC on MDCT, but not detected on histopathology and False Negatives (FN) were those histopathology detected HCC, but not found on CT.

Statistical software IBM SPSS Statistics Data Editor (version 21) was used for data analysis. Mean and

standard deviation was calculated for Age. Frequency and percentage was calculated for gender, Risk factor Hepatitis B & C. A 2x2 table was constructed to find sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy of Tri-phasic MDCT taking histopathology as gold standard. Post stratification kappa test was applied. Kappa value greater than or equal to 0.8 was considered as significant.

Results

The results showed that there were 128 male and 55 female patients in the study. The mean age was 52.03 ± 13.42 years. The Histogram representing distribution of age is shown in (Graph 1). Among total study subjects, Hepatitis B was observed in 29.0%

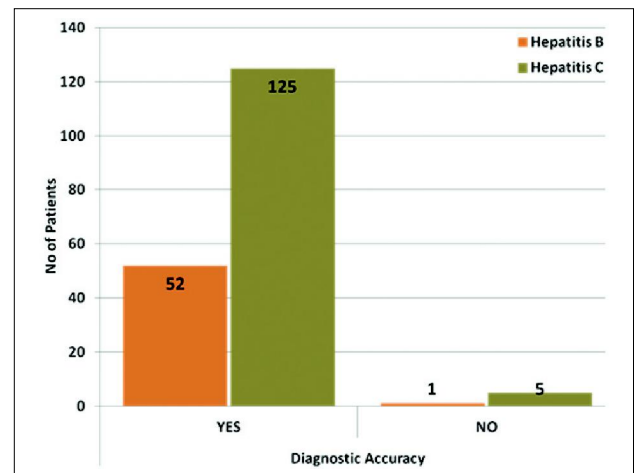


Graph 1: Histogram presenting distribution of age (years) n = 183

cases and Hepatitis C was observed in 71.0% cases. The frequency of diagnostic accuracy according to risk factors is shown in (Graph 2).

By Tri-phasic MDCT scan, positive findings were observed in 61.2% cases and histopathology showed positive findings in 62.3% cases. With the findings of tri-phasic MDCT and histopathology, the diagnostic accuracy of CT for the detection of HCC was found to be 96.7%.

Sensitivity, Specificity, Predictive values and diagnostic accuracy of tri-phasic MDCT scan for the detection of hepatocellular carcinoma taking histopathology as gold standard were calculated. The results showed



Graph 2: Frequency of diagnostic accuracy according to risk factors (n=183)

that there were 110 patients were true positive, correctly diagnosed and 67 patients were true negative, correctly diagnosed. Sensitivity, Specificity, PPV and NPV were 96.5%, 97.1%, 98.2%, and 94.4% respectively. These detailed results along with agreement between the two procedures are presented in (Tab.1). Post stratification Chi square test and Kappa test was also applied to see the association and agreement of two procedures considered Kappa value ≥ 0.8 and P-value ≤ 0.05 was considered as significant.

	Histopathology Findings			Kappa Value	P value
	Yes (n=114)	No (n=69)	Total		
MDCT Findings				0.931*	0.000**
Yes (n=112)	110 (TP)	2 (FP)	112		
No (n=71)	4 (FN)	67 (TN)	71		
Total	114	69	183		
Sensitivity	Specificity	PPV	NPV	Accuracy	
96.5%	97.1%	98.2%	94.4%	96.7%	

$$\text{Sensitivity} = \frac{TP}{TP + FN} * 100$$

$$\text{Specificity} = \frac{TN}{TN + FP} * 100$$

$$\text{PPV} = \frac{TP}{TP + FP} * 100$$

$$\text{NPV} = \frac{TN}{TN + FN} * 100$$

$$\text{Diagnostic accuracy: } \frac{TP + TN}{TP + FP + TN + FN} * 100$$

Kappa Test was applied

* Kappa Value > 0.8 was considered as significant

Chi Square Test was applied

P-value = 0.05 considered as Significant** Significant at 0.001 levels

Table 1: Diagnostic accuracy of triphasic MDCT findings to diagnose hepatocellular carcinoma with histopathology as gold standard (n=183)

Discussion

The aim of our study was to determine the diagnostic accuracy of MDCT in detection of Hepatocellular carcinoma in patients with viral hepatitis B and C using histopathology as gold standard. We evaluated diagnostic accuracy on the basis of sensitivity, specificity, positive predictive and negative predictive values. If these values were favorable for MDCT, then the latter could be proposed as the examination of choice for diagnostic imaging of hepatic lesions, and histopathology could then be reserved for therapeutic intervention alone via surgical resection or transplantation.

MCDT is a non-invasive and safe alternative to histopathology for investigating the hepatic malignancies, its extent, complications as well as imaging of benign hepatic lesions. It is also cost effective and available widespread as compared to MRI. With the advent of MDCT, diagnostic approach in a patient with chronic liver disease has been completely revolutionized with accuracy of radiological diagnosis of hepatocellular carcinoma approaching 99.6%.⁸

In the international study conducted by Torzilli G. et al reported high accuracy, sensitivity and specificity of CT over 95% for diagnosis of hepatocellular carcinoma (HCC).⁸ In view of these results, the fact that the real risks of fine needle biopsy have yet to be established and the possibility that tumor seeding has a major impact on patient prognosis, the use of biopsy should be drastically limited. Liver biopsy need not be performed under circumstances in which the diagnosis of HCC is certain after clinical, laboratory, and radiographic evaluation.⁹ In patients with cirrhosis with a 1-2 cm nodule detected during surveillance, a single imaging technique showing a typical contrast pattern confidently permits the diagnosis of HCC, thereby reducing the need for FNB examinations.¹⁰

In present study, sample population is restricted to hepatic lesion equal to or greater than 2 cm to re-emphasize the phenomena according to AASLD, EASL and EORTC guidelines¹¹⁻¹³ that typical CT findings can be used to diagnose HCC in high-risk patients (e.g. hepatitis B/C risk factor) without biopsy, when a nodule larger than 2 cm displays a typical vascular pattern on contrast enhanced CT or contrast-enhanced MRI. In 2011, a 6 month retrospective study conducted by Nam CY et al¹⁴ shows that res-

pective lesion-based sensitivity of CT was 65% (>2 cm) HCC and 40% for small (<2 cm) HCC. Patient-based specificity of CT was 96%. It was concluded that CT did not detect small HCC lesions with high levels of sensitivity. In one study conducted by Addley HC et al, analysis demonstrated a sensitivity of 65-75% and specificity of 47-88% for detection of HCC lesions. The sensitivity dropped to 48-57% for lesions of size ≤ 20 mm.¹⁵

There is paucity of Local literature regarding the accuracy of tri-phasic MDCT in detection of hepatocellular carcinoma. In 2004, J Yaqoob et al at evaluated HCC with Biphasic CT at AKUH in Pakistan. On HAP, imaging diagnostic accuracy was 84% while on PVP, imaging diagnostic accuracy was only 48%. In present study, we added delayed phase to the liver protocol for MDCT to increase the diagnostic accuracy. Lim JH et al¹⁶ at Sungkyunkwan University School of Medicine, Korea also reported that diagnostic accuracy of triple-phase helical CT including delayed phase for HCC was significantly higher than that of dual-phase helical CT. The mean sensitivity of triple-phase CT (89%) was significantly higher than that of dual-phase CT (86%).

In 2011, a local study conducted by Hafeez S et al at AKUH¹⁷ in Pakistan Concluded that tri-phasic CT Scan is a good non-invasive tool in characterizing and differentiating benign from malignant liver lesions with sensitivity of 100%, specificity of 80%, positive predictive value of 94.5%, negative predictive value of 100% and diagnostic accuracy of 95.5%.

In one study done in 2014, Choi JY et al¹⁸ reported 100% sensitivity for nodular HCCs larger than 2 cm on both modalities (CT and MR imaging). From the subsequent studies, the trend shows that diagnostic accuracy and sensitivity of MDCT in the detection of hepatocellular carcinoma has been increased with passage of time.

In our study, the mean age of the patients was 52.03 \pm 13.42 years. As compared with the study of Furlan A, Marin D et al,¹⁹ the mean age of the patients was 57 years-analogous to our study. There were 69.9% male patients and 30.1% female patients in our study which is compatible with the research of Abbas Z,²⁰ in which there were 78% male and 21% female patients. In our study, there were 29.0% Hepatitis B patients and 71.0% Hepatitis C patients which is comparable to a research study that examined trends

in the incidence of HCC among a population-based cohort of people infected with HBV or HCV at New South Wales Health Department between 1992 and 2007,²¹ there were 49% Hepatitis B patients and 51% Hepatitis C patients.

In present study, the positive predictive value of MDCT was 98.2% and diagnostic accuracy was 96.7% with sensitivity of 96.5% and specificity of 97.1%. Torzilli G et al⁸ reported accuracy, sensitivity, specificity, and positive and negative predictive values of CT were 99.6%, 100%, 98.9%, 99.3%, and 100% of CT for diagnosis of hepatocellular carcinoma (HCC) respectively which is comparable to our study.

Conclusion

The aim of our research was to re-emphasize the internationally studied fact that MDCT is a better diagnostic investigation in comparison to histopathology for diagnosing HCC. It is cheap, readily available and non-invasive imaging modality. MDCT proved high diagnostic accuracy as well as positive predictive value in the detection of HCC taken histopathology as gold standard. MDCT has the potential to replace histopathologic determination of HCC in hepatitis B and C patients, thereby avoiding possible complications related to histopathology.

Conflict of Interest: Authors declare no conflict of interest.

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