Journal of BUON **15:** 378-381, 2010

ORIGINAL ARTICLE

Ultrasonographic examination of the liver circulation in patients with liver metastasis from colorectal cancer

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Summary

Purpose: *Conventional imaging modalities are presently recommended for the detection of liver metastases. However, the presence of liver micrometastases is a major diagnostic problem. It has been known that micrometastases could be associated with changes in the liver blood flow.*

Methods: *We examined several parameters by color Doppler ultrasound to estimate hepatic artery flow in 30 patients without and 17 patients with liver metastases from colon cancer.*

Results: *Mean values of hepatic artery diameter (4.25± 0.81 mm in patients with liver metastases were not statistically different from those in patients without metastases (3.98±0.81). Patients with liver metastasis had significantly higher (p=0.007) mean values of systolic speed (61.33±30.01 cm/s) in comparison to patients without metastasis (41.38±16 cm/s).*

Conclusion: *Based on these results we suggest that color Doppler examination can be an additional quick noninvasive method in the detection of circulatory changes in the estimation of liver metastases.*

Key words: colorectal cancer, liver circulation, liver metastases, resistive index, systolic and diastolic speed, ultrasound

Introduction

Doppler ultrasonographic technique may be used for analysis of physiological and pathological changes of hepatic artery blood flow and allows noninvasive hemodynamic examination of the portal circulation [1-3]. Examination of splanchnic arteries, including the hepatic artery, provides new information on the flow in the parenchyma of abdominal organs [4]. Normal hepatic arterial flow has anterograde direction in diastole, indicating low resistance in the hepatic blood vessels. Hepatic artery predominates in liver tumor vascularization compared with portal vein. Primary liver tumors or metastatic changes lead to impairment of hepatic vascular network [5]. Vascular circulation in patients with a tumor is complex and different in comparison with the circulation in healthy people, and consists of double-origin blood vessels: one from the existing vascular net of the liver (peripheral blood vessels with small radial branches at tumor margins) and newly developed (central) vessels, which are generated as angiogenic response to tumor cell stimuli, such as peptides, cytokines and the most important among them – vascular endothelial growth factor (VEGF) [6-8]. Histological examinations have revealed that tumor blood vessels have characteristic architecture: they are primitive, with thin incomplete endothelial wall, and poor or absent muscular layer (tunica muscularis). A small number of studies [6,7] evaluates the density and distribution of blood vessels within the tumor by histological examinations, typically based on biopsy specimens. The future of better analysis of circulatory changes probably lies in the utilization and development of new techniques such as tridimensional ultrasonography. The number of blood vessels in the tumor is often, but not always, higher, and accordingly, hypervascularization is generally signifi-

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Received 20-03-2009; Accepted 15-04-2009

cant. Power color and Doppler ultrasonography have been used in many published studies on hepatic artery perfusion in liver tumors, with varying results [9,10].

Methods

This study analysed the arterial circulation of the liver in patients with colon and rectal cancer with and without liver metastasis. The study included 17 patients with metastatic changes and 30 patients without liver metastases immediately after surgery, confirmed by imaging methods and surgical exploration. The patients underwent clinical and biochemical examinations, including serum CEA determination. Diagnosis of colorectal cancer was verified by histopathological examination. Stage was determined according to Dukes' classification. The size of liver and number of metastatic changes were measured. Hepatic artery flow was measured by Toshiba Core Vision color Doppler duplex ultrasonography device, using the convex duplex 3.75 MHz ultrasound tube, at the ultrasonography department, Institute of Digestive System Diseases, Clinical Center of Serbia, Belgrade. Quantitative analysis included measurement of systolic and diastolic flow rate in the right hepatic artery because it manifests circulation changes much better than the extrahepatic trunk. Doppler indices were calculated from Doppler spectrum which enabled direct examination of vascular resistance in blood vessels, expressed also as resistive index (RI).

Statistical analysis

The obtained data were analyzed by Mann-Whitney U-test, ANOVA, and Spearman correlation test.

Results

The median age of 30 patients without metastases was similar with the median age of 17 patients with liver metastases (Table 1). Gender distribution was identical in metastatic and non metastatic patients (Table 1). Serum CEA levels were significantly higher in metastatic patients. Ultrasonography of the liver size showed (Figure 1) that the average size of the right liver lobe (longitudinal diameter) was 14.71±1.76 cm in non metastatic patients, while it was slightly bigger (15.43±2.41 cm) in metastatic patients, but without significant difference (Mann-Whitney U-test, p=0.25). Measurements of the right hepatic artery diameter demonstrated that its average diameter was

Table 1. Patient characteristics

Characteristics	*Liver metastases*	
	Without	*With*
Number of patients	30	17
Age (years)		
Median	61.88	57.81
Range	29-81	30-69
Gender (%)		
Male	45	41
Female	55	59
CEA (serum, ng/ml)*	7.98	132.69

*normal < 2.5; < 5 in smokers

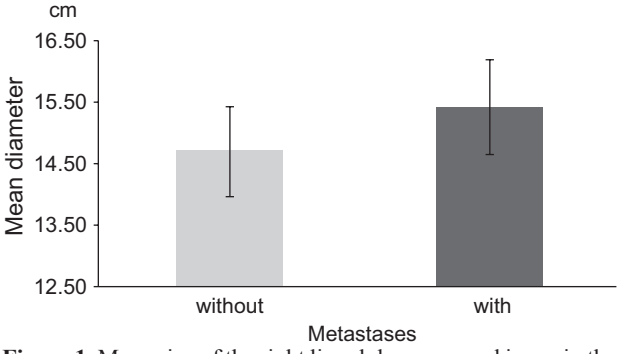

Figure 1. Mean size of the right liver lobe expressed in cm in the studied groups (p=0.25).

3.98 ±0.81 mm in patients without metastases, while in metastatic patients it was a little bigger (4.25±0.92 mm), but without significant difference (Mann-Whitney U-test, p=0.30; Figure 2). The most important analyses in this study were based on measurements of hepatic blood flow rate. In the group of patients without metastases, the mean systolic rate in the right hepatic artery was 41.38±16.82 cm/sec, and the mean diastolic rate 13.36±9.41 cm/sec. In patients with metastases, the mean systolic rate in the right hepatic artery was 61.33±32.01 cm/sec, and the mean diastolic rate 18.10±9.77 cm/sec (p=0.007 for systolic and p=0.05 for diastolic speed; Figure 3).

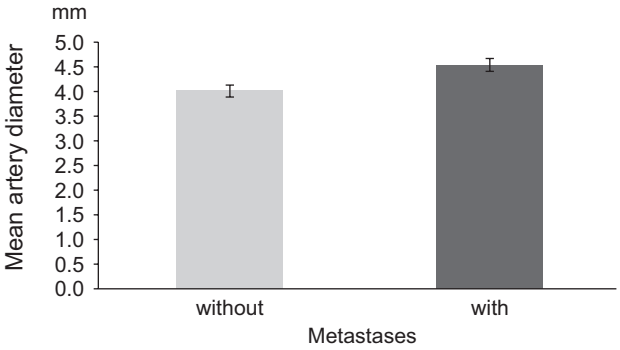

Figure 2. Mean diameter of the hepatic artery expressed in mm in the studied groups (p=0.30).

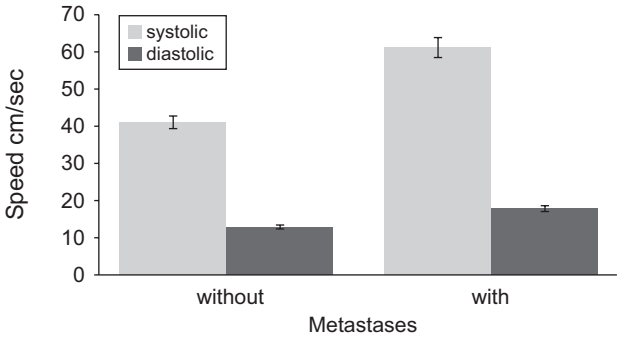

Figure 3. Mean blood flow rates in hepatic artery (cm/sec), measured by Doppler ultrasonography in the studied groups (p=0.007 for systolic and p=0.05 for diastolic speed).

Discussion

The objective of our study was to analyse the hepatic circulation through specific hemodynamic parameter determination (flow rate of the right hepatic artery). The predominant part of our investigation was focused on Doppler analysis of hepatic artery flow in two groups of patients, with and without liver metastases.

Since the second half of 1980s, a large number of studies on Doppler examination of blood flow in primary liver tumors or metastases has been published, frequently with varied results, probably due to the use of different equipment. New generation of ultrasound devices have provided more accurate data and better flow signals, which generally may present very low flow rate, originating from poorly vascularized parts of the liver tissue. Doppler indices are calculated from Doppler spectrum and allow indirect analysis of vascular resistance in blood vessels having pulsatile flow. Hepatic arterial RI varies (0.55-0.81) in fasting subjects, and increases with aging. RI is regularly decreased in distal arterial branches. Recent studies have shown that Doppler indices are altered in liver diseases both in hepatic and splanchnic arteries [11-13]. Many authors believe that the systolic rate in the hepatic artery is the most reliable parameter of hepatic arterial perfusion [14].

In hepatic arterial stenosis the systolic rate is pretty high (>2 cm/sec) as well as poststenotic tardus-parvus wave, with fall of the RI to less than 0.55 cm/sec. Mechanisms inducing Doppler index modifications in the hepatic artery are mostly associated with liver architecture changes, but are also related to changes of dilatation or constriction of hepatic arteries. Alterations of diameter occur most probably due to the release of certain substances from tumor tissue, and some of them are inflammation mediators, i.e. cytokines and factors affecting the blood vessel tonus, among which the most significant are nitric oxide, tumor necrosis factor, interleukin-1, and VEGF. Vascular flow resistance is one of the main phenomena in the investigation of tumor hemodynamics. Blood vessels in malignant tumors have lower flow resistance (low RI) in relation to benign tumors, but there are also variations of RI and pulsative index (PI) values within the tumor itself because of different vascularization areas (present and newly-formed blood vessels).

Current visualization diagnostic methods cannot detect occult metastases to liver due to limited resolution and poor contrast [15]; however, hepatic micrometastases may be analysed via liver circulation. Both in non-visible and clearly discernible metastases, the arterial resistance is being altered with lowering of hepatic artery RI due to structural and hemodynamic changes (increased vascularization). Such a finding often indicates the presence of colorectal metastases in the liver as well, that cannot be viewed either by ultrasonography or other diagnostic methods. Some authors have investigated the value of tumor markers for colon cancer in relation with changes in circulation and found that patients in advanced disease stage and increased values of tumor markers showed increase in systolic speed along with short survival [11,13]. In primary liver tumors, the systolic blood flow rate in blood vessels is abnormally high, something that distinguishes these vessels from metastatic flow. However, arteriovenous shunts are often pathognomonic of liver tumors (anastomoses between adjacent arteries and veins, mostly at the tumor periphery), which is the anatomic basis of high diastolic rate and lower RI [16,17]. It is analogue to studies on arterial flow in tumors of other organs (ovary, breast, prostate). Only few studies have addressed this problem [18,19], and our study is the first to investigate this topic in our country.

Metastases to the liver causing changes of vascularization may originate from kidney cancer, melanoma and endocrine tumors, and extremely rapid and turbulent blood flow is characteristic for these conditions. Nevertheless, such a flow may be observed in considerable arterial stenosis as well [17].

Liver metastases are supplied by blood from the hepatic artery which has increased blood flow, with relative drop of blood flow rate in portal vein affected by humoral factors to splanchnic vascular resistance [20]. Investigations conducted in this study constituted a new approach to detecting colorectal metastases in the liver by means of duplex color Doppler technique. Significantly reduced hepatic artery RI was found in the studied patients.

Based on data obtained from the relevant literature [16-20], as well as on our own results [1-4,21], we recommend the determination of these parameters as an additional non-invasive method for early detection of metastatic changes in the liver.

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