

## Treatment of hepatocellular carcinoma: Steps forward but still a long way to go

Liat Mlynarsky, Yoram Menachem, Oren Shibolet

Liat Mlynarsky, Yoram Menachem, Oren Shibolet, Liver unit, Department of Gastroenterology, Tel-Aviv Medical Center and the Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv 64239, Israel

**Author contributions:** Mlynarsky L wrote the paper; Menachem Y critically reviewed and revised it; and Shibolet O wrote, revised and finally approved the version to be published.

**Conflict-of-interest:** The authors have no conflict of interest.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Correspondence to:** Oren Shibolet, MD, Director of the Liver Unit, Department of Gastroenterology, Tel-Aviv Sourasky Medical Center and Tel-Aviv University, 6 Weizman St. Tel-Aviv 64239, Israel. [orensh@tasmc.health.gov.il](mailto:orensh@tasmc.health.gov.il)

Telephone: +972-3-6973984

Fax: +972-3-6966286

Received: August 9, 2014

Peer-review started: August 11, 2014

First decision: August 28, 2014

Revised: October 6, 2014

Accepted: December 29, 2014

Article in press: December 29, 2014

Published online: March 27, 2015

### Abstract

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and the third cause of tumor associated deaths worldwide. HCC incidence rates are increasing in many parts of the world including developing and developed countries. Potentially curative treatments for HCC are resection and liver transplantation, but these are only suitable for patients with small tumors, meeting strict pre-defined criteria, or well-compensated liver disease. Early diagnosis of HCC

can be achieved by surveillance of at-risk populations. For patients with non-resectable disease treatments modalities include loco-ablative and systemic therapies. In this review we focus on treatment options in HCC and their allocation. Although significant research is in progress, to this date, the results are unsatisfactory with limited long-term survival. In the fight against this deadly disease, there is still a long way to go.

**Key words:** Hepatocellular carcinoma; Liver resection; Liver transplantation; Loco-ablative therapies; Sorafenib

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** We chose to focus on the aspect of treatment modalities of hepatocellular carcinoma (HCC) and discuss the benefits and disadvantages of each modality. We report on the diversity of treatments and the allocation of patients with HCC to the different modalities according to the Barcelona-Clinic Liver Cancer. Moreover, we discuss novel treatments currently under investigation and not yet recommended by acceptable guidelines.

Mlynarsky L, Menachem Y, Shibolet O. Treatment of hepatocellular carcinoma: Steps forward but still a long way to go. *World J Hepatol* 2015; 7(3): 566-574 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v7/i3/566.htm> DOI: <http://dx.doi.org/10.4254/wjh.v7.i3.566>

### INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third leading cause of cancer-related deaths<sup>[1]</sup>. The highest HCC rates are found in East and South-East Asia and in Middle and sub-Saharan Africa (age-standardized incidence rates

35.5/100000 in men and 12.7/100000 in women and 16.6/100000 in men and 8/100000 in women respectively), whereas rates are low in Northern and Eastern Europe and United States (3.8/100000 in men and 1.6/100000 in women). Among primary liver cancers, HCC is the most common histological subtype, accounting for 70%-85% of all liver cancers worldwide<sup>[2]</sup>. Unlike most solid cancers, HCC incidence rates are increasing in many parts of the world including the United States and Europe, possibly due to hepatitis C virus (HCV) associated cirrhosis acquired *via* intravenous drug injection in the sixties and the obesity epidemic leading to non-alcoholic steatohepatitis (NASH) and NASH cirrhosis<sup>[2]</sup>. Approximately 90% of HCCs are associated with cirrhosis or a known underlying risk factor for chronic liver disease. Worldwide, approximately 54% of cases can be attributed to hepatitis B virus infection, 31% to Hepatitis C virus infection leaving approximately 15% associated with other causes such as chronic alcohol intake, non-alcoholic steato-hepatitis and environmental factors<sup>[3]</sup>. Patients are usually asymptomatic until they present with decompensation of their cirrhosis due to venous extension or replacement of functional liver tissue by tumor tissue. Extra-hepatic spread is present at the time of diagnosis in up to 15% of cases. The most common sites for metastases are the lungs, abdominal lymph nodes, bone, and adrenal glands<sup>[4]</sup>.

Early diagnosis of HCC can be achieved by surveillance of populations at high risk<sup>[3,5]</sup>. Ultrasonography (US) is the imaging modality most widely used with sensitivity ranging from 58% to 89% and specificity greater than 90%<sup>[6]</sup>. Multiphase computerized tomography (CT) (sensitivity 68% and specificity 93%) or dynamic magnetic resonance imaging (MRI) (sensitivity 81% and specificity 85%)<sup>[7]</sup>, can be used in specific cases<sup>[3]</sup>. Alpha-fetoprotein (AFP) is the most widely tested biomarker in HCC. It is generally accepted that serum levels greater than 500 µ/L in high-risk patients are diagnostic for HCC. However, negative values do not rule out tumor presence<sup>[8]</sup>. Due to its low sensitivity and specificity the use of AFP as a surveillance tool is not recommended by the European association for the study of the liver (EASL) and American association for the study of liver disease (AASLD)<sup>[3,5]</sup>.

According to the EASL and AASLD guidelines, one dynamic imaging technique (CT or MRI) showing defined radiological features suffices for diagnosing tumors > 1-2 cm in diameter. An approach utilizing two techniques is recommended when imaging is suboptimal or in centers not routinely treating patients with HCC. The role of contrast-enhanced ultrasound (CEUS) with Sonazoid for detecting HCC is gaining popularity (sensitivity of 95% and specificity of 93%)<sup>[9]</sup>, while angiography and positron emission tomography (PET)-scan are not routinely used for early diagnosis<sup>[3,5]</sup>. Liver biopsy is the gold

standard for diagnosis in cases where imaging results are equivocal.

---

## HCC STAGING

Several staging systems have been proposed to provide a clinical classification of HCC.

Currently, EASL and AASLD guidelines support the Barcelona-Clinic Liver Cancer (BCLC) classification for prognostic prediction and treatment allocation in HCC<sup>[10]</sup>. BCLC staging classification is comprised of 4 stages that are based on the extent of the primary lesion, performance status, presence of constitutional symptoms, vascular invasion, extrahepatic spread, and Okuda stage. The Okuda classification takes into account tumor size (imaging or surgery) and liver function status (ascites, jaundice and serum albumin)<sup>[11]</sup>.

BCLC early stage (A) includes patients with asymptomatic small tumors suitable for resection, transplantation or per-cutaneous treatments. Intermediate stage (B) comprises patients with asymptomatic multinodular HCC. Advanced stage (C) includes patients with symptomatic tumors and/or an invasive tumoral pattern (vascular invasion/extrahepatic spread). End-stage disease (D) contains patients with advanced tumor and liver disease (Okuda stage III or Eastern Cooperative Oncology Group performance status of 3 or 4) that should receive best supportive care.

---

## TREATMENT STRATEGIES AND ALLOCATION

The potentially curative treatments for HCC are resection and liver transplantation. However, most patients with HCC present with advanced disease and underlying liver dysfunction and are not suitable candidates for these treatments. Thus, they generally have a poor prognosis with median survival time of less than 1 year<sup>[12]</sup>. Other treatments are loco-ablative and systemic therapies. Treatment allocation is preferably performed through a multi-disciplinary team according to the BCLC allocation system.

---

## RESECTION

Hepatic resection is the treatment of choice for HCC in non-cirrhotic patients. In well-selected candidates the expected 5-year survival is 60%-80%. In cirrhotic patients, the expected 5-year survival rate post-resection is 60%, with a peri-operative mortality of 2%-3% and blood transfusion requirements of less than 10%<sup>[3,13,14]</sup>. Patient selection was traditionally based on the Child-Pugh classification, but this may significantly underestimate the severity of the liver disease. Portal hypertension is a major risk factor for post-operative hepatic decompensation<sup>[5]</sup>. Patients with hepatic venous pressure gradient (HVPG) value

< 10 mmHg have a small chance of developing clinical decompensation (< 10%). For each 1 mmHg increase in HVPG there is an 11% higher risk of clinical decompensation, thus HVPG of 15 mmHg has 55% higher chance of developing decompensation compared with a HVPG of 10 mmHg at equivalent MELD and albumin values<sup>[15]</sup>. Platelet count has also been confirmed as an independent predictor of survival in resected HCCs<sup>[3,5]</sup>.

In patients properly selected for resection, the main predictors of survival are tumor size, number of tumor nodules and the presence of microsatellites and vascular invasion<sup>[16]</sup>. Microscopic vascular invasion involves 20% of tumors of up to 2 cm in diameter, 30%-60% of cases in nodules 2-5 cm and up to 60%-90% in nodules above 5 cm in size<sup>[16]</sup>. As for the number of tumors, multivariate analyses revealed that the presence of multiple tumors is an independent risk factor for postoperative recurrence<sup>[13]</sup>.

Tumor recurrence represents the major complication of liver resection. Post-resection tumor recurrence rate exceeds 70% at 5 years<sup>[13,17]</sup>. For macroscopically solitary HCC, anatomic resection aiming at 2 cm margins provides better survival outcome and reduces recurrence rate as compared to narrow resection margins.

Another factor that may influence recurrence rate is the primary tumor location. HCC recurrence rates were found to be significantly higher in left-sided resection (41% at 1 year and up to 90% at 5 years), compared with right-sided resection (18% at 1 year and up to 72% at 5 years)<sup>[18]</sup>. Long-term survival was also significantly lower in patients with left-sided resection<sup>[18]</sup>. The hypothesized reason is the larger size of liver remnants harboring a risk for local recurrence, as opposed to right hepatectomy which harbors a higher risk for hepatic decompensation<sup>[5]</sup>.

Several adjuvant treatments to prevent post operative recurrence have been assessed. Interferon was the most frequently evaluated adjuvant with conflicting results. Other strategies such as systemic chemotherapy, chemoembolization, internal radiation, immune therapies and retinoids were also tested with disappointing results. According to EASL and AASLD guidelines, pre or post-resection adjuvant therapy is currently not recommended<sup>[3,5]</sup>.

Recently, laparoscopic liver resection (LLR) for HCC has been assessed. The best indications for LLR are solitary lesions, less than 5 cm in diameter, located in the anterior segments, at a distance from the line of transection, the hepatic hilum, and the vena cava<sup>[19]</sup>. However, surgical indications have continued to evolve and tumor size and posterior location are no longer considered contraindication to laparoscopic surgery<sup>[14]</sup>. According to a recent meta-analysis<sup>[20]</sup>, LLR had a significantly lower hazard ratio of mortality (HR = 0.64;  $P = 0.04$ ) with similar rates of recurrence (HR = 0.79;  $P = 0.37$ ) as compared to open liver resection (OLR). Furthermore, the LLR group had a lower operative

blood loss and lower relative risk of total postoperative complications, lower duration of hospital stay and fewer days of intravenous narcotic use. A literature review of western and Middle Eastern LLR experience concluded that comparative studies did not demonstrate any significant difference in terms of overall survival and recurrence rate between LLR and OLR. No seeding was reported<sup>[21]</sup>. Moreover, the main clinical advantage of laparoscopy for cirrhotic patients is a significantly lower rate of postoperative decompensation and lower blood transfusion requirement<sup>[14]</sup>.

## LIVER TRANSPLANTATION

Liver transplantation combines tumor removal with treatment of the underlying liver disease and cirrhosis. Initial enthusiasm for this modality in HCC was hampered by high rates of tumor recurrence. In 1996, a prospective cohort study defined restrictive selection criteria that led to superior survival for transplant patients in comparison to other treatment options for HCC<sup>[22]</sup>. Since then, these selection criteria have become universally known as the Milan criteria.

An international consensus conference held in 2010 in Zurich, Switzerland, re-affirmed the Milan criteria as the reference benchmark for selection of HCC patients for liver transplantation, and the basis for comparison with other suggested criteria. In addition, they recommended that liver transplantation should be reserved for HCC patients who have a predicted 5-year survival comparable to non-HCC patients<sup>[23]</sup>.

Currently, liver transplantation achieves excellent results in patients with limited tumor load. Patients fulfilling the Milan criteria (HCC nodule less than 5 cm or up to three nodules of less than 3 cm) have a 1-year survival exceeding 85% and a 5-year survival of 75% after liver transplantation, with tumor recurrence in less than 10%. This survival matches post-transplant survival of most other transplantation indications<sup>[24,25]</sup>. Survival is significantly reduced in patients undergoing liver transplantation for HCV-associated HCC as compared to HCC associated with other liver disease. The evidence of a beneficial effect of post-transplantation antiviral treatment and viral clearance on liver fibrosis, tumor recurrence, and survival is encouraging but has to be confirmed<sup>[26]</sup>.

The model for end stage liver disease (MELD) score is the most clinically used tool for organ allocation to patients on the liver transplantation waiting list<sup>[27]</sup>. In order to give patients with HCC equal opportunity for transplantation, those patients meeting the Milan criteria are given 22 calculated MELD points and a 10% point increase for every 3 mo on the waiting list.

Patients on the liver transplantation waiting list have a high cumulative probability to drop-out from the list due to intra or extrahepatic tumor progression. This probability has been reported to be 7%-11% at 6 mo and 38% at 12 mo following enrollment<sup>[17]</sup>.

Adjuvant therapies for patients within the Milan criteria while on the waiting list are used in most centers to prevent tumor progression. However, the impact of these treatments on drop-out rate, recurrence and survival is only estimated from non-randomized studies. Considering the strength of evidence available, the EASL and AASLD recommendation is to treat patients waiting for transplantation with percutaneous local ablation, and as a second choice with chemoembolization when the waiting period is estimated to exceed 6 mo<sup>[3]</sup>.

Down staging is a term used to describe treating tumors and decreasing their size to within the Milan criteria to allow transplantation. Two prospective studies showed that in patients with large tumors that were successfully down-staged, the post transplantation survival was similar to patients who initially met the criteria for transplantation<sup>[28,29]</sup>. Patients with progressive disease, in whom loco-regional therapy intervention is not considered appropriate or is ineffective, should be removed from the waiting list.

In some countries, mainly in Asia, living-donor liver transplantation (LDLT) using the right, or less often, the left liver lobe is the only option for liver transplantation. Currently, LDLT comprises less than 5% of adult liver transplants<sup>[30]</sup>. Some studies have suggested a higher risk of tumor recurrence in LDLT as compared to deceased donors, but no difference in outcome could be identified according to type of graft. A higher risk of recurrence was noted in patients with a short delay between diagnosis and liver transplantation, not allowing enough time for the biological behavior of the tumor to manifest<sup>[23]</sup>.

Salvage liver transplantation (SLT) for patients with HCC recurrence after initial liver resection is becoming more widely accepted in centers around the world. In a Korean multicenter study, the prognosis of patients following SLT was affected not only by the Milan criteria at the time of SLT, but also by the biological behavior of the recurrent HCC after initial liver resection<sup>[31]</sup>. The interval between initial resection and HCC recurrence, AFP level at the time of SLT and the Milan criteria at SLT were independent risk factors for low overall and recurrence-free survival of the salvage LT recipient.

## LOCO-ABLATIVE THERAPIES

Local ablation is considered the first line treatment option for patients at early stages (BCLC 0-A) not suitable for surgical therapies. Destruction of the tumor is achieved by injection of chemical substances (ethanol, acetic acid, or boiling saline) or by modifying the temperature (radiofrequency, microwave, laser, cryotherapy).

### **Percutaneous local injection**

Percutaneous ethanol injection (PEI) is the most studied method of local treatment. PEI can achieve

necrosis of 90-100% of HCC smaller than 2 cm, 70% in tumors of 2-3 cm and to 50% in HCC of 3-5 cm<sup>[32,33]</sup>. Patients with Child-Pugh A and successful tumor necrosis may achieve a 5-years survival of 50%, comparable with the outcome of resection in those candidates<sup>[33]</sup>. PEI requires repeated injections on separate days and is less effective in tumors larger than 3 cm, because the injected ethanol cannot access the entire tumor volume. This may be due to the presence of intra-tumoral septa, resulting in 43% local recurrence rates in lesions exceeding 3 cm<sup>[34]</sup>.

### **Radiofrequency ablation**

Radiofrequency ablation (RFA) induces thermal injury to the tissue through electromagnetic energy deposition. RFA requires fewer treatment sessions as compared to PEI in order to achieve comparable anti-tumoral effects. In randomized controlled trials comparing RFA to PEI for the treatment of early-stage HCC, RFA had a higher anti-cancer effect, leading to a lower recurrence rate (2 year local recurrence rate: 2%-18% vs 11%-45%, respectively)<sup>[35-37]</sup>. The best RFA outcomes have been reported in Child-Pugh A patients with early-stage HCC. Five-year survival rates as high as 51%-64%, may be reached in selected patients<sup>[33]</sup>. The main drawback of radiofrequency is its higher cost and the higher rate (up to 10%) of adverse events (mainly pleural effusion and peritoneal bleeding)<sup>[5,33,37]</sup>. Procedure-related mortality is 0%-0.3%. Sub-capsular location and poor tumor differentiation have been associated with increased risk of peritoneal seeding. According to EASL practice guidelines, RFA is recommended in most instances as the main ablative therapy in tumors less than 5 cm while PEI is recommended in cases where RFA is not technically feasible (around 10%-15%)<sup>[3]</sup>. For the RFA procedure to be considered technically successful, the tumor and at least a 5 mm safety margin must be included in the ablation zone<sup>[38]</sup>. Kudo *et al.*<sup>[39]</sup> reported that the local recurrence rate at 2 years after RFA was 2.6% in HCC patients with a  $\geq 5$  mm safety margin, as opposed to 20.8% in HCC patients without such a safety margin ( $P = 0.01$ ).

### **Transarterial chemoembolization**

Arterial obstruction of branches of the hepatic artery by transarterial chemoembolization (TACE) induces ischemic tumor necrosis with a high rate of objective responses. The procedure combines trans-catheter delivery of chemotherapy emulsion with lipiodol followed by vascular occlusion with embolic agents. TACE achieves partial responses in 15%-55% of patients, and significantly delays tumor progression and macro-vascular invasion<sup>[3]</sup>. Overall, the median survival after TACE for intermediate HCC is about 20 mo, an improvement over conservative therapy. TACE is the standard of care for patients with non-surgical HCC that are ineligible for per-cutaneous ablation, provided there is no extra-hepatic tumor spread and no portal



vein thrombosis. Patients with advanced liver disease (Child-Pugh class C) and/or intermediate-BCLC staging should not be considered for this treatment due to increased risk of liver failure and death<sup>[3,5]</sup>.

Possible side effects of TACE are nausea, vomiting, bone marrow suppression, alopecia and potentially renal failure. "Post-embolization syndrome" appears in more than 50% of the patients and consists of fever, abdominal pain and a moderate degree of ileus. The syndrome is usually self-limited and lasts less than 48 h. A minority of patients may develop severe infectious complications such as hepatic abscess or cholecystitis.

Chemoembolization with Drug-Eluting Beads (TACE-DEB) improves anti-tumoral activity and reduces systemic exposure, *via* well-controlled embolization with accurate size beads. Embolic microspheres release chemotherapeutic agents in a controlled mode over a 1-wk period. A randomized phase II study comparing TACE and TACE-DEB reported a significant reduction in liver toxicity and drug-related adverse events for the latter arm, associated with a non-significant trend of better anti-tumoral effect<sup>[40]</sup>.

Treatment response is assessed by the decrease in the concentration of tumor markers and by specific imaging characteristics on CT or MRI one month after therapy. Persistence of contrast uptake at the tumor edge indicates treatment failure.

Adverse outcome of TACE can be predicted by the response to the first TACE utilizing the Assessment for Retreatment with TACE score. An increase of aspartate aminotransferase and Child-Pugh score and the absence of radiologic tumor response after the first TACE, all predict poor response to another TACE<sup>[41]</sup>.

### **Radio-embolization**

Radio-embolization also known as selective internal radio-embolization (SIRT) is defined as the trans-arterial delivery of radioactive substances in the form of microspheres containing yttrium-90 (<sup>90</sup>Y), iodine-131 (<sup>131</sup>I) iodized oil, or similar agents. Currently, the most popular radio-embolization technique uses microspheres coated with <sup>90</sup>Y, a beta-emitting isotope<sup>[33]</sup>. <sup>90</sup>Y microspheres have minimally embolic effect, thus, treatment can be safely used in patients with portal vein thrombosis<sup>[42]</sup>. Contraindications for the use of <sup>90</sup>Y microspheres include significant hepatopulmonary shunting and the risk of deposition in the gastrointestinal tract. Therefore, <sup>99m</sup>Tc macro-aggregated albumin scan prior to treatment is mandatory. Post-radio-embolization syndrome (PRS) can range from mild flu-like symptoms, abdominal discomfort, and cachexia, to hepatic dysfunction, development of portal hypertension, radiation pneumonitis, pancreatitis and vascular injury. The incidence of PRS ranges from 20% to 55%<sup>[33,43]</sup>.

There are currently two commercially available <sup>90</sup>Y microspheres: TheraSphere (MDS Nordion, Ottawa, Canada) is made of glass and SIR-Spheres

(Sirtex Medical, Sydney, Australia) are made of resin. Glass microspheres are minimally embolic with higher specific activity and lower number of spheres as compared to resin microspheres<sup>[44]</sup>.

In a cohort study reporting long-term outcomes, the median survival time following radio-embolization was 17.2 mo for patients with Child-Pugh A disease and 14.8 mo in patients with Child-Pugh B without portal vein thrombosis (PVT) or extra-hepatic disease. Evidence of PVT decreased the median survival time to 10.4 mo in Child-Pugh A patients and to 5.6 mo in Child-Pugh B patients<sup>[45]</sup>. Similar results were observed in a phase II study where the median survival was 18 mo in non-PVT Child-Pugh A patients and 6 mo in patients with Child-Pugh B disease and PVT<sup>[46]</sup>.

To date, there was only one comparative study that assessed the relative safety and efficacy of TACE vs SIRT in patients with un-resectable HCC. In the SIRTACE open-label study, single-session SIRT appeared to be as safe and effective as multiple sessions of TACE<sup>[47]</sup>.

## **STEREOTACTIC BODY RADIOTHERAPY**

The use of radiation therapy for the treatment of HCC has been limited by the poor tolerance of the whole liver to radiation, allowing no more than 30-35 Gy to be delivered and a subsequent high risk of developing radiation induced liver disease; a clinical syndrome characterized by an anicteric hepatomegaly, ascites and elevated liver enzymes, 2 wk to 4 mo after hepatic irradiation<sup>[48]</sup>. However, technological developments in radiotherapy planning and treatment delivery have offered a significant benefit for patients with advanced HCC. The characteristics of stereotactic body radiotherapy (SBRT) include highly conformal radiation, iso-dose distribution around the planned treatment volume with minimal collateral damage to critical structures and organs by very tight margins and rapid fall-off of the radiation dose in the normal liver parenchyma outside of the treatment field<sup>[49]</sup>. Proper patient selection for this therapy includes unresectable HCC patients with Child-Pugh class A-B8 how are able to remain immobile in the radiation suite for a potentially extended period of time, tumors of up to 6 cm in diameter and a distance of at least 5 mm from neighboring organs such as the stomach wall or the small intestine<sup>[50]</sup>. To date, only small phase I/II and retrospective studies have been performed, but with encouraging results<sup>[48,51]</sup>. SBRT can be a complementary treatment to TACE, since the ischemic effects of TACE are less potent in the surrounding well-oxygenated periphery of the HCC tumor where radiation is the most effective. A retrospective study suggests a survival advantage in large tumors for the combination of SBRT and TACE as compared to TACE alone<sup>[52]</sup>. Due to the limited data regarding SBRT, it is considered under investigation, and not yet recommended by the EASL guidelines as part of the

HCC therapy regimen.

## SYSTEMIC THERAPIES

Sorafenib, is an oral multi-tyrosine kinase inhibitor (TKI), the first and only drug that demonstrated a survival benefit in patients with advanced HCC. The Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol study was a large double-blinded placebo controlled phase III study that demonstrated improved survival for treated patients. Sorafenib increased the median overall survival from 7.9 mo in the placebo group to 10.7 mo in the treatment group, a 31% decrease in the relative risk of death<sup>[53]</sup>. A similar survival benefit was demonstrated in a parallel phase III trial conducted in the Asian-Pacific population<sup>[54]</sup>. Median overall survival was 6.5 mo in the sorafenib group vs 4.2 mo in the placebo group. The most common grade 3 drug-related adverse events observed in these studies were diarrhea and hand-foot skin reaction, which occurred in 8%-9%, and 8%-16% of patients, respectively. Drug discontinuation due to adverse events was 15% in the sorafenib arm and 7% in the placebo arm.

Sorafenib is indicated for patients with well-preserved liver function (Child-Pugh A class) and with advanced tumors (BCLC C) or tumors progressing despite loco-regional therapies<sup>[3,5,55]</sup>.

Two randomized controlled trials and four cohort studies assessed the combined treatment of TACE and sorafenib<sup>[55]</sup>. Despite encouraging initial results, this treatment combination is not recommended by any of the HCC treatment guidelines.

## TARGETED MOLECULES UNDER CLINICAL DEVELOPMENT

Angiogenesis is currently the most extensively studied therapeutic target of HCC. The efficacy of novel anti-angiogenic TKIs for advanced HCC has been investigated in several phase III RCTs. However, to date, none of these drugs has shown superior efficacy to sorafenib<sup>[56]</sup>.

Sunitinib is an oral multi-TKI approved for the treatment of renal cell carcinoma, gastrointestinal stromal tumors and pancreatic neuroendocrine tumors. Although phase II studies showed potential efficacy, overall objective response rate was < 3%. Grade 3/4 adverse events were observed in 5%-10% of patients and hematologic adverse events in approximately 20%. Treatment-related deaths due to severe liver dysfunction were recorded in 5.8%-10.8%<sup>[57,58]</sup>. A phase III, multicenter, randomized open-label study of sunitinib vs sorafenib was prematurely discontinued for safety issues and futility reasons. Overall survival with sunitinib was significantly inferior to sorafenib<sup>[59]</sup>. This drug is presently not recommended for treatment of HCC.

Linifanib is an oral TKI targeting vascular endothelial growth factor (VEGF) and platelet-derived growth factor. One open-label, phase III trial, compared Linifanib with sorafenib as first-line therapy in advanced Child-Pugh A HCC patients. Overall survival was similar among the two groups and predefined superiority and non-inferiority overall survival targets were not met for Linifanib. Secondary endpoints such as time to progression favored Linifanib while safety results favored Sorafenib<sup>[60]</sup>. This drug is presently not recommended for treatment of HCC.

Brivanib, an oral VEGF receptor and fibroblast growth factor receptors (FGFR) TKI was evaluated in a multinational, randomized, double-blind, phase III trial as compared to sorafenib for first-line treatment of HCC. Overall survival for brivanib in the per-protocol population did not meet non-inferiority targets. However, both agents had similar antitumor activity, based on secondary efficacy end points. Grade 3/4 adverse events were more frequent in Brivanib treated patients<sup>[61]</sup>.

Everolimus (RAD001), an mTOR Inhibitor, has been extensively studied for the treatment of HCC. The EVOLVE-1 trial was a phase III study that evaluated everolimus vs placebo for advanced HCC following sorafenib failure. Everolimus did not improve overall survival as compared to placebo<sup>[62]</sup>.

## CONCLUSION

In conclusion, HCC is a growing cause of mortality in cirrhotic patients and is one of the only solid tumors whose incidence is rising. Currently the best chance for prolonged survival is early diagnosis. This can be achieved by strict adherence to surveillance protocols. Unfortunately, only a small percentage of eligible patients adhere to such programs<sup>[63]</sup>, although preliminary data imply increased adherence in recent years. Patients with active alcohol consumption and those with previous injection-drug abuse are the groups with highest risk for poor adherence to surveillance and as a result may present with more advanced tumors at diagnosis<sup>[64]</sup>.

The only curative therapies currently available are hepatic resection or liver transplantation which are only suitable for a small number of patients. RFA in small tumors may also be curative. The large majority of patients are not candidates for these therapies and for them treatment is only palliative. Successful treatment of HCC relies on adherence to protocols and on advancing knowledge through enrolling patients into clinical trials. In our institution treatment decisions are made by a multi-disciplinary team based on EASL guidelines following the BCLC criteria for treatment allocation. We recommend enrollment into clinical trials with new systemic medications to any patient who has failed conventional loco-ablative therapy and sorafenib. Significant research is being conducted to develop other agents and combinations that may help improve

outcomes for these patients, but so far results have been disappointing. In the battle against this deadly disease, we are on the right path, but there is still a long way to go.

## REFERENCES

- 1 **Centers for Disease Control and Prevention (CDC).** Hepatocellular carcinoma - United States, 2001-2006. *MMWR Morb Mortal Wkly Rep* 2010; **59**: 517-520 [PMID: 20448528]
- 2 **Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D.** Global cancer statistics. *CA Cancer J Clin* 2011; **61**: 69-90 [PMID: 21296855 DOI: 10.3322/caac.20107]
- 3 **European Association For The Study Of The Liver,** European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012; **56**: 908-943 [PMID: 22424438 DOI: 10.1016/j.jhep.2011.12.001]
- 4 **Uchino K, Tateishi R, Shiina S, Kanda M, Masuzaki R, Kondo Y, Goto T, Omata M, Yoshida H, Koike K.** Hepatocellular carcinoma with extrahepatic metastasis: clinical features and prognostic factors. *Cancer* 2011; **117**: 4475-4483 [PMID: 21437884 DOI: 10.1002/cncr.25960]
- 5 **Bruix J, Sherman M.** Management of hepatocellular carcinoma: an update. *Hepatology* 2011; **53**: 1020-1022 [PMID: 21374666 DOI: 10.1002/hep.24199]
- 6 **Bolondi L.** Screening for hepatocellular carcinoma in cirrhosis. *J Hepatol* 2003; **39**: 1076-1084 [PMID: 14642630]
- 7 **Colli A, Fraquelli M, Casazza G, Massironi S, Colucci A, Conte D, Duca P.** Accuracy of ultrasonography, spiral CT, magnetic resonance, and alpha-fetoprotein in diagnosing hepatocellular carcinoma: a systematic review. *Am J Gastroenterol* 2006; **101**: 513-523 [PMID: 16542288 DOI: 10.1111/j.1572-0241.2006.00467.x]
- 8 **Cris sien AM, Frenette C.** Current management of hepatocellular carcinoma. *Gastroenterol Hepatol (N Y)* 2014; **10**: 153-161 [PMID: 24829542]
- 9 **Zheng SG, Xu HX, Liu LN.** Management of hepatocellular carcinoma: The role of contrast-enhanced ultrasound. *World J Radiol* 2014; **6**: 7-14 [PMID: 24578787 DOI: 10.4329/wjr.v6.i1.7]
- 10 **Llovet JM, Brú C, Bruix J.** Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis* 1999; **19**: 329-338 [PMID: 10518312 DOI: 10.1055/s-2007-1007122]
- 11 **Okuda K, Ohtsuki T, Obata H, Tomimatsu M, Okazaki N, Hasegawa H, Nakajima Y, Ohnishi K.** Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. *Cancer* 1985; **56**: 918-928 [PMID: 2990661]
- 12 **Fong ZV, Tanabe KK.** The clinical management of hepatocellular carcinoma in the United States, Europe, and Asia: a comprehensive and evidence-based comparison and review. *Cancer* 2014; **120**: 2824-2838 [PMID: 24897995 DOI: 10.1002/cncr.28730]
- 13 **Ishizawa T, Hasegawa K, Aoki T, Takahashi M, Inoue Y, Sano K, Imamura H, Sugawara Y, Kokudo N, Makuuchi M.** Neither multiple tumors nor portal hypertension are surgical contraindications for hepatocellular carcinoma. *Gastroenterology* 2008; **134**: 1908-1916 [PMID: 18549877 DOI: 10.1053/j.gastro.2008.02.091]
- 14 **Gaillard M, Tranchart H, Dagher I.** Laparoscopic liver resections for hepatocellular carcinoma: current role and limitations. *World J Gastroenterol* 2014; **20**: 4892-4899 [PMID: 24803800 DOI: 10.3748/wjg.v20.i17.4892]
- 15 **Ripoll C, Groszmann R, Garcia-Tsao G, Grace N, Burroughs A, Planas R, Escorsell A, Garcia-Pagan JC, Makuch R, Patch D, Matloff DS, Bosch J.** Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. *Gastroenterology* 2007; **133**: 481-488 [PMID: 17681169 DOI: 10.1053/j.gastro.2007.05.024]
- 16 **Llovet JM, Schwartz M, Mazzaferro V.** Resection and liver transplantation for hepatocellular carcinoma. *Semin Liver Dis* 2005; **25**: 181-200 [PMID: 15918147 DOI: 10.1055/s-2005-871198]
- 17 **Llovet JM, Fuster J, Bruix J.** Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. *Hepatology* 1999; **30**: 1434-1440 [PMID: 10573522]
- 18 **Valenzuela A, Ha NB, Gallo A, Bonham C, Ahmed A, Melcher M, Kim LH, Esquivel C, Concepcion W, Ayoub WS, Lutchman GA, Daugherty T, Nguyen MH.** Recurrent hepatocellular carcinoma and poorer overall survival in patients undergoing left-sided compared with right-sided partial hepatectomy. *J Clin Gastroenterol* 2015; **49**: 158-164 [PMID: 24804988 DOI: 10.1097/MCG.0000000000000144]
- 19 **Buell JF, Cherqui D, Geller DA, O'Rourke N, Iannitti D, Dagher I, Koffron AJ, Thomas M, Gayet B, Han HS, Wakabayashi G, Belli G, Kaneko H, Ker CG, Scatton O, Laurent A, Abdalla EK, Chaudhury P, Dutson E, Gamblin C, D'Angelica M, Nagorney D, Testa G, Labow D, Manas D, Poon RT, Nelson H, Martin R, Clary B, Pinson WC, Martinie J, Vauthey JN, Goldstein R, Roayaie S, Barlet D, Espat J, Abecassis M, Rees M, Fong Y, McMasters KM, Broelsch C, Busuttill R, Belghiti J, Strasberg S, Chari RS.** The international position on laparoscopic liver surgery: The Louisville Statement, 2008. *Ann Surg* 2009; **250**: 825-830 [PMID: 19916210]
- 20 **Croome KP, Yamashita MH.** Laparoscopic vs open hepatic resection for benign and malignant tumors: An updated meta-analysis. *Arch Surg* 2010; **145**: 1109-1118 [PMID: 21079101 DOI: 10.1001/archsurg.2010.227]
- 21 **Piardi T, Sommacale D, Baumert T, Mutter D, Marescaux J, Pessaux P.** Laparoscopic resection for hepatocellular carcinoma: comparison between Middle Eastern and Western experience. *Hepatobiliary Surg Nutr* 2014; **3**: 60-72 [PMID: 24812597 DOI: 10.3978/j.issn.2304-3881.2014.04.03]
- 22 **Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L.** Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**: 693-699 [PMID: 8594428 DOI: 10.1056/NEJM199603143341104]
- 23 **Clavien PA, Lesurtel M, Bossuyt PM, Gores GJ, Langer B, Perrier A.** Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. *Lancet Oncol* 2012; **13**: e11-e22 [PMID: 22047762 DOI: 10.1016/S1470-2045(11)70175-9]
- 24 **European Liver Transplant Registry.** Available from: URL: <http://www.eltr.org/>
- 25 **Organ Procurement and Transplantation Network.** Available from: URL: <http://optn.transplant.hrsa.gov/>
- 26 **Dumortier J, Boillot O, Scoazec JY.** Natural history, treatment and prevention of hepatitis C recurrence after liver transplantation: past, present and future. *World J Gastroenterol* 2014; **20**: 11069-11079 [PMID: 25170196 DOI: 10.3748/wjg.v20.i32.11069]
- 27 **Kamath PS, Wiesner RH, Malincho M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR.** A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001; **33**: 464-470 [PMID: 11172350]
- 28 **Ravaioli M, Grazi GL, Piscaglia F, Trevisani F, Cescon M, Ercolani G, Vivarelli M, Golfieri R, D'Errico Grigioni A, Panzini I, Morelli C, Bernardi M, Bolondi L, Pinna AD.** Liver transplantation for hepatocellular carcinoma: results of down-staging in patients initially outside the Milan selection criteria. *Am J Transplant* 2008; **8**: 2547-2557 [PMID: 19032223 DOI: 10.1111/j.1600-6143.2008.02409.x]
- 29 **Yao FY, Kerlan RK, Hirose R, Davern TJ, Bass NM, Feng S, Peters M, Terrault N, Freise CE, Ascher NL, Roberts JP.** Excellent outcome following down-staging of hepatocellular carcinoma prior to liver transplantation: an intention-to-treat analysis. *Hepatology* 2008; **48**: 819-827 [PMID: 18688876 DOI: 10.1002/hep.22412]
- 30 **Brown RS.** Live donors in liver transplantation. *Gastroenterology* 2008; **134**: 1802-1813 [PMID: 18471556 DOI: 10.1053/j.gastro.2008.02.092]
- 31 **Lee S, Hyuck David Kwon C, Man Kim J, Joh JW, Woon Paik S, Kim BW, Wang HJ, Lee KW, Suh KS, Lee SK.** Time of hepatocellular carcinoma recurrence after liver resection and



- alpha-fetoprotein are important prognostic factors for salvage liver transplantation. *Liver Transpl* 2014; **20**: 1057-1063 [PMID: 24862741 DOI: 10.1002/lt.23919]
- 32 **Sala M**, Llovet JM, Vilana R, Bianchi L, Solé M, Ayuso C, Brú C, Bruix J. Initial response to percutaneous ablation predicts survival in patients with hepatocellular carcinoma. *Hepatology* 2004; **40**: 1352-1360 [PMID: 15565564 DOI: 10.1002/hep.20465]
- 33 **Lencioni R**. Loco-regional treatment of hepatocellular carcinoma. *Hepatology* 2010; **52**: 762-773 [PMID: 20564355 DOI: 10.1002/hep.23725]
- 34 **Khan KN**, Yatsuhashi H, Yamasaki K, Yamasaki M, Inoue O, Koga M, Yano M. Prospective analysis of risk factors for early intrahepatic recurrence of hepatocellular carcinoma following ethanol injection. *J Hepatol* 2000; **32**: 269-278 [PMID: 10707867]
- 35 **Lin SM**, Lin CJ, Lin CC, Hsu CW, Chen YC. Radiofrequency ablation improves prognosis compared with ethanol injection for hepatocellular carcinoma &lt;lt;math>\leq 4\text{ cm}</math>. *Gastroenterology* 2004; **127**: 1714-1723 [PMID: 15578509]
- 36 **Lin SM**, Lin CJ, Lin CC, Hsu CW, Chen YC. Randomised controlled trial comparing percutaneous radiofrequency thermal ablation, percutaneous ethanol injection, and percutaneous acetic acid injection to treat hepatocellular carcinoma of 3 cm or less. *Gut* 2005; **54**: 1151-1156 [PMID: 16009687 DOI: 10.1136/gut.2004.045203]
- 37 **Shiina S**, Teratani T, Obi S, Sato S, Tateishi R, Fujishima T, Ishikawa T, Koike Y, Yoshida H, Kawabe T, Omata M. A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma. *Gastroenterology* 2005; **129**: 122-130 [PMID: 16012942]
- 38 **Minami Y**, Nishida N, Kudo M. Therapeutic response assessment of RFA for HCC: contrast-enhanced US, CT and MRI. *World J Gastroenterol* 2014; **20**: 4160-4166 [PMID: 24764654 DOI: 10.3748/wjg.v20.i15.4160]
- 39 **Kudo M**. Local ablation therapy for hepatocellular carcinoma: current status and future perspectives. *J Gastroenterol* 2004; **39**: 205-214 [PMID: 15064996 DOI: 10.1007/s00535-003-1280-y]
- 40 **Lammer J**, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, Pitton M, Sergeant G, Pfammatter T, Terraz S, Benhamou Y, Avajon Y, Gruenberger T, Pomoni M, Langenberger H, Schuchmann M, Dumortier J, Mueller C, Chevallier P, Lencioni R. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. *Cardiovasc Intervent Radiol* 2010; **33**: 41-52 [PMID: 19908093 DOI: 10.1007/s00270-009-9711-7]
- 41 **Sieghart W**, Huckle F, Pinter M, Graziadei I, Vogel W, Müller C, Heinzl H, Trauner M, Peck-Radosavljevic M. The ART of decision making: retreatment with transarterial chemoembolization in patients with hepatocellular carcinoma. *Hepatology* 2013; **57**: 2261-2273 [PMID: 23316013 DOI: 10.1002/hep.26256]
- 42 **Kulik LM**, Carr BI, Mulcahy MF, Lewandowski RJ, Atassi B, Ryu RK, Sato KT, Benson A, Nemecek AA, Gates VL, Abecassis M, Omary RA, Salem R. Safety and efficacy of 90Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis. *Hepatology* 2008; **47**: 71-81 [PMID: 18027884 DOI: 10.1002/hep.21980]
- 43 **Riaz A**, Lewandowski RJ, Kulik LM, Mulcahy MF, Sato KT, Ryu RK, Omary RA, Salem R. Complications following radioembolization with yttrium-90 microspheres: a comprehensive literature review. *J Vasc Interv Radiol* 2009; **20**: 1121-1130; quiz 1131 [PMID: 19640737 DOI: 10.1016/j.jvir.2009.05.030]
- 44 **Ibrahim SM**, Lewandowski RJ, Sato KT, Gates VL, Kulik L, Mulcahy MF, Ryu RK, Omary RA, Salem R. Radioembolization for the treatment of unresectable hepatocellular carcinoma: a clinical review. *World J Gastroenterol* 2008; **14**: 1664-1669 [PMID: 18350597]
- 45 **Salem R**, Lewandowski RJ, Mulcahy MF, Riaz A, Ryu RK, Ibrahim S, Atassi B, Baker T, Gates V, Miller FH, Sato KT, Wang E, Gupta R, Benson AB, Newman SB, Omary RA, Abecassis M, Kulik L. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. *Gastroenterology* 2010; **138**: 52-64 [PMID: 19766639 DOI: 10.1053/j.gastro.2009.09.006]
- 46 **Mazzaferro V**, Sposito C, Bhoori S, Romito R, Chiesa C, Morosi C, Maccauro M, Marchianò A, Bongini M, Lanocita R, Civelli E, Bombardieri E, Camerini T, Spreafico C. Yttrium-90 radioembolization for intermediate-advanced hepatocellular carcinoma: a phase 2 study. *Hepatology* 2013; **57**: 1826-1837 [PMID: 22911442 DOI: 10.1002/hep.26014]
- 47 **Kolligs FT**, Bilbao JI, Jakobs T, <sup>1</sup>narrairaegui MI, Nagel J, Rodriguez M, Haug A, D'Avola D, Winkel Mod, Martinez-Cuesta A, Trumm C, Benito A, Tatsch K, Zech C, Hoffmann RT, Sangro B. SIRTACE: a randomised multicentre pilot trial of selective internal radioembolisation (SIRT) with yttrium-90 microspheres versus transarterial chemo-embolisation (TACE) in patients with unresectable hepatocellular carcinoma (HCC). *Journal of Hepatology* 2013; **58**: S45-S61
- 48 **Ursino S**, Greco C, Cartei F, Colosimo C, Stefanelli A, Cacopardo B, Berretta M, Fiorica F. Radiotherapy and hepatocellular carcinoma: update and review of the literature. *Eur Rev Med Pharmacol Sci* 2012; **16**: 1599-1604 [PMID: 23111978]
- 49 **Feng M**, Ben-Josef E. Radiation therapy for hepatocellular carcinoma. *Semin Radiat Oncol* 2011; **21**: 271-277 [PMID: 21939856 DOI: 10.1016/j.semradonc.2011.05.002]
- 50 **Lo SS**, Dawson LA, Kim EY, Mayr NA, Wang JZ, Huang Z, Cardenas HR. Stereotactic body radiation therapy for hepatocellular carcinoma. *Discov Med* 2010; **9**: 404-410 [PMID: 20515608]
- 51 **Yoon SM**, Lim YS, Park MJ, Kim SY, Cho B, Shim JH, Kim KM, Lee HC, Chung YH, Lee YS, Lee SG, Lee YS, Park JH, Kim JH. Stereotactic body radiation therapy as an alternative treatment for small hepatocellular carcinoma. *PLoS One* 2013; **8**: e79854 [PMID: 24255719 DOI: 10.1371/journal.pone.0079854]
- 52 **Jacob R**, Turley F, Redden DT, Saddekni S, Aal AK, Keene K, Yang E, Zarzour J, Bolus D, Smith JK, Gray S, White J, Eckhoff DE, DuBay DA. Adjuvant stereotactic body radiotherapy following transarterial chemoembolization in patients with non-resectable hepatocellular carcinoma tumours of  $\geq 3\text{ cm}$ . *HPB (Oxford)* 2015; **17**: 140-149 [PMID: 25186290 DOI: 10.1111/hpb.12331]
- 53 **Llovet JM**, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**: 378-390 [PMID: 18650514 DOI: 10.1056/NEJMoa0708857]
- 54 **Cheng AL**, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, Xu J, Sun Y, Liang H, Liu J, Wang J, Tak WY, Pan H, Burock K, Zou J, Voliotis D, Guan Z. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; **10**: 25-34 [PMID: 19095497 DOI: 10.1016/S1470-2045(08)70285-7]
- 55 **Zhang L**, Hu P, Chen X, Bie P. Transarterial chemoembolization (TACE) plus sorafenib versus TACE for intermediate or advanced stage hepatocellular carcinoma: a meta-analysis. *PLoS One* 2014; **9**: e100305 [PMID: 24945380 DOI: 10.1371/journal.pone.0100305]
- 56 **Shen YC**, Lin ZZ, Hsu CH, Hsu C, Shao YY, Cheng AL. Clinical trials in hepatocellular carcinoma: an update. *Liver Cancer* 2013; **2**: 345-364 [PMID: 24400222 DOI: 10.1159/000343850]
- 57 **Faivre S**, Raymond E, Boucher E, Douillard J, Lim HY, Kim JS, Zappa M, Lanzalone S, Lin X, Deprimo S, Harmon C, Ruiz-Garcia A, Lechuga MJ, Cheng AL. Safety and efficacy of sunitinib in patients with advanced hepatocellular carcinoma: an open-label, multicentre, phase II study. *Lancet Oncol* 2009; **10**: 794-800 [PMID: 19586800 DOI: 10.1016/S1470-2045(09)70171-8]
- 58 **Zhu AX**, Sahani DV, Duda DG, di Tomaso E, Ancukiewicz M, Catalano OA, Sindhvani V, Blaszkowsky JS, Yoon SS, Lahdenranta J, Bhargava P, Meyerhardt J, Clark JW, Kwak EL, Hezel AF, Miksad R, Abrams TA, Enzinger PC, Fuchs CS, Ryan DP, Jain RK. Efficacy, safety, and potential biomarkers of sunitinib monotherapy in advanced hepatocellular carcinoma: a phase II study. *J Clin Oncol* 2009; **27**: 3027-3035 [PMID: 19470923 DOI:



- 10.1200/JCO.2008.20.9908]
- 59 **Cheng AL**, Kang YK, Lin DY, Park JW, Kudo M, Qin S, Chung HC, Song X, Xu J, Poggi G, Omata M, Pitman Lowenthal S, Lanzaone S, Yang L, Lechuga MJ, Raymond E. Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized phase III trial. *J Clin Oncol* 2013; **31**: 4067-4075 [PMID: 24081937 DOI: 10.1200/JCO.2012.45.8372]
- 60 **Cainap C**, Qin S, Huang WT, Chung IJ, Pan H, Cheng Y, Kudo M, Kang YK, Chen PJ, Toh HC, Gorbunova V, Eskens F, Qian J, McKee MD, Ricker JL, Carlson DM, Nowiem SE. Phase III trial of linafinib versus sorafenib in patients with advanced hepatocellular carcinoma (HCC). *J Clin Oncol* 2013; **30** Suppl 4: abstr249
- 61 **Johnson PJ**, Qin S, Park JW, Poon RT, Raoul JL, Philip PA, Hsu CH, Hu TH, Heo J, Xu J, Lu L, Chao Y, Boucher E, Han KH, Paik SW, Robles-Aviña J, Kudo M, Yan L, Sobhonslidsuk A, Komov D, Decaens T, Tak WY, Jeng LB, Liu D, Ezzeddine R, Walters I, Cheng AL. Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized phase III BRISK-FL study. *J Clin Oncol* 2013; **31**: 3517-3524 [PMID: 23980084 DOI: 10.1200/JCO.2012.48.4410]
- 62 **Zhu AX**, Kudo M, Assenat E, Cattani S, Kang YK, Lim HY, Poon RTP, Blanc JF, Vogel A, Chen CL, Dorval E, Peck-Radosavljevic M, Santoro A, Daniele B, Furuse J, Jappe A, Perraud K, Anak O, Sellami DB, Chen LT. EVOLVE-1: Phase 3 study of everolimus for advanced HCC that progressed during or after sorafenib. *J Clin Oncol* 2014; **32** Suppl 3: abstr172
- 63 **Davila JA**, Henderson L, Kramer JR, Kanwal F, Richardson PA, Duan Z, El-Serag HB. Utilization of surveillance for hepatocellular carcinoma among hepatitis C virus-infected veterans in the United States. *Ann Intern Med* 2011; **154**: 85-93 [PMID: 21242365 DOI: 10.7326/0003-4819-154-2-2011101180-00006]
- 64 **González-Diéguez ML**, Mancebo A, Cadahia V, Pérez R, Varela M, Navascues C, Rodríguez M. Analysis of the adherence to a hepatocellular carcinoma (hcc) surveillance programme based on biannual controls. *Journal of Hepatology* 2014; **60** Suppl 1: S259 [DOI: 10.1016/S0168-8278(14)60732-7]

**P- Reviewer:** Gangl A, Kucherlapati MH, Kuo WH, Wang RB  
**S- Editor:** Tian YL **L- Editor:** A **E- Editor:** Wu HL





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>

