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# Current and future treatments for hepatocellular carcinoma

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## Abstract

Hepatocellular carcinoma (HCC) represents a unique challenge for physicians and patients. There is no definitively curative treatment. Rather, many treatment and management modalities exist with differing advantages and disadvantages. Both current guidelines and individual patient concerns must be taken into account in order to properly manage HCC. In addition, quality of life issues are particularly complex in patients with HCC and these concerns must also be factored into treatment strategies. Thus, considering all the options and their various pros and cons can quickly become complex for both clinicians and patients. In this review, we systematically discuss the current treatment modalities available for HCC, detailing relevant clinical data, risks and rewards and overall outcomes for each approach. Surgical options discussed include resection, transplantation and ablation. We also discuss the radiation modalities: conformal radiotherapy, yttrium 90 microspheres and proton and heavy ion radiotherapy. The biologic agent Sorafenib is discussed as a promising new approach, and recent clinical trials are reviewed. We then detail currently described molecular pathways implicated in the initiation and progression of HCC, and we explore the potential of each pathway as an avenue for drug exploitation. We hope this comprehensive and forward-looking review enables both clinicians and patients to understand various options and thereby make more informed decisions regarding this disease.

**Key words:** Hepatocellular carcinoma; Hepatoma; Hepatocellular cancer; Liver cancer; Adult; Liver cell carcinoma; Liver cell carcinoma; Adult; Liver neoplasm; Hepatic neoplasm

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**Core tip:** Hepatocellular carcinoma (HCC), depending on the stage, has several treatment options including surgery, radiotherapy and biological agents such as Sorafenib. For both practitioners and patients these treatment modalities all offer advantages and disadvantages over one another. The question of when to use each modality remains an active field of debate. In order to provide clarity in this regard, we review currently used treatment methods along with the relevant data supporting or refuting them. Additionally, we then discuss molecular pathways involved in HCC that could be, and in some cases already are being, exploited for potential future drug therapy.

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## INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cause of cancer and the most common type of hepatobiliary cancer with over 500000 new cases diagnosed yearly and having an annual death rate of 250000 people<sup>[1]</sup>. HCC is a highly angiogenic solid tumor characterized molecularly by cell cycle dysregulation, aberrant angiogenesis, and evasion of apoptosis. The molecular pathogenesis of HCC is very complex comprising of multiple genetic and epigenetic alterations, chromosomal aberrations, gene mutations, and altered molecular pathways<sup>[2]</sup>. Angiogenesis plays a vital role in the growth, invasiveness and metastatic potential of HCC. The angiogenic-nature of this tumor also contributes to its method of detection. As is known, both helical computed tomography (CT) and magnetic resonance imaging (MRI) utilizing arterial phase contrast administration can accurately diagnose HCC.

To date, liver transplantation comes the closest to cure by offering the potential for complete removal of the cancer, however in reality recurrence and adverse outcome rates remain high<sup>[3]</sup>. In the absence of a definitive "cure", many treatment options exist, each with their own advantages and disadvantages. The number of options available can be daunting for both patients and practitioners.

In this review, we discuss the various treatment modalities currently available for HCC, the various pros and cons for each approach and the differing outcomes obtained. We discuss the mechanism of action and clinical data behind new therapeutic options such as Sorafenib. We then discuss molecular pathways involved in HCC that could be, and in some cases already are being, exploited for potential future drug therapy. We hope this comprehensive and forward-

looking review enables both clinicians and patients to understand various options and thereby make more informed decisions regarding this disease.

## EARLY DISEASE THERAPY (BCLC STAGE 0/A): CURATIVE TREATMENTS

### Liver transplantation

Liver transplantation eliminates HCC and therefore is the best therapeutic approach for the treatment of HCC. Unfortunately, as is commonly known, demand for liver transplantation far exceeds the available supply. The guidelines outlined in the Milan criteria (solitary tumors of < 5 cm in diameter and up to three tumor nodules, each of which is < 3 cm) have helped establish this success<sup>[4]</sup>. The beneficial aspects of liver transplantation include wide margin tumor excision, removal of intrahepatic metastasis, curing of underlying cirrhosis and accurate pathologic staging and histological examination of the entire liver.

The Milan criteria are used for selecting and screening patients with HCC for transplantation. The recurrence of HCC post-transplantation poses the most significant hurdle with risk of mortality due to metastatic disease and the effect of immunosuppressant therapy. Despite this, transplantation remains the most effective treatment for solid HCC neoplasms. Vascular invasion, the size and number of nodules, serum alpha-fetoprotein levels and tumor differentiation guide the recurrence risk<sup>[5-8]</sup>. Although multiple groups have suggested less restrictive guidelines than currently established, the limited availability of liver grafts makes this a hotly debated topic. Further investigation would be needed to rationalize softening the criteria for transplantation in patients with advanced HCC. What is known is that many patients are listed for transplantation only to sit on a waiting list until their HCC advances to the point where they are no longer candidates. During this time, lack of treatment of HCC will invariably lead to vascular invasion and extrahepatic spread; both conditions of exclusion and overall poor prognosis. Estimates of exclusion/drop-out due to progression while on the wait list are in the area of 25% at 1 year<sup>[9]</sup>.

The Model for End-Stage Liver Disease (MELD) score has proved to be an objective and reliable marker of early mortality in transplant candidates. Prior to the MELD scoring system adoption in 2002, the United States based liver transplant allocation on urgency and wait time<sup>[10]</sup>. The Milan criteria were invoked to evaluate tumor progression and patient death without transplant for patients with Stage I or stage II tumors. At 3 mo, these patients had a dropout risk of 15% and 30%, respectively. Experts convened and assigned MELD scores of 24 and 29 to patients with Stage I and II tumors, respectively. Importantly, patients with Stage III or IV tumors did not receive a corresponding MELD score, but could be

**Table 1** Scoring/grading systems related to hepatocellular carcinoma

System	Description	When used
Milan Criteria <sup>[4]</sup> , 1996	Single tumor $\leq$ 5 cm, or 2-3 tumors $\leq$ 3 cm, and no vascular invasion and/or extrahepatic spread.	Staging HCC
UCSF Criteria <sup>[5]</sup> , 2001	Single tumor $\leq$ 6.5 cm, or 2-3 lesions, none exceeding 4.5 cm, with total tumor diameter $\leq$ 8 cm, no vascular invasion and/or extrahepatic spread.	Staging HCC
Model for End-Stage Liver Disease Score (MELD) <sup>[107]</sup> , 2000	Specific equation looking at the variables of bilirubin, INR and serum creatinine.	Transplant prioritization, End-stage liver disease severity by estimating 3 mo mortality
Barcelona Clinic Liver Cancer (BCLC) Staging <sup>[108]</sup> , 1999	Variables include tumor stage, liver functional status, physical status, and cancer-related symptoms	Widely accepted treatment algorithm of HCC
Child-Pugh-Turcotte <sup>[109,110]</sup> , 1964-1972	Variables include bilirubin, albumin, INR, Ascites and presence of encephalopathy	Prognosis/severity of liver disease including cirrhosis
Tumor-Node-Metastasis <sup>[111]</sup> , 1997	Variables include the classic tumor size/location, lymph node positivity, and presence of metastasis.	Standard and poorly predictive staging system not currently in use
Okuda <sup>[112]</sup> , 1985	Variables include albumin, ascites, bilirubin, and tumor stage (more or less than 50% of liver area involved)	Properly stratified patients with advanced/symptomatic stage and is useful to identify end-stage patients. Lacks early stage predictive capacity
Japan Integrated Staging (JIS) <sup>[113]</sup> , 2000	Combines TMN with Child-Pugh	Prognostic staging system for hepatocellular carcinoma

HCC: Hepatocellular carcinoma.

listed according to their “physiologic” MELD score. The initial results in the years that followed indicated that patients with HCC were receiving too high a priority in relation to other transplant candidates. In addition to this, a proportion of these high priority HCC patients were found to not have had HCC on pathological analysis and therefore the qualifying MELD scores were reduced to their current values, which for stage I HCC is 0 and for stage II is 22. For every three months a patient is listed, their MELD score increases by 10%<sup>[9]</sup> (Table 1).

Current data suggests that living-donor liver transplantation could reduce the dropout rate for patients suffering from HCC and has similar outcomes to cadaveric donor transplantation as well as those with HCC extended Milan criteria<sup>[11,12]</sup>. Additionally, decision analysis of living-donor liver transplantation considering cost, dropout and donor mortality proves beneficial at wait times beyond 7 mo<sup>[13]</sup>. Surgeons generally prefer living-donor liver transplantation for patients that fall outside of the criteria due to tumor size or the number of tumors as a possible option for transplantation.

### Hepatic resection

The most successful treatment for non-cirrhotic patients with appropriately staged HCC is hepatic resection. Extensive resections can be performed with minimal morbidity<sup>[14]</sup>. Strict selection criteria are needed to screen for presence of cirrhosis because post-operative complications more commonly occur and can include hepatic failure. Currently, to ensure successful treatment for resection of HCC, physicians routinely use multiple procedures that consist of intraoperative ultrasonography, vascular occlusion, hepatic parenchymal transection and appropriate drainage after transection of the liver. Ultrasonography and endoscopic ultrasound (EUS) allow liver resection

to be done safely by improving vessel detection of the tumors. Ultrasound can also detect lesions that were missed on pre-operative imaging, during both primary and repeat liver resection<sup>[15]</sup>. Procedures such as the inferior right hepatic vein-preserving hepatectomy and ultrasonically guided sub-segmentectomy would not be possible without ultrasound. A recent retrospective study of HCC has shown that resection-utilizing ultrasound is better in comparison to anatomical resection alone<sup>[16,17]</sup>. Intermittent inflow occlusion is a common and safe technique utilized in liver resection. The hemihepatic vascular occlusion and Pringle's maneuver minimize blood loss and have been shown not to affect post-operative liver function significantly as displayed in randomized controlled trials (RCT)<sup>[18]</sup>. Total hepatic vascular exclusion of both the inflow and outflow tracts is rarely performed due to the perioperative morbidity. Various flow patterns have been developed, but the general consensus remains that intermittent inflow occlusion is the most successful technique<sup>[19,20]</sup>.

Liver resection is an established treatment for HCC with significantly decreased surgical mortality. In a trial conducted by Llovet *et al.*<sup>[21]</sup> between 1989 and 1997, 164 patients underwent evaluation for surgical treatment of HCC. 77 underwent resection and 87 were selected for transplantation. Evaluation of one, three, and five-year survival in the resection group was 85%, 62% and 51%, respectively. This compared to 84%, 69% and 69% for those that underwent transplantation. Early diagnosis and treatment can be curative in some patients, but HCC often recurs. The post-operative 5-year recurrence rate nears 50%<sup>[22]</sup>. When recurrent HCC does result, the tumor tends to be more aggressive and harder to treat. Regardless of this, evaluation for repeat resection should occur. In a study conducted by Minagawa *et al.*<sup>[23]</sup> of 334 patients with primary resection of HCC, 67 received

repeat resection for recurrence. 1, 3, and 5-year survival rates of 94%, 75% and 56% were noted following repeat resection, respectively. In multivariate analysis, good prognostic factors for repeat resection included lack of portal vein invasion, a single HCC lesion during the primary hepatic resection, and a disease-free interval of at least one year or more following the primary resection. As in all therapeutic approaches, poor prognostic indicators included more than three tumors, a tumor size larger than 5 cm, portal vein invasion, intrahepatic metastases, absence of a tumor pseudocapsule, advanced TNM stage (III or IV), and a Child-Pugh class of C<sup>[24]</sup>. Pre-operative transhepatic artery chemoembolization (TACE) is not recommended. Despite some studies showing a potential survival benefit and reduced recurrence<sup>[25,26]</sup> most, including clinical practice guidelines, strongly advise against its use in this regard<sup>[27,28]</sup>.

### Ablation

Percutaneous ablative techniques have several foreseeable advantages over surgical resection. Along with an abbreviated recovery period, the minimally invasive and therefore well-tolerated approach of percutaneous ablation has provided a decision point for patients and physicians when initiating treatment of early stage HCC lesions. Although some studies suggest superiority of resection to ablation for the treatment of HCC, two RCT trials have shown equivalent long term and disease free survival.

Huang *et al.*<sup>[29]</sup> randomized 76 patients to undergo either resection ( $n = 38$ ) or ethanol ablation ( $n = 38$ ). In this study, equivalent recurrence, 18 and 15 and mortality, 3 and 5 was noted between the ethanol ablation and resection groups, respectively. Both elevated alpha-fetoprotein levels ( $> 200$  ng/mL) and Child-Pugh class B cirrhosis conferred higher recurrence and shorter survival. In the study comparing RFA to resection conducted by Chen *et al.*<sup>[30]</sup>, 161 patients were randomized to receive either resection ( $n = 90$ ) or RFA ( $n = 71$ ). Similar 1, 2, 3, and 4 year survival and disease free survival was noted between the groups. At 4 years following therapy, survival was 64% and 67.9% and recurrence-free survival was 51.6% and 46.4% in the resection and RFA groups, respectively. In both studies mentioned, immediate post-procedural complications were less in the percutaneous interventional group. When comparing the two treatment modalities to one another RFA appears to be superior to ethanol injection<sup>[31-33]</sup>.

Despite these promising results, wide adoption of ablative techniques remains absent. A prospective cohort conducted by the Liver Cancer Study Group of Japan, addressed some concerns with these studies and advised against complete adoption of this technique as an equally effective therapy<sup>[34,35]</sup>. This prospective study was conducted between

year 2000 and 2003 and identified 17149 patients with HCC who underwent treatment with either resection, percutaneous ethanol injection (PEI), or radio frequency ablation (RFA). Of this group, 7185 patients had no more than three tumors and Child-Pugh class A or B liver function. The two-year time to occurrence rate was 35.5%, 55.4%, and 73.3% in the resection ( $n = 2857$ ), RFA ( $n = 3022$ ), and PEI group ( $n = 1306$ ), respectively. Overall survival rates were not different between the groups. Similar results indicating decreased recurrence rates among patients who underwent hepatic resection compared to percutaneous ablative therapy were noted in retrospective analyses<sup>[36,37]</sup>.

Currently, a multicenter joint RCT is ongoing to address the controversial therapeutic topic between hepatic resection and RFA (SURF trial)<sup>[38]</sup>. Until the results of this data are known treating with hepatic resection if the patient is without evidence of liver cirrhosis or associated conditions is recommended. If the patient is not a surgical candidate or has underlying Child-Pugh A or B cirrhosis current guidelines recommend pursuit of RFA<sup>[28,39]</sup>.

## LATER DISEASE THERAPY (BCLC STAGE B, C): PALLIATIVE TREATMENTS

### TACE

TACE is a treatment modality employed for the management of patients with HCC who are deemed poor candidates for curative treatments. Traditionally, the procedure involves the intra-arterial injection of chemotherapeutic agents, usually suspended in lipiodol, into the hepatic artery followed by obstruction of the hepatic artery with embolizing particles. TACE using drug-eluting beads (DEB-TACE) is an expansion upon the traditional technique and includes the addition of embolizing particles into a cytotoxic agent. Despite the technique used, the ultimate goal is to both increase tumor cell exposure to cytotoxic agents and selectively tamponade the blood supply to the liver lobe affected by HCC. The procedure is performed under radiological guidance in order to maneuver the catheter from the main hepatic artery into sub-segmental branches specifically supplying blood to the tumor.

Although the liver is dually supplied by both the hepatic artery and the portal vein, vascularization of hepatocellular carcinoma typically arises from the hepatic artery alone<sup>[40]</sup>. TACE takes advantage of this pathophysiology by embolizing part or the entire hepatic artery, which is only responsible for approximately 30% of the blood supply to normal hepatic parenchyma, but the primary supply for HCC. For traditional TACE, chemotherapeutic agents are suspended in iodized oil, typically Lipiodol, and injected in the arterial supply closest to the tumor. Doxorubicin and Cisplatin are the most common agents used



today<sup>[28,41]</sup>. Tumor cells selectively uptake the chemotherapy/lipiodol cocktail which can remain active inside the cell from weeks to months<sup>[42]</sup>. Subsequent to chemotherapy, arterial embolization is performed using agents such as Gelfoam, polyvinyl alcohol particles, alcohol, starch microspheres, and less commonly metallic coils or autologous blood clots. There are advantages and disadvantages to each embolic agents. Therefore, agents are usually chosen for variables such as tumor size and provider preference. Gelfoam is the most common agent used in practice today. The advantages of Gelfoam over other agents include the ability to prepare various particle sizes, the temporary nature of the occlusion, and its safety profile.

TACE using drug-eluting beads (DEB-TACE) is similar in many ways to traditional TACE, however DEB-TACE uses embolizing particles which act as carriers for cytotoxic agents. The goals of these particles are both to embolize the hepatic artery and to provide a slow, controlled release of cytotoxic agents. Typical particles used include sulfonate-modified poly (vinyl alcohol) hydrogel, or a sodium acrylate and vinyl alcohol copolymer. Particles can then be loaded with chemotherapeutic agents, most commonly doxorubicin. The benefits of DEB-TACE over traditional TACE include but are not limited to a reduction in the total plasma concentration of these therapeutic agents. Optimal candidates for TACE are patients with large multifocal HCC, preserved liver function, an absence of cancer related symptoms, and no extrahepatic or intravascular spread who present with nonsurgical HCC and are also not eligible for percutaneous ablation<sup>[28]</sup>. Contraindications to TACE include decompensated liver failure, renal failure, poor hepatic blood flow, and portal vein thrombosis. Relative contraindications include tumor size greater than 10 cm, bile duct or papilla obstruction or incompetence, and untreated varices at high risk for bleeding.

Evidence supporting the benefits of traditional TACE over conservative management for both long-term survival and tumor response have been shown through randomized control trials<sup>[43,44]</sup> and confirmed through meta-analysis studies<sup>[45]</sup>. It should be noted that a patient's response to traditional TACE varies depending on several prognostic factors including response to therapy, vascular/portal vein invasion, liver function, and tumor burden<sup>[46]</sup>. The benefits to survival and tumor response of DEB-TACE over traditional TACE are not yet well defined. Although failing to show superiority of DEB-TACE over traditional TACE, a randomized controlled trial was able to report an improved tumor response rate of 52% for DEB-TACE vs 44% for traditional TACE<sup>[47]</sup>. Another recent systematic review, confirmed DEB-TACE offered no survival benefit over traditional TACE. However, this study once again observed an improved tumor response rate and additionally reported a slightly lower incident of adverse events for DEB-TACE as compared to traditional TACE<sup>[48]</sup>.

Transarterial chemoembolization is a relatively well tolerated procedure with major complications occurring in approximately 5% of cases<sup>[49]</sup>. Complications of TACE can be subdivided into vascular and nonvascular. Vascular complications include access site injuries, hepatic artery injury, non-target embolization, and pulmonary embolization of Lipiodol<sup>[50]</sup>. Access site injuries are fairly uncommon and include hematoma, pseudoaneurysm, and arteriovenous fistula formation. Hepatic artery injury and non-target embolization are among the most serious of the vascular complications. Variations in vascular anatomy, and inappropriate manipulation of the catheter and guide wire are major contributors to hepatic artery injury. Non-target embolization can occur through failure to recognize an arterial supply to non-hepatic structures or reflux of chemotherapeutic agents along the catheter. Finally, sequela of injury varies depending on the downstream tissues supplied by the compromised arterial supply, but includes ulceration, perforation, abscess formation, and organ dysfunction or failure<sup>[49]</sup>.

Nonvascular complications to TACE include post embolization syndrome, acute liver decompensation, bacteremia and sepsis, renal failure, variceal bleeding, and biliary/gastrointestinal tract complications<sup>[51]</sup>. Of these side effects, post embolization syndrome (PES) is the most common, occurring in approximately 90% of patients. It is marked by fever, malaise, nausea, vomiting, and right upper quadrant abdominal pain. Symptom severity is dependent on the dose of chemoembolic agents<sup>[52]</sup>, but can be controlled with adequate analgesics and antiemetics. Jaundice, sclera icterus, ascities, and encephalopathy are physical exam findings indicating acute liver decompensation after TACE. Elevated lactate dehydrogenase (> 425 mU/mL), serum bilirubin (> 2 mg/dL), aspartate transaminase (> 100 mL), and tumor burden > 50% of liver volume are criteria identifying patients at high risk for liver failure following TACE<sup>[46]</sup>. Individual patient risk for developing liver failure following TACE varies depending on preprocedural liver function, and can be transient or permanent<sup>[29]</sup>. Hepatobiliary abscess formation post TACE is hypothesized to develop following an intra-procedural or post-procedural ischemic event to local tissue with subsequent overgrowth of colonizing enteric flora<sup>[53]</sup>. Patients at greatest risk are those who surgically manipulated biliary tree such as bilioenteric anastomosis, biliary stents, or sphincterotomy. Closer perioperative monitoring and aggressive antibiotic prophylaxis may help to prevent abscess formation<sup>[54]</sup>. Once abscess formation has occurred, treatment with surgical drainage and prolonged intravenous antibiotic therapy is indicated.

Investigations into the complications and adverse effects of DEB-TACE are currently in their infancy. Vascular and procedural complications are identical to traditional TACE. However, early studies suggest non-vascular complications of DEB-TACE are less

frequent<sup>[48]</sup>. The current thought is this is secondary to a more localized release and lower serum concentrations of chemotherapeutic agents observed with DEB-TACE.

### **Sorafenib**

Sorafenib is the first oral multi kinase inhibitor approved for the treatment of “unresectable” HCC by FDA in 2007 based on the results of two large multicenters randomized controlled trials<sup>[55,56]</sup>. Sorafenib was noted to have inhibitory effects on cell growth, induction of apoptosis, and down regulation of anti-apoptotic protein Mcl-1 in preclinical models<sup>[57]</sup>. The drug was also found to reduce tumor angiogenesis, tumor cell signaling, and tumor growth in a dose dependent manner in mouse xenograft models of HCC by blocking Raf/MEK/ERK pathway and other extracellular receptor tyrosine kinases<sup>[58-60]</sup>.

### **SHARP trial (Llovet *et al*<sup>[55]</sup>, 2008)**

SHARP trial is a large multicenter phase III double blind RCT conducted at 121 centers in Europe, North America, South America, and Australia involving 602 patients with advanced HCC who have not received any previous systemic treatment. The patients received either Sorafenib (400 mg BID) or placebo. The primary outcomes were overall survival and the time to symptomatic progression and secondary outcomes included the time to radiologic progression, disease control rate, and safety. The patients had an ECOG score of 2 or less and belong to Child-Pugh class A based on liver function and BCLC stage B and C based on tumor staging. The underlying etiology for the HCC was Hep C followed by alcohol and Hep B<sup>[55]</sup>.

The overall median survival was 10.7 mo (95%CI: 9.4-13.3) compared to 7.9 mo (95%CI: 6.8-9.1) in placebo group ( $P < 0.001$ ). The one-year survival rate was also higher (44% vs 33%,  $P = 0.009$ ). There is significant improvement in time to radiologic progression (5.5 mo vs 2.8 mo) and time to symptomatic progression (4.1 mo vs 4.9 mo). Even though there was no complete response in sorafenib group, there was a significant difference noted in stable disease (71% vs 67%) and disease control rate (43% vs 32%).

Sorafenib was well tolerated and the adverse effects reported were predominantly grade 1 or 2 in severity related to gastrointestinal, constitutional, or dermatological in nature. Most frequently reported adverse effects were diarrhea, weight loss, hand-foot-skin reaction, alopecia, and anorexia. Hypophosphatemia and thrombocytopenia were most frequently noted laboratory abnormalities. Overall, sorafenib has shown considerable improvement in overall survival with acceptable side effects and tolerability.

### **Sorafenib Asia-Pacific Trial (Cheng *et al*<sup>[56]</sup>, 2005-2007)**

The other study conducted in the Asia-Pacific region

that concurred with the SHARP study findings was a randomized multicenter control trial done by Cheng *et al*<sup>[56]</sup>. The phase III double blind RCT was carried over at 23 centers in China, South Korea and Taiwan involving 271 patients with advanced HCC with no previous systemic therapy and belonging to Child Pugh class A and BCLC stage C. 400 mg of Sorafenib was given twice daily in six week cycles. There were no primary end points were set but overall survival, time to progression, time to symptomatic progression, disease control rate and safety were assessed at each cycle.

The median survival in Sorafenib group was 6.5 mo (95%CI: 5.5-7.5) compared to 4.2 mo (95%CI: 3.75-5.46) ( $P = 0.014$ ). The six months overall survival was also higher in Sorafenib group (53.3% vs 36.7%). Even though no complete response was seen in treatment group, there was a significant difference between the groups in terms of partial response (3.3% vs 1.3%), stable disease (54% vs 27.6%), progressive disease (30.7% vs 54%), and disease control rate (35.3% vs 15.8%). A similar adverse reaction profile was noted compared to SHARP trial including hand-foot-skin reaction, diarrhea, alopecia, fatigue, anorexia, hypertension and nausea. The patients in Asia-Pacific trial have more advanced disease with extra-hepatic spread, greater number of lesions, poorer performance status, and high AFP concentrations compared to SHARP trial.

### **Radioembolization: Yttrium 90 microspheres**

In many cases, advanced stage HCC is beyond the scope of curative treatments thus directing disease management to a more palliative approach aimed at increasing survival and improving the quality of life for patients. Microsphere brachytherapy is one such approach for patients who are not candidates for resection, which works by exploiting the increased arterial vasculature supplying many large metastatic and primary tumors of the liver<sup>[61,62]</sup>.

The liver is unique from many of the organs in the body in that it possesses a dual blood supply coming from the hepatic artery and portal vein. Despite the fact that the portal circulation supplies the majority of blood to the normal liver, it has long been accepted among the medical community that liver tumors of large size ( $> 3$  mm), metastatic neoplasms in particular, receive a majority of their blood supply from the hepatic artery<sup>[62-64]</sup>. Angiographic studies done under fluoroscopy are performed prior to microsphere implantation to determine tumor arterial flow. In addition, prophylactic embolization of extrahepatic vessels is performed prior to radioembolization to prevent the possibility of non-targeted deposition of radioactive microspheres elsewhere in the body<sup>[61]</sup>.

After review of arteriograms that show no revascularization of occluded extrahepatic vessels or anatomic variants, Yttrium-90 loaded glass or

resin microspheres, approximately 20-30  $\mu\text{m}$  in size, are infused *via* percutaneously inserted arterial catheters<sup>[61,65]</sup>. These spheres preferentially travel to and settle in tumor vasculature where they block the main source of blood flow and deliver dosed radiation to the tumor site<sup>[61,66,67]</sup>.

Microsphere dose ranges are based on CT imaging studies that determine total liver volume and a nominal target dose specific to the patient's tumor progression<sup>[68]</sup>. In addition, the type of microsphere, either resin or glass, must be considered due to significant differences in single sphere radioactivity as well as the amount of microspheres delivered<sup>[66,69-71]</sup>.

The first study to be performed to determine effective dose radiation as well as complications from Y-90 treatment of advanced HCC was performed by Lau *et al.*<sup>[68]</sup> in the mid 1990's. A total of 18 patients with inoperable advanced HCC were treated with the therapy. Patient median survival was found to be longer for those receiving a target dose of  $> 120$  Gy compared to those receiving doses of  $< 120$  Gy (55.9 wk vs 26.2 wk,  $P = 0.005$ ).

A more recent study by Geschwind *et al.*<sup>[72]</sup> in 2004 analyzed the median survival and 1-year survival rates of patients with unresectable HCC that received Y-90 treatment doses ranging from 47-270 Gy. Of the 80 patients treated in the trial, 50 were Okuda stage I and 26 were Okuda stage II. Okuda stage I patients experienced a median survival of 628 d with a 1-year survival of 63%. Stage II patients experienced a median survival of 384 days and a 1-year survival of 51%.

In 2008, Al-Kalbani *et al.*<sup>[73]</sup> reviewed some of the advantages and contraindications of Y-90 microsphere radioembolization therapy. The treatment is especially recommended for patients with HCC and portal vein thrombosis (PVT), where median survival was found to be significantly increased compared to PVT patients not receiving treatment (496 d vs 2.7-4 mo)<sup>[73-75]</sup>.

### Conformal radiotherapy

Determining which form of RT to implement in the treatment of HCC is often difficult since clinical experience with certain techniques is limited<sup>[76]</sup> in addition to considering the potential for radiation-induced liver disease (RILD) due to the low tolerability of the liver to radiation<sup>[77]</sup>. The tolerability of the liver to radiation depends largely on the total dose delivered but also on the volume of liver receiving the target dose throughout the treatment setting. According to data published in 1991 by Emami *et al.*<sup>[78]</sup>, the amount of radiation delivered to the whole liver, 2/3 liver, and 1/3 liver volume associated with a 5% normal tissue complication probability (NTCP) at 5 years was 30 Gy, 35 Gy, and 50 Gy, respectively.

In conjunction with modern imaging techniques a multitude of conformal radiotherapy techniques have been developed and tested that offer the ability

to deliver high dose radiation to tumor areas while reducing the exposure of healthy tissue to harmful rays. 3D conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT), stereotactic-body radiotherapy (SBRT), and RapidArc radiotherapy have been suggested to be favorable in the treatment of advanced HCC due to their ability to deliver high radiation doses that more accurately target the specific three-dimensional tumor volumes than whole liver RT.

Another study performed by Cheng *et al.*<sup>[79]</sup> examined the differences in dose-volume data between patients treated with 3D-CRT and patients treated with IMRT after subsequent development of RILD following an initial 3D-CRT course. The researchers found that IMRT significantly reduced volume fractions of radiation exposure to surrounding organs when compared to conventional 3D-CRT treatment for the spinal cord, stomach, and the right kidney (5.7% vs 33.4%,  $P = 0.009$ ; 3.7% vs 4.8%,  $P = 0.09$ ; 32.0% vs 34.8%,  $P = 0.007$ ; respectively). In addition, IMRT significantly increased the mean dose to the liver compared to 3D-CRT (2924 cGy vs 2504 cGy,  $P = 0.009$ ) while reducing the NTCP (23.7% vs 36.6%,  $P = 0.009$ ), both factors considered extremely desirable for disease treatment<sup>[79,80]</sup>.

The most recent conformal RT technique to be established, called RapidArc, is another volumetric intensity-modulated therapy that has shown promise as an equivalent or even superior therapy to IMRT for certain cancers<sup>[80,81]</sup>. Instead of the typical 5 gantry angle fractions used in conventional IMRT, RapidArc uses a one or two-arc gantry rotation while simultaneously modulating the beam intensity to accommodate for the three-dimensional tumor margins<sup>[82]</sup>. In their study, Kuo *et al.*<sup>[82]</sup> found that while RapidArc had a significantly higher conformity index (CI, relative volume covered by the prescribed dose compared to the prescribed target volume) than IMRT, it was not superior to IMRT in terms of reducing the NTCP (4.38% vs 3.98%). These and other studies highlight the potential for conformal radiotherapy in the treatment of advanced HCC as well as urge for future research to refine technical approaches.

### Proton and heavy ion radiotherapy

Proton therapy is currently being pursued as an additional treatment modality for advanced HCC due to its ability to deliver conformal, high dose treatments to tumor areas while at the same time significantly limiting dose exposure to uninvolved areas of the liver<sup>[83]</sup>. Protons have a much sharper peak of energy dissipation, termed the Bragg peak, than electrons or X-rays<sup>[84]</sup>. The sharpness of the peak corresponds to greater tissue absorption of ionizing radiation delivered to the target area over a shorter distance when compared to the peaks of other ionizing radiation. Additionally, the depth of the peak energy dissipation within the tissue is determined by the beam's initial

energy and the medium through which the beam is traveling. For proton therapy, the Bragg peak is very sharp and comes to its maximum over a short distance at the end of the beam length. This short distance over which a large portion of the beam's energy is absorbed contributes to a more accurately conformed dose volume that in theory reduces the normal tissue complication probability (NTCP) and risk of RILD<sup>[85]</sup>.

In 2005, Chiba *et al.*<sup>[86]</sup> published a retrospective review in which 162 patients were treated with proton beam therapy for advanced, unresectable HCC. The overall survival rate for the patient group was found to be 23.5% at 5 years, although the subset group of 50 patients presenting with solitary tumor and little hepatic impairment showed a 5-year survival of 53.5%.

Another 2005 study by Hata *et al.*<sup>[87]</sup> examined the effectiveness of proton therapy on HCC patients diagnosed with portal vein tumor thrombus (PVTT), a syndrome that has traditionally limited the capacity of radiotherapy in improving disease survival. Among their limited data set of 12 patients, the researchers found a 2-year and 5-year progression-free survival rate with a median progression-free survival of 67%, 24%, and 2.3 years, respectively.

Heavy-ion RT (H-IRT) is another treatment modality being explored for advanced HCC treatment. The advantages of heavy ions are similar to those that come from proton therapy; heavy ions follow an inverted dose profile that is much more effective in maintaining conformity of the beam to the target volume as opposed to non-heavy ion therapies<sup>[88]</sup>.

Research on H-IRT for HCC has been limited to date due to a number of factors including the expense of the procedure and the limited number of facilities world-wide capable of handling heavy-ion RT<sup>[88]</sup>. One of the first papers to be published on the effectiveness of heavy-ion RT for advanced HCC came from a prospective study by Kato *et al.*<sup>[89]</sup> in 2004. A total of 24 patients diagnosed with HCC of stage II (10), IIIA (6), and IVA (8) were each treated with 15 fractions of carbon ions over a 5-wk period. A 10% dose increment was also administered for each consecutive fraction over a range of 3.3 to 5.3 Gray equivalents (GyE). GyE was determined by multiplying the physical dose of the carbon ions in Gray by the relative biological effectiveness (RBE), determined by the researchers to be of the value 3.0 (RBE relativizes the physical damage to cells produced by heavy ions in comparison with megavoltage proton therapy)<sup>[90]</sup>. At the conclusion of the study, the overall tumor response rate was found to be 71% with 1, 3, and 5-year survival rates of 92%, 81%, and 25%, respectively<sup>[89]</sup>.

Currently, Phase I dose determining trials are underway in Germany at the University Hospital of Heidelberg, led by Combs *et al.*<sup>[88]</sup>. The Prometheus-01 trial is expected to deliver analysis on the safety and efficacy of the carbon ion radiotherapy procedure for patients diagnosed with advanced HCC. In addition,

the study's primary focus is to evaluate toxicity and determine the mean tolerable dose (MTD) for future clinical investigations. Promising results from this study could fuel research interest into more effective ways of targeting advanced HCC lesions with H-IRT.

## POTENTIAL MOLECULAR PATHWAYS OF INTEREST

Molecular pathways involved in the initiation and propagation of HCC have been well studied. Each pathway provides an opportunity to inhibit HCC progression. Through the development of molecular inhibitors specific to kinases, receptors and other integral proteins within these pathways, researchers are currently opening new potential avenues for treating HCC. Many inhibitors have been developed and are in various stages of clinical trials (Table 2). Key pathways and cascades associated with HCC are considered below.

### EGFR-RAS-MAPKK signaling pathway

Epidermal growth factor (EGF), hepatocyte growth factor (HGF), platelet derived growth factor (PDGF), and vascular endothelial growth factor (VEGF) participate in the activation of RAS/MAPKK signaling pathway playing a key role in cell proliferation<sup>[91]</sup>. The abnormal activation of RAS/MAPK pathway results from an aberrant upstream signals from EGFR and IGF<sup>[92]</sup>. VEGF, PDGF, and FGF are important proangiogenic factors that play role in neovascularization, invasiveness and metastatic potential of HCC<sup>[93]</sup>. VEGFR-1 and 2 are expressed on the endothelial cells and initiate the cascade. PDGF is helpful for angiogenesis by recruiting pericytes and smooth muscle cells around nascent vessel sprouts<sup>[94]</sup>. As VEGF, FGF, and PDGF expression correlates with metastatic potential of tumor cells, inhibitors of VEGF, FGF, and PDGF signaling pathways are useful as therapeutic agents<sup>[95]</sup>.

### c-MET signaling pathway

Mesenchymal epithelial transition factor (MET) is activated by receptor binding of HGF and their aberrant activity plays a significant role in HCC pathogenesis<sup>[95]</sup>. HGF/C-MET pathway plays vital role in cellular responses including invasive growth of cancer, tissue regeneration, angiogenesis, proliferation, and migration of cancer cells. HGF over expression and c-MET aberrant activation has been reported in HCC<sup>[96]</sup>. A number of therapeutic agents targeting the c-MET pathway are in various stages of development. These compounds can be found listed in Table 2.

### IGF signaling pathway

IGF- I and II have a limited role in the pathogenesis of HCC but down regulation of tumor suppressor IGFBP-1, IGFBP-2, IGFBP-3, and IGFBP-4 was found to be associated with HCC<sup>[97]</sup>. Over expression of IGF-1 and IGF-2 receptors and down regulation of IGF



**Table 2 Select current molecular inhibitors under investigation as standalone or combination therapies for treatment of hepatocellular carcinoma**

Drug name	Method of action	Clinical phase
Lenvatinib	VEGFR, PDGFR, FGFR, RET and c-Kit inhibitor	III, ongoing as 1 <sup>st</sup> line
Brivanib	VEGFR2 and FGFR tyrosine kinases	III, negative as 1 <sup>st</sup> line
Everolimus	mTOR inhibitor	III, negative
Tivantinib	c-MET inhibitor	III, ongoing as 2 <sup>nd</sup> line
Linifanib	RTK, VEGF and PDGF inhibitor	III, negative as 1 <sup>st</sup> line
Sorafenib (as adjuvant)	Raf/MEK/ERK inhibitor	III, negative
Ramucirumab	VEGFR2	II and III, negative
Foretinib	c-MET inhibitor	II
Refametinib	MEK1/2 inhibitor	II
Mapatumumab	TRAIL-receptor (death receptor 4)	II
Selumetinib	MAPK/ERK inhibitor	II
Erlotinib	EGFR tyrosine kinase inhibitor	II
Lapatinib	EGFR and HER2/neu inhibitor	II
Cabozantinib	VEGFR2, c-MET, RET, KIT, FLT4, AXL	III
MSC2156119J	c-MET/HGF	I b/ II
Lenalidomide	Immunomodulatory	II

HGF: Hepatocyte growth factor; VEGF: Vascular endothelial growth factor.

binding proteins contribute to proliferation of cancer cells, anti-apoptosis, and invasive behavior<sup>[95,96]</sup>.

### **P13K/Akt/mTOR signaling pathway**

P13K/PTEN/Akt/mTOR pathways regulate many processes like cell proliferation, differentiation, apoptosis, cell cycle progression, cell motility, tumor growth and angiogenesis. Akt activation can occur through EGF, IGF, or mTOR aberrant signaling or dysregulation of tumor suppressor gene PTEN<sup>[96,97]</sup>. The pathway is also involved in invasiveness and metastasis of HCC<sup>[98]</sup>.

### **Wnt-β-catenin signaling pathway**

Aberrant Wnt-β-catenin signaling activity has been demonstrated in up to one third of cases of HCC secondary to HCV. The pathway is dysregulated primarily as a result of mutations in CTNNB1 or AXIN1, or altered expression of WNT receptors inducing changes in oncogenes like CCND1, Cmyc or BIRC<sup>[99,100]</sup>. The pathway can be exploited as a target for treatment of HCC.

### **Apoptotic signaling pathways**

Abnormal apoptotic activity has been shown to play a role in the pathogenesis of HCC and agents have been in developmental phases targeting pro-apoptotic receptors. Apoptosis can occur intrinsically or extrinsically. In HCC some pro-apoptotic molecules like p53, PTEN, Bax are down regulated and anti-

apoptotic signals like Snail, β-catenin, NF-κB, Ras/ERK are over expressed leading to imbalance and evasion of apoptosis<sup>[91,96]</sup>.

### **Hedgehog signaling pathway**

Hedgehog (Hh) pathway is crucial for fetal liver development, regeneration and stem cell differentiation. Over expression of Sonic Hh and smoothened Hh can activate an aberrant Hh pathway and lead to carcinogenesis of HCC<sup>[91]</sup>.

### **Jak/STAT pathway**

It is activated by number of cytokines and growth factors and is involved in multiple cell functions such as differentiation, proliferation and apoptosis<sup>[101]</sup>.

Over expression of genes representing VEGFR, PDGF, Angiopoietin-2 leads to increased angiogenesis. Increased expression of MMP-9, osteopontin, MMP-14, cyclin D1 leads to metastasis of HCC<sup>[96]</sup>.

## **CONCLUSION**

HCC represents a uniquely challenging cancer requiring a multifactorial approach. Other than possibly a liver transplant, there is no definitive cure. Instead, clinicians are faced with multiple management strategies, each with different risks and rewards. The sheer number of current treatment approaches can be overwhelming to both physicians and patients. New breakthroughs such as Sorafenib offer great promise, yet even these new approaches must be weighed against radiation, surgery and other better-established treatment modalities. The tumor stage and extent of liver damage are key factors in the evaluation of an appropriate HCC treatment strategy. Choosing the most appropriate modality requires doctors to follow the most advanced guidelines to date.

The surgical options available are partial liver resection, percutaneous ablation, TACE and either living or cadaveric donor transplantation<sup>[102]</sup>. Surgical treatments have represented the most successful approaches to HCC. In addition, HCC patients today are benefiting from significant improvements in tumor identification, patient survival and patient selection. However, these advances in HCC treatment are riddled with high mortality as a result of cancer recurrence with unacceptable survival rates<sup>[103]</sup>.

Radiation therapies for advanced HCC are limited in their capacity to improve disease prognosis. Historically, one of the most difficult problems to overcome with the use of radiotherapy in HCC was the delineation of tumor margins. However, modern radiotherapy for HCC utilizes multiphase CT for tumor visualization<sup>[104]</sup>. Additionally, the multiphase CT of HCC produces a unique pattern of enhancement that can be used as a diagnostic marker in the absence of biopsy<sup>[28]</sup>. MRI and positron emission tomography can also be used to identify tumor margins as well as detect additional foci of HCC<sup>[105]</sup>.

The recent advances in understanding the pathogenesis of HCC have led to the successful development and approval of Sorafenib, currently the only drug shown to increase survival in randomized controlled trials. While more long term clinical data would be welcomed, Sorafenib represents a promising first step in the use of biological agents in the treatment of HCC.

Many molecular pathways have been well described in the development and progression of HCC. These molecular pathways could theoretically be exploited to slow down, halt or reverse the progression of HCC. Based on gene expression studies, HCC is classified into three molecular subsets consisting of different sets of genes altering signaling pathways responsible for cell proliferation and survival<sup>[96,106]</sup>. The key signaling pathways identified to play a role in HCC pathogenesis are Wnt- $\beta$ -catenin pathway, EGFR/RAS/MAPKK pathway, c-MET pathway, IGF signaling, Akt/m TOR pathway, and VEGF/PDGFR signaling pathways<sup>[95,96]</sup>. Several Phase II and III clinical trials are underway for novel drugs aimed at treating advanced HCC using some of these pathways. Further research into drugs targeting these pathways may lead to future breakthroughs in the treatment of HCC.

A comprehensive review such offers an opportunity for clinicians and patients to better understand, compare and contrast established, cutting edge and future treatment modalities. We hope this review will assist both physicians and patients in their decision-making regarding HCC. In early HCC, liver resection remains an established treatment for HCC owing to minimal surgical mortality and improved survival. Transplantation remains the most definitive treatment for HCC in patients who fulfill the selection criteria. Treatment guidelines for HCC will facilitate decision-making by both patients and physicians at every clinical step. By sharing the precise information in algorithm charts, physicians need to recommend treatment options and allow the patients to decide which treatment modality fits their desires.

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