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**Hepatocellular carcinoma: From diagnosis to treatment**

Waghray A *et al.* Hepatocellular carcinoma: From diagnosis to treatment

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**Abstract**

Hepatocellular carcinoma is the sixth most prevalent malignancy worldwide and is a rising cause of cancer related mortality. Risk factors for hepatocellular carcinoma are well documented and effective surveillance and early diagnosis allow for curative therapies. The majority of hepatocellular carcinoma appears to be caused by cirrhosis from chronic hepatitis B and hepatitis C virus. Preventive strategies include vaccination programs and anti-viral treatments. Surveillance with ultrasonography detects early stage disease and improves survival rates. Many treatment options exist for individuals with hepatocellular carcinoma and are determined by stage of presentation. Liver transplantation is offered to patients who are within the Milan criteria and are not candidates for hepatic resection. In patients with advanced stage disease, sorafenib shows some survival benefit.

**Key words:** Hepatocellular carcinoma; Hepatitis C virus; Liver transplantation; Tumor ablation; Sorafenib

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**Core tip:** Hepatocellular carcinoma is a rising cause of cancer related mortality and viral causes of cirrhosis appear to be a major cause. Surveillance helps to detect early stage disease and treatment options are determined by stage of presentation. Three potentially curative options are radiofrequency ablation, liver transplantation and tumor resection. Emerging therapies such as drug-eluting beads-TACE or sorafenib will continue to advance treatment options in hepatocellular carcinoma. The following will provide a concise review of hepatocellular carcinoma from prevention to treatment.

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**INTRODUCTION**

Hepatocellular carcinoma is the sixth most common malignancy and is the leading cause of mortality in patients with cirrhosis[[1](#_ENREF_1)]. An estimated half million new cases are diagnosed each year world-wide with disease burden highest in developing countries (85% of all cases)[[2](#_ENREF_2),[3](#_ENREF_3)]. The average age of diagnosis is 65 years with a shift in the last decade toward diagnosis at an earlier age[[4](#_ENREF_4)]. This trend is especially seen in developing countries and has implications for treatment. Rates of hepatocellular carcinoma are two to four times higher in men compared to women[[5](#_ENREF_5)]. Over the past 20 years there has been a 3 fold increase in the number of new hepatocellular carcinoma cases in the United States (estimated 33190 in 2014)[[2](#_ENREF_2),[6](#_ENREF_6),[7](#_ENREF_7)]. The rising incidence of hepatocellular carcinoma in Western countries appears to correlate with the increasing prevalence of hepatitis C virus (HCV). Currently, the incidence of hepatocellular carcinoma continues to rise and the 5 year survival rate remains low[[7](#_ENREF_7)]. Monotherapy agents targeting HCV have made curative therapy in chronic infection possible and may eventually translate into lower rates of hepatocellular carcinoma. One may presume that despite the high cost of the monotherapy agents, there will be a profound impact on the downstream costs and related complications from chronic HCV and HCC.

Risk factors for hepatocellular carcinoma are well documented and effective surveillance with early diagnosis allows for curative measures.

**RISK FACTORS**

Cirrhosis is the most important risk factor for developing hepatocellular carcinoma and is present in 80% to 90% of individuals[[8](#_ENREF_8)]. The annual incidence of liver cancer in patients with cirrhosis is 1% to 6 %[[8](#_ENREF_8)]. Although there exists wide regional variations in distribution and etiology of hepatocellular carcinoma, chronic hepatitis B virus (HBV) and HCV infection represent the majority of hepatocellular carcinoma cases worldwide[[9](#_ENREF_9)]. The highest incidence of HBV is in eastern Asia and sub-Saharan Africa where it accounts for the majority of cases (greater than 50%)[[10](#_ENREF_10)]. Viral load, duration of infection and rate of replication are related to the incidence of hepatocellular carcinoma[[11](#_ENREF_11),[12](#_ENREF_12)]. Further, a risk association between HBV and hepatocellular carcinoma is present in endemic areas where the pattern of transmission is from mother to newborn. Several mechanisms for HBV progression to hepatocellular carcinoma are proposed. Viral integration into liver cells may cause chromosomal instability and alteration of normal cellular replication resulting in hepatocellular carcinoma[[13](#_ENREF_13),[14](#_ENREF_14)]. Further, inflammatory and/or necrotic changes from HBV may alter hepatocyte genetic expression or directly induce malignancy[[15](#_ENREF_15)].

On the other hand, hepatocellular carcinoma cases in North America, Europe and Japan are highest among HCV infected patients. Annual incidence of hepatocellular carcinoma is 1% to 4% in patients with HCV related cirrhosis[[16](#_ENREF_16),[17](#_ENREF_17)]. Compared to HCV negative patients, individuals with chronic HCV infection have a 17 times higher risk of developing hepatocellular carcinoma. In the United States, it is estimated that the incidence of HCV will continue to rise in the following decades[[18](#_ENREF_18),[19](#_ENREF_19)]. It is hypothesized that the primary mechanism for hepatocellular carcinoma in HCV patients is inflammatory hepatocyte damage from oxidative stress, promoting cirrhosis[[20](#_ENREF_20)].

Alcohol related liver disease and non-alcoholic fatty liver disease increase the risk of hepatocellular carcinoma alone or in combination with HBV/HCV. Further, obesity and diabetes are independent risk factors for the development of hepatocellular carcinoma[[21-23](#_ENREF_21)]. In patients with chronic viral hepatitis, obesity may synergistically increase the risk of hepatocellular carcinoma by 100 fold[[24](#_ENREF_24)]. It has also been elicited that patients with a higher BMI often have a higher rate of mortality[[25](#_ENREF_25)]. In addition, the number of metabolic syndrome components in a given patient appears to correlate with an increased risk of hepatocellular carcinoma[[26](#_ENREF_26)]. As rates of patients diagnosed with metabolic syndrome rise around the world, even a small contribution to the development of hepatocellular carcinoma would have a devastating impact.

Finally, a number of less common risk factors for hepatocellular carcinoma include hereditary hemochromatosis, autoimmune hepatitis, glycogen storage diseases, primary biliary cirrhosis, alpha1-antitrypsin deficiency, and Wilson’s disease.

**PREVENTION**

Studies for preventive strategies have centered on viral causes of hepatocellular carcinoma and minimal data exists on risk reduction for other etiologies. Although vaccination and anti-viral treatment remain the primary means of prevention, counseling patients on dietary modifications, weight loss and tobacco/alcohol cessation remain important steps to address.

The HBV vaccine is effective at preventing hepatocellular carcinoma and vaccination programs have lowered rates of related malignancy[[27](#_ENREF_27)]. Over a 10 year period, the Taiwan universal vaccination program reduced the annual incidence of hepatocellular carcinoma from 0.70 to 0.36 per 100000 children. Thus, one would suspect that initiation of universal vaccination programs in children would have an overall reduction in hepatocellular carcinoma disease burden in adults. For adults with chronic HBV infection, vaccinations have no role in preventing hepatocellular carcinoma. Rather, one must focus on anti-viral treatment. Treatment with interferon alpha (IFN-α) reduced the risk of hepatocellular carcinoma by 6.4% in a meta-analysis of seven studies[[28](#_ENREF_28)]. Further analysis revealed that the protective effects of IFN-α were limited to patients with cirrhosis[[29](#_ENREF_29)]. Other treatment options include nucleoside/nucleotide analog treatments and most published data is on lamivudine or adefovir. Treatment with these agents appear to effectively suppress viral replication and decrease the risk of developing hepatocellular carcinoma[[30-32](#_ENREF_30)].

Antiviral treatment for HCV may also reduce the risk of hepatocellular carcinoma. In several studies, treatment by IFN with sustained viral response correlated with a decreased risk of hepatocellular carcinoma compared to non-responders or no treatment[[33](#_ENREF_33),[34](#_ENREF_34)]. Newer treatment options for HCV with improved viral response rates may effectively reduce progression to hepatocellular carcinoma.

**SURVEILLANCE**

Practice guidelines recommend standardized surveillance programs for hepatocellular carcinoma with decision analysis models showing that surveillance improves survival and is cost effective if the annual rate of hepatocellular carcinoma exceeds 1.5% in a given population[[35](#_ENREF_35),[36](#_ENREF_36)]. Diagnosis at an early stage of hepatocellular carcinoma confers a survival benefit compared to patients diagnosed with advanced disease[[37](#_ENREF_37)]. Curative treatment options such as liver transplantation available in early stage disease likely contribute to this survival benefit.

Hepatic ultrasound and alpha-fetoprotein (AFP) have historically played a prominent role in hepatocellular carcinoma surveillance. A randomized controlled trial of 18861 participants assessed the effect of screening on hepatocellular carcinoma mortality. All study participants had HBV and were divided into 2 groups: patients who underwent screening with ultrasound every 6 mo and alpha-fetoprotein (AFP) compared with no surveillance. Surveillance was associated with a 37% reduction in hepatocellular carcinoma mortality, despite sub-optimal adherence to surveillance (< 60%)[[38](#_ENREF_38)].

For over 40 years AFP has been used in the detection of hepatocellular carcinoma with variable sensitivity (39% to 65%), specificity (76% to 94%) and positive predictive value (9% to 50%)[[39-43](#_ENREF_39)]. Results from several studies have challenged the utility of AFP in screening. A randomized controlled trial of 5581 hepatitis B virus patients showed that AFP bi-annual screening improved detection rates of hepatocellular carcinoma but earlier detection did not translate to decreased mortality[[44](#_ENREF_44)]. Concurrent AFP and ultrasound testing increased false positive rates and led to unnecessary diagnostic testing. Further, data suggest that for lesions less than 2 cm in diameter, AFP will rarely be elevated[[41](#_ENREF_41),[45](#_ENREF_45),[46](#_ENREF_46)]. An inherent disadvantage of AFP is that it can be elevated in chronic hepatitis even without hepatocellular carcinoma, resulting in low specificity. Current AASLD guidelines do not recommend AFP for screening or diagnostic purposes. Research into novel biomarkers for early hepatocellular carcinoma detection continue. As more sensitive assays such as AFP-L3 are developed, the role of serology for surveillance maybe re-analyzed[[47](#_ENREF_47)].

The ideal modality for HCC screening remains an area of controversy. Although the recommended method of surveillance is liver ultrasonography, diagnosis by this modality remains operator and equipment dependent (sensitivity of 65% and specificity of 90%)[[45](#_ENREF_45)]. Older studies have shown ultrasonography to be equivalent to CT in detecting hepatic lesions[[48](#_ENREF_48),[49](#_ENREF_49)]. But more recently, research into CT and MRI for HCC screening have yielded promising results in lesions greater than 2 cm[[50](#_ENREF_50)]. Prospective trials are needed before CT or MRI can replace ultrasonography as the primary screening method for HCC. Specifically cost effectiveness, cumulative radiation exposure and mortality benefit will need to be addressed.

The 6 mo interval length for screening is based on tumor doubling time and is not dictated by risk factors for hepatocellular carcinoma. A shorter 3 mo interval increased small nodule detection without affecting survival rates[[51](#_ENREF_51)], while longer periods between screening (12 mo) showed an increased rate of advanced tumors[[52](#_ENREF_52)]. Once a lesion has been detected, the size of the lesion determines the next step. Hepatic nodules less than 1 cm should be followed with repeat ultrasonography every 3 mo. If the lesion is stable over 2 years then a return to routine 6 mo surveillance is acceptable[[53](#_ENREF_53)]. Liver lesions exceeding 1 cm warrant further evaluation as described below.

**DIAGNOSIS**

Definitive diagnosis via non-invasive testing includes four-phase multidetector CT (unenhanced, arterial, venous and delayed) or dynamic contrast enhanced MRI. The presence of arterial hyper-enhancement with a venous or delayed phase washout of contrast medium, confirms a diagnosis of HCC[35]. While MRI provides superior contrast resolution compared to CT, metallic implants, respiratory artifact, significant ascites, cost and availability all limit its use. Patients with atypical features for hepatocellular carcinoma either on CT or MRI should undergo the other imaging modality or lesion biopsy. Individuals with discordant CT/MRI findings or hepatic lesions without cirrhosis should also receive a liver biopsy. The imaging modalities above are valid for patients with cirrhosis or chronic HBV without cirrhosis. Contrast enhanced ultrasonography should not be used for diagnostic purposes as it lacks specificity for hepatocellular carcinoma[[16](#_ENREF_16)]. Unfortunately, biopsies also carry a high false negative rate (up to 30%) - attributed to inadequate sampling[[54](#_ENREF_54)]. Despite a negative biopsy, surveillance of the lesion at 3 to 6 mo intervals for changes characteristic for hepatocellular carcinoma or for lesion enlargement should be completed[[16](#_ENREF_16)]. Lesions less than 1 cm are difficult to assess even with the combination of imaging and biopsy.

**TREATMENT**

Several treatment options exist for patients with hepatocellular carcinoma and can be categorized as curative or palliative. The three potentially curative options are radiofrequency ablation, liver transplantation, or tumor resection. Given the heterogeneity of hepatocellular carcinoma and complexity of treatment options patients are optimally managed by a multi-disciplinary team. The best therapy is determined based on the stage of presentation. The barcelona clinic liver cancer staging system (BCLC), developed in 1999, is a common means to assess prognosis and select appropriate therapy for hepatocellular carcinoma[[55](#_ENREF_55)]. In general, surgical resection or liver transplantation is the first line treatment option for early stage hepatocellular carcinoma; whereas asymptomatic patients with intermediate stage disease benefit from chemoembolization. Patients with end stage hepatocellular carcinoma or extensive extrahepatic disease often have a less than 3 mo rate of survival. In these individuals, pain and symptom control to improve quality of life should be the primary focus[[35](#_ENREF_35)].

Other staging systems such as Cancer of Liver Italian Program (CLIP), Okuda stage, French staging system have been validated to a lesser extent. Biomarkers such as vascular endothelial growth factors may have prognostic value in the future[[56](#_ENREF_56)].

***Resection***

Surgical resection is the therapy of choice in early stage hepatocellular carcinoma without cirrhosis or in the absence of portal hypertension. Selection criteria have been refined over the years and include individuals with a tumor size less than 3 cm in diameter, normal bilirubin and absence of portal hypertension. In patients without cirrhosis, a 60% to 75% five year survival rate can be achieved[[57](#_ENREF_57),[58](#_ENREF_58)]. Hepatic function evaluated by MELD or Child-Pugh correlate with survival following resection. As expected, patients in Child-Pugh A classification have an improved survival rate following resection compared with those in class B or C[[59](#_ENREF_59),[60](#_ENREF_60)]. In the United States only 5% of individuals will qualify for resection, while in Asia younger age of presentation allows 40% of patients to qualify for surgical resection[[61](#_ENREF_61)]. Laproscopic liver resection accounts for 10%-20% of procedures in the United States and minimize postoperative morbidity compared to open resection. Patients with multiple intra-hepatic tumors are not ideal candidates for resection as this often represents intrahepatic metastasis[[62](#_ENREF_62)]. Although technically feasible in some patients, multiple hepatic lesion resection must be reviewed on a case by case basis[[63](#_ENREF_63),[64](#_ENREF_64)]. Further, vascular invasion significantly reduces the five year survival rate from around 50% to 10%[[65](#_ENREF_65)]. Individuals with a MELD score greater than 9 have a high mortality rate after resection and alternative therapies should be considered[[66](#_ENREF_66)].

Unfortunately, hepatic resection does not alter the course of underlying cirrhosis. At 2 years, 43% to 65% of patients will have a recurrent tumor and by 5 years post-resection 70% will have recurrent hepatocellular carcinoma[[67](#_ENREF_67),[68](#_ENREF_68)]. Pre-operative predictors of recurrent free survival include: Child-Pugh class, hepatic function, degree of fibrosis, total serum bilirubin, platelet count, portal hypertension, micro/macroscopic vascular invasion and tumor burden (number and size)[[69](#_ENREF_69)]. A case by case selection for patients with cirrhosis is essential to limit complications and mortality. Operative mortality ranges from 4% to 4.7% for resection with the majority of deaths likely in patients with underlying cirrhosis and large tumor burden[[70](#_ENREF_70)]. As newer treatment options for HCV are developed, treatment of underlying cirrhosis after resection may alter/delay the development of recurrent hepatocellular carcinoma.

***Liver transplantation***

Liver transplantation offers a potential cure of hepatocellular carcinoma as it treats the malignancy and the underlying cirrhosis. Given the scarcity of livers available for transplantation, one must carefully select patients to optimize outcomes.

Patients with hepatocellular carcinoma complicated by cirrhosis and/or portal hypertension should be evaluated for liver transplantation as it carries the lowest rate of tumor recurrence. Traditionally 3 scoring criteria are utilized to determine eligibility [Milan Criteria, University of California San Francisco (UCSF)] and prioritize patients for transplant [Model for End Stage Liver Disease (MELD)]. The Milan Criteria considers patients eligible for liver transplantation if they present with a single nodule less than 5 cm in diameter or 3 nodules with each less than 3 cm, without evidence of distant metastasis or vascular invasion. With the initial trial showing a 4 year survival rate of 75% and results verified in further studies, organ allocation societies including UNOS have adopted this criteria[[71-73](#_ENREF_71)]. Recurrent free survival for patients meeting Milan criteria is 90% with a 4 year overall survival rate of 85%[[71](#_ENREF_71)]. In contrast patients exceeding criteria parameters have a respective 59% and 50% rate of survival[[71](#_ENREF_71)]. The UCSF criteria proposed in 2001 expands the eligibility requirements set forth by the Milan criteria to include more patients with hepatocellular carcinoma. This criteria included individuals with a single tumor less than 6.5 cm or those with 3 nodules less than 4.5 cm (total diameter of no more than 8 cm). Experience with the UCSF criteria has shown similar survival rates compared to the Milan criteria[[74](#_ENREF_74),[75](#_ENREF_75)]. Unfortunately, the paucity of organs available for transplant remains a major obstacle.

Liver allocation is prioritized by the MELD score. All hepatocellular carcinoma patients have an adjusted MELD score of 22 with increases at each 3 mo interval. Prioritized allocation with MELD score adjustment has increased the number of hepatocellular carcinoma patients undergoing liver transplantation.

***Tumor ablation***

Chemical (ethanol, acetic acid) or thermal ablation (radiofrequency ablation (RFA), microwave, laser, cryoablation) are also used to treat hepatocellular carcinoma. Historically, percutaneous ethanol injection (PEI) had been used to induce cellular dehydration/necrosis in small hepatocellular carcinoma tumors. RFA has largely replaced PEI as studies have shown higher rates of complete response with fewer number of treatment sessions[[76-78](#_ENREF_76)]. RFA is superior to PEI in large and small lesions, although the benefit of using RFA is more pronounced in tumors larger than 2 cm in diameter[[79](#_ENREF_79)]. Combination RFA and PEI for high risk lesions is an area of ongoing research with promising results[[80](#_ENREF_80)].

***Radiofrequency ablation***

In cases of early stage hepatocellular carcinoma where surgical resection or liver transplantation are not feasible, radiofrequency ablation (RFA) is a minimally invasive approach to local ablation. Therapeutic effects are a result of thermal tumor necrosis, parenchymal and protein destruction[[81](#_ENREF_81)]. Overall complication rates for RFA are low and are minimized when performed by an experienced physician[[82](#_ENREF_82)]. Efficacy of RFA is limited by tumor size and location, with a less than fifty percent rate of ablation in tumors larger than 5 cm[[83](#_ENREF_83)]. RFA is also discouraged in large lesions as the risk of side effects may outweigh benefits[[81](#_ENREF_81)]. Further, therapy near large vessels may not achieve adequate temperature for coagulative necrosis[[84](#_ENREF_84)]. Tumors adjacent to intestine or large bile ducts may also preclude RFA.

Rate of recurrence for RFA is higher compared to surgical resection. For large and small tumors, RFA was associated with a significantly lower survival rate compared to surgical resection[[85](#_ENREF_85),[86](#_ENREF_86)]. Thus investigating RFA as a bridge to surgical intervention is logically area of research. Several retrospective studies have shown that pre-transplant RFA delays tumor progression and extends time on the liver transplant list[[87-90](#_ENREF_87)]. As a major limitation remains the number of organs available for transplant it remains unclear whether the extended time on the liver transplantation list will translate into improved clinical outcomes. Currently guidelines from AASLD support the use of RFA as a bridge to liver transplantation (level II evidence), although the exact role of bridging therapies has not been defined[[35](#_ENREF_35)].

***Transarterial chemoembolization***

Blood supply to hepatocellular carcinoma tumors are mainly from the hepatic artery. Transarterial chemoembolization (TACE) is the selective occlusion of the blood supply to the tumor with synergistic local distribution of chemotherapy and radioactive substances. The hypervascularity of hepatocellular carcinoma allows for this targeted therapy, minimizing side effects. The choice of chemotherapeutic agent is not standardized and may include agents such as doxorubicin, cisplatin or epirubicin.

For patients who are not candidates for liver transplantation or resection with tumors too large for local ablation, TACE is effective salvage therapy. Other criteria for treatment include: preserved liver function and no evidence of extrahepatic metastasis or vascular invasion. Approximately 35%-40% of patients will achieve a 25% decrease in tumor size with response rates as high as 60% when surrogate markers for response are utilized[[91-93](#_ENREF_91)]. A meta-analysis of six randomized controlled trials showed that patients who underwent TACE had a 2 year improved survival rate compared to those who only had supportive therapy[[93](#_ENREF_93)]. Interestingly, a meta-analysis of nine trials did not show a significant difference in survival based on chemotherapeutic agent used in TACE treatments[[94](#_ENREF_94)]. Growing literature supports the efficacy of TACE for hepatocellular carcinoma down-staging and bridging. The first study to use TACE prior to liver transplantation was published in 1997 and showed successful down-staging of tumors greater than 3 cm with a significant improvement in 5 year survival compared to no TACE[[95](#_ENREF_95)]. More recent studies show that 22% to 70% of patients were successfully downstaged with a 2 year post-transplant survival rate of 81%, and among advanced stage hepatocellular carcinoma (III/IV) patients a median survival of 20 mo[[96-101](#_ENREF_96)]. Based on response to therapy, repeat TACE treatments can be scheduled. More intense therapies may be associated with increased risk of acute hepatic decompensation and should be weighed against the potential gains from therapy[[91](#_ENREF_91)]. Transarterial radioembolization (TARE), a method of delivering internal radiation to the neoplasm using Yttrium 90, represents an alternative to TACE in intermediate stage HCC[[102](#_ENREF_102)]. This modality of treatment is indicated in patients with portal vein thrombosis where conventional TACE is contraindicated. Survival and response rates for TARE were comparable to TACE while a low side effect profile allows for treatment to be completed in the outpatient setting[[103](#_ENREF_103),[104](#_ENREF_104)].

Novel modalities such as drug-eluting beads-TACE (DEB-TACE) are being investigated in the non-transplant and as neo-adjuvant therapy in patients awaiting transplant. The drug-eluting beads appear to enhance medication delivery and reduce side effects by gradually releasing chemotherapy agents. The PRECISION trial compared non-transplant hepatocellular carcinoma patients who received DEB-TACE versus TACE. Sub-group analysis revealed a significantly lower hepatic/cardiac toxicity profile in the DEB-TACE group[[105](#_ENREF_105)]. A small retrospective analysis in transplant patients also showed that DEB-TACE had improved rates of response with minimal adverse effects compared to embolization alone[[106](#_ENREF_106)].

**CHEMOTHERAPY**

Systemic therapies for the management of patients with hepatocellular carcinoma continue to be researched. Cytologic agents such as tamoxifen, doxorubicin, everolimus and thalidomide have shown marginal success. Targeted molecular therapies such as bevacizumab, brivanib, erlotinib may be alternatives to conventional cytologic agents. To date, sorafenib is the only systemic therapy effective for treating advanced stage hepatocellular carcinoma. Sorafenib is an oral tyrosine kinase inhibitor with anti-angiogenic activity, and now is the standard of care in treating individuals with advanced stage hepatocellular carcinoma and Child’s A cirrhosis[[107](#_ENREF_107),[108](#_ENREF_108)]. Patients with minimal tumor related symptoms, vascular invasion and extrahepatic spread are considered ideal for treatment. Clinical experience has shown significant delay in tumor proliferation and angiogenesis with sorafenib therapy. Those with decompensated cirrhosis or those with a less than 3 mo life expectancy should not receive sorafenib. Adverse events include diarrhea, hand foot skin reaction, and fatigue and dose reduction achieves tolerance in most patients.

The Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) was a multi-center double-blinded controlled phase III trial that demonstrated a 31% decrease in risk of death with a median 3 mo delay in radiologic progression of disease in patients prescribed sorafenib[[108](#_ENREF_108)]. Further, the Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma (GIDEON) which included a heterogeneous population of unresectable HCC patients showed that sorafenib was generally well tolerated in the clinical setting[[109](#_ENREF_109)]. The role of sorafenib in treating early stage hepatocellular carcinoma and as neo-adjuvant therapy prior to liver transplantation is evolving. In pre-transplant patients, sorafenib combined with TACE may inhibit angiogenesis and induce tumor necrosis[[110](#_ENREF_110)]. Other targeted molecular therapies beyond sorafenib continue to be researched and may represent second line agents for patients that fail or are unable to tolerate sorafenib.

**CONCLUSION**

Hepatocellular carcinoma is a common cause of malignancy world-wide. Emphasis should be placed on surveillance and early diagnosis. Treatment of hepatocellular carcinoma has changed significantly over the past few decades with curative options such as liver transplantation, hepatic resection and radiofrequency ablation now available. Further, novel therapies such as DEB-TACE or sorafenib will continue to be areas of research. Despite these advances, there remains much to be learned about hepatocellular carcinoma. Research into effective prevention and factors that may mitigate malignant transformation should be further explored.

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