Advances in managing hepatocellular carcinoma

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Abstract   **Multiple modalities for treatment of hepatocellular carcinoma are available, depending on tumor size and number. Surgical resection remains the gold standard, so long as the residual liver function reserve is sufficient. In patients with advanced cirrhosis, liver transplantation is the preferred option, as these patients may not have adequate hepatic reserve after resection. Salvage liver transplantation has also become an option for a select few patients who recur after surgical resection. Ablative techniques have been used for palliation as well as to either completely destroy the tumor, act as an adjunct to resection, or downstage the tumor to meet Milan criteria such that a patient may be a candidate for liver transplantation. Radiofrequency ablation, microwave ablation, chemoembolization, radioembolization, and irreversible electroporation have all been used in this capacity. Currently, sorafenib is the only US Food and Drug Administration-approved chemotherapeutic for hepatocellular carcinoma. The efficacy of sorafenib, in combination with other agents, transarterial chemoembolization, and surgical resection is currently being investigated. Sunitinib and brivanib, tyrosine kinase inhibitors, have failed as potential first- or second-line options for chemotherapy. Bevacizumab in combination with erlotinib is also currently being studied. Final analysis for ramucirumab and axitinib are pending. Tivantinib, a selective mesenchymal-epithelial transition factor (MET) inhibitor, is also undergoing clinical trials for efficacy in MET-high tumors. This review serves to emphasize the current and new technologies emerging in the treatment of hepatocellular carcinoma.**

Keywords   hepatocellular carcinoma; radiofrequency ablation; microwave ablation; chemoembolization; radioembolization; sorafenib; irreversible electroporation

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide and is the third most common cause of cancer-related mortalities [1,2]. While HCC tumors tend to be slow-growing, they are often rapidly fatal since discovery usually occurs once the disease is advanced [3]. The major risk factors for HCC are male sex, cirrhosis, hepatitis B virus (HBV) infection, and hepatitis C virus (HCV) infection [4]. HCC rarely occurs before the age of 40 and reaches a peak at approximately 70 years of age. Cirrhosis is found in 67%–80% of autopsies on HCC patients [4,5]. Other risk factors involve alcoholic liver disease, non-alcoholic steatohepatitis (NASH), oral contraceptives, aflatoxins, and microcystin-contaminated water. There are multiple modalities available for management of HCC, depending on number and size of

tumors, disease stage, and previous treatments attempted. This review serves to emphasize current and new technologies emerging in the treatment of HCC.

Surgical resection

While some studies suggest that the best treatment for HCC is orthotopic liver transplantation (OLT) in that it allows for complete resection of the tumor as well as elimination of cirrhosis [6], surgical resection (SR) is still considered the gold standard and should be the first consideration in all cases. While hemihepatectomy, segmentectomy and non-anatomical wedge resection are all modalities for tumor resection, only 3% to 30% of patients are resectable at the time of diagnosis. Additionally, there are several factors affecting outcome after SR. Such factors include the size and number of nodules, microscopic or macroscopic vascular invasion, capsular invasion, lymph node involvement, and tumor grade. Although the operative mortality rate for

hepatectomy in the 1980s was 10%–20% [3], recent literature has shown a decrease to less than 5% in patients with early HCC meeting the Milan criteria [7] along with demonstration of good liver function [8]. Non-cirrhotic patients can tolerate extensive resections. Well-compensated patients with cirrhosis can tolerate resection of up to two segments; patients with cirrhosis who require resection of more than 2 functional segments should be considered for preoperative portal vein chemoembolization [3]. The 1-, 3-, and 5-year survival rates of patients undergoing SR are depicted in Table 1 [9–15]. However, as seen in Table 2 [10–14], the 1-, 3-, and 5-year recurrence-free survival rates of patients undergoing SR remain quite high. Two major factors contribute to high recurrence rates: (1) the actual inciting factor (e.g., HBV or HCV) is not completely removed at the time of SR [16]; (2) there are no established adjuvant chemotherapy protocols following SR.

Orthotopic liver transplantation

Orthotopic liver transplantation (OLT) remains the gold standard for patients with cirrhosis complicated by HCC. The Milan criteria [7] have traditionally defined eligibility for OLT, in which the presence of a tumor is $\leqslant$ 5 cm in diameter in patients with a single tumor or no more than 3 nodules each being $\leqslant$ 3 cm in diameter in patients with multiple tumors. While studies have shown that survival rates for OLT tend to be higher in patients meeting the Milan criteria than in patients exceeding them, several studies have also suggested

that survival rates in patients exceeding the Milan criteria are acceptable.

More recently, the "survival benefit" concept has become a guide used to evaluate OLT results. For patients with cirrhosis and a Model for End-state Liver Disease (MELD) score < 15, the 1-year mortality risk was greater with OLT than without OLT [17]. Therefore, the United States United Network for Organ Sharing (UNOS) instituted the "Share 15" rule, in which patients with MELD scores $\geqslant$ 15 have priority for OLT [18]. For HCC patients with MELD scores $\geqslant$ 15, OLT is therefore a reasonable option given their hepatic decompensation. For patients with HCC and MELD < 15, the situation is more complicated. Tandoi et al. [19] have demonstrated that the source of the underlying liver disease significantly influences the long-term survival in these patients, with hepatitis C recurrence being the most common cause of death.

There have been an increasing number of studies examining OLT in patients exceeding Milan criteria but meeting UCSF criteria [20,21]. UCSF criteria [21] are defined as the following: a solitary tumor $\leqslant$ 6.5 cm, or $\leqslant$ 3 nodules with the largest lesion $\leqslant$ 4.5 cm, and a total tumor diameter of $\leqslant$ 8 cm. Liu et al. [20] found that patients meeting Milan criteria undergoing OLT versus patients exceeding Milan criteria but meeting UCSF criteria experienced no difference in survival rates. Secondly, there have been a number of studies investigating the survival rates of OLT in patients who recurred after SR, otherwise known as salvage OLT (SLT), despite exceeding Milan criteria [22]. Such studies have found no significant differences in survival rates between

Table 1 Comparison of overall survival rates between surgical resection and radiofrequency ablation

Study (year)	n	1-year survival (%)	3-year survival (%)	5-year survival (%)
Hasegawa et al. (2013) [9]				
SR	5361	N/A	85.3	71.1
RFA	5548	N/A	81.0	61.1
Tohme et al. (2013) [10]				
SR	50	88	68	47
RFA	60	86	50	35
Feng et al. (2012) [11]				
SR	84	96.0	87.6	N/A
RFA	84	93.1	83.1	N/A
Huang et al. (2010) [12]				
SR	115	98.2	92.1	75.6
RFA	115	86.9	69.5	54.7
Chen et al. (2006) [13]				
SR	90	93.3	73.4	N/A
RFA	71	95.8	71.4	N/A
Lü et al. (2006) [14]				
SR	54	91.3	86.4	N/A
RFA	51	93.5	87.1	N/A
Chen et al. (2005) [15]				
SR	65	93.2	67.3	N/A
RFA	47	92.8	64.5	N/A

SR, surgical resection; RFA, radiofrequency ablation; N/A, not available.

patients undergoing OLT versus SLT. The 1-, 3-, and 5-year survival rates of these patient populations are depicted in Table 3 [20,23–28]. The 1-, 3-, and 5-year recurrence-free survival rates of these patient populations are depicted in Table 4 [24,26,29,30]. When compared to Table 2, OLT clearly shows lower recurrence rates when compared to SR.

Radiofrequency ablation

SR is often contraindicated in cases where there is limited hepatic function in patients with cirrhosis; hence, ablation has become increasingly common in treatment of HCC. Radiofrequency ablation (RFA) is the primary ablative therapy at most institutions. RF current causes molecular friction locally as a function of current density. Molecular friction adjacent to the electrode causes heat that is transmitted to the surrounding tissue. Temperatures are raised to 85–105°C to enable coagulation necrosis. Once running, RF current is monitored in real time with temperature recording and ultrasound.

RFA when used with intraoperative ultrasound yields better sensitivity for detecting and measuring tumors. While computed tomography (CT) is able to pick up most lesions, intraoperative ultrasound is extremely sensitive for picking up smaller lesions that may be missed on CT. Literature has shown that diagnostic laparoscopy, when used with intraoperative ultrasound, drastically altered the operative management in 32% of patients [31]. Laparoscopic ultrasound also upstaged the tumor in 32% of cases [32].

Survival rates after RFA when compared to SR are summarized in Table 1. Feng et al. [33] conducted a randomized controlled trial studying the efficacies of RFA versus SR on small HCC < 4 cm in diameter with ≤ 2 nodules. They found that the 1-, 2-, and 3-year survival rates for RFA and SR were 93.1%, 83.1%, 67.2% and 96.0%, 87.6%, 74.8%, respectively, with recurrence-free survival rates at 86.2%, 66.6%, 49.6% and 90.6%, 76.7%, 61.1% respectively. There were no differences between the groups in overall survival rate; however, the authors conclude that percutaneous RFA is more likely to be incomplete in treating small HCCs and that SR may still be a better option, as RFA may leave residual tumors more easily due to guidance system limitations. Despite use of ultrasonography with RFA for better results, RFA is limited by its high frequency of local recurrences. Local recurrence rates vary from 2% [34,35] to 60% [36]. Table 2 summarizes recurrence-free survival rates, demonstrating greater recurrence-free survival rates in the SR versus RFA groups. Meta-analysis of SR versus RFA has also demonstrated that SR is superior to RFA for treatment of early-stage HCC [37].

Additional drawbacks to RFA are the heat sink effect and the tissue charring. Heat adjacent to a great vessel dissipates into the great vessel, thereby preventing the target tissue from reaching an optimal temperature and altering ablation size and shape [38–40]. This phenomenon limits the area of ablation that RFA is able to achieve. Charring occurs when heat is rapidly deposited onto tissue, causing boiling and charring of the tissue, which increase tissue impedance and also alter ablation size and shape [41].

Microwave ablation

Microwave ablation (MWA) is the most recent development in thermal destruction of HCCs. MWA employs electromagnetic radiation to excite and thereby heat the intracellular water molecules of the surrounding tissue. This heat causes coagulation necrosis and destruction of the tissue. MWA is extensively used in the Asia and in the UK, whereas its use in the US remains in its infancy [42]. MWA can be delivered through open laparotomy, laparoscopically, or percutaneously.

Table 2 Comparison of recurrence-free survival rates between surgical resection and radiofrequency ablation

Study (year)	n	1-year recurrence-free survival (%)	3-year recurrence-free survival (%)	5-year recurrence-free survival (%)
Tohme et al. (2013) [10]				
SR	50	66	42	34
RFA	60	68	42	28
Feng et al. (2012) [11]				
SR	84	90.6	61.1	N/A
RFA	84	86.2	49.6	N/A
Huang et al. (2010) [12]				
SR	115	85.2	60.8	51.3
RFA	115	81.7	46.0	28.6
Chen et al. (2006) [13]				
SR	90	86.6	69.0	N/A
RFA	71	85.9	64.1	N/A
Lü et al. (2006) [14]				
SR	54	82.4	82.4	N/A
RFA	51	78.5	51.3	N/A

SR, surgical resection; RFA, radiofrequency ablation; N/A, not available.

Table 3 Comparison of overall survival rates of liver transplantation

Study (year)	n	1-year survival (%)	3-year survival (%)	5-year survival (%)
Liu *et al.* (2012) [20]				
PLT	180	90	81	72
SLT	39	88	78	61
SLT-MC	N/A	89	83	66
SLT-UCSF	N/A	88	69	55
Wu *et al.* (2012) [23]				
PLT-MC	147	98.0	86.4	75.5
PLT-BMC	156	96.2	64.7	48.7
SLT	36	97.2	80.6	69.4
Facciuto *et al.* (2008) [24]				
PLT	32	87	69	60
Scatton *et al.* (2007) [25]				
PLT	73	71	61	55
SLT	14	74	66	66
Vennarecci *et al.* (2007) [26]				
PLT	37	78	62.7	62.7
SLT	9	88.9	88.9	88.9
Margarit *et al.* (2005) [27]				
PLT	36	65	N/A	50
Adam *et al.* (2003) [28]				
PTL	195	N/A	N/A	61
SLT	17	N/A	N/A	41

PLT, primary liver transplantation; SLT, salvage liver transplantation; SLT-MC, salvage liver transplantation meeting Milan criteria; SLT-UCSF, salvage liver transplantation meeting UCSF criteria; PLT-MC, primary liver transplantation meeting Milan criteria; PLT-BMC, primary liver transplantation beyond Milan criteria; N/A, not available.

Table 4 Comparison of recurrence-free survival rates after liver transplantation

Study (year)	n	1-year recurrence-free survival (%)	3-year recurrence-free survival (%)	5-year recurrence-free survival (%)
Sapisochin *et al.* (2010) [29]				
PLT	191	97	93	89
SLT	17	100	88	75
Facciuto *et al.* (2008) [24]				
PLT	32	87	72	65
Vennarecci *et al.* (2007) [26]				
PLT	37	89	74	74
SLT	9	100	100	100
Belghiti *et al.* (2003) [30]				
PLT	70	N/A	82	59
SLT	18	N/A	82	61

PLT, primary liver transplantation; SLT, salvage liver transplantation; N/A, not available.

MWA has been shown in several clinical trials to be a safe and effective option for unresectable HCCs. Phase I clinical trials in the US demonstrated that MWA can achieve a maximal ablation zone of 50.8 cm^3 with gross and microscopic analysis demonstrating clear coagulation necrosis, even near large hepatic vessels [43]. Phase II clinical trials in the US [44] demonstrated that after MWA and a mean follow-up time of 19 months, 41% of patients were alive without evidence of recurrence. Martin *et al.* [45] reported a 100% ablation success rate for the 17 patients in their study with HCC, along with an ablation recurrence rate of 6%. They further report that their median disease-free survival was 18 months, with a median overall survival of 41 months. Another study showed that MWA yielded 1-, 3- and 5-year cumulative survival rates of 93%, 72%, and 51%, with tumor recurrence at 8% [46]. These survival rates are comparative to those of RFA, and these two modalities should be further compared for efficacy and successful ablation and recurrence rates.

MWA presents with some theoretical advantage over RFA in that microwave instrumentation operates between 900 MHz to 2.45 GHz, whereas RFA ranges from 300 kHz to 1 MHz, thus having lesser thermal destruction capability and at slower rates of destruction. Liu *et al.* [47] studied the effectiveness of the 915 MHz versus the 2.45 GHz models for ablation of HCC greater than 4 cm in diameter. They found that 85.7% of tumors ablated with the 915 MHz models

achieved complete ablation, whereas only 73.7% tumors were completely ablated with the 2.45 GHz models. Also, the 915 MHz group required fewer antenna insertions, which they attributed to its ability to penetrate deeper, thereby producing a larger ablation zone. Lastly, in the 915 MHz group, local tumor progression was seen in 14.3% cases, whereas the rate was 26.3% for the 2.45 GHz group. One recent study performed in the US utilized both 915 MHz and 2.45 GHz generators [48]. In this study, the 915 MHz model is preferred for multiple small volume ablations, while the 2.45 GHz model can target a larger ablation zone over a shorter period of time.

Along with its capacity to create larger zones of ablation compared to RFA, MWA is a good option for perivascular tumor treatment. MWA does not seem to be as susceptible to the heat sink effect that RFA is limited by, as MWA yields a greater power density in the targeted ablation zone [42]. Thus, MWA is able to achieve greater uniformity in the ablation zone. There has been some discussion about how large a target zone MWA can successfully ablate. RFA and MWA have been shown to be effective in treating HCC measuring less than or equal to 3 cm, but there is minimal literature comparing ablation success in small versus larger HCCs. Liu *et al.* [49] treated 52 patients with a main tumor measuring 3–5 cm and an additional 57 patients with a main tumor measuring 5–8 cm. Of the 52 patients with tumors measuring 3–5 cm, complete ablation was possible in 94.2% of patients. In patients with tumors measuring 5–8 cm, the complete ablation rate was 75%. There was a significant difference in complete tumor ablation rates between these two groups ($P = 0.033$). In addition, the local recurrence rate in patients with tumors measuring 5–8 cm was significantly higher than those between 3 and 5 cm ($P = 0.026$). The 1-, 2-, 3-, and 5-year overall survival rates for patients presenting with tumors 5–8 cm were 60.7%, 46.4%, 39.3%, and 13.1%. These data are consistent with other literature which recognize that tumor size is an important factor in determining local occurrence [50] and long-term survival [51].

Drug-eluting beads used in conjunction with transarterial chemoembolization

Transarterial chemoembolization (TACE) is a method in which chemotherapeutic drugs are combined with embolization particles and then injected into the hepatic artery that supplies the tumor. TACE has been used as treatment for HCC in cases where SR is not a viable option or a means of downstaging HCC to fit within Milan criteria for possibility of further management with OLT. TACE has traditionally been done with chemotherapeutics such as doxorubicin or cisplatin emulsed in lipiodol and gelatinin-sponge particles. Two randomized controlled trials have been done evaluating the efficacy of TACE. Table 5 [52,53] shows the survival rates for each of these studies. The trials performed by the Hong Kong [52] and Barcelona [53] groups showed a significant increase in survival rates when compared to the control groups ($P = 0.005$ and $P = 0.025$, respectively).

As discussed previously, a common chemotherapeutic agent used with TACE is doxorubicin. A more novel take on TACE is the use of drug-eluting beads (DEB) loaded with doxorubicin. Doxorubicin is loaded onto the beads *in vitro* prior to the procedure, and beads varying in size from 100 to 700 μm are injected into the artery feeding the tumor prior to embolization. However, it should be emphasized that there are no major studies demonstrating that systemic doxorubicin is efficacious against HCC. Since the advent of DEB-TACE, there has been question as to whether DEB-TACE is safer or more effective than conventional TACE. Varela *et al.* [54] have demonstrated in their pharmacokinetics study that systemic doxorubicin levels were significantly lower in DEB-TACE patients than in patients treated with conventional TACE, despite having delivered greater doses of doxorubicin via DEB-TACE. Furthermore, Recchia *et al.* [55] have shown that DEB-TACE allows for the gradual and continuous release of doxorubicin over 14 days post-procedure, allowing for prolonged antitumoral effect. This study further showed that AST and LDH levels were significantly lower in the DEB-TACE group versus the conventional TACE group. They also found that hospital stay was significantly shorter and postoperative complications were significantly less in the DEB-TACE group. The PRECISION V study [56] conducted a randomized trial comparing conventional TACE and DEB-TACE. In their study, the overall response rate, defined by complete response plus partial response, was 51.6% versus 43.5% for the DEB-TACE group versus the conventional TACE group. There were no significant differences between the disease control rates.

Table 5 Survival rates for chemoembolization as demonstrated in randomized clinical trials

Study	Survival rates (%)		
	1-year	2-year	3-year
Lo *et al.* (2002) [52]			
Chemoembolization	57	31	26
Control	32	11	3
Llovet *et al.* (2002) [53]			
Chemoembolization	82	63	29
Control	63	27	17

However, the study did find that in the 67% of patients with Child Pugh B, Eastern Cooperative Oncology Group (ECOG) stage 1, bilobar, or recurrent disease, the incidence of objective response and disease control rates were significantly greater in the DEB-TACE group. The same group found significantly lower serious liver toxicity postchemoembolization in the DEB-TACE group.

There has been some discussion as to whether DEB-TACE can be used to downstage T3N0M0 HCC to meet Milan criteria for transplantation. Patients undergoing locoregional treatments have been shown in prospective studies [57–60] to demonstrate acceptable disease-free survival after transplantation and that downstaging HCC with locoregional treatments predicts a favorable OLT result [61]. Green *et al.* [62] found that 77% of 22 patients undergoing DEB-TACE had their disease downstaged to meet Milan criteria per modified Response Evaluation Criteria In Solid Tumors (mRECIST) measurements, seven eventually undergoing OLT.

Transarterial radioembolization

Transarterial radioembolization (TARE) is an emerging treatment of HCC used for palliative measures or to bridge to OLT. Through TARE, micron-sized particles loaded with a radioisotope are injected transarterially. The most commonly studied and used radioisotope is Yttrium-90 infused microspheres [63].

Yttrium-90 microspheres are 20–40 μm sized particles that emit β radiation [63]. There are two modalities in which Yttrium-90 microspheres are introduced. Thera-Sphere® (MDS Nordion, Ottawa, Canada) consists of nonbiodegradable glass beads measuring between 20 μm and 30 μm. It was approved by the US FDA in 1999 through a Humanitarian Device Exemption (HDE) for patients with unresectable HCC and more recently approved for use in patients with HCC and portal vein thrombosis (PVT). SIR-Spheres® (Sirtex, Lane Cove, Australia) consists of biodegradable resin microspheres and was approved by the FDA for metastatic colon cancer to the liver. That being said, most centers in the US using TARE for HCC utilize TheraSphere®, while centers outside of the US have expanded to using SIR-Spheres® as well [64].

Prior to TARE, pretreatment evaluations must be performed, including angiography and testing for pulmonary shunting. Prophylactic embolization of the gastroduodenal artery and right gastric artery is recommended to minimize risks of hepato-enteric flow, particularly when using resin microspheres [63]. Shunting of Yttrium-90 microscrospheres to the lungs may cause radiation pneumonitis; hence, [99m]TC-MAA particles, which closely mimic Yttrium-90 particles in size, are utilized to predict splanchnic and pulmonary shunting to calculate the lung shunt fraction to minimize the risk of radiation pneumonitis.

TARE has been shown to downstage HCC to meet Milan criteria for OLT eligibility [65,66]. Furthermore, a retrospective analysis comparing TACE to TARE has shown that TARE may be a better tool for downstaging disease [65]. Also, patients presenting with PVT are considered ineligible for TACE because of concerns of interruption of hepatic arterial blood flow resulting in a large segment of hepatic necrosis in patients whose blood supply is already compromised [67,68]. As far as time to progression (TTP) of disease, TARE has been shown to be superior to TACE in that TARE leads to longer TTP with less toxicity than TACE and with similar survival times [69].

Complications with TARE include postradioembolization syndrome, which consists of fatigue, nausea, vomiting, anorexia, fever, abdominal discomfort, and cachexia. Radiation induced liver disease is a serious complication which occurs 4–8 weeks after TARE but usually occurs in only 0–4% of cases [63]. Liver fibrosis causing portal hypertension may also occur; thus it is recommended that patients are observed routinely for radiologic and clinical evidence of portal hypertension [70]. The incidence of radiation pneumonitis occurs in less than 1% if standard dosimetry protocols are followed [71]. Gastrointestinal complications have been reported at less than 5%, so long as proper percutaneous methods are used [72]. Microspheres may inadvertently spread to the gastrointestinal tract and cause ulceration [72,73]. Yttrium-90 induced ulcers usually originate from the serosal surface versus the mucosal surface [63].

Systemic chemotherapy

Sorafenib

Sorafenib (Nexavar, Bayer/Onyx) is currently the only US FDA approved systemic chemotherapeutic agent to treat advanced HCC. Sorafenib is an oral multikinase inhibitor which blocks tumor cell proliferation by targeting Raf/MEK/ERK signaling at the level of Raf kinase [74]. It also exerts an antiangiogenic effect by targeting vascular endothelial growth factor (VEGF) receptor-2/-3 and platelet-derived growth factor (PDGF) receptor-β tyrosine kinases [75] (Fig. 1). The phase III study conducted by Llovet *et al.* for the Sorafenib Hepatocellular Carcinoma Randomized Protocol (SHARP) Investigators [76] demonstrated that the median overall survival in the sorafenib group was significantly greater at 10.7 months versus 7.9 months in the placebo group. They also found that while there was no significant difference symptomatic TTP, the median time to radiologic progression was significantly greater at 5.5 months in the sorafenib group versus only 2.8 months in the placebo group. Llovet *et al.* noted similar toxicity profiles with sorafenib compared to the placebo as in the phase II study, with the added exception of hypophosphatemia. The phase III study of sorafenib among the Asia-Pacific population [77] showed that the sorafenib

group experienced a significantly increased medial overall survival at 6.5 months versus 4.2 months for the placebo group. Median TTP was significantly greater at 2.8 months in the sorafenib group versus 1.4 months in the placebo group. Toxicity profiles of sorafenib mirrored those reported in the phase II study. These data imply that despite the greater prevalence of HCV and alcohol cirrhosis contributing to HCC in the SHARP population and a greater prevalence of HBV contributing to HCC in the Asia-Pacific population, sorafenib is still relatively safe and efficacious as a systemic chemotherapeutic agent for both population groups. The discrepancies between the median overall survival rates and the median TTP between the SHARP and Asia-Pacific group have been postulated to be due to the more advanced disease in the Asia-Pacific group [78]. Fig. 2 depicts changes in tumor size after 15 months of sorafenib.

There have been efforts to combine sorafenib with other modalities used to treat HCC, such as TACE and RFA [79]. This study included patients in either stage B or C HCC according to Barcelona Clinic Liver Cancer (BCLC) criteria and ECOG ≤ 1 and yielded a disease control rate of 33.3% by RECIST criteria with a median TTP of 15.3 months,

median survival rate of 28.8 months. Previous studies have demonstrated that TACE-sorafenib yielded a median TTP of 8.5–10.6 months and a median overall survival of 12–18.5 months [80–82]. Li *et al.* [79] postulate that hypoxia induced by local treatment with modalities such as TACE (SPACE trial and ECOG1208) or Resction/RFA (STORM trial) is associated with production of VEGF and is thought to be a potential cause of recurrence. Therefore, the VEGF and PDGF receptor activity that sorafenib inhibits may contribute to the longer median survival rate and median TTP when compared to sorafenib alone. Final analysis of these two adjuvant studies is pending.

STOP-HCC, a phase III, open-label prospective, randomized clinical trial investigating efficacy of sorafenib with or without TheraSphere® for unresectable HCC, is currently underway. The YES-P trial is also currently in phase III and is studying the use of sorafenib versus TheraSphere® for the treatment of advanced HCC with PVT. Concurrently there is the SORAMIC trial in phase II, in which patients will either receive RFA followed by sorafenib or placebo or SIR-Spheres® with sorafenib or sorafenib alone. The Sirtex®-supported SorAfenib versus Radioembolization in Advanced
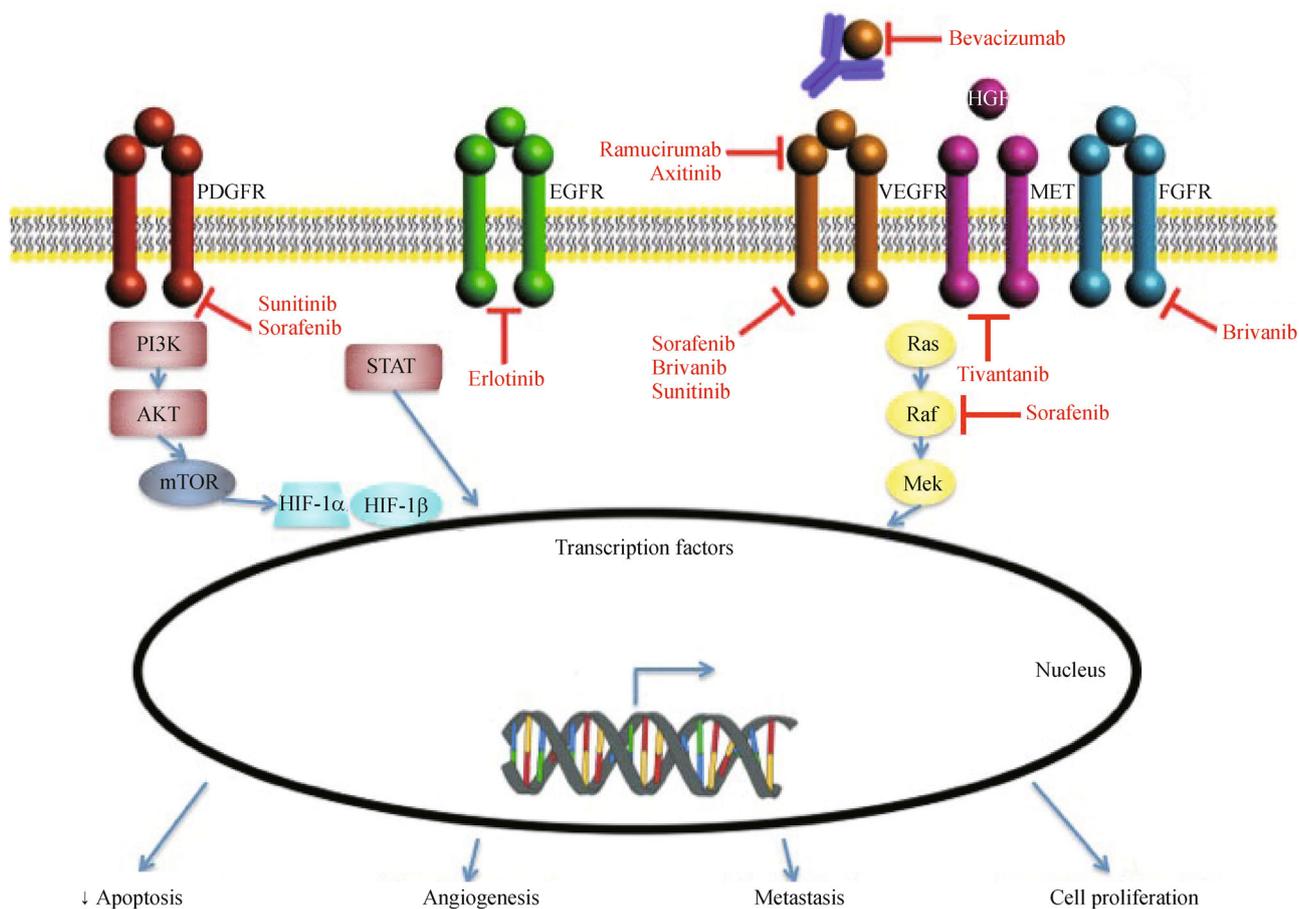

Fig. 1 Molecular pathways involved in chemotherapy used to treat hepatocellular carcinoma.
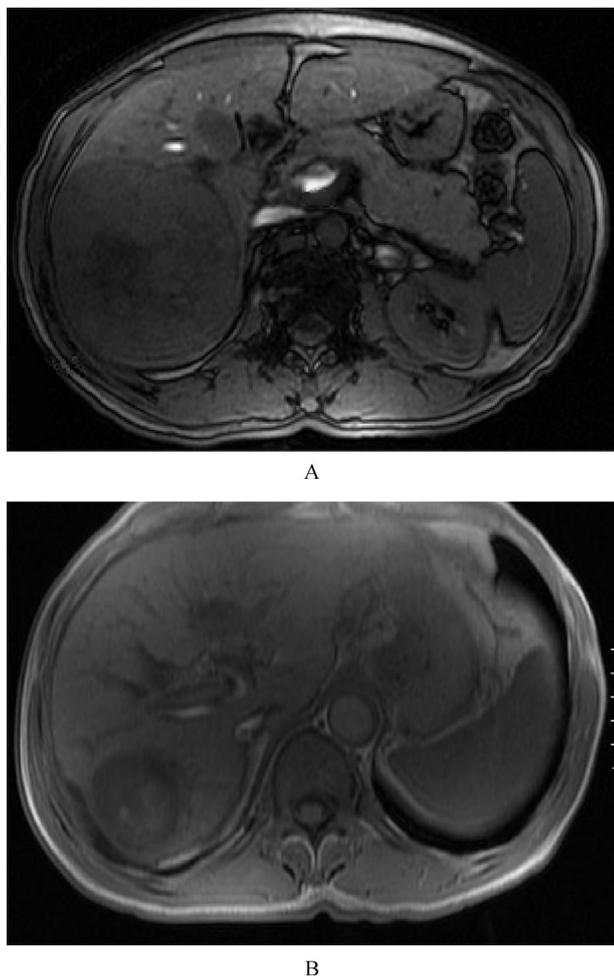
Fig. 2 MRI of liver tumor before and after 15 months of sorafenib. (A) Original lesion was measured at 10.4 cm × 10.0 cm × 10.0 cm. (B) The lesion is now at 4.2 cm × 4.0 cm × 3.8 cm. Biopsy shows no viable tumor.

Hepatocellular carcinoma (SARAH) trial is currently in phase III. In addition, the SIRveNIB trial is in phase III and is a multicenter open-label randomized controlled trial comparing sorafenib to SIR-Spheres® in advanced HCC.

Sunitinib

Sunitinib (Sutent, Pfizer, NY) is a multitargeted tyrosine kinase inhibitor of VEGF receptors and other receptor tyrosine kinases [83–89] (Fig. 1). It has demonstrated in three phase II studies antitumoral effects in patients with advanced HCC [90–92]. An open-label, phase III study comparing the efficacy of sunitinib versus sorafenib was terminated early due to significantly greater toxicity in the patients treated with sunitinib [93]. Median overall survival for sunitinib was 7.9 versus 10.2 months for sorafenib. However, median progression-free survival and TTP were comparable.

Brivanib

Brivanib (BMS-582664, Bristol-Myers Squibb, NY) is a tyrosine kinase inhibitor of the VEGF and fibroblast growth factor (FGF) signaling pathways [94] (Fig. 1). A phase II study in patients with advanced HCC who had failed previous antiangiogenic treatment demonstrated an overall response rate of 11%, disease control rate of 72% using mRECIST criteria, and a medial overall survival rate of 9.8 months [95,96]. Phase III conclusions from the BRISK-FL trial determined that brivanib was not inferior to sorafenib as first-line treatment for HCC, brivanib demonstrating a median overall survival of 9.5 months versus 9.9 months for sorafenib; TTP, objective response rate, disease control rate were similar between the two [96]. Despite these similarities and while expressing an acceptable adverse rate profile, sorafenib was better tolerated than brivanib, with adverse effects including anorexia, fatigue, hyponatremia, hypertension, nausea, vomiting, headache, dysphonia, and dizziness [97]. Additionally, phase III studies from the BRISK-PS trial showed that brivanib did not significantly improve the overall survival rate in patients previously treated with sorafenib [98].

Ramucirumab

Ramucirumab [IMC-1121B (LY3009806), ImClone Systems Inc.] is a human IgG1 monoclonal antibody that binds with high affinity to VEGFR-2 and blocks the interaction of VEGFR-2 and its ligands [99] (Fig. 1). In a phase II study of ramucirumab [99], median progression-free survival was 4.0 months, with median TTP at 4.2 months. Median overall survival was 12.0 months. Patients with BCLC stage C disease and Child-Pugh A cirrhosis were found to have greater median overall survival rates at 18.0 months versus patients at BCLC stage C disease and Child-Pugh B cirrhosis at 4.4 months. Ramucirumab is currently undergoing a phase III trial as a second-line option, post-sorafenib. The study is now closed to enrollment.

Axitinib

Axitinib (Inlyta, Pfizer) is a tyrosine kinase inhibitor which has been shown to inhibit VEGFR-1, -2, and -3 in *in vitro* and preclinical models [100] (Fig. 1). Currently axitinib is indicated in treatment for advanced renal cell carcinoma after failure of one systemic therapy but is currently undergoing phase II clinical trials in patients with unresectable HCC after having one prior antiangiogenic therapy. This study is a non-randomized, open-label trial with a primary end point of determining safety and efficacy and is now closed to enrollment.

Tivantinib as a selective MET inhibitor

The hepatocyte growth factor (HGF)/mesenchymal-epithelial

transition factor (MET) receptor tyrosine kinase pathway is often dysregulated in HCC [101] (Fig. 1). Patients may present with high MET versus low MET activity. Overexpression of HGF or MET is correlated with increased metastases, cancer aggressiveness, and poor prognosis [102]. Tivantinib (ARQ 197) is an oral, selective MET inhibitor which disrupts MET-dependent downstream signaling by blocking MET phosphorylation that is constitutive and HGF-regulated [103]. In a phase Ib study of tivantinib [101], 360 mg of tivantinib was administered twice daily to patients with Child-Pugh A and B liver cirrhosis until there was evidence of disease progression or unacceptable toxicity. In their study, the best response was stable disease at 5.3 months with a median TTP of 3.3 months. Further phase II studies [104] demonstrated that TTP was longer in the tivantinib group at 1.6 months versus 1.4 months in the placebo group. This difference was even more pronounced in MET-high tumors such that TTP in the tivantinib group was 2.7 months versus 1.4 months in the placebo group. In both studies [101,104], common adverse effects of tivantinib were neutropenia, anemia, asthenia, leukopenia, anorexia, diarrhea, and fatigue. In the phase II study [104], four deaths related to severe neutropenia were observed in the tivantinib group. In this study, the 38 patients receiving tivantinib 360 mg twice daily underwent dose reduction to 240 mg twice daily due to a high incidence of grade 3 or worse neutropenia. A population pharmacokinetic analysis of tivantinib, which included this study, revealed that tivantinib exposure is about three times higher in patients with HCC than in patients with other solid tumors; such exposure is correlated with the incidence of grade 3 or worse neutropenia [104]. The authors of the phase II study [104] propose that tivantinib could serve as a second-line option for treatment of HCC, particularly patients with MET-high tumors. Currently, there is a phase III trial with tivantinib dosed at 240 mg twice daily versus placebo administered to subjects with MET-high HCC treated with one prior systemic chemotherapeutic agent.

Bevacizumab plus erlotinib as antiangiogenesis agents

Increased HGF, epithelial growth factor receptor (EGFR), VEGF, insulin-like, and transforming growth factors have been implicated in the progression from normal liver to cirrhosis and HCC [104]. Bevacizumab (Avastin, Genentech BioOncology, South San Francisco) with erlotinib (Tarceva, OSI Pharmaceuticals, Boulder, CO) have been studied in Phase II clinical trials in the US and in Asia [105,106]. Bevacizumab is a monoclonal antibody that binds circulating VEGF-A ligand and is approved by the US FDA for treatment of metastatic colorectal, non-small cell lung, and breast cancers. Erlotinib is an oral tyrosine kinase inhibitor that blocks phosphorylation of the EGFR transmembrane receptor and is approved for advanced adenocarcinoma of the pancreas and non-small cell lung cancer [105] (Fig. 1). In the US phase II trial [105], patients with Child-Pugh A or B liver cirrhosis

and ECOG status 0, 1, or 2 were enrolled. The primary end point of progression-free survival at 16 weeks was 62.5%. With 40 patients treated, 10 patients experienced partial response, the median progression-free survival was 39 weeks, and the median overall survival was 68 weeks. However, in the Asia Phase II trial [106], the progression-free survival at 16 weeks was only 35.3%, the median progression-free survival was only 2.9 months, and the median overall survival was only 10.7 months. The variations between these two trials include the dosing of the bevacizumab and the population sampled: the Asia trial used a bevacizumab dose of 5 mg/kg whereas the US trial used a dose of 10 mg/kg, and the Asia trial enrolled more patients with BCLC stage C disease, more patients with HBV infection, and patients of Asian descent only. However, an additional two phase II studies [107,108] enrolling patients from the US reported less favorable efficacies than those of earlier phase II trial. Therefore, data are conflicting about the efficacies of bevacizumab with erlotinib. Currently, a randomized phase II study comparing bevacizumab with erlotinib and sorafenib is ongoing in the US [106].

Irreversible electroporation

Irreversible electroporation (IRE) is a novel ablative technique used to treat HCCs in cases where patients either fail or are not candidates for SR or ablative therapies such as RFA or MWA. During IRE, micro- to millisecond electrical pulses are delivered to targeted tissue, causing cell membrane permeabilization and eventual necrosis of the tissue. Davalos *et al.* [109] demonstrated application of IRE can reach temperatures up to 50°C. However, they suggest that its primary ablative technique is through direct damage of the cell membrane rather than thermal destruction. Further animal studies conducted by Lee *et al.* [110] show that IRE tissue, when examined histologically, tested positive for Bcl-2 oncoprotein staining and TUNEL assay, suggesting apoptotic cell death among the treated tissue. Guo *et al.* [111] demonstrated that 15 days post-IRE, 5 out of 6 treated lesions showed no remnant viable tumor, but did show giant cell reaction, hemosiderin-laden histiocyte reaction, and scarring fibrosis. This is consistent with the thought that the irreversibly permeabilized cells left *in situ* would be cleared by the immune system [109]. A preliminary study on the safety of IRE on humans demonstrated complete target tumor ablation of HCC in 82% tumors [112]. Overall recurrence free survival at 3, 6, and 12 months have been reported in a prospective study at 97.4%, 94.6%, and 59.5%, respectively; however, these values include colorectal metastasis to the liver (45% of tumors), hepatic metastases from non-small cell lung cancer, breast cancer, three carcinoid/neuroendocrine tumors, melanoma, renal cell carcinoma, soft tissue tumor, as well as HCC (35% of tumors) [113]. Both the preliminary study and the prospective study utilized the NanoKnife® system (Angiodynamics, Latham, NY), which was approved
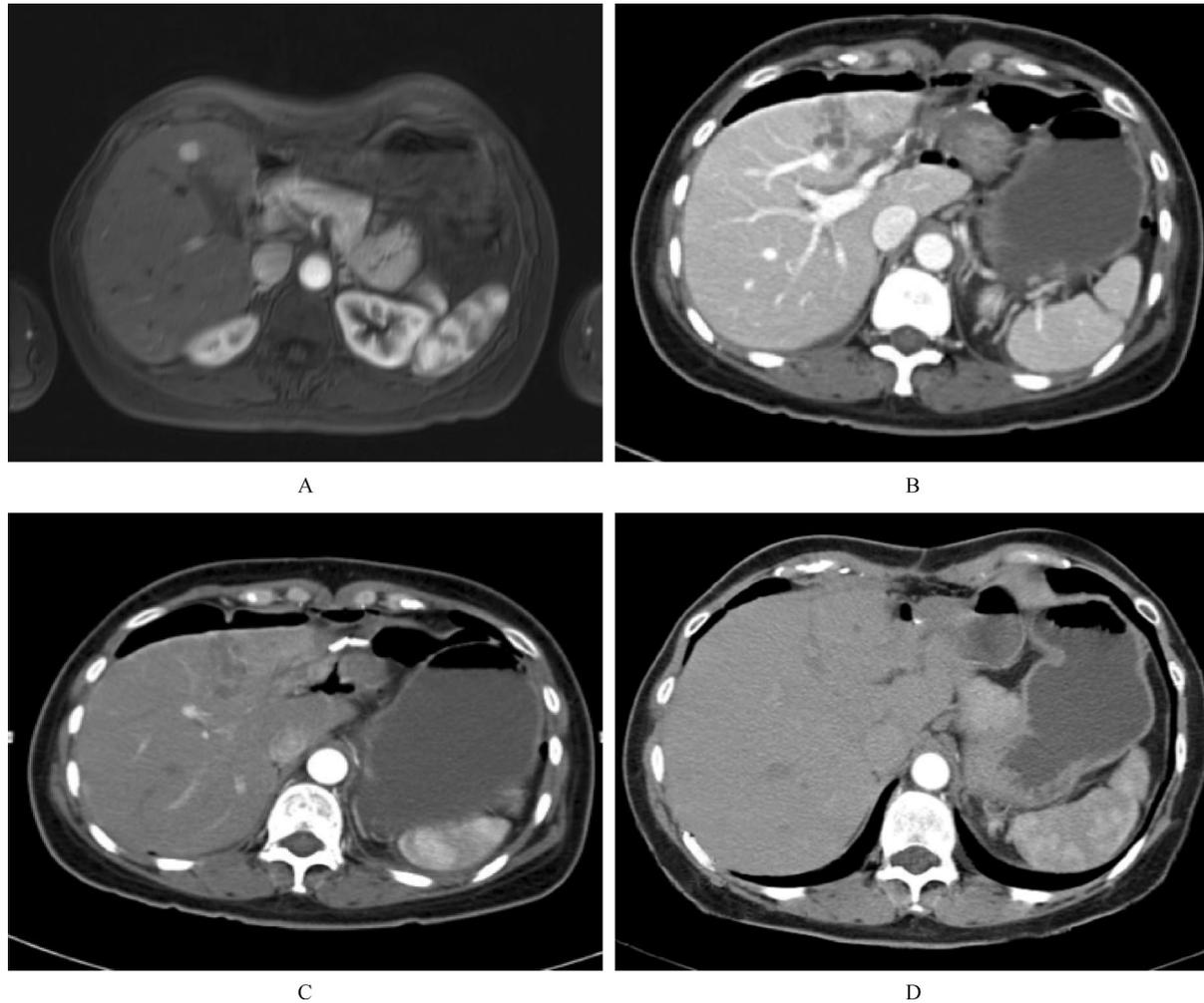
Fig. 3 (A) MRI of liver tumor prior to treatment. (B) CT of tumor at post-operative day 1 after treatment with NanoKnife® ablation. (C) CT of tumor at post-operative day 30 after treatment with NanoKnife® ablation. (D) CT of tumor at post-operative day 90 after treatment with NanoKnife® ablation.

by the US FDA for ablation in soft tissue, including cardiac and smooth muscle. Fig.3 depicts pre- and post-NanoKnife® ablation treatment of a liver tumor. Note the significant early edema zone seen at 24 h which ultimately resolves over time.

IRE also has advantages over RFA in that IRE does not seem to be affected by or damage blood vessels or bile ducts in the targeted area [111,113]. Lee *et al.* [110] further comment that the vessels in the ablated zone demonstrated intact endothelium with minimal endothelial damage in small vessels and preserved vessel integrity in large vessels. Furthermore, IRE does not seem to be subject to heat sink effects that RFA is limited by when near vasculature [109,113].

Potential adverse effects of IRE include cardiac arrhythmia. Delivery of the pulses must be synchronized to the patient's electrocardiogram such that the pulses are timed to be delivered during the absolute myocardial refractory period 50 ms after the R-wave; however, the NanoKnife® pulse

generator has incorporated this feature into its system [113]. That being said, cardiac arrythmias can still occur such that in the prospective study discussed earlier, two procedures were aborted before completion of the planned number of ablations due to arrhythmia, ventricular tachycardia in four patients, and transient supraventricular tachycardia in one patient.

Summary

Surgical resection and OLT are still the gold standards in managing hepatocellular carcinoma. However, most patients are not eligible for these treatement modalities. While there are several thermal ablative techniques and irreversible electroporation that may serve as a palliative means of care or as a means of downstaging tumors to fit criteria for OLT, such techniques themselves have relatively high survival rates on their own. Sorafenib has shown promise as a systemic

chemotherapeutic agent, and studies are investigating its efficacy with other chemotherapeutics.

Compliance with ethics guidelines

Marielle Reataza and David K. Imagawa declare that they have no conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

References

1. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology 2007; 132(7): 2557–2576

2. Dyer Z, Peltekian K, van Zanten SV. Review article: the changing epidemiology of hepatocellular carcinoma in Canada. Aliment Pharmacol Ther 2005; 22(1): 17–22

3. Song TJ, Ip EW, Fong Y. Hepatocellular carcinoma: current surgical management. Gastroenterology 2004; 127(5 Suppl 1): S248–S260

4. Simonetti RG, Cammà C, Fiorello F, Politi F, D'Amico G, Pagliaro L. Hepatocellular carcinoma. A worldwide problem and the major risk factors. Dig Dis Sci 1991; 36(7): 962–972

5. Unoura M, Kaneko S, Matsushita E, Shimoda A, Takeuchi M, Adachi H, Kawai H, Urabe T, Yanagi M, Matsui O, et al. High-risk groups and screening strategies for early detection of hepatocellular carcinoma in patients with chronic liver disease. Hepatogastroenterology 1993; 40(4): 305–310

6. Duan C, Liu M, Zhang Z, Ma K, Bie P. Radiofrequency ablation versus hepatic resection for the treatment of early-stage hepatocellular carcinoma meeting Milan criteria: a systematic review and meta-analysis. World J Surg Oncol 2013; 11(1): 190

7. 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(11): 693–699

8. Lim KC, Chow PK, Allen JC, Siddiqui FJ, Chan ES, Tan SB. Systematic review of outcomes of liver resection for early hepatocellular carcinoma within the Milan criteria. Br J Surg 2012; 99(12): 1622–1629

9. Hasegawa K, Kokudo N, Makuuchi M, Izumi N, Ichida T, Kudo M, Ku Y, Sakamoto M, Nakashima O, Matsui O, Matsuyama Y. Comparison of resection and ablation for hepatocellular carcinoma: a cohort study based on a Japanese nationwide survey. J Hepatol 2013; 58(4): 724–729

10. Tohme S, Geller DA, Cardinal JS, Chen HW, Packiam V, Reddy S, Steel J, Marsh JW, Tsung A. Radiofrequency ablation compared to resection in early-stage hepatocellular carcinoma. HPB (Oxford) 2013; 15(3): 210–217

11. Feng K, Yan J, Li X, Xia F, Ma K, Wang S, Bie P, Dong J. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. J Hepatol 2012; 57(4): 794–802

12. Huang J, Yan L, Cheng Z, Wu H, Du L, Wang J, Xu Y, Zeng Y. A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. Ann Surg 2010; 252(6): 903–912

13. Chen MS, Li JQ, Zheng Y, Guo RP, Liang HH, Zhang YQ, Lin XJ, Lau WY. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. Ann Surg 2006; 243(3): 321–328

14. Lü MD, Kuang M, Liang LJ, Xie XY, Peng BG, Liu GJ, Li DM, Lai JM, Li SQ. Surgical resection versus percutaneous thermal ablation for early-stage hepatocellular carcinoma: a randomized clinical trial. Nat Med J China (Zhonghua Yi Xue Za Zhi) 2006; 86 (12): 801–805 (in Chinese)

15. Chen MS, Li JQ, Liang HH, Lin XJ, Guo RP, Zheng Y, Zhang YQ. Comparison of effects of percutaneous radiofrequency ablation and surgical resection on small hepatocellular carcinoma. Nat Med J China (Zhonghua Yi Xue Za Zhi) 2005; 85(2): 80–83 (in Chinese)

16. Li F, Guo Z, Wang H. Influencing elements and treatment strategies associated with the relapse of hepatocellular carcinoma after surgery. Hepatogastroenterology 2013; 60(125): 1148–1155

17. Merion RM, Schaubel DE, Dykstra DM, Freeman RB, Port FK, Wolfe RA. The survival benefit of liver transplantation. Am J Transplant 2005; 5(2): 307–313

18. Organ Procurement and Transplantation Network. http://optn. transplant.hrsa.gov/PoliciesandBylaws2/policies/pdfs/policy_8. pdf. Accessed October 2013

19. Tandoi F, Ponte E, Saffioti MC, Patrono D, Mirabella S, Lupo F, Romagnoli R, Salizzoni M. Liver transplantation for hepatocellular carcinoma within Milan Criteria in patients with Model for End-Stage Liver Disease score below 15: the impact of the etiology of cirrhosis on long-term survival. Transplant Proc 2013; 45(7): 2711–2714

20. Liu F, Wei Y, Wang W, Chen K, Yan L, Wen T, Zhao J, Xu M, Li B. Salvage liver transplantation for recurrent hepatocellular carcinoma within UCSF criteria after liver resection. PLoS One 2012; 7(11): e48932

21. Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology 2001; 33(6): 1394–1403

22. Zhu Y, Dong J, Wang WL, Li MX, Lu Y. Short- and long-term outcomes after salvage liver transplantation versus primary liver transplantation for hepatocellular carcinoma: a meta-analysis. Transplant Proc 2013; 45(9): 3329–3342

23. Wu L, Hu A, Tam N, Zhang J, Lin M, Guo Z, He X. Salvage liver transplantation for patients with recurrent hepatocellular carcinoma after curative resection. PLoS One 2012; 7(7): e41820

24. Facciuto ME, Koneru B, Rocca JP, Wolf DC, Kim-Schluger L, Visintainer P, Klein KM, Chun H, Marvin M, Rozenblit G, Rodriguez-Davalos M, Sheiner PA. Surgical treatment of hepatocellular carcinoma beyond Milan criteria. Results of liver resection, salvage transplantation, and primary liver transplantation. Ann Surg Oncol 2008; 15(5): 1383–1391

25. Scatton O, Zalinski S, Terris B, Lefevre JH, Casali A, Massault PP, Conti F, Calmus Y, Soubrane O. Hepatocellular carcinoma developed on compensated cirrhosis: resection as a selection tool

for liver transplantation. Liver Transpl 2008; 14(6): 779–788

26. Vennarecci G, Ettorre GM, Antonini M, Santoro R, Maritti M, Tacconi G, Spoletini D, Tessitore L, Perracchio L, Visco G, Puoti C, Santoro E. First-line liver resection and salvage liver transplantation are increasing therapeutic strategies for patients with hepatocellular carcinoma and child a cirrhosis. Transplant Proc 2007; 39(6): 1857–1860

27. Margarit C, Escartín A, Castells L, Vargas V, Allende E, Bilbao I. Resection for hepatocellular carcinoma is a good option in Child-Turcotte-Pugh class A patients with cirrhosis who are eligible for liver transplantation. Liver Transpl 2005; 11(10): 1242–1251

28. Adam R, Azoulay D, Castaing D, Eshkenazy R, Pascal G, Hashizume K, Samuel D, Bismuth H. Liver resection as a bridge to transplantation for hepatocellular carcinoma on cirrhosis: a reasonable strategy? Ann Surg 2003; 238(4): 508–518, discussion 518–519

29. Sapisochin G, Bilbao I, Balsells J, Dopazo C, Caralt M, Lázaro JL, Castells L, Allende H, Charco R. Optimization of liver transplantation as a treatment of intrahepatic hepatocellular carcinoma recurrence after partial liver resection: experience of a single European series. World J Surg 2010; 34(9): 2146–2154

30. Belghiti J, Cortes A, Abdalla EK, Régimbeau JM, Prakash K, Durand F, Sommacale D, Dondero F, Lesurtel M, Sauvanet A, Farges O, Kianmanesh R. Resection prior to liver transplantation for hepatocellular carcinoma. Ann Surg 2003; 238(6): 885–892, discussion 892–893

31. Tsioulias GJ, Wood TF, Chung MH, Morton DL, Bilchik A. Diagnostic laparoscopy and laparoscopic ultrasonography optimize the staging and resectability of intraabdominal neoplasms. Surg Endosc 2001; 15(9): 1016–1019

32. Herbold T, Wahba R, Bangard C, Demir M, Drebber U, Stippel DL. The laparoscopic approach for radiofrequency ablation of hepatocellular carcinoma—indication, technique and results. Langenbecks Arch Surg 2013; 398(1): 47–53

33. Feng K, Yan J, Li X, Xia F, Ma K, Wang S, Bie P, Dong J. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. J Hepatol 2012; 57(4): 794–802

34. Curley SA, Izzo F, Delrio P, Ellis LM, Granchi J, Vallone P, Fiore F, Pignata S, Daniele B, Cremona F. Radiofrequency ablation of unresectable primary and metastatic hepatic malignancies: results in 123 patients. Ann Surg 1999; 230(1): 1–8

35. Pawlik TM, Izzo F, Cohen DS, Morris JS, Curley SA. Combined resection and radiofrequency ablation for advanced hepatic malignancies: results in 172 patients. Ann Surg Oncol 2003; 10 (9): 1059–1069

36. Mulier S, Ni Y, Jamart J, Ruers T, Marchal G, Michel L. Local recurrence after hepatic radiofrequency coagulation: multivariate meta-analysis and review of contributing factors. Ann Surg 2005; 242(2): 158–171

37. Ni JY, Xu LF, Sun HL, Zhou JX, Chen YT, Luo JH. Percutaneous ablation therapy versus surgical resection in the treatment for early-stage hepatocellular carcinoma: a meta-analysis of 21,494 patients. J Cancer Res Clin Oncol 2013; 139(12): 2021–2033

38. Patterson EJ, Scudamore CH, Owen DA, Nagy AG, Buczkowski AK. Radiofrequency ablation of porcine liver in vivo: effects of blood flow and treatment time on lesion size. Ann Surg 1998; 227

(4): 559–565

39. Schramm W, Yang D, Wood BJ, Rattay F, Haemmerich D. Contribution of direct heating, thermal conduction and perfusion during radiofrequency and microwave ablation. Open Biomed Eng J 2007; 1(1): 47–52

40. Chinn SB, Lee FT Jr, Kennedy GD, Chinn C, Johnson CD, Winter TC 3rd, Warner TF, Mahvi DM. Effect of vascular occlusion on radiofrequency ablation of the liver: results in a porcine model. AJR Am J Roentgenol 2001; 176(3): 789–795

41. Goldberg SN, Gazelle GS, Mueller PR. Thermal ablation therapy for focal malignancy: a unified approach to underlying principles, techniques, and diagnostic imaging guidance. AJR Am J Roentgenol 2000; 174(2): 323–331

42. Padma S, Martinie JB, Iannitti DA. Liver tumor ablation: percutaneous and open approaches. J Surg Oncol 2009; 100(8): 619–634

43. Simon CJ, Dupuy DE, Iannitti DA, Lu DS, Yu NC, Aswad BI, Busuttil RW, Lassman C. Intraoperative triple antenna hepatic microwave ablation. AJR Am J Roentgenol 2006; 187(4): W333–W340

44. Iannitti DA, Martin RC, Simon CJ, Hope WW, Newcomb WL, McMasters KM, Dupuy D. Hepatic tumor ablation with clustered microwave antennae: the US Phase II trial. HPB (Oxford) 2007; 9 (2): 120–124

45. Martin RC, Scoggins CR, McMasters KM. Safety and efficacy of microwave ablation of hepatic tumors: a prospective review of a 5-year experience. Ann Surg Oncol 2010; 17(1): 171–178

46. Liang P, Wang Y. Microwave ablation of hepatocellular carcinoma. Oncology 2007; 72(Suppl 1): 124–131

47. Liu FY, Yu XL, Liang P, Wang Y, Zhou P, Yu J. Comparison of percutaneous 915 MHz microwave ablation and 2450 MHz microwave ablation in large hepatocellular carcinoma. Int J Hyperthermia 2010; 26(5): 448–455

48. Swan RZ, Sindram D, Martinie JB, Iannitti DA. Operative microwave ablation for hepatocellular carcinoma: complications, recurrence, and long-term outcomes. J Gastrointest Surg 2013; 17 (4): 719–729

49. Liu Y, Zheng Y, Li S, Li B, Zhang Y, Yuan Y. Percutaneous microwave ablation of larger hepatocellular carcinoma. Clin Radiol 2013; 68(1): 21–26

50. Mulier S, Ni Y, Jamart J, Ruers T, Marchal G, Michel L. Local recurrence after hepatic radiofrequency coagulation: multivariate meta-analysis and review of contributing factors. Ann Surg 2005; 242(2): 158–171

51. Liang P, Dong B, Yu X, Yang Y, Yu D, Su L, Xiao Q, Sheng L. Prognostic factors for percutaneous microwave coagulation therapy of hepatic metastases. AJR Am J Roentgenol 2003; 181 (5): 1319–1325

52. Lo CM, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, Fan ST, Wong J. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002; 35(5): 1164–1171

53. Llovet JM, Real MI, Montaña X, Planas R, Coll S, Aponte J, Ayuso C, Sala M, Muchart J, Solà R, Rodés J, Bruix J, 0. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002; 359(9319): 1734–1739

54. Varela M, Real MI, Burrel M, Forner A, Sala M, Brunet M, Ayuso C, Castells L, Montañá X, Llovet JM, Bruix J. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. J Hepatol 2007; 46(3): 474–481

55. Recchia F, Passalacqua G, Filauri P, Doddi M, Boscarato P, Candeloro G, Necozione S, Desideri G, Rea S. Chemoemboliza-tion of unresectable hepatocellular carcinoma: Decreased toxicity with slow-release doxorubicin-eluting beads compared with lipiodol. Oncol Rep 2012; 27(5): 1377–1383

56. Lammer J, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, Pitton M, Sergent 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; PRECISION V Investigators. 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(1): 41–52

57. Yao FY, Kerlan RK Jr, Hirose R, Davern TJ 3rd, 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(3): 819–827

58. 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(12): 2547–2557

59. Lewandowski RJ, Kulik LM, Riaz A, Senthilnathan S, Mulcahy MF, Ryu RK, Ibrahim SM, Sato KT, Baker T, Miller FH, Omary R, Abecassis M, Salem R. A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization. Am J Transplant 2009; 9(8): 1920–1928

60. Gordon-Weeks AN, Snaith A, Petrinic T, Friend PJ, Burls A, Silva MA. Systematic review of outcome of downstaging hepatocellular cancer before liver transplantation in patients outside the Milan criteria. Br J Surg 2011; 98(9): 1201–1208

61. Majno PE, Adam R, Bismuth H, Castaing D, Ariche A, Krissat J, Perrin H, Azoulay D. Influence of preoperative transarterial lipiodol chemoembolization on resection and transplantation for hepatocellular carcinoma in patients with cirrhosis. Ann Surg 1997; 226(6): 688–701, discussion 701–703

62. Green TJ, Rochon PJ, Chang S, Ray CE Jr, Winston H, Ruef R, Kreidler SM, Glueck DH, Shulman BC, Brown AC, Durham J. Downstaging disease in patients with hepatocellular carcinoma outside of Milan criteria: strategies using drug-eluting bead chemoembolization. J Vasc Interv Radiol 2013; 24(11): 1613–1622

63. Memon K, Lewandowski RJ, Riaz A, Salem R. Yttrium 90 microspheres for the treatment of hepatocellular carcinoma. Recent Results Cancer Res 2013; 190: 207–224

64. Kim DY, Park BJ, Kim YH, Han K, Cho SB, Cho KR, Uhn S, Choe J, Choi JY, Chun HJ, Lee HC, Gown DI, Lee KH, Yoon J, Chung JW, Kim CW, Heo J, Kim JK, Joo YE. Radioembolization with Yttrium-90 resin microspheres in hepatocellular carcinoma: A multicenter prospective study. Am J Clin Onc 2013 Sep 21. [Epub ahead of print]

65. Lewandowski RJ, Kulik LM, Riaz A, Senthilnathan S, Mulcahy MF, Ryu RK, Ibrahim SM, Sato KT, Baker T, Miller FH, Omary R, Abecassis M, Salem R. A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization. Am J Transplant 2009; 9(8): 1920–1928

66. Tohme S, Sukato D, Chen HW, Amesur N, Zajko AB, Humar A, Geller DA, Marsh JW, Tsung A. Yttrium-90 radioembolization as a bridge to liver transplantation: a single-institution experience. J Vasc Interv Radiol 2013; 24(11): 1632–1638

67. Bruix J, Sherman M. AASLD practice guideline: management of hepatocellular carcinoma: an update (July 2010). http://www.aasld.org/practiceguidelines/Pages/NewUpdatedGuidelines.aspx Accessed 2012

68. Jelic S, Sotiropoulos GC; ESMO Guidelines Working Group. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010; 21(Suppl 5): v59–v64

69. Salem R, Lewandowski RJ, Kulik L, Wang E, Riaz A, Ryu RK, Sato KT, Gupta R, Nikolaidis P, Miller FH, Yaghmai V, Ibrahim SM, Senthilnathan S, Baker T, Gates VL, Atassi B, Newman S, Memon K, Chen R, Vogelzang RL, Nemcek AA, Resnick SA, Chrisman HB, Carr J, Omary RA, Abecassis M, Benson AB 3rd, Mulcahy MF. Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoemboliza-tion in patients with hepatocellular carcinoma. Gastroenterology 2011; 140(2): 497–507, e2

70. Gaba RC, Lewandowski RJ, Kulik LM, Riaz A, Ibrahim SM, Mulcahy MF, Ryu RK, Sato KT, Gates V, Abecassis MM, Omary RA, Baker TB, Salem R. Radiation lobectomy: preliminary findings of hepatic volumetric response to lobar yttrium-90 radioembolization. Ann Surg Oncol 2009; 16(6): 1587–1596

71. Leung TW, Lau WY, Ho SK, Ward SC, Chow JH, Chan MS, Metreweli C, Johnson PJ, Li AK. Radiation pneumonitis after selective internal radiation treatment with intraarterial 90yttrium-microspheres for inoperable hepatic tumors. Int J Radiat Oncol Biol Phys 1995; 33(4): 919–924

72. Murthy R, Brown DB, Salem R, Meranze SG, Coldwell DM, Krishnan S, Nunez R, Habbu A, Liu D, Ross W, Cohen AM, Censullo M. Gastrointestinal complications associated with hepatic arterial Yttrium-90 microsphere therapy. J Vasc Interv Radiol 2007; 18(4): 553–561, quiz 562

73. Carretero C, Munoz-Navas M, Betes M, Angos R, Subtil JC, Fernandez-Urien I, De la Riva S, Sola J, Bilbao JI, de Luis E, Sangro B. Gastroduodenal injury after radioembolization of hepatic tumors. Am J Gastroenterol 2007; 102(6): 1216–1220

74. Abou-Alfa GK, Schwartz L, Ricci S, Amadori D, Santoro A, Figer A, De Greve J, Douillard JY, Lathia C, Schwartz B, Taylor I, Moscovici M, Saltz LB. Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. J Clin Oncol 2006; 24(26): 4293–4300

75. Wilhelm SM, Carter C, Tang L, Wilkie D, McNabola A, Rong H, Chen C, Zhang X, Vincent P, McHugh M, Cao Y, Shujath J, Gawlak S, Eveleigh D, Rowley B, Liu L, Adnane L, Lynch M, Auclair D, Taylor I, Gedrich R, Voznesensky A, Riedl B, Post LE, Bollag G, Trail PA. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and

receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res 2004; 64(19): 7099–7109

76. 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; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008; 359(4): 378–390

77. 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(1): 25–34

78. Bruix J, Raoul JL, Sherman M, Mazzaferro V, Bolondi L, Craxi A, Galle PR, Santoro A, Beaugrand M, Sangiovanni A, Porta C, Gerken G, Marrero JA, Nadel A, Shan M, Moscovici M, Voliotis D, Llovet JM. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. J Hepatol 2012; 57(4): 821–829

79. Li Y, Zheng YB, Zhao W, Liu B, Hu BS, He X, Huang JW, Lu LG. Sorafenib in combination with transarterial chemoembolization and radiofrequency ablation in the treatment for unresectable hepatocellular carcinoma. Med Oncol 2013; 30(4): 730

80. Han G, Yang J, Shao G, Teng G, Wang M, Yang J, Liu Z, Feng G, Yang R, Lu L, Chao Y, Wang J. Sorafenib in combination with transarterial chemoembolization in Chinese patients with hepatocellular carcinoma: a subgroup interim analysis of the START trial. Future Oncol 2013; 9(3): 403–410

81. Cabrera R, Pannu DS, Caridi J, Firpi RJ, Soldevila-Pico C, Morelli G, Clark V, Suman A, George TJ Jr, Nelson DR. The combination of sorafenib with transarterial chemoembolisation for hepatocellular carcinoma. Aliment Pharmacol Ther 2011; 34(2): 205–213

82. Zhao Y, Wang WJ, Guan S, Li HL, Xu RC, Wu JB, Liu JS, Li HP, Bai W, Yin ZX, Fan DM, Zhang ZL, Han GH. Sorafenib combined with transarterial chemoembolization for the treatment of advanced hepatocellular carcinoma: a large-scale multicenter study of 222 patients. Ann Oncol 2013; 24(7): 1786–1792

83. Mendel DB, Laird AD, Xin X, Louie SG, Christensen JG, Li G, Schreck RE, Abrams TJ, Ngai TJ, Lee LB, Murray LJ, Carver J, Chan E, Moss KG, Haznedar JO, Sukbuntherng J, Blake RA, Sun L, Tang C, Miller T, Shirazian S, McMahon G, Cherrington JM. *In vivo* antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. Clin Cancer Res 2003; 9(1): 327–337

84. Murray LJ, Abrams TJ, Long KR, Ngai TJ, Olson LM, Hong W, Keast PK, Brassard JA, O'Farrell AM, Cherrington JM, Pryer NK. SU11248 inhibits tumor growth and CSF-1R-dependent osteolysis in an experimental breast cancer bone metastasis model. Clin Exp Metastasis 2003; 20(8): 757–766

85. O'Farrell AM, Abrams TJ, Yuen HA, Ngai TJ, Louie SG, Yee KW, Wong LM, Hong W, Lee LB, Town A, Smolich BD, Manning WC, Murray LJ, Heinrich MC, Cherrington JM. SU11248 is a novel FLT3 tyrosine kinase inhibitor with potent activity *in vitro* and *in vivo*. Blood 2003; 101(9): 3597–3605

86. Abrams TJ, Lee LB, Murray LJ, Pryer NK, Cherrington JM. SU11248 inhibits KIT and platelet-derived growth factor receptor beta in preclinical models of human small cell lung cancer. Mol Cancer Ther 2003; 2(5): 471–478

87. Kim DW, Jo YS, Jung HS, Chung HK, Song JH, Park KC, Park SH, Hwang JH, Rha SY, Kweon GR, Lee SJ, Jo KW, Shong M. An orally administered multitarget tyrosine kinase inhibitor, SU11248, is a novel potent inhibitor of thyroid oncogenic RET/papillary thyroid cancer kinases. J Clin Endocrinol Metab 2006; 91(10): 4070–4076

88. Kodera Y, Katanasaka Y, Kitamura Y, Tsuda H, Nishio K, Tamura T, Koizumi F. Sunitinib inhibits lymphatic endothelial cell functions and lymph node metastasis in a breast cancer model through inhibition of vascular endothelial growth factor receptor 3. Breast Cancer Res 2011; 13(3): R66

89. Faivre S, Demetri G, Sargent W, Raymond E. Molecular basis for sunitinib efficacy and future clinical development. Nat Rev Drug Discov 2007; 6(9): 734–745

90. 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(8): 794–800

91. Zhu AX, Sahani DV, Duda DG, di Tomaso E, Ancukiewicz M, Catalano OA, Sindhwani V, Blaszkowsky LS, 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(18): 3027–3035

92. Koeberle D, Montemurro M, Samaras P, Majno P, Simcock M, Limacher A, Lerch S, Kovàcs K, Inauen R, Hess V, Saletti P, Borner M, Roth A, Bodoky G. Continuous Sunitinib treatment in patients with advanced hepatocellular carcinoma: a Swiss Group for Clinical Cancer Research (SAKK) and Swiss Association for the Study of the Liver (SASL) multicenter phase II trial (SAKK 77/06). Oncologist 2010; 15(3): 285–292

93. 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, Lanzalone 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(32): 4067–4075

94. Cai ZW, Zhang Y, Borzilleri RM, Qian L, Barbosa S, Wei D, Zheng X, Wu L, Fan J, Shi Z, Wautlet BS, Mortillo S, Jeyaseelan R Sr, Kukral DW, Kamath A, Marathe P, D'Arienzo C, Derbin G, Barrish JC, Robl JA, Hunt JT, Lombardo LJ, Fargnoli J, Bhide RS. Discovery of brivanib alaninate ((S)-((R)-1-(4-(4-fluoro-2-methyl-1H-indol-5-yloxy)-5-methylpyrrolo[2,1-f][1,2,4]triazin-6-yloxy)propan-2-yl)2-aminopropanoate), a novel prodrug of dual vascular endothelial growth factor receptor-2 and fibroblast growth factor receptor-1 kinase inhibitor (BMS-540215). J Med Chem 2008; 51(6): 1976–1980

95. Park JW, Finn RS, Kim JS, Karwal M, Li RK, Ismail F, Thomas M, Harris R, Baudelet C, Walters I, Raoul JL. Phase II, open-label study of brivanib as first-line therapy in patients with advanced hepatocellular carcinoma. Clin Cancer Res 2011; 17(7): 1973–1983

96. Finn RS, Kang YK, Mulcahy M, Polite BN, Lim HY, Walters I,

Baudelet C, Manekas D, Park JW. Phase II, open-label study of brivanib as second-line therapy in patients with advanced hepatocellular carcinoma. Clin Cancer Res 2012; 18(7): 2090–2098

97. 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(28): 3517–3524

98. Llovet JM, Decaens T, Raoul JL, Boucher E, Kudo M, Chang C, Kang YK, Assenat E, Lim HY, Boige V, Mathurin P, Fartoux L, Lin DY, Bruix J, Poon RT, Sherman M, Blanc JF, Finn RS, Tak WY, Chao Y, Ezzeddine R, Liu D, Walters I, Park JW. Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: results from the randomized phase III BRISK-PS study. J Clin Oncol 2013; 31 (28): 3509–3516

99. Zhu AX, Finn RS, Mulcahy M, Gurtler J, Sun W, Schwartz JD, Dalal RP, Joshi A, Hozak RR, Xu Y, Ancukiewicz M, Jain RK, Nugent FW, Duda DG, Stuart K. A phase II and biomarker study of ramucirumab, a human monoclonal antibody targeting the VEGF receptor-2, as first-line monotherapy in patients with advanced hepatocellular cancer. Clin Cancer Res 2013; 19(23): 6614–6623

100. Inlyta Mechanism of Action. http://www.pfizerpro.com/hcp/inlyta/moa. Accessed December 2013

101. Santoro A, Simonelli M, Rodriguez-Lope C, Zucali P, Camacho LH, Granito A, Senzer N, Rimassa L, Abbadessa G, Schwartz B, Lamar M, Savage RE, Bruix J. A Phase-1b study of tivantinib (ARQ 197) in adult patients with hepatocellular carcinoma and cirrhosis. Br J Cancer 2013; 108(1): 21–24

102. Boccaccio C, Comoglio PM. Invasive growth: a MET-driven genetic programme for cancer and stem cells. Nat Rev Cancer 2006; 6(8): 637–645

103. Munshi N, Jeay S, Li Y, Chen CR, France DS, Ashwell MA, Hill J, Moussa MM, Leggett DS, Li CJ. ARQ 197, a novel and selective inhibitor of the human c-Met receptor tyrosine kinase with antitumor activity. Mol Cancer Ther 2010; 9(6): 1544–1553

104. Santoro A, Rimassa L, Borbath I, Daniele B, Salvagni S, Van Laethem JL, Van Vlierberghe H, Trojan J, Kolligs FT, Weiss A, Miles S, Gasbarrini A, Lencioni M, Cicalese L, Sherman M, Gridelli C, Buggisch P, Gerken G, Schmid RM, Boni C, Personeni N, Hassoun Z, Abbadessa G, Schwartz B, Von Roemeling R, Lamar ME, Chen Y, Porta C. Tivantinib for second-line treatment of advanced hepatocellular carcinoma: a randomised, placebo-controlled phase 2 study. Lancet Oncol 2013; 14(1): 55–63

105. Thomas MB, Morris JS, Chadha R, Iwasaki M, Kaur H, Lin E, Kaseb A, Glover K, Davila M, Abbruzzese J. Phase II trial of the combination of bevacizumab and erlotinib in patients who have advanced hepatocellular carcinoma. J Clin Oncol 2009; 27(6): 843–850

106. Hsu CH, Kang YK, Yang TS, Shun CT, Shao YY, Su WC, Sandoval-Tan J, Chiou TJ, Jin K, Hsu C, Cheng AL. Bevacizumab with erlotinib as first-line therapy in Asian patients with advanced hepatocellular carcinoma: a multicenter phase II study. Oncology 2013; 85(1): 44–52

107. Philip PA, Mahoney MR, Holen KD, Northfelt DW, Pitot HC, Picus J, Flynn PJ, Erlichman C. Phase 2 study of bevacizumab plus erlotinib in patients with advanced hepatocellular cancer. Cancer 2012; 118(9): 2424–2430

108. Govindarajan R, Siegel E, Makhoul I, Williamson S. Bevacizumab and erlotinib in previously untreated inoperable and metastatic hepatocellular carcinoma. Am J Clin Oncol 2013; 36(3): 254–257

109. Davalos RV, Mir IL, Rubinsky B. Tissue ablation with irreversible electroporation. Ann Biomed Eng 2005; 33(2): 223–231

110. Lee EW, Chen C, Prieto VE, Dry SM, Loh CT, Kee ST. Advanced hepatic ablation technique for creating complete cell death: irreversible electroporation. Radiology 2010; 255(2): 426–433

111. Guo Y, Zhang Y, Klein R, Nijm GM, Sahakian AV, Omary RA, Yang GY, Larson AC. Irreversible electroporation therapy in the liver: longitudinal efficacy studies in a rat model of hepatocellular carcinoma. Cancer Res 2010; 70(4): 1555–1563

112. Thomson KR, Cheung W, Ellis SJ, Federman D, Kavnoudias H, Loader-Oliver D, Roberts S, Evans P, Ball C, Haydon A. Investigation of the safety of irreversible electroporation in humans. J Vasc Interv Radiol 2011; 22(5): 611–621

113. Cannon R, Ellis S, Hayes D, Narayanan G, Martin RC 2nd. Safety and early efficacy of irreversible electroporation for hepatic tumors in proximity to vital structures. J Surg Oncol 2013; 107(5): 544–549