JANUS, Anita, ŁOŚ, Dawid, KAPTUR, Agata, DZIEDZIŃSKI, Dawid and NOWAK, Aleksandra. Guidelines for oncologic surveillance in a patient with established cirrhosis. Quality in Sport. 2024;16:52495. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.16.52495
https://apcz.umk.pl/QS/article/view/52495

The journal has had 20 points in Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 12.06.2024. Revised: 20.06.2024. Accepted: 01.07.2024. Published: 08.07.2024.

Guidelines for oncologic surveillance in a patient with established cirrhosis

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Abstract:

Cirrhosis is a chronic, diffuse disease process characterized by fibrosis and remodeling of the organ's normal architectonics into regenerative nodules. It is also one of the risk factors for cancers of the organ. One of the most common is hepatocellular carcinoma (HCC). The etiologic agent of HCC, which usually also causes cirrhosis, can be determined in more than 90% of patients. The annual risk of developing HCC ranges from 1% to 8%. It is estimated that about 1/3 of cirrhotic patients will develop HCC. By preventing cirrhosis and controlling its course, we reduce the risk of hepatocellular carcinoma [1].

Keywords: cirrhosis, hepatocellular carcinoma, oncologic surveillance

Introduction:

Cirrhosis is a chronic, diffuse disease process characterized by parenchymal fibrosis, abnormal liver cytoarchitectonics, and the formation of pseudotumors and secondary vascular lesions. Based on the size of regenerative nodules, we can divide cirrhosis into: fine nodule, large nodule and mixed nodule. However, in clinical practice, the etiologic (possibility of causal

management) and functional (prognostic significance) divisions are of particular importance [1].

The main causes of cirrhosis are hepatitis B and hepatitis C virus infection, alcohol and obesity [2]. Table 1 lists the known etiological factors of cirrhosis. In many cases, the etiology is complex. The number of deaths from cirrhosis is expected to increase in the next decade (in 2019 it was associated with 2.4% of deaths worldwide) [3].

Epidemiology

Liver diseases (i.e., cirrhosis, hepatitis B and C, and cancer) cause more than two million deaths annually and account for 4% of all deaths. About two-thirds of all liver-related deaths involve men [4]. In 2019, the number of cirrhosis-related deaths worldwide was nearly 1.5 million representing a 10% increase since 2010 [3].

Cirrhosis is the ninth cause of death in Europe and a significant cause of mortality among patients with chronic liver disease. In 2019, 223,000 people died from cirrhosis in Europe, accounting for 16 deaths per 100,000 population [3,4].

In Poland, diseases of the digestive system (including liver disease) are the seventh most common cause of death. It is estimated that 308,000-422,000 people suffer from chronic liver disease, although the number appears to be higher and is hard to estimate. The number of deaths from chronic liver disease including cirrhosis has been increasing over the past few years, and data show that in Poland in 2021 there were more than 8540 deaths from this cause. It is assumed that about one-third of the number of deaths is due to alcoholic cirrhosis with possible HCV co-infection. [5,6] Alcohol is one of the leading causes of cirrhosis worldwide and is responsible for nearly 60% of cirrhosis cases in Europe, North America and Latin America [3].

HCC prevention

Primary prevention of hepatocellular carcinoma (HCC) involves preventing the development of a cirrhotic liver. Nearly 90% of HCC cases develop in a cirrhotic liver, and about 90% of all cases of this cancer are associated with known risk factors: chronic HBV and HCV infection, regular alcohol consumption, exposure to aflatoxins and hormonal preparations (anabolics, contraceptives) [7].

The risk of developing HCC depends on the underlying disease: it is low, for example, when the underlying disease is autoimmune hepatitis (about 3% over 10 years) and high when the underlying disease is chronic hepatitis B with a viral load greater than 10^7 copies/ml (almost 20% over 13 years) [8]. For HBV infection, prevention can be achieved by implementing a vaccination program. Mandatory immunization covers all infants from birth to age one, as well as those in groups at higher risk of infection: medical school and university students, health care workers, people infected with hepatitis C and those at risk of infection (e.g., travelers to endemic areas, drug users and those who have sexual relations with multiple partners [7,9]. Treatment of patients infected with HBV and HCV should follow current guidelines. It is estimated that 240 million people worldwide are carriers of hepatitis B virus surface antigen (HBsAg) [10]. The 5-year risk of cirrhosis in untreated patients with chronic hepatitis B (HBsAg) is 8-20%, and decompensation in patients with cirrhosis in the following 5 years is 20%. [10]. The goal of treatment of HBV infection is to achieve complete suppression of HBV replication - permanent disappearance of DNA-HBV, as well as elimination of HBs antigen and production of anti-HBs antibodies [11]. Antiviral therapy uses drugs such as interferons, nucleoside analogs (lamivudine, telbivudine, entecavir) and nucleotide analogs (adefovir, tenofovir) [11]. The main goal of therapy for hepatitis C virus infection is to eliminate the virus from the body, leading to a halt in the progression or regression of liver lesions. To detect HCV infection, tests indicating the presence of anti-HCV antibodies are used, with subsequent confirmation of infection activity by detecting HCV RNA. The choice of treatment should take into account: availability, efficacy and safety profile of the drug [12].

It is also important to avoid other harmful factors that are causes of cirrhosis. Patients should be encouraged to modify their lifestyles to prevent obesity and prevent excessive alcohol consumption. In addition to abstinence from alcohol, all people with chronic liver disease should avoid cigarette smoking, which promotes the progression of fibrosis [8]. Among dietary components, coffee consumption has anti-tumor activity. Consuming two or more cups of coffee per day is associated with slower fibrosis [8]. In daily coffee drinkers, the risk of HCC was reduced regardless of etiology by about 50% [1].

Clinical picture and course of liver cirrhosis

Cirrhosis is a progressive disease. In clinical settings, patients are often categorized as having compensated (compensated) or uncompensated (decompensated) cirrhosis. Progression from early stage to extreme liver failure takes varying lengths of time and depends on etiology, treatment used, among other factors - usually several years. The rate of progression from compensated to uncompensated cirrhosis has been reported at 4% to 10% per year [13]. A patient with cirrhosis may develop organ failure suddenly as a result of triggering factors (in the course of esophageal or gastric variceal bleeding, sepsis, ischemia or direct liver damage by alcohol, hepatotoxic drugs or hepatotropic viruses). We can determine the severity of liver impairment using the Child-Pugh scale [14] or the British MELD (Model of End-stage Liver Disease) scale [15].

Most patients with compensated cirrhosis remain asymptomatic. The first symptoms may be nonspecific and include fatigue, weakness, loss of appetite, unexplained weight loss, among others. With the onset of decompensation, patients may report symptoms indicative of impaired liver function: jaundice, ascites, peripheral edema, confusion, sleep disturbances [2]. Physical findings that may be present in patients with cirrhosis are summarized in Table 3 [2, 16].

Diagnosis of cirrhosis and its complications

Identifying patients with cirrhosis, allows to implement surveillance and reduce the risk of cirrhotic complications, including the development of HCC. Liver biopsy remains the reference standard in the diagnosis of diseases of this organ [2,17].

To confirm or exclude cirrhosis, non-invasive, inexpensive and reproducible tests are used to monitor the degree of liver fibrosis and its complications [2,18].

These include blood tests (markers of fibrosis present in serum, laboratory variables), methods for assessing the physical properties of tissues, and imaging methods [17].

A test to measure liver stiffness is elastography, which can be performed using ultrasound (transient elastography (TE) and transverse wave elastography (SWE)) or magnetic resonance imaging [17]. Transient elastography is the most common test for assessing the

degree of fibrosis and its sensitivity for detecting cirrhosis has been estimated at 81%, with a specificity of 88%. Its negative predictive value of >90% allows the exclusion of cirrhosis with high accuracy [18,19]. The limitations of elastography are false-positive results in cases of acute hepatitis, congestion of this organ and extrahepatic cholestasis [20]. They may also be overestimated with food intake or exercise [17]. Transient elastography may not be sensitive enough in patients with ascites or obesity [2]. EASL (European Association for the Study of the Liver) guidelines suggest that transient elastography should not be used in patients whose laboratory aminotransferases exceed the upper limit of normal by a factor of 10 [21]. The choice of non-invasive tests should take into account their indications and limitations, and the different methods should complement each other to make a correct diagnosis [17].

Biopsy is recommended when the results of non-invasive tests are inconsistent with the patient's clinical condition, in patients with liver disease of unknown etiology and in autoimmune diseases. It may be indicated in the diagnosis of hepatitis of HBV etiology or in non-alcoholic steatohepatitis (NAFLD), due to their difficult differentiation by non-invasive tests [2,22]. The advantages and limitations of the most popular non-invasive tests are shown in Table 3 [17].

Patients with suspected chronic liver disease should first be checked for all possible risk factors (metabolic syndrome, alcohol, HBV, HCV, positive family history of liver disease, exposure to drugs and potentially hepatotoxic substances) and have basic laboratory tests (complete blood count, liver tests, bilirubin, and PT/INR) ordered. Initial investigations also include serologic markers for viral hepatitis, ferritin measurement, transferrin saturation, and abdominal ultrasound [2, 17].

In the case of a diagnosis of viral hepatitis, liver disease of other etiologies, or the presence of clinical signs indicative of cirrhosis, the patient should be immediately referred to a specialized center [17].

In a situation where the only risk factor is excessive alcohol consumption and/or metabolic syndrome, a non-patent FIB-4 test can be performed as an adjunct, the result of which can help assess the degree of liver fibrosis.

A FIB-4 value <1.30 indicates a low risk of advanced fibrosis. Patients with such a result are recommended to modify their lifestyle and repeat the test at 1-3 year intervals, without the need for referral to a specialist [17]. A FIB-4 value ≥ 1.30 is an indication for transient elastography. If the obtained liver stiffness result is ≥ 8 kPa, additional patent serum tests (ELF, FibroMeter, Fibrotest) should be performed, which can confirm cirrhosis. A biopsy can be

considered if the tests do not agree with elastography. Transient elastography and FIB-4 test can be performed before or after the patient is referred to a specialist, depending on availability and treatment. With an elastography result of <8 kPa, the risk of cirrhosis is low and should remain on observation and lifestyle modification. In patients with excessive alcohol consumption, with an elevated liver stiffness score, with signs of inflammation in laboratory tests, it is recommended to repeat elastography after at least 1 week of abstinence [17].

At the early stage of cirrhosis, laboratory test results may be normal or slightly deviate from it. Laboratory findings suggestive of cirrhosis are characterized by: decreased albumin levels < 3.5 g/dl, thrombocytopenia, AST/ALT ratio > 1, elevated bilirubin levels, and prolonged PT/elevated INR [23].

Ultrasound is useful in the diagnosis of cirrhosis and its complications (splenomegaly, portal hypertension, ascites, HCC) and concomitant liver diseases. The sensitivity for detecting hepatic steatosis is estimated at 94%, with a specificity of 84%, and the test is recommended as the first choice for the diagnosis of steatosis [2,24].

The most common fatal complication of cirrhosis is rupture of varices, a symptom of portal hypertension [25]. The preferred method of screening for esophageal and gastric varices is endoscopy. It is indicated in all patients with cirrhosis, especially in the presence of clinically significant portal hypertension (liver stiffness >20 kPa, increased spleen size and thrombocytopenia or lack thereof). Endoscopy is recommended at one to two year intervals if small varices are detected and every two to three years if none are present [26,2].

Therapeutic approach to the patient with cirrhosis

Patients with cirrhosis are often malnourished and have reduced physical activity. Both of these factors lead to sarcopenia - a loss of skeletal muscle volume and weakness [27]. Studies have shown that sarcopenia results in shorter survival in patients with cirrhosis [28]. Current guidelines recommend a daily energy intake of > 35 kcal/kg body weight and a protein intake of 1.2 - 1.5 g per kilogram of dry weight. [29] High-protein diets are well tolerated by patients, and it is not recommended to restrict protein intake in cases of acute hepatic encephalopathy[30]. It is recommended that the patient eat the last meal consisting of carbohydrates late in the evening due to the hypermetabolic state, which leads to muscle

exhaustion and thus counteracts this [31]. The daily limit for sodium intake is 2,000 mg [30]. The patient should be encouraged to be absolutely alcohol abstinent and to stop smoking [8].

Hyponatremia is common in cirrhosis and occurs most often in advanced stages of the disease. It is associated with poor clinical outcomes, including increased mortality, poor quality of life and increased health care utilization [32]. We may see hypovolemic or, more commonly, hypervolemic hyponatremia. The most common cause of hypovolemic hyponatremia in patients with cirrhosis is excessive diuretic treatment of ascites. It is recommended that daily weight reduction should not exceed 500-800g. Management of hyponatremia with hypovolemia consists of administration of 0.9% saline solution and treatment of the cause (most commonly, discontinuation of diuretics) [8A]. Hyponatremia with hypervolemia is an expression of conductance. Depending on the level of natremia, different measures are taken. Asymptomatic and mild symptomatic hyponatremia (sodium concentration > 130 mmol/L) generally does not require treatment. In the case of severe symptomatic natremia, which is defined as the presence of life-threatening symptoms (vomiting, lethargy, convulsions, coma), management consists of hypertonic saline supplementation [33].

Coagulation disorders are an integral component of cirrhosis and are a key aspect of most prognostic factors. Current guidelines do not recommend correction of the coagulation system by, among other things, administration of fresh frozen plasma (FFP) in patients without bleeding or with bleeding due to coagulation disorders; transfusion of platelet cell concentrate (PLC) when platelet count is < 50,000/ul before procedures with a low risk of bleeding [16]. Portal vein thrombosis (PVT) is the most common thromboembolic disease event in cirrhosis, with an increased rate in decompensated conditions. Two randomized controlled trials show the superiority of direct oral anticoagulants (DOACs: apixaban, dabigatran, edoxaban, rivaroxaban) over warfarin therapy. In addition, one study showed improved survival in patients treated with DOACs compared to patients treated with warfarin. [34] Patients with acute PVT are initially treated with unfractionated heparin, with maintenance treatment with low-molecular-weight heparin if tolerated, or DOACs for compensated cirrhosis [35].

Esophageal varices are a very important complication of portal hypertension and defines decompensation. Variceal bleeding often has a dramatic course, can recur and is associated with significant mortality. In patients without prior variceal bleeding, current guidelines only address prevention of the first bleeding episode. [30, 36]. Primary prevention includes the use of non-

selective beta-blockers (i.e., propranolol, nadolol, propranolol) or banding (treatments repeated every 2-8 weeks until the varices are completely eradicated). One or the other should be used, as combination therapy has no benefit and may exacerbate side effects [36]. Non-selective beta-blockers should be discontinued when the patient has refractory ascites, spontaneous bacterial peritonitis, severe alcoholic hepatitis or hypotension [30].

Spontaneous bacterial peritonitis (SBP) is a life-threatening condition in patients with cirrhosis and ascites. Its prevention is essential to improve prognosis. The most commonly used prophylactic strategy is continuous long-term intestinal decontamination with norfloxacin [37]. There are studies that have shown an increased risk of infection in patients taking proton pump inhibitors, so they should be used when strongly indicated [30]. Patients with SBP should be promptly treated with empiric antibiotic therapy. The first-line therapy is third-generation cephalosporins (cefotaxime). Treatment should be administered in the hospital setting. Acute kidney injury occurs in about one-third of patients diagnosed with SBP and is associated with increased mortality during hospitalization. With intravenous albumin infusion, we reduce the risk of renal impairment. According to the International Club of Ascites, the greatest benefit from prophylactic infusions in SBP is seen in patients with bilirubin levels > 4 mg/dl or creatinine levels > 1 mg/dl [38].

3-hydroxy-3-methylglutaryl A reductase inhibitors (statins) can be safely used in patients with cirrhosis. Statins have been shown to reduce the risk and complications of chronic liver disease (lower risk of decompensation, may reduce portal hypertension). In addition, epidemiological studies have observed a positive association between statin use and hepatocellular carcinoma [39].

Ascites is one of the most common complications of cirrhosis and involves the accumulation of ascitic fluid in the abdominal cavity. Ascites is divided according to the volume of ascitic fluid into: benign (detected only on ultrasound), moderate (fluid volume > 0.5, detectable on physical examination) and advanced (abdomen tight, umbilicus smoothened or presence of umbilical hernia). For mild and moderate ascites, dietary sodium should be limited to 4.6-6.9 grams of salt per day. It is not necessary to limit fluid intake in patients whose blood sodium levels are normal. The next step in the treatment of ascites is diuretics, which we use when there is no effect of previous measures. We first use spironolactone in a dose of 100 mg once a day, which we increase by 100 mg when there is no response to treatment (max. 400

mg/day). When the effect of therapy is unsatisfactory (i.e., body weight decreases by <2 kg/week), consider adding furosemide starting at 40 mg/day. The goal of diuretic therapy is to reduce body weight by 0.3-0.5 kg/d. In patients with advanced ascites, systematic puncture of the peritoneal cavity with simultaneous administration of intravenous albumin preparations is recommended. In refractory ascites, intrahepatic portal-systemic anastomoses (TIPS) are used, but this procedure is associated with a high risk of increased encephalopathy [40].

Hepatic encephalopathy is a syndrome of CNS dysfunction in the course of acute or chronic liver disease. Treatment is multidirectional, which aims, among other things, to reduce ammonia production and increase its metabolism. Dietary recommendations, which focus on limiting protein intake to 40 g/day, are also important. To reduce ammonia production, the following are used: lactulose, antibiotic therapy (rifaximin 550 mg twice a day orally for 1-2 weeks in episodic form or for 6 months in long-term form) and probiotics The only drug that increases ammonia metabolism is ornithine aspartate (it stimulates urea synthesis and further increases liver regeneration). Factors that aggravate liver failure should be eliminated: metabolic disorders, infections, constipation, and drugs that depress the central nervous system (such as benzodiazepines) [41].

Oncological surveillance of high-risk patients

Monitoring HCC, is an effective secondary prevention strategy aimed at early detection of tumor and prompt implementation of treatment. Guidelines around the world, agree on the need for surveillance among all patients with cirrhosis, regardless of the etiologic factor. This recommendation applies to patients with Child-Pugh class A and B cirrhosis, as well as patients with class C cirrhosis under the condition of eligibility for liver transplantation [42].
Attempting to detect early-onset HCC in patients with severe cirrhosis-Class C on the Child-Pugh scale who are not eligible for transplantation is considered overdiagnosis of HCC, which can lead to overtreatment, increased costs and psychological damage without improving overall survival or quality of life [43].

Continuity of oncologic surveillance in patients with cirrhosis on infectious grounds is an important aspect. It is also indicated after the virus has been eradicated and when antiviral drugs are taken, since the risk of developing HCC, although niched, continues [44].

Surveillance coverage also applies to patients with advanced fibrosis regardless of etiology, patients with congenital hemochromatosis and patients with chronic HBV or HCV infections. HBV infection must be accompanied by a positive family history of HCC or an active viral load while HCV infection must be accompanied by advanced fibrosis. Such patients are at high risk and, despite the absence of cirrhosis, should also be placed on surveillance, as should those with chronic HBV infection of Asian and African descent [42,1,45].

The EASL guidelines recommend monitoring patients with chronic HBV infection who are at intermediate or high risk according to the PAGE-B classification, based on platelet count, age and sex, developed to predict the 5-year risk of HCC in Caucasian patients receiving entecavir or tenofovir [43].

Surveillance is not recommended in patients with mild to moderate fibrosis due to a lower risk of developing HCC, in patients with metabolic fatty liver disease (MAFLD), and in NAFLD patients with current cardiovascular disease or diabetic complications with an unfavorable prognosis [1].

The primary and readily available test used for oncological surveillance is abdominal ultrasound performed at six-month intervals. The test result is considered positive if there is a lesion ≥ 10 mm in diameter, which is the basis for expanding the diagnosis. Such lesions have a high probability of malignancy compared to lesions < 10 mm, at the detection of which the test is considered non-diagnostic. Nodules < 10 mm are difficult to diagnose due to their small size, so monitoring under regular supervision is recommended, which is a safe option for the patient. If focal lesions are not visualized on ultrasound, or if benign lesions are found, the result of the examination is defined as negative [44].

CT and MRI are not recommended as the primary method of surveillance for HCC in patients with cirrhosis; however, they can be used in selected situations if the ultrasound result appears to be unreliable [44]. MRI appears to be a better test in identifying liver lesions, especially for smaller tumors. The sensitivity for detecting lesions <20 mm by MRI has been determined to be 62% with a sensitivity of 48% for CT. For larger tumors, the sensitivity of the two tests is similar at 95% and 92% for MRI and CT, respectively [46].

Some guidelines additionally recommend the determination of alpha-fetoprotein, which is considered a marker for some cancers, including HCC. Studies show that the use of ultrasound with simultaneous AFP determination increases the sensitivity of detecting early HCC to 63%

compared to ultrasound, whose sensitivity for detecting early lesions is estimated at 45% [47]. Available studies show that when both methods are used simultaneously, only less than 5% of HCC cases are missed, with approximately 15% false positives [48] .

Despite EASL guidelines that do not recommend routine determination of AFP, this glycoprotein remains a readily available marker that can be used in individual clinical situations and is included in guidelines worldwide. Its determination may be useful in obese patients when the ultrasound examination performed may be difficult [1].

Significant limitations of AFP determination as a single test include its inadequate sensitivity for the diagnosis of smaller tumors <3 cm, which is estimated at only 25%, with a sensitivity of 57% for tumors >3 cm, and the possibility of increased titers in other disease entities as well, including acute and chronic hepatitis, cirrhosis, or other cancers [1,49].

Research is currently underway on the efficacy of new markers that could soon help in the surveillance of patients at high risk of developing HCC.

In patients with cirrhosis, a baseline metabolic panel, liver tests, complete blood count and INR/PT should be determined every six months to recalculate Child-Pugh score and MELD score [2]. Patients with a score >15 on the MELD scale should be referred for liver transplant evaluation. Patients with refractory ascites, variceal bleeding, hepatic encephalopathy and HCC should also be referred for such evaluation [50,2].

Diagnosis of HCC in patients diagnosed with a focal lesion in the cirrhotic liver

In patients with cirrhosis, all suspicious liver lesions should be monitored. Unlike other cancers, the diagnosis of HCC can be made based on imaging studies alone if patients are in a high-risk group. Such a group includes patients with known cirrhosis, chronic hepatitis with a viral (HBV) background and those with a history of HCC. This neoplasm should be differentiated from adenomas and metastases, due to the similar radiologic appearance on imaging studies resulting from shared vascularization from the hepatic artery [1].

If a lesion <10 mm in size is detected by ultrasound, it is recommended to repeat the examination no later than 4 months. Such a patient should have three follow-up ultrasound examinations within a year. If the image of the lesion is stable within a year, one can consider extending the period of frequency of its monitoring and perform the examination every 6 msc [51,1].

If the lesion on follow-up ultrasound has changed echogenicity or become enlarged, a multiphase contrast-enhanced CT or MR imaging study is indicated to verify its nature [51,1].

When a pattern of post-contrast enhancement characteristic of HCC, defined as enhancement of the lesion after contrast administration in the arterial phase (wash-in) and wash-out effect in the venous phase (wash-out), is visualized in one of the above studies, HCC can be accepted as the diagnosis. Unfortunately, most tumors <20 mm, do not show all the characteristic features of HCC on radiography, due to the insufficient sensitivity of imaging studies. If this is the case, multiphase CT or MR imaging with contrast should be repeated using the latter modality [51,52]. Obtaining an image characteristic of HCC on the second examination, the diagnosis of HCC can be made. If HCC cannot be confirmed on both of these examinations then a coarse-needle biopsy is indicated to help verify the nature of the lesion. If the biopsy is inconclusive, a repeat biopsy should be considered [51]. When this is not possible, the lesion should be returned to be monitored by imaging studies every 3-4 months [1].

An equivocal image is often seen in HCC with a diameter of <1-2 cm, so further diagnosis should not be overlooked according to the above algorithm. This is important because of the increased risk of treatment failure in tumors that reach >2 cm in diameter [53]. Biopsy of the lesion is also indicated in patients who have a diagnosed focal lesion but no cirrhosis or its presence is difficult to evaluate. In this case, imaging alone will not be sufficient. With the typical enhancement pattern seen on CT or MR, characteristic of HCC, biopsy is not required in patients with cirrhosis, but can be considered when a higher level of certainty of diagnosis is expected [51,1].

When a lesion >10 mm is detected, it is important to expand the diagnosis and perform imaging studies (multiphase CT or MR with contrast). Biopsy may be considered in special situations depending on the patient's individual clinical history, when a higher level of certainty about the nature of the tumor is necessary, or in the absence of typical HCC features on radiographic studies and uncertainty about the nature of the lesion. As with smaller tumors, biopsy should be repeated if unsuccessful, and when this is not possible, monitoring of the lesion by imaging studies should be implemented every 3-4 months.[51,1]

Summary

Cirrhosis is the end stage of chronic liver disease, with a variety of etiologies. In most patients it remains asymptomatic until the development of severe complications such as ascites, esophageal variceal bleeding, spontaneous bacterial peritonitis, hepatic encephalopathy or

HCC. Education, prevention and early diagnosis in high-risk patients play an important role to reduce morbidity and mortality associated with complications.

In primary care patients, it is important to pay attention to potential risk factors - alcohol, risky sexual behavior, diet, lifestyle, medications, dietary supplements, and early identification of patients with abnormal test results indicating liver disease. Early detection of liver-related diseases, in most cases, allows for their effective treatment. ALT testing remains a readily available marker in the diagnosis of liver damage regardless of the cause and should be routinely performed on a large scale as a screening test for liver disease.

Patients with cirrhosis should receive oncologic surveillance, which includes abdominal ultrasound at 6-month intervals, and be under the supervision of a specialized center. A complete cure for cirrhosis is not possible. The goal is to slow down the fibrosis process and treat the symptoms and complications.

Statement of the authors' contribution

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Receiving funding - no specific funding.

All authors have read and agreed with the published version of the manuscript.

Financing Statement

This Research Received No External Funding

Institutional Review Board Statement

Not Applicable

Informed Consent Statement

Not Applicable

Data Availability Statement

Not Applicable

Conflict Of Interest

The authors deny any conflict of interest.

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