DIAGNOSTIC ACCURACY OF ULTRASONOGRAPHY FOR DIAGNOSIS OF HEPATOCELLULAR CARCINOMA IN PATIENTS WITH LIVER CIRRHOSIS

SANDEELA SATTAR,[1] MAMOONA CHIRAGH,[2] MUHAMMAD SALEEM AKHTAR[3] AND BASMA SHAHID[4]
Departments of Radiology, [1]Combined Military Hospital, [2]Nawaz Sharif Social Security Hospital
[3]Punjab Institute of Cardiology, Lahore and [4]Aga Khan University Medical College, Karachi

ABSTRACT

Objective: To determine the diagnostic accuracy of USG for diagnosis of hepatocellular carcinoma in comparison to histopathology taking it is as gold standard, in patients with liver cirrhosis.

Study Design: Cross – sectional.

Place and Duration of Study: Radiology Department of Combined Military Hospital, Lahore, from 15 Nov., 2009 to 15 May 2010.

Patients and Methods: Seventy patients with liver cirrhosis with a known mass, referred to the Radiology department, fulfilling the inclusion criteria were included. Ultrasonography was done with TOSHIBA NEMIO and LOGIC 2000 ultrasound machines, using low frequency curvilinear probe with a frequency of 3.5 MHz. Ultrasound guided aspiration was performed using an 18G needle under full aseptic measures. Ultrasonographic findings were validated by histopathology reports.

Results: Mean age of the study population was 60.39 ± 10.9 years. 47 (67.1%) of the patients were males and 23 (32.9%) were females. Risk factors for hepatocellular carcinoma were HCV infection in 27 (38.6%), HBV infection in 11 (15.7%). Mean size of the lesions was 4.59 ± 1.08 cm. The lesions were characterized as being isoechoic, hypoechoic or hyperechoic as compared to the liver parenchyma. Compared to histopathologic findings, accuracy of the ultrasound findings was determined. Sensitivity of ultrasonography in detection of hepatocellular carcinoma was 92.3%. Specificity was 55.5%. Positive predictive value was 85.7% and negative predictive value was 71.4%.

Conclusion: Conventional ultrasonography can be used as a screening tool in patients with advanced liver cirrhosis and for surveillance purposes. However further workup is required for definitive diagnosis.

Key Words: Liver cirrhosis, hepatocellular carcinoma, ultrasonography, histopathology.

INTRODUCTION

Hepatocellular Carcinoma (HCC) is a high grade malignancy showing rapid infiltrative growth, early stage metastasis, poor therapeutic response and disappointing prognosis even after successful curative resection.[1]

HCC is considered the third deadliest and fifth known cancer all over the world.[1] Its incidence in developing countries is high [1,2],where the incidence rate is two to three folds higher than the developed countries.[2]

Cirrhosis of the liver is a major contributor to Hepatocellular carcinoma, comprising almost 80% of the affected individuals. Therefore any agent leading to chronic liver damage and, ultimately cirrhosis should be considered as a potential risk factor for HCC. HBV, HCV, and alcohol are the main causes of cirrhosis, hence risk factors for HCC. In addition, less prevalent conditions, such as Hereditary Hemochromatosis, Non-Alcoholic Steatohepatitis, Primary Biliary Cirrhosis (PBC) and Wilson's disease have also been associated with HCC.[3]

Previously, most hepatocellular carcinomas were diagnosed at an advanced stage, when cancer related symptoms were already present and a large mass could easily be detected by physical examination[4]. Now-a-days, the development of Ultrasonography (USG), Computerized Tomography (CT) and Magnetic Resonance Imaging (MRI) has allowed diagnosis at an earlier stage.[3,4]

USG combined with Color Doppler is the primary imaging modality used for surveillance in patients who are at increased risk of developing HCC. USG is a relatively cheap, noninvasive and simple technique with advantages of real time observation, ability to assess hepatic blood supply and presence of vascular invasion[5]. Although accuracy of percutaneous needle is around 90% but its use in diagnosis of HCC is controversial due to potential for complications such as bleeding and seeding of tumor cells along the needle track.[5,6] The sensitivity of ultrasonography for detecting HCC reported in previous studies ranges from 55% – 85% and specificity is between 90% –94%.[7]

HCC causes significant morbidity and mortality in cirrhotic patients. However the overall survival of the patients with HCC is influenced by severity of underlying liver dysfunction and tumor size at initial detection. Those individuals whose tumors are identified prior to the development of hepatic decompensation or other complications are more likely to be better candidates for aggressive interventions proven to prolong survival.[8] The rationale of this study is to find out the sensitivity of Doppler Ultrasonography in diagnosing HCC in cirrhotic patients for early tumor detection.

MATERIAL AND METHODS

Study Design
Cross – sectional.

Setting
Radiology Department of Combined Military Hospital, Lahore.

Duration
Six months from 15 Nov 2009 to 15 May 2010.

Sample Size
Sample size of 70 cases was calculated with 95% confidence level and 15% margin of error, taking expected percentage of HCC 35% with sensitivity and specificity of USG 85% and 94% respectively and taking histopathology as gold standard.

Sampling Technique
Non probability purposive sampling.

Inclusion Criteria
- Age above 40 years.
- Both genders.
- Liver cirrhosis with mass.
- Raised AFP levels.

Exclusion Criteria
- Nodular lesion less than 3 cm in size on USG.
- Lesion with non-specific vascular profile on USG.
- Poor visualization on USG.
- Patients in which FNA / biopsy can cause complications (ascites deranged coagulation profile, INR > 1.4).
- Patients not willing for histopathology.

Data Collection
According to guide lines of ethical committee of CMH Lahore, 70 cases of liver cirrhosis with a mass referred from outpatient department and indoor fulfilling the inclusion criteria were taken. Ultrasonography was done free of cost after taking informed consent from the patients. Liver Ultrasound was done on TOSHIBA NEMIO and LOGIC 2000 using low frequency curvilinear probe with frequency of 3.5 MHz. Scanning was done in supine and left lateral position. Images were taken in both radial and anti-radial projections. The position of lesion was described according to segmental anatomy of liver. All lesions were carefully descrybed sonographically according to their shape, orientation, margins, lesion boundary, interface, echo pattern, posterior acoustic features and surrounding tissue alterations. Ultrasonographic guided aspiration from the lesion was done by 18G needle under full aseptic measures. The aspirate was spread on glass – slide and fixed in absolute alcohol. The slides were sent for histopathological examination. Ultrasonographic findings were validated by histopathology reports. To exclude observer bias results were verified by another radiologist. All of the above information including histopathological reports was recorded on performa.

Analysis
The collected data was entered and analyzed by using software SPSS version 11.0. The variables to be analyzed were age, gender, risk factors (HBV, HCV infection, Alcohol intake). Age was numeric variable and mean and standard deviation were calculated. Gender and risk factors, were qualitative variables and were presented as frequency distribution table. 2x2 tables was generated for the calculation of sensitivity, specificity, positive predictive value and negative predictive value of ultrasonography for diagnosis of hepatocellular carcinoma taking histopathology as gold standard.

RESULTS
Mean age of the study population was 60.39 ± 10.9 years. Males were 47 (67.1%) and females were 23 (32.9%). Risk factors for hepatocellular carcinoma were HCV infection in 27 (38.6%), HBV infection in 11 (15.7%). There were no identifiable risk factors in rest of the patients. None of the patients gave history of alcohol intake.

Table 1 reveals ultrasonographic lesion characteristics. Mean lesion size was 4.59 ± 1.08 cm. The les-

Table 1: *Ultrasonographic Lesion Characteristics.*

Characteristics	*Numbers (Frequencies)*
Lesion size mean cm	4.59 ± 1.08
Lesion size groups	
3 cm	14 (20%)
4 cm	19 (27.1%)
5 cm	19 (27.1%)
6 cm	18 (25.7%)
Echogenecity	
Hyperechoic	43 (61.4%)
Isoechoic	3 (4.3%)
Hypoechoic	28 (40%)
Mixed	0

ions were divided into 3, 4, 5 and 6 cm sizes for accuracy of size. The lesions were isoechoic, hypoechoic or hyperechoic as compared to the liver parenchyma (Fig. 1). All lesions were hyper-vascular, whereas none showed portal vein invasion.

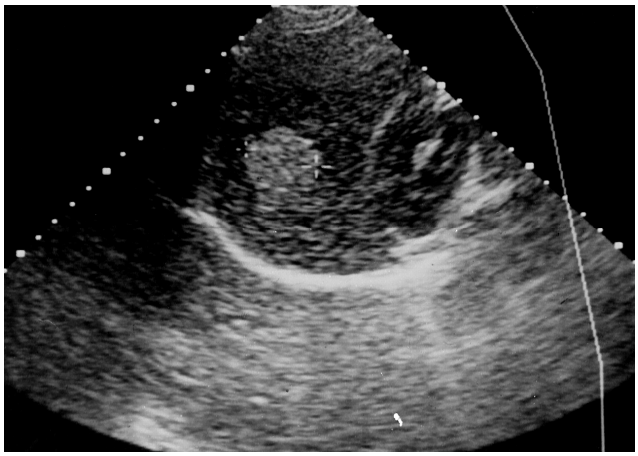

Figure 1A: *Hyperechoic lesion in liver in liver.*

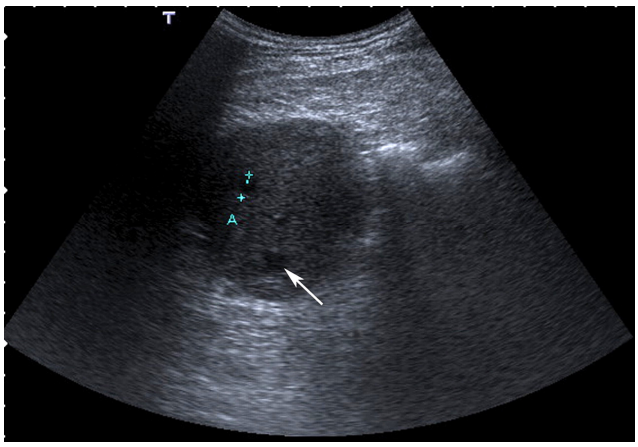

Figure 1B: *Hypoechoic lesion in liver.*

Table 2: *Presence of Hepatocellular Carcinoma on Ultrasonography vs. Histopathology.*

Ultrasound			
		Positive	*Negative*
Histopathology	Positive	48	4
	Negative	8	10

Table 2 reveals presence of hepatocellular carcinoma on ultrasonography vs. histopathology. Hepatocellular carcinoma was detected on ultrasonography in 56 (80%) and on histopathology in 51 (72.9%) patients. Keeping histopathology as gold standard parameters of diagnostic accuracy was calculated. True positive were 48, false positive were 8, true negative were 10 and false negative were 4. From these parameters 2X2 tables were drawn and sensitivity, specificity, positive and negative predictive values were calculated. Sensitivity of ultrasonography in detection of hepatocellular carcinoma was 92.3%. Specificity was 55.5%. Positive predictive value was 85.7% and negative predictive value was 71.4%.

DISCUSSION

Diagnostic confirmation and assessment of disease extent are crucial for proper clinical management of patients with hepatocellular carcinoma (HCC).The diagnosis of hepatocellular carcinoma is based on imaging in combination with clinical and laboratory findings i.e. raised AFP levels. With recent technological development in imaging, imaging studies play a crucial role in diagnosis and staging of HCC. The imaging techniques most commonly used for diagnosis of HCC include ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), and angiography. Although ultrasonography is widely accepted for HCC surveillance, spiral computed tomography (CT) or dynamic magnetic resonance imaging is required for diagnostic confirmation and intrahepatic tumor staging. CT arteriography is a more invasive yet effective option to improve accuracy as a result of higher quantity of contrast administered at a faster rate. However, the invasive and costly nature of this approach tends to restrict its use.[9] MRI produces results comparable to those of CT hepatic arteriography[10] and has become the diagnostic imaging mode of choice for HCC at many institutions worldwide. However, this facility was not available for our study. Also currently MRI is not a cost effective option.

Currently, with developments in imaging modalities, invasive biopsy is infrequently required prior to treatment, and diagnosis of HCC is strongly dependent on hemodynamic features (arterial hypervascularity and washout in the venous phase) on dynamic imaging. And biopsy is reserved only for lesions atypical on imaging. However, until now, despite technological advances, imaging cirrhotic patients remains a challenging issue, since pre neoplastic hepatocellular lesions, such as dysplastic nodules, mimic a small hepatocellular carcinoma. Further improvement of imaging technologies including functional imaging such as perfusion imaging and diffusion imaging, and development of new contrast media will undoubtedly improve detection and characterization of small tumors.

Diagnostic evaluation of hepatic lesions with liver biopsy has been practiced for over half a century to confirm suspicious lesions for HCC. Cytologic and histologic samples can be obtained by percutaneous fine–needle aspiration (FNA) and needle core biopsy, respectively, under US guidance. The diagnostic accuracy of liver biopsy is greater when both FNA and core biopsy

techniques are used simultaneously than when either is used alone. Early small HCC are usually composed of well – differentiated hepatocytes[11] and this turns the diagnosis through examination of FNB samples into a pathology challenge. Their reading requires major expertise, and even so, it is usual to assume a high rate of false – negative reports. Accordingly, some unique studies where such false – negative results are not observed have not been reproduced elsewhere and should be looked at with caution.[12] Liver biopsy should be avoided when platelet counts are 50,000 per mm^3 or the international normalizing ratio (INR) is greater than 2. The potential for spread of tumor from the biopsy needle track is of great concern and fuels much of the controversy surrounding the need for liver biopsy.

Studies to evaluate the diagnostic capacity of imaging techniques offer limited information because they just include patients with already diagnosed HCC, either by imaging techniques or by biopsy. In that way, the population is biased by excluding those with nontypical imaging or negative biopsy. Such studies merely serve to validate the usefulness of any technique to establish vascularization but provide no data about diagnostic sensitivity and specificity of any technique for the diagnosis of small nodules within a cirrhotic liver.[12] This information is critical to establish reliable diagnostic criteria for HCC, and for this reason this prospective study was designed.

The reported sensitivities of unenhanced US for HCC detection are scattered broadly between 34% and 100%.[13,14] This wide range undoubtedly reflects not only differing levels of sonographer skill and experience but also varying study methodologies.[15-17]

In a recent systematic meta – analysis by Colli et al,[18] selected studies with acceptable methodological quality and using explant histology as reference standard, demonstrated an average unenhanced US sensitivity of 48% for all size lesions. This result is in contrast to this study and the only explanation is histopathological examination of the lesion in explanted liver. The pathological examination of an explanted liver allows detecting even sub-centrimetric neoplastic nodule in an advanced nodular pattern. Furthermore sensitivity is also decreased in end stage liver disease (those undergoing organ liver transplants) and severely shrunken liver parenchyma.

In a study by Yu, et al[19], which compared the different imaging modalities like US, CT and MRI, the sensitivity of USG in comparison to these varied from 46–85% depending upon the lesion size. It was lowest for the lesion size less than 2 cm which was 46% and with the lesion size greater than 4 cm it was 85%. So sensitivity improved with the increased lesion size. While specificity was 96% and 89% positive predictive value. In this study, most of the patients with early HCC diagnosis were included with the help of advanced imaging technology. So many patients were with the smaller lesion size were included which are not readily diagnosed on ultrasonography.

In another study by Tanaka et al,[20] the overall sensitivity ,specificity and accuracy of US was found to be 58.9%, 99.9%, and 99.3% respectively.

In a study by Sbolli et al,[21] 138 patients underwent ultrasound followed by fine needle aspiration biopsy. The diagnosis of HCC was obtained in 132 cases with sensitivity of 95.6% and specificity of almost 100% and in this study the sensitivity closely resembles to this study.

In a study by Takayasu et al,[22] efficacy of different imaging modalities in diagnosis of HCC was considered among the Japanese population. The sensitivity of ultrasound was found to be 84%. Takayasu et al[22] included patients with smaller tumor size that is less than 3 cm. if they would have included the patients with larger size than sensitivity would have been even higher than this.

Possible explanations for this wide variation in results of above mentioned studies may be due to differences in the tested populations, different indications for performing the test and / or differences in the stage of liver disease. It is known that population selection seems to affect the operative characteristic of diagnostic tests in an unpredictable manner, for example, in a selected population of HBs Ag chronic carriers with high AFP levels, Ultrasonography was more sensitive (86%) and less specific (82%) in diagnosing HCC.

Moreover, differences in the tumor size may also have been responsible because large HCC are more easily detectable, and the definition of minimal detectable diameter of a given focal liver lesion can be greatly affected by the technical performances of ultrasound equipment.

This study inevitably has a number of limitations i.e. most of the patients were having a larger lesion size i.e. almost 80% of the patients were having a lesion that was greater than or equal to 4 cm in size. In most of the studies with this size of lesion USG has better sensitivity for detection of hepatocellular carcinoma.

Another limitation of the study is that it used only conventional ultrasonography instead of contrast enhanced ultrasonography which has higher and better results for the early detection of HCC. So results can be improved with the use of contrast enhanced ultrasonography instead of conventional ultrasonography alone.

According to Feinstein, a diagnostic test should not only confirm the presence or absence of a given disease, but may also be useful in staging it or detecting the related risk factors and / or concomitant diseases. In this study the usefulness of noninvasive techniques in staging HCC was not considered.

It is ***Concluded*** the conventional ultrasonography, because of increased sensitivity, can only be used as a screening tool in patients with advanced liver cir-

rhosis for surveillance purpose.

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