UNIVERSITY OF MEDICINE AND PHARMACY CRAIOVA

FACULTY OF MEDICINE

PhD Thesis

IMAGISTIC INVESTIGATION ALGORITHM FOR HEPATOCELLULAR CARCINOMA

-ABSTRACT-

Scientific coordinator,

Professor ADRIAN SĂFTOIU, MD, PhD

PhD Student,

CRISTIANA IULIA DUMITRESCU

CRAIOVA
2013

CONTENTS

Key words: hepatocellular carcinoma, standard ultrsonography, contrast enhanced ultrasonography, real-time elastrography, hybride techniques, computed tomography, magnetic resonance.

INTRODUCTION

From the vast area of hepatocellular carcinoma, this thesys is focusing on the study of the imagistic exploration of the disease. The present workpaper is a potential answer to the unmet need of an early diagnosys of the hepatocellular carcinoma.

STAGE OF KNOWLEDGE

CHAPTER I - LIVER TUMORS CLASSIFICATION

BENIGNE TUMORS

- Hepatocellular hyperplasia:
  - macroregenerative nodule
  - nodular hyperplasia
  - mixed hamartoma
- Hepatocellualr adenoma
  - typical
  - associated with anabolic steroids
- Hepatic cysts
  - simple
  - polycystic
- Bile duct adenoma
- Benign mesenchymal tumors and tumor like conditions
  - mesenchymal hamartoma
  - hemangioma
  - infantile hemangioendothelioma
  - lymphangiomatosis
  - lipoma
  - leiomioma
  - fibroma
  - inflammatory pseudotumor
  - myxoma

TUMOR OF HETEROTOPIC TISSUE AND UNCERTAIN ORIGIN

- adrenal rest tumor,
  - pheocromocytoma
  - pancreatic rests
  - carcinoid
  - neuroendocrine infantile sinusoidal tumor
  - teratoma
  - yolk sac tumor
  - malignant trophoblastic tumor
  - hepatic malignant mixed tumor

PRIMARY MALIGNANT EPHITELIAL TUMOR

- hepatocellualar carcinoma variants
  - childhood
  - fibrolamellar
  - combined
  - spindle cell
  - clear cell
  - giant cell
  - carcinosarcoma
  - sclerosing hepatocellular carcinoma
- hepatoblastoma
- cholangiocarcinoma and cholangiocellular carcinoma
- billiary cystadenocarcinoma
- squamous cell carcinoma
- primary malignant mesenchymal tumor

SECONDARY MALIGNANT TUMORS (METASTASES)

CHAPTER II - HEPATOCELLULAR CARCINOMA ETIOPATHOGENY

CIRRHOSIS

- Viral hepatitis B
- Viral hepatitis C
- Alcohol
- Autoimmune active chronic hepatitis
- Cryptogenic cirrhosis
- Cirrhosis due to non-alcoholic fatty liver disease
- Primary biliary cirrhosis
- Hereditary hemochromatosis
- α1-antitripsine deficiency
- Wilson disease

METABOLIC DISEASES (WITHOUT CIRRHOSIS)
- Hereditaru tyrosinemia
- Ataxia teleangiecatsia
- Types 1 and 3 glycogen storage disease
- Galactosemia
- Citrullimenia
- Hereditary hemorrhagic teleangiecatsia
- Porphyria cutanea tarda
- Orotic aciduria
- Congenital cholestatic syndome

ENVIRONMENTAL
- Thorotrast
- Andogenic steroids
- Smoking
- Aflatoxin

CHAPTER III - CLINICAL ASPECTS IN HEPATOCELLULAR CARCINOMA

Are described multiple clinical forms:

- classical: hepatomegaly, epigastric discomfort and the sensation of a fullness in the abdomen;
- cirrhotic: ascites, hepatic failure, superior digestive hemmorhage;
- occult: no simptoms – accidentally founded;
- febrile: abdominal pain;
- metastatic: the simptomathology is driven by the presence of the metastases;
- hepatitis: jaundice, pruritus, increases in the transaminase levels;
- acute abdomen: severe abdominal pain installed abruptely accompanied by peritoneal reaction;
- cholestatic: severe obstructive jaundice.

CHAPTER IV - IMAGISTIC TESTS IN HEPATOCELLULAR CARCINOMA

The current screening tests used at the patients with cirrhosis are alfa-fetoproteine level (AFP) and ultrasonography (US), with 50%-60% sensibility [6]. Magnetic resonance imaging (IRM) and computed tomography (CT) are the best imagistic techniques available for hepatocellular carcinoma (HCC) diagnosis, in the cases of patients with modified AFP level or ultrasonography abnormalities [7].

OBJECTIVE

- evaluation of the demographic features of the patients with hepatocellular carcinoma
- patients evaluation based on diagnostic algorithm wich includes: ultrasonography, elastography, computed tomography and magnetic resonance imaging;
- identification the histologic and imunohistochemic aspects most frequent encounted in clinical practice of the patients with hepatocellular carcinoma.

PERSONAL RESEARCH

CHAPTER V - MATERIAL AND METHODS

The study was:

- retrospective - time interval 2008 June 1st – 2010 June 30th . This retrospective study has permitted: to highlite the risk factors involved in HCC etiopathogeny and especially in the relation cirrhotic lesion – HCC preneoplasic lesions; identification of histopathologyc, imunohistochemical and ultrasonographyc features of the HCC and these aspects correlation.
- prospective – between 2010 July 1st – 2013 July 3th. This study made possible the evolution surveillance and identification of the predictive factors for survival and mortality of the patients with HCC.

Patients distribution was :

Group A: 371 patients with focal hepatic lesions, imagistic explored;

Group B: 240 patients with focal hepatic lesions ultrasonographic investigated in Clinica I Internal Medicine, Gastroenterology compartment.

Group C: 30 patients with HCC explored trough ultrasonography and computed tomography;

Group D: 126 patients examined trugh contrast enhanced ultrasonography and MRI, from which 76 confirmed with HCC

Group E: 215 patients evaluated with CT and MRI. This group has included 150 patients diagnosed with HCC.

Group F: 15 patients with pathologic confirmation of the HCC.

All 371 patients have completed a protocol for diagnosis which is composed from clinical, biological and imagistic tests.

Imagery has included ultrasonography and elasography for all cases, and selectively contrast enhanced ultrasonography and/or CT and/or MRI. The maximum time interval between explorations was 7 days.

Study inclusion criteria

- Patients with 1- 3 focal hepatic lesions diagnosed trough bidimensional ultrasonography;
- 18 to 65 years of age.

Exclusion criteria:

- Patients with cardiac conditions: heart failure NYHA III/IV, acute myocardial infarctation;
- Hepatic cysts with classic aspect at the conventional ultrasonography (biliar cysts or hydatic cysts);

- Patients known with focal hepatic lesion percutaneously treated and at which contrast ultrsonography is used to monitorisation;
- Pregnancy and postpregnancy period.

Final diagnosys was established by coordinating clinical, biological and imagistic data (contrast CT or contrast MRI).

CHAPTER VI - RESULTS

The most affected age group is 60-80 years, 147 cases, representing 65,33%. Regarding the disease distribution based on sex 169 patients with HCC were men and only 57 women. Demographyc analysis has revealed that 134 patients are from rural area and 92 are from urban population.

240 patients have been examined ultrasonographycally and presented unic lesion, with a mean age of 56 ± 1,6 years.

From the patients with hepatocellular carcinoma 73 (74,48%) already have had a cirrhosis diagnostic. 75 (76,53%) from the 98 patients with HCC (98) have had lesions >2 cm diameter.

When we considered only conclusive cases at the contrast enhanced ultrasonography, HCC accuracy was 88,2%, sensitivity 80,9%, specificity 93,8% and predictive positive value was 88,9%.

In the case of 10 patients with hepatic focal lesions we have performed hybrid imagistic techniques (computed tomography/ultrasonography in 7 cases and in 3 cases magnetic resonance imagining – ultrasonography).

Computed tomography and magnetic resonance imaging were applied at a number of 215 patients. Statistic analisys has revealed next data: sensitivity, secificity, VPP, VPN, PDRL, NDRL and accuracy for each of the analised methods. For a value of the area under curve of 0,879 (CI95%, 0,828 - 0,920) (P<0.0001) sensibility and specificity for computed tomography in hepatic focal lesions diagnosys were 86,6% and 89,2% respectively. According to disease prevalence the accuracy for computed tomography was 87,4%.

In order to evaluate the value of MRI for the differential diagnosys of liver focal lesions I have used ROC analisys, and the value resulted was 0,940 (CI95%, 0,899 - 0,968) (P<0.0001) for area under curve. For this value, the sensibility and specificity obtained were 92,6% and 95,4% respectively, and the accuracy was 93,4%.

Comparing values of the ROC curves for the two imaging techniques for liver focal lesions I have observed that aria under curve (AUC) for MRI with contrast is

larger than AUC for contrast CT (0,940 versus 0,879), with statistic significance p=0,001 (CI95%, 0,0247 - 0,0972).

So, from the 74 patients, contrast CT has detected 14 nodules with HCC pattern from wich 11 were real positive and 3 were false positive, resulting a sensitivity of 57,9 % and a specificity of 90,9%. Paramagnetic contrast MRI has detected 17 nodules with HCC aspect with only 1 false positive result.

MRI sensibility and specificity for the liver focal lesion diagnosys, in the case of the lesions smaller than 2 cm diameter was 84,2% and 94,5% respectively (CI95%, 0,800 - 0,953, p=0,0001).

Comparing AUC corresponding to the two imagistic techniques it can be observed also larger bigger values for MRI cs. CT, 0,894 versus 0,744, with statistic significance p = 0,011 (CI 95%, 0,0343 - 0,265).

I have included in this study 76 cases diagnosed with HCC using the two imagistic methods – contrast enhanced ultrasonography and magnetic resonanace imaging (CEUS și RMN), 69 patients had one single lesion, 5 had 2 lesions and 2 patients multiple lesions, most of the patients being diagnosed in advanced stages of the disease. HCC was detected in the context of a viral B hepatitis in 2 cases, viral C hepatitis in 3 cases and cirrhosis in 30 cases. 66 from de 126 cases were diagnosed with HCC at CEUS and 73 out of 126 cases trough MRI. When I compared the ROC curves I have identified a higer area under curve for MRI (0,952) versus CEUS (0,835), with a value for statistical significance (p) of 0,005, and CI 95% = 0,0343 - 0,199.

I haven't found a statistical semnificative difference between CEUS and MRI characterising LHF and, also, I observed a good concordance between the two imagistic techniques with a k value of 0,78.

According to WHO classification criteria (2010), most frequent hystopatologic subtype was the trabeculat form – 8 cases representing 53,4%, followed by pseudoglandular subtype – 3 cases representing 20%, and less frequent were the solid and pleiomorphyc subtypes – each identified in 2 cases.

CHAPTER VII - DISCUSSION

Demography has constituted criteria for patients stratification due to the fact that factors as low quality alcohol consumption, nonfilter cigarettes smoking and delayed presentation at a doctor are factors that certainly influence the development and evolution of the hepatocellular carcinoma.

Ultrasonography was performed at 240 patients with hepatic focal lesions. The proportion of malignant lesions was bigger than that of benign lesions, similar

to multicentre studies performed in Romania, Germany and France [4, 5, 6].

As a result from the statistic analisys of all cases included in the study, considering the non-concludent ones at contrast enhanced ultrasonography as diagnosys mistakes, I have observed that CEUS has an accuracy of aprox. 87% in differentiating malignant lesions from benign lesions. [4, 5].

Focal lesions dimension (≤ 2 cm and > 2cm) has no influence on contrast enhaced ultrasonography accuracy with regard to differential diagnosys between malignant and benign. [5, 6].

Sensibility and specificity of the obtained results for CT or MRI were similar with those obtained at contrast enhanced ultrasonography: sensibility - 86%, 0,85, 0,87 and specificity 82%, 87%, 89%.

Hybrid techniques play an important role in the non-invasive diagnosys of liver focal lesions because imagistic techniques used (ultrasonography, CT and MRI) have different mechanisms.

In the present study I have examined 10 patients with hepatic focal lesions using hybrid imagistic techniques. I have observed the optimum efficacy of these techniques. Also, togheter with CT and MRI I have used complementar ultrasonography techniques (Doppler and contrast enhanced) which proved to be very usefull for hepatic focal lesions diagnosys.

215 patients were explored trough computed tomography and magnetic resonance imaging techniques and 150 were finally diagnosed with hepatocellular carcinoma: 139 correctly diagnosed by MRI and 130 at CT.

Concurently I have introduced in the study 74 patients with hepatic lesions less than 2 cm diameter, from witch contrast CT has revealed 14 nodules with HCC pattern and from the last ones 11 were real positive and three were false positive, resulting a sensitivity of 57,9% and a specificity of 90,9%. Contrast MRI has detected 17 nodules with HCC patter and has 1 false positive result.

Utilisation of diffusion sequences (DWI) and apparent diffusion coefficient (ADC) are very usefull for the study of the hepatocellular nodules [10]. DWI is a sequence which permite a non-invazive quantification of water diffusion and microcapillar blood perfusion [11]. Always interpreted in parallel with conventional MRI.

Regarding the comparation between ROC curves corresponding for the two imaging techniques, I have identified a sensitivity and a specificity bigger for contrast MRI – referring to HCC. MR has the advantage to permite identification of

smaller nodules and giving more data regarding vascular implication. When chi square test was used, no significant statistical difference (p>0,05) was identified between CEUS and MRI regarding focal hepatic lesions features identification. Moreover, a correlation coefficient of 0,78 was observed between the 2 techniques.

Regarding the stage of the disease at the diagnosys, I have observed that HCC was more frequently diagnosed in stage III (66,7%) and in more advanced stages (stage IV) for solid and pleiomorphyc subtypes.

CONCLUSIONS

Clinical expression of hepatocellualar carcinoma is variable, rarely specific, most of the time ignored by the patient all these heaving as consequence an late diagnosys.

Analizing the sex distribution, hepatocellular carcinoma is predominantly developing in male population.

66,82% from the cases of hepatocellualar carcinoma are, unfortunately diagnosed in advanced stages: stage C or stage D, which makes therapeutic decision very difficult.

Contrast enhanced ultrasonography had a 80% accuracy in diagnostic when we took into consideration all cases included in the study.

Real time elastography had an accuracy of 89% for distinguishing between benign lesions and malignant lesions.

Medium value histogram obtained after examination of the sonoelastographic films was 187 for HCC and statistically different from the medium value of histogram for benign tumors.

Hybrid techniques played an essential role in identifying the lesions difficult to see with standard ultrasonography, remaining especially important for ultrasonographic guided ablation. The advantages are represented by a better procedure control and avoidance to radiation exposure.

ROC curves for contrast enhanced ultrasonography and magnetic resonance imaging have demonstated a better specificity for HCC diagnosys in favour of magnetic resonance imaging.

Regarding the diagnosys of hepatocellular carcinoma, computed tomography had a smaller accuracy 87% when compared with margetic resonance imaging – 93%.

The role of MRI is increased when adding DWI and also specific hepatobiliary contrast agents. We have to take into consideration a review of the current diagnostic algorithm for hepatocellular carcinoma.