Evaluation of Diagnostic Accuracy of Ultrasound to Detect Hepatocellular Carcinoma in Chronic Liver Disease (CLD) Patients

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Abstract

Objective: To determine diagnostic accuracy of ultrasound to detect hepatocellular carcinoma (HCC) in chronic liver disease (CLD) patients by taking histopathology as the gold standard.

Methods: Descriptive study was done in which a total of 246 patients, of either sex (age range: 20-70 years) with diagnosis of CLD for 6 months or more, were enrolled at the department of radiology, Abbasi Shaheed Hospital, Karachi from January to June 2015. Abdominal ultrasound was performed to detect any mass lesion in liver, following which all patients underwent liver biopsy under ultrasound guidance. The ultrasound diagnosis was then compared with the histopathology result to assess sensitivity, specificity and accuracy of ultrasound examinations. Informed consent was taken from all the patients.

Results: Mean age of patients was 46.98 ± 6.20 years. Mean duration of chronic liver disease was 11.58 ± 3.22 months. Among 246 patients, in 102 (41.5%) patients single lesions were seen, while in 67 (27.2%) patients multiple lesion were seen. Mean size of mass was found to be 4.05 ± 1.37cm. The diagnostic accuracy of ultrasound for the diagnosis of HCC was 81.71%. Sensitivity and specificity of ultrasound for the diagnosis of HCC was 86.21% and 75.25% respectively. However, in this study positive and negative predictive values for ultrasound were 83.33% and 79.19% respectively. Statistical analysis was performed using SPSS version 10.0.

Conclusion: These results are in acceptable range suggesting that ultrasound can be used for the screening and detection of HCC in patients of chronic liver disease.

Keywords: Ultrasound, histopathology, hepatocellular carcinoma, chronic liver disease.

IRB: Dissertation approved by Research Evaluation Unit, College of Physicians and Surgeons Pakistan. Ref no. CPSP/REU/RAD-2009-174-1093. Dated: 9th December 2015.

(ASH & KMDC 21(4):206;2016).

Introduction

Hepatocellular carcinoma (HCC) is the most frequent malignant liver tumor, which occurs in the setting of chronic liver disease (CLD) and cirrhosis. It is the fifth most common tumor worldwide[1]. It is currently the third leading cause of cancer-related deaths worldwide, resulting in over 600,000 deaths per year. Despite the high numbers of patients diagnosed worldwide, HCC continues to pose challenging clinical problems. Good-quality ultrasound with careful evaluation of the entire liver can be a screening examination for HCC in patients at risk. Despite advances in technology and available therapies, very little improvement in survival rate is reported i.e. 5-year survival of 5% of patients[2].

Its incidence is increasing in Europe and America because of increasing hepatitis B and C infections[3,4]. While, literature indicates that in Pakistan it has an incidence of 8/100,000 per annum.

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Date of Submission: 29th September 2016
Date of Acceptance: 6th December 2016

The prevalence of viral hepatitis in Pakistan is 3.7%, however, this varies in the international data up to 39%[2].

HCC classically arises and grows in silent fashion, making its detection challenging prior to the development of later stage disease. Considering recent advances in HCC treatments, early and accurate detection of hepatocellular carcinoma is critical while tumors are small enough for the indication of curative treatments such as surgical resection, liver transplantation, percutaneous ethanol injection, laser, radiofrequency ablation and cryotherapy[5,6]. Although serum alpha-fetoprotein levels are used to screen the hepatocellular carcinoma in CLD patients, which is supportive but sometime remains inconclusive. Therefore, imaging plays a very crucial and effective role in the diagnosis and management of HCC[7].

Ultrasound is the most common method for the screening of HCC because of various advantages such as ease of performing it, non-invasiveness and real time observation. However, there have been variety of results in the application of ultrasound for HCC surveillance. Wide variety of imaging techniques like ultrasound, computerized tomography (CT) and magnetic resonance imaging (MRI) are being used for CLD patients, but ultrasound is the most commonly used imaging modality for screening CLD patients for detection of tumor because it is widely accessible, reliable, cost effective, relatively quick, safe and a non-invasive imaging technique[5,8,9].

Data from other studies showed the sensitivity of ultrasound for HCC detection in CLD was 65%, specificity was 85%, and accuracy was 70%[10] and another study reported sensitivity of 92%, specificity 65% and accuracy 85%[11]. Cirrhotically damaged liver inherently harbors benign lesions such as areas with fatty degeneration, circumscribed fibrosis, scar tissue, necrosis or vascular malformations that may imitate HCC and may pose diagnostic dilemma[8]. The reported accuracy and reliability of ultrasound has been inconsistent across studies[10]. It will be beneficial for patients as well as helpful for the physicians to find a more improved, refined and accurate way which is widely available, non-invasive, inexpensive and easy to do method. Therefore, the main objective of this study was to analyze the diagnostic accuracy of ultrasound in detection of HCC in CLD patients.

Patients and Methods

A Study was conducted at department of Radiology, Abbasi Shaheed Hospital, Karachi, from January to June 2015. It was a cross sectional study and sampling technique was non probability, consecutive sampling. The sample size was (n) 246, estimated using 95% confidence level and 8% margin of error with expected prevalence of HCC 39%, taking sensitivity 65% and specificity 85% of ultrasound. Informed consent was taken.

Patients (age range: 20 to 70 years) of both sexes were referred to the Department of Radiology for ultrasound of liver. Patients were already diagnosed with chronic liver disease for 6 months or more. After taking a brief history and informed consent, the liver ultrasound was performed by a consultant sonologist with more than 5 year of experience. Then the patient underwent liver biopsy under ultrasound guidance by a consultant radiologist and specimens were sent for histopathological examination. Patients who were already diagnosed cases of hepatocellular carcinoma, in whom histopathological results were inconclusive or patients who refused to give informed consent were not included in this study.

Ultrasound diagnosis of HCC was made if any two or more than two of the following findings were seen in the liver; size of lesion smaller than 30mm in diameter which appears hypo-echoic, lesion more than 50mm showing heterogeneous mixed echogenicity pattern (Fig 1), thrombosed portal vein (no blood flow, contains echogenic material) infiltrating lesion with irregular and diffused margins, presence of pseudo-capsule (thickening of surrounding parenchyma) (Fig 2), mass protruding beyond the surface of liver (exophytic lesion) and displacement or compression of intrahepatic blood vessels (Fig 3). Histopathological diagnosis was taken as gold standard.

Data was collected on a structured performa. Ultrasound diagnosis was then compared with the histopathology report. The statistical analysis was performed using SPSS version 10.0. Descriptive analysis i.e. frequency and percentage for categorical variables like sex, hepatocellular carcinoma, and mean and standard deviation for the continuous variables like age, number of masses, size of tumor, duration of CLD, sensitivity, specificity, positive and negative predictive values (PPV, NPV) and diagnostic accuracy of detection of hepatocellular carcinoma was calculated against histopathological findings by using a 2/2 table. Stratification of number of masses, size of tumor, and duration of CLD was performed. Post-stratification chi-square was applied. p-value $\leq$0.05 was taken as significant.

Results

Among 246 patients 161 (65.4%) patients were male and 85 (34.6%) were female. Mean age of patients was 46.98 ± 6.20 years, minimum and maximum age of patients was 39 and 60 years respectively. Mean duration of chronic liver disease was 11.58 ± 3.22 months, the minimum and maximum durations of disease were 6 and 20 months, respectively. In 102 (41.5%) patients single lesion was seen while in 67 (27.2%) patients multiple lesions were seen. There were 77 (31.3%) patients in which no definite mass was seen, mean size of mass was 4.05 ± 1.37cm. Minimum and maximum size of mass was 3 and 6 cm, respectively.

On ultrasound 145 (58.9%) patients were diagnosed with HCC and on histopathological examination 150 (61%) patients were diagnosed with HCC. Diagnostic accuracy of ultrasound for the diagnosis of HCC was 81.71%. Sensitivity and specificity of ultrasound for the diagnosis of HCC was found to be 86.21% and 75.25% respectively. Whereas positive and negative predictive values for ultrasound were 83.33% and 79.19 % respectively (Table1).

For single mass sensitivity, specificity, PPV, NPV and diagnostic accuracy of ultrasound was 86.05%, 0%, 82.22%, 0% and 72.55%, respectively. However in case of patients with multiple mass sensitivity, specificity, PPV, NPV and diagnostic accuracy of ultrasound was 87.93%, 0%, 85%, 0% and 76.12% respectively (Table 2).

Sensitivity, specificity, PPV, NPV and diagnostic accuracy of ultrasound for mass size of 3-4 cm was 86.05%, 0%, 82.22%, 0% and 72.55%. For the mass size 5-6 cm sensitivity, specificity, PPV, NPV and diagnostic accuracy of ultrasound was 87.93%, 0%, 85%, 0% and 76.12% respectively (Table 2).

Sensitivity, specificity, PPV, NPV and diagnostic accuracy of ultrasound for duration of disease with range: 5 to 10 months was 88.14%, 68.29%, 80%, 80% and 80% respectively. For duration of disease range:11 to 15 months sensitivity, specificity, PPV, NPV and diagnostic accuracy of ultrasound was 85.29%, 81.25%, 86.75%, 79.59% and 83.62% respectively. For duration of disease range:16 to 20 months sensitivity, specificity, PPV, NPV and diagnostic accuracy of ultrasound was 83.33%, 75%, 83.33%, 75% and 80% respectively (Table 2).
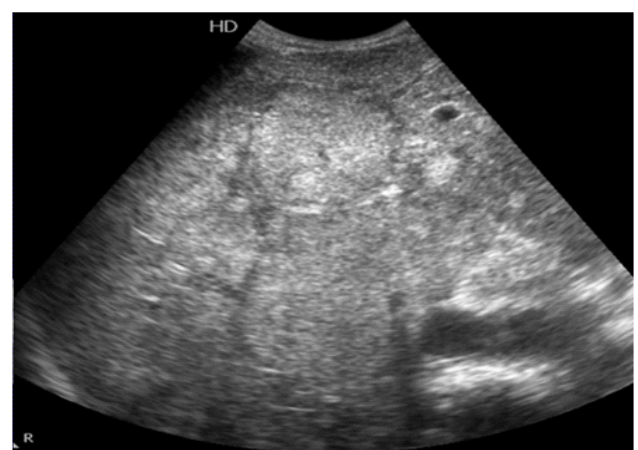

Fig 1. Ultrasound image shows mass in right lobe of liver with heterogenous echotexture.

Table 1. Diagnostic accuracy of ultrasound for HCC while takinghistopathology as gold standard

HISTOPATHOLOGY		ULTRASOUND		TOTAL
		YES	NO	
	YES	125	25	150
	NO	20	76	96
TOTAL		145	101	246

Sensitivity= 86.21%   Specificity= 75.25%   Positive predictive value= 83.33%
Negative predictive Value= 79.17%   Diagnostic accuracy= 81.71%

Table 2. Diagnostic accuracy of ultrasound for of HCC in relation to number, size of mass and duration of disease

Histopathology		Ultrasound		Sens	Spec	PPV	NPV	DA
		YES	NO					
NUMBER OF MASS								
Single	YES	74	16	86.05%	0%	82.22%	0%	72.55%
	NO	12	0					
Multiple	YES	51	9	87.93%	0%	85%	0%	76.12%
	NO	7	0					
SIZE OF MASS								
3-4 cm	YES	74	16	86.05%	0%	82.22%	0%	72.55%
	NO	12	0					
5-6 cm	YES	51	9	87.93%	0%	85%	0%	76.12%
	NO	7	0					
DURATION OF DISEASE								
5-10 Month	YES	52	13	88.14%	68.29%	80%	80%	80%
	NO	7	28					
11-15 Month	YES	58	9	85.29%	81.25%	86.75%	79.59%	83.62%
	NO	10	39					
16-20 Month	YES	15	3	83.33%	75%	83.33%	75%	80%
	NO	3	9					

Sens=Sensitivity   Spec= Specificity   PPV= Positive predictive value
NPV= Negative predictive value   DA= Diagnostic accuracy

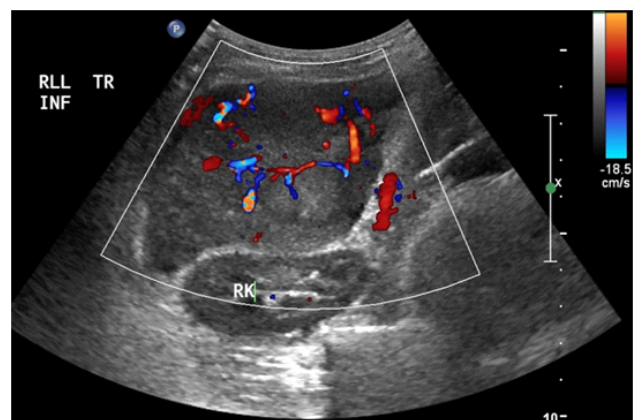**Fig 2.** Ultrasound image shows hypoechoic mass in liver with pseudocapsule.

Fig 3. Color doppler ultrasound shows increased vascularity in hepatic mass and displacement of surrounding vessels.

Discussion

Non invasive approaches for assessment of liver histology include routine laboratory tests and radiological evaluation. The common causes of chronic liver disease are viral hepatitis, alcohol abuse, and metabolic disorders. These causes lead to the damage of hepatocytes,subsequently it may contribute to the development of liver fibrosis, cirrhosis, and/or HCC[12]. This disease is a substantial cause of morbidity and mortality in the developing countries. Accurate evaluation of the severity of disease is crucial for treatment planning i.e. commencement of antiviral treatment and prognostication[13].

Non-invasive approaches such as routine laboratory tests like serum markers, liver function test, and radiological evaluation of liver are in routine use. Liver histological diagnosis based on needle biopsy determines the inflammatory activity (grading), the extent of fibrosis (staging), and other comorbidities[14]. But the procedure of ultrasound guided liver biopsy is invasive with about 1% risk of significant complications like post-interventional hemorrhage, bile leak, infection and injury to adjacent organs with less than 0.1% mortality[15]. Sampling errors may also be encountered since the liver parenchymal damage in chronic hepatitis is not homogeneous. In addition there is a possibility of inter- and intra-observer variability[16].

Diagnostic confirmation and assessment of disease extent are crucial for proper clinical management of patients with HCC. The diagnosis of HCC is based on imaging in combination with clinical and laboratory findings i.e. elevated AFP levels. With recent technological development, imaging plays a crucial role in diagnosis and staging of HCC. The imaging techniques that are 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 (Triphasic CT) or dynamic magnetic resonance imaging is required for diagnostic confirmation and intrahepatic tumor staging. Catheter arteriography DSA is a more invasive yet effective option to improve accuracy, however, the invasive and costly nature of this approach tends to restrict its use[17]. 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[18]. The reported sensitivities of unenhanced ultrasound for HCC detection are scattered broadly between 34% and 100%[19,20]. This wide range undoubtedly reflects not only the differing levels of a sonographer's skill and experience but also varying study methodologies[21-23].

A systematic meta-analysis by Colli et al, selected studies with acceptable methodological quality and using explant histology as reference standard, demonstrated an average unenhanced ultrasound sensitivity of 48% for leions of all sizes[24]. In our study it was observed that sensitivity and specificity of ultrasound for the detection of HCC was 86.21% and 75.25%, respectively. While positive and negative predictive values for ultrasonography for the diagnosis of HCC was 83.33% and 79.17%, respectively. Overall diagnostic accuracy was turned out to be 81.71% which shows that ultrasound can be used successfully for the diagnosis of HCC in patients of chronic liver disease.

In a study by Yu et al, which compared the different imaging modalities like ultrasound, CT and MRI, the sensitivity of ultrasound 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[25]. Results of this study regarding sensitivity of ultrasound was 86.21% which is almost similar to sensitivity reported by Yu et al. However, in this study when mass size was stratified for small masses (3-4 cm), the sensitivity was found to be 86.05% and for larger mass sizes (5-6 cm) the sensitivity increases up to 87.93%. These findings regarding

mass sizes were also consistent with the results reported by Yu, et al. The same trend was seen in this study that with the increase in mass size, sensitivity increases for ultrasound.

In another study by Tanaka et al, the overall sensitivity, specificity and accuracy of US was found to be 58.9%, 99.9% and 99.3% respectively[26]. In this study, sensitivity of ultrasonography was greater i.e. 86.21% as that of reported by Tanaka et al. However specificity and over all diagnostic accuracy of this study was lower than that reported by Tanaka et al.

In a study by Sbolli et al, 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%[27]. Although results regarding sensitivity and specificity of ultrasonography in this study do not exactly match the results reported by Sbolli et al. but these results are in acceptable range which indicates or permits the use of ultrasound for the detection of HCC in chronic liver disease.

In a study by Takayasu et al, 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 included patients with smaller tumor size, that is less than 3cm. If they would have included the patients with larger size then sensitivity would have been even higher than this[28]. The results of this study are in line with the results reported by Takayasu et al. However in this study mass size ranges in between 3-6cm. It was also observed that as with the increment in mass size there were increases in the sensitivity of ultrasound. This finding was also reported by Yu et al in his study[18].

Possible explanation for variations in the 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 char-

acteristic of diagnostic tests in an unpredictable manner, for example, in a selected population of HBs Ag chronic carriers with high AFP levels, ultrasound 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.

Ultrasound and serum alpha-fetoprotein (AFP) have been most widely used in screening, in part because of wide accessibility and low cost. Reported accuracies of ultrasound vary greatly, likely as a result of dependence on operator experience, attention to detail during scanning, and choice of transducer and equipment. However, poor sensitivity for small nodules is a uniformly recognized concern.

The strength of this study showed that the results were stratified based on number, size of mass and duration of CLD. In stratified analysis, there is no statistically significant difference of sensitivity and specificity, however, slight improvement of diagnostic accuracy noted with increase in number and size of mass. Significant increase noted in specificity and diagnostic accuracy noted in relation to duration of disease. The limitations of this study are small sample size and patients belonging to specific region, therefore, general implication of result is restricted. However, keeping in view the prevalence of CLD and socioeconomic factors this study shows that ultrasound can be a reliable diagnostic tool for early detection of HCC.

Conclusion

Based on results of this study ultrasound sensitivity and specificity, PPV, NPV and diagnostic accuracy was turn out to be 86.21%, 75.25%, 83.33%. 79.17% and 81.71%, respectively. Stratification of mass size, duration of disease and lesion status also showed good and acceptable diagnostic accuracy of ultrasonography. These results are in

acceptable range where it can be said that ultrasound can be used for the screening and detection of HCC in patients of chronic liver disease.

Conflict of interest

Authors have no conflict of interests and no grant/funding from any organization for this study.

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