INTRODUCTION
The incidence of malignant tumors increases from year to year, with more than 10 million new cases annually, and more than 5 million deaths (directly or indirectly). Primary liver tumors are in 6th place in the hierarchy incidence worldwide, with 749,000 new cases in 2008, representing 7% of the total, and 694,000 deaths.[1,2] Hepatocellular carcinoma (HCC) represents 70-90% of all primary liver tumors.[3,4] Of the approximately 694,000 deaths in 2008 worldwide, 477,000 were men and 217,000 women; because of its high mortality (mortality/incidence ratio of 0.93) liver cancer is the third leading cause of cancer death worldwide, and the distribution of mortality rate is similar to that of incidence.[5]

The incidence of HCC has doubled or even tripled compared to the 1978 in some countries (USA, Western European countries), a development likely linked to increased prevalence of cirrhosis caused by hepatitis C virus infection (HCV) and nonalcoholic steatohepatitis (NASH).[6]

According to GLOBOCAN 2008, Romania does not occupy one of the top spots as the value of HCC incidence (7th place) however, we situate ourselves on mortality in an unwanted second place. By contrast, it should be noted the cases of countries with infrastructure, adequate ser-ration (in hemochromatosis). Overall, one third of patients with cirrhosis will develop HCC during life, the latter being one of the leading causes of death in people with cirrhosis.[6,12]

Cirrhosis is often diagnosed late (years after onset) due to the enormous functional reserve of the liver and once confirmed diagnosis of cirrhosis surveillance and screening of these patients is the best strategy to limit mortality from HCC. However, despite the existence of well-defined programs and strategies in this regard, only 30% of cases of HCC are diagnosed at an early stage, stage allowing efficient therapeutic approach (surgical resection, radioablation, percutaneous ethanol injection) and avoid liver transplantation, with a 5-year survival rate superior to the cases diagnosed late.[13,14]

THE PURPOSE AND OBJECTIVES OF THE PRESENT STUDY
The aim of the study was to highlight the important role of early imaging diagnosis of HCC in the management of patients with HCC.
Specific Objectives
- Identification of clinical and demographic conditions associated HCC (sex and age of patients, cirrhosis of alcohol abuse, chronic viral hepatitis B / C, toxic hepatitis, etc.).
- Evaluation of HCC screening ultrasound technique in conjunction with MRI issues highlighted in the same patients (given that there are structural changes in hepatic parenchyma detectable on imaging examinations routinely performed in liver cirrhosis, and recognition of these changes is the first step in the direction to a possible diagnosis of HCC).
- Determination of the diagnostic value of MRI imaging in patients with HCC (relative to clinical and biological parameters and/or to the "gold-standard" liver biopsy with histopathological examination).

MATERIALS AND METHODS

The group of patients studied was represented by patients of the Clinic of Gastroenterology of Emergency Clinica Hospital “Floreasca” Bucharest for a period of two years (2007-2009). Patients were initially selected based on the presence of specific diseases, cirrhosis of different etiologies, patients with chronic hepatitis or hepatic decompensation. Were further evaluated by MRI examination patients with suspected HCC on earlier imaging exams or clinico-biological profile. Of these, we included in the study patients in which confirmation of the results obtained from MRI was achieved by:
a) pathological examination of the tumor formation detected on MRI (echo guided biopsy, laparoscopic exploration with biopsy or liver resection - removal of intraoperative biopsy fragments) or
b) Clinical and biological criteria (alpha-fetoprotein> 400 IU) or
c) tracking imaging over a period of 6 months (diagnostic imaging positive).

We analyzed data of 79 patients, obtaining an assessment of clinical and laboratory, as well as some aspects of imaging. The observed parameters were age and sex, clinical presentation (ascites, encephalopathy), chronic liver disease history (with etiology when it was known), biological parameters with the classification of cirrhosis in a Child-Pugh stage, alpha-fetoprotein level (when appropriate), aspects of abdominal ultrasound imaging and MRI (lesion type, size, number of lesions).

After assessing demographic parameters (age, sex), we studied the presence of underlying liver pathology, clinical presentation, overall look of the hepatic parenchymal determined by MRI, characterization of the type of nodular lesions detected (non-regenerative, dysplastic, carcinoma), presence of satellite nodules, the presence and location of parenchymal fibrosis. I also highlighted the need for a histo-pathological examination of a biopsy fragment to test the MRI performance related to the "gold-standard".

Hepatic ultrasonography
Ultrasound is an imaging technique based on the reflection of ultrasound on the tissues of different densities. Ultrasound examination of the liver involves assessing liver parenchyma, blood vessels and bile ducts. Liver parenchyma is homogeneous except of contained vascular and bile structures. Liver echogenicity is expressed in relation to nearby organs (spleen, right kidney), so it is isoechogen or hyperechoic to the renal cortex, or hypoecogen to the spleen. Portal vein is easily identified, in the liver branching into two. Intrahepatic bile ducts are sometimes difficult to distinguish from small blood vessels.

The ultrasound can observe changes in size (hepatomegaly in the initial stages of alcoholic liver disease, liver decreases in advanced cirrhosis), changes of shape (in particular the anterior edge by examining the oblique incidence), nodular formations associated with cirrhosis and nodular regeneration, diffuse echogenic changes (nonspecific hyperecosgenous of steatosis, cirrhosis, hyperecogenitate in diffuse cancers).

Changes in focal echogenicity may suggest the presence of cysts, bleeding, abscesses, focal fibrosis/necrosis, granulomas, nodular hyperplasia, dysplastic nodules, hepatic primary or metastatic tumor nodules. I followed especially nodular lesions focusing on number, character benign/malignant and localization. Examination was done with 3.5 MHz transducer.

HCC presents mixed echogenic, the solid is hipoecogen, fat transformation - hyperechoic. In the encapsulated HCC, the capsule appears as a thin band hipoecogen. HCC can be identified as small hyperechoic hemangioma (source of false negative).

Liver Biopsy- The Fine Needle Aspiration technique
The histopathological specimen examination after the liver biopsy, currently is considered the „gold standard” for evaluation of suspicious liver nodules, and also it has role in confirmation or infirmation of HCC. It is not the perfect method, for the examination of the samples EASL is recommending that it is best to be done by an expert in liver histology, because there are a number of issues related to the interpretation, issues about the degree of the tissue architecture (the grade of dysplasia) and/or issues about the appearance of the hepatocyte. Usually thru this technique a sample is obtained (about 1-4cm length, wide ~ 1mm), and it represents about 1/50.000 from the liver mass.

Regarding the liver biopsy technique it can be done by a percutaneous approach, transjugal or by laparoscopy. In day to day practice the most used by far is the
peculiar pattern of hypervascula rity aspect in so called ar-

MRI is one of the best methods to evaluate HCC, with its

Magnetic Resonance Imaging - MRI

MRI is one of the best methods to evaluate HCC, with its peculiar pattern of hypervascularity aspect in so called arterial phase, than the late washout (sometimes pseudo-

washout by enhancing of the liver parenchyma in the portal phase, when HCC remains hypodense). In small lesions the washout phenomenon is more discreet than in larger ones.

We used Gyroscan Intera Philips, Netherland, 1.0 T, with phased array-coil for transmission and receiving the signal. We also included pre contrast sequences in the examina-

tion protocol which was consisted of axial sections

T1 TFE in-phase and out-of-phase, T2 TSE with fatness suppression and coronal sections T2 TSE. For the contrast-enhanced MRI of the liver we used Resovist, (Schering AG, Germany), a super paramagnetic iron oxide, bolus injection with 1,4 ml (0.5 mmoli Fe/ml).

The images were recorded at 10 minutes after the injection of the contrast agents, and were used the axial sections T2 TSE with fatness suppression and/or coronal sections T2 TSE, with respiratory trigger. For the examination of the extracellular compartment, we used i.v. injection of Mag-

nevist (Schering AG, Germany) a gadopentetate dimeglu-

mine 0,1 mmoli/kg body, sequences used for recording the images were T1 3d TFE – the axial sections or coronal. Suppressed respiration is needed.

For obtaining of the images we used dynamic examination, there were 4 sets of sequences : before injection of the agent, on 20 seconds after the injection (arterial phase), on 40 seconds (portal phase), and after 4 minutes (late phase). The complete protocol that involved all of the sequences lasted about 45 minutes. Every lesion of the liver paren-

chyma who was obtained on the pre contrast phase (T1 TFE in-phase, out-of-phase and T2 TSE with or without fatness suppression) subsequent was analyzed for captiva-

tion (resovist) and its dynamic properties (Margnevist).

We considered that nodules are non neoplastic (regenerative ) if: hypo captivation in T1 and T2, homogene-

ous captivation of Resovist, nodules that did not modifi-

cate on dynamic examination, regular contour.

We considered the newly discovered nodules as a dys-

plastic nodules if: Hypercaptivation in T1, hypocaptiva-

tion in T2, nodules that did not presented charging in the arterial phase.

Nodules with high grade dysplasia were characterized by moderate hypercaptation in arterial phase. These type of nodules are hard to differentiate with HCC on imaging criteria, both types of lesions have: Hypercaptivation in T1., intense arterial load)

We used the following criteria for the diagnosis of hepatocellular carcinoma: formations with various sizes, encapsulated nodules, with variant captivation in T1, moderate hypercaptivation in T2 sequence, homogeneous hyper vascularization in the arterial phase, the late washout phe-

nomenon, nodules that did not captivated Resovist, eventu-

ally nodules who presented vascular invasion.

RESULTS

Total of 79 patients were selected for this study, 54 males (31,65%) and 25 females (68.35%) (figure 1), ratio ~2:1.

Distribution by age revealed a high incidence of HCC on patients with advanced age (figure 2), with a peak at 60-69 years (36,71% from patients).

From the group of 79 patients, 68 (86,1 %) had liver cir-

rhosis, a number of 9 (11,4%) had chronic hepatitis without cirrhosis, and a number of 2 (2,5%) had no disease. (figure 3)

The most frequent etiology in majority of the cases was (figure 4) chronic hepatitis B virus infection (30,4%) re-

spectively chronic hepatitis C viral infection (56,96%), 2 patients with dual HBV/HCV infection, and 10 patients (all of them males) with mixed etiology – viral and etha-

nol.

With the MRI, we were able to determine the location, type and severity of liver damage, and also the degree of fibrosis and nodularity. The vast majority of lesions were located in the right lobe (34 of cases, 43,04%), left +right lobe36 of cases, 45,57%). ( figure 5)

In relation to the degree of liver nodularity detected on MRI, 7 patients(8,86%) had livers without any nodules In a large number of cases, 30 patients, 37,97%) we noticed a multinodular liver appearance (table 1, figure 6).

From the total of 79 HCC patients, we detected with MRI, carcinomatous lesions on 47 patients, which means 59,49% (with histo-pathological confirmation – true posi-

tive – TP). Most of these cases (24 patients, 51 % of TP), were solitary liver nodules (figure 7). One
particular aspect who indicates the real diagnostic potential of the MRI is the evaluation of the liver nodules less than 1 cm (8 cases, 17% from the TP). Patients with multinodular HCC (8 cases) were correctly classified (TP) by the MRI (malignancy criteria), 6 of them had general multinodular aspect, and 4 of them were identified in the early stages of clinical and biological evaluation. Patients with diffuse HCC (nr.4), 2 were with general multinodular aspect, and 2 with diffuse lesions.

We compared the potential of MRI for classification of the liver lesions to the current "gold-standard" which is fine needle punctation of the liver with a histopathological exam represented by liver biopsy (see contingency table 2x2).

Calculation of the validity to the MRI in diagnosis of HCC, reports high sensitivity of this test, which associated with good specificity and good predictive values, it is recommended for use of MRI in diagnosis of HCC in early stages.
By interpreting the MRI tests, we obtained the following results:

- **True positive cases TP (47 cases, 59.49% from HCC patients), with malignant characteristics identified on MRI, later confirmed as hepatocellular carcinoma on biopsy;**

- **False positive cases FP (7 cases, 8.86%), with malignant characteristics identified on MRI, but later this diagnosis was denied by the histopathologist. All of the FP patient had solitary liver nodule on MRI, without any significant degree of parenchyma fibrosis. Anatomopathologists described these lesions as benign (5 cases) and 2 cases as metastases of renal carcinoma;**

- **True negative cases TN (22 patients, 27.85%), without malignant characteristics identified on MRI, later confirmed as normal results by the anatomopathologist.**

- **False negative cases FN (3 cases, 3.80%), without malignant characteristics for HCC, identified on MRI (without multinodular aspect of the liver parenchyma), 1 case was interpreted as liver metastases and the other two as cholangio-carcinoma, but later biopsies showed poorly differentiated hepatocellular carcinoma.**

**DISCUSSIONS**

Hepatocellular carcinoma is a disease with increasing rate in Romania, Europe and worldwide also. It represents up to 90% of primary liver tumors.[3,4] In 80% of cases, hepatocellular carcinoma is associated with cirrhosis. From 79 patients, 68 (86.1%) had liver cirrhosis, which is the condition with the highest risk of development of HCC.

From the group of 79 patients, 25 females and 54 males, patients with HCC were classified by their existent liver pathology (cirrhosis Child Pugh A, B, C, only hepatitis, or without cirrhosis / hepatitis). Male / female ratio was ~ 2: 1 which is consistent with the already existent data from the Globoscan 2008 project, who estimates incidence of hepatocellular carcinoma in central and East Europa.

It is expected that the rate of hepatocellular carcinoma to continue to grow in the upcoming years. The peak incidence of HCC associated with HCV infection has not been occurred yet.[16]

One of the most important issues, at this moment is appearance of cirrhosis on patients with non alcoholic fatty liver disease which is frequent on those who suffer from obesity, diabetes, dyslipidemia and high blood pressure, wherefore it is such a significant problem in the US.[17]

Thereby, the development of an effective support for patients with end-stage liver disease and those with HCC should be a primary goal.

The role of imaging in cirrhotic patients is to identify the morphological changes (size, degree of liver fibrosis, nodularity), to evaluate internal and external vascularisation and to determinate the degree of portal hypertension. Seeing that, majority of HCC (80%) occur on a background of existing cirrhosis, there can be some problems about the certainty on the diagnosis and the staging of HCC in the condition of many other diffuse or focal imagistic anomalies.[3]

We followed the general appearance of the liver determined by MRI, characterization of nodular lesions...
(regenerative, dysplasia, carcinoma), presence of satellite nodules and the presence and location of parenchyma fibrosis.

The MRI determined the location, type and severity of liver damage, i.e., the degree of fibrosis and nodularity. The vast majority of lesions were located in the right lobe (34 of cases, 43.04%), left + right lobe (36 of cases, 45.57%). From the point of view of nodularity, the typical presentation of cirrhosis in Europe and USA is micro-nodular (alcoholic) cirrhosis.[18]

The management of hepatocellular carcinoma should be multidisciplinary, performed by collaboration between hepatologist, hepato-biliary surgeon, transplant surgeon, oncologist, interventional radiologist and experts in palliative medicine. Overall, transplantation still remains the best solution for patients with HCC. Unfortunately, the number of available organs for transplantation are limited. Thereby, alternative therapies such as resection, radiofrequency ablation, and systemic therapy with sorafenib should be attempt for delaying of recurrences. Patients with post-transplant relapse, seems to benefit the most from aggressive surgical treatments.

Due to the difficulties to make an accurate diagnosis of HCC and also the complicated therapeutic management, many strategies are needed to limit the outbreaks (HBV, HVC) and for implementation of therapeutic strategies to prevent HHC.

The immunization campaigns against HBV that were conducted in Taiwan, have reduced incidence of hepatocellular carcinoma. Moreover, the patients who did not completed the vaccination programs, were at higher risk for developing HCC.[19]

Other strategies for reducing the incidence of HCC include HBV and HVC treatments with pegylated interferon, the nucleoside analogs and ribavirin. The protease inhibitors are in phase of clinical studies.[20] HALT-C Study (The Hepatitis C Antiviral Long-term Treatment against Cirrhosis) showed that long-term therapy with pegylated interferon did not reduce the incidence of HCC, on patients with HCV hepatitis who hadn’t sustained viral response.

Other methods for reducing the incidence of HCC, could be reducing of the obesity or diabetes. Major efforts are made to raise awareness in patients with cirrhosis about their alcohol consumption. Hemochromatosis, also should be recognized and treated as early as possible. Mass vaccinations should be the goal for prevention programs with the use of biological molecules to delay the occurrence of HCC in cirrhotic patients.

Most common obstacles for implementation of these programs are the high cost and limited therapeutic resources. It is indicated that the patients with liver cirrhosis patient should be examined with imagistic every 6 months and also blood test for the level of alpha-fetoprotein. With aggressive screening, resectability of the HCC reaches 30-50% which is almost two times higher than those who do not participate in these programs.

Serum AFP screening is an attractive option, given its low cost. Unfortunately, the sensitivity is only 40-64% as many tumors do not produce AFP or occur very late in the development. When there are elevated levels of AFP the specificity is 75-91%, and in the appropriate clinical context values above 400ng/mL are considered diagnostic of HCC.

It is not yet decided which screening program is the best solution. Ultrasound of the liver is a cheap investigation in comparison to MRI or CT scan and also it has not the nephrotoxicity side effects of the contrast agents. [21,22,23]

Ultrasound of the liver has sensitivity of 60% and specificity of 97% in cirrhotic population with already demonstrated cost-effectiveness.[24,25] Any suspicious image found on liver ultrasound or biopsy should be further investigated by a superior imaging method. As well, we recommend investigation in the extra hepatic areas (pulmonary metastases), as this would exclude loco-regional curative treatment.

Surgical therapy is the best option for patients with a small number of tumor nodules. No pre-operate treatment can be declared efficient. Chemotherapy, chemo-embolization or intra-arterial infusions did not increase the survival rate, while immunotherapy such as retinoid, antiangiogenic therapy and radioactive isotopes seem promising.

Local treatment such as ethanol injection, crio-therapy and radiofrequency ablation are indicated to end-stage patients and should be combined with other therapeuticall methods. Systemic therapy with cyto-toxic agents is not recommended. Also goes for hormone therapy with tamoxifen or androgens, because this therapy is not effective and may even be harmful.

**CONCLUSIONS**

We recommend that for the screening of patients who are at high risk of developing HCC, ultrasound of the liver should be performed by an experienced operator, who can detect and accurately locate any suspect nodules. It seems that both tests, MRI and the liver ultrasound have great role in identifying liver nodules and fibrotic processes. For definitive diagnosis of hepatocellular carcinoma MRI is superior to liver ultrasound.

Despite encouraging clinical reports and some studies from referral centers who show obviously efficacy of antiviral therapy for HBV or HCV infection and hepatocellular carcinoma surveillance and treatment, in clinical practice their effectiveness is low.

In addition to the development of new biomarkers and drugs, several steps must be taken to improve outcomes for patients with hepatocellular carcinoma.
This can be done by increasing the number of patients who receive a diagnosis in the early stages of the disease - implementation of surveillance programs, ensuring optimal treatment for each patient (for instance rehabilitation programs for patient with drug and alcohol use), implementation of validated staging systems and perhaps most importantly improved access to specialty care.

References

1. IARC. <http://www-dep.iarc.fr/>; 2011;