# Tissue Harmonic Imaging Compared with Conventional B-Mode Ultrasound, Biphasic CECT and Tissue Diagnosis in Evaluation of Pancreatic Masses.

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Received: March 2018
Accepted: April 2018



## ABSTRACT

**Background:** Tissue harmonic imaging (THI) is a newer method that can diagnose and differentiate various types of pancreatic masses. The aim of this study was to evaluate the efficacy of tissue harmonic imaging for detection and differentiation of pancreatic masses and its comparison with conventional B-mode ultrasound, biphasic CECT abdomen and tissue diagnosis. **Methods:** 31 patients who presented with a suspicion of pancreatic mass clinically or radiologically were enrolled in this study. All patients underwent both conventional B-mode ultrasound abdomen and THI. Biphasic CECT abdomen was done for diagnostic reference. Pancreatic lesions were documented regarding site, size, internal architecture, and status of peri-pancreatic vessels. The USG diagnosis was compared with biphasic CECT and tissue diagnosis. **Results:** There was statistically significant difference between THI and conventional B-mode USG in visualization of image quality (p<0.001) and solid-cystic differentiation (SCD) (p=0.001). Taking tissue diagnosis as the standard, out of the 25 (80.6%) cases which were diagnosed as malignant on USG and biphasic CECT, 18(72%) cases were confirmed to be malignant on tissue diagnosis. There was no statistically significant difference between biphasic CECT and USG (conventional B-mode and THI) in the diagnosis of benign and malignant masses in pancreas (p=1). **Conclusions:** THI is superior to conventional B-mode USG in the Sonography of pancreatic masses because THI has better overall image quality, lesion conspicuity, visualization of lesion margin and fluid–solid differentiation. It should be routinely utilized as part of the diagnostic workup of patients with pancreatic masses.

***Keywords:*** Tissue harmonic imaging, pancreatic solid cystic masses, B-mode ultrasound, tissue diagnosis.

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## INTRODUCTION

Adenocarcinomas and pancreatitis associated masses are the most common pancreatic masses. Neuroendocrine lesions, cystic tumors and metastasis to the pancreas occur less frequently.[1] Pancreatic tuberculosis, and chronic pancreatitis including autoimmune pancreatitis also present as pancreatic masses. Pancreatic tuberculosis can also mimic pancreatic tumors.[2] Neuroendocrine tumors, mucin producing cystic tumors and pseudocyst also present as pancreatic mass. The differentiation of pancreatic masses is very important for the planning of appropriate treatment.[3,4] Radiological evaluation in a suspected case of a pancreatic mass generally begins with conventional ultrasound followed by CECT abdomen or CEMR depending on clinical scenario. The limitations of transabdominal ultrasound in the diagnosis of pancreatic diseases are in cases of tumors < 10mm in diameter and in the assessment of the necrotic and ischemic areas in acute pancreatitis.[5] At present, biphasic CECT abdomen is the modality of choice for the detection of pancreatic masses and also to determine the resectability in cases of pancreatic malignancy.[6] CEMR has also been shown to have comparable performance to CECT in these areas. However, in many situations, it is difficult to differentiate benign from malignant masses, particularly in cases of focal chronic pancreatitis or pancreatic tuberculosis. Another problematic situation is the differentiation of benign cystic lesions from cystic degeneration in malignant lesions.[7] Endoscopic ultrasound is a recent modality which has been shown to be superior to CECT or CEMR for the detection of small pancreatic lesions. The internal architecture of the lesion, status of peripancreatic vessels as well as

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loco-regional lymphadenopathy are also better visualized with EUS. However, it is invasive and operator dependent.[8]

A new approach to combat the inherent limitations of conventional ultrasound is tissue harmonic imaging. This technique can increase spatial and contrast resolution over that of conventional B-mode ultrasound.[5] Especially in pancreatic imaging, it has been shown that THI provides an enhanced overall image quality, better lesion conspicuity and advantages in fluid-solid differentiation in comparison to conventional B-mode ultrasound.[5] It therefore holds the potential for better characterization of focal pancreatic lesions.

**Aim**

To determine the performance of tissue harmonic imaging in pancreatic masses in comparison to B-mode conventional sonography taking biphasic CECT as the gold standard.

## MATERIALS & METHODS

A total of 31 patients who presented with suspicion of mass in the pancreas on the basis of clinical examination or imaging were enrolled in the study after taking written informed consent. Patients with evidence of metastases at presentation, those who refused to participate in the study and patients with deranged renal parameters were not included.

These patients underwent ultrasound abdomen on either Philips HD-11 or Philips iU-22 (USG machines). Similar views of the pancreatic mass lesions were obtained using both tissue harmonic imaging and conventional B-mode USG. Scanning parameters were optimized for each method, and all images were obtained with the use of the same focal zone. Harmonic images were acquired at a transmitted frequency of 2.0 MHz, and a receiving harmonic bandwidth of 4.0MHz. Conventional US images were obtained at a frequency of 3.5 MHz which is the commonly used frequency for abdominal imaging in adults. The harmonic and conventional modes were switched by means of a toggle switch on the scanner control panel. This was followed by biphasic CECT on a multidetector scanner.

The pancreatic lesions were documented regarding the site, size, internal architecture and status of peri-pancreatic vessels on both conventional B-mode ultrasound and THI and biphasic CECT in a blinded manner. The operator interpreting the tissue harmonic imaging was not aware of the details of findings on other imaging modalities. Three point grading scheme was used to classify the image quality on conventional B-mode and THI, i.e. "poor", "satisfactory" and "good" regarding overall image quality, lesion conspicuity as a measure of contrast between anatomical and pathological structures, cystic- solid differentiation and lesion margin as the criteria. The patients were kept under follow up and an ultimate tissue diagnosis was obtained either by US/CT guided FNAC, histopathology of resected specimen or biopsy obtained during surgery.

The ultrasound diagnosis (whether benign or malignant) was compared with the biphasic CECT and ultimate tissue diagnosis to calculate sensitivity, specificity and diagnostic accuracy of the ultrasound modalities. Furthermore, the sensitivity and specificity of both techniques were correlated to the size of the lesions which were classified into <1cm, 1-3cm and >3cm.

Statistical analysis: Data was filled in a proforma and arranged on a Microsoft excel sheet. Continuous variables were summarized by means and standard deviations. Chi square test was performed for discrete variables. Wilcoxon's signed-ranks test was applied to see the significant differences between grades of image qualities of two modalities (THI and BM) and p-value of <0.05 was considered as significant. The statistical analysis was carried out by SPSS 16.0 version.

## RESULTS

Among 31 patients enrolled in this study, 20 were male (64.5%) and 11 females (35.5%) with mean age of 53.65 years (ranges 14-76 years). The presenting complaints consisted of pain abdomen associated with nausea/vomiting in 24 (77.4%) patients, loss of weight and appetite in 19(61.3%), jaundice in 18 (58.1%), itching in 13(41.5%), clay colored stools in 8(25%), diabetes mellitus in 2(6.5%), abdominal lump in 2(6.5%) and fever in 1(3.2%) patients.

Lesions were identified both on conventional B-mode USG , THI and biphasic CECT in the head of the pancreas in 23 patients (74.2%), as shown in [Figure 1a, 1b and 1c respectively], tail of pancreas in 2 patients (6.5%), and uncinate process in 2 patients (6.5%), 1(3.2%) in head and uncinate process, 1(3.2%) in body, 1(3.2%) in body and tail and 1(3.2%) in neck and proximal body of pancreas.

Lesions were solid in internal architecture in 19(61.3%) patients on both USG (conventional BM and THI) and biphasic CECT abdomen. Lesions were solid- cystic in 11(35.5%) and cystic in 1(3.2%) patients on USG (conventional BM and THI) while on biphasic CECT these lesions were solid-cystic in 9 (29%) patients and pure cystic in 3(9.7%) patients.

Lesion >3 cm in size were found in 22(70.9%) patients, size between 1-3 cm was found in 9(29.1%) and <1 cm was found in none on both USG (conventional BM and THI) and biphasic CECT, (sensitivity=100%, specificity=100%). There was no statistically significant difference between THI and conventional BM in the visualization of lesions with size >3cm, between1-3cm and <1cm (p=1).

Calcification was found in lesions in 3(9.7%) patients. Two out of three were diagnosed as benign and one as malignant on both USG (conventional BM and THI) and biphasic CECT and on tissue diagnosis all three were found to be benign. Lesion conspicuity (LC) was found to be "good" in 31(100%) patients on THI while it was found to be "good" in 3(9.7%), "satisfactory" in 27(87.1%), and "poor" in 1(3.2%) patients on conventional B mode USG. There was statistically significant difference between THI and conventional B mode USG in the visualization of lesion conspicuity (LC) in pancreatic masses (p<0.001).

Visualization of the lesion margin (LM) was found to be "good" in 30(96.8%) patients and "satisfactory" in 1(3.2%) patient on THI and it was found to be "good" in 1(3.2%), "satisfactory" in 29(93.5%) and "poor" in 1(3.2%) patient on conventional BM USG. There was statistically significant difference between THI and conventional BM in the visualization of lesion margin (LM) in pancreatic masses (p<0.001).

Overall image quality was found to be "good" in the lesions of 31(100%) patients in THI while on conventional BM USG, it was found to be "good" in 3(9.7%) and "satisfactory" in 28(90.3%) of patients. There was statistically significant difference between THI and conventional BM in the visualization of overall image quality in pancreatic masses (p<0.001).

Solid-cystic differentiation (SCD) among 12 patients with either solid-cystic(11, 35.5%) or cystic (1, 3.2%) lesions on both conventional BM and THI, solid-cystic differentiation of the lesions were found to be "good" on THI in all the patients while on conventional B-mode USG the visualization of the SCD of the lesion was "good" in 1(8.3%), "satisfactory" in 7(58.3%) and "poor" in 4(33.3%) patients. There was statistically significant difference between THI and conventional B-mode in the visualization of the solid-cystic differentiation (SCD) in pancreatic masses (p=0.001) [Table 1].

Main pancreatic duct was dilated in 22(70.1%) patients on both USG (conventional BM and THI) and biphasic CECT and common bile duct was dilated in 19(61.3%) patients on both USG (conventional BM and THI) and biphasic CECT.

Peripancreatic vessels were found to be involved in the form of compression of the portal vein/superior mesenteric artery by the tumour in 2(6.5%) patients. On both USG and biphasic CECT, lesions in 25(80.1%) patients were diagnosed as malignant and 6(19.4%) were diagnosed as benign. On tissue diagnosis, out of 31 patients, 18(58.1%) were confirmed to have malignancy and rest, 13(41.9%) were found to have benign etiology. On tissue diagnosis, adenocarcinoma was found in 16 (88.9%) patients predominantly from the head of pancreas and 2(11.1%) patients showed indeterminate malignant cells. Of the 13 benign masses, 6(46.2%) diagnosed as having benign cells, 2(15.4%) as benign cyst, 2(15.4%) as tuberculosis, 1(7.6%) as granulomatous inflammation, 1(7.6%) as mass forming chronic pancreatitis and 1(7.6%) as autoimmune pancreatitis (IgG4=5.94g/u) on cytology/histology.

**Table 1: Mean value (x) and standard deviation (σ) of average values for overall image quality, lesion conspicuity, cystic–solid differentiation, lesion margin and size.**

| | BM | THI | P-value |
|---|---|---|---|
| Overall Image Quality | x=2.100 σ=0.301 | x=3.000 σ=0.000 | <0.001** |
| Lesion Conspicuity | x=2.060 σ=0.359 | x=3.000 σ=0.000 | <0.001** |
| Cystic Solid Differentiation | x=1.770 σ=0.599 | x=3.000 σ=0.000 | 0.001** |
| Lesion Margin | x=2.000 σ=0.258 | x=2.970 σ=0.180 | <0.001** |
| Size | x=2.770 σ=0.425 | x=2.770 σ=0.425 | 1.000 |

p value for Wilcoxon's signed-ranks symmetry test: 1=poor; 2=satisfactory; and 3=good and for size 1=<1cm; 2=between 1-2cm; and 3=>3cm.

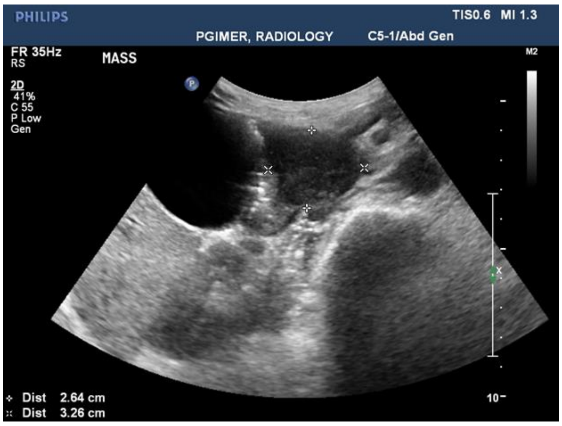


**Figure 1a: Axial B-mode USG image showing >3 cm sized heterogeneous mass lesion in the head of the pancreas. No calcification is seen.**

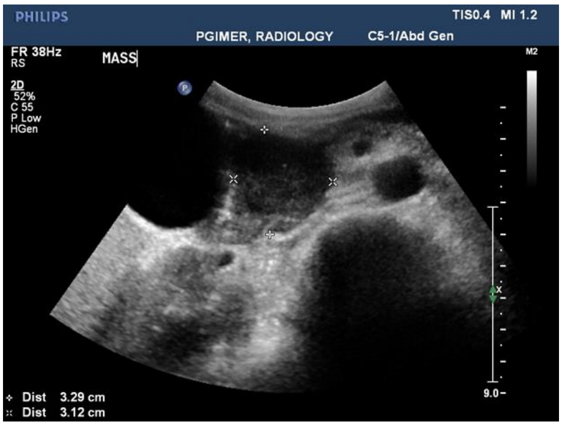


**Figure 1b: Axial THI showing >3 cm sized heterogeneous mass lesion in the head of the pancreas.**

Keeping biphasic CECT as the standard, USG (conventional BM and THI) showed a sensitivity and specificity equal to that of biphasic CECT in the diagnosis of pancreatic masses. There was no statistically significant difference between biphasic CECT and USG (conventional BM and THI) in the diagnosis of benign and malignant masses in the pancreas (p=1).

Taking tissue diagnosis as the gold standard, of the 25 cases which were diagnosed as malignant on USG and biphasic CECT, 18(69.2%) cases were confirmed to be malignant on tissue diagnosis. Rest 7(28%) were confirmed to be benign on tissue diagnosis (False positive) giving a sensitivity of 100% , positive predictive value of 72%, specificity of 46.2% and diagnostic accuracy of 75%.

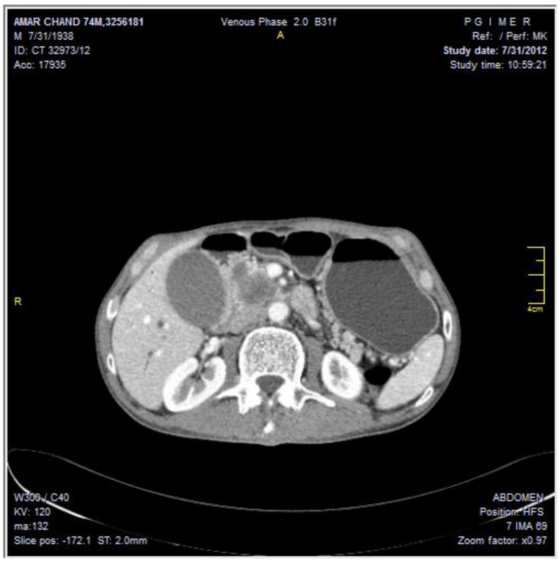


**Figure 1c: Axial CECT image showing >3 cm sized solid mass lesion in the head of the pancreas. CBD and MPD were dilated.**

## DISCUSSION

In a suspected case of pancreatic mass radiological evaluation generally begins with ultrasound but diagnostic difficulties with conventional B-mode ultrasound are artifacts, which can degrade image quality.[4] A new approach to combat the inherent limitations of conventional ultrasound is tissue harmonic imaging. These harmonic beams are whole-numbered multiples of a fundamental frequency that are transmitted by an ultrasound probe.[3] The peaks and troughs of the transmit pulse cause the tissue to alternatively expand and contract, distorting its shape. During tissue contraction, tissue density increases causing the peak of the second wave to travel slightly faster than trough. The result of this process, called non-linear propagation, is that the wave becomes progressively more asymmetrical. This asymmetrical distortion results in harmonics.

In pancreatic imaging, it has been shown that THI provides an enhanced overall image quality, better lesion conspicuity and advantages in solid-cystic differentiation in comparison to the conventional BM ultrasound.[4] In previous studies THI has been proven to be superior in ultrasound of the heart, vascular system, liver, biliary system, kidneys and female pelvis because harmonic imaging show a superior image quality, fewer artifacts and better delineation of normal and pathological structures compared with B-mode ultrasound.[9-13] Tanka et al,[13] showed that THI was significantly better in detecting and correctly characterizing focal masses of the liver than with BM ultrasound, especially for hepatocellular carcinoma in cirrhotic parenchyma.

In a study of 60 cases of pancreatic examinations by Shapiro et al,[9] THI was graded the best technique for penetration in 45, detail in 56 and total image quality in 50 cases. Whereas in 68 examinations of other anatomic areas THI was the best technique for penetration in 42, detail in 57, and total image quality in 58 cases. THI was significantly better than conventional sonography. Schmidt T et al,[15] found that THI (phase inversion tissue harmonic imaging) is a real advance in sonographic technique for imaging the kidney because of its higher sensitivity for overall image quality, lesion conspicuity and fluid solid differentiation. While analyzing lesions <10 mm they found low sensitivity for both the modalities (THI and conventional BM) without a statistically significant difference between the BM and THI. These researches found sensitivities between 0% and 26% for focal renal lesions 1-10 mm size but THI was better than fundamental B-mode sonography in terms of overall image quality, lesion conspicuity and fluid solid differentiation. So they concluded that sonography including THI is currently not sufficient for assessing very small lesions, which also holds true for small pancreatic lesions.

In our study, there was no statistically significant difference between THI and conventional B-mode in the visualization of lesions with size >3cm, between 1-3cm and <1cm (p=1). Out of 31 patients pancreatic lesions >3 cm were found in 22(70.9%), 1-3 cm in 9(29.1%) and <1 cm in 0% both on conventional B-mode and THI. Hohl C et al,[3] in their study of 107 patients using phase-inversion tissue harmonic imaging compared with conventional B-mode ultrasound in the evaluation of pancreatic lesions proved that THI was superior to BM regarding overall image quality (p<0.0001), lesion conspicuity (p=0.0045), and fluid–solid differentiation (p=0.0002) as well as the delineation of the pancreatic tail (p<0.0001) these differences were statistically significant. This statistically significant improvement favors the use of THI when evaluating the pancreas with USG. They found that 60 pancreatic lesions (cystic, acute pancreatitis, dilatation of the pancreatic duct, calcifications, and solid tumors) were diagnosed by CTor MRI. Tissue harmonic imaging had a sensitivity of 70% (14 of 20) compared to BM 60% (24 of 40) for the detection of pancreatic lesions; however the difference was not statistically significant (p=0.46). In the assessment of lesions <1cm of size, tissue harmonic imaging had a sensitivity of 70%, and conventional B-mode ultrasound 46.7%, with out statistically significant difference.

We also found that there was statistically significant difference between THI and conventional BM USG in the visualization of lesion conspicuity (LC) ($p<0.001$), the lesion margin (LM) ($p<0.001$), overall image quality (OIQ) ( $p<0.001$) and solid-cystic differentiation (SCD) ($p=0.001$) of the lesions, as calculated by Wilcoxon's signed- ranks test in [Table 1].

We also compared the USG diagnosis (whether benign or malignant) with the diagnostic reference, i.e. biphasic CECT to calculate sensitivity and specificity of the USG modalities which were found to be statistically insignificant ($p=1$). Then we compared the USG diagnosis (whether benign or malignant) with the tissue diagnosis (FNAC/ cytology/histopathological reports) to calculate sensitivity and specificity of the USG/CT modalities. On USG (conventional BM and THI) and biphasic CECT, lesions in 25(80.1%) patients were diagnosed as malignant and 6(19.4%) were diagnosed as benign. On tissue diagnosis, out of 31 patients, 18(58.1%) were confirmed to have malignancies and rest 13(41.9%) were found to be benign. So we over diagnosed 7 cases as malignant.

Limitations of our study were: Firstly the USG examination is subjective and operator dependent, secondly excessive bowel gases limit the study in some cases. Though tissue harmonic imaging is better for demonstrating most pancreastic lesions regarding overall image quality, lesion conspicuity, lesion margin and solid cystic differentiation but at the same time it did not have any additional benefit over conventional USG for improving diagnostic confidence, or altering clinical management.

## CONCLUSION

Tissue harmonic imaging is superior to conventional B-mode sonography in the sonography of pancreatic masses because tissue harmonic imaging has better overall image quality, lesion conspicuity, visualization of lesion margin and fluid–solid differentiation. It should be routinely utilized as part of the diagnostic workup of patients with pancreatic masses.

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**How to cite this article:** Devi G, Iqbal J, Kang M, Bhasin DK, Gupta R. Tissue Harmonic Imaging Compared with Conventional B-Mode Ultrasound, Biphasic CECT and Tissue Diagnosis in Evaluation of Pancreatic Masses. Ann. Int. Med. Den. Res. 2018; 4(3):RD19-RD23.

**Source of Support:** Nil, **Conflict of Interest:** None declared