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ORIGINAL ARTICLE

Diagnostic Role of Contrast-Enhanced Ultrasound (CEUS) in Characterizing Indeterminate Liver Lesions

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ABSTRACT

Background: Indeterminate lesions of the liver are commonly detected in abdominal imaging and in most instances they are cause of diagnostic ambiguity when traditional ultrasound, CT, or MRI fails to clearly define them as benign or malignant. Contrast-Enhanced Ultrasound (CEUS) has become a promising, real-time imaging modality, which does not expose ionizing radiation or any exposure of nephrotoxic contrast to visualize the microvascular perfusion. It is especially useful in the assessment of hepatic lesion evaluation because of its capacity to show characteristic enhancement and a wash-out effect.

Objectives: The objective of the study was to assess the diagnostic utility of CEUS as a tool to characterize indeterminate liver lesions as well as compare patterns of its improvement with ultimate diagnosis made using CT/MRI, histopathology, or imaging follow-up.

Methods: The study was a cross-sectional diagnostic accuracy study, which was carried out among tertiary care hospitals in Punjab, Pakistan between June 2024 and May 2025. There were 80 adult patients with unspecified hepatic lesions identified after the first grayscale imaging who were enrolled. Secondary generation microbubble contrast agent was used to perform the CEUS and a lesion was evaluated at the arterial, portal venous and late stages. Behavioral enhancements, wash-in behavior, wash-out behavior and perfusion were studied. Contrast-enhanced CT/MRI, biopsy or 6-month follow-up imaging were used to confirm the final diagnoses.

Results: CEUS correctly detected 47 out of 52 benign lesions and 26 out of 28 malignant lesions and had a diagnostic accuracy of 91.2 with high sensitivity (92.8) and specificity (90.4). Typical patterns in persistent or isoenhancing late phase were observed in benign lesions (hemangiomas and focal nodular hyperplasia). Malignant lesions such as hepatocellular carcinoma and metastases showed hyperenhancement of the arteries and then early or late wash-out.

Conclusion: CEUS is an effective, safe, cost effective modality, which can distinguish between benign and malignant liver lesions. It can play a crucial role in eliminating unnecessary biopsies and supplement CT/MRI in routine liver examination, since its application in diagnostic algorithms can greatly decrease the number of unnecessary biopsies.

Keywords: Contrast-enhanced ultrasound, CEUS, liver lesions, hepatocellular carcinoma, hemangioma, FNH, washout pattern, diagnostic imaging, microbubble contrast.

INTRODUCTION

Indeterminate liver lesions are common on routine and high-risk clinical imaging, and may appear incidentally in the course of abdominal ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI)[1]. These lesions can be either a wide range of benign (hemangiomas, focal nodular hyperplasia (FNH)) or malignant (hepatocellular carcinoma (HCC), cholangiocarcinoma, and metastatic disease). Proper description of this type of lesions is important since incorrect classification could result in unnecessary biopsy, malignancy diagnosis being delayed, over-treatment of benign lesions and higher psychological and financial impact on patients[2].

The standard grayscale ultrasound continues to be the most appropriate imaging modality in the assessment of the liver because of its access, cost, and safety[3]. In many cases grayscale ultrasound however does not disclose the difference between benign and malignant lesions as most of them reveal similar echogenicity and morphologic features. Although cross-sectional modalities like CT and MRI offer better diagnostic accuracy their application has a number of limitations including radiation exposure (CT), exposure to contrast induced nephropathy (CIN) contraindicated in cases of renal impairment, high cost, and limited availability in low and middle-income nations[4].

Contrast-Enhanced Ultrasound (CEUS) has proven to be an attractive, real-time, dynamic imaging modality, which offers detailed visualization of microvascular perfusion with the help of intravascular microbubble contrast agents. CEUS has a high temporal resolution, can continuously track the arterial, portal venous, and late phases, and has characteristic patterns of enhancement that are extremely helpful in the characterization of the lesions. In comparison to CT and MRI contrast agents, CEUS microbubbles are non-nephrotoxic, do not diffuse across the vascular endothelium, and offer an excellent safety profile, which makes the modality a particularly promising choice with patients with renal dysfunction, contrast allergies, or radiation contraindications[5,6].

During the past few years, CEUS has been included in the international guidelines such as the European Federation of Societies of Ultrasound in Medicine and Biology (EFSUMB) as one of the significant diagnostic methods to assess focal liver lesions. It is especially useful in the distinction of hemangiomas, FNH, HCC, and hypervascular metastases, using different enhancement appearances of peripheral nodular fill-in, spokes/wheel arterial structure, and wash-out. In addition, the application of CEUS in the follow up of liver lesions, guidance of biopsy, and measurement of treatment response following ablation or embolization treatment is also becoming a common practice[7,8].

Considering its benefits of safety, real-time imaging, cost-effectiveness, and diagnostic accuracy, CEUS is becoming an inseparable part of liver imaging algorithms, particularly in the cases when the CT or MRI images are inconclusive. The work will discuss the diagnostic efficacy of the CEUS in the characterization of indeterminate liver lesions, and also emphasize how the latter may be used as a valid, non-invasive method in the current hepatic imaging practice[9].

MATERIAL AND METHOD

Study Design and Setting

The research was aimed to be a cross-sectional study of diagnostic accuracy that was carried out in various tertiary care hospitals in Punjab, Pakistan. The hospitals were chosen according to the presence of high-tech radiology units including contrast-enhanced ultrasound (CEUS) units in these hospitals. The study was conducted in a span of 12 months, between June 2024 and May 2025 where all qualified patients who presented with the indeterminate liver lesions were assessed.

Study Population

The study involving 80 adult patients was conducted. All respondents were persons who showed an indeterminate lesion of the liver on initial grayscale ultrasound or had undergone CT/MRI scans earlier. Any localized hepatic defect that was not indefinitely classifiable as benign or malignant on the basis of routine imaging alone was referred to as an indeterminate lesion. The patients that were included were older than 18 and could undergo CEUS with informed written consent. Patients who had been found to have a history of primary or metastatic liver malignancy, those with severe cardiopulmonary pathology contraindicating the use of contrast agents, pregnant or lactating women and those whose lesions could not be well visualized because of poor acoustic windows were not excluded by the study.

Ethical Considerations

All tertiary care hospitals that were involved in the study in Punjab provided ethics approval to the study. The character and aim of the study were communicated to all patients who then provided written consent as per the ethical standards of research involving human beings.

Contrast Agent/ Imaging Equipment.

The modern and high resolution ultrasound machines with contrast specific image software and low mechanical index capability were used to carry out CEUS examination. The

contrast agent that was used in the entire study was a second-generation microbubble agent, which contained sulfur hexafluoride gas in a phospholipid shell. The contrast was injected intravenously as per the normal dosing schedule given by the manufacturer.

CEUS Imaging Protocol

All patients initially had a baseline grayscale and Doppler ultrasound scan to identify the location of the lesion, size, acoustic qualities and vascularity. This was followed by the intravenous bolus injection of the microbubble contrast agent which was followed immediately by saline. Real-time CEUS was activated during the time of injection and was carried to arterial, portal venous and late vascular phases. Arterial phase was measured at an approxim 10-30 seconds when the injection was done, the portal venous phase was measured at 30-120 seconds and the late phase was measured at 120-300 seconds. During these phases, the cine-loops were continuously recorded to enable a subsequent detailed interpretation of perfusion patterns, enhancing properties, and wash out properties. The lesions were assessed in terms of the extent of arterial improvement, homogeneity, rim improvement or not, and wash-out timing and intensity. Where feasible, these were interpreted according to the guidelines of CEUS LI-RADS, in order to facilitate reporting consistency particularly in patients with possible at-risk of hepatocellular carcinoma.

Reference Standard

The ultimate diagnosis of every liver lesion followed the comparison with one or more reference standards. These incorporated the results of contrast-enhanced CT or MRI, of histopathology results of the cases elicited by fine-needle aspiration or core needle biopsy, and an interval imaging greater than six months in the cases which were believed to be benign. This cross-modal validation provided a valid comparison with interpretations by CEUS.

Collection and Statistical Analysis of Data.

All clinical and imaging information were documented in a structured proforma which was specifically designed to be used in the study. Demographic data, clinical appearance, the nature of the lesion and CEUS was recorded in an orderly manner. The accuracy of diagnosis was evaluated based on the comparison of the results of CEUS to those of the reference standard diagnosis allowing the calculation of the sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy. Statistical information was done using SPSS version 26. The variables of the type of continuous were presented in the form of the mean and standard deviation, whereas the variables of the type of categorical presented their frequencies and percentages. The quality of CEUS in the discriminating between benign and malignant liver lesions was analysed via standard 2x2 contingency table.

RESULTS

The final analysis used 80 patients who had indeterminate liver lesions. The average age of the research population was 52.62=13.4 years and the male to female ratio was 1.3:1. The majority of patients were chiefly complaining of pain in the right upper quadrant, the identification of those abdominal scans, or were being examined as to whether they had chronic liver disease. According to the ultimate reference standard (CT / MRI, biopsy, and follow up imaging), 52 (65) lesions were benign and 28 (35) were malignant out of the total lesions detected.

The contrast-enhanced ultrasound was able to characterize all the lesions showing distinctive patterns of arterial, portal venous, and late-phase enhancing. The benign enhancement in hemangiomas and focal nodular hyperplasia showed normal CEUS, though the malignant lesions, such as hepatocellular carcinoma and metastatic deposits, had early arterial enhancement, with progressive washout. CEUS was able to identify 47/52 benign lesions and 26/28 malignant lesions and this makes the diagnostic accuracy of the device very high.

The median lesion size recorded on CEUS was 3.2 ± 1.6 cm, with the range of 0.8 cm to 8.6 cm. Benign lesions tended to have persistent late-phase enhancement, with malignant lesions recording a consistent washout at the late phase. Metastases were very much linked with early washout (<60 sec), and delayed mild washout is typical of hepatocellular carcinoma. All in all, CEUS was shown to be very sensitive, specific, PPV and NPV in distinguishing benign and malignant lesions. The table 1 below presents a summary of the demographic and baseline lesion features of all the participants. A balance in the number of adult males and females was used in the study, and the number of benign lesions outweighed the number of aggressive lesions. The variation in the size of the lesions indicates the broad range of manifestations in tertiary care. This table -2 indicates the diagnostic breakdown of the lesions after the confirmation of the CT/MRI or histopathology. The most common benign lesions were hemangiomas but hepatocellular carcinoma had the highest percentage of malignant cases. The table-3 is the description of hallmark CEUS vascular patterns in each category of lesion. Improvement of behavior is observed at the arterial, portal venous, and late stages to establish the CEUS-based distinction between benign and malignant focal liver lesions. CEUS proved to be a high-quality diagnostic tool with a very high sensitivity and NPV, which is very effective at eliminating malignancy in case of benign patterns.

Specificity and PPV also show a high level of reliability in detecting malignant lesions as presented in table 4.

Table 1. Baseline Characteristics of Study Participants (n = 80)

Variable	Value
Mean Age (years)	52.6 ± 13.4
Gender (Male/Female)	45 / 35
Total Lesions	80
Benign Lesions	52 (65%)
Malignant Lesions	28 (35%)
Mean Lesion Size (cm)	3.2 ± 1.6

Table 2. Final Diagnosis of Liver Lesions Based on Reference Standard (n = 80)

Category	Type of Lesion	Frequency (%)
Benign (n = 52)	Hemangioma	22 (27.5%)
	Focal Nodular Hyperplasia (FNH)	14 (17.5%)
	Hepatic Adenoma	7 (8.8%)
	Simple Cyst	9 (11.3%)
Malignant (n = 28)	Hepatocellular Carcinoma (HCC)	16 (20%)
	Metastases	10 (12.5%)
	Intrahepatic Cholangiocarcinoma	2 (2.5%)

Table 3. CEUS Enhancement Patterns Observed in Different Lesions (n = 80)

Lesion Type	Arterial Phase	Portal Venous Phase	Late Phase	CEUS Pattern Interpretation
Hemangioma	Peripheral nodular	Progressive fill-in	Persistent enhancement	Benign
FNH	Homogeneous hyperenhancement	Isoenhancing	Isoenhancing	Benign
Adenoma	Rapid homogeneous enhancement	Iso/hypo	Mild washout (variable)	Indeterminate–Benign leaning
Simple Cyst	No enhancement	No enhancement	No enhancement	Benign
HCC	Non-rim hyperenhancement	Mild hypoenhancement	Late washout	Malignant
Metastases	Rim-like enhancement	Hypoenhancement	Early marked washout	Malignant
Cholangiocarcinoma	Irregular rim enhancement	Hypoenhancement	Early washout	Malignant

Table 4. Diagnostic Accuracy of CEUS in Differentiating Benign vs. Malignant Lesions

Parameter	Value
Sensitivity	92.8%
Specificity	90.4%
Positive Predictive Value (PPV)	86.7%
Negative Predictive Value (NPV)	94.8%
Overall Diagnostic Accuracy	91.2%

The findings of this paper indicate that CEUS is a very dependable imaging modality in characterization of indeterminate liver lesions. The overall diagnostic accuracy of CEUS in distinguishing benign and malignant lesions was found to be 91.2 out of 80 cases, which included them. Benign lesions always exhibited typical enhancement patterns, especially the constant enhancement of late stages found in hemangiomas and the stable isoenhancement of focal nodular hyperplasia. Contrastingly, the malignant lesions such as hepatocellular carcinoma, metastases, and cholangiocarcinoma exhibited the anticipated characteristics of early arterial uptake and gradual washout with the metastases portraying the earliest and profoundest washout.

The diagnostic performance in all categories was high and CEUS was more effective in differentiating between hemangiomas and FNH, which showed typical enhancement patterns. The large NPV of CEU in this research also confirms that it is a safe, efficient and cost effective alternative to CT and MRI in characterizing the liver lesion or follow-up of lesions in any environment where an advanced imaging might not be easily accessible.

DISCUSSION

This study is a multicenter diagnostic accuracy study that was done across tertiary care hospitals in Punjab, Pakistan, where Contrast-Enhanced Ultrasound (CEUS) was able to perform very well in characterizing indeterminate liver lesions with a total diagnostic accuracy of 91.2[9]. The results support the accumulating global data that CEUS is a dependable, non-invasive, and economical modality that can be used to characterize hepatic lesions in areas where CT or MRI is inconclusive, contraindicated, or less available[10].

The significant diagnostic accuracy in the present study is related to the published literature in which CEUS has been found to be associated with diagnostic accuracy equal to the contrast-enhanced CT and MRI in the diagnosis of most focal liver lesions. The high temporal resolution to real-time visualization of microvascular perfusion is the advantageous characteristic of the CEUS, and it is essential in identifying the enhancement dynamics at the arterial, portal venous, and late phases. The classical CEUS enhancement patterns observed in our study including peripheral nodular fill-in and homogeneous arterial hyperenhancement with isoenhancement during later stages were observed in benign lesions, including hemangiomas and focal nodular hyperplasia (FNH), and is consistent with the agreed-upon CEUS profiles[11,12].

Our cohort demonstrated sustained enhancement of hemangiomas at late ages, which is characteristic and allowed distinguishing it almost perfectly between hypervascular malignancies and others. Likewise, FNH also

showed the typical centrifugal "spoke-wheel" arterial appearance and constant isoenhancement, and could be positively diagnosed without additional studies[13]. Such findings reiterate CEUS as the initial modality of choice in the assessment of benign vascular lesions and underline its ability to decrease unnecessary CT/MRI scans and invasive procedures like biopsy.

The expected CEUS behavior of malignant lesions of the present study was observed, that is initial hyperenhancement of the arteries and subsequent extent of washout during the portal venous phase and late phase. Hepatocellular carcinoma (HCC) had mild and delayed washout, and metastases had rapid and pronounced washout, which fits with published international data. The capability of CEUS to distinguish between washout time and intensity is especially useful because the features of washout can be considered one of the most effective signs of malignancy. Even though the CEUS LI-RADS system was not actively used with all the study participants, it offers a standardized framework that can be compared with the features of enhancement that were evident in this cohort[14,15].

Adenomas came as an intermediate with irregular improvement and slight washout. This tendency reflects the diagnostics complexity of hepatic adenoma known in the ultrasound assessment. Although CEUS is a useful method in the evaluation of adenoma, CT and MRI, particularly, hepatobiliary contrast agents, can still be relevant as supplementary methods. Nevertheless, CEUS was influential in the reduction of differential diagnosis as well as directing the further imaging choices[16,17].

The finding that CEUS may be useful with renal impaired patients or those that cannot be given iodinated or gadolinium contrast was found to be an advantage in our cohort. Microbubble agents, CEUS, are entirely intravascular, with a great safety record, which has specific benefits of repeated imaging, treatment monitoring, and follow-up in oncology patients. Also, CEUS offered superior timing of enhancement visualization flexibility when compared to CT since the latter could depend on the variability in acquiring delay or breath-hold[18].

Although CEUS had some advantages, it had some weaknesses. Lesions that were deep-seated, lesions beneath the diaphragm, and lesions covered by bowel gas were difficult. Diagnostic confidence was also affected by the dependency on the operator and the necessity to possess the skills in reading patterns of the improvement. Moreover, CEUS is not able to substitute CT or MRI in the case of whole-liver surveying especially in multifocal or metastatic disease. Nevertheless, as demonstrated in this paper, these shortcomings do not negate the fact that CEUS is a useful complementary modality especially when it comes to lesion specific characterization[19].

Altogether, the results of this paper highlight CEUS as a useful, safe, and precise imaging method to assess indeterminate lesions of liver. The growing clinical significance of contrast imaging in the contemporary hepatobiliary imaging can be attributed to its diagnostic strength particularly when integrated with conventional imaging procedures or in patients who have contraindications to other contrast modalities[20].

CONLUSION

The use of Contrast-Enhanced Ultrasound (CEUS) was shown to be a very precise and clinically useful aspect of characterizing indeterminate lesions in the liver in this population of tertiary care hospitals in Punjab, Pakistan. CEUS has a high-diagnostic accuracy of over 90 and is useful in distinguishing benign and malignant tumors using dynamic improvement pattern and washout features. Predictable behavior of enhancement was observed in benign lesions, especially hemangiomas and focal nodular hyperplasia but hepatocellular carcinoma and metastases were observed to have early arterial enhancement and progressive wash out.

The use of CEUS can be considered a good alternative/supplement to CT and MRI due to its safety profile, real-time imaging, lack of ionizing radiation, and affordability. Its utility is mostly critical among patients who have renal impairment, contraindication of contrasts, and in a setting that requires bedside characterization to be rapid. Despite the limitations (dependence of operators and difficulties in visualizing deep or hidden lesions), the clinical utility of CEUS in general is significant.

To sum up, the use of CEUS in the diagnostics of hepatic lesions should be extended into the scope of diagnostic pathways. It can help decrease the amount of unnecessary biopsies, decrease exposure to nephrotoxic contrast agents, and enhance the confidence in diagnosis in the management of focal liver lesions. Future research using larger multicenter samples and standardized CEUS-based diagnostic models will add to its importance in the liver imaging practice.

DECLARATION

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