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Hepatocellular Carcinoma

Authors

Kwabena O. Asafo-Agyei[1]; Hrishikesh Samant[2].

Affiliations

[1] MCG Augusta University
[2] Ochsner Multiorgan Transplant Center

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Continuing Education Activity

Hepatocellular carcinoma (HCC) is a primary tumor of the liver. Hepatocellular carcinoma constitutes more than 90% of the primary tumor of the liver. This activity describes the evaluation and management of hepatocellular carcinoma and highlights the role of the interprofessional team in evaluating and treating patients with this condition.

Objectives:

- Identify the etiology of hepatocellular carcinoma.
- Summarize the evaluation of hepatocellular carcinoma.
- Outline the management options available for hepatocellular carcinoma.
- Discuss interprofessional team strategies for improving care coordination and communication to advance hepatocellular carcinoma and improve outcomes.

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Introduction

Hepatocellular carcinoma (HCC) is a primary tumor of the liver and constitutes more than 90% of the primary tumor of the liver. Hepatocellular carcinoma occurs in approximately 85% of patients diagnosed with cirrhosis.[1] HCC is now the fifth most common cause of cancer worldwide.[2] The second leading cause of cancer death after lung cancer in men is HCC.[2] Five-year survival of HCC is 18% and second to pancreatic cancer.[3] Significant risk factors for hepatocellular carcinoma include viral hepatitis (hepatitis B and hepatitis C), alcoholic liver disease, and non-alcoholic liver steatohepatitis/non-alcoholic fatty liver disease. HCC occurs in 80%-90% of patients with cirrhosis. The annual incidence of HCC in patients with cirrhosis is 2-4%.[1]

Etiology

Hepatitis B, hepatitis C, alcoholic liver disease, and non-alcoholic liver steatohepatitis/non-alcoholic fatty liver disease are the etiological factors for the development of hepatocellular carcinoma.

Viral Hepatitis

Chronic hepatitis B virus and chronic hepatitis C virus is associated with more than 70% of cases of hepatocellular carcinoma.

Hepatitis B virus- Hepatitis B virus (HBV) is an enveloped virus, partially double-stranded virus, circular DNA genome, and belonging to the family Hepadnavirus. Hepatitis B affects more than 250 million individuals worldwide and is the most common cause of chronic hepatitis worldwide. Integration of the hepatitis B virus genome into the host genome is the primary pathogenesis for oncogenesis in HBV. Insertion of viral genome in telomerase reverse transcriptase (TERT) promoter sites of the human genome resulting in mutation accounting for 60% of HCC cases.[4] Other genetic alterations include mutations in TP53 (affecting cell cycle), beta-1 catenin (CTNNBI), axis inhibitor-1 (AXINI), AT-rich interaction domain-containing protein 1A (ARID1A), and ARID2(chromatin proliferation). The Hepatitis B virus and the Hepatitis C virus infection accounts for 56 % and 20% of HCC cases diagnosed worldwide, respectively.[5] HCC can occur in the absence of cirrhosis in patients infected with the hepatitis B virus infection. More than 80% of HBV-related HCC have underlying cirrhosis.[6] A strong risk predictor for hepatocellular carcinoma in patients with HBV includes elevated serum HBV DNA levels (equal to or more than 10,000 copies/mL).[7] This is independent of the hepatitis B e antigen (HBeAg) status of the patient.[8] Also, the positivity of the hepatitis B e antigen is associated with an increased incidence of HCC. This may be an indicator of a prolonged replication phase. HBV genotype C is associated with an increased risk for HCC.[9] Patients with low hepatitis B virus load but high levels of hepatitis B surface antigen (HBsAg) with levels of more than 1000 IU/mL are significantly associated with HCC.[10] Viral coinfection with the hepatitis C virus and the hepatitis delta virus increases the risk for the development of HCC.[11]

Hepatitis C virus- Hepatitis C virus (HCV) is a partially double-stranded, plus-sense RNA virus with 11 major genotypes, and 15 different subtypes. HCV genotype 1b is frequently associated with HCC.[12][13] HCV does not integrate with the host genome. Cirrhosis is a significant step in viral carcinogenesis for HCC. Chronic inflammation in chronic hepatitis C virus infection with subsequent fibrosis, necrosis, and regeneration contributes to HCC development. Molecular markers noted in liver carcinogenesis include viral structural and non-structural proteins (NS3, NS4A, NS4B, NS5A, and NS5B). HCV-associated HCC mostly occurs in patients with cirrhosis or advanced stages of fibrosis.[14] Fewer cases of HCV-related HCC have been documented in patients without cirrhosis.[15] 20% of HCC cases diagnosed worldwide are caused by HCV. Viral coinfection with the hepatitis B virus is associated with increased risk for HCC.[16]

Non-Alcoholic Liver Steatohepatitis (NASH) and Non-Alcoholic Fatty Liver Disease (NAFLD)

Non-alcoholic fatty liver disease is excess fat in the hepatocytes in the absence of a history of alcohol. NAFLD mostly occurs in the setting of metabolic syndrome. Metabolic syndrome occurs in patients with insulin resistance, hypertension, hypertriglyceridemia, and abdominal obesity, which increases cardiovascular risk. NAFLD is now a leading cause of HCC worldwide, especially in western countries.[17] 13% of patients noted to have HCC without background cirrhosis were noted to have NAFLD.[18] The incidence of HCC is expected to increase by 122% in the United States due to the increase in obesity and diabetes between 2016 and 2030.[19]

Alcohol

30% of HCC is related to a history of excessive alcohol ingestion in the United States. Alcohol can, directly and indirectly, cause HCC. Alcohol can indirectly cause HCC through cirrhosis. Alcohol leads to increased reactive oxidative stress and inflammation.[20][21] Drinking more than 80 g/day of alcohol increases HCC risk by fivefold.

Aflatoxins

Aflatoxin B1 is a mycotoxin produced by *Aspergillus flavus* and *Aspergillus parasiticus*. This is mostly found in Sub-Saharan Africa and Southeast Asia, where the fungus contaminates grains. Carcinogenesis is mostly through the mutation of the tumor suppressor gene (p53).[22] Aflatoxin B1 is associated with increased risk for HCC in patients with chronic hepatitis B virus.[23][24]

Other risk factors include iron overload, Glycogen storage disease, Wilson disease, alpha one antitrypsin disease, hypercitrullinemia, Alagille syndrome, and acute intermittent porphyrias.

Epidemiology

Hepatocellular carcinoma (HCC) is now the fifth most common cause of cancer worldwide.[2] Almost 841,000 new cases of HCC were diagnosed in 2018. The second leading cause of cancer death after lung cancer in men is HCC.[2] 780,000 deaths in 2018 were caused by HCC. HCC is thrice as common in males compared to females.[25] More than 80% of new cases of HCC occur in developing countries such as Sub-Sahara Africa, South-East Asia, and China, which have high burdens of the hepatitis B virus infection.

NAFLD is now a leading cause of HCC worldwide, especially in western countries.[17] The incidence of HCC is expected to increase by 122% in the United States due to the increase in obesity and diabetes between 2016 and 2030.[19]

The median age of HCC in the US is 64 years. HCV infection is mostly diagnosed in patients who were born between 1945 and 1965. Five-year survival of HCC is 18% and second to pancreatic cancer.[3]

Pathophysiology

Cirrhosis is a significant step in viral carcinogenesis for hepatocellular carcinoma. Integration of the hepatitis B virus genome into the host genome is the primary pathogenesis for oncogenesis in HBV. Insertion of viral genome in telomerase reverse transcriptase (TERT) promoter sites of the human genome resulting in mutation accounting for 60% of HCC cases.[4] Other genetic alterations include mutations in TP53 (affecting cell cycle), beta-1 catenin (CTNNBI), axis inhibitor-1 (AXINI), AT-rich interaction domain-containing protein 1A (ARID1A), and ARID2(chromatin proliferation).

Chronic inflammation in chronic hepatitis C virus infection with subsequent fibrosis, necrosis, and regeneration contributes to HCC development. Molecular markers noted in liver carcinogenesis include viral structural and non-structural proteins (NS3, NS4A, NS4B, NS5A, and NS5B).

HCV-associated HCC mostly occurs in patients with cirrhosis or advanced stages of fibrosis.

Histopathology

Hepatocellular carcinoma is a malignant tumor of the hepatocytes. Cytological features depend on the differentiation of hepatocytes. From well-differentiated to poorly differentiated HCC. The trabecular architectural pattern is the commonest. Other patterns include pseudoacinar (acinar with proteinaceous material), compact and sarcomatoid.

Histology may show variation, according to the differentiation of the tissue:

- Well-Differentiated: cells smaller than normal, minimal nuclear atypia, nuclear density two times of normal liver
- Moderately Differentiated: larger tumor cells with more eosinophilic cytoplasm, pseudoglands, distinct nucleoli, bile, and giant tumor cells
- Poorly Differentiated: large tumor cells with hyperchromatic nuclei prominent pleomorphism may have spindle cell or small-cell areas

History and Physical

The presentation of hepatocellular carcinoma (HCC) is dependent on the stage of the tumor and background cirrhosis.

- Non-cirrhotic related HCC may present asymptomatic in the early stage of the disease. The median age of the clinical presentation of HCC is 69 years.
- Cirrhotic-related HCC patients may present with symptoms of decompensated liver failure, including worsening jaundice, pruritus, hepatic encephalopathy, ascites, palpable mass in the upper abdomen, fever, malaise, weight loss, early satiety, abdominal distension, and cachexia. Abdominal pain is the commonest presentation for HCC.
- Paraneoplastic syndrome in HCC patients may present with hypoglycemia, erythrocytosis, hypercalcemia, diarrhea, and cutaneous findings such as pemphigus foliaceous, pityriasis rotunda, dermatomyositis, and Leser-Trelat sign.
- Symptomatic patients may present with variceal bleeding, intraperitoneal bleeding, obstructive jaundice, pyogenic liver abscess, and hepatic encephalopathy.
- The most common extrahepatic metastasis of HCC is to the lung, intra-abdominal lymph node, bone, and adrenal, respectively.[26]

Evaluation

Biochemistry

Liver function tests including bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and albumin may be elevated on the initial evaluation. This may indicate the severity of the disease. Other abnormal laboratory findings noted in patients with decreased synthetic liver function or reserve include an elevated international normalized ratio (INR), prothrombin time (PT), thrombocytopenia, anemia, hyponatremia, or hypoglycemia. Patients with advanced HCC, chronic hepatitis, or cirrhosis-related HCC are likely to present with these findings. Patients with early non-cirrhotic-related HCC may present with normal LFTs on the initial encounter. Patients with paraneoplastic features of HCC could present with hypoglycemia, hypercalcemia, erythrocytosis.

Other laboratory investigations to evaluate the etiology of HCC include hepatitis B surface antigen, anti-HCV antibody, alpha antitrypsin level, copper levels, and iron saturation.

Serum Alpha-Fetoprotein (AFP)

Alpha-fetoprotein is a serum glycoprotein produced by the fetal yolk sac and fetal liver during gestation. Elevated serum levels of AFP are typical for advanced HCC. This does not correlate with tumor size or vascular invasion. About 40% of small HCC do not secrete AFP. Early non-cirrhotic HCC have normal serum AFP levels.[27] The sensitivity of serum AFP is approximately 66% and specificity of 80% with a cut-off of 10.9 ng/ml (normal value between 10 and 20 ng/mL).[28] Markedly elevated serum alpha-fetoprotein levels of more than 200 ng/ml are highly specific but with moderate sensitivity for detecting HCC.[29] Detecting HCC in patients with coexisting liver disease using a cut-off point of 500 ng/mL has a specificity of more than 90%.[30] Serum alpha-fetoprotein levels may be elevated in patients with chronic hepatitis, cirrhosis, pregnancy, and other germ and non-germ line tumors.[31] [32] Alpha-fetoprotein is used with ultrasound for surveillance.

Other biomarkers include des-gamma-carboxyprothrombin (DCP) and lectin-bound alpha-fetoprotein, which may be elevated in HCC.[33]

Imaging

HCC may be diagnosed with ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI).

Ultrasound: Ultrasound (US) is a non-invasive, widely used screening test for HCC and surveillance. Sensitivity and specificity range from 51%-87% and 80-%100% respectively.[34] Non-contrast US determines the size, morphology, location, and vascular invasion of HCC. HCC can be hypoechoic or hyperechoic depending on the background of fatty infiltration or fibrosis. HCC demonstrates increased blood flow and neovascularity. USG is limited for the detection of tumors less than 2 cm.[35]

Contrast-enhanced ultrasound (CEUS) is used for the characterization of lesions detected on non-contrast ultrasound. CEUS has specificity greater than 97% and sensitivity and sensitivity of 90% in diagnosing lesions previously demonstrated on the non-contrast US as HCC.[36][37]

Ultrasound with or without serum alpha-fetoprotein is recommended every six months for HCC surveillance in high-risk patients.

Computed Tomography (CT): Diagnostic imaging criteria for detecting HCC with triphasic CT scan include hyperenhancement in the arterial phase and rapid washout during the portal venous phase relative to the liver background.[38][39] Contrast CT has sensitivity and specificity per lesion of 65% and 96%, respectively.[40] Sensitivity decreases to 40% for lesions less than 2cm. The positive predictive value increases to more than 92% for lesions greater than or equal to 2cm.

MRI: T1-weighted images may be isointense to hyperintense depending on the degree of fibrosis, fat, and necrosis. Hyperintense images on T1 are mostly well-differentiated tumors and appear as isointense on T2 images. Poorly or moderately differentiated tumors appear as isointense on T1 images and hyperintense on T2 images. Contrast MRI has a sensitivity of 77%-90% and a specificity of 84-97%.

American radiology association (ARA) has developed a liver imaging reporting and data system (LI-RADS) for classifying hepatic nodules and has been adopted by several societies including the American association for the study of liver disease (AASLD) in 2018. The lesion should demonstrate a non-peripheral washout appearance in the portal venous or delayed phase, non-rim arterial phase hyperenhancement in relation to the background liver parenchyma, smooth enhancing capsule appearance, and growth of more than 50% increase in size in less than 6 months.[41] High-risk patients include patients with chronic hepatitis B virus infection, cirrhosis, concurrent or prior diagnosis of HCC, and lesion identified on a surveillance US for HCC.

Liver Biopsy

Liver biopsy is not routinely done for HCC as the procedure is associated with the risk of tumor seeding and bleeding, and false negative on failure to obtain tissue from the appropriate site. Liver biopsy has a sensitivity of 66%-93% depending on the size of the tumor, positive predictive value, and specificity of 100%.[42]

AASLD recommends biopsy in lesions not typical for HCC on contrast-enhanced imaging and categorized as LI-RADS-M or LI-RADS-4. Several biomarkers to increase the accuracy of the diagnosis of HCC from high-grade dysplastic nodules include heat shock protein 70 (HSP70), glypican-3 (GPC3), and glutamine synthetase (GS).[43][44]

Treatment / Management

Surgical Resection

Patients with Barcelona-clinic liver cancer (BCLC) classification of very early (0) and early-stage (A) are ideal candidates for surgical resection. Very early (0) stage has preserved liver function, European cooperative oncologic group performance status (ECOG-PS) score of 0, and solitary nodule of 2 cm. For patients with early-stage (A) with preserved liver function and ECOG-PS score of 0 and with a solitary nodule of more than 2 cm are appropriate surgical resection candidates.[45]

Patients with Child–Turcotte–Pugh A and without clinically significant portal hypertension have favorable surgical resection outcomes. Patients with small HCC (tumors less than 5 cm) and Child-Pugh A have survival rates of 70% and 35% at 5 and 10 years, respectively, and recurrence-free survival rates of 36% and 22%.[46] Predictors of HCC recurrence after surgical resection include micro-and macrovascular invasion, tumor differentiation, and the presence of satellite nodules. Five years risk of recurrence is up to 70%.[47] Adjuvant therapies have not been shown to reduce the risk of recurrence.[48]

Liver Transplantation

Liver transplantation is associated with the removal of tumors and the potential for cure. Milan criteria for liver transplantation is a single nodule less than or equal to 5 cm in diameter or not more than three nodules, with none large than 3 cm in diameter without macrovascular invasion and extrahepatic spread.[49] A patient who meets Milan criteria for liver transplantation is associated with a 60%-80% and 50% survival at 5 and 10 years, respectively. Posttransplantation recurrence of HCC is less than 15%. Milan criteria have been the benchmark for liver transplantation in patients with HCC and embraced by the united network for organ sharing (UNOS). Adjuvant therapy has been shown to be cost-effective in patients with HCC awaiting liver transplantation. There is a moderate gain in life expectancy whiles waiting for liver transplantation.[50]

Tumor Ablation

Patients with BCLC classification of very early (0) and early-stage (A) who do not meet surgical resection criteria are appropriate for ablation.[51][52][51] Ablation is by modifying the local tumor temperature by using either radiofrequency ablation (RFA), cryotherapy, microwave, or laser therapy or injection of chemical substances, including ethanol, boiling saline, and acetic acid. Radiofrequency ablation has been shown to have superior ablative therapy in patients with tumors greater than 2 cm as compared to percutaneous ethanol and acetic acid injection. [53] Fewer complications have been associated with ablation as compared to surgical resection.

Transarterial Therapies

Transarterial therapies are considered for patients with BCLC intermediate stage (B). Intermediate stage (B) has preserved liver function, ECOG-PS 0, and multinodular without macrovascular invasion or extrahepatic spread. Transarterial chemoembolization (TACE) is the intraarterial infusion of cytotoxic agents and subsequent embolization of the feeding artery to the tumor. TACE is contraindicated in patients with decompensated cirrhosis. Metanalysis revealed an objective response rate of 52.5% and overall survival of 70.3%, 40.4%, and 32.4% at 1, 3, and 5 years respectively.[54] Selective internal radiation therapy (SIRT) is an intraarterial infusion of radioisotope yttrium-90 microspheres. This is considered for patients with BCLC intermediate stage (B).[55][56] No benefit has been shown with patients with BCLC advanced stage (C).

Systemic Chemotherapy

Sorafenib is the first-line treatment for the patient with BCLC advanced stage (C) with preserved liver function, ECOG-PS score of 1-2, and macrovascular invasion or extrahepatic spread. Sorafenib is a multikinase inhibitor. Sorafenib hepatocellular carcinoma assessment randomized protocol (SHARP) trial demonstrated a median survival of 10.7 months for patients receiving sorafenib as compared to 7.9 months in the placebo group.[57] In addition, sorafenib was shown to be effective in the Asia-Pacific region with patients having advanced HCC.[58] Common side effects of sorafenib include palmar-plantar erythrodysesthesia, diarrhea, weight loss, and hypertension. Lenvatinib was demonstrated noninferiority, but not superior to sorafenib.[59] Lenvatinib has been approved as the second agent for the first-line treatment of advanced HCC by the food and drug authority (FDA). Lenvatinib is associated with significant weight loss but less palmar-plantar erythrodysesthesia when compared to sorafenib. Patients who are intolerant or have tumor progression on sorafenib are started on the second line of treatment. Regorafenib, which is a multikinase inhibitor, has been approved by the FDA as the second-line of treatment for advanced HCC.[60] Other

second-line medications include cabozantinib, ramucirumab, and nivolumab, which is a programmed cell death 1 (PD-1) immune checkpoint inhibitor.[61][62]

Differential Diagnosis

Differential diagnosis of hepatocellular carcinoma (HCC) includes the following:

- Cholangiocarcinoma
- Fibrous nodular hyperplasia
- Dysplastic/Regenerative nodules in cirrhosis
- Hepatic adenoma
- Primary hepatic lymphoma
- Cirrhosis
- Metastatic cancer

Ultrasound with doppler typically demonstrates fine branching patterns with increased vascularity and greater flow velocity as compared to hemangioma and metastatic disease to the liver. HCC appears hypervascular on the arterial phase with portal venous washout while regenerative nodules appear isoechoic or hypoechoic in contrast to the rest of the parenchyma. Cholangiocarcinoma may present on multiphasic CT with both arterial and delayed enhancement.

Staging

The prognosis of hepatocellular carcinoma depends on both tumor burden and liver dysfunction. Tumor-node-metastasis (TNM) does not account for the degree of performance status and liver dysfunction. The most widely staging system is the Barcelona clinic liver cancer (BCLC). Among other staging systems include the Chinese University Prognostic Index, Japan Integrated Staging, Cancer of the Liver Italian Program.

The BCLC offers the most prognostic information, including patients' performance status, liver burden, and liver function.[63][64] The system stratifies patients with HCC in one of five stages. Substrata of 0, A, B, C, and D providing treatment recommendations depending on the stage. Tumor burden is assessed according to the size and number of nodules, extrahepatic spread, or presence or absence of macrovascular tumor invasion. The liver function test is assessed with Child–Turcotte–Pugh score, Model for End-Stage Liver Disease, and albumin–bilirubin grade.

Prognosis

Five-year survival of hepatocellular carcinoma is 18% and second to pancreatic cancer. The prognosis of patients with HCC is dependent on the tumor size, differentiation or grade of the tumor on histopathology, severity of the underlying liver disease, presence or absence of metastases, and tumor extension to adjacent structures. HCC with high levels of alpha-fetoprotein is associated with poorly differentiated HCC and confers a poor prognosis.[65] Patients with hepatitis B virus-related HCC and positive serum hepatitis B e antigen(HBeAg) are associated with poor prognosis and higher recurrence of HCC.[66][67] High levels of serum hepatitis B virus DNA are associated with a higher risk for HCC and recurrence.[68][69] Diabetes mellitus is a risk factor for the development of HCC and also associated with a poor prognosis.[70]

Complications

Hepatic complications of hepatocellular carcinoma include hepatic encephalopathy, portal vein thrombosis, worsening ascites, variceal bleeding, obstructive jaundice, and pyogenic liver abscess.

Intraperitoneal bleeding is a life-threatening complication of HCC. Patients present with worsening abdominal girth and pain, hypotension, and anemia. Emergent angiography with embolization and surgery for control of bleeding. CT abdominal scan without contrast is required for diagnosis and CT abdominal scan with angiography for emergency angiography studies.

The most common extrahepatic metastasis of HCC is to the lung, intra-abdominal lymph node, bone, and adrenal, respectively.[26] The brain tumor is a rare extrahepatic manifestation of HCC.

Deterrence and Patient Education

- Hepatocellular carcinoma is the fifth leading cause of cancer worldwide and the second cause of cancer deaths in men.
- Risk factors for HCC include chronic hepatitis B virus infection, chronic hepatitis C virus infection, alcohol abuse, and non-alcoholic fatty liver disease.
- NAFLD is now a leading cause of HCC worldwide, especially in western countries. This is due to the increase in metabolic syndrome. Metabolic syndrome occurs in patients with insulin resistance, hypertension, hypertriglyceridemia, and abdominal obesity, which increases cardiovascular risk.
- HCC is diagnosed by elevation of serum biomarkers, including alpha-fetoprotein, imaging including ultrasound, contrast CT/MRI, and biopsy.
- Five-year survival of HCC is 18% and second to pancreatic cancer.

Pearls and Other Issues

- Universal hepatitis B vaccination is likely to decrease the incidence of hepatocellular carcinoma worldwide.
- Direct antiviral for the treatment of chronic hepatitis C cirrhosis and the achievement of sustained viral response is likely to decrease the incidence of HCC.
- Non-cirrhotic chronic hepatitis B virus infection with high-risk for the development of HCC include patients with elevated ALT and high serum hepatitis B virus DNA, family history of HCC, patients older than age 20 years from sub-Saharan Africa, Asian men and women older than 40 and 50 years should undergo surveillance.[51]
- Surveillance with ultrasound and with or without alpha-fetoprotein every 4-6 months is likely to increase the detection of early HCC.

Enhancing Healthcare Team Outcomes

Hepatocellular carcinoma is the second leading cause of cancer deaths in males worldwide. NAFLD is now a leading cause of HCC worldwide, especially in western countries. The incidence of HCC is expected to increase by 122% in the United States due to the increase in obesity and diabetes between 2016 and 2030. Chronic hepatitis B virus infection is the leading cause of HCC worldwide. Universal hepatitis B vaccination is likely to decrease the incidence of HCC worldwide.

Five-year survival of HCC is 18% and second to pancreatic cancer. Management of HCC is complex, and there is a variety of treatments for HCC from different specialties. An interprofessional team, including medical oncology, surgery, radiation oncology, interventional radiology, and lead by hepatologist is important in providing a holistic and integrated approach to patients with hepatocellular carcinoma and achieving the best possible outcomes.

Review Questions

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