

# Ultrasonography Contribution to the Detection and Characterization of Hepatic Restructuring: Is the “Virtual Biopsy” Taken into Consideration?

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## Abstract

Generally, the evolution of diffuse liver diseases is variable but quite long. Even the severe types of chronic hepatitis have a slow progression which implies decades, often over 20-30 years. Cirrhosis is the principal long time complication of chronic hepatopathies. It represents a major risk factor for the development of hepatocellular carcinoma. Ultrasonography plays an important role among the methods used for detecting diffuse liver diseases, for placing them and identifying supplementary risk factors for carcinogenesis and of hepatocellular carcinoma itself. The two- and especially the three-dimensional exploration allow the characterization of hepatic texture and the identification of certain changes which may suggest hepatic restructuring.

## Keywords

Liver – ultrasonography – fibrosis – cirrhosis – textural analysis – virtual biopsy

## Rezumat

Evoluția afecțiunilor hepatice difuze este variabilă dar, în general, destul de îndelungată. Chiar și formele mai severe de hepatită cronică au o tendință lent progresivă care necesită decade, adesea peste 20 – 30 de ani. Principala complicație pe termen lung a hepatopatiilor cronice este ciroza. Aceasta, la rândul ei este un factor de risc major pentru dezvoltarea carcinomului hepatocelular. Ultrasonografia are un rol important în cadrul metodelor de detecție a bolilor hepatice difuze, pentru încadrarea acestora și identificarea unor factori de risc suplimentari de carcinogeneză și a carcinomului hepatic însuși. Explorarea bidimensională, dar mai ales cea tridimensională permit caracterizarea texturii

hepatice și identificarea unor modificări care pot sugera existența unei restructurări hepatice.

## Introduction

Chronic liver diseases represent an important public health problem. Infections with hepatitis B, C or D viruses, non-alcoholic fatty liver disease or alcoholic hepatopathy represent the majority of the liver diseases, the rest of them (genetic, metabolic or autoimmune) having a minor contribution.

Hepatic fibrosis represents the cicatriceal response to the chronic injury, regardless of its cause. Fibrosis progression is non-linear, occurring more likely consecutive to the active episodes. Cirrhosis is the main long term complication of chronic hepatopathies. During the cirrhotogenous process, there is a diffuse nodular transformation of the hepatic parenchyma which represents a significant risk factor for hepatocellular carcinoma (HCC) development (1).

The pathogenesis of the malignant tumor is not entirely elucidated, but it is known that there are early preneoplastic/ neoplastic changes. There are two types of lesions usually recognized as preneoplastic lesions. One type is represented by nodular lesions called dysplastic nodules (2). There is evidence suggesting the risk of malignant transformation of these nodules (3-6). The second type is represented by hepatocyte dysplasia (presence of atypical hepatocytes).

Understanding the dynamic process of evolution of chronic hepatitis from fibrosis to the restructuring phase, i.e. cirrhosis, and then to HCC is very important in order to “place” the imaging techniques among the methods to detect diffuse liver diseases, to locate them and to identify supplementary risk factors for carcinogenesis and the HCC itself.

## Liver biopsy

Liver biopsy is now “the gold standard” in the diagnosis of fibrosis and chronic hepatopathies. Although it is an

investigation that brings useful information, it has also shortcomings. It is quite difficult to be accepted by the patients because of its invasiveness and also its possible side-effects (pain in one third of the patients, severe complications in 0.3% and even death in 0.03%). Moreover, the diagnostic value of hepatic biopsy is limited by the sampling variability; the average size of the prelevated fragment is 15 mm, which represents 1/50,000 of the entire organ. There is a quite significant variability of intra and interobserver interpretation and it is quite expensive (7, 8).

### Ultrasonography contribution to the detection and characterization of hepatic restructuring

European researchers tend to replace the invasive diagnostic methods with non-invasive or less invasive methods but with similar performances. Non-invasion is a principle which should be applied in any situation, but related to chronic liver diseases, it plays a significant part in selecting the patients with hepatic cirrhosis among those with chronic hepatitis (with different fibrosis grades) and the patients with dysplastic nodules generated by the hepatic cirrhosis. The imaging methods and ultrasonography (US) in particular, play an important role as non-invasive diagnostic methods.

US exploration of textures is an increasingly exciting field. It is well known that the substratum of the image provided by the hepatic parenchyma starts from the lobule, which means that the exploration accuracy reaches the size of 1 mm (9). There are many factors which can disturb the US image, such as: special speculative reflections, refractions, interferences, attenuation, distortions, non-linear propagation etc. There is also the tissue movement, its non-homogeneous structure and even the fluid movement at the vessel level. In addition, there are many techniques providing useful information related to liver exploration: gray-scale exploration, vascular investigation (pulsed and codified color Doppler, in different ways), harmonious investigation (by using frequencies superior to the conventional ones) or the exploration with contrast (allowing the evaluation of the circulatory characteristics of the tissues) (10).

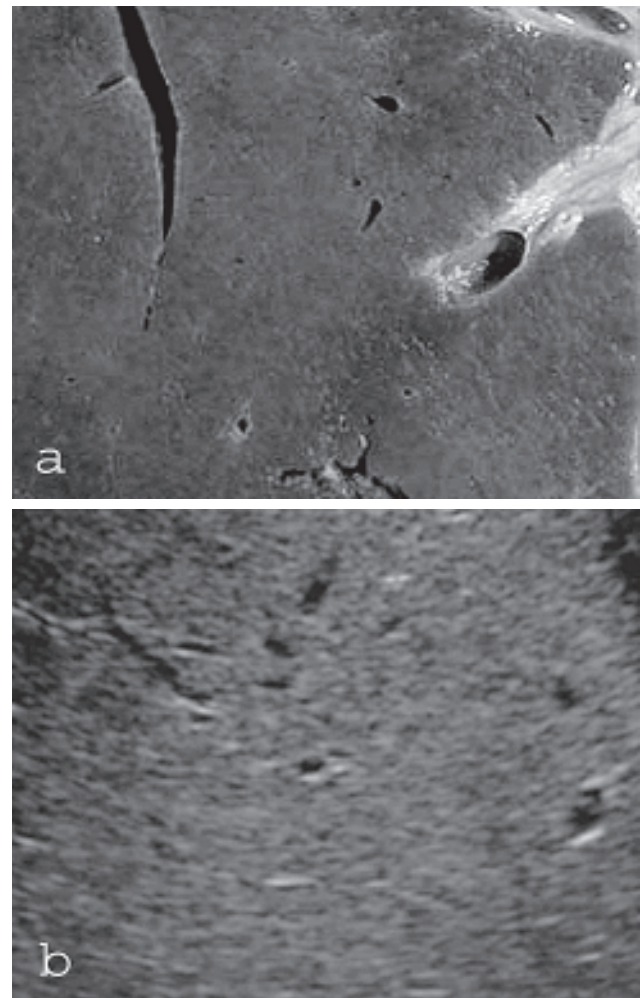
### Two-dimensional ultrasound

Two-dimensional (2D) US provides the plane representation of echoes coming from the ultrasound reflection at the interface level. There are an infinity of interfaces in the liver. Sectionally, it provides a complex textural pattern composed of echogenic structures corresponding to the hepatic matrix (mainly a fibrous structure but also vascular and biliary elements) and of hypoechoic structures from the hepatic lobules. This structural pattern is very similar to the one existing on a

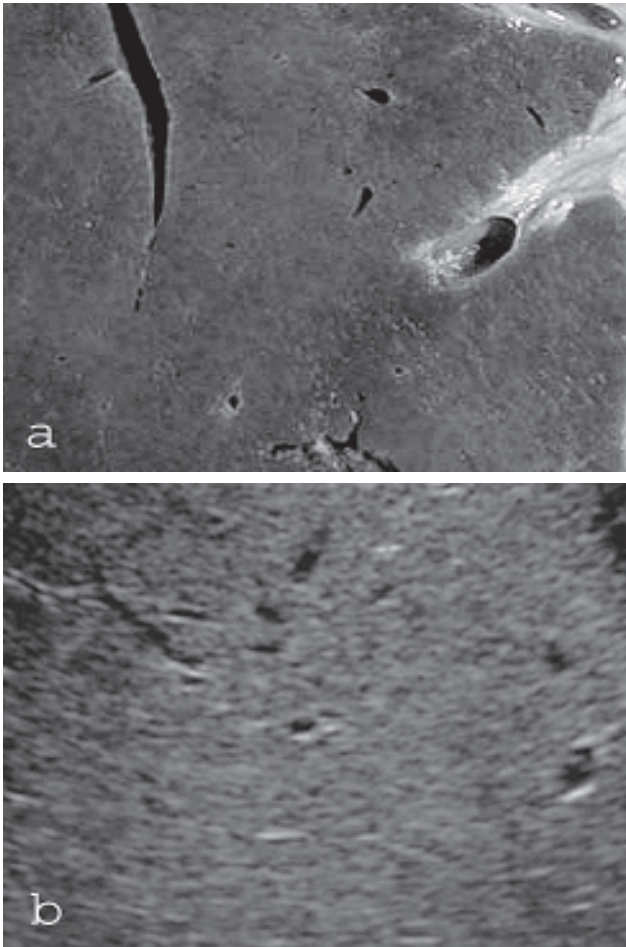
section of hepatic parenchyma examined with a magnifying glass (Fig.1). On the whole, the echographic aspect is characterized by a "relative homogeneity" of a "diffuse non-homogeneous" pattern which means that the distribution of hypoechogenic (hepatic lobule) and hyperechogenic structures with reticular aspect (the fibrous matrix) is similar on all section plans. Then, the parenchyma is penetrated into the surface structures and into the deeper ones, by using a competitive equipment providing echoes equal in surface and depth, and by compensating for the ultrasound attenuation. Because the parenchyma restructuring in chronic hepatopathies is characterized by thickening and disorganization of fibrous matrix, there is an "accentuated" non-homogeneous pattern on the US sections, with an unequal aspect on different section plans. The echogenicity of the parenchyma, depending on the extent of fibrosis and steatosis is modified.

This structural change occurs in a variable proportion and corresponds to the cicatricial transformation process of the liver.

For example, in concordance with the clinical and biochemical variability of chronic hepatitis, the US examination varies from the normal aspect to changes similar to



**Fig.1** Aspect of normal hepatic texture on an enlarged section on an anatomic part (a) and on an echographic image (b).

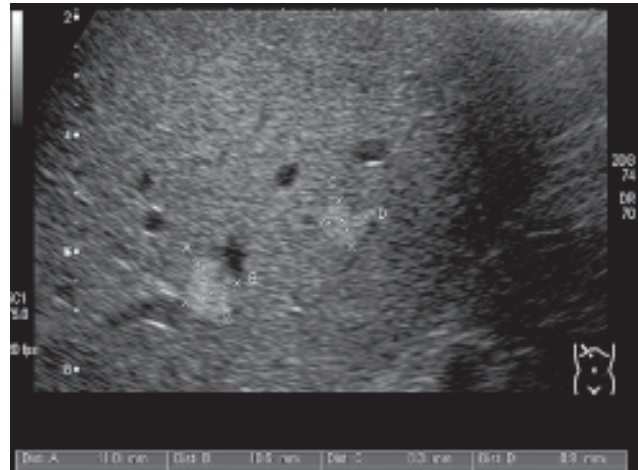


**Fig.2** Aspect of hepatic texture from cirrhosis on an enlarged section: anatomic (a) and US image (b).

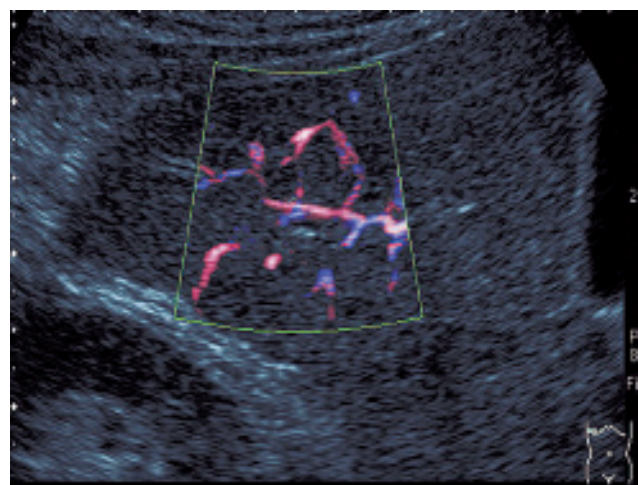
those of hepatic cirrhosis. The most frequent changes are: hepatomegaly, slightly increased echogenicity, sometimes with a moderate attenuation (exogenous toxic factor), homogeneous structure, granular or even non-homogeneous but without clear focal images, regular capsular contour. However, there are non-specific changes suggestive for etiology. US is useful in this situation in order to exclude (with probability) portal hypertension; it cannot exclude the incipient portal fibrosis. At the same time, the differential diagnosis with incipient cirrhosis is difficult to establish and the patient needs a periodical US reevaluation every 6-12 months.

The structural changes in diffuse hepatopathies eventually lead to hepatic cirrhosis (Fig.2). The liver restructuring pattern may be visualized with highly competitive equipments. The dysplastic nodules have an echographic aspect characterized by variable echogenicity. They may be directly (Fig.3) or indirectly identified by showing the vascular replacements (Fig.4).

The general model of the cirrhotic liver may be qualitatively evaluated, depending to a great extent on the experience of the examiner and on the quality of the equipment. The present imaging techniques – US, computerized tomography, nuclear magnetic resonance – may identify nodular transformations of the hepatic parenchyma larger than 1 mm. The disadvantage of such



**Fig.3** Hepatic cirrhosis. Dysplastic nodules (size of 8-10 mm).



**Fig.4** Vascular replacements made by dysplastic nodules (color codified exploration).

techniques is their lack of specificity, which means that a large dysplastic nodule with low risk has the same aspect as a hepatocellular carcinoma. Anyway, a histological diagnosis is possible in this case. Moreover, even if from the histological point of view the nodule has a high cellular differentiation, the presence of malignant cellular islands inside should still be considered.

The morphologic elements identifiable by the US image (fibrosis, steatosis, hepatomegaly, arterialization of micro or macronodular restructuring parenchyma) define some US cirrhosis patterns connected to its etiology. Hepatic cirrhosis of alcoholic etiology induces an echogenic and quite homogeneous pattern, while the viral B and C type induce a textural transformation, progressively accentuated, sometimes even diffuse “pseudotumoural” patterns.

### Three-dimensional ultrasound

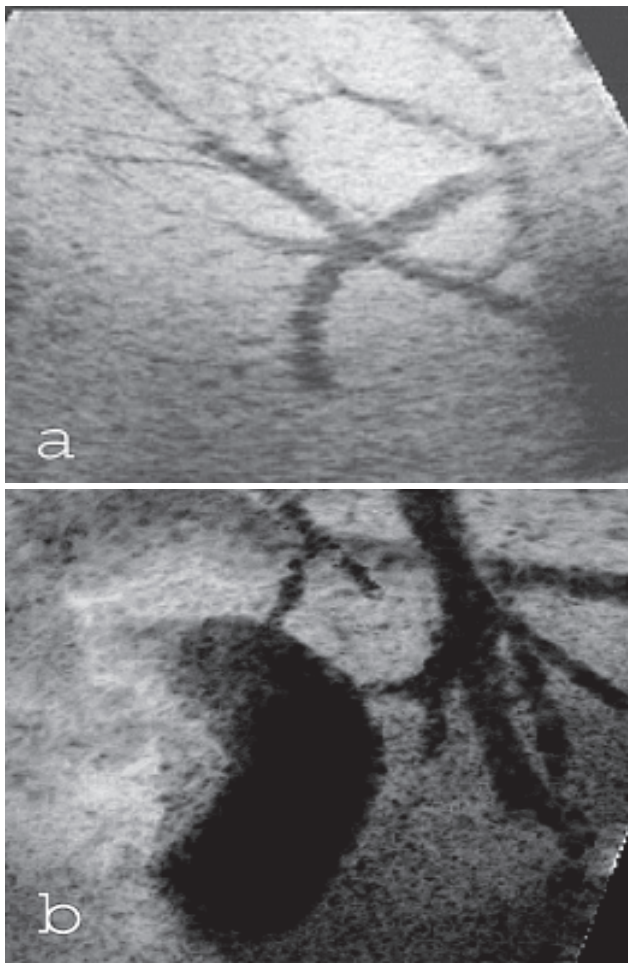
Three-dimensional (3D) ultrasound is a virtual representation of structures. As for the liver, the image is created by joining a great number of almost parallel plane sections in a “pseudovolume”. The structure obtained is the result of

high-technology. It consists of a special transducer permitting the creation of concomitant perpendicular planes and extremely quick processor, capable of reconstructing the image with a very little time difference. Finally, the visual perception of “volume” movement is obtained, namely 4D or 3D live technique (9).

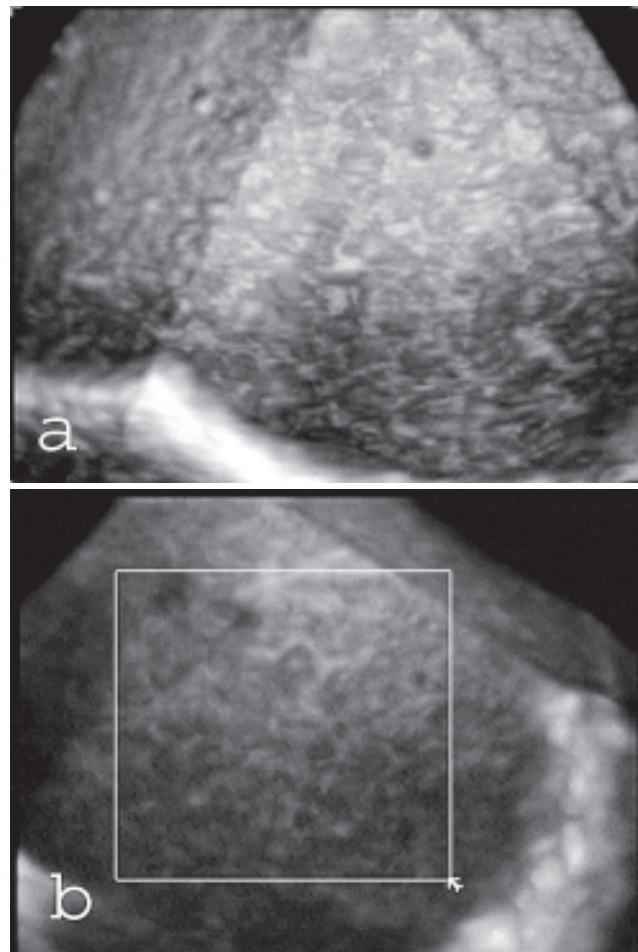
Such a volume of the liver represents the total of a large amount of real information completed by a significant number of artifacts (9). The present equipment is able to obtain a “decantation” of these error factors and to supply the image almost in real time.

3D ultrasound is performed with a special transducer obtaining sections without the scanning used for the conventional exploration. The volume is obtained in short time, between 5-10 seconds, being preregulated by the examiner. The exploration may focus on any segment of the liver, depending on the optimal window. The information may be gathered from variable depths and may be related to the subcapsular or deep parenchyma.

Before the examination, a volume is collected and then reconstructed on the same equipment or on an external working station. The information may be supplied in “transparent” mode (Fig.5), identifying the spatially placed vascular and tubular elements of the liver, or in “surface”



**Fig 5** “Transparent mode” examined hepatic volume. To observe the hepatic vascularization (a) and the biliary ducts and the cholecyst (b).



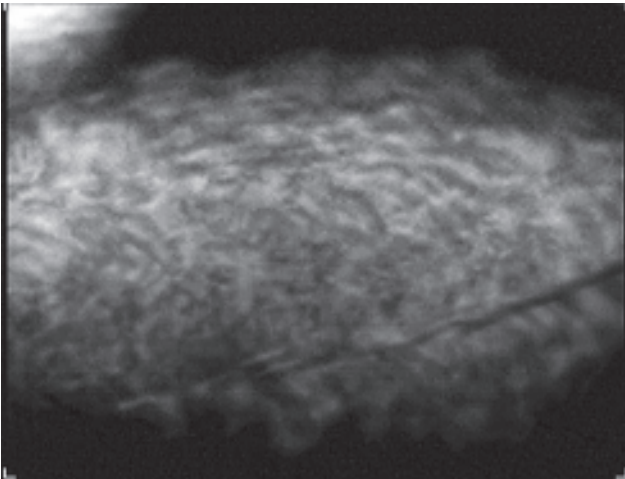
**Fig.6** “Surface mode” examined hepatic volume. To observe the separation of the volume surfaces, through margins (a) and the textural pattern on one of the volume side (b), selected and prepared for analysis by means of a predefined right-angled sample.

mode, by watching the extracted parenchyma, its surface and the separating limits (Fig.6).

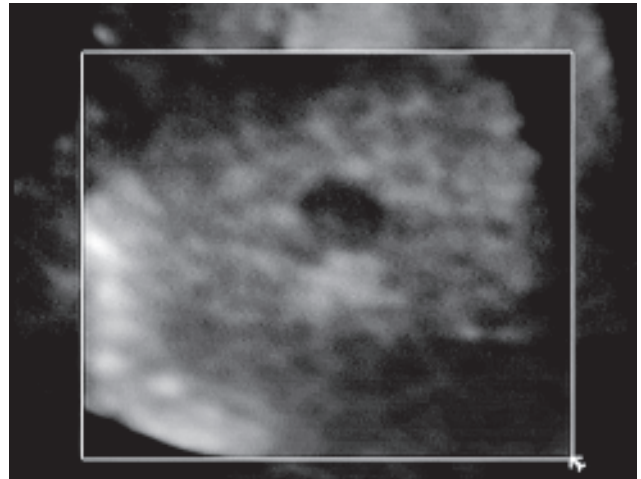
Related to the cirrhotic nodules, the deformed hepatic surface may be quite successfully examined (Fig.7). The method allows the selection of an area of interest in order to create a progressive “framing”, at predefined distances, so that the hepatic texture may be examined in depth, both in the antero-posterior approach and from the side part (Fig. 8). This framing allows the virtual biopsy in any depth and may identify the tumoural nodules (Fig. 9). At the same time, the internal surfaces of the framing inside the volume may also be evaluated (Fig.10).

### Computerized analysis of the data included in the ultrasonic image

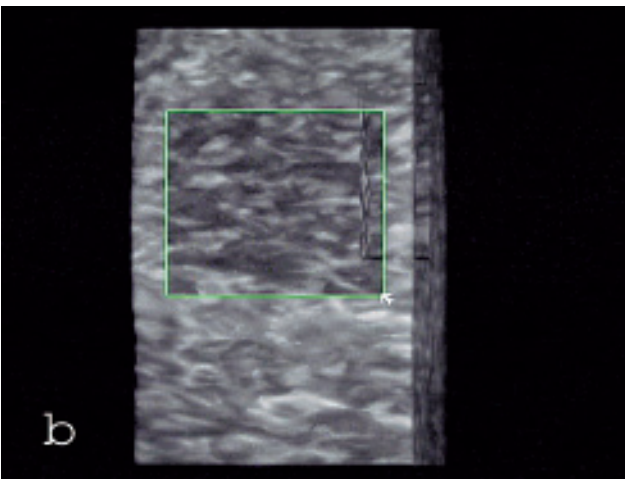
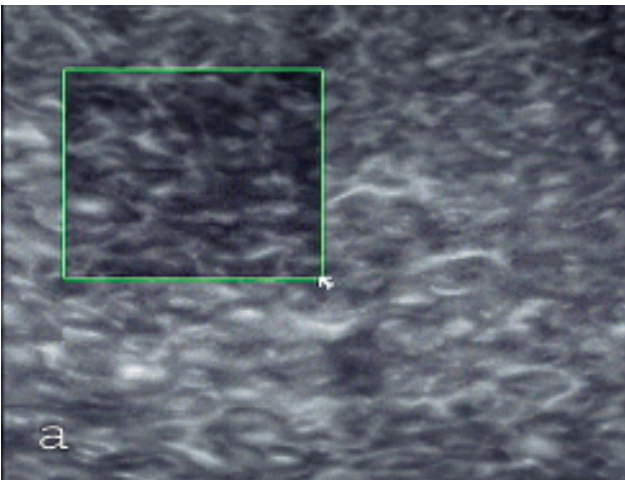
When diagnosing diffuse hepatopathies, US is a simple method bringing useful information but it is not safe enough when determining the difference between certain diseases (steatosis, chronic hepatitis or incipient cirrhosis) or quantifying their severity. Although these pathological conditions are different as a substratum, the main obstacle



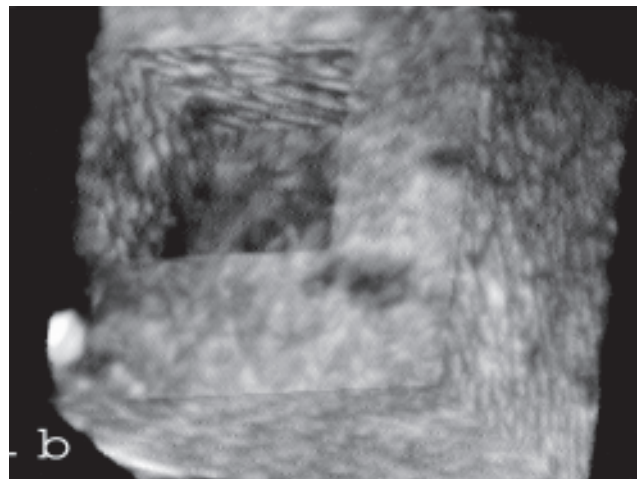
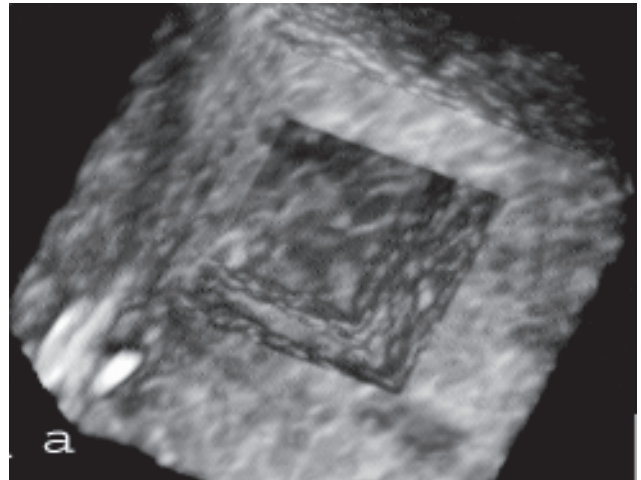
**Fig.7** Visualization of bosselated hepatic surface of the cirrhotic liver (ascites facilitates the exploration).



**Fig.9** Detection of tumoural nodules through successive and predefined framing of the volume.



**Fig.8** Examination of hepatic texture on predefined surfaces on the anterior side of the volume (a) and on the right side of the volume (b).



**Fig.10** Exploration of internal surfaces of the framing in the volume by rotating the extracted volume (a, b).

for their differentiation is the extremely subtle visual differences on the US image (11). The visual discrimination criteria depend on the subjective interpretation of the examiner which may lead to the limitation of the method reproducibility and diagnostic errors. This is the reason why the conventional US examination attempts to be optimized

(12). One approach may be the computer processing data forming the US image, taking into consideration the fact that all information related to the tissue characteristics already exists in the echoes sent back to the transducer.

We consider the principles according to which the pathological tissular changes due to a specific disease

determine the alterations of the physical and micro-architectural features (density, thickness, elasticity, homogeneity etc.). These are very difficult to visualize, but because they interfere with the propagation of the ultrasounds, they can be perceived through the complex analysis of the image (the US tissular characterization) as a different textural pattern as opposed to the healthy one (13).

The simple inspection of the US image is not always able to define a difference between the nature of certain diffuse hepatopathies or their severity. However, the statistic methods of image analysis combined with neuronal networks highly increase the diagnostic precision. They may also offer a graduation of the fibrosis severity or a separation between the benign and malignant hepatic formations (14, 15).

Computer-aided diagnosis methods (CAD) may offer a second opinion and increase the positive predictive value of the examination. These methods may be extrapolated from 2D to 3D examination. From the CAD point of view, 3D ultrasonography is able to represent the entire textural information, by using the textural analysis, much better than 2D ultrasound (16). Moreover, the volume sample may be transferred through telemedicine networks to be evaluated in an expert center.

## Conclusions

When diagnosing diffuse hepatopathies, the conventional US is a simple method bringing useful information but largely dependent on the examiner. 3D ultrasound may offer supplementary information. It provides characterization of the hepatic texture and the identification of certain changes suggesting restructuring by adding information from a third plan, inaccessible to 2D ultrasound. At the same time, 3D - US technique gathers information from any part of the liver, for a volume much larger than the one investigated through biopsy.

Computerized analysis of the US data objectifies the examination and makes easier and more accurate the early diagnosis of certain diseases which usually provide similar US images. It represents a “virtual biopsy” of the liver, offering a more precise monitoring of the disease evolution, by avoiding as much as possible the harmfulness of invasive diagnostic methods.

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