INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most frequent carcinomas. According to the World Health Organization (WHO) it is the fifth most common carcinoma in the world, with a male to female ratio of 2 : 1 [1–5]. HCC is a neoplasm with a very poor prognosis, unless it is detected in its early stage or adequate state-of-the-art radical treatment is applied, i.e. surgical resection or radiofrequency ablation (RFA) [6, 7]. The five year survival rate among patients diagnosed with HCC is about 15% [8]. The incidence of HCC has been on a constant rise over the last decades not only in undeveloped countries but in the United States as well, which can be attributed primarily to the epidemic of hepatitis C virus [1, 2, 7]. In addition to hepatitis C virus infection, a number of other risk factors have been associated with this tumor, which develops most frequently in patients having chronic liver disease, i.e. cirrhosis [2–6]. Therefore, etiological factors of chronic liver disease overlap with the factors contrib-
uting to the development of HCC. Apart from hepatitis C and B virus, autoimmune hepatitis and alcohol consumption, the most recent data suggest an association with metabolic diseases – non-alcoholic fatty liver disease (NAFLD) and metabolic syndrome. In different parts of the world other etiological factors have been mentioned (alpha toxin, contraceptives, etc.) as well as the possibility of developing HCC from a subclass of adenoma. HCC rarely develops in a previously intact liver [2, 3, 7, 9–12].

Imaging methods have a crucial role in the diagnosis of HCC. It has become a clinical trend to use characteristic findings, most frequently computed tomography (CT)/magnetic resonance imaging (MRI), i.e. noninvasive criteria, whereas biopsy for the purpose of pathohistological verification is taken only in case of inconclusive imaging findings. Such a decision should be made by a multidisciplinary team [1–3, 6–9, 13–17].

Being non-invasive and widely available in clinical practice, ultrasound examination is the most frequently applied method in surveillance of groups at high risk for developing HCC [4, 5, 15, 18]. Screening protocols include mostly patients with chronic liver disease and cirrhosis, and they usually combine ultrasound monitoring at certain intervals (mostly from 3 to 6 months) with determination of specific biomarkers, most often alpha fetoprotein (AFP) [3, 6, 7, 9]. Generally speaking, AFP seems to be insufficiently reliable, because it is not significantly higher in all patients with HCC, and it can be slightly elevated in chronic liver diseases as well as in some other carcinomas (embryonic, gastric and lung carcinomas) [1, 6]. The American Association for the Study of Liver Diseases (AASLD) recommends ultrasound monitoring at six month intervals with or without determination of AFP [2, 4, 6].

On ultrasound, HCC presents with nodular or multinodular lesions of various size and structure, rarely as diffuse lesions. These focal lesions may have different structures, i.e. echogenicity: hypoechogenic, isoechochogenic, hyperechogenic, heterogeneous (mosaic) pattern, and they can also have a halo around the lesion, lateral acoustic shadows as well as posterior acoustic enhancement [19]. As it is well known, posterior acoustic enhancement is one of the ultrasound characteristics of cystic focal lesions, and in a certain percentage of liver hemangiomas. However, some authors have found this ultrasound phenomenon to be present in diagnosed HCC [1, 20–22].

The aim of this study was to determine the frequency of posterior acoustic enhancement which was found to be a sonographic feature in some cases of diagnosed HCC. This is even more important because the availability of ultrasound enables detection of various liver lesions, which may often imitate or resemble HCC and vice versa by their ultrasonographic characteristics. The ultrasonographic characteristics of HCC found in the presence of other abnormal lesions in the liver may considerably impede the differential diagnosis and thus hinder early detection of HCC.

**Material and Methods**

This retrospective study included 120 patients treated at the Oncology Institute of Vojvodina and MC Polyclinic “Simed” in Novi Sad during a 15-year period. These patients had a histopathologically verified HCC. The diagnosis was based on ultrasound guided biopsy or examination of material obtained by surgical resection. The study sample included 88 men and 32 women, whose mean age was 62 years (the youngest and the oldest patients were 28 and 92 years old, respectively). The majority of patients were in the sixth decade of life;

**Graph 1.** Distribution of HCC according to the tumor size

**Graph 2.** Incidence of posterior acoustic enhancement in the group of histopathologically verified nodular HCC

**Legend/Legenda:**

1 - HCC with posterior acoustic enhancement/hepatocelularnih karcinoma sa posteriornim pojačanjem zvuka;
2 - HCC without posterior acoustic enhancement/hepatocelularnih karcinom bez posteriornog pojačanja zvuka

**Abbreviations**

HCC – hepatocellular carcinoma
RFA – radiofrequency ablation
CT – computed tomography
MRI – magnetic resonance imaging
AFP – alpha fetoprotein

0 - 3 cm 3 - 5 cm 5 - 10 cm Over/preko 10 cm
however, it should be noted that female patients were in younger age groups. Histopathological findings indicated a trabecular type of HCC in 91% of cases, whereas the remaining 9% had other types (mixed trabecular-adenoid, adenoid, trabecular-tubular and solid type). Only ¼ of cases (25.5%) presented with HCC in a previously intact liver. In other cases, HCC developed from a histopathologically verified chronic liver lesion, i.e. micronodular, macronodular, mixed (micro-macronodular) cirrhosis, chronic active hepatitis, chronic persistent hepatitis, steatosis as well as hemochromatosis in one patient.

There were no data on the presence of any known etiological factor in about 26.1% of the patients, while in others there was evidence of chronic alcohol consumption, viral hepatitis, and long-term use of contraceptives, antilipemic agents or exposure to pesticides. Hepatitis B virus markers were positive in 73% of the patients (HBsAg was found in 21.8% of the patients, while others had positive Anti-HBc or Anti-HBs). Hepatitis C virus was not included in our study due to the lack of sufficient data available for the period covered by our study.

Ultrasound examinations were performed using real time machines, routinely used in the above mentioned institutions (Siemens Sonoline SL -2, Hitachi EUB-525, Toshiba SSA-770A - Apio, Toshiba Xario SSA 660A) using probes in the frequency range of 3.5 - 5 MHz. The examiners were experienced in the field of abdominal ultrasound imaging. There was no strict protocol of follow-up, whereas the follow-up interval was determined by the attending doctor-specialist. Ultrasound examinations focused on analyzing the size, location, number and echogenicity of the newly found tumor lesions, as well as the presence or absence of posterior acoustic enhancement, as areas of increased echogenicity behind the lesions.

Results

Out of the 120 histologically verified cases of HCC, ultrasound examination revealed a macroscopic nodular type of HCC (Eggel’s classification) in 110 patients, i.e. 91.6% of cases, while the rest were diffuse (infiltrative) and massive tumors. Tumor size could only be determined in the group of nodular lesions, with lesions less than 3 cm being found in 10.2% of cases, tumors ranging from 3 to 5 cm observed in 32.1%, while tumors in the range of 5 to 10 cm were detected in the highest percentage of patients (43.2%). Tumors exceeding 10 cm were found in 14.5% of cases (Graph 1). In 73 patients (60.8%), tumors developed in histologically verified cirrhotic livers, moderately differentiated tumors being considerably more frequent. The multinodular type of HCC was statistically considerably more frequent in cirrhotic livers than solitary forms of HCC. Multinodular type was found in 21.7% of all HCC cases. Posterior acoustic enhancement was observed in 47% of all nodular HCC (Graph 2), whereas this ultrasound phenomenon was statistically significantly more often seen in the group of tumors ranging from 3 to 5 cm (Figures 1 and 2). Posterior acoustic enhancement was detected in 70% of multinodular tumors, whereas this phenomenon was absent in the rest of them. In the group of tumors smaller than 3 cm, hypoechogenic solitary tumors were significantly more frequent than hyperechogenic ones. They were most often well differentiated and statistically significantly more common in women than in men. Posterior acoustic enhancement was observed only in one case in this group, that being the case of hyperecho-
genic HCC. Statistically significantly elevated values of AFP were found in 45% of cases.

Discussion

Posterior acoustic enhancement is the result of good transmission of ultrasound waves through a tumor of soft consistency, i.e. acoustic enhancement results from any lesion attenuating the sound less than the surrounding tissue. The intensity of the transmitted ultrasound beam is relatively preserved distal to the lesion.

It is not known for sure which histological substrate leads to the development of this ultrasound phenomenon, but it is assumed that a lesion with a simple structure or homogenous cell population found also in HCC, shows posterior acoustic enhancement in the cirrhotic liver. This phenomenon may result either from tissue characteristics of the lesion or cirrhosis itself.

Posterior acoustic enhancement is usually mentioned in the context of cystic lesions which attenuate sound less than any other soft tissue. This phenomenon is also found in the presence of hemangioma, and this is what we ourselves had observed during ultrasound monitoring of lesions with inconclusive CT/MRI findings until the final diagnosis was established. Maturen et al. [20] observed a typical sono-graphic image of hemangioma in 31 cases with hyperechogenic lesions with posterior acoustic enhancement which overlapped with HCC.

We observed the highest percentage (almost 50%) of posterior acoustic enhancement in the group of tumors between 3 and 5 cm and less frequently in tumors exceeding 5 cm and only once in a tumor smaller than 3 cm. Khan et al. [1] have also not found posterior acoustic enhancement in a group of tumors (which were mostly hypoechogenic) smaller than 3 cm. Maturen et al. [20] found this ultrasound phenomenon in a group of advanced, bigger HCC’s, which is in accordance with our results; however, Choi et al. [21] found the same phenomenon much more frequently in smaller tumors (smaller than 3 cm). This difference could be explained by the recognized differences in etiological factors in various regions where these studies were performed, i.e. by the presence or absence of chronic disease, with the majority of cases being underlying cirrhosis [9]. Another reason could be the fact that in various regions of the world with more advanced screening programs, HCC is detected when its dimensions are still rather small, and therefore bigger tumors seem to be less frequent.

The multinodular HCC’s, being considerably more common in the cirrhotic liver, were found in 21.7% of our cases, whereas Okuda et al. [23] found them in 19% of cases in the United States and only in 12% of cases in Japan and Africa, which suggests a possible influence of various etiological factors in development of this type of HCC. In the group of multinodular tumors, the ratio of 70% of cases with posterior acoustic enhancement versus 30% of cases without it is considered interesting, because histopathological analysis of tumor tissue in the 70% revealed that the presence of clear (lucidocellulare) cells was smaller (48%), and these cells are thought to be the cause of tumor hyperechogenicity [24, 25]. Multinodular type of HCC without detectable posterior acoustic enhancement had a considerably higher percentage (66.7%) of clear cells. These results contribute to the actuality of the dilemma whether posterior acoustic enhancement occurs as a result of the tumor structure itself or underlying cirrhosis.

In the group of tumors smaller than 3 cm (more common in women) no considerable presence of posterior acoustic enhancement was detected. In this group, there was no statistically significant presence of clear (lucidocellulare) cells. Thus, the question arises regarding the correlation between both, the appearance of the lesion itself (hypohyperechogenicity) and the occurrence of a phenomenon such as posterior acoustic enhancement related to gender. There are other various possible etiological factors, as well as the possibility that women in our region go for check-ups earlier/more often so the disease is detected at its early stage, since it is known that early HCC are usually hypoechogenic [1, 19, 21].

Since these small hypoechogenic lesions (smaller than 3 cm) did not present with posterior acoustic enhancement in our results, we came to the conclusion that posterior acoustic enhancement was associated with advanced HCC. We agree with other authors that the changes in the structure of early HCC, when the tumor is growing, may cause the appearance of this ultrasound phenomenon (neovascularization, fatty changes, fibrosis, central necrosis, content of Kupffer cells, sinusoidal dilatation, etc.) [1, 3, 7, 14, 21, 23, 26]. However, in the context of early diagnosis, this fact could diminish the importance of posterior acoustic enhancement, so this could be a limiting factor of the significance of this ultrasound phenomenon in screening, i.e. early detection of HCC. Nevertheless, findings of posterior acoustic enhancement in the detection of focal liver lesions are considered very important since HCCs of bigger dimensions are still more often detected in our population. And last but not least, it is necessary to establish standardized ultrasound examination techniques, given the possible role of the examination technique itself, i.e. the importance of the examination without spatial compounding [21].

Conclusion

Posterior acoustic enhancement may be an important finding in the ultrasound diagnosis of hepatocellular carcinoma. Its occurrence within the monitored groups at risk for the development of hepatocellular carcinoma (cirrhosis, chronic liver disease), or particularly its presence in case of interval increase of a previously observed focal lesion, may be the reason to suggest more frequent ultrasound controls, indicate computed tomography or magnetic resonance imaging, as well as tumor biopsy in case of inconclusive imaging findings.
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