Role of Ultrasonic Transient Elastography (Fibroscan) in Assessment of Hepatic Tumor Stiffness

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ABSTRACT
Diagnosis of the nature of hepatic focal lesion is essential for making a proper management decision. Hepatic tumors differ in their tissue composition and thus in the degree of tumor stiffness accordingly tumor stiffness measurement can help in detection of the nature of hepatic focal lesion.

Aim of work: Evaluate the role of ultrasonic transient elastography (fibroscan) in assessment of hepatic tumor stiffness so that it can be used as a potential diagnostic modality in detection of HCC from other focal lesion.

Patients and methods: Our study included 34 patients with different types of hepatic focal lesions (26 with HCC, 4 patients with lymphoma, 3 patients with metastasis and one patient with sarcoidosis) for them routine investigations, ultrasound and liver stiffness measurement using fibroscan were done.

Results: 1- The median stiffness for the HCC was 72.5 kPa, for lymphoma was 17.2 kPa, for metastasis was 6.5 kPa and sarcoidosis was 10.5 kPa.
2- Fibroscan is a sensitive tool in detection of nature of the focal hepatic lesion based on the difference in tissue stiffness.

Key words: Hepatic focal lesions, Transient elastography (Fibroscan), Hepatocellular carcinoma, Lymphoma.
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LIST OF ABBREVIATIONS

AASLD : American association of study of liver disease

: Aveolar echinococcosis AE

: Alpha-l-fucosidase AFU

: Alpha fetoprotein AFP

: Alanine aminotransferase ALT

: Alkaline phosphatase ALP

: Aspartat aminotransferase AST

: The area under the Roc curve AUROCs

: Total bilirubine BIL-T

: Body mass index BMI

: Complete blood count CBC

: Cholangiocarcinoma CCA or CCC

: Cystic Echinococcosis CE

: Contrast enhanced ultrasound CEUS

: Cytokeratins 7 CK7

: Chronic liver disease CLD
CRYL1: Crystallin, lambda 1

CT: Computed tomography

ELISA: Enzyme-linked immunosorbent assay

ERCP: Endoscopic retrograde cholangiopancreatography

FHL: Focal hepatic lesion

FNAB: Fine needle aspiration biopsy

FNH: Focal nodular hyperplasia

GGT: Gamma glutamyle transeferase

GJB2: Gap junction beta-2

GP73: Golgi protein 73

HA: Hepatic adenoma

HB: Hemoglobin

HBV: Hepatitis B virus

HCV: Hepatitis C virus

HCC: Hepatocellular carcinoma

HGF: Hepatocyte growth factor

HSP-70: 70 kilodalton heat shock proteins

HVPG: Hepatic vein portal gradient
: International normalization ratio INR
: Interquartile range IQR
: kilopascals kPa
: Large tumor suppressor, homolog 2 LATS2
: Lens culinaris agglutinin LCA
: Liver stiffness LS
: Magnetic resonance MR
: Magnetic resonance cholangiopancreatography MRCP
: Magnetic resonance imaging MRI
: Non alcoholic fatty liver disease NAFLD
: Prothrombine concentration PC
: Positron emission tomography PET
: Platlets PLT
: Prothrombine time PT
: Primary hepatic lymphoma PHL
: Protein induced by vitamin K absence or antagonist-II PIVKA-II
: Positive predictive value       PPV

: Percutaneous transhepatic cholangiography     PTC

ROI      : Region of interest

: Squamous cell carcinoma antigen     SCCA

: Standard deviation       SD

SELDI-TOF: Surface-enhanced laser desorption/ionization time of flight mass spectrometry

: Transient Elastography       TE

: Transforming growth factor-beta 1      TGF-β1

: Ultrasound       US

: Vascular endothelial growth factor      VEGF

: White blood cells       WBCS

: World health organization     WHO
INTRODUCTION

The increased use of radiologic imaging, particularly ultrasound examination, has led to much more frequent identification of nodules in the liver. Hepatocellular carcinoma (HCC) is increasingly associated worldwide with estimates of hepatitis B and hepatitis C prevalence (Bosch et al., 2004).

Over the last 5 to 8 years, evidence has been accumulating in different countries that the incidence of hepatocellular carcinoma (HCC) is rising. Traditionally, the care of patients with HCC has been undertaken by hepatobiliary surgeons, interventional radiologists, and oncologists (Bosch et al., 2004).

The tests used to diagnose HCC include radiology, biopsy and AFP serology. Which tests should be used depends on the context. Some form of imaging such as CT scan or MRI is always required to determine the extent of disease. In the setting of a patient with known hepatitis B or cirrhosis of other etiology, a mass found incidentally or on screening ultrasound has a high likelihood of being HCC. The sequence of tests used to diagnose HCC depends on the size of the lesion (Bruix and Sherma, 2005).

Tissue stiffness is related to tissue composition. Physicians have used palpation as a part of the physical examination to detect pathology. The ubiquitous presence of stiffer tissue associated with pathology often represents an early warning sign for disease, as in the cases of breast or prostate cancer. This implies that methods for estimating stiffness of tissues would add a weapon to the medical arsenal. It is therefore of interest to measure the stiffness in an objective and noninvasive way, and techniques to estimate the mechanical response of deep tissues to external excitations have been proposed (Masuzaki et al., 2007).
Transient elastography (Fibroscan) is a novel rapid, noninvasive, reproducible method for measuring liver stiffness (Foucher et al., 2006).

The principle is one in which a painless, mechanical impulse is delivered to the skin above the liver, using a low-frequency elastic wave. This produces a wave of mechanical deformation that propagates towards the liver. By monitoring the wave’s progression in real time an echographic transducer determines the propagation speed. Waves propagate more quickly in stiff tissue (Sandrin et al., 2003).

This study is a step toward the provision of a noninvasive measurement of hepatic tumor stiffness by transient elastography.
The aim of this study is to determine the role of Fibroscan in assessing the degree of stiffness of hepatic tumors.
CHAPTER (1)
FOCAL HEPATIC LESIONS

• INTRODUCTION:
Focal liver lesions are defined as solid or liquid-containing masses foreign to the normal anatomy of the liver. Their nature is widely varying, and may range from benign lesions with an indolent clinical course to aggressive malignant tumors (Schwartz and Kruskal, 2007).

• CLASSIFICATION OF FOCAL HEPATIC LESIONS:(Pons and Llovet, 2004).

• Benign tumors

  Hepatocellular: Focal nodular hyperplasia, hepatocellular adenoma
  Biliary: Biliary cystadenoma, biliary hamartoma
           (von Meyemburg complex).
  Cystic: Simple cyst, hydatid cyst, pyogenic/amebic abscess
  Mesenchymal: Cavernous hemangioma, lipoma, angiomyolipoma,
               leiomyoma, fibroma, teratoma, solitary fibrous tumor,
               myelolipoma, myxoma
  Other lesions: Focal fatty infiltration, inflammatory pseudotumor
• **Malignant tumors:**
  
  **Primary**

  Hepatocellular: Hepatocellular carcinoma, hepato-cholangiocarcinoma, Hepatoblastoma
  Biliary: Cholangiocarcinoma, cystadenocarcinoma
  Mesenchymal: Angiosarcoma, epithelioid hemangioendothelioma, fibrosarcoma, leiomyosarcoma, liposarcoma, undifferentiated sarcoma, carcinosarcoma, rhabdomyosarcoma
  Other: Lymphoma

  **Metastatic**

  Adenocarcinomas: Colon, lung, breast, stomach, pancreas, prostate, ovary. Urinary tract tumors, thyroid tumors
  Squamous cell: Lung, esophagus, larynx, perineal tumors.
  Other: Sarcomas, lymphomas, melanomas, neuroendocrine tumors

There is another classification of focal hepatic lesions: “WHO histological classification of the liver and intrahepatic bile ducts tumors” *(Enjoji, 2008):*

  □ **Epithelial tumors:**

  • **Benign:**
• Hepatocellular adenoma
• Focal nodular hyperplasia
• Intrahepatic bile duct adenoma
• Intrahepatic bile duct cystadenoma
• Biliary papillomatosis

• Malignant:

• Hepatocellular carcinoma
• Intrahepatic cholangiocarcinoma
• Bile duct cystadenocarcinoma
• Combined hepatocellular and cholangiocarcinoma
• Hepatoblastoma
• Undifferentiated carcinoma

☐ Non-epithelial tumors:

• Benign:
  • Angiomyolipoma
  • Lymphangioma and lymphangiomatosis
  • Hemangioma
  • Infantile hemangioendothelioma

• Malignant:
  • Epithelioid hemangioendothelioma
  • Angiosarcoma
  • Embryonal sarcoma
  • Rhabdomyosarcoma
  • Others

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Miscellaneous tumors

- Solitary fibrous tumor
- Teratoma
- Yolk sac tumor
- Carcinosarcoma
- Rhabdoid tumor

Hematopoietic and lymphoid tumors

Secondary tumors

Epithelial abnormalities

- Liver cell dysplasia
- Dysplastic nodules
- Bile duct abnormalities

Miscellaneous lesions

- Mesenchymal hamartoma
- Nodular transformation
SOME COMMON AND IMPORTANT BENIGN LIVER MASSES:

- **Cavernous Hemangioma:**

  Cavernous hemangiomas are the most common benign liver tumors, occurring in 7% of adults in autopsy series, with a 1.5-5:1 female-to-male predominance, being diagnosed most frequently in multi-parous women in their third to fifth decades ([Fallon, 2000](#)) and frequently coexist with focal nodular hyperplasia ([Roberts, 2008](#)).

  Histologically, cavernous hemangioma is a non-encapsulated lesion that consists of thin-walled vascular spaces separated by fibrous septae and lined by flattened epithelium. Large hemangiomas may have areas of thrombosis, scarring and calcification ([Benhamo, 1996](#)).

  In most cases, it is a haphazard finding in a patient with no symptoms or unspecific abdominal complaints. Of indolent natural history, it remains stable during follow-up but may grow in the presence of pregnancy or estrogenic therapies. It rarely causes symptoms and only exceptionally associates with thrombopenia, consumption coagulopathy and microangiopathic anemia (Kassabach-Merritt syndrome) ([Pons and Llovet, 2004](#)).

  Diagnosis is radiographic. Ultrasonography (US) shows a hyperechogenic, well-defined lesion that may be more heterogeneous in case of intratumor thrombosis ([Horton et al., 2002](#)).

  On dynamic contrast-enhanced multiphasic CT, there is peripheral nodular enhancement during the arterial phase, with later filling-in toward the center of the lesion ([Roberts, 2008](#)).

  Technetium 99m-labeled red blood cell scintigraphy can be used to confirm the diagnosis in lesions that are atypical on other imaging studies. There is low perfusion on early images, and the isotope gradually accumulates to a high
concentration within the lesion on late images. Biopsy may be useful for small lesions that show uniform enhancement and resemble primary tumors or metastases and also for large lesions that have pronounced scarring and atypical imaging features. Biopsy specimens are typically relatively acellular "dry aspirate" with occasional vascular elements seen on histologic study (Roberts, 2008). The role of percutaneous fine needle aspiration biopsy (FNAB) of a suspected hemangioma is still being debated, the procedure has been associated with fatal hemorrhage, and large superficial lesions in subcapsular locations appear to pose the greatest risk. In addition, there is a low diagnostic yield from FNABs (Heilo and Stenwig, 1997)

- **Hepatic Adenomas:**

Hepatic adenoma (HA) is a mass lesion of the liver characterized by the benign proliferation of hepatocytes. There is evidence linking these lesions to the use of oral contraceptives, the risk sharply increases to 25 times greater after 9 or more years of use (Roberts, 2008).

An important feature of hepatic adenomas is that they can undergo malignant transformation, although this seems to be relatively unusual. Recent evidence suggests that adenomas that stain positive for increased cytoplasmic or nuclear Beta catenin are more likely to transform to hepatocellular carcinoma (Roberts, 2008). Most adenomas are not specifically diagnosed at US and are usually further evaluated with CT or other imaging modalities. Color Doppler US may help to differentiate hepatocellular adenoma from focal nodular hyperplasia. Hepatocellular adenomas are typically bright on T1-weighted magnetic resonance images and predominantly hyperintense relative to liver on T2-weighted images (Grazioli et al., 2001).
On technetium 99m sulfur colloid scintigraphy, there is usually no uptake because adenomas do not contain Kupffer cells. This feature also helps to differentiate adenomas from focal nodular hyperplasia in the delayed phase after MRI with gadolinium in which adenomas show decreased retention of the contrast when compared with surrounding liver. One characteristic of hepatic adenoma seen on all imaging studies is the well-encapsulated features of the hepatic adenoma with well-defined borders (Trotter and Everson, 2001).

At pathological analysis, hepatocellular adenoma is usually a well-circumscribed, non-lobulated lesion, and at gross examination, resected adenomas frequently demonstrate areas of hemorrhage and infarction. Adenomas are characterized by the presence of sheets of hepatocytes without bile ductules, fibrous septa, portal tracts or central veins (Grazioli et al., 2001).

![Gadolinium enhanced magnetic resonance image of hepatic adenoma](image.jpg)