Is identification of malignant lesions of the liver and of hemangiomas possible by Doppler ultrasonography and radionuclide angiography?

Mirjana Stojković MD, PhD,
Milica Stojković MD,
Vera Artiko MD, PhD,
Marinko Žuvela MD, PhD,
Nebojša Lekić MD MSc,
Milorad Petrović MD PhD,
Andrija Antić MD PhD,
Mirko Kerkez MD PhD,
Dragana Šobić MD PhD,
Vladimir Obradović MD PhD

Clinical Center of Serbia, Belgrade University School of Medicine, Višegradska 26, 11 000 Belgrade, Serbia

***

Keywords: Color Doppler ultrasonography
- Radionuclide angiography
- Liver tumors
- Hepatic perfusion index
- Arterial hepatic inflow

Correspondence address:
Vera Artiko MD, PhD,
Center for Nuclear Medicine,
Clinical Center of Serbia,
Visegradska 26,
11 000 Belgrade, Serbia.
Tel: + 381 11 3540891
Fax: + 381 11 3540891
E-mail: veraart@beotel.rs;
vartiko@sbb.rs

Received:
21 December 2010
Accepted revised:
28 February 2011

Abstract

The aim of this study was to try to diagnose malignant liver lesions and hemangiomas by means of vascularisation and perfusion studies. The *study was performed* in 32 patients with hepatocellular carcinoma (HCC), in 74 with metastatic liver carcinoma (MLC) and in 40 with hemangiomas (H). Color Doppler ultrasonography (DUS) was done with an ATL Ultramark 9 apparatus with convex probe 2.5 MHz using pulse and DUS. Hepatic radionuclide angiography (HRA) was performed with bolus injection of 740MBq ^{99m}Tc-pertechnetate, (1min, 1f/s), using ROTA scintillation camera and MicroDelta computer. Hepatic perfusion index (HPI) indicated the percentage of the portal blood inflow to the liver. *Our results showed that* in HCC and MLC there was a decrease of portal inflow while arterial inflow was increased resulting in pulse arterial wave velocity increase and in continuous venous waves velocity in the tumors. There was significant linear correlation between the increase of the arterial inflow and the arterial pulse wave found in the center and in the margin of the tumors. In hemangiomas, hepatic perfusion index related to arterial inflow was within normal range. *In conclusion*, our results suggest that HCC and MLC have specific characteristics in vascular and/or perfusion studies while hemangiomas show normal liver parenchyma findings.

Hell J Nucl Med 2011; 14(1): 38-42 *Published on line: 26 March 2011*

Introduction

The liver can be affected by both benign and malignant tumors. The benign ones are usually of no clinical importance. Malignant tumors of the liver, on the contrary need immediate and intensive management. Correct diagnosis is of essential clinical importance. Malignant tumors resection is limited to tumors of 5cm diameter with no invasion of the blood vessels and provided that the remaining portion of the liver is sufficient not to induce liver failure. Even in the most appropriately selected patients, about 10% are expected to develop liver failure after surgery. Pulsed and color Doppler ultrasonography (DUS) may be useful in the differential diagnosis of focal liver lesions. Hepatic parenchyma normally shows no DUS signals other than small signals corresponding to the hepatic artery, portal and hepatic veins [1-3]. The aim of this study was the assessment of vascularization by DUS [4] and of perfusion by hepatic radionuclide angiogram (HRA) [5], in focal lesions due to hepatocellular carcinoma (HCC) to liver metastases(MLC) and to liver hemangiomas, in order to support their diagnoses.

Patients and methods

Patients were divided into three groups: HCC (n=32), MLC (n=74) and hemangiomas (H) (n=40). In the HCC group, there were 18 males and 14 females of mean age 49 years (range 30-68 years), in the MLC group there were 38 males and 36 females, mean age 46 years (29-62 years), while in H group there were 20 males and 22 females, mean age 46 years (27-65 years). Most of the patients (30/32 HCC, 70/74 MLC and 37/40 H) had only one lesion. In the patients with multiple lesions, one most approachable lesion was studied. Informed consent was obtained from each patient, and the study protocol was approved by the Hospital Ethics Committee.

All patients, as described below, underwent US, Color DUS, radiocolloid scintigraphy, hepatic radionuclide angiography (HRA) and blood pool scintigraphy. All patients with HCC and LC were histologically diagnosed after laparoscopy and biopsy. Hemangiomas were diagnosed by blood pool scintigraphy, CT, MRI and clinical follow up. Additional tests

like contrast CT, MRI, and selective angiography were also performed in doubtful HCC cases and final diagnosis was proved by biopsy.

All patients were tested for sedimentation rate, hemoglobin, hematocrit, white blood cells count, fibrinogen, C-reactive protein, serum iron, serum sodium and potassium, serum albumin (reference range 3.5 to 5.0g/dL), alkaline phosphatase (30-120IU/L), gamma glutamyl transpeptidase (0-42IU/L), aspartate aminotransferase (10-40IU/L), alanine aminotransferase (9-60IU/L), bilirubin (total 0.2-1.2mg/dL and direct 0-0.3mg/dL), and tumor markers like alpha fetoprotein (<10 μg/L), carcinoembryonic antigen (<2.5ng/mL) and carbohydrate antigen 19-9 (<40U/mL) in order to evaluate their liver function, their hemostatic condition and any other latent disease.

Doppler US were performed by the ATL Ultramark 9 apparatus (USA) with convex probe 2.5MHz using pulse and color Doppler. Examination of vascularisation involved the measurement of blood flow in the center of each lesion, as well as in the periphery especially in a of 8-10cm of scanning per square centimeter counting and registering specific characteristics performed by the detection of DUS signal on a certain depth of scanning per square centimeter. Two types of spectral curved lines were analyzed according to their velocities (cm/s): pulse-arterial wave (PW) and continuous-venous wave (CW). Cross sectional area of the portal vein in cm, volume of blood flow through portal vein in mL/min and number of blood vessels per cm of tumor zone were estimated.

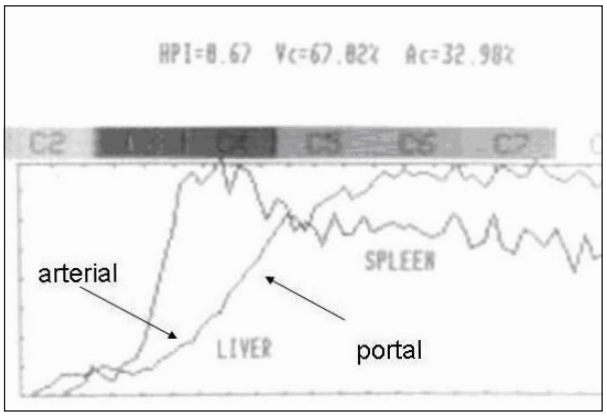
For all radionuclide investigations, ROTA scintillation camera and MicroDelta computer (Siemens, Germany) were used. Radiocolloid scintigraphy was performed 30min after the intravenous injection of 150MBq ^{99m}Tc-$SnCl_2$ in the anterior, posterior and two lateral positions with matrix size 128x128 pixels and 500000imp/view. Immediately before blood pool scintigraphy, hepatic radionuclide angiography (HRA) was estimated after bolus injection of 740MBq ^{99m}Tc-pertechnetate (^{99m}Tc-P), (1min, 1frame/sec). Regions of interest (ROI) encountered the whole liver parenchyma. The arterial-hepatic and portal-venous phase of the HRA, were separated at the moment when maximal activity over the left kidney ROI was registered [5]. The arterial (Ba) slope of the liver time activity (TA) curve was determined from the time of the first activity in the liver ROI till the next 7sec. Portal (Bp) slope was determined from the liver TA curve from the time of maximal activity in the left kidney ROI was determined till the next 7sec. Hepatic perfusion index (HPI) was calculated according to Sarper's method [HPI=Bp/(Ba+Bp)], [5, 6]. Thus, HPI reflected the value of the relative portal contribution to liver blood flow. Blood pool scintigraphy was performed from 20min to 180min after the injection of 740MBq ^{99m}Tc-P and 15min after the intravenous application of Sn-pyrophosphate, in the above four positions 1000,000 impulses/view. Blood pool single photon emission tomography (SPET) was performed in every patient (at 360° with 6 degrees/view, in step and shoot manner). Reconstruction was done using filtered back projection using Butterworth filter order 6.

Statistical analysis, besides the mean values (M) and standard deviation (SD) included Student's test, Wilcoxon's, Kruskal-Wallis and χ^2 tests.

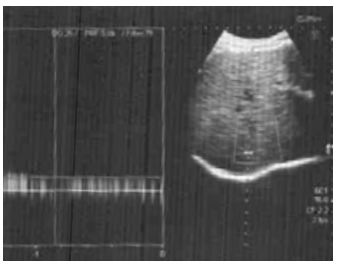
Results

The lesions were classified according to their color flow patterns into two main categories: lesions with internal vascularity (n=106, 72.6%) and lesions without internal vascularity (n=40, 27.4%).

Arterial PW (cm/s) estimated in the center and the periphery of HCC and MLC are shown in Figure 1 and Table 1.



A.



B.

Figure 1. A: Color Doppler ultrasonography: normal liver parenchyma. Normal liver blood flow, continuous, low speed (12cm/s). **B**: Hepatic radionuclide angiography: hepatic perfusion index in a normal liver parenchyma is within normal range (HPI=0.67).

Table 1. Pulse and continuous waves in focal lesions and hepatic perfusion index in liver parenchyma

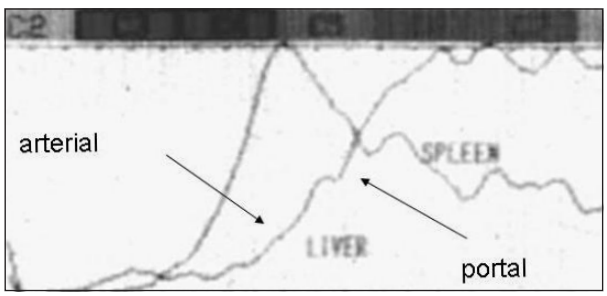
Diagnosis	No. of patients	Pulse wave velocity in the center (cm/s)	Pulse wave velocuty at the margin (cm/s)	Continuous wave velocity in the center (cm/s)	Continuous wave velocity at the margin (cm/s)	Hepatic perfusion index in liver parenchyma
Hepatocellular carcinomas	32	82±24	87±24	65±30	49±20	0.26±0.20
Metastatic liver carcinomas	74	38±18	47±29	28±12	31±13	0.34±0.26
Hemangiomas	40	Not detected	Not detected	Not detected	Not detected	0.64±0.15

Hepatic perfusion index between MCC-LM and between H/normal were not different

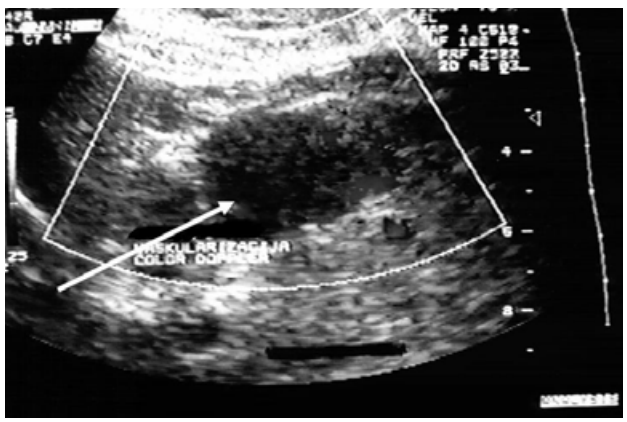
Table 2. Pulse and continuous waves in focal lesions and hepatic perfusion index in liver parenchyma

No. of patients	Dg	No. of leasions		Radiocolloid scintigraphy		Blood pool scintigraphy			
		solitary	multiple	photopenic	isoactive	photopenic	isoactive	hyper vascularized	hot
32	HCC	30	2	32	0	0	14	18	0
74	MLC	66	8	74	0	66	8	0	0
40	H	37	3	40	0	0	0	0	40

HCC-hepatocellular carcinoma; MLC-metastatic liver carcinoma; H-hemangioma



A.



B.

Figure 2. A: Color Doppler ultrasonography: liver hemangioma, with vascularisation on the periphery. Flow is not registered. **B:** Hepatic radionuclide angiography: hepatic perfusion index in a patient with hemangioma is within normal range (HPI=0.64).

Continuous waves (cm/s) in the center and the periphery of the HCC and MLC are shown in Figure 2 and Table 2.

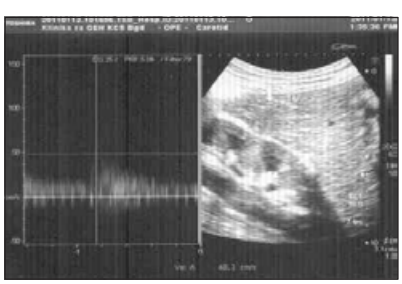
In 98% of H patients we did not detect internal vascularity (Fig. 2). Continuous waves and PW were registered in H and in the necrotic tumor centers of HCC and of MLC lesions (Table 1).

In HCC and MLC cross sectional area (CSA) of the portal vein was increased (1.45±0.39cm, 1.41±0.36cm) while blood flow velocity was decreased (11±2.9cm/s and 13±4.3cm/s).

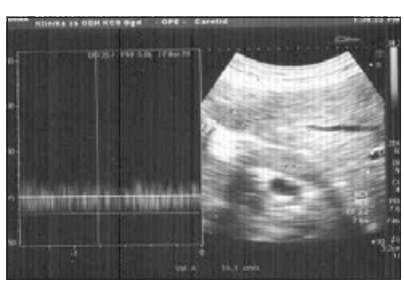
The volume of blood flow through portal vein ranged from 800-1200mL/min in HCC and 900-1250mL/min in MLC while in H lesions was about normal (800±290mL/min).

In tumor lesions larger than 5cm the DUS targets per cm^2 in the center of HCC and MLC were 1-4 and 1-2, while at the periphery were 1-6 and 1-4, respectively. The characteristics of tumor lesions on radiocolloid and blood pool scintigraphy are shown in Table 2. Hepatic perfusion index was decreased in both HCC and MLC 0.26±0.20 and 0.34±0.26, respectively. In both groups the values of HPI were significantly decreased ($P<0.05$) in comparison to those in the patients with H (0.64±0.15). Values of HPI in H did not differ from physiological liver tissue values (0.68±0.06)[14] ($P>0.05$), while values between HCC and MLC differed ($P<0.05$).

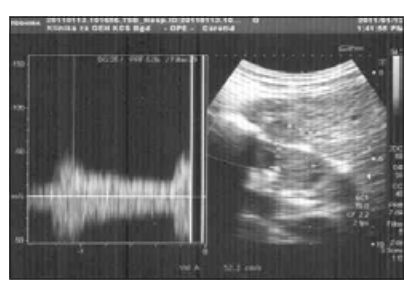
There was a significant linear correlation between the increase of the Ba inflow estimated by HRA and the PW velocity found in the center and in the periphery ($p<0.01$) of HCC and MLC lesions ($P< 0.01$) (Fig. 3 and 4, Table 1).



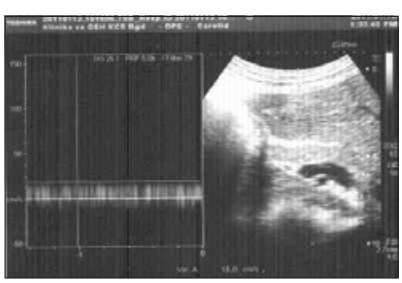
A.



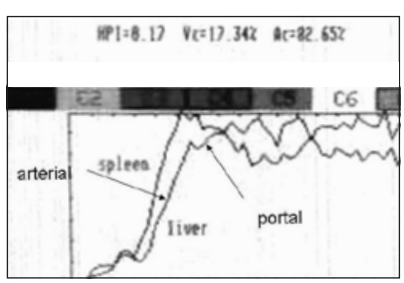
B.



C.

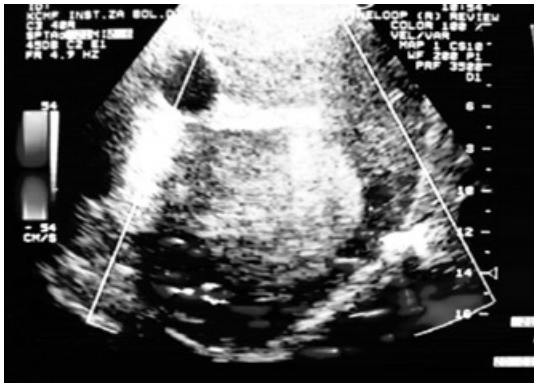


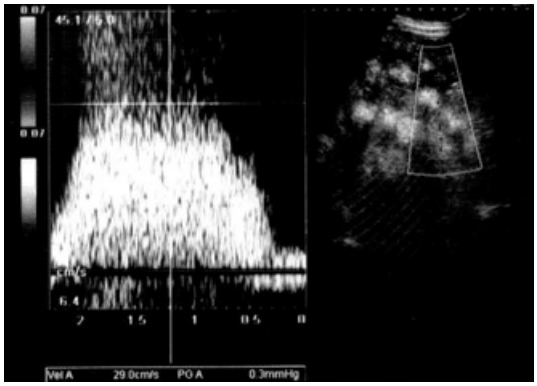
D.

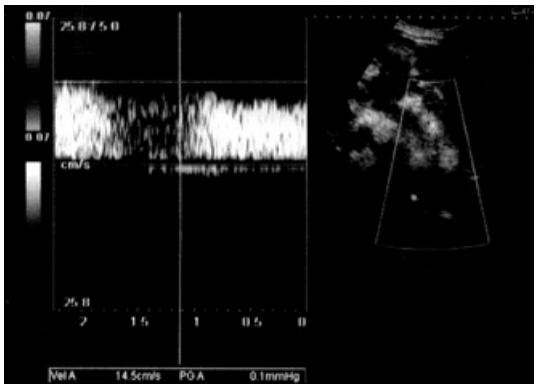


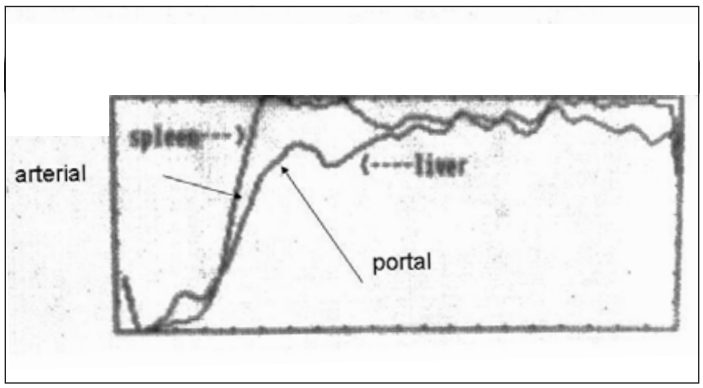
E.

Figure 3. Color Doppler ultrasonography: hepatocellular carcinoma, with vascularisation in the centre and periphery. **A:** Pulse flow velocity 48cm/s is registered on the periphery. **B:** Continuous flow velocity 19cm/s is also registered on the periphery. **C:** Pulse flow velocity 48cm/s is registered in the center. **D:** Continuous flow velocity 18cm/s is also registered in the center. **E+:** Hepatic radionuclide angiography: highly decreased hepatic perfusion index (HPI=0.17), in a patient with hepatocellular carcinoma.


A.


B.


A.



A.

Figure 4. A: Color Doppler ultrasonography: colon carcinoma, with vascularisation on the periphery. **B:** Pulse flow velocity 29cm/s is registered on the periphery. **C:** Continuous flow velocity 14.5cm/s is also registered on the periphery. **D:** Hepatic radionuclide angiography: highly decreased hepatic perfusion index (HPI=0.05), in a patient with metastases from colon carcinoma.

Discussion

According to our results, using above mentioned characteristics of DUS signal, as well as of the parameters obtined by HRA, it is possible to diagnose HCC and MLC but not H lesions. Many others have found results similar to ours [7-9].

Some investigators have found a basket pattern (a fine blood-flow network surrounding the tumor nodule) mainly in HCC, as well as an indication of vessels within liver tumor. In patients with multiple MLC, a "detour" pattern i.e. a dilated portal vein around the tumor nodules was found , while in H, a "spot" pattern i.e. color-stained dots or patches in the central region of the tumor was seen [10, 11]. We were unable to describe these findings in H.

Others, recommend DUS [12] for the early detection of occult liver metastases. By studying pulsatile and countinious flows they found differences between well-differentiated and moderately or poorly differentiated HCC [13], an increase of the Ba and diminished Bp of hepatic blood flow assessed on the liver TA curve. Similar to our results, others found in MLC enhanced Ba flow at the rim of the tumor, in HCC throughout the tumor and in H lesions no signal enhancement [14, 15]. Results by using HPI were also similar [16-23].

In a previous paper we showed that HRA can also early diagnose the hepatic lesions of Hodgkin's lymphoma [24]. Rarely, HRA can be false positive, as reported by others in two cases of actinomycosis, in which hypervascular hepatic masses were observed in the arterial phase [25].

Others have shown high HRA sensitivity, even for very small focal liver lesions for both HCC, MLC and H (80%-96%) with low specificity (50%-70%) due to diffuse liver disease or portal system disfunction [16, 17, 20, 26]. Others describe a specifity of 91% [27] for the same lesions. Assessment of specificity vary between researchers from 50%-70% [15, 17, 20, 26] even to 92% [27], while sensitivity is mainly very high (80%-96%) [17, 20]. This may be due to the different methodology performed like the choice of the radiopharmaceutical, the method for the estimation of the onset of the portal phase of the liver curve, the method of calculation and also to the the size of the lesion, the position of the patient during dynamic imaging and the presence of diffuse liver disease [5-6, 15-24].

Others have recently estimated differential arterial and portal contribution to liver lesions, by PET radiopharmaceuticals [28]. Both the HRA and US methods for liver perfusion estimation have not yet found wide acceptance, partly because they are time consuming, not available in every hospital and because of difficulties in reproducibility [29].

In conclusion, according to our study by DUS and HRA, the HCC and MLC lesions can well be diagnosed while characteristics of hemangiomas are not different from those of normal liver parenchyma.

Supported by grant(M 175 018) of the Republic of Science of Serbia
The paper was translated by Miloš and Jelena Petrović.
The authors declare that they have no conflicts of interest

Bibliography

1. Grgurević I, Boozari B, Kujundzić M et al. Color Doppler ultrasound of the liver circulation. *Lijec Vjesn* 2009; 131: 211-7.
2. Giorgio A, Di Sarno A, de Stefano G et al. Hepatocellular carcinoma with cirrhosis: are patients with neoplastic main portal vein invasion eligible for percutaneous radiofrequency abla-

tion of both the nodule and the portal venous tumor thrombus? *AJR Am J Roentgenol* 2009; 193: 948-54.
3. Luo W, Zhou X, Zheng X et al. Role of sonography for implantation and sequential evaluation of a VX2 rabbit liver tumor model. *J Ultrasound Med* 2010; 29: 51-60.
4. Tanaka S, Kitamura T, Fujita M et al. Color doppler flow imaging of liver tumors. *AJR* 1990; 154: 509-14.
5. Sarper R, Faraj BA, Tarcan YA et al. Assessment of splanchnic blood flow in alcohol and drug abuse using radionuclide angiography. *J Subst Abuse* 1993; 5: 295-303.
6. Sarper R, Fajman WA, Rypins EB et al. A noninvasie method for measuring portal venous/total hepatic blood flow by hepatosplenic radionuclide angiography. *Radiology* 1981; 141: 179-84.
7. Kudo M, Tochio H, Zhou P. Differentiation of Hepatic Tumors by Color Doppler Imaging: Role of the Maximum Velocity and the Pulsatility Index of the Intratumoral Blood Flow Signal. *Intervirology* 2004; 47: 154-61.
8. Tanaka S, Kitamura T, Fujita M et al. Color Doppler flow imaging of liver tumors. *American Journal of Roentgenology* 2004;154: 509-14.
9. Numata K, Tanaka K, Kiba T et al. Use of hepatic tumor index on color Doppler sonography for differentiating large hepatic tumors. *AJR Am J Roentgenol* 1997; 4: 991-5.
10. Choi BI, Kim TK, Han JK et al. Vascularity of hepatocellular carcinoma: assessment with contrast-enhanced second-harmonic versus conventional power Doppler US. *Radiology* 2000; 200: 55-8.
11. Ren XL, Yan RL, Yu XH et al. Biliary cystadenocarcinoma diagnosed with real-time contrast-enhanced ultrasonography: report of a case with diagnostic features. *World J Gastroenterol* 2010; 16: 131-5.
12. Makuuchi M, Abe H. Mini-mesohepatectomy for colorectal metastasis invading the middle hepatic vein at the hepatocaval confluence: educational video demonstrating IOUS use in modern hepatic surgery. *Ann Surg Oncol* 2010; 17: 356-7.
13. Kumada T, Nakano S, Toyoda H et al. Assessment of tumor hemodynamics in small hepatocellular carcinoma: comparison of Doppler ultrasonography, angiography-assisted computed tomography, and pathological findings. *Liver Int* 2004; 24: 425-31.
14. Ernst H, Hahn EG, Balzer T et al. Color Doppler ultrasound of liver lesions: Signal enhancement after intravenous injection of the ultrasound contrast agent Levovist. *Journal of Clinical Ultrasound* 2002; 1: 31-5.
15. Strobel D, Raeker S, Martus P et al. Phase inversion harmonic imaging versus contrast-enhanced power Doppler sonography for the characterization of focal liver lesions. *Int J Colorectal Dis* 2003; 26: 63-72 .
16. Petrović N, Artiko V, Obradović V et al. Study of blood flow in liver hemangiomas using radionuclide angiography. *Acta Chir Iugosl* 2001; 48: 25-9.
17. Dragoteanu M, Cotul SO, Pîgleşan C et al. Liver angioscintigraphy: clinical applications. *Rom J Gastroenterol* 2004;13: 55-63.
18. Dragoteanu M, Cotul SO, Tamas S et al. Nuclear medicine dynamic investigations of diffuse chronic liver diseases and portal hypertension. *Rom J Gastroenterol* 2004; 4: 351-7.
19. Dragoteanu M, Balea IA, Dina LA et al. Staging of portal hypertension and portosystemic shunts using dynamic nuclear medicine investigations. *World J Gastroenterol* 2008; 24: 3841-8.
20. Muroff LR, Freedman GS. Radionuclide angiography. *Semin Nucl Med* 1976; 121: 217-30.
21. Volkov AA, Granov AM, Iakovleva LA et al. Comprehensive radionuclide method of studying focal liver lesions. *Med Radiol (Mosk)* 1983; 28: 49-53.
22. Rudberg U, Hesser U, Udén R. Generalized increase of arterial blood flow to the liver observed at visceral radiocolloid angiography. *Acta Radiol* 1989; 30: 597-601.
23. Shiomi S, Kuroki T, Kim K et al. Diagnosis of hepatocellular carcinoma by factor analysis. *Eur J Nucl Med* 1990; 121: 601-5.
24. Stojković M, Artiko V, Radoman I et al. Color Doppler sonography and angioscintigraphy in hepatic Hodgkin's lymphoma. *World J Gastroenterol* 2009; 15: 3269-75.
25. Ueno K, Kabuto H, Haseda Y et al. Radionuclide angiography in two cases of hepatic actinomycosis. *Clin Nucl Med* 1986; 11: 44-8.
26. Ballantyne KC, Charnley RM, Perkins AC et al. Hepatic perfusion index in the diagnosis of overt metastatic colorectal cancer. *Nucl Med Commun* 1990; 1: 23-8.
27. Wraight EP, Barber RW, Ritson A. The role of liver blood flow measurement in the equivocal liver scan. *Nucl Med Commun* 1982; 3: 273-4.
28. Chen S, Feng D. Noninvasive quantification of the differential portal and arterial contribution to the liver blood supply from PET measurement using the ^{11}C- acetate kinetic model. *IEEE Trans Biomed Eng* 2004; 9: 1579-85.
29. Robinson PJA. Imaging liver metastases: current limitations and future prospects. *Brit J Radiol* 2000; 73: 234-41.