ORIGINAL RESEARCH PAPER VOLUME-6 | ISSUE-8 | AUGUST - 2017 | ISSN No 2277 - 8179 | IF : 4.176 | IC Value : 78.46

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

Comparison of Tissue Harmonic Imaging, Phase Inversion Harmonic Imaging, Conventional Ultrasound in Focal Hepatic Lesions-ORIGINAL ARTICLE

Radiodiagnosis

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ABSTRACT

Sonography plays a major role in the diagnostic workup of the liver. Present study was designed to compare the role of three techniques i.e. CUS, THI and PIHI. PIHI showed high sensitivity (98.08%), specificity (100%) and overall accuracy (99%) in conspicuity of visualization of solid lesions than both THI (94.23%, 100% and 97% respectively) and CUS (92.31%, 100% and 96% respectively).Both PIHI and THI were found to be of better than CUS in sensitivity, specificity and overall accuracy of visualization of cystic lesions. THI showed better sensitivity, specificity, overall accuracy in conspicuity of visualization than CUS in both solid and cystic lesions. PIHI ($p<0.05$) was found to be better than THI and CUS in lesion conspicuity, internal architecture, margins and overall image quality of solid lesions. PIHI ($p<0.05$) was also found to be better than THI and CUS on posterior enhancement, side lobe artifact and overall image quality of cystic lesions and showed no difference than THI in lesion conspicuity in cystic lesions.

KEYWORDS:

Harmonic images, Conventional ultrasound (CUS), Phase inversion, Focal hepatic lesion

Introduction:

Ultrasound is an incredible diagnostic tool in abdominal diseases. Though it has become the first line investigation in focal hepatic lesions, yet at times it remains silent to differentiate benign from malignant lesions. Tissue harmonic imaging (THI) and Phase inversion harmonic imaging (PIHI) have attributed a lot to minimize artifacts and offer higher contrast resolution.

PRINCIPLE OF TISSUE HARMONIC: It is based on the phenomenon of non linear distortion of an acoustic signal as it travels through the body (fig1). Tissues first compress and then relax as each pulse of sound passes which produces peaks and troughs in the pulse wave pattern because the speed of sound is slightly higher in compressed than in non-compressed tissues. These repetitive alterations in the sound wave create low-amplitude harmonic echoes that increase in intensity as the beam propagates deeper. Multiple harmonics are produced, but the second— the initial echo of the fundamental transmitted pulse—is the only one strong enough to be captured and used by current clinical sonography equipment[1,2]. The processed image is formed with use of the harmonic-frequency bandwidth in the received signal after the transmitted frequency spectrum is filtered out[3,4,5] (Fig 2).

In Phase Inversion Harmonic Imaging (PIHI), fundamental sonographic signal is removed maximally which can be done by either frequency-based or phase inversion methods[6,7,8,9]. In our study phase inversion technology is being used. Thence two consecutive wide-bandwidth pulses are transmitted. The phase of the second is inverted 180° relative to the first. The returning echoes are summed. The linear responses from the fundamental beam and odd harmonic echoes are suppressed. Even harmonic echoes, especially the second, are amplified. This amplification allows wideband filtering to more effectively eliminate the fundamental signal with less harmonic loss. Multifrequency capacity is maintained. (Fig. 3)

Material and method:

The study included 100 consecutive patients with focal liver lesion on CUS. All examinations were performed on Toshiba Xario, Nemio US system (Toshiba Medical System Corporation, Japan) (Using convex broadband 2.5-4.0 MHz transducer). All lesions were first scanned by CUS, followed by THI and PIHI at the same level, magnification, depth and focus which was optimized during scanning using conventional imaging. Gray scale gain was adjusted in each mode. Images obtained by CUS, THI, PIHI were evaluated qualitatively at maximum magnification and repeated independent examination to alienate interobserver variability.

Solid lesions of liver and all cystic lesions were evaluated for: A) Conspicuity and visualization, (B) Internal architecture, © Rim/margins and periphery, (D) Overall image quality.

Each of the above variables was assigned a grade with a score of 0-2:- 0: Poor, 1: Good, 2: Excellent

Inter-observer variability was determined by using inter-observer Kappa analysis and Kappa value determined for measurement of agreement between the observers for CUS, THI and PIHI. Kappa value between 0.75-1 meant very high, between 0.5-0.75 high, between 0.25-0.50 moderate, <0.25 meant low agreement between the observers.

The final diagnosis was made by Contrast Enhanced Computed Tomography, Magnetic Resonance Imaging or Fine Needle Aspiration Cytology performed as a part of diagnostic work up of the patient.

The data from the three groups was statistically analyzed. Sensitivity, specificity & overall accuracy for each of the 3 techniques was determined separately for solid and cystic lesions using statistical software, Analyse-IT (Leeds UK). The sum scores for each of the category of lesions by three different techniques was analyzed by non parametric Kruskal-`wallis test to determine the statistical difference in the visualization of the focal lesions of the liver by the use of above techniques. Image analysis was further statistically analysed using Wilcoxon signed rank test. Interobserver Kappa analysis was done between observations made by three different observation sets & Kappa value was calculated to determine inter-observer variability. The results were then discussed and final conclusion drawn.

Observation and Results:

The study of 100 consecutive patients included 40 females and 60 males. Mean age being 45.7+/-14.7 years.

LESION	USG	SENSITIVITY (%)	SPECIFICITY (%)	POSITIVE PREDICTIVE VALUE (%)	NEGATIVE PREDICTIVE VALUE(%)	ACCURACY (%)
SOLID	CUS	92.31	100	100	92.31	96
	THI	94.23	100	100	94.12	97
	PIHI	98.08	100	100	97.96	99
METASTASIS	CUS	91.30	100	100	97.47	98
	THI	91.30	100	100	97.47	98
	PIHI	100	100	100	100	100
HEMANGIOMA	CUS	100	100	100	100	100
	THI	100	100	100	100	100
	PIHI	100	100	100	100	100
HEPATOMA	CUS	80	100	100	98.96	99
	THI	100	100	100	100	100
	PIHI	100	100	100	100	100
REGENERATIVE NODULE	CUS	100	100	100	100	100
	THI	100	100	100	100	100
	PIHI	100	100	100	100	100
FATTY SPARING /INFILTRATION	CUS	100	100	100	100	100
	THI	100	100	100	100	100
	PIHI	100	100	100	100	100
CYSTIC	CUS	97.92	98.08	97.92	98.08	98
	THI	100	98.08	97.96	100	99
	PIHI	100	98.08	97.96	100	99
ABSCESS	CUS	96.77	98.55	96.77	98.55	98
	THI	100	98.55	96.88	100	99
	PIHI	100	98.55	96.88	100	99
HEPATIC CYST	CUS	100	100	100	100	100
	THI	100	100	100	100	100
	PIHI	100	100	100	100	100
HYDATID CYST	CUS	100	100	100	100	100
	THI	100	100	100	100	100
	PIHI	100	100	100	100	100

TABLE I: SENSITIVITY, SPECIFICITY, POSITIVE PREDICTIVE VALUE,NEGATIVE PREDICTIVE VALUE AND ACCURACY IN CONSPICUITY OF FOCAL HEPATIC LESIONS

Focal lesions of the liver were divided into solid and cystic lesions. 51 patients had solid lesions, 49 had cystic lesions. The commonest solid lesion was liver metastasis in 23 (45%), hemangiomas 5 (10%), HCC 5 (10%) and regenerative nodules 4 (8%), focal fatty sparing/ infiltration 3 (6%). The most common focal cystic lesion detected was hepatic abscess, hepatic cyst and hydatid cyst in 65, 21 and 14 percent respectively.

There was a high to very high correlation between all the three observers in conspicuity, internal architecture, margins and overall quality with kappa value varying between 1 and 0.52 on CUS, THI, PIHI in solid lesions.

There was also a moderate to very high inter-observer agreement between all the three observers on posterior enhancement, side lobe artifact and overall quality with kappa value varying between 0.86 and 0.30 in cystic lesions on CUS,THI,PIHI except for overall image quality which showed only poor agreement with kappa value of 0.23 on PIHI. Kappa value was indeterminate between observer 1 and observer 3, observer 2 and observer 3 in conspicuity as kappa analysis required a 2-way table in which values of first variable match the values of the second variable.

To determine whether the use of PIHI was better in detection and characterization of focal hepatic lesions over CUS and THI statistical analysis was done using Kruskal Wallis test.

For both solid lesions and cystic lesions p-value was <0.001 which was statistically significant. PIHI was better than THI and CUS. THI was also significantly better than CUS.

For liver metastases and hemangiomas p-value was <0.001, which was statistically significant with PIHI and THI being significantly better than CUS.

In HCC liver, regenerative nodules, fatty sparing/infiltration, hydatid cysts p-value was 0.267, 0.111, 0.061, 0.825 respectively which shows that there was no statistically significant difference in the image quality between these three modalities.

In hepatic cysts, the mean ranks for CUS, THI, and PIHI were 9.50, 15.50, 21.50 respectively with p-value of 0.002 which shows that there was statistically significant difference in the image quality between them in which PIHI was better than THI and CUS. THI was also significantly better than CUS.

Image analysis was further statistically analysed using Wilcoxon signed rank test, which shows that solid lesions were better seen on PIHI than both THI and CUS on all the parameters with p-value being <0.05 [TABLE 2] and in cystic lesions, PIHI was judged better than both THI & CUS (p<0.05) for all parameters, except for conspicuity in which it was equal to THI (p=0.1797). THI was judged better than CUS on all parameters (p<0.05) except for side lobe artifact (p=0.0702) [TABLE 2].

LESION	PARAMETERS	P-VALUE ON CUS & THI	P-VALUE ON CUS& PIHI	P-VALUE ON THI& PIHI	RESULT
OVERALL SOLID	CONSPICUITY	0.0003	<0.0001		
	INT.ARCHITECTURE	0.0046	<0.0001	0.0293	P>T>C
	RIM/MARGINS	<0.0001	<0.0001	0.0004	P>T>C
	OVERALL	<0.0001	<0.0001	0.0054	P>T>C
				0.0029	P>T>C
METASTASIS	CONSPICUITY	0.4609	0.0078	0.1563	P=T,P>C, T=C
	INT.ARCHITECTURE	0.6250	0.0020	0.0273	P>T=C
	RIM/MARGINS	0.0215	<0.0001	0.0977	P=T>C
	OVERALL	0.1289	0.0002	0.1289	P=T,P>C, T=C
HEMANGIOMA	CONSPICUITY	0.0039	0.0020	0.7500	P=T,P>C, T>C
	INT.ARCHITECTURE	0.0625	0.0078	0.1250	P=T,P>C, T=C
	RIM/MARGINS	0.0156	0.0010	0.1641	P=T>C
	OVERALL	0.0039	0.0002	0.0625	P=T>C
HEPATOMA	CONSPICUITY	0.2500	0.2500	1.0000	P=T=C
	INT.ARCHITECTURE	0.1250	0.1250	1.0000	P=T=C
	RIM/MARGINS	0.5000	0.5000	-	P=T=C
	OVERALL	0.2500	0.2500	-	P=T=C
REGENERATIVE NODULE	CONSPICUITY	0.5000	0.5000	-	P=T=C
	INT.ARCHITECTURE	0.7500	0.5000	1.0000	P=T=C
	RIM/MARGINS	0.5000	0.2500	1.0000	P=T=C
	OVERALL	0.5000	0.2500	1.0000	P=T=C
FATTY SPARING/ INFILTRATION	CONSPICUITY	0.5000	0.2500	1.0000	P=T=C
	INT.ARCHITECTURE	1.0000	0.2500	0.5000	P=T=C
	RIM/MARGINS	0.7500	0.2500	1.0000	P=T=C
	OVERALL	0.5000	0.2500	1.0000	P=T=C
OVERALL CYSTIC	CONSPICUITY	0.0009	0.0005		
	POST.ENHANCEMENT	<0.0001	<0.0001	0.1797	P=T>C
	SIDE LOBE ARTIFACT	0.0702	0.0018	0.0196	P>T>C
	OVERALL	<0.0001	<0.0001	0.0339	P>T=C
				0.0023	P>T>C

ABSCESS	CONSPICUITY	0.0047	0.0005	0.0455	P>T>C
	POST.ENHANCEMENT	<0.000	<0.000	0.0588	P=T>C
	SIDE LOBE	1	1	0.5637	P=T,P>C,
	ARTIFACT	0.0956	0.0339	0.0143	T=C
	OVERALL	0.0002	<0.000		P>T>C
			1		
HEPATIC CYST	CONSPICUITY	0.2500	0.2500	-	P=T=C
	POST.ENHANCEMENT	0.0625	0.0313	1.0000	P=T,P>C,
	SIDE LOBE	0.7500	0.0625	0.1250	T=C
	ARTIFACT	0.1250	0.0078	0.1250	P=T=C
	OVERALL				P=T,P>C,
					T=C
HYDATID CYST	CONSPICUITY				
	POST.ENHANCEMENT	-	1.0000	1.0000	P=T=C
	SIDE LOBE	-	1.0000	1.0000	P=T=C
	ARTIFACT	-	1.0000	1.0000	P=T=C
	OVERALL	-	0.7500	0.7500	P=T=C

P:-PIHI, T:-THI, C:-CUS, > :- BETTER THAN, = :- EQUAL TO
TABLE 2: P-VALUES IN DIFFERENT MODALITIES BY WILCOXON SIGNED RANK TEST.

Discussion:

The study was designed to evaluate three sonographic modalities –CUS, THI, and PIHI for focal liver lesions. Sonography is often one of the initial imaging studies for evaluation of the liver because it is simple, inexpensive, and noninvasive[10,11]. Recent advances in ultrasound technology, such as THI, have made ultrasound even more widely used in the liver imaging than previously.

In the present study, the conspicuity of visualization of solid lesions on PIHI showed sensitivity , specificity and accuracy of 98.08%, 100% and 99% respectively while CUS showed sensitivity, specificity and accuracy of 92.31%, 100% and 96% respectively and THI showed sensitivity, specificity and accuracy of 94.23%, 100% and 97% respectively.

While Tanaka et al[12], showed that THI has a higher accuracy of 82.3% than CUS 79.6%. Our results showed a better trend than those of Tanaka, presumably due to improved hardware of sonographic imaging used in all these three different modalities compared to year 2000.

Metastasis remained the commonest type of solid focal lesion in the liver in the present study; CUS showed a sensitivity of detection of 91.3%, while it missed detection of lesions less than 1.5mm in size (8.7%), while all the lesions were detected by PIHI. This improved sensitivity of PIHI was attributed to improved contrast by the use of harmonic imaging using PIHI, the effect of which is more conspicuous in obese patients; thus improving the rate of detection of small lesions.

We found HCC in 5 patients by THI and PIHI, which CUS could detect in only 4 (80%) lesions with sensitivity, specificity and accuracy being 80%, 100% and 99% while THI and PHI showed 100% sensitivity, specificity and overall accuracy, respectively.

All the patients were having cirrhosis with coarse echotexture since harmonic imaging uses narrow band width of second harmonic; it had improved lateral resolution, with reduced side lobe artifacts, resulting in improved lesion detection. Tanaka et al[12] also observed an improved count rate detection of number of focal HCC lesions with THI (42.5%) than with CUS (36.8%), which was statistically significant.
Regarding detection of other focal solid lesions, present study exhibited that all the three sonographic modalities had similar results and these included patients of hemangiomas of liver, regenerative nodules and focal fatty infiltration. PIHI, THI provided additional lesion information for solid lesions in 12% patients which altered the patient management. In a study by Sodhi et al[13] showed by use of harmonic imaging improved lesion detection in 61% of patients.
Compared with CUS, THI and PIHI also showed improved lesion conspicuity, internal architecture and morphology.

A good interobserver agreement was seen in all the modalities in the present study.

PIHI had the highest kappa value for overall image quality (0.73-0.93). Statistical analysis of results done using Kruskal Wallis test, showed that for metastasis detection, mean rank of PIHI (43.02) was significantly higher (p=0.008) than that of THI and CUS which were 35.24 and 26.74. Thus, PIHI was judged to be better than other two modalities. Similar results were also seen by Jang et al[14]. This was attributable again to the improved visualization of internal architecture and morphology of lesions by using PIHI.

Although for detection of hemangiomas, the sensitivity and specificity of all the three modalities were the same, but improved visualization of lesions was seen due to better posterior acoustic enhancement in PIHI and THI in the present study. Kruskal Wallis test showed mean rank of PIHI of 33.5 while that of CUS was 13.69 ($p < 0.001$).
Jang et al[14] also reported an improved posterior acoustic enhancement in liver hemangiomas.

In our study, results of Wilcoxan signed rank test showed that PIHI was better than THI and CUS in detection of focal solid liver lesions (p value < 0.05) and best showed the internal architecture of lesions than both THI and CUS, while THI showed only improved visualization of lesion margins than CUS (p=0.02) while no statistical difference was seen for other lesion parameters i.e. conspicuity, internal architecture and overall image quality when compared to CUS.

To our knowledge and review of literature, there was no study eliciting such a detailed comparison of all the three modalities for solid liver lesions.

In the present study, out of 49 cystic lesions, CUS detected 47 (95.91%) lesions with 1(2.04%) false positive and 1(2.04%) false negative. Sensitivity, specificity of cystic liver lesions for conspicuity of visualization on CUS were 97.92%, 98.08% with overall accuracy of 98%. Both THI and PIHI detected 48 (97.95%) cystic lesions with 1(2.04%) false positive with sensitivity, specificity of 100%, 98.08% and overall accuracy of 99%. The false positive cystic lesion was diagnosed as hepatic abscess on all the three ultrasound modes while on FNAC, it was found to be hepatic adenoma.

Hepatic abscess, remained the commonest cystic focal liver lesion in the present study, CUS showed a sensitivity of detection of 96.77%, while it missed one of lesions (3.12%) where as THI and PIHI were able to detect. One lesion (3.12%) which was diagnosed as abscess on all the three modes of sonography was found to be hepatic adenoma on FNAC. The sensitivity and specificity of detection of hepatic abscess was equal for both THI and PIHI.

All the three sonographic modalities had similar results in focal cystic lesions.

A moderate to high interobserver agreement was seen in all the modalities in the present study, with Kappa value varying between 0.773-0.232 for overall image quality. Statistical analysis of results done using Kruskal Wallis test showed that for detection of cystic lesions PIHI was significantly better ($p<0.001$) than that of THI and CUS, which were 77.15 and 51.31. Thus PIHI was judged to be better than the other two modalities. Similar results were also seen by Jang et al14. This was attributable to the improved visualization of cystic lesions by using PIHI.

Similar results were also seen in hepatic cysts in the image quality, with p value of 0.002 and hepatic abscesses with p value of 0.0001. In hydatid cysts, there was no statistical significant difference in the image quality with p value of 0.825.

In the present study, the results of Wilcoxan signed rank test showed that, for cystic lesions, PIHI was better than THI and CUS ($p<0.005$), except for lesion conspicuity on THI (0.1797) in which no significant difference was seen between PIHI and THI. However, side lobe artifact were less in THI than CUS, but the results were not statistically significant (p=0.0702). Improved lesion conspicuity is due to high contrast and spatial resolution and better signal to noise ratio in harmonic imaging.

While Jang et al[14] concluded that for all parameters except posterior enhancement, PIHI was the best among the three techniques, followed by THI ($p<0.05$) and CUS ($p<0.0001$). For posterior enhancement both PIHI and THI were better than CUS ($p<0.05$) but showed no significant difference between them.

Kim et al[15] concluded in their study that for posterior enhancement and

internal artifacts within the cyst, harmonic sonography was significantly better than fundamental ultrasound ($p<0.0001$). These results matched with the results of the present study which also shows that posterior acoustic enhancement was better with THI than CUS ($p<0.05$) and side lobe artifacts were less in THI than CUS but the results were not statistically significant ($p=0.0702$).

Compared with CUS in hepatic abscess, THI and PIHI showed improved lesion conspicuity, posterior enhancement and overall image quality ($p<0.05$) except for side lobe artifact with THI showing no significant difference than CUS ($p=0.0956$). PIHI showed better lesion conspicuity and overall image quality than THI ($p<0.05$). However no significant difference was seen in posterior enhancement and side lobe artifact between THI and PIHI ($p<0.05$).
For hepatic cysts no significant difference was seen between all the modalities for all parameters ($p>0.05$), except for better posterior enhancement and overall image quality on PIHI compared to CUS ($p<0.05$).
For hydatid cysts no significant difference was seen among the three modalities for all the parameters ($p>0.05$). This could be attributed to small sample size of the hydatid cysts and large lesion size.

LIMITATIONS

First, since the image characteristics of the three different techniques were recognizably different, the readers were not blinded, during their analysis, to which technique had been employed.

Second, for reasons of standardization, we did not account for changes in imaging and postprocessing parameters for image gain and location of focal zone. We had to compromise in our definitions of fixed parameters, such as using the same gray scale presetting and dynamic range for all three sonographic modalities. These parameters might have been in favor of one or the other imaging modality.

Third, as for study methods, only solo examiner performed all 3 sets of sonograms in this study and this can in some cases compromise the external validity of the results. However, the use of solo examiner allowed for the acquisition of consistent images with similar high quality from patient to patient. Multiple images of the same view were obtained in both modalities to alleviate this bias.

Conclusion:

Sonography plays a major role in the diagnostic workup of the liver. Improvements in sonography technology, especially those that enable better depiction and characterization of smaller and more subtle abnormal findings, is therefore welcome in the evaluation of focal liver lesions. Present study was designed to compare the role of three techniques i.e. CUS, THI and PIHI, the following conclusions were made:

1. PIHI showed high sensitivity (98.08%), specificity (100%) and overall accuracy (99%) in conspicuity of visualization of solid lesions than both THI (94.23%, 100% and 97% respectively) and CUS (92.31%, 100% and 96% respectively). However, both PIHI and THI were found to be of better than CUS in sensitivity, specificity and overall accuracy of visualization of cystic lesions.
2. THI showed better sensitivity, specificity, overall accuracy in conspicuity of visualization than CUS in both solid and cystic lesions.
3. PIHI ($p<0.05$) was found to be better than THI and CUS in lesion conspicuity, internal architecture, margins and overall image quality of solid lesions. PIHI ($p<0.05$) was also found to be better than THI and CUS on posterior enhancement, side lobe artifact and overall image quality of cystic lesions and showed no difference than THI in lesion conspicuity in cystic lesions.

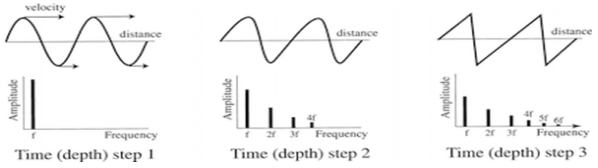

Figure 1: Time Sequence Illustrates the Generation of Harmonic Frequencies

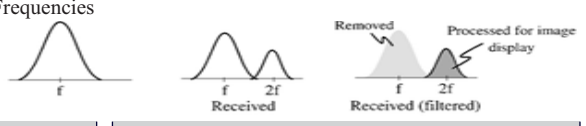

Figure 2: Frequency Spectrum of the Transmitted And Received Waves

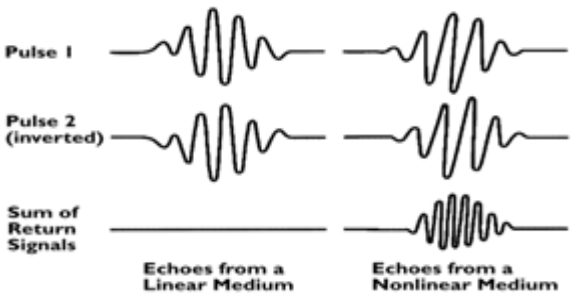

Figure 3: Schematic Diagram of Phase Inversion Harmonic Sonography

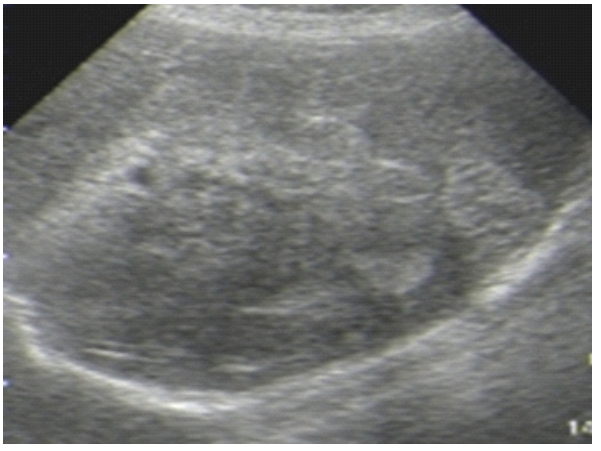

Figure 4: CUS shows a large rounded ecogenic mass in the right lobe of liver with areas of degeneration. No calcification is seen.

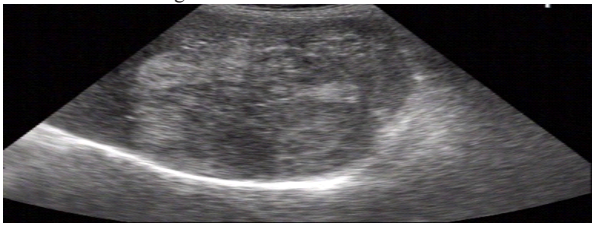

Figure 5: THI shows a large rounded ecogenic mass in the right lobe of liver with areas of degeneration. No calcification is seen.

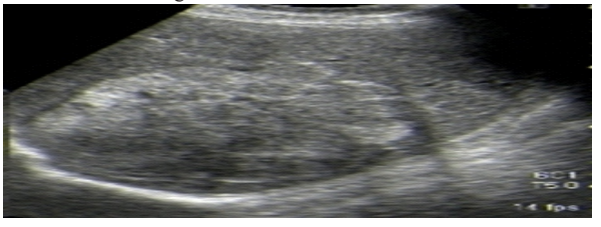

Figure 6: PIHI shows a large rounded ecogenic mass in the right lobe of the liver with areas of degeneration. No calcification is seen alongwith another small hypoechoic mass which was not seen on CUS and THI

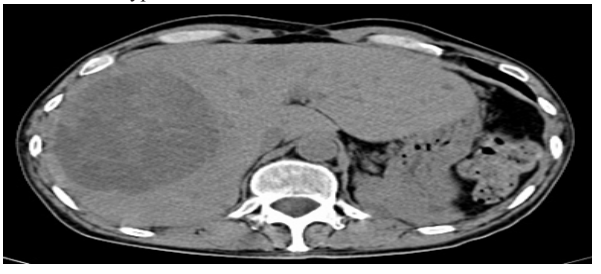

Figure 7: CECT on portal phase shows an isodense mass in the right lobe of the liver.

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