ORIGINAL ARTICLE

Diagnostic Performance of Quadruple Phase Multidetector Row Computed Tomography in Hepatoma: Comparison with Histopathological Diagnosis

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ABSTRACT

Objective: To determine diagnostic accuracy of quadruple phase helical computed tomography scan in detection of hepatocellular carcinoma in individuals with hepatitis B and C, keeping histopathology as the gold standard. **Methods:** A cross-sectional study was performed in the Radiology and Imaging department of a tertiary care university hospital during 2014 to 2016. All serologically positive patients were included. Quadruple phase computed tomography scan was done and results were interrelated with histological diagnosis. **Results:** Hepatocellular carcinoma was accurately diagnosed in 76 out of 80 patients using Quadruple phase computed tomography scan (sensitivity, 95%). It was correctly excluded in 70 of 72 patients (specificity, 97.2%). The overall diagnostic accuracy of Quadruple phase computed tomography scan for diagnosing hepatocellular carcinoma was 96.05%. The positive and negative predictive values were 97.4% and 94.59% respectively. **Conclusion:** Quadruple phase computed tomography is more effective in evaluating hepatocellular carcinoma than conventional biphasic and triphasic computed tomography scans. We propose it as the technique of first preference for imaging workup in patients with Hepatitis B and C.

Key words: Hepatocellular carcinoma, Computed Tomography, Diagnostic accuracy.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the commonest primary carcinoma of hepatic parenchyma. It is the fifth most common malignant neoplasm worldwide, and the third principal cause of cancer-related mortality. Majority of the HCC reported in Asia especially in East Asia.[1]

With increasing age, its incidence increases, with highest prevalence is observed for above than 65 years of age. In Western countries, HCC tends to be more common in cirrhotic patients. However, in Asia and Africa, the pattern is reverse.[2,3] According to World Health Organization (WHO), Hepatitis B Virus (HBV) is regarded as the second known human carcinogen after tobacco. The incidence of HBV related HCC in East Asian countries reported to be 2.7%.[4,5] Hepatitis C Virus (HCV) associated cirrhosis has a higher prevalence of developing HCC and only few cases of non-cirrhotic HCC have been reported with HCV, that indicates a possible mutagenic effect of the virus.[2,6,7]

HCC diagnosis is based on serological determination of Alpha Feto-protein (alpha-FP) levels, ultrasonography (U/S), Computed Tomography (CT) scan and Magnetic Resonance Imaging (MRI) techniques. Existing literature does not support the use of U/S as diagnostic tool because of wide variations in sensitivity and specificity.[8] MRI is more time consuming and needs a compliant patient. In past, conventional CT of liver was done which included only the portal venous phase imaging. Introduction of helical CT enabled biphasic scanning which included both arterial and portal venous phase acquisition.[9,10] Several studies showed that the addition of initial non-enhanced and delayed phases enabled the discovery of hepatomas that were missed on arterial and venous phase images.[11]

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Currently, scanning of cirrhotic liver suspected of having hepatocellular carcinoma is done by quadruple phase CT in which examination is carried out with precontrast or unenhanced images followed by hepatic artery dominant, portal venous phase and delayed phase images. Ricardo et.al has claimed 97.3% sensitivity and Agostino et.al has showed 93% specificity of quadruple phase CT.[8,10] Unenhanced phase ensures that the small siderotic regenerating nodules, that appear hyperdense than liver parenchyma, are not mistaken for enhancing nodules in the arterial phase.[12] HCC shows typical intense arterial enhancement with contrast washout in venous phase. Delayed phase CT enables to detect fibrous HCC capsule.[13]

It has already been established that hepatic cirrhosis is associated with manifold increased risk of hepatoma in hepatitis B or C positive cases. In Pakistan, the prevalence of HCC in cirrhosis is reported to be as high as 16.7%.[13] Elevation in serum alpha-fetoprotein is found in 90% of patients and is strongly suggestive of HCC in patients with cirrhosis. Various studies have realized that HCC in Pakistan detected more frequently in males of middle-aged group and there has been a positive correlation between lengthy interval between HCV infection and the development of HCC.[14]

Dual phase post contrast CT in helical format is a valuable diagnostic modality in recognition and characterization of HCC.[15] This is routinely practiced in the radiology departments for characterization of hepatic masses. Data acquisition is planned to get the arterial phase at around 20-50 second and portal venous phase at around 60-100 seconds after intravenous infusion of contrast agent. However, when conducting quadruple-phase protocol, two more phases are added. First, an unenhanced phase before commencement of intravenous contrast injection and an additional delayed phase after 180 seconds of contrast injection.[16]

The objective of this study was to evaluate all serologically positive hepatitis B and C patients for early detection of HCC by performing helical CT, keeping histopathology as gold standard. Local literature is relatively scarce on this subject. Therefore, this study will be a valuable addition to the local data.

METHODS

This cross-sectional study was conducted in tertiary care university hospital in the Radiology Department for two years from Feb 2014 to Feb 2016. All patients were recruited through non-probability consecutive sampling technique. Study was designed for adult patients of either gender and between age ranges of 40-65 years. All the patients who were diagnosed to have Hepatitis B and C on surface antigen test / surface antibodies were included in the study and serologically negative patients were excluded. Patients with HCC due to other causes like alcohol, alpha-1 antitrypsin deficiency and hemochromatosis were also not included. The duration of the disease process should be more than six months.

The study was conducted after the approval of ethical review committee of the institution. The purpose, procedure, risks and benefits of the study was explained to the patients and informed written consent was taken. All the CT scans were performed on 16 slicer ASTEON-4 CT scanner (Toshiba Japan) with slice thickness of 5mm and pitch of 5mm. Oral contrast (1 lit. of 2% gastrografin) was given to all the patients 1 hour before the examination. All the CT Scans were performed on quadruple phase technique that include unenhanced, arterial, portovenous and delayed phases. Initially, unenhanced CT scan was performed followed by 100 ml of nonionic intravenous contrast administration. Contrast was given by power injector at the flow rate of 2.5 ml/sec and arterial phase was planned 25 sec after the start of contrast injection. Venous phase was taken at 60-70sec and delayed phase was performed after 5 mins of contrast injection. All the images were reviewed by two Senior Consultant Radiologists having an experience of more than 5 years. A proforma was used to record the radiological findings. Histopathological reports were collected and then later on compared with CT findings to evaluate Hepatocellular Carcinoma.

The collected data were analyzed by using SPSS version 16 software. A 2x2 table was constructed. Specificity, sensitivity, negative and positive predictive values, and accuracy of quadruple phase CT scan in the diagnosis of HCC was calculated by keeping histopathological findings as gold standard. Frequency and percentage were computed for gender, mean ± SD was computed for age and duration of disease. Stratification to control the effect modifiers such as age and gender to see the outcome.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

RESULTS

A total of 152 cases were enrolled to determine the diagnostic accuracy of the Quadruple Phase CT for hepatic carcinoma in patients with hepatitis B and C, taking Histopathology as gold standard. Out of total 152 patients, 110 (72.36%) patients were male while

42 (27.63%) patients were female. 110 (72.36%) patients were < 50 years of age while, 42 (27.63%) patients were > 50 years of age. (Table 1) Mean age of the patient was 43.08 years with the standard deviation of ± 9.98 years. Similarly, duration of symptom was 11.5 months (mean) with the standard deviation of ±4.8 months. The minimum duration of symptom in patients was 9 months while the maximum duration was 48 months.

Based on quadruple phase CT scan findings, HCC was diagnosed in 78 patients (51.32%) and 74 patients (48.68%) were not found positive on QPCT. Of the 78 patients diagnosed with HCC, 76 were positive and 2 were negative on histopathological examination. Similarly, of the 74 patients not showing features of hepatocellular carcinoma, 70 were also negative on histopathological examination. In 4 patients, HCC was misinterpreted as negative. Correct assessment was made in 146 out of 152 patients (96.05%). Incorrect assessment was made in 6 out of 152 patients (3.94%) only. (Table 2)

HCC was correctly diagnosed prospectively in 76 of 80 patients using QPCT (sensitivity, 95%). It was correctly excluded prospectively in 70 of 72 patients (specificity, 97.2%). The overall diagnostic accuracy of Quadruple phase CT scan for diagnosing hepatocellular carcinoma was 96.05%. The PPV and NPV were 97.4% and 94.59% respectively.

Diagnostic accuracy of Quadruple Phase CT in patient <12 months of duration of symptom was 93.75% Sensitivity, 83.33% specificity, 90.91% PPV while NPV was 88.24% and p-value found to be significant i.e. <0.001. In patients with >12 months of duration of symptom, sensitivity was 93.75%, specificity 83.33%, PPV 90.91%, NPV 88.24%. (p-value <0.001).

Diagnostic accuracy of Quadruple Phase CT in age group <50 years was 96.43% and 95.29% sensitivity and specificity respectively. Similarly, PPV and NPV were 93.10% and 96.15% (p-value <0.001). In age group > 50 years, sensitivity, specificity, PPV and NPV were 92.13%, 87.50%, 92.13% and 87.50% respectively (p-value <0.001).

Diagnostic accuracy of Quadruple Phase CT in male patients showed the sensitivity, specificity, PPV and NPV of 93.33%, 88.0%, 90.32% and 91.67% respectively while in females, it was 90.91%, 90.00%, 90.91% and 90.00% respectively (p-value <0.001). (Table 3)

Table 1: Frequency & Percentage of the Age, Quadruple Phase Findings, Histopathology Findings & Duration of Sypmtom (n=152)

Variable	Frequency	Percentage
Age		
<50	110	72.36
>50	42	27.64
Qpct Finding		
Yes	78	51.84
No	74	48.16
Histopathology Finding		
Yes	80	52.63
No	72	47.36
Duration Of Symptom		
< 12 Months	100	65.78
> 12 Months	52	34.21

Table 2: Diagnostic Accuracy of Quadruple Phase CT in the Diagnosis of Hepatocellular Carcinoma Keeping Histopathology as Gold Standard (n=152)

Results of Quadruple Phase CT	Histopathology		Total
	Positive	Negative	
CT (Positive)	True Positive 76	False Positive 02	78
CT (Negative)	False Negative 04	True Negative 70	74
Total	80	72	152

Sensitivity = 95%
Specificity = 97.2%
Positive Predictive Value = 97.4%
Negative Predictive Value = 94.59%
Diagnostic Accuracy = 96.05%

Table 3: Stratification of Results According to Gender, Age and Duration of Symptoms

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Gender				
Male	93.33	88.00	90.32	91.67
Female	90.91	90.00	90.91	90.00
Age				
<50 Years	96.43	95.29	93.10	96.15
>50 Years	92.31	87.50	92.13	87.50
Duration				
<12 Months	93.75	83.33	90.91	88.24
>12 Months	93.33	72.73	82.35	88.88

DISCUSSION

Worldwide, HCC is one of the frequently reported cancers and is a considerable health risk with increasing incidence. The background hepatic cirrhosis is the vital contributing risk factor that is largely due to chronic HCV and HBV infection globally. Although histopathology is considered to be the gold standard for diagnosing liver malignancy, quadruple-phase CT is less invasive, easy to perform and yields results which draw similarities with histopathology. At present, CT is the diagnostic modality most frequently used by

radiologists for studying the liver. The introduction of single-detector helical (spiral) CT (HCT) during the last decade and, more recently, the development of multidetector CT (MDCT) have significantly improved the ability to study the liver.[17]

Dual phase contrast enhanced spiral CT is considered to be a valuable method in recognition and characterization of HCC.[10] This is routinely practiced in the radiology departments for characterization of hepatic masses. Data acquisition is planned to get the arterial phase at around 20-50 second and portal venous phase at around 60-100 seconds after intravenous infusion of contrast agent.[12] However, when conducting quadruple-phase protocol, two more phases are added. First an unenhanced phase before commencement of intravenous contrast injection and an additional delayed phase after 180 seconds of contrast injection.

In the current study, MDCT using quadruple-phase protocol for detection of hepatocellular carcinoma taking histopathological gold standard showed 97.16% sensitivity, 70% Specificity, 97.52% Positive PV and 76.92% Negative PV. These findings are in agreement with a study conducted by Lannaccone R and workers.[10]

Another study conducted by Kim HC and colleagues,[18] showed that inclusion of initial noncontrast sections improve diagnostic yield to detect HCC, increase level of confidence assessing the viability of tumor cells, in comparison to dual phase spiral CT only, in patients with prior TACE (transcatheter arterial chemoembolization). It is also very important in distinguishing variant lesions such as simple hepatic cysts, regenerating nodules, focal fat sparing and confluent focal fibrosis from HCC nodules.

The increased ability to detect HCC is that we may have missed a considerable number of tumors because we did not have pathologic correlation for all individual focal lesions that we thought to be HCC. However, all our cases had at least one histologically confirmed neoplasm (either at partial surgical resection or biopsy), each extra nodule seen at nonenhanced and/or delayed phase scanning had pathologic confirmation. This study was not only intended to test the sensitivity of CT as a screening tool in cases with cirrhosis without clinical suspicion of HCC but also to assess the additional value of nonenhanced and/or delayed phase imaging. To our knowledge very few studies have been done on quadruple-phase protocol for detection of hepatocellular carcinoma worldwide generally and in Pakistan specifically, and the results of the current study in support of other studies mentioned above demonstrate the increased accuracy of MDCT using quadruple-phase protocol for detection of hepatoma in cases of cirrhosis taking histopathology as a gold standard.

The enhancement pattern of the tumor depends upon the hepatic arterial supply whereas the portal venous supply is responsible for enhancement of the surrounding liver parenchyma. The tumor may appear isoattenuating if the arterial supply of the lesion is not sufficient to enhance the tumor than the surrounding liver parenchyma. Most of the moderately and poorly differentiated HCC are solely supplied by hepatic arteries; however, few do not possess sufficient supply therefore, remaining isoattenuating on arterial, portal and delayed phases. Nodules that had same degree of hepatic arterial and slightly decreased portal venous supply appear iso-attenuating on hepatic arterial and venous phases and hypo-attenuating on delayed phase due washout.[19]

Our analysis may be partially clarified by the observing the progression of tumour and liver attenuation over the different imaging phases. In our research, both liver parenchyma and HCC attained their extreme enhancement during venous phase. Past data have suggested that this outcome is a result of the intratumoral persistence of the iodinated contrast throughout the arterial phase.[20] The reason behind lesion washout remains unclearly understood, but according to the prevailing theory, this sign reflects diminished intranodular portal blood supply.[21,22] Consequently, it can be restated as, compared to the venous phase, the longer interval related with delayed phase results in more heightened drainage of contrast substance from the lesion and elucidating the higher frequency of tumour washout during the late phase.[23,24]

Hwang et al.[25] explained that in cirrhotic patients with portal hypertension, the ultimate enhancement of the liver tissues on late phase increases contrast between relatively hypovascular HCC and surrounding liver parenchyma. Well differentiated HCCs have a normal or increased hepatic supply and decrease portal supply, so these can only be seen on delayed phase images. Thus, it is suggested by Takayasu et al.[26] that delayed phase CT is more valuable in detecting early hepatocellular carcinoma.

Addition of delayed phase CT scan has many practical implications in detecting hepatocellular carcinoma, especially for tumors less than 2cm in size. It is also valuable in detecting lesions that are equivocal on arterial and portovenous phases thus increasing the confidence level. It has also shown great advantage in visualization of tumor capsule of HCC than with Dual phase helical CT. This is a pivotal prognostic indicator as presence of a capsule has lately been established to be a favorable prognostic factor for having enormous tumor necrosis after TACE.[27] Delayed phase imaging also helps to differentiate the cholangiocarcinoma and

haemangiomas from HCC due to their typical delayed enhancement pattern.

Lim et al,[19] related triple phase dynamic CT with dual phase dynamic CT with combination of arterial and venous phase imaging for lesion detection and concluded that although HCC less than 2 cm in size were more obvious on late phase than on porto-venous phase and some were detected only on late phase images. However they concluded that delayed image did not increase sensitivity in detecting large tumors more than 2 cm.

The major pitfall of inclusion of additional phases in any CT examination of cirrhotic patients remains to cause concern due to accentuated radiation exposure and tube loading. This study reveals, no washout that was visible in venous phase was missed in the delayed phase, but we were unable to provide adequate evidence to suggest the elimination of venous phase. In this study Quadruple Phase CT had a positive and negative predictive value of 97.4% and 94.59% respectively and diagnostic accuracy of Quadruple Phase CT for the detection of Hepatocellular carcinoma 96.05%, which correlates well with results obtained in other parts of the world.

CONCLUSION

In cases of hepatocellular carcinoma, imaging plays an essential role in the detection, diagnosis, staging, treatment, and surveillance. Spiral MDCT using quadruple-phase has high diagnostic accuracy for better detection of hepatocellular carcinoma in comparison to conventional dual phase CT. Therefore, we propose Quadruple phase CT as the method of first choice for the diagnostic imaging of HCC in patients with Hepatitis B and C.

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