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THE ROLE OF ULTRASOUND IN THE DIFFERENTIAL DIAGNOSIS OF LIVER NEOPLASMS

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Introduction Among the focal neoplasms of the liver, there are both benign and malignant tumors, the approach to the treatment of which is fundamentally different. Ultrasound examination (ultrasound) is usually one of the first and most frequently used tools in the diagnosis of liver diseases. The method is accessible, non-invasive, harmless, relatively inexpensive and allows for a real-time assessment of the liver using a combination of various ultrasound techniques. The result of this was the emergence of the term "multiparametric ultrasound". Using various imaging methods, it is possible to obtain multimodal information about the organ under study, which increases the diagnostic value of ultrasound. There are no works in the modern literature where a comprehensive analysis of the possibilities of ultrasound diagnostics in the format of multiparametric ultrasound using modern and affordable technologies in the diagnosis of solid liver neoplasms would be carried out.

The aim is to evaluate the possibilities of multiparametric ultrasound in the differential diagnosis of liver neoplasms.

Material and methods A retrospective analysis of the results of examination and treatment of 172 patients with the most common liver neoplasms (172 nodes) who were on inpatient treatment at the Research Institute - Regional Clinical Hospital No. 1 named after Prof. S.V. Ochapovsky in 2019-2021 was carried out. The final diagnosis was formed on the basis of histological examination. By gender and age, the patients were distributed as follows: 82 (47.7%) men and 90 (52.3%) women aged 25 to 86 years (Me = 62 years). According to the morphological forms, according to the biopsy data, patients were divided into groups: hemangioma – 26 (15.1%), focal nodular hyperplasia (FNG) – 22 (12.8%), hepatocellular adenoma (HCA) – 15 (8.7%), liver metastases - 51 (29.7%), hepatocellular carcinoma (HCC) – 58 (33.7%) people. After receiving prior informed consent, all patients underwent multiparametric ultrasound in the following volumes: in-mode examination, color and energy Doppler mapping, pulse-wave Doppler scanning, contrast-enhanced ultrasound (CUSI). Ultrasound devices Aixplorer (SuperSonic Imagine, France) with a 1-6 MHz convexic sensor and Acuson S2000 (Siemens, Germany) with a 2-6 MHz convexic sensor were used, having modes of operation with an ultrasonic contrast preparation (USCP). The preparation SonoVue (Bracco Suisse SA, Switzerland) was used as a contrast. Subsequently, all

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patients underwent percutaneous biopsy of liver neoplasms under ultrasound control. Statistical processing of the results was carried out using Statistica 7 application software packages. Qualitative variables were described by absolute and relative frequencies, quantitative variables were presented in the form of median, interquartile range (25-75 th percentile) and minimum/maximum values. Comparison of qualitative features was carried out using the criterion $\chi 2$. The critical level of significance when testing statistical hypotheses was assumed to be $p < 0.05$.

Results Generalized data obtained using traditional ultrasound diagnostic methods are presented. Hemangiomas Most of the hemangiomas (14; 53.8%) had clear contours and increased echogenicity (20; 76.9%). In the overwhelming majority, when using color-coded ultrasound modes, the formations were avascular. In 4 (15.4%) patients, single vessels with venous, mainly peripheral, blood flow spectrum were detected. Spectral analysis of blood flow in the intranodular vessels is difficult. FNG In B-mode FNG was characterized by average echogenicity (20; 90.9%) and inhomogeneous echostructure (20; 90.9%). When using color mapping modes of blood flow in 18 (81.8%) patients, characteristic ultrasound signs were found – the presence of a feeding vessel and radially diverging arteries in the center of the neoplasm, the so-called wheel spokes symptom. It was possible to study the spectral characteristics of blood flow in 5 (22.7%) patients. According to the results of the study of the velocity parameters of blood flow, the following indicators were obtained: the average value of the linear velocity of blood flow is 56 cm/s (41-74) (34-81), Ri = 0,48 (0,42–0,58) (0,4–0,6) (Me, 95% CI, min–max). HCA Ultrasound picture of adenomas was nonspecific. This nosological form, along with metastases and HCC, is represented by all types of echogenicity. Only in 3 (20.0%) cases, single arterial vessels were detected in the formation. Vascular pattern is represented by peri- and intranodular vessels. Spectral analysis of blood flow in the intranodular vessels is difficult. MTS Ultrasound picture of metastases obtained in the In-study mode was characterized by polymorphism. Due to the predominance of a- and hypovascularization (42; 82.4%), spectral analysis of blood flow in intra-tumor vessels is difficult. It was possible to study the spectral characteristics of blood flow in 6 (11.8%) patients. There were no significant differences in the velocity parameters of blood flow in the intracellular arteries and the surrounding parenchyma. HCC According to echographic types of neoplasms were distributed as follows: nodular form of HCC – 32 (55.2%), diffuse-nodular – 17 (29.3%), diffuse – 9 (15.5%). The dependence of tumor echogenicity on the echographic type was not revealed ($p > 0.05$). The overwhelming number of nodes – 55 (94.8%) – had an inhomogeneous echostructure. It was possible to study the spectral characteristics of blood flow in 21 (36.2%) patients. According to the results of the study of the velocity parameters of blood flow in the intracellular arteries, the following indicators were obtained: the average value of the linear velocity of blood flow is 78

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cm/s (41-92) (35-115), Ri = 0,62 (0,52–0,68) (0,5–0,72) (Me, 95% CI, min–max). All patients of the study group underwent CUZI. The time parameters of the admission of ultrasound into the tumor were studied. Indicators of the dynamics of the intake and leaching of UZCP in the focus are presented in Table 2. According to the data obtained, the wash-out phenomenon was not observed in groups of patients with FNG, hemangiomas and in 9 patients (60%) with HCA, which in turn is a distinctive feature of MTS and HCC. In order to determine the presence or absence of differences in the indicators of admission and leaching of UZCP in the focus, depending on the nosology, a comparative analysis of the values between the groups was carried out. The data obtained are presented in Table 3. When analyzing the data obtained, it is obvious that statistically significant differences in the parameter "the beginning of contrast in the focus" were revealed between the groups "FNG & hemangioma" ($p < 0.000046$), "FNG & HCA" ($p < 0.006293$), "MTS & FNG" ($p < 0.028125$), "FNG & HCC" ($p < 0.024933$), "the time of maximum accumulation of ultrasound in the focus" – "FNG & hemangioma" ($p < 0.012590$), "FNG & HCC" ($p < 0.007983$), "MTS & HCC" ($p < 0.000243$). There were no significant differences between the parameters "onset of contrast in the focus", "time of maximum accumulation of ultrasound in the focus" and "time of alignment of contrast in the focus and liver parenchyma" between the groups "MTS & hemangioma", "MTS & HCA", "HCA & hemangioma", "hemangioma & HCC". Considering that 40% of patients with adenomas had a wash-out phenomenon, as in the group with MTS, a comparative analysis was carried out between these groups. Statistically significant differences in the time of the wash-out onset were revealed: the parameters "the beginning of washout" ($p < 0.000041$) and "the time of maximum washout of the UZCP" ($p < 0.001543$). According to none of the criteria selected for comparison, there were no differences between the groups "HCA & HCC".

Discussion of ultrasound-signs of focal formations obtained using a combination of traditional ultrasound methods are extremely variable and highly specific. The sign of "contour clarity" is characteristic of hemangiomas, HCA and metastases and was recorded in 82, 100, 96% of cases, respectively. The most common (in all nosological forms), therefore, the least specific feature was the "average echogenicity of education". Almost all nosological forms were characterized by the characteristic "heterogeneous echostructure". It is known that, in addition to the signs that unite all focal neoplasms of the liver, each of the echographic types of metastases has its own specific signs [1]. In our study, characteristic ultrasound symptoms – "target" and "bull's eye" – were recorded in 9 (18%) and 7 (14%) cases, respectively. Ultrasound data obtained using Doppler techniques were not reliable enough. It was possible to conduct a study of the spectral characteristics of the intracellular blood flow in only 32 (18.6%) patients. Such a low reproducibility of the method does not allow us to make a quantitative assessment of blood flow in a volumetric formation one of the

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differential diagnostic criteria. Characteristic features of FNG are: hypercontrusting and vascular pattern in the form of wheel spokes. The frequency of their combination reaches from 71.4 to 97% (Y. Yen et al. [4] and D. Strobel et al. [5]). According to the data obtained by us, with the "classical" type of FNG, the frequency of each of these signs can reach 96%. In our opinion, important differential diagnostic signs of this nosology are: 1) early onset of contrast formation in the arterial phase (AF) of the study (parameter "onset of contrast in the focus"); the use of this feature allows reliable differentiation of FNG from hemangiomas ($p < 0.000046$), HCA ($p < 0.006293$) and MTS ($p < 0.028125$); 2) accumulation of ultrasound from the center to the periphery (86% of neoplasms); 3) filling of the narrow central parts of the focus (77% of cases). The leaching of the contrast agent in the portal and late phases of the study (9% of cases) is uncharacteristic for this nosological group [6]. According to our observations, the hemangioma group in comparison with the FNG group was characterized by a later onset of contrast. In 42% of cases, the formation contrast was absent throughout the AF and the beginning of contrast was in the portal and late phases of the study, in addition, the nature of the accumulation of ultrasound in the neoplasm was less intense (57% of cases). According to C.F. Dietrich et al. (2007) [7], a specific symptom of visualization of contrast lumps on the periphery of the formation, which is characteristic of hemangiomas, occurs in 74% of cases, in our study the frequency of this sign was higher (92% of patients). According to D. Strobel et al. (2009) [8], the combination of two symptoms is quite informative in the diagnosis of hemangiomas: tumor contrast "from the periphery to the center" and complete filling of the formation with contrast in the late phases of the study. The data obtained by us are comparable with the opinion of the author. In our study, this type of contrast was observed in 75% of cases, however, complete contrast of the focus was recorded somewhat less frequently (which is probably due to the size of the neoplasms we studied) – in 65% of cases versus 78% [6, 8]. According to the results we obtained (Table. 3), HCA are the only neoplasms that lacked any specific vascular contrast patterns during CUSI. This significantly complicates differential diagnosis with other nosological forms and makes the choice of the next diagnostic step questionable. According to our data, HCA is characterized by complete and more intensive (100 and 80%, respectively) filling of the UZCP focus in the direction "from the periphery to the center" (80% of cases). The most difficult cases of HCA in terms of differential diagnosis are those where the phenomenon of washing out of the contrast agent is registered during the study, because, as is known, the combination of hypercontrusting of the neoplasm with the phenomena of washing out of the ultrasound is extremely suspicious of the malignant nature of the neoplasm [8, 9]. In our study, the wash-out phenomenon was registered in 6 (40%) patients with HCA. At the same time, according to the time of onset, the parameters "the beginning of leaching" and "the time of maximum leaching of the

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UZCP" had statistically significant differences with the MTS group ($p < 0.000041$ and $p < 0.001543$, respectively). According to the data of the World Federation for Ultrasound in Medicine and Biology (World Federation for Ultrasound in Medicine and Biology) 2020, the characteristic signs of metastatic liver damage are the phenomenon of hypocontrastation of the focus in the portal and late phases of the study, early and intensive onset of leaching [9]. The results obtained by us are generally comparable with international literature data. The MTS group is characterized by polymorphism of the identified signs, vascular contrast patterns in the arterial phase of the study are not specific. In more than half of all cases (55.8%), neoplasms accumulated UZCP completely and more intensively in comparison with unchanged liver parenchyma (46.5%). At the same time, only a third of the studied neoplasms had a specific sign of annular amplification. In our opinion, the most important differential sign of metastatic lesion is the phenomenon of early leaching (100% of cases, the sign of "beginning of leaching" Me (LQ–UQ) – 40 (35-56) p.). Of the most specific signs, the black hole symptom can be noted – 50% of all cases, asymmetric vascular pattern – 39.5% of cases [6]. A typical sign of HCC on the background of liver cirrhosis is increased contrast in the arterial phase, followed by contrast washout in the late phase of the study [10]. The results obtained in a number of key positions, namely hypercontrusting of the tumor and the possible presence of hypoperfusion zones, are quite comparable with the data of foreign colleagues [11]. We found that the contrast parameters of HCC nodes in patients with and without cirrhosis are comparable. In 2/3 of cases, the onset of contrast in the tumor was slowed down, the foci were characterized by an asymmetric vascular pattern (86.2%) and a more intense nature of the accumulation of contrast medium (91.4%). In more than 30% of cases, the central parts of neoplasms were not contrasted throughout all phases of the study. When comparing the FNG & HCC groups, statistically significant differences were revealed in the parameter "the beginning of contrast in the focus" ($p < 0.024933$), as well as in the parameter "the time of maximum accumulation of UZCP in the focus" between the groups "FNG & HCC" ($p < 0.007983$), "MTS & HCC" ($p < 0.000243$). According to the time of the wash-out onset – the parameters "the beginning of leaching" ($p < 0.001$) and "the time of maximum leaching of UZCP" ($p < 0.001$) – significant differences in HCC with metastatic liver damage were revealed. No differences were found in any of the criteria selected for comparison when comparing the "HCA & HCC" groups. In our opinion, the most important differential diagnostic signs of HCC are: in the arterial phase of the study, the accumulation of contrast agent is somewhat delayed, but more intense in comparison with the surrounding liver parenchyma; asymmetric, chaotic vascular pattern. In about half of the cases of highly and moderately differentiated tumors, the wash-out effect may be absent throughout the study. Regardless of the degree of differentiation of the tumor, HCC is characterized by the beginning of the

washout of the ultrasound contrast agent after 62 s. from the beginning of the study, than it significantly differs from MTS. The greatest difficulties are the differential diagnosis of this nosological group with liver adenomas.

Conclusions Ultrasound has not lost its relevance and remains an accessible and quite informative method of diagnosing liver neoplasms. Traditional ultrasound methods make it possible to establish the presence of a liver neoplasm, localize, evaluate its size and echographic criteria. They should be used as a basic screening in the diagnosis of liver neoplasms, dynamic observation, selection of acoustic access and navigation during biopsy. KUUZI in the framework of multiparametric ultrasound examination expands the possibilities of the method and allows for reliable differential diagnosis between benign and malignant liver neoplasms, with a sufficient degree of reliability to judge the morphological nature of the tumor. A reasonable combination of ultrasound methods can reduce the time of diagnosis, reduce the need for invasive and cost-effective methods of instrumental diagnostics.

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