VALIDITY OF COLOR DOPPLER SONOGRAPHY IN EVALUATION OF MALIGNANT PORTAL VEIN THROMBOSIS IN HEPATOCELLULAR CARCINOMA

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ABSTRACT

Objective: *The objective of this study was to assess the validity of color doppler sonography in the evaluation of malignant portal vein thrombosis in hepatocellular carcinoma (findings on biphasic spiral computed tomography were used as the gold standard).*

Methodology: *This study was conducted in the Department of Diagnostic and Interventional Radiology at Shifa International Hospital, Islamabad from March 2009 to November 2009. A total of 100 patients those who were already diagnosed cases of HCC or those having high suspicion of HCC based on clinical criteria (e.g., chronic hepatitis B or C, liver cirrhosis, increased alpha fetoprotein level [>400ng/dl]) and / or Imaging findings (e.g., sonography, MRI, CT) were included in this study.*

Results: *Color doppler sonography had 80.7% sensitivity and 100% specificity in the detection of arterial flow in the portal vein thrombus (i.e., malignant thrombus) in comparison with biphasic CT (taken as gold standard).*

Conclusion: *Color doppler sonography is an effective, noninvasive method for evaluating the presence of malignant portal vein thrombosis associated with HCC.*

Key Words: *Spiral computed tomography, Doppler sonography, Portal venous thrombosis, Hepatocellular carcinoma.*

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INTRODUCTION

Hepatocellular carcinoma (HCC), also called hepatoma, is a malignant tumor of hepatocytes. It is the most common primary hepatic tumor and also the fifth most common tumor in the world[1]. Among cancer-related deaths, HCC is the third most common cause after lung and stomach cancer[2]. Since the mid-1980s, the incidence of hepatocellular carcinoma has been rising at an alarming rate. Much of this increase is likely due to hepatitis C infection, a known risk factor for HCC. Areas such as Asia and sub-Saharan Africa with high rates of infectious hepatitis have increased incidence of HCC. Length of survival depends largely on the extent of cirrhosis in the liver; cirrhotic patients have shorter survival times with limited therapeutic options; portal vein occlusion, which occurs commonly, portends an even shorter survival.

HCC has greater propensity for portal venous invasion as compared to metastatic or other primary liver neoplasms. Portal vein invasion in HCC has important implications in the management of patient. Firstly, it is a bad prognostic factor and in its presence mean survival time of patient decreases even more. Secondly, it is associated with increased risks of complications e.g., it can lead to tumour spread throughout the liver, increase portal venous pressure, variceal formation and increased risk of their rupture, ascites, hepatic encephalopathy and liver failure. Thirdly, the presence of portal vein thrombus is an important staging criterion in systems such as TNM and Cancer of the Liver Italian Program. These patients are not good candidates for surgical resection and transplantation, having a poor prognosis.

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Incidence of portal vein thrombosis (PVT) in HCC varies. It is about 20-30% in small HCC (<3cm) and up to 50-75% in HCC>5cm[3]. This has important implications for therapy. Patients with invasion of major branches of portal vein (PV) are graded as stage IV by the TNM classification and have poor prognosis as they are not candidates for surgical resection and transplantation[4,5]. Although some reports indicate a tendency toward aggressive management of advanced HCC such as extending partial hepatic resection and liver transplantation to patients with documented PV tumor thrombus, macroscopic tumor thrombus is still the most significant predictor of tumor recurrence in patients undergoing orthotopic liver transplantation[6]. Some authors suggest better results with transcatheter arterial chemotherapy with or without radiotherapy, and systemic chemotherapy[7].

Ultrasound is generally the first imaging technique used to detect PVT. Thrombi appear on sonography as solid intraluminal material that may have a hypo-,iso-, or hyperechoic pattern. Recent developments and continuing refinement in color doppler imaging techniques have made possible high-quality color doppler sonography for showing blood flow and local hemodynamics in various organs. On color doppler sonography the presence of arterial waveforms signals within the thrombus on doppler spectral examination is considered a highly specific sign of thrombus malignancy[8]. The overall sensitivity and specificity of color doppler sonography for PV involvement is 86.5% and 97.4%[9].

CT also helps to differentiate between benign and malignant PVT by assessing PV diameter and subjective enhancement of the thrombus. In the presence of hepatic tumors, enhancing expansile PVT is highly suggestive of hepatocellular carcinoma.

Hepatitis B & C is almost endemic in Pakistan with rising incidence of HCC. PVT directly affects the management of patients with HCC. Ultrasound is a readily available modality and this study is carried out to assess the validity of color doppler sonography in evaluation of portal venous system.

METHODOLOGY

This Cross-sectional (validation) study was conducted at Radiology department of Shifa International Hospital (SIH), Islamabad. The study included both OPD and IPD patients. Duration of study was 9 months i.e., from March 2009 to Nov 2009. Purposive sampling technique was used.

Patients with diagnosed Diagnosed cases of HCC or those having high suspicion of HCC based on clinical criteria (e.g., chronic hepatitis B or C, liver cirrhosis, increased alpha fetoprotein level [>400ng/dl]) and/or imaging findings (e.g., sonography, MRI, CT or angiography) were included in the study.

Patients of chronic liver disease with no evidence of any focal hepatic lesion; those with portal vein thrombosis of etiologies other than HCC; pregnant females; patients having history of allergic reaction to contrast or iodine; and patients with inadequate peripheral intravenous access were excluded from the study.

Written informed consent was obtained from the patients. Initially examination was done with a preliminary gray-scale sonography of the upper abdomen. Portal vein and its branches were examined with color doppler sonography. A number of flow settings were used depending on the underlying flow velocity and color gains were adjusted during each examination to select the highest value allowing artifact-free images. If a thrombus was detected, the doppler encoded area was restricted to maximize color sensitivity and frame rate and the thrombus was carefully examined for internal color signals. Any signals detected were subjected to doppler spectral examination.

CT imaging of each patient was then performed on a 64-slice CT scanner (Aquilion 64, Toshiba). An upper extremity 18- or 20-gauge IV cannula was used for venous access. Non-ionic contrast (Iopamidol) was administered with the dose of 1ml/kg at the rate of 4-5 ml/s. The following parameters were used. Collimation, 0.5mm; tube voltage, 120mV; and rotation time, 0.5 seconds. The tube current was adjusted according to patient characteristics (mean, 235 mA; range, 100-440mA). Scanning during both arterial and venous phases was performed in the cranio-caudal direction during a single breath-hold at deep inspiration. Arterial phase was done by placing Sure Start at abdominal aorta (150HU) in automatic mode. Portal venous phase imaging was initiated 65 seconds after the start of contrast material injection. Reconstructions were performed on an offline workstation (Vitrea, Vital Images) for multiplanner reformations (MPRs) and maximum intensity projections (MIPs).

Data was collected using proformas of patients after taking informed consent. Characterization of the PVT was done by delineating visualization of PV and its branches and detection of flow in the thrombus. The findings of color doppler sonography were then compared with that of spiral CT. To remove bias, findings were reviewed by a senior radiologist. All data was entered and analyzed using SPSS version

10.0. For continuous data (i.e., age), mean±S.D was calculated. For categorical data (i.e., arterial flow in the thrombus) frequency (percentage) was calculated for both doppler sonography and spiral CT. Sensitivity, specificity, positive predictive value and negative predictive value of color doppler sonography in comparison with spiral CT were reported as shown by 2x2 table below:

		Biphasic spiral CT (gold standard) +	Biphasic spiral CT (gold standard) –
Color doppler Sonography	+	a	b
	–	c	d

$$\text{Sensitivity} = \frac{a}{a+c} \times 100$$

$$\text{Specificity} = \frac{d}{d+b} \times 100$$

$$\text{Positive predictive value} = \frac{a}{a+b} \times 100$$

$$\text{Negative predictive value} = \frac{d}{d+c} \times 100$$

RESULTS

A total of 100 patients were included in this study which were diagnosed cases of HCC or were highly suspicious of HCC based on clinical, laboratory and imaging findings. The mean age was 53 years with range of 12–87 years. Maximum number of patients were in the age group of 51-60 years (38%) followed by age group of 61-70 (29%). Out of 100 patients, PVT was visualized on CT in 28 patients.

Diagnosis of tumour (malignant) thrombus was established when arterial flow was detected in the thrombus i.e., pulsatile flow on doppler sonography and arterial waveforms on spectral analysis within the thrombus, and on spiral CT, enhancement in the thrombus on arterial phase. Out of 28 cases of portal vein thrombosis, 26 (92.8%) were tumour thrombus, as they showed arterial phase enhancement on CT. Doppler ultrasound successfully detected tumour thrombus in 21 patients (80.7%) labeling benign thrombus in rest of 5 cases i.e., false negative. None of the cases of benign tumor thrombosis on CT were labeled as malignant thrombosis on U/S. Specificity of doppler U/S was 100% (Table 3). The positive and negative predictive values of the doppler ultrasonography in depicting malignant PVT as compared to CT scan are 100% and 28.6% respectively (Table 4).

The area under receiver operator curves (AUROC) of doppler sonography was calculated for diagnosing malignant PVT in patients as compared to the CT scan (Figure 3). Receiver operator characteristic curves were used to evaluate the diagnostic values. The diagnostic accuracy values of sensitivity (SN), specificity (SP), predictive value (PV) and likelihood ratio (LR) are given above for this curve. The Area under receiver curve (AURC) at admission for the doppler sonography was 0.90 (95 % CI= 0.78-1.03).

Figure 1: Color doppler sonography of patient with HCC revealed portal vein thrombosis (arrows) with internal arterial flow i.e., malignant thrombus

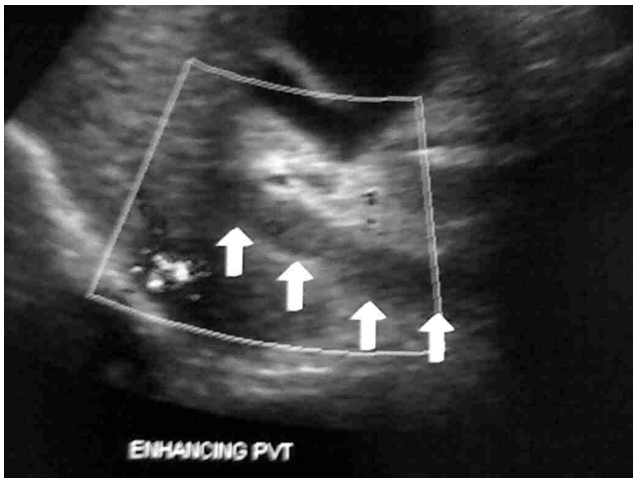


Figure 2 : Color doppler sonography of another patient revealed arterial flow in portal vein thrombus (i.e malignant thrombus)

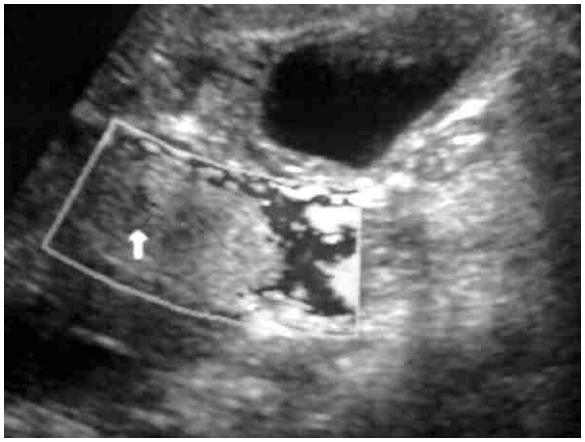


Table 1: Arterial Flow in Thrombus on Doppler U/S

Nature of Thrombus	Frequency	Percent
Yes (Malignant)	21	75
No (Benign)	7	25
Total	28	100.0

Table 2: Arterial Flow in Thrombus on CT

Nature of Thrombus	Frequency	Percent
Yes (Malignant)	26	92.8
No (Benign)	2	7.2
Total	28	100.0

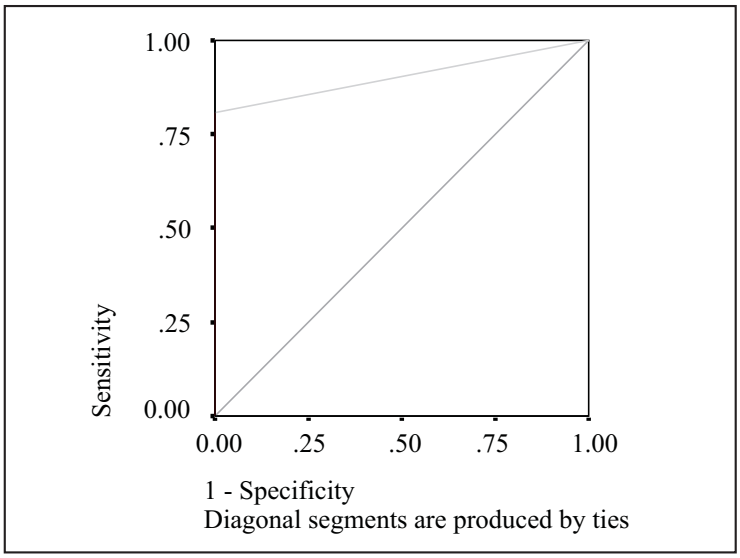
Table 3: Sensitivity and Specificity of the Doppler Ultrasonography in depicting Malignant Portal vein thrombosis as compared to the CT Scan (Gold Standard)

		CT of the Portal Vein		Total
		Malignant Portal Vein Thrombosis (n)	No Malignant Portal Vein Thrombosis (n)	
Doppler U/S of Portal Vein	Malignant Portal Vein Thrombosis (Sensitivity%=a/a+c)	21 (80.7%)	0	21
	No Malignant Portal Vein Thrombosis (Specificity%=d/b+d)	5	2 (100%)	7
Total		26	2	28

Table 4: PPV and NPV of the Doppler Ultrasonography in depicting Malignant Portal vein thrombosis as compared to the CT Scan (Gold Standard)

		CT of the Portal Vein		Total
		Malignant Portal Vein Thrombosis (n)	No Malignant Portal Vein Thrombosis (n)	
Doppler U/S of Portal Vein	Malignant Portal Vein Thrombosis (PPV%= a/a+b)	21 (100%)	0	21
	No Malignant Portal Vein Thrombosis (NPV%=d/c+d)	5	2 (28.6%)	7
Total		26	2	28

Figure 3: ROC Curve



Area Under the Curve

Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.904	0.065	0.061	0.777	1.031

The test result variable(s): Ultrasound of the Arterial Flow has at least one tie between the positive actual state group and the negative actual state group.
Statistics may be biased.
a Under the nonparametric assumption
b Null hypothesis: true area = 0.5

Case Processing Summary

CT of the arterial flow	Valid N (list wise)
Positive	26
Negative	2

Larger values of the test result variable(s) indicate stronger evidence for a positive actual state.
The positive actual state is Malignant Thrombus.

DISCUSSION

The reported incidence of PVT in association with HCC ranges from 5% to 44% (10,11). In our study comprising of 100 patients, incidence of portal vein thrombosis was 28%. As for thrombus characterization, doppler sonography is helpful tool in detecting vessels within thrombus. Arterial neovascularization within a neoplastic thrombus appears as enhancing signals, which are easily distinguishable from those of venous flow by their pulsation. The high visibility of these signals also facilitates doppler spectral examination confirmation of their arterial nature. However, spectral examination during color doppler sonography was sometimes impossible because of the location of the thrombus (e.g., left hepatic lobe or deep in the right hepatic lobe); in other cases, it was difficult because of a lack of patient cooperation. In our study, sensitivity of doppler sonography in detecting arterial flow in the thrombus i.e malignant portal vein thrombosis was 80.7%. Tanaka K, et al[12] in their study, found 89% sensitivity, while Rossi S, et al[13] determined 86.7% sensitivity of color doppler sonography. The specificty of doppler sonography in detecting malignant thrombus was 100% in our study which was equal to that of Tanaka K, et al[12].

In this preliminary clinical experience, color doppler sonography appears to be a reliable technique for not only evaluating the patency of the portal venous system but also characterization of the thrombus. Ultrasound is of paramount help especially in our setup. Firstly, it has the advantage of convenience and availability. In Pakistan, multi-slicer CT machines are not frequently available not even in some of the major tertiary care hospitals of the country. As proper CT liver dynamic scans, especially the arterial phase, are only possible on these machines, hence evaluation of arterial flow in portal vein tumor thrombus is not routinely done in every HCC patient. In such scenario, doppler ultrasound can be an alternative scanning procedure for evaluation of malignant tumor thrombus in portal venous system. Secondly, ultrasound is very cost effective as most of the population of our country consists of poor people. They cannot afford expenses of CT liver dynamic even if the facility is available. In such cases, doppler sonography can be done to fulfill the deficiencies. Ultrasound has also the advantage over CT as there are no radiations and contrast material risks in it. It is also beneficial in terms of the elimination of additional diagnostic procedures, particularly invasive ones such as liver biopsy, and also the avoidance of inappropriate therapies. However, we must note that color doppler sonography can be affected by several factors, such as operator's experience, the patient's body habitus and patient's condition like breathlessness and poor response to command. In such cases, confirmation by other modalities like CT/MRI of portal vein patency or thrombus may be required.

CONCLUSION

Considering reasonable sensitivity, specificity and cost effectiveness, the color doppler sonognaphy is a reliable investigation for evaluating the presence of malignant thrombus in portal vein associated with HCC. It is an effective, noninvasive, cost effective method with no risk of contrast material and ionizing radiation hazards.

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CONTRIBUTORS

SA conceived the idea & planned the study. RP did the analysis of the study. SR, AR & MG did the data collection, & helped in write up of the manuscript. All the authors contributed significantly to the research that resulted in the submitted manuscript.