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Screening and Early Diagnosis of Hepatocellular Cancer and Optimization of Diagnostic Imaging Techniques: a Review of the Literature and Conclusion of the Expert Panel

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Aim: to describe modern approaches for screening and early diagnosis of hepatocellular carcinoma (HCC).
Key points. Screening for HCC in high-risk groups (cirrhosis of any etiology, patients with chronic viral hepatitis B and patients with F3 liver fibrosis) should be organized as regular (every 6 months) liver ultrasound in combination with determination of the serum alpha-fetoprotein (AFP) level. At an AFP level of ≥ 20 ng/ml, even in the absence of changes according to ultrasound data, it is advisable to perform MRI with a hepatospecific contrast agent (gadoxetic acid) which makes it possible to detect very small focal liver lesions. If focal liver lesions of 1–2 cm are detected on ultrasound, additional imaging of the liver using MRI with a hepatospecific contrast agent gadoxetic acid helps to identify HCC at an earlier stage or high degree dysplastic nodes. When planning surgical treatment and liver transplantation, it is preferable to use MRI with a hepatospecific contrast agent, since the presence of the hepatobiliary phase may allow the detection of additional smaller focal liver lesions and assess the nature of the focal liver lesion. When a patient is included in the waiting list for liver transplantation, the optimal frequency of liver MRI is 1 time in 3 months.
Conclusion. MRI with hepatospecific contrast agent gadoxetic acid is effective in screening, early diagnosis and treatment planning for HCC.
Key words: hepatocellular carcinoma, liver cancer, MRI, hepatospecific contrast, screening, early diagnosis, gadoxetic acid
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Скрининг и ранняя диагностика гепатоцеллюлярного рака и оптимизация методов диагностической визуализации: обзор литературы и заключение совета экспертов

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Цель обзора: описать современные подходы, используемые для скрининга и ранней диагностики гепатоцеллюлярного рака (ГЦР).

Основные положения. Следует организовать проведение скрининга ГЦРв группах высокого риска его развития (цирроз печени любой этиологии, больные хроническим вирусным гепатитом В и пациенты с фиброзом печени F3) в виде регулярного (каждые 6 мес.) проведения УЗИ печени в сочетании с определением уровня альфа-фетопротеина (АФП). При уровне АФП ≥20 нг/мл даже в случае отсутствия изменений по данным УЗИ целесообразно провестиМРТ с гепатоспецифическим контрастным средством – гадоксетовой кислотой, которая позволяет выявить более мелкие очаговые поражения печени, в том числе в цирротически измененной. При выявлении на УЗИ очаговых поражений печени размером 1–2 см дополнительная визуализация печени с помощью МРТ с гепатоспецифическим контрастным средством – гадоксетовой кислотой будет способствовать выявлению ГЦР на более ранних стадиях или диспластических узлов высокой степени дисплазии. При планировании хирургического лечения и трансплантации печени следует предпочтительно использовать МРТ с гепатоспецифическим контрастным средством, поскольку наличие гепатобилиарной фазы может позволить выявить дополнительные более мелкие очаговые поражения печени, оценить характер очагового поражения печени. При включении пациента в лист ожидания на трансплантацию печени оптимальная кратность проведения МРТ печени составляет 1 раз в 3 месяца.

Заключение. ПроведениеМРТ с гепатоспецифическим контрастным средством – гадоксетовой кислотой эффективно при скрининге, ранней диагностике и при планировании лечения ГЦР.

Ключевые слова: гепатоцеллюлярный рак, рак печени, МРТ, гепатотропный контраст, скрининг, ранняя диагностика, гадоксетовая кислота

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Problems of early diagnosis of hepatocellular cancer

Hepatocellular carcinoma (HCC) accounts for up to 85 % of all primary malignant liver tumors. According to the GLOBOCAN assessment, primary malignant liver diseases occupied the 6th position in terms of prevalence in the world among all cancers, and the 3rd in terms of mortality in 2020 [1]. 10,349 new cases and 11,192 deaths were registered in the Russian Federation in 2020 [2]. The main possible reason for the excess (more than 8 %) in the number of deaths over the number of newly diagnosed cases can be a late diagnosis of the disease — about 60 % of cases are detected already in stage IV [3]. There is also a negative trend in an increase in the mortality rate by 23.18 % over the past 10 years among males in this group of malignant diseases in the Russian Federation [3].

A significant proportion of post-mortem diagnosis reflects the extremely unfavorable situation with the diagnosis of this disease. 66–80 % of patients with newly diagnosed disease die within 1 year. The main reason for late diagnosis is difficulties in detecting this low-symptomatic tumor in the patients with chronic hepatitis and cirrhosis [4].

The main risk factors for the development of HCC were viral hepatitis, but there is a trend towards an increase in the proportion of HCC due to metabolic associated fatty liver disease in various countries now [5].

According to a retrospective analysis of a group (n = 380) of HCC patients the main risk factors for the development of HCC were: viral (58 %, with a predominance of hepatitis C — 30.5 %), alimentary-metabolic (diabetes, obesity, metabolic syndrome — 17.4 %) and toxic (alcohol — 8.7 %); cirrhosis was detected in 203 (53.4 %) of these patients [6].

The absence in the Russian Federation of widely used screening programs for HCC in risk groups (cirrhosis of any etiology) inevitably leads to late diagnosis of cancer. HCC was detected in the result of the prophylactic examinations only in 3.7 % of the cases of this cancer in 2012. Late diagnosis determines a small number of cases of radical surgical treatment that accounts less than 7 % of patients with HCC in the Russian Federation [7].

Imaging methods for early detection of hepatocellular cancer

The system of active detection of HCC at an early stage in high-risk groups has been successfully used in many countries around the world. It has been shown that screening for HCC in risk groups can increase the detection of this disease at an early stage and increase survival [8].

The development of HCC is associated with the presence of chronic liver diseases, which are characterized by the presence of a long-term inflammatory process and the development of fibrosis. The degree of risk of developing HCC depends on the nature and duration of chronic disease [9]. The risk groups for developing HCC include patients with cirrhosis of any etiology, chronic viral hepatitis B and/or C, metabolic associated fatty liver disease (MAFLD) combined with diabetes mellitus and obesity [10–12]. According to the risk of developing HCC, patients can be divided into groups of very high, high and low risk. Various scales are used to assess the risk of development: they are the THRI index for cirrhosis, the Reach-B model for hepatitis B in patients not receiving antiviral therapy, the PAGE-B scale for hepatitis B in patients after antiviral therapy, and the Fib-4 index for NAFLD. HCC risk assessment and differentiated approach to its screening can increase the detection of HCC at an early stage and positively affect the cost of managing such patients. The follow-up interval should depend on the degree of risk of developing HCC and on the average time of tumor doubling, which in HCC is about 80-117 days. Thus, the frequency of screening in the high-risk HCC group every 6 months seems reasonable [10, 12]. When observing patients at low risk for developing HCC, it is possible to reduce the frequency of the examination to 1 time in 6–12 months. [13]. According to various studies, focal lesions in a cirrhotic liver with a diameter < 2 cm are most often benign [14, 15]. But such lesions can be precancerous one including dysplastic nodes of a high degree of dysplasia. The risk of the development of HCC during the year increases to 46.2 % in this case [13]. Therefore, the frequency of examination should be every 4 months in these patients [12].

The sensitivity of detecting focal liver lesions with a diameter < 2 cm with ultrasound, contrast-enhanced CT, and MRI with extracellular contrast agent is low (37.3 %, 59.1 %, and 63.8 %, respectively). Therefore, it seems reasonable to use the most sensitive methods at initial imaging. It was shown that the sensitivity of MRI with a hepatospecific contrast agent gadoxetic acid (Gd-EOB-DTPA, Primovist®, Bayer, Berlin, Germany) is 83.6 % in detecting small HCC in cirrhotic liver [13, 16]. Currently, it is possible to detect HCC by observing the patients with premalignant focal lesions of a diameter < 2 cm and achieve the goal of early diagnosis and treatment of liver cancer. The use of MRI with gadoxetic acid in clarifying the nature of focal liver lesions of 1–2 cm can increase the detection of HCC at a very early stage or dysplastic nodes of a high degree of dysplasia [13, 17].

The stage of detected HCC determines the management of the disease. The Barcelona Clinical

Liver Cancer (BCLC) is a widely used guideline for treatment selection. Updated in 2018, the BCLC system includes both an assessment of the tumor process and the condition of the patient with its liver function. The Child-Pugh scale should be used in all cases for assessing liver function. In the early stages of HCC (1–3 nodes < 3 cm, intact liver function, functional status 0), radical treatment methods (resection or transplantation) are recommended. The expected median life expectancy after this treatment of this patients is > 5 years [18].

Imaging data provides the information about the location of HCC, the number of the nodes, their size, and the stage of the disease. Therefore, they are the basis for selection of treatment option. The imagine sign of HCC is the accumulation of contrast agent during the arterial phase combined with its washout during the portovenous or delayed phases with dynamic computed tomography or MRI. In nodules of 1–2 cm in size, these typical imaging features for HCC have a specificity and positive predictive value of almost 100 %, but low sensitivity (71 %) [19]. Several studies have shown that MRI is more sensitive than CT in the diagnosis of HCC in patients with chronic liver disease [20, 21].

Gadoxetic acid contrast-enhanced MRI for early detection of hepatocellular cancer

Gadoxetic acid contrast-enhanced MRI (GA-MRI) demonstrated better accuracy in diagnosing HCC than CT [22, 23] and significantly higher sensitivity in detecting focal lesions (87 %) than MRI performed with other contrast media [20, 21]. In a large (n = 700) retrospective study, Kim et al. showed that GA-MRI compared with standard dynamic computed tomography led to the detection of additional HCC and clarification of the stage of HCC and, as a result, to a decrease in the number of relapses and a decrease in overall mortality in patients [24]. When planning treatment, it is critically important to establish the stage and extent of the process as accurately as possible. It allows to select the most optimal management and reduce the risk of disease recurrence in radically treated patients at an early stage.

In the SORAMIC study, GA-MRI provided superior accuracy in treatment decisions (83 % and 81 %, respectively, for R1 and R2 radiologists; population of all randomized patients by treatment n = 538; p < 0.001) compared with contrast-enhanced CT (74 % and 71 %) and routine dynamic MRI (76 % and 70 %, respectively) [21]. In their study, Lee et al. noted that the presence of hypointense focal liver lesions without hyperintense signal in the arterial phase according to GA-MRI is a significant predictor of disease-free survival after liver resection and radiofrequency ablation [25].

Currently, the Milan criteria are most widely used to determine the possibility of liver transplantation for HCC. Independent predictors of HCC recurrence outside the Milan criteria include a hypointense signal from the peritumoral area during the hepatobiliary phase (RR: 18.30; p < 0.001). The presence of a hepatobiliary phase on MRI increased accuracy up to 90 % in addition to the Milan criteria compared to explanted liver pathology. A hypointense signal from the peritumoral area during the hepatobiliary phase was significantly associated with more advanced tumor stage (p = 0.01) and microvascular invasion (p < 0.001) [26]. The accuracy of grouping patients according to the Milan criteria (completely meet; meet, but there are additional exceptions; do not meet) also increased from 89 % to 92 % when the hepatobiliary phase of GA- MRI was assessed [27]. GA-MRI also increases the accuracy of the assessment of the HCC recurrence risk after liver transplantation [26]. The patients waiting liver transplantation should be underwent liver GA-MRI every 3 months.

The LI-RADS® system is widely used in the world for assessing the probability that focal liver lesion is malignant according to various imaging methods [28]. On the one hand, this system has a number of advantages for the early diagnosis of HCC (determination of risk groups, probability assessment, verification), uniformity in terminology, approaches to performing image studies and interpretation rules, algorithms for managing patients, and integration into various international guidelines (ACR, NCCN, AASLD, UNOS-OPTN, ESMO, EASL, Clinical guidelines of the Ministry of Health of the Russian Federation) [12, 28–33]. On the other hand, this system is only suitable for patients with cirrhosis and/or hepatitis B and/or a history of HCC. There are also technological variations (how to measure dimensions, various technical parameters of MRI and a number of other parameters), insufficient staff training, which can adversely affect the results of imagine studies and reduce the accuracy of conclusions. Therefore, it is advisable to use this system in specialized centers.

Abdominal ultrasound, the most common methods of liver imaging in the Russian Federation, has the lowest sensitivity and positive predictive value (PPV) in detecting focal liver lesions. Sensitivity and PPV of contrast-enhanced CT and MRI with extracellular gadolinium-containing contrast agents do not differ significantly. GA-MRI is characterized by higher sensitivity and PPV (85.6 % and 94.2 %, respectively) in detecting focal liver lesions and can be used as the optimal method for imagine diagnosis of HCC [16]. This increase in the sensitivity of the

GA-MRI method is due to the ability of gadoxetic acid to accumulate in hepatocytes at 10–20 minutes after the injection of this contrast agent in patients with healthy liver parenchyma, and at 20–30 minutes in patients with cirrhosis (the hepatobiliary phase). Therefore, focal lesions are distinguished from normal liver cells in this phase because the former have hypointense signal and the latter have hyperintense one. Thus, gadoxetic acid allows obtaining additional information about the nature of the lesion and identifying additional foci [34].

Conclusion of the expert panel

Based on these data, on May 28, 2021, the expert panel composed of the authors of this article proposed the following approach to increase the rate of the detection of HCC in the early stages in order to increase the survival of these patients:

1. Organization of screening in high-risk groups for developing HCC (cirrhosis of any etiology, chronic hepatitis B, F3 liver fibrosis) as regular (every 6 months) ultrasound examinations of the liver in combination with the assessment of serum alpha-fetoprotein (AFP) levels.

a. If the level of AFP is ≥ 20 ng/ml, the additional study should be performed even if there are no changes according to the ultrasound data. In this case, It is preferable to use GA-MRI, which allows you to identify very small focal liver lesions, incl. in cirrhotic changed liver [13, 35].

b. If focal liver lesions of 1–2 cm are detected on ultrasound, GA-MRI can help to identify HCC at an earlier stage or dysplastic nodes of a high degree of dysplasia. If these dysplastic nodes are detected, the interval between imaging examination should be reduced to 4 months.

2. It is necessary to standardize the description and assessment of the focal liver damage. The LI-RADS® system, which is widely used in the world, is suitable for the assessment of liver lesions in patients at high risk of developing HCC, including patients with cirrhosis and viral hepatitis. The LI-RADS® system is preferred for use in expert clinics that specialize in the treatment of patients with HCC.

3. The use of imagine criteria for establishing the diagnosis of HCC in patients with cirrhosis is possible on the conclusion by experienced medical imagine specialists based on the results of multiphase CT or dynamic MRI with contrast enhancement.

4. The selection of the optimal treatment for HCC should be based on a multidisciplinary approach with the involvement and interaction of a liver surgeon, a chemotherapist, a medical imagine specialist, a pathologist, and, if it is possible, an interventional radiologist and transplantologist who have sufficient experience in treating patients with primary liver cancer.

5. When planning surgical treatment or transplantation, it is preferable to use GA-MRI, since the presence of the hepatobiliary phase can reveal additional smaller focal liver lesions and assess the nature of focal liver damage. When a patient is included in the waiting list for liver transplantation, the optimal frequency of liver MRI is 1 time in 3 months. In disputable cases, the consultation at a specialized oncology center should be requested.

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