Integrative diagnostic and evolution prediction model of focal liver lesions

-ABSTRACT-

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KEYWORDS: Hepatocellular carcinoma, diagnostic model, contrast enhanced
ultrasonography, neural network, fractal image analysis.
STATE OF THE ART

Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver are diagnosed worldwide each year over 500 000 new cases [1-4]. HCC is a major cause of mortality worldwide, representing the third leading cause of death from cancer and that the second cause of death in gastrointestinal cancers in the field [5-8].

Although ultrasound cannot distinguish between HCC and other solid tumors of the liver, it is a widely available technique, noninvasive, and commonly used for HCC screening [9-13]. Current guidelines recommend Contrast Enhanced diagnostic UltraSonography (CEUS), together with other imaging techniques (computed tomography or magnetic resonance imaging with contrast) among the techniques that can be used for the noninvasive diagnosis of HCC [12, 13].

Analysis by a human operator of native CT images during the filling phase of contrast agents provides a sufficiently precise localization and morphological characteristics of liver tumors [14].

Combining analysis of morphometric nuclear arrangement of angiogenesis markers are an absolute novelty in histological investigations for primary and secondary liver tumors [15-18].

Computer-aided diagnosis systems may offer new possibilities in the diagnosis and staging of tumor pathology [19-21].
MATERIALS AND METHODS

Study lot. Selection of risk factors

We included in a prospective study 112 patients (69 men, 43 women) aged between 28 and 87 years (mean age 61 ± 4.01 years) who underwent CEUS between January 2009 and May 2011, following the observation of focal liver lesions standard ultrasound.

Fractal analysis of hystological images

Fixed tissue sections were included in paraffin blocks with a thickness of 2 micrometers, standard techniques were subjected to hematoxylin staining of nuclear chromatin and immunohistochemical staining to detect vascular patterns.

Images were acquired with a Nikon Eclipse 90i microscope (Apidrag, Bucharest, Romania) and a 5 megapixel camera with CCD (Charge-Coupled Device), equipped with Apo-chromatic objective with 40x magnification and 60x respectively. We captured a series of 100 images for each case studied. A signature red-green-blue DAB signal was created and all images were automatically segmented masks obtained were then saved as binary images containing information about the texture of each original image.

Binary images thus obtained were further analyzed using Image J software (Wayne Rasband, National Institutes of Health, Bethesda) with plug-in FracLac (A. Karperien - Charles Sturt University, Australia). Finally, all raw data were exported to Excel (Microsoft Corporation, Redmond, Washington, USA) and analyzed with GraphPad Prism software package 5.0 for statistics.

Analisys of CEUS movies

Patients were examined using a Hitachi EUB-8500 ultrasound and ultrasound Preirus Hitachi, models equipped with an examination possibilities B, M, Color Doppler, pulsed Doppler. Convex probes were used for model C516
with 2.5 to 5 MHz frequency range. We used a bolus injection of 2.4 ml SonoVue (Bracco, Germany), followed by injection of 5 ml saline.

After B-mode scanning was performed prior to injection of contrast agent, at which time began and low mechanical index CEUS examination.

Movies (AVI format, 6 frames per second) and transferred into the offline (notebook) were analyzed using Image Pro Plus software (Media Cybernetics, Bethesda, USA). The film was full investigation initially segmented into three representative portions, depending on transit times of liver contrast agent. Has selected two regions of interest: tumor area surrounding a segment of normal parenchyma, the tumor located at the same depth. Results were exported into Microsoft Excel (Microsoft Corp., USA) for filing and subsequent plot. Distinct sets of data were also exported to GraphPad Prism 5 program (GraphPad, USA).

Track parameters in this study were represented: maximum intensity (IMAX), represented by the average intensities at each point of the target's AOI, mean transit time (MTT), which approximates the time the contrast agent is not represented as a significant increase in light intensity in the AOI, area under curve (AUC), which provides a parallel interpretation of the impact of changes in intensity, perfusion index (PI), and an assessment of the vasculature in the area of interest, rise time (RT) and measurement growth rate until the threshold of higher intensity, and time to peak (TTP), made from time zero intensity.

**Computer tomography (CT) imagistic study**

Patients were investigated multidetector helical CT with a Siemens SOMATOM Emotion 6 (Siemens ltd., Germany) using a standard protocol in four phases, depending on the timing of iodinated contrast agent: pre-contrast, arterial time for portal-venous and late phase (phase equilibrium). Each patient received a bolus of contrast agent up to 100 ml. Four recordings were made cranio-caudal direction complete with the following parameters: range 1-5 mm
sections, the number of bits to store 24, 512x512 resolution, 220 mA and 120 KVP effective power. Phase pressure was recorded up to about 50-51 seconds from the time of injection (range 37-65 seconds), portal phase in 65 seconds (range 60-70 seconds), since the terminal phase is 180 seconds (range 170-190).

Images were taken back and analyzed using a multi-step protocol semi-automatic segmentation. The series of images were entered into the free software ImageJ.

Classifiers selection was made by a neural network subsystem based on automatic selection and parallel involvement by a human operator. We used a model based on co-location matrix on shades of gray (Gray Level Co-occurrence Matrix - GLCM) proposed by Haralick model, plug-in model implemented in the "Texture Analyzer" (Cabrera, United States) developed ImageJ software (Bethesda, USA). We calculated as three texture descriptors: the contrast, the correlation coefficient and the coefficient of entropy, for each set of texture classifiers chosen as positive.

Rețelele neuronale aplicate în modelul de diagnostic și predicție

With a set of clinical and laboratory parameters of a sufficient number of patients, we continued by using a neural network model for classification, staging and determining optimal therapeutic indication for HCC patients with focal liver tumors or other, either malignant or benign.

Neural networks were designed and applied in the toolbox of the application site dedicated MatLab (MathWorks, Massachusetts, USA). With the introduction of complex parameters neural network training, they were stored in a dedicated database.

The collaboration between system and neural network processing modules movies CEUS, CT image analysis and automated analysis moduleul fractal images, we populated the database with a range of values for these investigations.
RESULTS

Descriptive statistics

Subjects ages ranged between 28 and 87 years with a mean age of 61 ± 4.01 years (age ± SD - standard deviation). Prevailed subjects over 50 years (n = 82 and 73.2% of the entire lot). Of the 73 patients with malignant liver tumors (HCC and liver metastases) a number of 68 patients (93.15%) were aged over 50 years. In patients with hepatocarcinom sublot was observed predominantly affecting men (n = 30, the ratio men: women was 2.72: 1).

The relative risk (RR) of developing HCC was calculated for a 95% confidence interval (CI 95%) in patients with liver cirrhosis, HBV, HCV and alcohol consumption. We observed a statistically significant increased risk for HCC in patients with liver cirrhosis (RR = 6.53, CI95% = 3.18 to 13.38), HBsAg positive patients (RR = 4.51, CI95% = 2 , 48 to 8.21) in patients with anti-HCV positive Atc (RR = 4.91, 95% CI 1.84 to 4.33) and in patients of alcohol (RR = 9.165, CI95% 4.43 -18.92). We have identified a correlation between alcohol abuse and HBsAg positivity both in patients with liver cirrhosis and those with chronic (chi-square test, p <0.001). HBsAg positive and high alcohol consumption were more common in rural population (chi-square test, p <0.001).

Risk factors identified in the sublot with HCC were represented by HBV (n = 17 patients, 41.46%), HCV (n = 13 patients, 31.70%), association of HBV and HCV (n = 6, 14, 63%), alcohol abuse without pathology associated viral (n = 5 patients, 12.19%). Alcohol abuse was detected in 30 patients (73.1%) of which 15 patients with HBV, HCV 7 patients, 3 patients with HBV and HCV association and 5 patients without associated viral pathology. Liver cirrhosis was present in 36 patients with HCC in sublot (87.8%) of which 15 patients with HBV, 13 HCV patients, 6 patients with HBV + HCV association and 5 patients with alcohol abuse and without chronic viral infection.
Fractal analysis of hystological images

We observed distinct variations of the mean value for each specific type of pathology, as well as variations in HCC vasculature as this neuroendocrine differentiation (HCCn). Record minimum and maximum values and 95% CI gave us a better picture of the spread of values in each interval.

Regarding the disposal of nuclear chromatin, we observed significant differences between the five pairs of intratumoral tissue groups [one-way ANOVA, F (5, 594) = 205.2, p <0.0001]. Post-hoc analysis using Bonferroni test for multiple comparison showed that the median differences between FD sites for metastases of gastric adenocarcinoma and colon were not statistically significant (t = 0.2164, p> 0.05). Also, as expected, HCC cases studied showed variations minimal inter-group (p> 0.05). All other media FD sites differed significantly (p <0.0001).

We used to highlight axis imunomarcarea vascular CD34 in both tumor samples and in the surrounding parenchyma. Fractal dimension calculated for all different types of tumors, metastases and primary tumors clearly different [one-way ANOVA, F (5, 594) = 2.441, p <0.0001]. Because hepatocarcinomul with neurodiferențiere (HCCn) was poorly vascularized compared with other cases of HCCs studied in post-hoc analysis we have seen significant variations between them (t = 5.139, p <0.0001).

Imagistic CEUS study

Hepatocellular carcinoma

Graphical representation of the intensity-time curves of the two corresponding tumor area and an area of interest that parenchymal revealed significant differences between average intensity values recorded during arterial and portal phase during (p <0.0001). These differences were not statistically significant but during the late phase, where the curves have different intensities,
recorded values of similar intensities, which corresponds to early wash-out tumor (p = 0.6755).

**Hypervascular liver metastases**

Using the Wilcoxon signed rank test, we observed significant differences between mean values obtained in each of the three phases of load contrast agent (p <0.0001). The differences were maintained during the late phase, but there are wash-out phenomenon, with the balance curves, but late than the time necessary "money" for tumor metastasis (p <0.0001). Mean values were significantly different during the three phases, probably due to the aspect that these were well perfused liver metastases.

**Hypovascular liver metastases**

Hypovascular metastases average values were significantly different during the three phases (p <0.001). Variation in each pair was significant, with positive values of Spearman coefficients, due mainly to reverse phenomenon curves between the two areas of interest, charging parenchyma is faster and higher values compared with the region tumorală. Variația area under curve showed the existence of significant differences between high-normal parenchyma area and tumor area (p <0.0001).

**Hepatic hemangiomas**

Graphical representation of the intensity-time curves of the two corresponding areas of interest located at the same depth, revealed significant differences between the average intensity values recorded during the three stages of loading (p <0.0001). The differences were maintained during the late phase, where the curves were different intensities, missing wash-out phenomenon of early tumor specific for malignancy (p = 0.0002).
**Focal fatty sparring**

By comparing successive pair of two sets of values of intensity in areas of interest during the three phases of action of contrast agent, we observed significant differences in the degree of filling (p > 0.05). IMAX had a slightly higher value for the steatosis, compared to normal parenchyma, but with no significant differences statistically (p > 0.05). In contrast to the tumors studied, TTP was approximately equal in the two areas. MTT also had similar values in both areas here pursued.

**CT image analysis**

Prin By applying successive Sobel and LOG filters, we obtained an automatic representation liver limits. This method correctly selected the liver parenchyma area in 91.57% of cases (n = 1641 images correctly selected out of 1792. We observed significant differences between the values of all elements studied histograms and thus distinguish between each type of pathology and the time of the contrast. The late phase helped to identify a significant percentage correct increased hemangiomas, without wash-out phenomenon (87.5% correct classification, peak for this type of formations). We obtained an accuracy of 85.7%, with a sensitivity of 90.6%, specificity 70%, positive predictive value 90.6% and negative predictive value of 70%. It can be seen that maximum accuracy is achieved for hipovascularizate liver metastases (100%), followed by accuracy for hepatocarcinom (85.7%), hepatic hemangiomas (70%) and finally well vascularized metastases (66.6%).

**Testing neural networks in HCC diagnosis. Classification and prognosis of focal liver lesions**

We trained neural networks in parallel two worked together to achieve a final result as accurate. The first network received only clinical and laboratory data of patients, thus obtaining a distribution of tumors according to malignancy. The second neural network processed according to the parameters resulting from
imaging with contrast agent. Diagnosis of benign simple network attribute if the cumulative score weights lies closer to the value 0 and the diagnosis of malignancy when the values are around 1. Since the cumulative scores for each diagnosis varies between 0 and 100% probability for a diagnosis, values between 0 and 0.49 are interpreted as benign, while scores above 0.50 to 1.50 are interpreted as malignant. Complex network showed superior performance of simple, properly classifying a total of 109 cases of 112, compared with 103 positive ratings for the network simple. For all three cases the network has offered a degree of safety but dropped below 80%. However, the simple network shown very good reliability, with a sensitivity of over 93% of malignant tumors in evidence, also with a specificity of almost 90%.
CONCLUSIONS

• The introduction of fractal analysis, fractal dimension to measure, is a new method to quantify histological markers of tissue samples taken from malignant liver tumors. Its use in the context of differentiation of several types of malignant liver tumors is a new global offering in the future can accurately quantify the status of your tumor, and also proved useful in determining the origin of liver tumors.

• Study conducted allowed me to develop a medical expert system, able to use fractal analysis techniques to medical images to identify and quantify specific prognostic markers for corroborating clinical and laboratory data in a complex neural networks.

• These parameters (maximum intensity of contrast agent, time to achieve this value, the mean transit loading slope and area under curve) were studied in each class, and the results could be entered into the expert based on neural networks, significantly increasing its diagnostic accuracy.

• The best results were obtained in evaluating the dynamics of vascular CT stages where neural networks were able to classify a significant increased tumor formation (102 of 112 configurations correctly classified, compared with only 34 of 112 configurations for native images).

• Adding data from intensity-time curves analysis results from the analysis of records CEUS significantly increased diagnostic accuracy of the network (sensitivity and specificity significantly higher - 97.3% and 97.4%).
SELECTED REFERENCES


LIST OF PUBLICATIONS

In extenso publications in ISI indexed journals with an impact factor:


In extenso publications in peer-reviewed indexed journals:

1 Vere Cristin Constantin; Streba Costin Teodor; Rogoveanu Ion; Nita-Stefanescu Liliana; Ionescu Alin Gabriel. Cirrhosis and chronic viral hepatitis as risk factors for Hepatocellular Carcinoma: Romanian single-clinic experience. Maedica. 5(4), pp 265–270, 2010

Papers published as abstracts in supplements of ISI indexed journals, presented at international conferences:


4 Streba CT, Rogoveanu I, Sandulescu LD, Mogoanta L, Comanescu M,

Papers published as abstracts in supplements of ISI indexed journals, presented at national conferences:

1 Streba CT, Vere CC, Niță-Ștefănescu Liliana, Salan E, Ionescu AG, Țapu F. Epidemiology and risk factors of the hepatocellular carcinoma associated with cirrhosis or viral hepatitis: a retrospective study in a single Romanian clinic. Volum rezumate: A II-a Sesiune de comunicări științifice „Victor Babeș” 3-4 iunie, București. Pag. 41-42. 2010


5 Costin Teodor Streba, Ion Rogoveanu, Cristin Constantin Vere, Daniel Pirici, Cristina Baloseanu. Correlations between fractal dimension of vascular axel disposition and dimension in immunostained images of hepatocellular carcinoma and various liver metastasis. Journal of Gastrointestinal and Liver Disease, vol. 29, Suppl. 1: p 149, 2010

Patent claim resulting from the Ph D research:

CURRICULUM VITAE

Personal information

First name(s) / Surname(s) St. Streba Costin Teodor
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E-mail(s) costinstreba@gmail.com
Nationality Romanian
Date of birth 26 March 1983
Gender Male

Work experience

Dates 01 October 2008 – 30 September 2011
Occupation or position held Ph D Student
Main activities and responsibilities Research activities in the field of hepatocellular carcinoma diagnostic and curative procedures. Histological image analysis. Experience in interpreting Contrast-Enhanced Ultrasonography movies. Biostatistics and epidemiology-related tasks, with a focus on hepatocarcinoma.
Name and address of employer University of Medicine and Pharmacy of Craiova St. Petru Rares No. 2, 200349 Craiova (Romania)
Type of business or sector Education

Dates 01 January 2009 → Present
Occupation or position held Resident physician
Main activities and responsibilities Patient care. Diagnosis and treatment in the field of Internal Medicine, Gastroenterology, Pneumology and Cardiology.
Name and address of employer County Emergency Hospital of Craiova St. Tabaci No. 1, 200642 Craiova (Romania)
Type of business or sector Medical

Education and training

Dates 01 October 2008 – 30 September 2011
Title of qualification awarded Ph D Degree
Principal subjects / occupational skills covered Devising and applying novel computer-based image manipulation techniques for the quantification of histological elements. Devising medical-oriented database systems for patient information registration. Interpretation and computer-aided quantification of contrast enhanced ultrasonography
recordings of hepatocellular carcinomas, liver metastasis, haemangiomas and focal steatosis.

Devising a novel, computer-based medical expert system for diagnosis and classification of focal liver masses by using neural networks and logic algorithms (patent pending).

<table>
<thead>
<tr>
<th>Name and type of organisation providing education and training</th>
<th>Dates</th>
<th>Title of qualification awarded</th>
<th>Principal subjects / occupational skills covered</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Medicine and Pharmacy of Craiova (Medical University)</td>
<td>01 October 2002 – 15 September 2008</td>
<td>Doctor Medic</td>
<td>Training in fundamental research techniques. Training in diagnostic techniques and methods. Training in patient care and treatment modalities for general medicine. Gained extensive theoretical and practical knowledge in the field of general medicine.</td>
</tr>
<tr>
<td>&quot;Charles the 1st&quot; National College (College)</td>
<td>15 September 1998 – 17 July 2002</td>
<td>Bachelor Degree</td>
<td>General subjects and basic general occupational skills.</td>
</tr>
</tbody>
</table>
providing education and training

Personal skills and competences

**Mother tongue(s)**
- Romanian

**Other language(s)**
- English: Proficient user
- French: Independent user
- Italian: Proficient user

**Self-assessment**
- **Understanding**: Proficient user
- **Speaking**: Proficient user
- **Writing**: Proficient user

**Social skills and competences**
- Team spirit gained through over 12 years of working in various settings, during student and professional exchanges and internships.
- Good ability to adapt to multicultural environments, gained through six years as voluntary in an international student's association.
- Good communication skills gained through multiple local, national and trans-national collaborations and meetings.
- Good social adaptability gained through multiple internships and bursaries abroad.

**Organisational skills and competences**
- Good experience in project management (six years of voluntary work in regional, national and international student associations, coordinator of an international project while member of the International Federation of Student Medical Associations - IFMSA).
- Good experience in team management, as President and Vice-President of the "Medical Student Society of Craiova" (2004-2005), censor of said organization (2007-2008) and Censor of the IFMSA-Romania branch (2007-2008).
- Good sense of organization, as secretary of the "Medical Student Society of Craiova" (2005-2006).
- Experienced in organizing medium and large scale events (President of the Organization Committee of the "7th International Medical Student Conference of Craiova, 2006"; member of the Organizing Committee of the International Medical Student Conference of Craiova for in 2003, 2004, 2005, 2007 and 2008; member of the Organizing Committee of the "Morphology and Light Microscopy Conference in Craiova (2010 and 2011).

**Technical skills and competences**
- Experience in operating various types of Nikon microscopes gained through various courses and international bursaries.
- Experience in operating the Leica confocal microscope (three months bursary in the Klinik für Neurologie, Ernst-Moritz-Arndt-Universität Greifswald, Germany).
- Experience in immunohistochemistry and immunofluorescence techniques and laboratory apparatus (three years' experience in the Histology laboratory, University of Medicine and Pharmacy of Craiova, Romania).
- Experience in using polymerise-chain-reaction (PCR) techniques (one month internship, Department of Molecular Biology and Genetics, University of Lund, Sweden).
- Experience in interpreting videocapsule endoscopy results (two years involved as collaborator in the national research grant "Comparison between video capsule endoscopy and push-and-pull enteroscopy in patients with small bowel pathology".
- Experience in analyzing native abdominal Ultrasonography and liver-specific Contrast Enhanced UltraSonography recordings (gained through my Ph D related studies).
Experience in general clinical patient management, gained through my medical residency.

**Computer skills and competences**
- Good command of image and sequence analysis, with special focus on histology and medical imaging (ImageJ, Image Pro Plus, Amira, Leica and Nikon microscopy suites).
- Computer-aided fractal analysis of medical images.
- Basic programming skills and Neural networks implementation for medical usage (MatLab).
- Good command of advanced editorial and image manipulation techniques (Microsoft Office, Adobe Creative Suite, Corel applications etc).
- Good knowledge of web design and site creation and administration (creator and former administrator of www.ssmc.ro, website of the "Medical Student Society of Craiova"; co-creator and current administrator of www.rjme.ro - official site of the Romanian Journal of Morphology and Embryology; creator and current administrator of www.srm-ro.ro, site of the "Romanian Association of Morphology").

**Artistic skills and competences**
- Drawing and painting as leisure activities (charcoal and water-based painting).
- Amateur photographer.

**Other skills and competences**
- Chess (B-level grade competitive title. 2nd place in team events 1997).
- Basketball (semi-professional competitive play during college).
- Two years of voluntary work during college years in student oriented organizations.
- Six years of voluntary work in local, national and international Medical Students Organizations (attended in over 20 annual projects and events).

**Driving licence(s)**
- B

**Additional information**

**Publications**

Ph. D. Thesis:
Integrative diagnosis and prediction on the evolution of focal liver lesions.

**Articles published in ISI journals as first author:**


*=equal shared contribution and/or corresponding author.
Articles published in ISI journals as co-author:


Articles published as first author in peer-reviewed indexed journals:


* = corresponding author.

Abstracts published in ISI indexed supplements as first author:

2. C.T. Streba, D. Pirici, L. Mogoanta, M. Comanescu, I. Rogoveanu, L. Sandulescu, A. Bold; Fractal Analysis Differentiation Of Nuclear And Vascular Patterns In Hepatocellular
Carcinomas And Hepatic Metastasis. J of Hepatol, Suppl. 1 (52), 2010: S351.


Abstracts published in ISI indexed supplements as co-author:


Book chapters in international publishing houses, indexed by worldcat.com:


Book chapters in national publishing houses, indexed by CNCSIS:


Courses and diplomas

1999: Certificate in Advanced English Cambridge: maximum qualification obtained (A/A)
2004: One month IFMSA internship in Molecular Genetics, University of Lund, Sweden, under the supervision of Prof. Lo Persson.
2005: One month IFMSA Clinical internship at the County Hospital of Coimbra, Portugal.
2006-2008: Training course organized by the Department of Teacher Training in UMF Craiova.
2004-2006: Completed all three levels of Advanced Project Management training courses organized by the International Federation of Medical Students' Organizations (IFMSA).
2008-2011: Ph. D. Student in Internal Medicine at the University of Medicine and Pharmacy of Craiova, Romania. Beneficiary of a POS-DRU bursary.
2008-2010: Master in Management of Health Medical Units, University of Medicine and Pharmacy of Craiova. Successful defense of thesis in July 2010 (maximum qualification obtained, 10/10).
2010: Special Prize awarded by Roche during the 30th Gastroenterology and Hepatology Congress Craiova, Romania, for the abstract “Differentiation between normal hepatic parenchyma, hepatocellular carcinoma and metastasis, on histological images, using image fractal analysis”.
2010: Invited observer at the Program for the Advancement of Therapy in Hepatocellular
Carcinoma (PATH). Bologna Liver Oncology Group 22-24th November 2010, Bologna, Italy.

2011: Three months bursary internship in the Department of Neurology, Brain Aging and Repair, under the supervision of Prof. Aurel Popa-Wagner, Ph. D. Acquired extensive knowledge of confocal laser microscopy, various immunohistochemistry techniques including immunofluorescence, dissection and handling of ice-embedded tissue.

Grants and Research contracts obtained through competition:


1. 2007-2010, grant participant, Ministry of Education and Research, (PNCD II Programme), Comparison between video capsule endoscopy and push-and-pull enteroscopy in patients with small bowel pathology (ENTERODIAG), multicentric grant with 3 participants, total amount 2.000.000 RON (= 570.000 EURO).

Patents


Membership of professional organizations:

2009-Present: Member of the European Association for the Study of the Liver (EASL).
2008-Present: Member of the Romanian Society of Histology and Morphology
2008-Present: Honorary member of the "Medical students' organization of Craiova"
2002-2008: Member of the "Medical students' organization of Craiova"
2002-2008: Member of the "International Federation of Medical Students' Associations - Romanian branch"