Annals of Gastroenterology (2017) **30,** 23-32

Novel implications in the treatment of hepatocellular carcinoma

Jan Best[a], Clemens Schotten[a], Jens M. Theysohn[b], Axel Wetter[b], Stefan Müller[c], Sonia Radünz[d], Maren Schulze[d], Ali Canbay[a], Alexander Dechêne[a], Guido Gerken[a]

University Hospital Essen, Essen, Germany

Abstract

Worldwide hepatocellular carcinoma remains one of the leading causes of cancer-related death, associated with a poor prognosis due to late diagnosis in the majority of cases. Physicians at care are frequently confronted with patients who are ineligible for curative treatment such as liver resection, transplantation or radiofrequency ablation. Besides established palliative locoregional therapies, such as ablation or chemoembolization, new treatment options, such as microwave ablation, drug-eluting bead transarterial chemoembolization or selective internal radiation therapy, are emerging; however, data from randomized controlled trials are still lacking. In order to achieve optimal tumor control, patients should receive tailored treatment concepts, considering their tumor burden, liver function and performance status, instead of strictly assigning patients to treatment modalities following algorithms that may be partly very restrictive. Palliative locoregional pretreatment might facilitate downstaging to ensure later curative resection or transplantation. In addition, the combined utilization of different locoregional treatment options or systemic co-treatment has been the subject of several trials. In cases where local tumor control cannot be achieved, or in the scenario of extrahepatic spread, sorafenib remains the only approved systemic therapy option. Alternative targeted therapies, such as immune checkpoint inhibitors have shown encouraging preliminary results, while data from phase III studies are pending.

Keywords Hepatocellular carcinoma, liver surgery, locoregional therapy, systemic therapy, individualized treatment concept

Ann Gastroenterol 2017; 30 (1): 23-32

Introduction

The worldwide incidence of hepatocellular carcinoma (HCC) is almost equaled by its mortality; HCC is the second most common cause of cancer-related death [1]. Despite the prospectively decreasing prevalence of HCC in the context of viral hepatitis, globally it is on the rise [1]. Predominantly in Europe, HCC incidence related to non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (NAFLD/NASH) is dramatically increasing, mainly because of the rising prevalence of metabolic syndrome and its hepatic manifestation NAFLD (Fig. 1). Furthermore, the high HCC mortality throughout western civilization results from the majority of HCC cases being diagnosed at late stages when curative therapies are no longer available. The future will show whether strict surveillance strategies employing risk group stratification - as in the Japanese HCC surveillance guidelines - will result in earlier diagnosis and longer overall survival (OS) in Europe as well. The role of novel biomarkers, such as α-fetoprotein-L3 (AFP-L3) and des-γ-carboxyprothrombin (DCP), has been well validated in Japanese populations and also shows promising performance in European populations [2,3]. Patients suffering from chronic hepatitis B are well known to be at high risk for HCC development, even in the absence of cirrhosis, with the same phenomenon having been reported lately for NASH-related HCC [4] (Fig. 1).

In consequence, physicians are mostly confronted with intermediate or advanced stage HCC when only palliative treatment strategies are applicable. Of numerous staging systems, only the Barcelona Clinic Liver Cancer (BCLC) algorithm has found broad clinical acceptance as a basis for

Departments of [a]Gastroenterology and Hepatology (Jan Best, Clemens Schotten, Ali Canbay, Alexander Dechêne, Guido Gerken); [b]Diagnostic and Interventional Radiology and Neuroradiology (Jens M. Theysohn, Axel Wetter); [c]Nuclear Medicine (Stefan Müller); [d]Transplant and General Surgery (Sonia Radünz, Maren Schulze), University Hospital Essen, Essen, Germany

Conflict of Interest: Jan Best, Jens M. Theysohn, Alexander Dechêne, Stefan Müller: Speaker honoraria and advisory board meetings BTG Intl.; Jan Best: Travel grant Bayer; Alexander Dechêne: Speaker honoraria and advisory board meetings Bayer

Correspondence to: Prof. Dr. Med. Guido Gerken, Department of Gastroenterology and Hepatology, University Hospital Essen, Hufelandstr 55, 45147 Essen, Germany, Tel.: +49 201 723 3611, Fax: +49 201 723 5971, e-mail: guido.gerken@uk-essen.de

Received 23 June 2016; accepted 29 August 2016; published online 30 September 2016

DOI: http://dx.doi.org/10.20524/aog.2016.0092

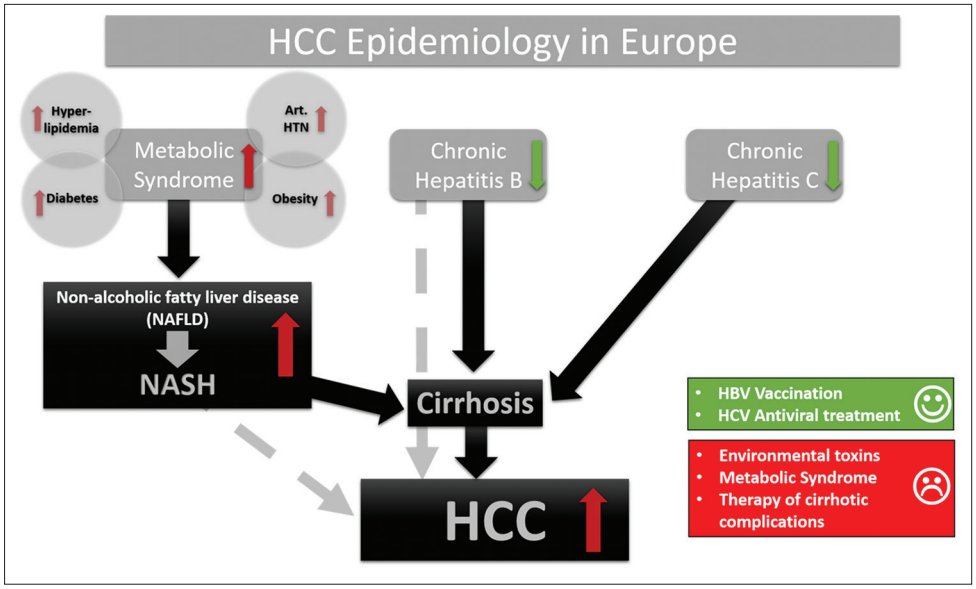

Figure 1 Hepatocellular carcinoma (HCC) epidemiology in Europe. Prospectively, because of hepatitis B vaccination programs and new highly effective anti-HCV therapies the incidence of HCC in the context of viral hepatitis will gradually decrease. In contrast, the global prevalence of the metabolic syndrome, encompassing hyperlipidemia, type-2 diabetes, arterial hypertension and obesity, will result in a concomitant strong increase in its hepatic equivalent, non-alcoholic fatty liver disease (NAFLD), which culminates in non-alcoholic steatohepatitis (NASH). This persistent hepatic inflammation is a prerequisite for HCC development, even in the absence of liver cirrhosis; therefore, the worldwide incidence of HCC is predicted to increase despite the improved prevention and treatment of viral hepatitis
Art. HTN, arterial hypertension

diagnosis and treatment decision making. The European Association for the Study of Liver Disease (EASL) and the American Association for the Study of Liver Diseases (AASLD) guidelines endorsed the BCLC classification system as favorable for treatment allocation and prognosis estimation. It encompasses the size and number of liver and extrahepatic lesions, patients' clinical performance status, and the stage of liver disease. Whether this algorithm should be amended to offer a more customized treatment concept, matched with the patients' individual health condition and tumor burden, is controversial.

In summary, there is an urgent need to address the critical challenges faced in HCC treatment to improve the poor clinical outcome we currently see.

Treatment of HCC

To ensure the optimal treatment strategy for each patient, staging of HCC is mandatory, assessing intra- and extrahepatic tumor burden, liver function tests, extent of portal hypertension and performance status. HCC size and focality should be assessed, preferably by contrast-enhanced MRI or alternatively CT scanning, and in case of advanced disease this should be augmented by chest CT and bone scan to rule out extrahepatic metastases. After thorough staging, according to all national and international guidelines, the treatment decision has to be made by an interdisciplinary tumor board, consisting of a hepatobiliary surgeon, interventional radiologist, nuclear medicine specialist, oncologist, pathologist and hepatologist. Curative treatment strategies encompass liver resection, liver transplantation, and under certain circumstances ablative regimens such as radiofrequency (RFA) or microwave ablation (MWA) (BCLC stage 0/A). Palliative treatments are represented by locoregional and systemic treatment strategies, but also individualized concepts that can combine different modalities (BCLC B/C). The decision regarding treatment should always aim to increase patients' OS [5] by identification of the best personalized therapy concept [6] (Fig. 2).

Curative treatment options

Role of surgical procedures

Resection is the treatment of choice for HCC patients without advanced fibrosis and associated evidence of portal hypertension. However, liver surgery in patients with chronic liver disease demands expert hepatobiliary surgeons because of the risk of hepatic failure, especially after extended resection. Recently Bruix *et al* refined their BCLC treatment algorithm, stating that surgery is no longer the only first-line treatment in very early-stage HCCs, since case-control studies have shown ablation to be noninferior and more cost-effective for patients with BCLC 0 stages [7]. Still, even in the case of cirrhosis, in the absence of portal hypertension, resection reveals low mortality rates (<5%) in BCLC stages 0 and A [8,9].

The multicenter BRIDGE study, which enrolled 8656 patients, aimed to elucidate whether straying from guideline recommendations impacted survival, when differentiating

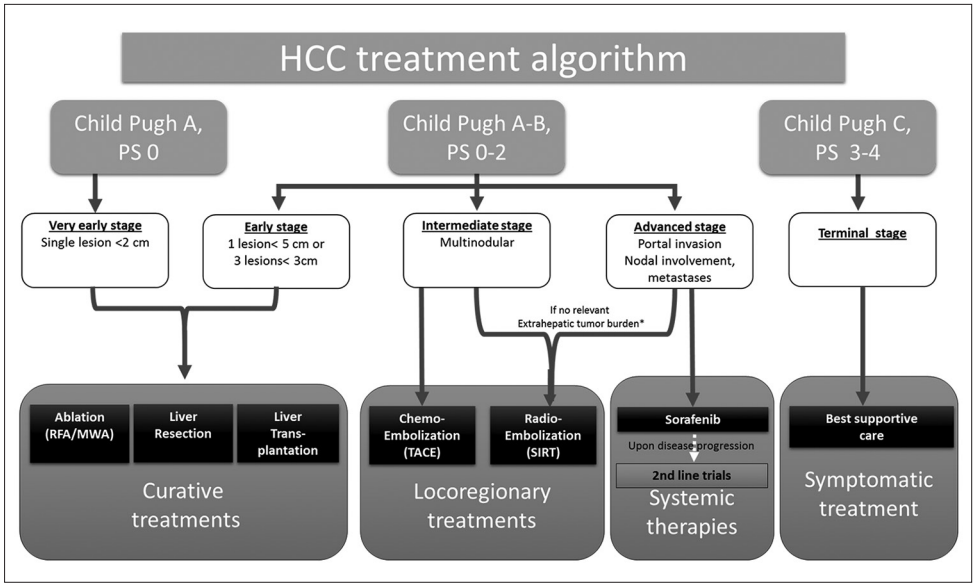

Figure 2 BCLC staging system with hepatocellular carcinoma (HCC) treatment recommendation by the authors.
Patients in very early and early HCC stages should receive either ablation, resection or liver transplantation. Resection should be offered only to those patients in Child-Pugh A condition in the absence of portal hypertension, otherwise liver transplantation should be offered, if the Milan criteria are fulfilled. Radiofrequency (RFA) or microwave (MWA) ablation should be restricted solely to lesions ≤2 cm in size.
During intermediate-stage disease, TACE should be performed. In cases where TACE is technically infeasible, SIRT can be offered.
In advanced stages, SIRT can be offered, if patients have no prognostically relevant tumor burden (*Pulmonary filiae ≤1 cm, lymphonodular filiae ≤2 cm), otherwise systemic therapy with sorafenib is indicated until clinical progression or intolerable toxicity. In this case, second-line systemic therapy trials should be offered to patients.
During terminal stage disease, patients should be offered best supportive care.

between formally ideal and non-ideal resection candidates, who either underwent surgery or not. The study concluded that not resecting ideal candidates was associated with increased mortality and that even a proportion of non-ideal candidates might benefit from resection over other treatment modalities [10]. In individual cases, multifocal HCCs can also be subjected to resection, however, this scenario entails a markedly increased risk of postoperative morbidity and mortality.

Portal hypertension and related post-resection deterioration

There is controversial discussion concerning the criteria for reliably estimating the risk of post-hepatectomy liver failure. In particular, resection should be reserved for patients with preserved liver function: no hyperbilirubinemia, platelet count >100,000/μL, endoscopically confirmed absence of esophageal varices and no splenomegaly. However, some authors claim that the measurement of the hepatic venous pressure gradient (HPVG) remains the gold standard of risk estimation [11,12]. A recent single-center, longitudinal observational study enrolling 217 patients undergoing HCC resection concluded that HPVG >10 mmHg was associated with a higher risk of ascitic decompensation early after surgery. On the other hand, such restrictive selection criteria might exclude a large proportion of potentially resectable patients, since liver function has recovered markedly 3 months post-surgery. Therefore, the authors conclude that HPVG measurement should rather facilitate the modulation of treatment planning, avoiding highly extended resection in patients with significant portal hypertension [13], rather than preventing surgery in general.

Strategies inducing preoperative hypertrophy of the future liver remnant

Over the past decades, multiple approaches have been applied in order to prevent post-hepatectomy liver failure, a result of extended tumor burden, insufficient amount of future liver remnant (FLR) and, in elderly patients (>75 years of age), a negative hepatic proliferation index (apoptosis > regeneration).

Frequently applied methods for enhancing FLR in primary non-resectable liver tumors are portal vein ligation (PVL) and portal vein embolization (PVE). A meta-analysis from 2008, involving 1088 patients, demonstrated that on average 29 days passed from PVE to resection. In 14% of PVE patients, resection was not feasible because of either disease progression or insufficient hypertrophy [14]. A systematic review comparing both procedures concluded that the increase in FLR was 39% for PVE and 27% for PVL; however, the difference between the treatments was non-significant. Both procedures had comparable post-resection morbidity and mortality, similar time to hepatectomy, and similar time-to-disease progression [15]. Associating Liver Partition and PVL for Staged hepatectomy (ALPPS) is a novel 2-stage surgical strategy [16]. In the first step, surgical exploration, right

PVL, and *in situ* splitting of the liver parenchyma along the falciform ligament is performed. In the scenario of bilobar tumors, the FLR is cleared from all tumor tissue by partial resection. ALPPS can induce pronounced and rapid growth of the FLR within a short period [17] and is clearly superior to PVE/PVL alone. Here, the FLR is able to enlarge by 40-80% within 6-9 days [18]. During the second step, the right artery is dissected and ligated. The bile duct and the venous drainage of the right and middle vein into the vena cava are divided and the deportalized liver is removed to render the patient completely tumor-free. The indications for ALPPS encompass patients with an FLR of less than 30% in healthy liver and an FLR of less than 40% in diseased liver parenchyma. Contraindications are unresectable lesions in the FLR, extrahepatic tumor burden, portal hypertension, and poor performance status [19].

Since unilobar Yttrium-90 selective internal radiation therapy (SIRT) has been reported to induce hypertrophy of the contralateral, untreated liver lobe, another emerging strategy of preparing small FLR patients with bilobar HCC lesions for later resection has been called radiation-lobectomy. In 2016, Lewandowski *et al* conducted a study (HCC n=10, cholangiocarcinoma n=2, metastatic colorectal cancer n=1), where right-lobar +/- segment-4 radioembolization was performed prior to lobectomy/tri-segmentectomy in patients with a bilobar tumor in the setting of inadequate FLR. The median time between SIRT and resection was 86 days, resulting in a median FLR hypertrophy of 30%, and the median post-resection follow-up time was 604 days. The authors concluded that, in this preliminary study, radiation lobectomy prior to resection provided adequate FLR hypertrophy, while promising improved tumor control [20].

HCC recurrence risk following resection

Even following resection with a curative intent, HCC shows recurrence rates of approximately 50% during the first 3 years and more than 70% during the first 5 years [21-23], which constitutes either intrahepatic metastasis (early recurrence) or a *de novo* HCC in the cirrhotic remnant liver (late recurrence). In particular, microvascular invasion is a known predictor of recurrence, likewise histological grading, multifocality and the size of lesion(s).

A multicenter phase III double-blind, placebo-controlled study called "Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM)" assessed the safety and efficacy of an adjuvant treatment with sorafenib for a maximum of 4 years with the primary endpoint of recurrence-free survival following resection or ablation. There was no significant difference in recurrence-free survival between sorafenib and placebo (33.3% months in sorafenib group vs. 33.7% in the placebo group). Therefore, sorafenib is not an effective intervention in the adjuvant setting for HCC following resection or ablation [24].

In a cohort of 164 HCC patients, Ferrer-Fabrega *et al* prospectively validated an *ab initio* liver transplantation (LT) after liver resection in cases where histology of the resected specimen revealed risk factors for recurrence (microvascular invasion and/or satellites). They concluded that *ab initio* LT should be offered to those patients with a histologically proven risk of recurrence, there being no benefit in waiting for clinical evidence of recurrence by imaging. However, to avoid aggressive disease recurrence associated with poor prognosis, they proposed a waiting time of at least 6 months between resection and enlistment for transplant.

LT

LT is the treatment of choice in patients with early HCC according to the Milan criteria (MC), at BCLC stage 0 or A, with evidence of portal hypertension and/or hepatic dysfunction, who are therefore ineligible for resection. Despite its limited access, it represents a unique strategy to cure HCC, resolving both the tumor and the underlying cirrhosis.

Selection criteria for HCC patients for LT listing

If the MC are fulfilled (single lesion ≤5 cm or 3 lesions ≤3 cm) [25], 70% of transplanted HCC patients reach 5-year survival. There have been multiple attempts to extend the MC, considering them to be too restrictive. Therefore, various alternative LT selection criteria have been evaluated in trials. Criteria such as Up-to-7 (5-year OS 71.2%) [26], Tokyo (5-year OS 75%) [27] and UCSF (5-year OS 75.2%) [28] are mainly based on tumor size and number and achieve comparable results compared to the MC. Other selection scores contain additional variables, such as AFP in combination with histopathological grading (Hangzhou) [29], DCP (Kyoto) [30], vascular/lymphonodular invasion, and extrahepatic tumor burden (Shanghai) [31], each in combination with tumor size and number. Among those criteria utilizing additional variables, the Kyoto score has achieved a superior 5-year OS (86.7%) [30].

The "Metroticket calculator" represents another prognostic tool, endorsed by the International Liver Transplantation Society (ILTS) and by the international liver cancer association (ILCA), to estimate survival based on a survey of more than 1200 HCC patients transplanted outside the Milan/Unos Criteria (https://www.hcc-olt-metro-ticket.org/calculator). This calculator predicts the 3- and 5-year survival of a given patient with HCC undergoing LT, based on morphological characteristics of the tumor: 1) the size of the major nodule; and 2) the total number of HCC nodules. The 5-year forecast can optionally be adapted to take account of the absence or presence of vascular invasion.

HCC downstaging prior to LT

Liver-directed transcatheter therapy is commonly applied to bridge patients to LT or to downstage HCC lesions to fulfill the MC (outside EUROTRANSPLANT).

The rationale for bridging patients to LT is to prevent dropout from the waiting list due to tumor progression [32]. Recently,

Yao *et al* were able to confirm that after successfully downstaging tumors to within the MC criteria, post-transplant survival was comparable to that of those patients who fulfilled the MC without prior downstaging [33]. The choice of therapeutic modality is based on lesion size and location, a common strategy involves a combination of transcatheter and local ablative therapy. Most commonly, bridging involves conventional transarterial chemoembolization (cTACE) and RFA [34]. Studies evaluating the efficacy of cTACE prior to LT have reported complete tumor necrosis rates of 38-57% for lesions in the liver explant [35], compared to 36-70% after SIRT prior to LT [36-38]. Most commonly, cTACE is utilized for downstaging; however, Lewandowski *et al* retrospectively compared the effectiveness of SIRT and cTACE in 86 patients and concluded that downstaging to within the MC was achieved in 31% of cTACE and in 58% of SIRT patients [39]. Certainly those data warrant verification in a prospective randomized controlled trial.

RFA and MWA

The effect of RFA is based on the heat generated using high-frequency alternating current, resulting in heat-induced cell necrosis. RFA treatment of small HCC lesions in patients with preserved liver function has been recognized as safe, easy to use and less invasive than surgical resection [40,41], and is now accepted as a curative treatment for very early or early-stage HCC according to the recent BCLC treatment strategy [42]. In BCLC 0 stages (single lesion <2 cm) resection is no longer the treatment of choice; recent studies have provided evidence that RFA has comparable efficacy to resection in very-early stage HCCs, with better cost-effectiveness [43,44]. In BCLC A stages (single lesion or 3 lesions <3 cm), if resection or transplantation is not feasible, because of portal hypertension or comorbidities, respectively, RFA is the first-line ablation technique. Survival of patients with HCC lesions <3 cm treated with RFA is comparable to that after surgical resection [45]. For lesions exceeding 3 cm in diameter or in multifocal HCCs, pretreatment with TACE prior to RFA has been proposed [46]. However, given the lack of robust data, in the scenario of unifocality resection remains the treatment of choice, if technically feasible [47].

MWA is a strong rival to RFA, using electromagnetic waves to kill the tumor by direct hyperthermic injury. MWA has the advantage of a higher thermal efficiency and the time required for ablation is shorter than for RFA. There is no heat-sink effect and it can be utilized for ablation of tumors adjacent to major blood vessels. A recent multicenter study, in which 1007 patients with malignant liver tumors underwent MWA, showed a 1- and 5-year OS of 91.2% and 59.8%, respectively [48,49].

Palliative treatment regimens

Locoregional transcatheter therapies

TACE and SIRT are utilized in scenarios when curative treatment approaches, such as resection, LT or RFA, are no longer applicable, but the tumor burden is still confined to the liver in the absence of relevant extrahepatic tumor spread (BCLC B/C).

TACE

Taking advantage of the liver's dual blood supply via the artery and portal vein on the one hand, and the arterial hypervascularization of HCC as a mandatory prerequisite for local tumor therapy on the other, cTACE can deliver highly concentrated doses of chemotherapeutic agents into hypervascularized neoplastic tissue, while the surrounding liver parenchyma remains unaffected if superselective catheterization of the tumor feeder can be achieved. In addition, the embolic agent induces local ischemia and consecutive necrosis and decelerates the washout of previously administered antineoplastic drugs.

According to the AASLD [50] and EASL [51] guidelines, cTACE is the therapy of choice for intermediate stage HCC patients who are ineligible for resection, LT and ablation (BCLC B). Some authors promote a BCLC B subclassification (B1-B4) to facilitate the TACE decision, mainly taking into account liver function, Eastern Cooperative Oncology Group performance status, and fulfillment of the MC [52]. Sieghart *et al* consider patients with well-preserved liver function and a low tumor burden (BCLC B1) to be optimal candidates for TACE. In contrast, subclasses B2 and B3/4 consist of very heterogeneous patients and thus still need prospective evaluation [53].

A data-based approach to the TACE treatment decision was the establishment of the Hepatoma Arterial Embolization Prognostic score (HAP) [54], which is based on serum-albumin, AFP, bilirubin and maximum tumor diameter. It is divided into 4 risk groups, ranging from HAP A to HAP D (HAP A=best liver function, lowest AFP and lowest tumor diameter). Accordingly, patients in HAP-score groups A and B are considered to be the most suitable for TACE [53].

Finally, the Selection for Transarterial chemoembolization treatment (STATE) [55] score was developed in a training-cohort using a stepwise Cox regression model and was validated in an external validation cohort. The STATE score is based on serum albumin, C-reactive protein and up-to-seven in/out criterion, which enables identification of a subgroup of patients with long survival after chemoembolisation, and is divided into two groups (<18, >18 points). A STATE score <18 points was associated with increased mortality and thus reflects an absolute contraindication for TACE.

Different TACE regimens

Conventional TACE encompasses the selective injection of a chemotherapeutic agent - e.g. doxorubicin (36%), cisplatin (31%), epirubicin (12%), mitoxantrone (8%), mitomycin C (8%) [56] - emulsified in a viscous carrier, followed by selective obstruction of the tumor feeding vessel. There are numerous

embolizing agents that can be utilized: gelatin sponge particles, polyvinyl alcohol particles, degradable starch microspheres, and Embospheres®, even though there is no evidence for benefit compared to the use of lipiodol [56].

Cumulative meta-analyses confirmed that cTACE reduced the overall 2-year mortality compared to controls receiving conservative treatment [57,58]. However, it remains unclear which is the most effective chemotherapeutic drug, which is the most appropriate embolization agent, and which is the best treatment schedule. Complete responses are mostly achievable after approximately two to four repetitive procedures. The intervals can be either fixed or dependent on therapy response. Decision on treatment continuation following first TACE can be guided by the Assessment for Retreatment with TACE (ART) score [59]. The score encompasses objective radiological tumor response (absence or presence), parenchymal liver damage (increased aspartate aminotransferase), and impairment of liver function (increase in Child-Turcotte-Pugh [CTP] score) after the first TACE session. The ART score discriminates between two patient groups (0-1.5 vs. ≥2.5 points). Sequential assessment prior to each further TACE session identifies patients likely to have a poor prognosis (ART score ≥2.5 points) were TACE treatment to be continued [53].

Alternatively, TACE may be performed with microspheres loaded with a chemotherapeutic agent, known as drug-eluting bead TACE (DEB-TACE). This method facilitates the delivery of large amounts of drugs into the tumor over a prolonged time period. It is postulated that this results in an ameliorated antineoplastic activity on the one hand and in decreased peak plasma concentrations of the chemotherapy agent [60] on the other, resulting in less systemic side effects [61,62].

Contraindications for TACE

Because of the lack of arterial hyperarterialization, TACE is not recommended during very early HCC stages. Relative contraindications for TACE are hepatic encephalopathy, biliary obstruction, and a large tumor burden (in terms of multifocality, massive size of singular lesion, or technical obstacles such as multiple tumor feeders) [63]. Absolute contraindications are decompensated liver cirrhosis and branch or main portal vein thrombosis (PVT), since additional occlusion of the remaining arterial blood supply might result in liver failure. Nevertheless, TACE might be considered even in the context of PVT, if a supraselective approach is technically feasible [64].

Side effects/complications of TACE

A common side effect of cTACE is a usually transient post-embolization syndrome encompassing abdominal pain and fever [65]. This is frequently accompanied by a mostly self-limiting decline in liver function. Severe hepatic decompensation with jaundice, ascites and hepatic encephalopathy is rather rare. The most serious complication is liver failure, which can potentially be prevented by a more selective procedure, sparing most of the tumor surrounding liver parenchyma. This should be considered especially in the patient with borderline compromised liver function prior to treatment.

Combined therapies

The sequential combination of TACE and RFA has found broad clinical acceptance for several indications. The most relevant is that cTACE may facilitate downstaging of HCC lesions larger than 3 cm in diameter to permit subsequent potentially curative RFA treatment. A meta-analysis was able to clearly demonstrate that the combination of cTACE with RFA resulted in significantly improved OS and recurrence-free survival compared to RFA alone [66,67]. Furthermore, it has been demonstrated that the application of cTACE prior to RFA increases the volume of the ablation area [68].

The combination of TACE with sorafenib also has a rationale: TACE-associated local ischemia induces upregulation of vascular endothelial growth factor (VEGF) [69], which is associated with HCC proliferation and thus disease progression. This effect might be attenuated by the sequential systemic administration of sorafenib, utilizing its systemic antiangiogenetic properties mediated by inhibition of VEGF receptors 2 and 3. In the phase II SPACE trial (safety and efficacy of sorafenib vs. placebo associated with DEB-TACE) a cohort of patients with intermediate stage HCC received DEB-TACE in combination with either sorafenib or placebo. The combinatory treatment resulted in a better time to progression in the sorafenib treated group [70].

SIRT and ongoing studies

Another emerging transcatheter irradiation-based HCC therapy is SIRT. Despite the fact that SIRT has not yet been adequately taken into account in international guideline recommendations, it may have a broad range of clinical applications, such as HCC patients who are ineligible for TACE because of a high tumor burden (lesions >7 cm in diameter), presence of vascular invasion (especially PVT), or lack of response to previous TACE. Since SIRT only targets intrahepatic tumors, this treatment should be limited to patients without prognostically relevant extrahepatic metastases (Fig. 2).

SIRT is performed by injecting microspheres into the arterial circulation of the liver. The microspheres are loaded with a β-emitting radioisotope, such as ^{90}Yttrium (^{90}Y), which delivers the radiation close to the origin of the particle. Because of the higher arterial blood flow in many malignant liver neoplasms compared to the liver parenchyma, this results in higher tumor doses without selective catheterization of the tumor feeding arteries, extending the applicability of SIRT beyond the limits of superselective TACE. In addition, the incidence of post-embolization syndrome is lower compared to TACE [71-73].

There are two products with ^{90}Y-microspheres commercially available: SIR-Spheres® consist of non-biodegradable resin-based microspheres (Sirtex Medical Europe, Bonn, Germany) and TheraSpheres® (BTG International, London,

United Kingdom) are glass microspheres. Both methods show differences in terms of diameter, activity per particle, spheres per 3 GBq, specific gravity and embolic effect. Treatment planning is based on avoiding toxicity to the liver tissue, but also to extrahepatic organs that may be targeted as a result of intratumoral arteriovenous shunts, e.g. the lung, or anatomical variants of the hepatic vasculature, e.g. gastrointestinal organs.

Clinical evidence on SIRT and ongoing studies

Evidence supporting the benefit of SIRT in HCC treatment derives from consistent, large-cohort series involving patients with more advanced stage HCC, who are ineligible for other locoregional interventions or who have progressed under previous TACE. Recent studies have reported various response rates (any response encompassing partial response, complete response, stable disease after SIRT ranging from 79-94% with an OS of 15-16.4 months [74-76]. These studies also clearly demonstrate that liver function is a relevant predictor of OS, since patients in a CTP A condition reveal markedly better OS compared to those in a CTP B condition (median OS CTP A: 17.2-17.4 vs. CTP B: 6-7.7 months) [74,75]. Furthermore, PVT and extensive extrahepatic disease appear to negatively impact prognosis [75,77].

SIRT candidates are frequently ineligible for TACE because of their high tumor burden, the presence of macrovascular invasion, or a lack of response to previous TACE. The only randomized controlled trial (RCT) comparing DEB-TACE to SIRT (24 patients) showed no significant difference in OS [78]. Other large case series also show no significant difference between TACE and SIRT (median OS 17.4 vs. 16.9 months), but they reveal the problem of comparability, since SIRT patients tend to be in more advanced disease stages compared to TACE patients [79,80].

At present there are several ongoing phase III RCTs investigating irresectable HCC in the absence or presence of PVT, treated with either SIR-Spheres®—SORAMIC (NCT01126645), SARAH (NCT01482442), SIRveNIB (NCT01135056)—or TheraSpheres®—STOP-HCC (NCT01556490), YES-P (NCT01887717)—against or in combination with sorafenib; the results of all trials mentioned above are still pending.

Contraindications and adverse events in SIRT patients

SIRT is a technically demanding procedure, given the risk of non-target embolization. One absolute contraindication is a significant hepatopulmonary shunt, because of the risk of radiation pneumonitis and lung fibrosis that may require treatment with steroids [81]. A retrospective study demonstrated that, in patients with a high hepatopulmonary shunt, sorafenib treatment was able to reduce the shunt from 26.5% to 7.5% on average prior to anticipated SIRT, thus making patients eligible for SIRT who otherwise would have been excluded from this locoregional treatment option [82].

Furthermore, the predicted deposition of microspheres in the gastrointestinal tract, which may result in gastrointestinal ulceration, is a contraindication. Pre-interventional coiling of vessels with hepatofugal flow helps to reduce the risk of GI complications but may itself create risks due to collateral formation [83,84]. Proton pump inhibitors are the treatment of choice in the case of gastrointestinal ulceration, while in refractory cases surgical intervention may be required.

Post-radioembolization syndrome, encompassing fatigue, nausea, fever and abdominal discomfort, is the most frequent, mostly transient (lasting no longer than 2-4 weeks post-procedure) side effect following SIRT [85]. A short-term elevation of the liver enzymes alkaline phosphatase, alanine transferase and bilirubin are normal side effects of this treatment.

SIRT in patients with compromised liver function may lead to radioembolization-induced liver disease (REILD) [86], defined as jaundice and ascites appearing 1 to 2 months after radioembolization in the absence of tumor progression or bile duct occlusion. A judicious selection of patients by liver function in terms of ascites and evidence of compromised liver function tests is crucial for avoiding liver failure [85,86]. Sequential lobar treatment, instead of single-session treatment of the entire liver, might reduce the risk of REILD and should be considered especially in patients with compromised liver function. The periprocedural administration of ursodeoxycholic acid and low-dose steroids may reduce the risk of REILD.

Biliary toxicity encompassing bilioma, abscesses or post-radiogenic cholecystitis, occurs in less than 2% of patients [87]. Cholecystitis often shows no correlating clinical manifestation and can be self-limiting.

Systemic therapies

In patients at BCLC stage C, and when locoregional treatment options have been exhausted or extrahepatic tumor spread is present, systemic antiproliferative therapy is indicated. At present, the only guideline-recommended antiangiogenetic substance is sorafenib, which reduces tumor cell proliferation and angiogenesis, and increases apoptosis by targeting receptor tyrosine kinases, including VEGF and platelet-derived growth factor receptor signaling pathways [88].

The SHARP (Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol) trial, published in 2008 by Llovet *et al*, demonstrated improved OS in patients with advanced HCC on treatment with sorafenib. In this trial, 602 patients with well-preserved liver function (>95% CTP A) were randomized to receive either sorafenib 400 mg b.i.d. or matching placebo. In the sorafenib group the median OS was 10.7 months, compared with 7.9 months in the placebo group [89]. Sorafenib therapy is frequently limited by side effects such as "hand-foot-syndrome", arterial hypertension, diarrhea, hair loss and myocardial ischemia. Dose de-escalations and treatment interruptions are frequent.

Other tyrosine kinase inhibitors targeting pathways promoting angiogenesis, such as brivanib, sunitinib and linifanib [90-92], have failed during phase III trials. Recently, hepatocyte growth factor and its corresponding tyrosine kinase receptor (MET) have been identified as other promising targets

of HCC-directed therapy [93]. The results of two phase III trials with tivanitinib (MET inhibitor) and cabozantinib (combined-MET and VEGFR2 inhibitor) are still pending.

Immunological mechanisms are assumed to play a pivotal role in the regulation of HCC proliferation [94]. A postulated mechanism of tumor immune tolerance in HCC is an increase in regulatory T-cells (Tregs). Tregs are a target of immune checkpoint-inhibiting antibodies, such as ipilimumab (anti-CTLA-4), pembrolizumab (anti PD-1), and nivolumab (anti PD-1). All of these antibodies have already received FDA approval for the treatment of other cancer entities [95]. In HCC, PD-L1 expression is assumed to represent a biomarker predicting drug sensitivity. A recent publication by Calderaro *et al* indicates that PD-L1 expression by neoplastic cells in HCC is related to tumor aggressiveness (high AFP levels, satellite lesions, micro- and-macrovascular invasion and poor differentiation) and implies that the response to treatments targeting the PD-L1/PD-1 immune checkpoint could be restricted to particular HCC subtypes [96].

Concluding remarks

Clinicians are faced with the heterogeneity of patients presenting with a variable extent of intra-and extrahepatic HCC tumor burden, liver function and clinical performance status. Current staging systems, such as the BCLC algorithm, aim at patient classification and recommendation of treatment modalities. Patients with early-stage HCCs without portal hypertension are recommended for surgical resection; patients with portal hypertension and HCC within MC should be evaluated for LT. In case of ineligibility for both, ablation should be performed. In intermediate-stage HCC, TACE is the treatment of choice; in advanced-stage HCC, BCLC recommends sorafenib treatment. Terminal-stage patients should not be treated with anti-cancer therapies. However, this strict assignment has several limitations: disagreement surrounds the care of the heterogeneous intermediate BCLC stage patient population, which according to BCLC is restricted to TACE, neglecting to consider that under certain circumstances they might be eligible for resection or LT. Patients at intermediate stages might also be offered sorafenib, RFA or SIRT. Many of the newer treatment options discussed above are not yet covered in guidelines, because of the lack of evidence supporting their utilization. Therefore several groups have demanded subclassifications of the BCLC intermediate stage, in order to add treatment regimens not included to date. Ongoing RCTs on treatment strategies, including new locoregional treatments as well as new systemic targeted therapies, will serve to extend guideline recommendations in the near future.

References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015;**136**:E359-E386.
2. Berhane S, Toyoda H, Tada T, et al. Role of the GALAD and BALAD-2 serologic models in diagnosis of hepatocellular carcinoma and prediction of survival in patients. *Clin Gastroenterol Hepatol* 2016;**14**:875-886.
3. Johnson PJ, Pirrie SJ, Cox TF, et al. The detection of hepatocellular carcinoma using a prospectively developed and validated model based on serological biomarkers. *Cancer Epidemiol Biomarkers Prev* 2014;**23**:144-153.
4. Ertle J, Dechêne A, Sowa JP, et al. Non-alcoholic fatty liver disease progresses to hepatocellular carcinoma in the absence of apparent cirrhosis. *Int J Cancer* 2011;**128**:2436-2443.
5. Romagnoli R, Mazzaferro V, Bruix J. Surgical resection for hepatocellular carcinoma: Moving from what can be done to what is worth doing. *Hepatology* 2015;**62**:340-342.
6. Chan SL, Wong AM, Lee K, Wong N, Chan AK. Personalized therapy for hepatocellular carcinoma: Where are we now? *Cancer Treat Rev* 2016;**45**:77-86.
7. Bruix J, Reig M, Sherman M. Evidence-based diagnosis, staging, and treatment of patients with hepatocellular carcinoma. *Gastroenterology* 2016;**150**:835-853.
8. Llovet JM, Schwartz M, Mazzaferro V. Resection and liver transplantation for hepatocellular carcinoma. *Semin Liver Dis* 2005;**25**:181-200.
9. Belghiti J, Hiramatsu K, Benoist S, Massault P, Sauvanet A, Farges O. Seven hundred forty-seven hepatectomies in the 1990s: an update to evaluate the actual risk of liver resection. *J Am Coll Surg* 2000;**191**:38-46.
10. Roayaie S, Jibara G, Tabrizian P, et al. The role of hepatic resection in the treatment of hepatocellular cancer. *Hepatology* 2015;**62**:440-451.
11. Berzigotti A, Reig M, Abraldes JG, Bosch J, Bruix J. Portal hypertension and the outcome of surgery for hepatocellular carcinoma in compensated cirrhosis: a systematic review and meta-analysis. *Hepatology* 2015;**61**:526-536.
12. Capussotti L, Ferrero A, Viganò L, Muratore A, Polastri R, Bouzari H. Portal hypertension: contraindication to liver surgery? *World J Surg* 2006;**30**:992-999.
13. Cucchetti A, Cescon M, Golfieri R, et al. Hepatic venous pressure gradient in the preoperative assessment of patients with resectable hepatocellular carcinoma. *J Hepatol* 2016;**64**:79-86.
14. Abulkhir A, Limongelli P, Healey AJ, et al. Preoperative portal vein embolization for major liver resection: a meta-analysis. *Ann Surg* 2008;**247**:49-57.
15. Pandanaboyana S, Bell R, Hidalgo E, et al. A systematic review and meta-analysis of portal vein ligation versus portal vein embolization for elective liver resection. *Surgery* 2015;**157**:690-698.
16. Schadde E, Ardiles V, Robles-Campos R, et al; ALPPS Registry Group. Early survival and safety of ALPPS: first report of the International ALPPS Registry. *Ann Surg* 2014;**260**:829-836; discussion 836-838.
17. Govil S. Rapid improvement in liver volume induced by portal vein ligation and staged hepatectomy: the ALPPS procedure. *HPB (Oxford)* 2012;**14**:874.
18. Song T. Recent advances in surgical treatment of hepatocellular carcinoma. *Drug Discov Ther* 2015;**9**:319-330.
19. Alvarez FA, Ardiles V, Sanchez Claria R, Pekolj J, de Santibañes E. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): tips and tricks. *J Gastrointest Surg* 2013;**17**:814-821.
20. Lewandowski RJ, Donahue L, Chokechanachaisakul A, et al. (90) Y radiation lobectomy: Outcomes following surgical resection in patients with hepatic tumors and small future liver remnant volumes. *J Surg Oncol* 2016;**114**:99-105.
21. Sakon M, Nagano H, Nakamori S, et al. Intrahepatic recurrences

of hepatocellular carcinoma after hepatectomy: analysis based on tumor hemodynamics. *Arch Surg* 2002;**137**:94-99.
22. Belghiti J, Panis Y, Farges O, Benhamou JP, Fekete F. Intrahepatic recurrence after resection of hepatocellular carcinoma complicating cirrhosis. *Ann Surg* 1991;**214**:114-117.
23. Nagasue N, Uchida M, Makino Y, et al. Incidence and factors associated with intrahepatic recurrence following resection of hepatocellular carcinoma. *Gastroenterology* 1993;**105**:488-494.
24. Bruix J, Takayama T, Mazzaferro V, et al; STORM investigators. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2015;**16**:1344-1354.
25. Mazzaferro V, Bhoori S, Sposito C, et al. Milan criteria in liver transplantation for hepatocellular carcinoma: an evidence-based analysis of 15 years of experience. *Liver Transpl* 2011;**17** Suppl 2:S44-S57.
26. Mazzaferro V, Llovet JM, Miceli R, et al; Metroticket Investigator Study Group. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. *Lancet Oncol* 2009;**10**:35-43.
27. Sugawara Y, Tamura S, Makuuchi M. Living donor liver transplantation for hepatocellular carcinoma: Tokyo University series. *Dig Dis* 2007;**25**:310-312.
28. Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology* 2001;**33**:1394-1403.
29. Zheng SS, Xu X, Wu J, et al. Liver transplantation for hepatocellular carcinoma: Hangzhou experiences. *Transplantation* 2008;**85**:1726-1732.
30. Ito T, Takada Y, Ueda M, et al. Expansion of selection criteria for patients with hepatocellular carcinoma in living donor liver transplantation. *Liver Transpl* 2007;**13**:1637-1644.
31. Fan J, Yang GS, Fu ZR, et al. Liver transplantation outcomes in 1,078 hepatocellular carcinoma patients: a multi-center experience in Shanghai, China. *J Cancer Res Clin Oncol* 2009;**135**:1403-1412.
32. Fujiki M, Aucejo F, Choi M, Kim R. Neo-adjuvant therapy for hepatocellular carcinoma before liver transplantation: where do we stand? *World J Gastroenterol* 2014;**20**:5308-5319.
33. Yao FY, Mehta N, Flemming J, et al. Downstaging of hepatocellular cancer before liver transplant: long-term outcome compared to tumors within Milan criteria. *Hepatology* 2015;**61**:1968-1977.
34. Yao FY, Kerlan RK Jr, Hirose R, et al. Excellent outcome following down-staging of hepatocellular carcinoma prior to liver transplantation: an intention-to-treat analysis. *Hepatology* 2008;**48**:819-827.
35. Stampfl U, Bermejo JL, Sommer CM, et al. Efficacy and nontarget effects of transarterial chemoembolization in bridging of hepatocellular carcinoma patients to liver transplantation: a histopathologic study. *J Vasc Interv Radiol* 2014;**25**:1018-1026.
36. Tohme S, Sukato D, Chen HW, et al. Yttrium-90 radioembolization as a bridge to liver transplantation: a single-institution experience. *J Vasc Interv Radiol* 2013;**24**:1632-1638.
37. Riaz A, Kulik L, Lewandowski RJ, et al. Radiologic-pathologic correlation of hepatocellular carcinoma treated with internal radiation using yttrium-90 microspheres. *Hepatology* 2009;**49**:1185-1193.
38. Kulik L, Vouche M, Koppe S, et al. Prospective randomized pilot study of Y90+/-sorafenib as bridge to transplantation in hepatocellular carcinoma. *J Hepatol* 2014;**61**:309-317.
39. Lewandowski RJ, Kulik LM, Riaz A, et al. A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization. *Am J Transplant* 2009;**9**:1920-1928.
40. Rossi S, Di Stasi M, Buscarini E, et al. Percutaneous RF interstitial thermal ablation in the treatment of hepatic cancer. *AJR Am J Roentgenol* 1996;**167**:759-768.
41. Shiina S, Teratani T, Obi S, Hamamura K, Koike Y, Omata M. Nonsurgical treatment of hepatocellular carcinoma: from percutaneous ethanol injection therapy and percutaneous microwave coagulation therapy to radiofrequency ablation. *Oncology* 2002;**62** Suppl 1:64-68.
42. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. *Lancet* 2012;**379**:1245-1255.
43. Cho YK, Kim JK, Kim WT, Chung JW. Hepatic resection versus radiofrequency ablation for very early stage hepatocellular carcinoma: a Markov model analysis. *Hepatology* 2010;**51**:1284-1290.
44. Cucchetti A, Piscaglia F, Cescon M, et al. Cost-effectiveness of hepatic resection versus percutaneous radiofrequency ablation for early hepatocellular carcinoma. *J Hepatol* 2013;**59**:300-307.
45. Cho YK, Kim JK, Kim MY, Rhim H, Han JK. Systematic review of randomized trials for hepatocellular carcinoma treated with percutaneous ablation therapies. *Hepatology* 2009;**49**:453-459.
46. Peng ZW, Zhang YJ, Chen MS, et al. Radiofrequency ablation with or without transcatheter arterial chemoembolization in the treatment of hepatocellular carcinoma: a prospective randomized trial. *J Clin Oncol* 2013;**31**:426-432.
47. Germani G, Pleguezuelo M, Gurusamy K, Meyer T, Isgrò G, Burroughs AK. Clinical outcomes of radiofrequency ablation, percutaneous alcohol and acetic acid injection for hepatocelullar carcinoma: a meta-analysis. *J Hepatol* 2010;**52**:380-388.
48. Liang P, Wang Y, Yu X, Dong B. Malignant liver tumors: treatment with percutaneous microwave ablation--complications among cohort of 1136 patients. *Radiology* 2009;**251**:933-940.
49. Liang P, Yu J, Yu XL, et al. Percutaneous cooled-tip microwave ablation under ultrasound guidance for primary liver cancer: a multicentre analysis of 1363 treatment-naive lesions in 1007 patients in China. *Gut* 2012;**61**:1100-1101.
50. Bruix J, Sherman M; Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. *Hepatology* 2005;**42**:1208-1236.
51. European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012;**56**:908-943.
52. Bolondi L, Burroughs A, Dufour JF, et al. Heterogeneity of patients with intermediate (BCLC B) Hepatocellular Carcinoma: proposal for a subclassification to facilitate treatment decisions. *Semin Liver Dis* 2012;**32**:348-359.
53. Sieghart W, Hucke F, Peck-Radosavljevic M. Transarterial chemoembolization: modalities, indication, and patient selection. *J Hepatol* 2015;**62**:1187-1195.
54. Kadalayil L, Benini R, Pallan L, et al. A simple prognostic scoring system for patients receiving transarterial embolisation for hepatocellular cancer. *Ann Oncol* 2013;**24**:2565-2570.
55. Hucke F, Pinter M, Graziadei I, et al. How to STATE suitability and START transarterial chemoembolization in patients with intermediate stage hepatocellular carcinoma. *J Hepatol* 2014;**61**:1287-1296.
56. Marelli L, Stigliano R, Triantos C, et al. Transarterial therapy for hepatocellular carcinoma: which technique is more effective? A systematic review of cohort and randomized studies. *Cardiovasc Intervent Radiol* 2007;**30**:6-25.
57. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. *Hepatology* 2003;**37**:429-442.
58. Cammà C, Schepis F, Orlando A, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials. *Radiology* 2002;**224**:47-54.
59. Sieghart W, Hucke F, Pinter M, et al. The ART of decision making: retreatment with transarterial chemoembolization in patients with hepatocellular carcinoma. *Hepatology* 2013;**57**:2261-2273.

60. Varela M, Real MI, Burrel M, et al. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. *J Hepatol* 2007;**46**:474-481.
61. Matsui O, Miyayama S, Sanada J, et al. Interventional oncology: new options for interstitial treatments and intravascular approaches: superselective TACE using iodized oil for HCC: rationale, technique and outcome. *J Hepatobiliary Pancreat Sci* 2010;**17**:407-409.
62. Facciorusso A, Di Maso M, Muscatiello N. Drug-eluting beads versus conventional chemoembolization for the treatment of unresectable hepatocellular carcinoma: A meta-analysis. *Dig Liver Dis* 2016;**48**:571-577.
63. Raoul JL, Sangro B, Forner A, et al. Evolving strategies for the management of intermediate-stage hepatocellular carcinoma: available evidence and expert opinion on the use of transarterial chemoembolization. *Cancer Treat Rev* 2011;**37**:212-220.
64. Xue TC, Xie XY, Zhang L, Yin X, Zhang BH, Ren ZG. Transarterial chemoembolization for hepatocellular carcinoma with portal vein tumor thrombus: a meta-analysis. *BMC Gastroenterol* 2013;**13**:60.
65. Shin SW. The current practice of transarterial chemoembolization for the treatment of hepatocellular carcinoma. *Korean J Radiol* 2009;**10**:425-434.
66. Liu Z, Gao F, Yang G, et al. Combination of radiofrequency ablation with transarterial chemoembolization for hepatocellular carcinoma: an up-to-date meta-analysis. *Tumour Biol* 2014;**35**:7407-7413.
67. Peng ZW, Chen MS. Transcatheter arterial chemoembolization combined with radiofrequency ablation for the treatment of hepatocellular carcinoma. *Oncology* 2013;**84** Suppl 1:40-43.
68. Mostafa EM, Ganguli S, Faintuch S, Mertyna P, Goldberg SN. Optimal strategies for combining transcatheter arterial chemoembolization and radiofrequency ablation in rabbit VX2 hepatic tumors. *J Vasc Interv Radiol* 2008;**19**:1740-1748.
69. Shim JH, Park JW, Kim JH, et al. Association between increment of serum VEGF level and prognosis after transcatheter arterial chemoembolization in hepatocellular carcinoma patients. *Cancer Sci* 2008;**99**:2037-2044.
70. Lencioni R, Llovet JM, Han G, et al. Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: The SPACE trial. *J Hepatol* 2016;**64**:1090-1098.
71. Salem R, Lewandowski RJ, Kulik L, et al. Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma. *Gastroenterology* 2011;**140**:497-507.
72. Kennedy A, Nag S, Salem R, et al. Recommendations for radioembolization of hepatic malignancies using yttrium-90 microsphere brachytherapy: a consensus panel report from the radioembolization brachytherapy oncology consortium. *Int J Radiat Oncol Biol Phys* 2007;**68**:13-23.
73. Dezarn WA, Cessna JT, DeWerd LA, et al; American Association of Physicists in Medicine. Recommendations of the American Association of Physicists in Medicine on dosimetry, imaging, and quality assurance procedures for 90Y microsphere brachytherapy in the treatment of hepatic malignancies. *Med Phys* 2011;**38**:4824-4845.
74. Salem R, Lewandowski RJ, Mulcahy MF, et al. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. *Gastroenterology* 2010;**138**:52-64.
75. Hilgard P, Hamami M, Fouly AE, et al. Radioembolization with yttrium-90 glass microspheres in hepatocellular carcinoma: European experience on safety and long-term survival. *Hepatology* 2010;**52**:1741-1749.
76. Mazzaferro V, Sposito C, Bhoori S, et al. Yttrium-90 radioembolization for intermediate-advanced hepatocellular carcinoma: a phase 2 study. *Hepatology* 2013;**57**:1826-1837.
77. Sangro B, Iñarrairaegui M, Bilbao JI. Radioembolization for hepatocellular carcinoma. *J Hepatol* 2012;**56**:464-473.
78. Pitton MB, Kloeckner R, Ruckes C, et al. Randomized comparison of selective internal radiotherapy (SIRT) versus drug-eluting bead transarterial chemoembolization (DEB-TACE) for the treatment of hepatocellular carcinoma. *Cardiovasc Intervent Radiol* 2015;**38**:352-360.
79. Sangro B, Carpanese L, Cianni R, et al; European Network on Radioembolization with Yttrium-90 Resin Microspheres (ENRY). Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. *Hepatology* 2011;**54**:868-878.
80. Lewandowski RJ, Mulcahy MF, Kulik LM, et al. Chemoembolization for hepatocellular carcinoma: comprehensive imaging and survival analysis in a 172-patient cohort. *Radiology* 2010;**255**:955-965.
81. Wright CL, Werner JD, Tran JM, et al. Radiation pneumonitis following yttrium-90 radioembolization: case report and literature review. *J Vasc Interv Radiol* 2012;**23**:669-674.
82. Theysohn JM, Schlaak JF, Müller S, et al. Selective internal radiation therapy of hepatocellular carcinoma: potential hepatopulmonary shunt reduction after sorafenib administration. *J Vasc Interv Radiol* 2012;**23**:949-952.
83. Abdelmaksoud MH, Hwang GL, Louie JD, et al. Development of new hepaticoenteric collateral pathways after hepatic arterial skeletonization in preparation for yttrium-90 radioembolization. *J Vasc Interv Radiol* 2010;**21**:1385-1395.
84. Lam MG, Banerjee S, Louie JD, et al. Root cause analysis of gastroduodenal ulceration after yttrium-90 radioembolization. *Cardiovasc Intervent Radiol* 2013;**36**:1536-1547.
85. Riaz A, Lewandowski RJ, Kulik LM, et al. Complications following radioembolization with yttrium-90 microspheres: a comprehensive literature review. *J Vasc Interv Radiol* 2009;**20**:1121-1130; quiz 1131.
86. Gil-Alzugaray B, Chopitea A, Iñarrairaegui M, et al. Prognostic factors and prevention of radioembolization-induced liver disease. *Hepatology* 2013;**57**:1078-1087.
87. Atassi B, Bangash AK, Lewandowski RJ, et al. Biliary sequelae following radioembolization with Yttrium-90 microspheres. *J Vasc Interv Radiol* 2008;**19**:691-697.
88. Wilhelm S, Carter C, Lynch M, et al. Discovery and development of sorafenib: a multikinase inhibitor for treating cancer. *Nat Rev Drug Discov* 2006;**5**:835-844.
89. Llovet JM, Ricci S, Mazzaferro V, et al; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;**359**:378-390.
90. Llovet JM, Decaens T, Raoul JL, et al. 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**:3509-3516.
91. Cheng AL, Kang YK, Lin DY, et al. Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized phase III trial. *J Clin Oncol* 2013;**31**:4067-4075.
92. Cainap C, Qin S, Huang WT, et al. Linifanib versus Sorafenib in patients with advanced hepatocellular carcinoma: results of a randomized phase III trial. *J Clin Oncol* 2015;**33**:172-179.
93. Venepalli NK, Goff L. Targeting the HGF-cMET Axis in Hepatocellular Carcinoma. *Int J Hepatol* 2013;**2013**:341636.
94. Makarova-Rusher OV, Medina-Echeverz J, Duffy AG, Greten TF. The yin and yang of evasion and immune activation in HCC. *J Hepatol* 2015;**62**:1420-1429.
95. Mahoney KM, Freeman GJ, Mcdermott DF. The next immune-checkpoint inhibitors: PD-1/PD-L1 blockade in melanoma. *Clin Ther* 2015;**37**:764-782.
96. Calderaro J, Rousseau B, Amaddeo G, et al. Programmed death ligand 1 expression in hepatocellular carcinoma: relationship with clinical and pathological features. *Hepatology* 2016;**64:**2038-2046.