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Evaluation of CT Perfusion for the Diagnosis of Hepatocellular Carcinoma in a Teaching Hospital

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Abstract **Original Research Article**

CT perfusion, the measurement of blood flow characteristics through dynamic CT acquisitions following intravenous administration of contrast agents, can easily be integrated into routine CT imaging protocols within the same imaging session. Clinical applications of CT perfusion imaging for earlier detection of hepatocellular carcinoma are being assessed in this study. The study was conducted in the department of Radiodiagnosis MOSC medical college, Kolencherry from January 2018 to March 2020. Total 56 patients were included in the study. Imaging done on 64 slice CT. For Analysis, data were processed at a workstation. Functional maps of HBF (hepatic blood flow), HBV (hepatic blood volume), MTT (mean transit time), TTP (time to peak), HPI (hepatic perfusion index) and PSAP (permeability surface area product) were generated. Statistical analysis has been carried out in the present study. Wilcoxon signed rank test was used to compare the perfusion parameters of HCC (hepatocellular carcinoma) and background liver parenchyma. All data were expressed as mean ± SD, and statistical analysis was performed with RStudio. Wilcoxon-signed ranks test (nonparametric test) of variance was used to compare the differences in CT perfusion parameters. $P < 0.05$ was considered statistically significant. Wilcoxon signed rank test was used to compare the perfusion parameters between the background liver and HCC. In our study there was significant increase in HBF, HBV, PSAP, and HPI whereas TTP and MTT was significantly reduced in HCC compared to background liver.Our results were comparable to the reference studies.

Keywords: Hepatocellular carcinoma, CT perfusion, tumour vascularity, hepatic perfusion index, means transit time.

INTRODUCTION

Primary liver cancer is a major contributor to both cancer incidence and mortality globally. It is the sixth most commonly occurring cancer in the world and the third largest cause of cancer mortality [1]. HCC can be diagnosed in cirrhotic patients non-invasively based on radiologic findings if imaging characteristics are present. CT, MRI and contrast-enhanced US (CEUS) have largely replaced biopsy and conventional angiography for diagnosis of HCC. CT perfusion, the measurement of blood flow characteristics through dynamic CT imaging following intravenous administration of contrast agents, can be done along with routine CT imaging protocols within the same imaging session. Several studies have shown that CT perfusion parameters correlate well with the presence and extent of tumour vascularity.

CT perfusion is assessed using sequential scanning of same volume over time [2]. Region of interest ROI is kept in a vessel supplying the area to be assessed, to obtain a time-intensity curve (for hepatic perfusion imaging, ROI kept in hepatic artery and the portal vein.) [3]. Kinetic models are used to calculate various perfusion parameters in the tissues being analysed. For liver CT perfusion, one of the three methods are used including model-free maximum slope method, compartment model-based method, and distributed parameter model-based method or their combination can be used [3].

In the model-free maximum slope method, time to peak splenic enhancement (the end of arterial phase and beginning of the portal venous phase of liver perfusion) is used for separating HAP (hepatic arterial perfusion) and PVP (portal venous perfusion). The maximal slope of the liver time-intensity curve in both the arterial and portal venous phase is divided by the peak aortic and portal enhancement to calculate arterial and portal liver perfusion, respectively. The HPI, which is the ratio of the arterial perfusion to the total hepatic

perfusion, can also be calculated [4-7]. In single-compartment model it is assumed that the intravenously administered contrast agent is confined to only one compartment (i.e., the vascular space), however in dual-compartment models it is assumed that there is dynamic distribution of contrast agent between two compartments which are the vascular space and the interstitial space [3, 7]. In the distributed parameter model analytic solution in the time domain is used by which four perfusion parameters i.e., blood flow, blood volume, MTT, and permeability can be calculated [8, 9].

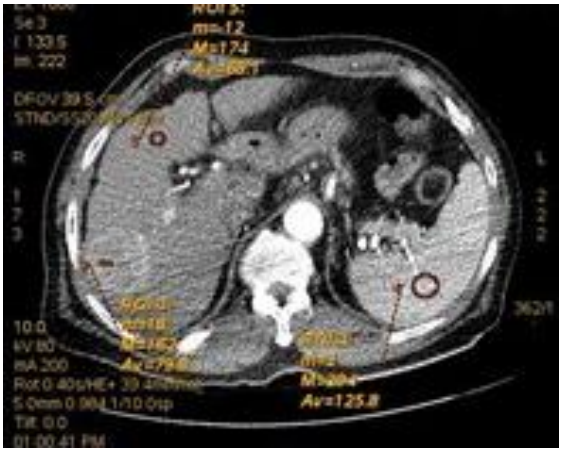
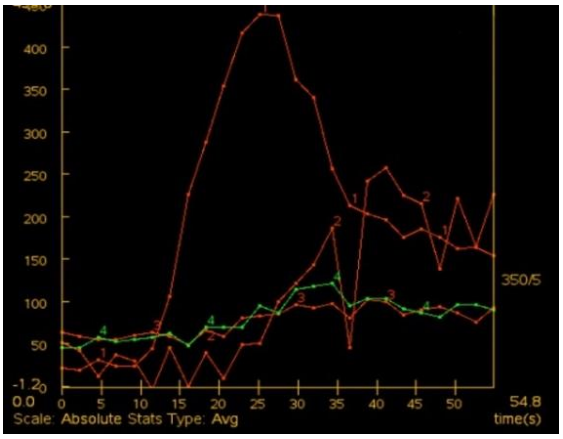


Fig-1(a)



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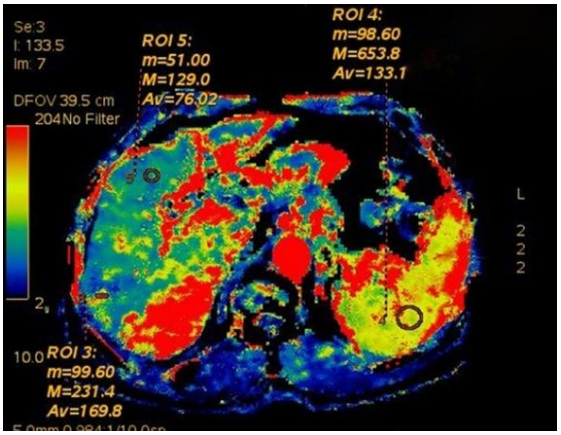

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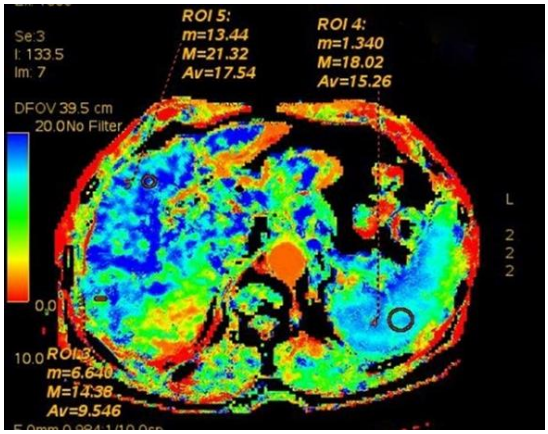

Fig-1(d)

Fig-1: Dynamic CT perfusion imaging of 77year old male with arterial phase enhancing lesion in right lobe of liver. The lesion shows increased hepatic blood flow, hepatic blood volume while the mean transit time is decreased. Lesion later biopsied before TACE. Histopathology was hepatocellular carcinoma Fig 1 (a) Arterial phase. Fig 1(b) time intensity curves with ROI in aorta, portal vein, HCC, spleen and in background liver. Fig 1 (c) Hepatic blood flow map. Fig 1 (d) mean transit time map.

CT perfusion parameters are HBF (hepatic blood flow), HBV (hepatic blood volume), MTT (mean transit time), TTP (time to peak), HPI (hepatic perfusion index) and PSAP (permeability surface area product). Hepatic blood flow is the rate of flow. Blood volume is the volume of blood within the vasculature. MTT is average time it takes for blood to traverse between the arterial inflow and the venous outflow. Permeability surface area product is the product of permeability and the total surface area of capillary endothelium in a unit mass of tissue or tumour [3]. Permeability-related values such as permeability surface area product is due to vascular leakiness due to poorly formed vascular basement membrane. Reduced MTT usually reflects the presence of arteriovenous shunts, seen commonly in tumour [10]. Time to peak which is the time to reach the maximum value in contrast material concentration [11]. Many studies have shown that contrast enhancement dynamics of a tissue can indirectly reflect the microenvironment of the tissue. Sahani et al. [12], Ippolito et al. [13] and Bayraktutan et al. [14] in their studies reported that hepatic CT perfusion imaging is a useful modality to assess tumour vascularity and angiogenesis in HCC.

MATERIAL AND METHODS

The study was conducted in the department of Radiodiagnosis MOSC medical college, Kolencherry from January 2018 to March 2020. The patients selected for the study were referred from Gastromedicine/Gastrosurgery/Medicine departments at our hospital, who were clinically suspected to have Hepatocellular carcinoma based on history of alcohol intake, hepatitis B virus infection, with raised AFP (alpha fetoprotein) levels and detected to have

Cirrhosis/focal lesion on USG. Total 56 patients were included in the study. Inclusion criteria were patients with liver cirrhosis and raised AFP and patients with liver focal lesions detected on ultrasound. Exclusion criteria were postoperative patients and patients who took prior treatment. Imaging methods: Imaging done on 64 slice CT scanner. Unenhanced acquisition with 120kV and 160 mA (whole abdomen). Dynamic acquisition with 80kV and 160mA (32 cm coverage which includes liver, pancreas and both kidneys). First pass study is done every one second. PV and venous phase with120kV and 160mA (whole abdomen) Contrast media used had iodine content of 370mg/ml, Contrast administration was as a bolus of 70ml at the rate of 4-5ml/sec. Scan delay of 5 seconds is used. Post processing using deconvolution technique and ROIs kept in abdominal aorta and portal vein for assessing liver perfusion and a third ROI is drawn in spleen. After drawing additional ROIs over lesions in liver and background normal liver, quantitative perfusion parameters are displayed. All cases were reported by experienced radiologists. For Analysis, data were processed at a work station functional maps of HBF, HBV, MTT, HPI, TTP and PSAP were generated. Analytical statistical analysis has been carried out in the present study. Wilcoxon signed rank test was used to compare the perfusion parameters of HCC and background liver. All data were expressed as mean ± SD, and statistical analysis was performed with R studio. Wilcoxon-signed ranks test (nonparametric test) of variance was used to compare the differences in CT perfusion parameters and $P < 0.05$ was considered statistically significant.

RESULTS

Out of 56 samples studied, 87.5% of the patients (49 cases) were male and 12.5% were female (7 cases). The male to female ratio being 49:7. It is noted that a greater number of samples was seen in the age group 61-70 years (42.8.0%) followed by 51-60 years (26.7%). While 5.3% cases were in age group 30-40 years. 14.2% cases were in age group 41-50 years and 11% cases were in age group 71-80years. Alcohol was associated risk factor in 80% of the patients (45 cases)followed by hepatitis B in 20% (11).

In our study all patients had AFP level above 20ng/ml. AFP level in maximum number of patients 77% (43 cases) were between 400-1000 ng/ml. While 7% patients (4 cases) had AFP< 400ng/ml and 16% patients (9 cases) had AFP > 1000ng/ml. In our study HBV was the cause of cirrhosis in only 20% cases and alcohol intake being associated risk factors in 80% cases. In present study 20 out of 56 patients were detected to have focal lesion on USG making it 35.7% sensitive for the diagnosis of HCC in cirrhosis patients. On CT perfusion imaging, there was significant increase(pvalue< 0.05) in HBF, HBV, PSAP and HPI whereas TTP and MTT was significantly reduced in HCC compared to background liver.

Table-1: Comparisons of computed tomography (CT) perfusion parameters between hepatocellular carcinomas (HCCs) and their surrounding non-tumour background liver parenchyma (BLP).

Perfusion parameter	BLP	HCC	Wilcoxon signed-rank test
HBF (mL/min/100ml)	15.36 ± 1.14	148.86 ± 15.68	p<0.05
HBV (mL/100 ml)	2.79 ± 0.58	5.51 ± 0.802	p<0.05
PSAP (mL/min/100ml)	22.82 ± 4.08	36.29 ± 5.63	p<0.05
MTT (sec)	14.81 ± 1.202	8.13 ± 1.42	p<0.05
TTP (sec)	34.94 ± 0.89	29.02 ± 1.04	p<0.05
HPI%	29.43 ± 4.43	94.66 ± 6.77	p<0.05

Data are presented as mean ± standard derivation.

Wilcoxon signed rank test was used to compare the perfusion parameters between the background liver and HCC. This table shows that there was significant increase in HBF, HBV, PSAP,and HPI whereas TTP and MTT were reduced in HCC compared to background liver.

DISCUSSION

Cirrhosis is the most important clinical risk factor for HCC, with approximately 80% of cases of HCC developing in patients with cirrhosis. In most high-risk HCC regions, HBV infection is associated with most cases of cirrhosis and causes at least 80% of the cases of HCC [15]. In our study 100% HCC patients had associated cirrhosis of liver. However, unlike the usual trend reported in other studies, in our study HBV was the cause of cirrhosis in only 20% cases and with alcohol intake being associated risk factor in 80% cases.

With the widespread use of imaging modalities, the usefulness of alpha-fetoprotein assay in the diagnosis of hepatocellular carcinoma (HCC) has decreased however AFP and liver US are the most widely used tools for HCC surveillance. Normal AFP levels are present in as many as 30% of patients at time of diagnosis and usually remain low, even with advanced HCC [16]. AFP >400–500 ng/ml is considered diagnostic for HCC, although fewer than half of patients may generate levels that high. In this study AFP level in maximum number of patients(77%) was between 400-1000 ng/ml.All 56 patients had AFP level > 20ng/mL.

According to AASLD (American Association for the Study of Liver Diseases) recommendations, patients who have cirrhosis and those who do not have cirrhosis but are at high risk for HCC should be screened by USG at 6monthly interval [17].In a meta-analysis of19 studies evaluating the accuracy of USG for HCC surveillance, the pooled data showed that USG had a sensitivity of 94% for identifying HCC at all stages and 63% for detecting HCC at an early stage [18]. In present study 20 out of 56 patients were detected to have focal lesion on USG making it 35.7% sensitive for the diagnosis of HCC in cirrhosis patients.

Contrast enhancement dynamics of a tissue can indirectly reflect the microenvironment of the tissue and helps in early detection of HCC. In the study by Sahani et al. [12], HCC had significantly higher blood flow, blood volume and PSAP values and lower MTT values than background liver. In the study by Ippolito et al. [13], hepatic perfusion, blood volume, HPI, and arterial perfusion values were elevated, whereas portal perfusion and TTP were lower, in HCCs relative to the surrounding liver. In the study by Bayraktutan et al. [14], the values of perfusion parameters, like HBF, HBV, arterial perfusion, and HPI, were more in the lesion in comparison to the normal liver parenchyma. A study by Fischer et al. on cirrhotic patients showed high sensitivity of perfusion CT in the detection of HCC in cirrhotic liver [19]. Zhu et al. [20] demonstrated that HCC shows higher blood flow, blood volume, and permeability surface area product and shorter MTT than the background liver parenchyma on CT perfusion images. Findings in our study concurred with the other studies and there was significant increase in HBF, HBV, PSAP and HPI whereas TTP and MTT was significantly reduced in HCC compared to background liver ($p<0.05$).

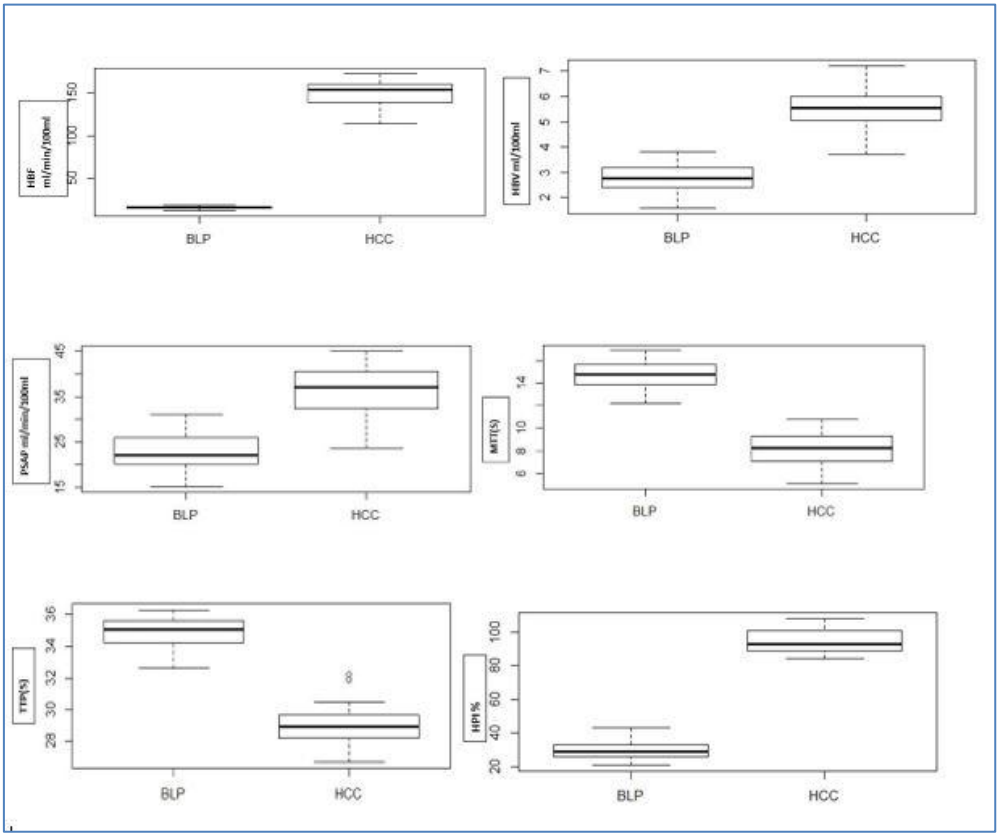

Fig-2: Box plots of perfusion parameters in which edge of boxes closest to zero is 25th percentile, line within boxes marks median, and edge of boxes farthest from zero is 75th percentile. Errors bars above and below boxes indicate maximum and minimum values, respectively. There is significant increase in HBF, HBV, PSAP,and HPI whereas TTP and MTT was reduced in HCC compared to background liver. BLP (background liver parenchyma), HCC (hepatocellular carcinoma) HBF (hepatic blood flow), HBV (hepatic blood volume), PSAP (peak systolic arterial pressure), MTT (mean transit time) TTP (time to peak), HPI (hepatic perfusion index)

CONCLUSION

The prognosis of patients with untreated HCC is very poor. Ultrasonography and conventional cross-sectional imaging methods such as CT and MRI, may not be adequate for detection of tumour vascularity. A dysplastic lesion gradually converts to HCC by a gradual increase in vascularity. CT perfusion imaging is a non-invasive imaging technique that allows both qualitative and quantitative evaluation of tumour vascularity by using several perfusion parameters in normal and pathologic tissues and thereby helps in early detection of HCC.

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