ROLE OF DELAYED PHASE TUMOR CONTRAST WASHOUT IN PATIENTS OF HEPATOCELLULAR CARCINOMA ON COMPUTED TOMOGRAPHY

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ABSTRACT

Objective: To evaluate role of delayed phase tumor contrast washout in patients of hepatocellular carcinoma on computed tomography.

Study Design: Comparative - cross-sectional study.

Place and Duration of Study: Study was conducted in Department of Radiology, Pakistan Institute of Medical Sciences and Islamabad, from Jan 2017 to Jul 2017.

Material and Methods: A total of 54 patients with diagnosed HCCs on the basis of clinical, radiological and histopathological findings were included in the study. All the patients of HCC underwent Multiple detector computed tomography (MDCT) examination. A standard liver CT protocol was followed in all patients. All patients were given a non-ionic contrast medium having 350mg per ml concentration. The CT images were studied by two radiologists. Data was analyzed by SPSS version 20.

Results: Total 79 hepatic cellular carcinomas were detected in 54 patients on MDCT on at least one imaging phase. The overall mean tumor size was 5.2 ± 1.79 cm, 64 (81%) were hypervascular and 15 (19%) were hypo-vascular. The subjective washout was found statistically significant (2=16.80, *p*-value=0.0001) for more tumors on delayed phase images (77.3% vs. 22.67%) as compared to hepatic venous phase images. The absolute value of mean tumor to liver contrast was significantly (*p*-value <0.05) higher on delayed phase images, (15 HU) in comparison to hepatic venous phase images (4 HU).

Conclusion: On multiphasic MDCT the delayed phase has appreciably higher rate of detection of tumor washout in comparison to hepatic venous phase.

Keywords: Delayed phase, Hepatocellular carcinoma, Multiple detector computed tomography, Tumor Washout.

INTRODUCTION

The most common liver tumor is hepatocellular carcinoma (HCC), and 85-90% liver carcinomas are HCCs. This cancer is the fifth most common carcinoma globally and it stands on third position as a most common cause of death due to cancers in the world. It is the most common cancer among males of Pakistan. Usually patients having chronic parenchymal liver disease present with HCC, the most common cause of HCC is cirrhosis of the liver[1].

It has been found that etiology of HCC is multifactorial and there are different risk factors which cause the development of HCC including in majority, viral infections as well as non-viral infections to environmental and dietary exposures which are also responsible for growth of HCC. The most common cause found throughout the world is chronic hepatitis B infection[2].

Cirrhosis is the foremost risk factor that causes hepatocellular carcinoma. The incidence of this malignancy is rising worldwide. In HCC non-excisional biopsies are not preferred therefore, this malignancy is usually diagnosed on the basis of different imaging techniques alone[3]. Imaging characteristics are the main source for the diagnosis of HCC. It is diagnosed on the basis of its appearance after administration of contrast medium on images taken at late arterial, portal venous and delayed phase through MDCT[4].

Many different imaging technique like computed tomography (CT) and magnetic resonance imaging (MRI) are in common use for liver imaging and diagnosis of HCC. The

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evaluation of cirrhotic liver and assessment of masses in liver are usually done through computed tomography. The assessment of liver through computed tomography is different form ultrasound because the CT evaluates the entire liver, which is not done through ultrasound. The CT evaluation is also not affected due to ribs or gas. Similarly, the CT evaluates extrahepatic metastasis more systematically as compared to ultrasound evaluation[5,6].

The hypoattenuation with respect to adjoining hepatic parenchyma on hepatic venous or delayed phase is known as tumor washout and is identified as a strong prognostic indicator of HCC. The late hepatic arterial phase is recognized as best time to visualize tumor enhancement[7,8]. But the correct timing for identification of tumor washout on multiphasic MDCT of liver is disputed. A time range of 2 to 8 minutes after the administration of contrast material is called a delayed phase, it can trail the hepatic venous phase or can occur alone post hepatic arterial phase[9,10].

The studies on identification of best timing and phase sequence are limited in our setup. Limited data is available in our country which can compare the hepatic venous phase or delayed phase in terms of detection of tumor washout among the patients presenting with HCC. So, the present study was planned to assess the effect of delayed phase tumor contrast washout in patients of hepatocellular carcinoma on computed tomography.

MATERIAL AND METHODS

Approval of the study was taken from hospital ethical committee prior to start the study. The setting for this study was department of Radiology, Pakistan Institute of Medical Sciences, Islamabad. The study duration was about seven months from Jan 2017 to Jul 2017. In this comparative - cross-sectional study, a total of 54 patients of diagnosed HCCs on the basis of clinical and radiological findings visiting or referred to the department for dynamic liver computed tomography, were included in the study. Patients with clinical and radiological features of HCC under went MDCT examination then followed for their histopathological findings. Patients with positive histopathological findings were then retrospectively analyzed on MDCT. Patient with radio frequency or transarterial chemoembolization were excluded from the study. All the patients in the sample were selected by non-probability consecutive sampling technique. Sample size was calculated by WHO sample size calculator for comparing two independent means while keeping mean difference of 5.6 and SD of 10[11]. Estimated minimal sample size was 51.

All the patients of HCC underwent MDCT examination with 16-slice MDCT scanner. During the examination, a standard liver CT protocol was followed in all patients. All patients were given a non-ionic contrast medium having 350 mg per ml concentration. This contrast medium was given in a dose of 2 ml per kg of the total body weight and through intravenous root. This contrast medium was followed by a flush of 40 ml saline administered with the same flow. The CT was performed instantly pre and post administration of contrast medium in hepatic arterial, hepatic venous and delayed phase. The hepatic arterial phase began after 20-35s of trigger threshold. The hepatic venous phase started after 55-65s and delayed phase started after (2-8 minutes) after the trigger threshold.

The CT images were studied by two radiologists having at least 3 years' experience in this field. Lesions attenuation was assessed by the observers during the reading sessions in comparison with the contiguous hepatic parenchyma. The categorization of lesions was made as hyper-, iso- or hypoattenuating in contrast to adjacent parenchyma.

All the collected data was entered and analyzed through SPSS version 20. Mean along with standard deviation was calculated for numerical data. Frequency and percentages were presented for categorical data. Independent sample t-test was applied to compare means of

quantitative variables and chi-square test for qualitative variables. The level of significance was set at *p*-value ≤0.05.

RESULTS

Total 79 of the hepato-cellular carcinomas were detected in 54 patients on MDCT on at least one imaging phase. In majority 33 (61.1%) patients one lesion was detected and in 21 (38.88%) patient two or more lesions were detected on MDCT examination. The overall mean tumor size was noted 5.2 ± 1.79 cm with a range of 3-7cm. Most 34 (43.04%) of the tumors were of size 5-6 cm, 23 (29.11%) carcinomas were less or equal to 4 cm, and 22 (27.85%) tumors were of size of 6 cm or more.

Table-I: Characteristics of the tumor lesions.

Characteristics	Frequency	Percentage (%)
Over all mean size of the tumor		
Mean ± SD	5.2 ± 1.79 cm	
Range	3-7 cm	
Size of the Tumor		
≤4 cm	23	29.11
5-6 cm	34	43.04
≥6 cm	22	27.85
Tumor attenuation relative to surrounding liver		
Hypervascular	64	81.00
Hypovascular (Iso - and hypoattenuating)	15	19.00

Among 79 hepatic cellular carcinomas 64 (81%) were hypervascular and 15 (19%) were hypovascular containing 11 lesions of Iso- and 4 hypoattenuating to the surrounding liver parenchyma on hepatic arterial phase imaging. The diagnosis of washout was not possible in 4 HCCs having hypoattenuating lesions due to hypoattenuation on hepatic arterial phase images. The subjective washout was found statistically significant (*p*-value=0.0001) for more tumors on delayed phase images (77.3% vs. 22.67%) as compared to hepatic venous phase images among 75 tumor lesions of hypervascular or Isoattenua-ting tumors. Among 64 hyper-vascular HCCs it was found that subjective washout was detected significantly (*p*-value = 0.00008) more tumors on delayed phase images 51 (79.7%) as compared with 13 (20.1%) hepatic venous phase images (table-I).

Table-II: Comparison of Hepatic Venous phase with Delayed Phase on the basis of Washout, TLC and mean attenuation value.

Characteristics	Hepatic Venous Phase		Delayed Phase		Calculated Value of Statistic	*p*-value
	Frequency	Percentage (%)	Frequency	Percentage (%)		
Subjective washout in hyperattenuating and isoattenuating HCCs (n=64)						
Achieved n (%)	19	30	50	78	30.2175*	<0.001
Not Achieved n (%)	45	70.31	14	21.87		
Subjective washout in hyperattenuating HCCs (n = 64)						
Achieved n (%)	21	32.81	43	67.18	15.125*	<0.001
Not Achieved n (%)	43	67.19	21	32.81		
Mean tumour attenuation value (n=64)						
Mean ± SD	75.6 ± 13.8		45.6 ± 10.67		13.7922**	0.0001
Mean attenuation measurement for hepatic Parenchyma (n=64)						
Mean ± SD	79.24 ± 5.76		60.18 ± 10.05		13.1506**	0.0001
Mean tumor-to-liver contrast (TLC) values						
Mean ± SD	4 ± 1.36		15 ± 2.53		30.6367**	0.0001

*Calculated value of chi-square, **Calculated value of Paired Sample t-test

The comparison of mean tumor attenuation value for each imaging phase showed that its

value in hepatic arterial phase was 80.45 ± 15.3 HU, in contrast to hepatic venous phase in which it was noted to be 75.6 ± 13.8 HU and it decreased to 45.6 ± 10.67 HU on delayed phase images. Similarly, the mean attenuation measurement of hepatic parenchyma was highest on porto-venous phase images with mean value of 79.24 ± 5.76 HU, and decreased significantly to 60.18 ± 10.05HU in delayed phase images. It was noted that absolute value of mean Tumor to Liver Contrast (TLC) was significantly (t=-30.637 *p*-value <0.05) higher on delayed phase images in which mean TLC value was 15 HU in comparison to hepatic venous phase images having mean TLC value of 4 HU (table-II).

DISCUSSION

Chronic liver disease and cirrhosis are main instigator of HCC. A small proportion of patients of HCC have non-cirrhotic livers and it is estimated that this proportion is not more than 10%. The other main causes are chronic infections of hepatitis B and C, which are increasing incidence of HCC globally[12].

Although these chronic infections are main cause of this disease but many lifestyle factors including obesity, diabetes, use of aflatoxin contaminated foods and excessive consumption of alcohol, also play a considerable role in development of HCC. But provided all these factors still more than 90% cases of HCC are those patients who have chronic inflamed liver due to hepatitis infections. Diabetes and obesity are cause of non-alcoholic fatty liver disease[13]. The etiology of the hepatocellular carcinoma shows that it is a hypervascular neoplasm and its main blood supply is from hepatic artery, which make the lesions to enhance during arterial phase imaging. The hypervascularity of arteries is very important because the treatment options of HCC are determined on the basis of this feature[14].

The sign of washout kinetics reveals that in the tumor intravascular space is greater than interstitial space. Many studies have revealed the importance of contrast washout during portal or delayed phase for classification of hepatocellular carcinoma. This characterization is independent of size of lesions in the patients[15].

According to the results this present study it can be concluded that in patients of HCC the detection of washout signs of HCC on MDCT are more excellent as compared with hepatic venous phase. The results were significantly better in delayed phase images in contrast to hepatic venous phase images. The subjective washout was found in statiscally significant (2=16.80, *p*-value =0.0001) for more tumors on delayed phase images (77.3% vs. 22.67%) as compared to hepatic venous phase images among 75 tumor lesions of hypervascular or Isoattenuationg tumors. Among 64 hypervascular HCCs it was found that subjective washout was detected in significantly (2=11.28, *p*-value=0.00008) more tumors on delayed phase images 51 (79.7%) as compared with 13(20.1%) hepatic venous phase images. Some studies like study of Lee *et al*, have reported higher rate 63% of washout detection as compared to our study in which we found washout only in 22.67% HCCs during hepatic venous phase. The rate of delayed phase washout detection has also reported to be greater in study of Lee *et al*, in which he found 86% versus 7.3% in this present study during delayed phase[16,17].

The reasons of this difference might be that since we have compared both phases images in the same tumors for detection of HCC washout. The second reason might be the difference between time of getting images of delayed phase, which vary from 2-10 minutes in other studies[18,19].

Another reason which can affect our findings might be difference in tumor sizes which were different from previous study. The mean tumor size was comparatively small in this study (mean size 5.0 ± 1.79 cm) as compared to those studied by Lee *et al*[20,21].

When the presence of HCC is indicated clinically by screening or surveillance tests the first line diagnostic tool, which is most frequently used is assessment of HCC through imaging modalities like multiphasic dynamic contrast

enhanced computed tomography MDCT or MRI. The diagnosis of HCC is based upon the presence of hyper enhancement of contrast agent in late arterial phase with succeeding sign of washout of HCC during portal venous or delayed phases or in both phases will confirm the diagnosis of HCC[18].

In this present study, it was noted that in HCC tumor lesions in which hypervascular lesions were detected the rate of washout significantly increased from 20.1% on images taken during hepatic venous phase to 79.7% on the images taken during delayed phase. These results are in accordance with previous studies of Furlan et al and Peterson *et al*[7,20].

The diagnosis of HCC is a difficult task and imaging techniques play vital role for this purpose. In patients who are at risk of HCC arterial enhancement trailed by washout sign is a main indication for diagnosis of HCC. This feature is also a basis of guidelines currently available for diagnosis of this disease. The main difficulties in accurately diagnosing HCCs are faced when lesions are of small sizes[21].

CONCLUSION

In patients of hepatocellular carcinoma, imaging has a great importance for detection, diagnosis and management of patients. The results of our study showed that on multiphasic MDCT the delayed phase has appreciably higher rate of detection of tumor washout in comparison to hepatic venous phase.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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