

Hepatocellular carcinoma: a review

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Abstract: Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and is a leading cause of cancer-related death worldwide. In the United States, HCC is the ninth leading cause of cancer deaths. Despite advances in prevention techniques, screening, and new technologies in both diagnosis and treatment, incidence and mortality continue to rise. Cirrhosis remains the most important risk factor for the development of HCC regardless of etiology. Hepatitis B and C are independent risk factors for the development of cirrhosis. Alcohol consumption remains an important additional risk factor in the United States as alcohol abuse is five times higher than hepatitis C. Diagnosis is confirmed without pathologic confirmation. Screening includes both radiologic tests, such as ultrasound, computerized tomography, and magnetic resonance imaging, and serological markers such as α -fetoprotein at 6-month intervals. Multiple treatment modalities exist; however, only orthotopic liver transplantation (OLT) or surgical resection is curative. OLT is available for patients who meet or are downstaged into the Milan or University of San Francisco criteria. Additional treatment modalities include transarterial chemoembolization, radiofrequency ablation, microwave ablation, percutaneous ethanol injection, cryoablation, radiation therapy, systemic chemotherapy, and molecularly targeted therapies. Selection of a treatment modality is based on tumor size, location, extrahepatic spread, and underlying liver function. HCC is an aggressive cancer that occurs in the setting of cirrhosis and commonly presents in advanced stages. HCC can be prevented if there are appropriate measures taken, including hepatitis B virus vaccination, universal screening of blood products, use of safe injection practices, treatment and education of alcoholics and intravenous drug users, and initiation of antiviral therapy. Continued improvement in both surgical and nonsurgical approaches has demonstrated significant benefits in overall survival. While OLT remains the only curative surgical procedure, the shortage of available organs precludes this therapy for many patients with HCC.

Keywords: hepatocellular carcinoma, cirrhosis, α -fetoprotein, orthotopic liver transplantation

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and is a leading cause of cancer-related death worldwide. In the United States, HCC is the ninth leading cause of cancer deaths.¹ A total of 30,640 new liver and intrahepatic bile duct cancers were estimated to occur in 2013 in addition to 21,670 deaths.² HCC occurred more often in males than females (2.4:1), with a higher incidence in Eastern and Southern Asia, Middle and Western Africa, Melanesia, and Micronesia/Polynesia.³ The age-adjusted incidence of liver cancer has risen from 1.6 per 100,000 individuals to 4.6 per 100,000 individuals among American Indians and Alaskan Natives followed by blacks, Whites, and Hispanics.⁴ There are pockets in the United States where certain ethnic groups have

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significantly increased incidence of HCC. Importantly, the incidence of HCC will continue to escalate as hepatitis C reaches its maturity and as nonalcoholic steatohepatitis (NASH) and obesity become more prevalent in the United States.

Risk factors

Chronic liver disease and cirrhosis remain the most important risk factors for the development of HCC of which viral hepatitis and excessive alcohol intake are the leading risk factors worldwide.

Chronic viral hepatitis can lead to cirrhosis and/or HCC. Hepatitis B and C are the most common causes of chronic hepatitis in the world. Hepatitis B virus (HBV) is a double-stranded, circular DNA molecule with eight genotypes (A to H). Genotypes A and D are more common in Europe and the Middle East, while genotypes B and C are more common in Asia.⁵ Hepatitis B is transmitted via contaminated blood transfusions, intravenous injections, and sexual contact. Vertical transmission from mother to fetus is the leading cause for HBV infection worldwide. Five percent of the world's population is infected with hepatitis B.⁶

Several epidemiological studies have demonstrated significant hepatocarcinogenicity with chronic HBV infection.⁷ Hepatitis B carriers have a 10%–25% lifetime risk of developing HCC. Unlike other causes of chronic hepatitis, HBV is unique in that HCC can develop without evidence of cirrhosis.² Genotype C has been associated with a higher risk of HCC than genotypes A, B, and D.⁸ Active infection with HBV carries an independent risk of HCC with HBV DNA levels $>10^5$ /mL viral copies associated with a 2.5–3 times increased risk of developing HCC in 8–10 years follow-up.⁹ Hepatitis B surface antigen (HBsAg) is not the only hematological marker that carries a significant risk for development of HCC. Patients with positive hepatitis B core antibody (anti-HBc) who are HBsAg-negative also remain at risk for development of HCC. The hepatocarcinogenicity of HBV can be significantly reduced with antiviral treatment for hepatitis B. Suppression of the virus can result in a significant 5-year reduction of the incidence of HCC from 13.7% (controls) to 3.7%, with the greatest reduction occurring in cirrhotic patients.¹⁰ The use of HBV vaccination has resulted in significant declines in the incidence of HCC from HBV.¹¹ The East Asian neonatal vaccination program is estimated to result in a 70%–85% decrease in the incidence of hepatitis B-related HCC.¹² Despite perinatal immunization, 5%–10% of infants remain at risk of acquiring hepatitis B infection. The use of nucleoside analogs in treating chronic hepatitis B mothers in their third trimester of pregnancy has demonstrated superiority to vaccination alone in preventing neonatal transmission.^{13,14}

Hepatitis C virus (HCV) is a small, single-stranded RNA virus, which exhibits high genetic variability.¹⁵ There are six different genotypes of HCV isolated. Genotypes I, II, and III are predominant in the Western countries and the Far East, while type IV is predominant in the Middle East. The highest rates of chronic hepatitis C infection occur in Egypt (18%), with lower rates occur in Europe (0.5%–2.5%), the United States (1.8%), and Canada (0.8%).¹⁶ Once infected with HCV, 80% of patients progress to chronic hepatitis, with ~20% developing cirrhosis.¹⁷ In hepatitis C, the development of HCC occurs almost exclusively in the liver with established cirrhosis; however, in the HALT-C trial, 8% of HCC occurred in patients with only advanced fibrosis.¹⁸ Dual infection with HBV and HCV in a cirrhotic patient increases the risk of HCC with an odds ratio (OR) of 165 compared to 17 for hepatitis C and 23 for hepatitis B alone.²¹⁹ A synergistic effect with alcohol increases the incidence of HCC between 1.7- and 2.9-fold when compared to HCV–HCC alone.^{20,21} The risk of HCC is reduced significantly in patients who obtained a sustained viral response after treatment of HCV with a 54% reduction in all-cause mortality.²² While advances in medications recently have made treating HCV easier, vaccinations against the virus remain elusive.

Alcohol consumption remains an important risk factor for the development of HCC.²³ The relationship between alcohol and liver disease correlates with the amount of alcohol consumed over a lifetime, with heavy alcohol use rather than social drinking being the main risk of HCC.²⁴ The prevalence rate of alcohol abuse in the United States is five times higher than that of hepatitis C.²⁵ Alcohol abuse accounts for 40%–50% of all HCC cases in Europe.²⁶ Studies in Europe reported an increase in the relative risk of developing liver disease above 7–13 drinks per week in women and 14–27 drinks per week in men.^{25,27} In the United States, studies showed that the risk of liver cancer is increased two- to fourfold among persons drinking more than 60 g/d of ethanol.²⁸ A meta-analysis of 19 prospective studies showed that consumption of three or more drinks per day resulted in a 16% increase risk of liver cancer and consumption of six or more drinks per day resulted in a 22% increase risk.²⁹

Diabetes and nonalcoholic fatty liver disease

Sixty percent of patients older than 50 years with diabetes or obesity are thought to have NASH with advanced fibrosis.³⁰ Chronic medical conditions such as diabetes mellitus and obesity increase the risk of HCC. Diabetes mellitus directly affects the liver because of the essential role the liver plays in glucose metabolism. It can lead to chronic hepatitis, fatty

liver, liver failure, and cirrhosis. Diabetes is an independent risk factor for HCC.^{19,31} Patients with diabetes have between a 1.8- and 4-fold increased risk of HCC. When compared to HCV, NASH-related HCC liver transplants increased by nearly four times in the decade from 2002 to 2012.³² In 2006, El-Serag et al³³ reviewed several cohort and case-control studies showing that diabetes mellitus is significantly associated with HCC. Hyperinsulinemia has been associated with a threefold increased risk of HCC. It is believed that the pleiotropic effects of insulin that regulate the anti-inflammatory cascade and other pathways inducing cellular proliferation play a role in carcinogenesis. Insulin-like growth factor and insulin receptor substrate-1 promote cellular proliferation and inhibit apoptosis, respectively.^{34,35} It is well-known that obesity is associated with many hepatobiliary diseases, including nonalcoholic fatty liver disease (NAFLD), steatosis, and cryptogenic cirrhosis all of which can lead to the development of HCC.^{36,37} Obesity itself increases the risk of HCC to 1.5- to 4-fold. The relative risk of HCC is 117% for overweight subjects and 189% for obese patients.³⁸ The majority of HCC-NAFLD occurs in men. Compared to women, men developed HCC with less fibrosis and cirrhosis.³⁹ The mean age of presentation is 70 years. Up to 50% of cases of NAFLD-related HCC may occur in the absence of cirrhosis.²⁹ These tumors tend to have lower α -fetoprotein (AFP) synthesis but are more likely to have elevated des- γ -carboxy prothrombin (DCP) than HCV-related HCC.^{40,41}

Other predisposing conditions

Sex may play a role in the development of HCC. HCC occurs more often in males, with a ratio of 2:1–4:1; however, this may not be due to sex alone.⁴² Males are more likely to be infected with viral hepatitis, consume greater quantities of alcohol, smoke cigarettes, and have a higher body mass index than women. It may be the higher testosterone levels that account for the higher incidence in males. It is known that high testosterone levels have been linked to HCC in hepatitis B carriers and to advanced hepatic fibrosis in males with chronic hepatitis C infection.^{43,44} Elevated testosterone or intake of anabolic steroids has been associated with an increased incidence of HCC and liver adenomas.

Aflatoxin produced by *Aspergillus* species (molds) found on grains, corn, peanuts, or soybeans stored in warm humid conditions is a potent hepatocarcinogen. The risk of HCC with aflatoxin is dependent on the dose and duration of exposure. Aflatoxin exposure is more prevalent in rural United States. Aflatoxin exerts a synergistic effect on hepatitis B- and C-induced liver cancer, the risk being 30 times greater with chronic hepatitis B plus aflatoxin exposure than with aflatoxin exposure alone.⁴⁵ The most potent aflatoxin, AFB1,

when removed from the environment has resulted in a reduction of the incidence of HCC.⁴⁶

Metabolic and genetic diseases associated with HCC include hemochromatosis, Wilson's disease, α -1 antitrypsin disease, tyrosinemia, glycogen-storage disease types I and II, and porphyrias.

The risk of HCC with hereditary hemochromatosis is estimated to be between 100- and 200-fold.⁴⁷ Other iron overload states such as thalassemia have not only been associated with HCC but also have a high prevalence of HCV that may contribute to the increased risk of primary liver cancer. South African blacks who consume beer brewed in nongalvanized steel drums have increased iron stores leading to an increase in the risk of HCC 10 times that of people with normal iron stores.^{48,49}

Other risk factors may include smoking. Cigarette smoking is associated with a significant increase in the development of HCC. A recent meta-analysis that reviewed the association between smoking and liver cancer demonstrated an OR of 1.6 (95% confidence interval [CI], 1.3–1.9) for current smokers and 1.5 (95% CI, 1.1–2.1) for former smokers. Studies investigating the use of oral contraceptive pills and the risk for development of HCC have previously been inconclusive; however, a recent review of six studies showed a significant increase in HCC risk with a longer duration (>5 years) of exposure to oral contraceptives.⁵⁰

Screening

Surveillance (Table 1) for HCC should have the goal of decreasing mortality and improving patient outcomes. Studies have found a survival benefit for early screening of patients for HCC.^{51,52} Patients who are identified early consequently have multiple treatment options leading to improved outcomes. Defining the target population should be a priority in today's rising health care costs, as surveillance for the general population is not recommended. An intervention (screening modality) is considered clinically effective if it provides at least 100 days increase in longevity.

Table 1 Screening guidelines for HCC

Screening guidelines for HCC	
All patients with cirrhosis (any age)	
Patients with HBsAg	
Asian females >50 yr	Males >40 yr
Africans/North American Blacks >20 yr	Family history of HCC
Non-Asians/Black females >50 yr	Non-Asians/Black males >40 yr with active disease ^a

Notes: ^aHBV-DNA >100,000 copies/mL and/or elevated ALT. Data from Bruix et al.⁵
Abbreviations: HCC, hepatocellular carcinoma; HBV, hepatitis B virus; ALT, alanine transaminase; yr, years.

Cost-effectiveness would be defined as an intervention costing <\$50,000/yr of life gained.⁵ Screening intervals for HCC are based on the average tumor doubling time of 3–5 months and a cost-effective threshold of an expected annual incidence exceeding 1.5% in cirrhosis and 0.2% in noncirrhotic hepatitis B patients.⁵³ Given these criteria, any patient with cirrhosis should be screened for HCC, although screening in autoimmune hepatitis cirrhosis and primary biliary cirrhosis may be of less value. Another exception to this rule may be patients with advanced/decompensated cirrhosis who are not transplant candidates. Their life expectancy is too short to receive any survival benefit from surveillance.⁵⁴

Persistent infection with HBV, in both noncirrhotic and cirrhotic patients, is a major risk factor for developing HCC. HBV carriers have a 223-fold higher risk of developing HCC than noncarriers.⁵⁵ The risk of HCC in Asian males exceeds the threshold for screening starting at the age of 40 years. HCC in Caucasians with hepatitis B is more related to virus inflammatory activity in noncirrhotic livers.⁵⁶ Active disease is defined as an elevated alanine transaminase (ALT) and/or a high viral load (>20,000 IU/mL). Screening for noncirrhotic HBV in Caucasian males with active disease should start at 40 years of age, while screening for Asian and Caucasian females should start at 50 years of age. African noncirrhotic hepatitis B carriers, in particular sub-Saharan Africans, have the highest incidence of HCC occurring particularly at a younger age.⁵⁷ Screening in these individuals should begin at the time of diagnosis or upon reaching the age of 20. Hepatitis B carriers with a family history of HCC are also at increased risk. The risk increases with age (23% with HCC at 70 years vs 8.9% without family history) and the number of family members affected (risk 5.6 times with >2 family members).⁵⁸ The age at which to start surveillance, however, has not been well-defined by guidelines. At our institution, we begin surveillance for males at age 40 and females at age 50 or 10 years before the index cancer developed in a family member.

Screening modalities

Modalities available for HCC screening include both radiographic tests and serological markers. Radiological tests commonly used for surveillance include ultrasonography (US), multiphase computerized tomography (CT), and magnetic resonance imaging (MRI) with contrast. US has historically been utilized to identify intrahepatic lesions since the early 1980s.⁵⁹ Sensitivity of US imaging is variable, ranging from 35% to 84%, and is operator and equipment dependent; however, studies have reported a specificity >90% when used for screening.^{60,61} Small HCC nodules ≤ 2 cm represented 85% of the lesions that failed to be detected by US.⁶² Furthermore,

central obesity hampers ultrasound's ability to detect small lesions.⁶³ HCC lesions exhibit increased arterialization as well as decreased presence of contrast agents during the portal phase of imaging (washout) on both CT and MRI scans.⁶⁴ Tumors ≥ 2 cm are detected by CT and MRI at 90% sensitivity, while sensitivity detection of tumors between 1 and 2 cm is 65% and 80%–92% and that for tumors <1 cm is 10% and 34%–71%, respectively.⁶⁵ CT and MRI is preferred in patients who have equivocal results utilizing US as their initial modality.

AFP's main function is the regulation of fatty acids in both fetal and proliferating adult liver cells.⁵⁵ Since 1968, AFP has been used as a serum marker for the detection of HCC.³² Several studies have evaluated the sensitivity and specificity of utilizing AFP with ranges of 21%–64% and 82%–93%, respectively.^{65–69} One major disadvantage is that AFP levels can be falsely raised in patients who have active hepatitis but no evidence of HCC. The upper limit of normal that is often adopted is 20 ng/mL because AFP levels in healthy individuals rarely exceed this level. In chronic hepatitis C patients without HCC, AFP can be >20 ng/mL in 16% of patients.⁷⁰ Furthermore, the sensitivity of AFP >20 ng/mL may have racial differences, being found to be 42.9% among blacks and 60% among nonblacks.⁷¹ AFP sensitivity is lower with small HCC lesions. It can be elevated in acute hepatitis, cirrhosis, colitis, germ cell tumors, and intrahepatic cholangiocarcinoma. AFP levels above 400 ng/mL can be considered definitive in diagnosing HCC, but sensitivity is lower at this higher cutoff value.⁵⁵ Lin et al⁷² demonstrated that surveillance with AFP and ultrasound was cost-effective regardless of the incidence of HCC.

In 2011, American Association for the Study of Liver Diseases (AASLD) published updates to its guidelines for surveillance of HCC. Cost-effectiveness is achieved if the expected HCC risk exceeds 1.5% per year in patients with HCV and 0.2% per year in patients with HBV. Ultrasound is the most cost-effective modality when performed at 6-month intervals. Some studies show that 6-month ultrasound with AFP exceeds cost-effectiveness, while biannual AFP/annual contrast CT exceeds the threshold by \$1,750.⁷² AFP lacks adequate sensitivity and specificity for surveillance, and therefore surveillance has to be based on US examination every 6 months.⁵³

While standard AFP levels are of variable benefit in identifying patients with HCC, other assays are available. Lens culinaris agglutinin-reactive fraction of α -fetoprotein (AFP-L3) expressed as a percentage of AFP has been found to be elevated in patients with HCC. It is highly specific for HCC when AFP levels are >20 ng/mL. A level >10% may identify patients with increased risk of developing HCC. AFP-L3 is associated with a more aggressive tumor, shorter

doubling time, infiltrative growth pattern, vascular invasion, and intrahepatic metastasis.⁷³

DCP is produced by malignant hepatocytes from an acquired posttranslational defect in vitamin K-dependent carboxylase system. The specificity of the DCP is 91% compared to 70% for AFP; however, sensitivity is low at 41%.⁷⁴ DCP normalizes with successful tumor resection. DCP levels >125 mAU/mL is sensitive and specific for differentiating HCC from chronic hepatitis and cirrhosis.⁷⁵ The highest accuracy for diagnosing HCC occurs when all three markers with appropriate cutoff values are used together. A DCP >40 mAU/mL + AFP >20 ng/mL and AFP-L3 >10% yield a sensitivity of 82.2% with a specificity of 82.4%.⁷⁶

Diagnosis

To obtain the best treatment result for HCC, early diagnosis is the key. Chronic hepatitis leads to the development of cirrhosis. Cirrhotic livers exhibit regenerative nodules, which result from increased proliferation of hepatocytes. Differentiation between these regenerative nodules and HCC can vary based on the size of the nodules. Nodules <1 cm (Figure 1) detected via US that cannot be defined

should be followed up with a repeat US in 3–4 months. Nodules >1 cm detected via US should have further radiologic investigation including either contrast-enhanced triple or quadriphasic CT or MRI. The diagnosis of HCC is based on the contrast enhancement in the arterial phase (wash-in) followed by disappearance of the contrast in the venous phase (washout) (Figure 2).⁷⁷ A recent meta-analysis of the diagnostic performance of CT and MRI for evaluating HCC has demonstrated that MRI has a higher per-lesion sensitivity than multidetector CT and should be the preferred imaging modality for the diagnosis of HCC in patients with chronic liver disease.⁷⁸ If the first radiologic test is equivocal, then confirmation with a different technique is recommended. If the diagnosis still remains uncertain, a serum AFP level >400 ng/mL has a high positive predictive value.⁷⁹ Percutaneous biopsy should be limited to those nodules that are radiologically nontypical on CT or MRI for HCC.⁸⁰

Staging

Stratification of patients diagnosed with HCC into groups is the primary aim of staging systems. Staging systems will assist

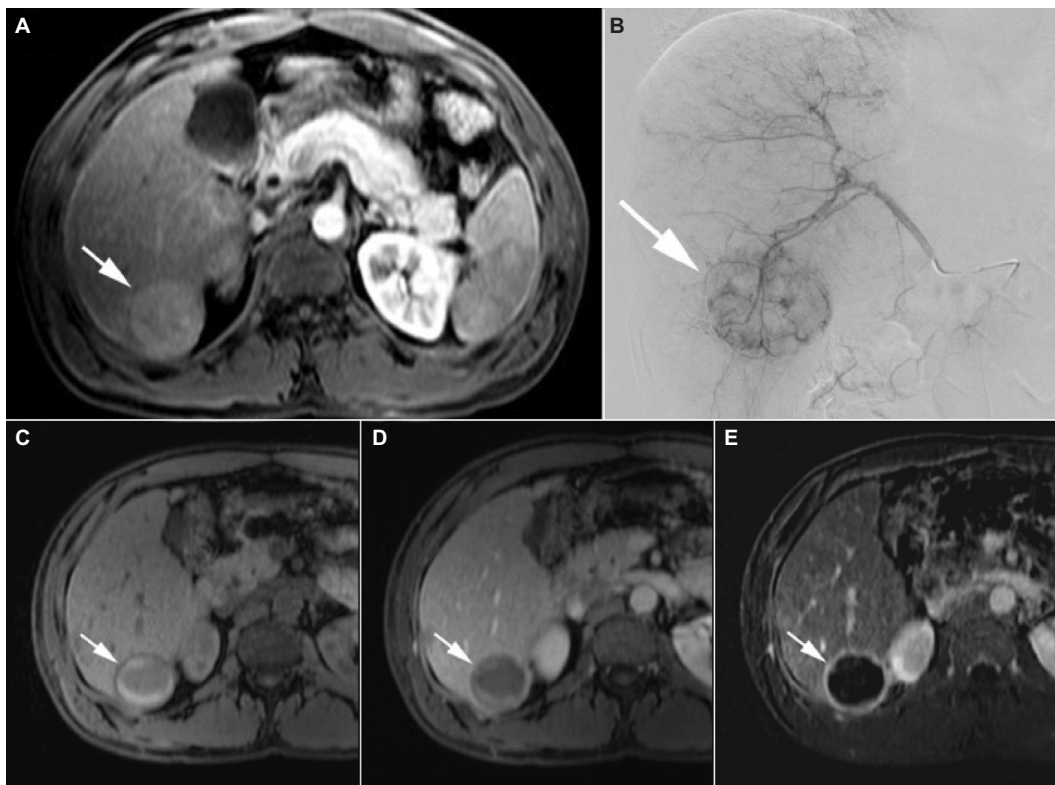


Figure 1 TACE.

Notes: Pretreatment MRI of a 43-year-old male with hepatitis C shows (A) a 4-cm T2-hyperintense solitary mass (arrow [A–E]) in segment VI of the liver with enhancement features compatible with hepatocellular carcinoma. The patient was treated with TACE with drug-eluting beads (B). A follow-up MRI 6 months after TACE shows intrinsic T1 peripheral hyperintensity (C) within the treated lesion with no residual internal enhancement (D), confirmed on subtracted imaging (E). Reproduced from Cochrane Miller J. Bridging procedures prior to liver transplantation. *Radiology Rounds*. 2015;13(1).¹⁴⁵

Abbreviations: TACE, transarterial chemoembolization; MRI, magnetic resonance imaging.

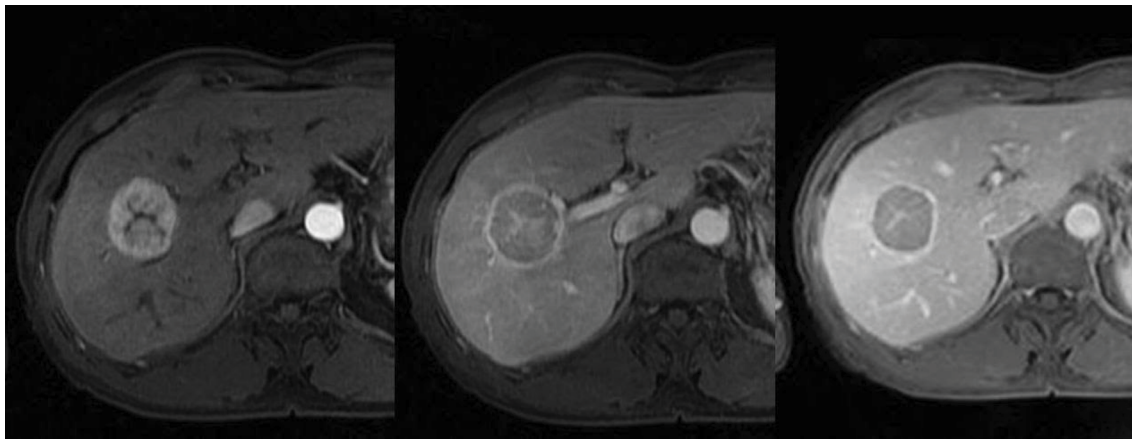


Figure 2 Typical HCC shows arterial phase hypervascularity with washout of contrast on portal venous and equilibrium phase.

Note: There is delayed pseudocapsule enhancement.

Abbreviation: HCC, hepatocellular carcinoma.

in organizing patients into groups based on prognosis and can guide clinicians in a choice of therapy, aid patient counseling, and facilitate patient selection and randomization for research protocols.⁸¹ Currently, there are three clinical and four pathologic staging systems. Pathologic staging systems include the Liver Cancer Study Group of Japan, Japanese Integrated, Chinese University Prognostic Index, and American Joint Committee on Cancer/International Union Against Cancer Staging System. Clinical staging systems include the Okuda Staging System, Cancer of the Liver Italian Program score, and the Barcelona Clinic Liver Cancer Staging System (BCLC). The BCLC staging system is widely accepted in clinical practice and is also at the forefront of many clinical trials used to establish the effectiveness of new HCC drugs.⁵³ The BCLC staging system has become the de facto staging system that is used. In the United States, there are additional staging systems commonly used, including the Model for End-Stage Liver Disease (MELD) score, the tumor–node–metastasis (TNM) staging system, or the simplified TNM staging system.^{82–85} In 2010, the AASLD published their recommendations regarding staging systems for HCC. Staging systems should best assess the prognosis of HCC in that a staging system should take into account tumor stage, liver function, and physical status. BCLC is the only system that takes into account all of these factors.⁵

CT scan of the chest, abdomen, and pelvis in addition to bone scan is vital to look for secondary disease and staging. Tumor characteristics such as size, maximum diameter, and number of lesions, location of tumors, vascular invasion, and any extrahepatic disease should be documented.

Treatment

Unfortunately, the diagnosis of HCC is too often made with advanced disease when patients have become symptomatic

and have some degree of liver impairment. At this late stage, there is virtually no effective treatment that would improve survival. In addition, the morbidity associated with therapy is unacceptably high. The unfortunate truth is that many patients are not properly screened. In a study looking at MarketScan claims database, over 700,000 patients with at least one claim for NAFLD/NASH/HCV over one-quarter of those diagnosed with HCC had no knowledge of liver disease prior to their diagnosis.⁸⁶ HCC screening was regularly performed on 21.1% of NASH and 22.3% of hepatitis C patients in this study. Even when patients are followed by expert hepatologists at academic centers, up to one-third of the patients had inconsistent HCC surveillance.⁸⁷ With proper screening and vigilance, many patients can and should be diagnosed with early disease and preserved liver function. Currently, there are several treatment options, both surgical and nonsurgical, that can have a positive impact on survival.⁸⁸ The best outcomes are achieved when patients are carefully selected for each treatment option. Regardless of the treatment approach, patients with HCC require a multidisciplinary approach to care to ensure optimal outcome. The multidisciplinary team typically consists of a hepatologist, a radiologist, a pathologist, a medical oncologist, an interventional radiologist, a transplant surgeon, and a hepatobiliary surgeon. Each specialty will have unique contributions to ensure optimal long-term outcomes for patients with HCC.

Surgical approaches

Resection

Surgical resection is the accepted treatment of choice for noncirrhotic patients and offers the best curative rate with a 5-year survival of 41%–74%.⁸⁹ The resectability of the

tumor is dependent on the tumor size, location, underlying liver function, and whether or not the remaining liver volume will allow for resection without drastically increasing postresection morbidity and mortality. Resection is considered the first-line treatment as long as R0 resection can be accomplished. The candidates for this therapy are patients with a solitary tumor confined to the liver, no radiologic evidence of vascular invasion, and well-maintained liver function.^{90,91} Optimum candidate selection is crucial to limit surgical morbidity and mortality. In patients with normal synthetic function, the size of the tumor does not necessarily affect the outcome when residual volume (volume of remaining liver) is adequate and technical aspects of the surgery are achievable.⁹² Operative mortality is affected by the presence (10%) or absence (5%) of cirrhosis.⁹³ Over the previous decades, Child–Pugh classification has been utilized in the guidance of resection candidates. However, Child–Pugh classification is far from accurate in predicting postoperative liver failure and some authors argue that Child–Pugh A patients already have functional liver impairment, significant portal hypertension, and minor fluid retention necessitating diuretic use.⁹⁴ Utilizing the MELD, a score of ≤ 8 has been shown to have no mortality as compared to a perioperative mortality of 29% for a score of >9 .⁹⁵ Many Japanese groups rely on the indocyanine green retention test to assess whether surgery is possible. The feasibility of surgery or degree of possible liver resection can be determined by the degree of indocyanine dye retention. In the United States and Europe, selection of ideal candidates for resection is usually based on the assessment of portal hypertension, which is assessed by cannulation of the hepatic vein and calculation of the hepatic portal venous gradient. Significant portal hypertension is evident when the portocaval gradient is >10 mmHg. A significant gradient can also be clinically surmised with evidence of gastroesophageal varices, splenomegaly, and a platelet count $<1 \times 10^{11}/L$ that leads to an increase in postoperative morbidity and mortality.⁹⁶

Perioperative portal vein embolization (PVE) is a technique utilized to cause hypertrophy of the anticipated residual liver remnant, thus permitting a more extensive liver resection. When PVE is performed, an overall increase in the liver volume of 10%–12% can be achieved.⁹⁷ Perioperative PVE has less major complications (10% vs 36%) and 90-day mortality (0% vs 18%) compared to patients who have had major resection without PVE.⁹⁸

Postresection 5-year survival rates range from 41% to 74% for patients who have a solitary tumor confined to

the liver without radiologic evidence of vascular invasion and preserved liver function.^{17,99,100} In contrast, patients who exhibit significant portal hypertension will develop postoperative decompensation with a 5-year survival rate of $<50\%$. Finally, survival in patients who exhibit both adverse predictors (portal hypertension and elevated bilirubin) and multifocal disease is $<30\%$ at 5 years.^{101,102} Cirrhotic patients have a perioperative mortality rate between 3% and 8% after resection, and a 5-year survival rate ranging from 30% to 50%.⁹⁶ Despite increasing overall survival in patients undergoing hepatic resection (HR) to treat HCC, the disease-free survival has not changed.¹⁰³ Recurrence rates may be as high as 70% after 5 years. Predictors of early recurrence include AFP levels $>2,000$ ng/dL, nonanatomic resection, micro- or macrovascular invasion, positive resection margins, and poorly differentiated tumors.¹⁰⁴ While de novo tumor development can occur after resection, the majority of HCC recurrences occurs within 1–2 years and is believed to be a result of dissemination or micrometastasis from the primary tumor and not inadequate surgical resection.² Contraindications to resection are the presence of extrahepatic metastasis or invasion of the main portal trunk by the tumor. Generally, neoplastic invasion of the portal vein leading to thrombosis is a poor prognostic indicator; however, in certain cases, hemihepatectomy can be feasible, especially when thrombosis of the main branch of the portal vein resulted in the hypertrophy of the contralateral hemiliver.¹⁰⁵

In comparison to traditional open surgery, laparoscopic liver resection is safe^{106,107} and effective in cirrhotic patients and now plays a key role in the treatment of HCC. Resection is also the primary treatment for advanced tumors and can be used as an alternative or a bridge to liver transplantation.^{108–111} Technical feasibility is the only limiting factor when offering laparoscopic vs open resection. Two criteria have been proposed to assist in the selection of appropriate candidates for surgery: size and location of the tumor and liver function.¹¹²

Liver transplantation

Orthotopic liver transplantation (OLT) is the best curative option for patients with decompensated cirrhosis, and HCC is the only solid cancer that can be treated with transplantation. Mazzaferro et al¹¹³ published a landmark study with <50 patients who were transplanted for HCC with specific criteria, which became known as the Milan criteria. These specific criteria included single HCC tumors <5 cm or three tumors all ≤ 3 cm each and demonstrated a 4-year survival rate of 75%. A recent systemic review of 90 studies that followed 17,780

patients over a 15-year period identified the Milan criteria as an independent prognostic factor of outcome after OLT.¹¹⁴

Expansion of the Milan criteria, particularly by liberating the restrictions on tumor size, has also been studied. The University of California San Francisco (UCSF) criteria, which includes 1) a single lesion ≤ 6.5 cm, or 2) three or fewer nodules with the largest lesion ≤ 4.5 cm and with a total diameter ≤ 8 cm, have been studied both retrospectively and prospectively and have shown survival and recurrence rates equal to those patients using the Milan Criteria.⁴⁹ The 1- and 5-year survival rates were 90% and 75%, respectively.¹¹⁵ Both the Milan and UCSF criteria consider the number and size of the tumor regardless of tumor biology. The University of Toronto developed a protocol for biopsying large tumors up to 10 cm, and poorly differentiated tumors were excluded. These patients were treated aggressively prior to transplantation with ablative therapies, with survival being similar in both the Milan criteria and expanded criteria patients.¹¹⁶

Locoregional therapies have been used to downsize patients with HCC exceeding current transplant criteria with the goal to decrease the tumor burden in order to meet transplant criteria.^{117–119} Yao et al¹¹⁹ published a downstaging protocol consisting of transarterial chemoembolization (TACE) and/or radiofrequency ablation (RFA) and demonstrated survival rates of 96.2% at 1 year and 92.1% at 4 years among patients who received transplantation. In compensated livers, locoregional therapy is utilized to downsize the tumor to an acceptable size and within standard criteria. Posttransplant survival data are comparable in patients who underwent downsizing with those within conventional criteria.¹¹⁸ Ablative therapies can also be used as bridging therapies for transplantation, deceleration of tumor progression, minimization of dropout, and improvement of posttransplant survival.⁸ Long waiting time, and a shortage in available organs, is one of the major disadvantages of OLT as a treatment option in HCC. Under the current United Network of Organ Sharing policy, patients who are diagnosed with HCC and are within the Milan criteria receive a MELD score of 22. This starting score increases in a stepwise fashion every 3 months after the results of repeated imaging (CT or MRI) reconfirm that criteria is still met.¹²⁰ This can result in a waiting time of >2 years in certain areas of the country. An alternative to deceased donor liver transplantation is living donor liver transplantation; however, the mortality to the donor is approximately 0.3% and life-threatening morbidity is 2%. Because of the risk to the donor, living donor liver transplantation should be restricted to centers of excellence.¹²¹

Nonsurgical approaches

Transarterial chemoembolization

The most commonly used initial treatment for locoregional HCC as well as for downstaging tumors that exceed criteria is TACE.¹²² TACE can also be considered prior to HR and RFA as neoadjuvant therapy to either reduce tumor volume or even target micrometastasis.¹²³ The rationale for using TACE is the neoangiogenic properties of HCC and its mechanism of action on the hepatic arterial supply of the tumor. During its initial development, the tumor derives its blood flow from the portal system. As the tumor increases in size, the blood supply becomes arterialized, so even a well-differentiated HCC is mostly dependent on hepatic arterial supply. This tumor characteristic provides the pathologic basis for the radiologic features used to diagnose HCC. Embolization of the hepatic artery branch leads to selective tumor hypoxia and eventually tumor necrosis. This is accomplished by a significant reduction in arterial blood flow through the use of image-guided catheter-based infusion of particles.¹²⁴ Potential agents including polyvinyl alcohol beads, alcohol, starch microspheres, metallic coils, autologous blood clots, and gelfoam have all been used for embolization.⁵ Prior to arterial embolization, a chemotherapeutic agent is injected. Several chemotherapeutic agents have been historically used, including doxorubicin, cisplatin, mitomycin, and epirubicin.² In addition, doxorubicin-eluting beads have recently become an alternative to traditional TACE. Drug-eluting beads are considered an improvement in both treatment response rates and tumor necrosis compared to traditional TACE.¹²⁵ Contraindications for TACE are decompensating cirrhosis (Child–Pugh B), massive tumor with extensive replacement of both lobes, severely reduced portal flow (portal vein occlusion or hepatofugal blood flow), and a creatinine clearance of <30 mL/min.¹²⁶ Llovet et al¹²⁷ found that survival probabilities for TACE were 82% and 63% for 1 and 2 years, respectively, for unresectable HCC. The response to TACE is an independent predictor of survival. Additional studies have shown an improvement in survival in TACE-treated patients in the range of 20%–60% at 2 years.¹²⁸ Morbidity with embolization is relatively low ($<5\%$), and common complications include abdominal pain, nausea, ileus, and fever, which are consistent with postembolization syndrome.¹²⁹ Historically, portal vein tumor thrombosis has been considered a contraindication to the performance of TACE therapy. This interruption of hepatic arterial blood flow which can lead to significant hepatic necrosis when combined with a portal vein occlusion from tumor thrombus which already compromised blood flow to the affected area of the liver. Several prospective and reactive retrospective

studies have shown that TACE can improve overall survival in Child–Pugh's A cirrhotic HCC patients with portal vein tumor thrombosis. Furthermore, the combination of TACE and sorafenib may have synergistic value.¹³⁰

Transarterial radiation

Transarterial radioembolization is a form of catheter-directed internal radiation that delivers small microspheres with radioisotopes directly into the tumor. Yttrium-90 (Y-90) microspheres or iodine-131-labeled lipiodol¹²⁷ are administered in a procedure similar to TACE. This procedure has been shown to be safe and effective in cirrhotic patients with HCC.^{131,132} One major advantage of Y-90 over TACE is that it is indicated in the case of portal vein neoplastic thrombosis, while TACE traditionally has been considered a contraindication.¹³³ The side effects are usually well tolerated.¹³⁴ The most common side effects include fatigue, nausea and vomiting, and abdominal pain. Postembolization syndrome (fever, unremitting nausea, general malaise, loss of appetite, and abdominal pain) is seen less frequently with TACE. A pretreatment evaluation that often includes an arteriogram, superior mesenteric angiogram, and celiac trunk angiogram is necessary to evaluate for the presence of arterioportal shunting. Coil embolization of these collateral vessels may be necessary to decrease unintended deposition of microspheres outside the targeted area. Vessels most often embolized include the inferior esophageal, left inferior phrenic, accessory left gastric, supraduodenal, and retroduodenal arteries. Y-90 is contraindicated in patients with hepatopulmonary shunting, which can lead to extremely high levels of pulmonary radiation exposure and the development of radiation pneumonitis. The reported rate of complete tumor necrosis in patients with tumors <3 cm was 90%.⁹¹ The 2010 AASLD clinical practice guidelines stated that radioembolization with Y-90 glass beads has been shown to induce extensive tumor necrosis with an acceptable safety profile; however, no studies demonstrating an impact on survival have been established.⁵

Percutaneous local ablation

Percutaneous local ablation, which includes both RFA and percutaneous ethanol injection, is the standard of care for BCLC stage 0-A HCC not suitable for surgery.² RFA is the treatment of choice for local destruction of liver tumors. RFA produces coagulative necrosis of the tumor while leaving a safety margin around the tumor, leading this to be the most common local ablative therapy. RFA can be performed both percutaneously under radiological guidance using CT or US or during surgery guided by intraoperative US. Complete

ablation of tumors <2 cm is possible in >90% of cases.¹³⁵

There are several limitations of RFA:

1. for tumors >3 cm, complete necrosis is rarely observed;
2. there is difficulty in ablating tumors that are adjacent to major blood vessels;
3. it is difficult to reach certain segments of the liver (ie, Segment 1) percutaneously;
4. subcapsular lesions can rupture into peritoneum;
5. bladder injury can occur with ablation of segment IVb; and
6. in livers with multinodular cirrhosis, targeting lesions under ultrasound guidance can be difficult.¹⁰⁵

The treatment of HCC has been well demonstrated in multiple series with overall 5-year survival rates between 33% and 55%.¹³⁶ Ethanol injection requires multiple injections on separate days and rarely induces significant necrosis in tumors >3 cm largely because the injected ethanol rarely reaches the entire tumor volume. Tumor necrosis rates are 90%–100% for tumors <2 cm, 70% for 2- and 3-cm tumors, and 50% in HCC tumors between 3 and 5 cm.⁵ In one prospective nonrandomized study, RFA achieved higher ablation rates on HCC tumors <3 cm than percutaneous ethanol injection (90% vs 80%) with fewer treatments.

Microwave ablation

Microwave ablation (MWA) can be utilized both percutaneously and intraoperatively and is a potentially curative ablative procedure.¹³⁷ It is a method very similar to RFA, except MWA utilizes electromagnetic waves with frequencies >900 kHz to irradiate and ablate tumor foci.⁹⁰ This leads to rapid elevation of temperatures within the MWA field to excess of 100°C without the damaging effects of tissue impedance, leading to a more rapid and uniform ablation.⁵³ This carries an increased risk of more severe injury to adjacent structures when compared to RFA. Earlier studies comparing MWA and RFA demonstrated no statistical difference in efficiency, and more recent studies using improved MWA modalities show potential.⁹⁰ Clinical advantage of MWA over RFA and its potential to demonstrate increased rates of tumor necrosis with a reduction in overall treatments need to be evaluated.

Systemic therapy

The majority of patients diagnosed with HCC present with advanced disease. Prior to 2008, no systemic therapy was available that demonstrated an improvement in survival. With the publication of two randomized placebo-controlled Phase III trials, the oral multitargeted tyrosine kinase inhibitor

sorafenib has become the new standard of treatment for advanced HCC with an increased median survival from 7.9 months in the placebo group to 10.7 months in the treatment group.^{138,139} Sorafenib blocks the activity of Raf serine/threonine kinase isoforms, as well as the receptor tyrosine kinases vascular endothelial growth factor receptor 2 and 3, platelet-derived growth factors receptor β , c-KIT, FLT-3, and RET, to inhibit tumor angiogenesis and tumor cell proliferation.¹⁴⁰ Currently, sorafenib is recommended in patients with advanced HCC and preserved liver function who are not candidates for either resection or liver transplantation and have failed to respond to locoregional therapies.¹⁴¹ The main side effects include anorexia, nausea, vomiting, weight loss, hoarseness of voice, esthesia, and hypertension.¹⁴² Sorafenib can be difficult to tolerate because of the side effect profile, dose reduction (54%) or treatment interruption (40%) is often needed.¹⁴³ Despite the side effects, treatment is recommended to be continued until progression of the tumor is demonstrated. Currently, studies are continuing in an attempt to identify the best responders to sorafenib; c-Jun N-terminal kinase activity was positively correlated with the CD133 expression level and inversely correlated with the therapeutic response to sorafenib.¹⁰⁵ Consequently, c-Jun N-terminal kinase activity may be considered as a new predictive biomarker for response to sorafenib.¹⁰¹

Conclusion

HCC is an aggressive cancer that occurs in the setting of chronic liver disease and cirrhosis that frequently presents in advanced stages. Concomitant liver dysfunction with advanced tumor stages further impedes curative therapies. HCC as well as other cancers, can be prevented if appropriate measures, including HBV vaccination, universal screening of blood products, use of safe injection practices, treatment and education of alcoholics and intravenous drug users, and initiation of antiviral therapy, have shown to be effective.^{102,144}

Continued improvement in both surgical and nonsurgical approaches has demonstrated significant benefits in overall survival. While OLT remains the only curative surgical procedure, the shortage of available organs precludes this therapy for many patients with HCC. Sorafenib has shown to be a unique neoantigenic targeting agent with encouraging results. Studies need to further investigate other biomarkers both alone and in conjunction with other modalities to assess survival and tumor regression.

Disclosure

The authors report no conflicts of interest in this work.

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