# Choice of Intra-arterial Therapy for Hepatocellular Carcinoma: Evidence and Future Horizons

Mansur A. Ghani, BS[1] Vinayak Thakur, MD[1] Jean-François Geschwind, MD[1]

[1] Department of Radiology and Biomedical Imaging, Yale University School of Medicine, New Haven, Connecticut

Dig Dis Interv 2017;1:105–114.

**Address for correspondence** Jean-François Geschwind, MD, Department of Radiology and Biomedical Imaging, Yale University School of Medicine, 333 Cedar Street, TE 2-230, New Haven, CT 06520 (e-mail: jeff.geschwind@yale.edu).

## Abstract

Hepatocellular carcinoma is the second most common cause of cancer-related deaths worldwide. Along with viral and alcoholic hepatitis, obesity is the leading cause for increasing incidence in the western world, specifically in the United States. As most patients initially present with intermediate to advanced stage disease, curative therapies such as ablation, surgical resection, or liver transplantation cannot usually be applied. Thus, intra-arterial therapies (IATs), such as transarterial chemoembolization (TACE), have become a mainstay of treatment. Several variations of transarterial embolotherapy, such as bland transarterial embolization or drug-eluting bead TACE, are currently available and used in clinical practice. Yttrium-90 radioembolization is a distinct IAT that relies on delivery of radiation to surrounding tissue for tumor death. However, no clear guidelines or evidence exist that would favor one of these options over the other, leaving the decision-making process open to influence by local expertise and experience. In addition, combining TACE with systemic antiangiogenic agents, such as the multityrosine kinase inhibitor sorafenib, has been investigated in several prospective clinical trials without clearly demonstrating substantial survival benefits of the combination over TACE alone. This review will summarize and discuss the available clinical evidence and indications for each treatment modality with the goal of facilitating clinical decision-making processes, and provide an overview of the ongoing efforts to compare different IAT modalities.

**Keywords**
- intra-arterial therapy
- HCC
- cTACE
- TAE
- DEB-TACE

Hepatocellular carcinoma (HCC) is the fifth most common malignancy in males and the seventh in females.[1] This disease carries a dismal prognosis, and is the second most common cause of cancer-related deaths worldwide.[2] The incidence of HCC is rising worldwide and has almost tripled in the past three decades in the United States.[3] Most patients with HCC are diagnosed with disease that is not amenable to curative treatment options, such as ablation, liver transplantation, or surgical resection.[4] In response, there have been advances in several image-guided, catheter-based intra-arterial therapies (IATs) such as transarterial embolization (TAE), transarterial chemoembolization (TACE), drug-eluting beads TACE (DEB-TACE), and yttrium-90 (Y90) radioembolization.[5] IATs have been adopted into consensus treatment algorithms due to advantages over most systemic therapies; they mitigate drug toxicity and yield more robust local tumor control by targeting the most arterially supplied tumor tissue while sparing nontumoral liver parenchyma which is mainly fed through the portal vein.[6] Irrespective of what chemotherapeutic agent is delivered, embolization is considered a critical step, achieving necrosis through ischemic insult.[7] In turn, however, this also causes a hypoxic

**received**
December 17, 2016
**accepted after revision**
May 11, 2017
**published online**
June 12, 2017

**Issue Theme** Hepatocellular Carcinoma; Guest Editors, Ron C. Gaba, MD, and R. Peter Lokken, MD, MPH.



**DOI** https://doi.org/10.1055/s-0037-1603891.
**ISSN** 2472-8721.

tumor microenvironment, which stimulates the upregulation of neoangiogenic pathways soon after embolization. The subsequent expression and secretion of vascular endothelial growth factor (VEGF) leads to rebound neovascularization, tumor progression, and ultimately reduced overall survival (OS).[8,9] With the advent of molecular targeted agents that are able to specifically target proangiogenic molecules and pathways, combining such systemic therapies with IATs was supported by a clear biological rationale to prevent post-embolization recurrence. Sorafenib, a multityrosine kinase inhibitor with a strong antiangiogenic activity, was chosen by most investigators primarily because this drug was the only agent to significantly prolong patient survival when given as a monotherapy.[10,11]

In this review, we provide a brief update on TACE, TAE, DEB-TACE, and Yttrium-90 (Y-90) radioembolization, and discuss potential benefits of each modality. Additionally, we summarize the evidence for the role of sorafenib in combination with each of these therapies. Finally, future directions and unmet needs are discussed.

## Transarterial Chemoembolization

Conventional TACE (cTACE) was introduced more than 30 years ago.[12] cTACE delivers an emulsion of conventional chemotherapeutic agents carried by Lipiodol to the tumor-feeding artery. Lipiodol is an iodinated poppy seed oil-based medium that works at once as an effective drug carrier, tumor-seeking embolic agent, and contrast agent which is easily visualized under fluoroscopy and by computed tomography (CT), helping to confirm targeting and complete tumor coverage.[13] Additionally, it can remain within tumor nodules for weeks because of the absence of Kupffer's cells and inherent hypervascularity of HCC, and penetrate distally into the capillary bed, reaching the tumor portions invading the venous blood vessels.[14] No cTACE chemotherapy regimen is universally accepted for HCC; however, cisplatin, doxorubicin, and mitomycin C are typically employed.[15] While only a few studies have investigated the optimal drug cocktail, this trio has been shown to have a higher response rate and lower rates of tumor progression compared with doxorubicin alone.[16] However, in one recent study, doxorubicin alone was shown to demonstrate longer mean OS compared with triple-drug therapy, possibly due to decreased toxicities associated with single-drug therapy.[17] The subsequent administration of embolic material, such as Gelfoam, polyvinyl alcohol (PVA) particles, or trisacryl gelatin (TG) microspheres, causes stasis in segmental and subsegmental arterial branches, more effectively preventing washout of the previously administered chemotherapy-lipiodol emulsion.[18] Gelfoam is a biodegradable gelatin sponge that is safe and effective for the occlusion of larger blood vessels.[19] However, this has mostly been replaced by nonbiodegradable TG microspheres which can occlude very distal tumor-supplying blood vessels.[20] While no consensus exists about the number of cTACE procedures that are needed to achieve satisfactory treatment, at least two sessions should be performed before treatment is abandoned or alternative therapies are considered.[21] Multiple TACE procedures can be administered either at regular intervals (on schedule) or when there is poor tumor response or disease progression (on demand).[22] On-schedule TACE should provide the greatest opportunity for tumor necrosis; however, repeated chemotherapy insults may precipitate liver atrophy and vascular damage.[23,24] On the other hand, while an on-demand treatment schedule may risk undertreatment, it allows for proper patient selection each cycle and minimizes liver toxicity and complications.[24] Current consensus guidelines recommend an on-demand treatment schedule.[22] Patients are typically followed up 6 weeks after the procedure for clinical, blood work, and cross-sectional imaging evaluation. Contraindications to cTACE and most common toxicities are summarized in ►**Table 1**.[25,26]

TACE is usually considered in patients who are not eligible for curative resection or ablation, and have Barcelona Clinic Liver Cancer (BCLC) class B or intermediate-stage (Hong Kong Liver Combined Liver Cancer or HKCLC Stage IIIa/IIIb) disease.[27] Studies have shown improved survival in patients with Child-Pugh class A disease and albumin level greater than 3.4 g/dL when treated with TACE in comparison with those with Child-Pugh class B or C disease. However, laboratory data are not solely used in any exclusion criteria.[28]

Early studies casted doubt on the benefit of cTACE in patients with unresectable HCC. Four randomized controlled trials (RCTs) did not show any survival benefit of cTACE versus best supportive care.[21,29,30] However, in 2002, two RCTs clearly demonstrated the survival benefit of cTACE over symptomatic treatment in selected HCC patients who were not eligible for surgical therapy.[31,32] These two studies, along with a systematic review of RCTs,[33] led to the inclusion of cTACE into the official treatment guidelines for HCC and endorsement by the American Association for the Study of the Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL).[15,34] After the introduction of cTACE, the median OS for intermediate-stage HCC patients increased from approximately 16 to 20 months, establishing this treatment modality as the standard of care.[33] More recently, the BRISK trial, a Phase III RCT, achieved an OS of 26.1 months in mostly intermediate-stage patients treated with cTACE.[35]

Portal vein invasion classifies a patient as advanced stage according to the BCLC classification and no IAT is recommended. However, several noncontrolled studies of patients with portal vein thrombosis (PVT) treated with cTACE have shown a potential benefit in survival compared with best supportive care.[36–38] In one recent study, cTACE patients who matched the SHARP trial inclusion criteria for advanced HCC had a median OS of 8.1 months. This was similar to the life expectancy of comparable patients treated with sorafenib within the SHARP trial, but showed a better toxicity profile.[39] In another study of 508 BCLC C patients treated with cTACE, median OS was 11.9 months.[40] As a comparison, OS in advanced-stage HCC patients treated with sorafenib ranged from 5 to 10.7 months.[10,41] Subgroup analysis of low-risk advanced-stage patients demonstrated even better

**Table 1** Main contraindications to cTACE and common toxicities

| Relative contraindications | Absolute contraindications | Most common adverse events | Rare adverse events |
|---|---|---|---|
| Diffuse tumor burden involving >50% of liver | ECOG performance status >2 | Postembolization syndrome (fever, pain, nausea, transaminitis, vomiting) | Biloma |
| Segmental or branch PVT | Severely reduced portal flow by branch or main PVT | | Abscess formation |
| Extrahepatic metastases | Active systemic infection | | Cholecystitis |
| Ascites | Uncorrectable bleeding disorder | | Arterial dissection |
| Serum bilirubin >3 ng/dL | Uncorrectable contrast medium sensitivity | | Hepatic failure |
| Lactate dehydrogenase >425 U/L | Leukopenia | | Gastrointestinal bleed |
| AST and ALT >5 × upper limit of normal | Renal insufficiency (creatinine clearance <30 mL/min) | | |
| Biliary obstruction | Hepatic encephalopathy | | |
| Severe uncorrectable thrombocytopenia (<50,000/μL | | | |
| Recent variceal bleeding | | | |
| Intractable arteriovenous fistula | | | |
| Right-to-left cardiopulmonary shunting | | | |

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; cTACE, conventional transarterial chemoembolization; PVT, portal vein thrombosis.

outcomes as compared with systemic therapy. Thus, there are significant indications that treatment guidelines should be re-evaluated, and cTACE considered as an option for advanced-stage patients.

## Drug-Eluting Beads–Transarterial Chemoembolization

Polymer-based DEBs were developed with the hopes of delivering higher concentrations of chemotherapy to the tumor while improving systemic toxicities caused by cTACE.[42] The pharmacodynamic benefits of this technique led to a shift away from cTACE toward DEB-TACE in the treatment of patients with HCC, especially in the United States and Europe.[43,44] Two major types of drug-eluting microspheres are available (DC/LC Beads made by BTG International, London, UK, and Quadraspheres/HepaSpheres made by Merit Medical Systems Inc., South Jordan, UT), but both are approved as embolic material, not a drug delivery system. Although these microspheres can be loaded with several ionic agents, doxorubicin (DEBDOX) is the most commonly used in the treatment of HCC.[45,46] Most clinical trials utilize DC beads, which are made of non-biodegradable materials, such as PVA and are soft, compressible, spherical particles. They range in size from 75 to 900 μm. The smaller bead diameters achieve a more distal embolization and more extensive necrosis as compared with larger beads.[47] The use of small caliber beads (100–300 μm) in tumors of less than 6 cm was not associated with an increase in liver toxicity or complications when compared with larger beads (300–500 μm).[48] Recently, even smaller beads called M1 (LC Bead M1; BTG International) have been developed which are 70 to 150 μm in diameter. In animal models, LC Bead M1 demonstrates greater tumor penetration and drug delivery than larger beads, with a similar pharmacokinetic profile.[49] They also have a favorable short-term safety profile and demonstrate promising results in terms of objective response, tumor down-staging, and necrosis.[50] An ongoing clinical trial is currently assessing the feasibility and safety of doxorubicin-eluting LC Bead M1 for HCC (NCT 02007954).

The drug uptake of the DEBs occurs through an ion-exchange mechanism. Pharmacokinetic studies have demonstrated that drug elution occurs gradually and only in an ionic environment once the microspheres are delivered to the tumor. Several in vitro and animal experiments demonstrated the continuous release of doxorubicin from DC beads to the tissue.[42,51] Most of the drug is eluted over the first 24 hours, but higher local drug concentrations and longer drug–tumor contact may allow targeting of more resistant tumor cell populations. Furthermore, histopathological analysis found a high efficiency of DEB-mediated drug delivery and release to the tumor tissue, causing local coagulative necrosis and an inflammatory fibrotic reaction.[52]

In clinical practice, DEB-TACE has the same indications and contraindications as cTACE (►**Table 1**). In 2007, Varela et al investigated the safety, pharmacokinetics, and efficacy

of DC Bead loaded with doxorubicin (DEBDOX; 500–700 μm) in 527 patients with HCC (Child–Pugh A, BCLC B).[53] The procedure was well tolerated; postembolization syndrome was observed in 37% of patients after the first DEB-TACE, and only 18% after the second. Two patients developed liver abscesses. Of note, peak plasma concentrations of doxorubicin were significantly lower compared with those measured in cTACE. In the same year, results of a combined Phase I/II study in more than 500 HCC Child-Pugh A patients were reported.[54] In the Phase I trial, the dose was escalated from 25 to 150 mg of doxorubicin, and showed no dose-limiting toxicity. The Phase II trial showed an objective response in 70% of the patients according to the modified response evaluation criteria in solid tumors (mRECIST). Six patients had treatment-related complications. In 2008, similar results were reported in an open-label, single-center, single-arm study including 62 patients with unresectable HCC.[55] Patients received up to three sessions of DEBDOX (300–500 μm). At 9-month follow-up, the objective response was 80.7%. All patients reported postembolization symptoms, although severe procedure-related complications were observed in only 3.2%. The first prospective Phase II pilot study evaluating the safety and efficacy of DEBDOX (100–300 or 300–500 μm) in the United States included 20 patients (Child–Pugh A, 75%; BCLC C, 60%).[44] Only 10% experienced grade III toxicities. Objective response at 1 month was 60% (EASL) and disease control at 6 months was 95% (RECIST). More importantly, this study reported encouraging outcomes in patients with more advanced disease with a median progression-free survival (PFS) of 13 months and OS of 26 months. Two studies in 2012 demonstrated unparalleled outcomes in HCC patients with early-and intermediate-stage disease. In one study, 173 HCC patients had a mean OS of 43.8 months;[56] in the other study, 104 HCC patients had a median OS of 48.6 months.[57]

The safety and survival outcomes of DEB-TACE in patients with advanced-stage HCC have also been investigated. Two retrospective studies combining 201 patients (Child–Pugh A/B: 123/78, BCLC C: 100%, Eastern Cooperative Oncology Group [ECOG] score 0/1/2: 22/139/40) reported 19 patients with grade III toxicities.[58,59] Neither grade IV toxicities nor 30-day mortality was observed. Similar median OS was obtained with 13.3 and 13.5 months, respectively.[58,59] Because most clinical studies regarding DEB-TACE have used DC Bead, doxorubicin-loaded HepaSphere microspheres have less clinical validation, but similar results to DC Bead have been shown.[60,61]

A prospective randomized multicenter trial of 212 patients across Europe (PRECISION V) compared efficacy and safety of DEB-TACE using DEBDOX to cTACE.[43] Although response rates were higher in the DEB-TACE group, this study failed to show any statistically significant difference in efficacy compared with cTACE in the entire study population. However, patients with more advanced (ECOG 1, BCLC B, bilobar lesions) and recurrent disease showed better objective response when treated with DEB-TACE. With a significant decrease in liver toxicity and doxorubicin-related adverse events, this trial confirmed the better tolerability profile of DEB-TACE over cTACE. Similarly, an RCT of 177 patients undergoing either DEB-TACE or cTACE found no difference in safety or efficacy, but cTACE was associated with more frequent and severe postprocedural abdominal pain.[62] In a retrospective study, Song et al reported a better treatment response in patients who received DEBDOX versus cTACE with no differences in treatment-related liver toxicity.[63] Longer time to progression (TTP) and better OS were also seen with DEBDOX. In a recent meta-analysis, DEB-TACE increased the tumor complete response rate, OS rate, and survival time with less common adverse events. However, DEB-TACE has similar partial response rate, objective response rate, disease control rate, and serious adverse events, compared with cTACE.[64]

Despite some promising results, DEB-TACE has not yet fulfilled the promised benefits over cTACE. Recently, this has led to another shift back to cTACE, especially since the considerable expense of DEB-TACE is not justified by outcomes. Another important factor is that while Lipiodol in cTACE is easily visualized, DEB-TACE is radiolucent. In light of the growing importance of intraprocedural imaging biomarkers for embolization endpoints and deposition control, the imageability of Lipiodol represents a major advantage over non-imageable DEBs. In response, LC Bead LUMI (BTG International), which is a radiopaque imageable microsphere labeled with iodine that can be visualized by fluoroscopy and CT, was developed. Compared with conventional beads, LUMI beads have demonstrated better real-time geographic localization to determine target and nontarget embolization in preclinical studies[65] and early case reports.[66] The imaging characteristics of LUMI beads are now studied in an ongoing clinical trial of hepatic tumors (NCT 02649868). However, it is not yet clear if this or other advancements will be enough to establish DEB-TACE as a superior treatment modality over cTACE.

## Transarterial Embolization

In TAE, embolic agents are deposited without a prior or consecutive chemotherapy dose. Bead Block (BTG, London, Great Britain) is among the most commonly used embolic device in TAE. The most common sizes used are in the 100–300 μm and 300–500 μm ranges; however, larger microspheres can be used if stasis is not achieved.[67] Some investigators operate according to the hypothesis that the ischemic insult induced by embolization may be sufficient to cause tumor cell death, and the addition of chemotherapeutic agents may thus contribute unnecessary toxicity, while not providing the crucial tumoricidal effect. As with cTACE, the technique for TAE varies among individuals and institutions. The main embolization endpoint in TAE is complete stasis of the tumor-feeding vessels to achieve ischemia-induced death of the tumor cells using embolic agents varying in size and physical capabilities. TAE has similar patient selection criteria to those for TACE and mostly includes BCLC class B disease or intermediate-stage (HKLC Stage IIIa/IIIb) disease, and there are no TAE-specific laboratory exclusion criteria. Similar absolute and relative contradictions exist for TAE as with TACE (►**Table 1**). With the exception that chemotherapy-related side effects (e.g.,

alopecia) are not seen with TAE, complications for TAE are similar to those for TACE. In addition, the presence of hepatic arterial-systemic venous shunts in patients undergoing small-particle TAE using 40- to 120-μm tris-acryl gelatin microspheres has resulted in fatal pulmonary vessel blockade. Pancreatitis, pulmonary edema, and cardiac arrhythmias also have been reported.[68]

In 1998, a very large prospective single-center RCT compared TAE ($n = 540$) with best supportive care ($n = 540$) in patients with unresectable HCC. While a partial response of 55% was observed in the TAE group, there was no benefit in survival compared with untreated patients.[69] In 2008, a single-arm retrospective analysis of 322 patients treated with TAE was conducted and the median OS was 21 months (16–26 months).[68] The 1-, 2-, and 3-year survival rates were 66, 46, and 33%, respectively. In the absence of PVT or extrahepatic disease, the median survival was 40 months (31–52 months) and the 1-, 2-, and 3-year survival rates were 84, 66, and 51%, respectively. These promising results heightened the need for an RCT. Marelli et al compared three RCTs and concluded that TACE did not demonstrate a survival benefit compared with TAE.[26] Similarly, a meta-analysis of RCTs conducted by Xie et al[70] found that 6-, 9-, 12-, 24-, and 36-month OS of the TACE group was not significantly different than that of the TAE group.

Comparisons between TAE and DEB-TACE have not demonstrated significant differences between these therapies. In 2010, an RCT was performed that compared TAE (Bead Block, 100–300 and 300–500 μm) in 43 patients with DEB-TACE (DC Bead, 100–300 and 300–500 μm) in 41 patients with intermediate-stage HCC.[71] Patients were randomized by tumor size and treated every 2 months, up to three procedures. Complications were similar in both groups. DEB-TACE did yield a better local tumor response with higher response rates at 6, 9, and 12 months, and reached statistical significance at 9 months. DEB-TACE had fewer recurrences at 9 and 12 months and longer TTP compared with TAE ($10.6 \pm 2.7$ vs. $9 \pm 2.3$ months, respectively). However, the short 12-month follow-up makes it difficult to draw definitive conclusion from this data. A Phase II study comparing 51 patients treated with TAE (Bead Block) versus 50 patients treated with DEB-TACE (LC Beads—150 mg doxorubicin) was recently published.[67] No difference in adverse events, response or disease control rate, PFS, or OS (6.2 vs. 2.8 months [$p = 0.11$] and 19.6 vs. 20.8 months [$p = 0.64$] for TAE and DEB-TACE, respectively) were found between both groups. However, there are several notable issues with the trial design. First, stasis was chosen as the embolization endpoint, which precluded retreatment. It also potentially induced hypoxia, likely contributing to the very short PFS (6.2 months for DEB-TACE vs. 2.8 months for TAE). Second, Bead Block microspheres were used in the DEB-TACE arm to achieve stasis instead of LC Beads as recommended in DEB-TACE. This drastically minimized the true technological difference between DEB-TACE and TAE and made the results difficult to generalize in a clinical context. Third, as the authors acknowledged, the study may not have had enough power to detect small to moderate differences in outcome. Therefore, it is too early to conclude that TAE is truly equal to DEB-TACE.

These results demonstrate that TAE by itself has a clear antitumor effect and suggest that the main driver of tumor toxicity in IATs is ischemia through embolization. However, further studies are needed to evaluate TAE in comparison to other catheter-based therapies before abandoning the added chemotherapy. Indeed, a large potential difference between TAE and cTACE/DEB-TACE may be among patients with portal vein thrombus (BCLC C), where the ischemic insult may not be sufficient to improve survival alone,[69] and chemotherapy is necessary to cover the PVT. These patients are often excluded in studies of TACE,[26,68] while increasing evidence is suggesting efficacy of cTACE[36–39] and DEB-TACE[58,59] in this population. These patients should be the target population of future prospective studies comparing these modalities.

## Radioembolization

Yttrium-90 radioembolization involves delivery to the tumor of radioactive microspheres that emit β-radiation to the surrounding tissue. TheraSphere (MDS Nordion), where Y-90 is an integral constituent of the glass, and SIR-Sphere (Sirtex), where Y-90 is directly bound to the resin, are the two most common radioembolic agents that are used.[72] Patients who are not candidates for surgical resection and have life expectancies longer than 3 months should be considered for radioembolization. Contraindications include the presence of pulmonary shunts that potentially allow more than 30 Gy of radiation to be delivered to the lungs or extrahepatic blood flow to the gastrointestinal tract that cannot be corrected with catheter embolization, total serum bilirubin greater than 2 mg/dL, severely reduced portal vein flow, and poor hepatic reserve.[73] The utilization of radiation leads to toxicities of radioembolization that are distinct from TACE and TAE, including portal hypertension, radiation pneumonitis, gastrointestinal ulcers, and radiation-induced liver disease. As with TACE and TAE, postembolization syndrome and abscess are possible toxicities as well.[74]

Determining the relative efficacy of radioembolization compared with other IATs is currently an area of intense investigation. In a nonrandomized cohort comparison, Lewandowski et al found that radioembolization was superior to cTACE for downstaging of disease (58% vs. 31%).[75] A recent randomized phase 2 study of patients with BCLC stages A or B HCC found that Y-90 radioembolization gave a significantly longer time to progression (TTP) than cTACE (>26 months vs. 6.8 months; $p = 0.0012$), but OS was not different.[76] However, criticisms of this study include the challenge of comparing tumor progression criteria between radioembolization and cTACE, a relatively small sample size that may not be representative of patients most commonly eligible for IAT, and a short follow-up period.[77,78] Direct comparisons of radioembolization with TAE or DEB-TACE are even more sparse. However, a meta-analysis comparison of DEB-TACE and radioembolization demonstrated a one-year survival benefit of DEB-TACE, but not at two or three years.[79] While recent trials

have generated important results on the efficacy of radioembolization compared with other IATs, a clear consensus has yet to be reached, and future studies will hopefully add clarity to this.

## Sorafenib/IAT Combination Therapy

Sorafenib in combination with IATs could be a promising strategy in advanced-stage HCC treatment. The high rate of HCC recurrence after TACE may be due to its enhancement of angiogenesis and upregulation of VEGF and platelet-derived growth factor receptor expression. Therefore, combination of antiangiogenic agents with TACE could potentially decrease the recurrence of HCC and improve survival. A Phase III study has been conducted in Japan and Korea using TACE with sorafenib versus TACE alone. However, combination therapy failed to show any benefit in terms of TTP (sorafenib vs. placebo 5.4 vs. 3.7 months) or OS.[80] A Phase II study investigated safety and efficacy of sorafenib with DEB-TACE treatment, and demonstrated an objective response of 58% according to EASL criteria and mostly minor toxicities.[81] The results of the SPACE trial comparing sorafenib and placebo in patients undergoing TACE revealed the combination of sorafenib with DEB-TACE was technically feasible, but the combination did not improve TTP in a clinically meaningful manner.[82] This result is in part due to the conservative TACE treatment protocol used in the study in which more than one-third of the patients in the experimental group received only one TACE. Furthermore, a greater proportion of non-Asian patients in the sorafenib arm received only one TACE (42 vs. 18% in placebo arm), while TACE among Asian patients was more equally distributed. This heterogeneity may have contributed to the similar outcomes in the two groups, especially considering that greater TTP and a trend toward increased OS were observed in the Asian patients. Finally, median OS, the ultimate endpoint in cancer research, was not reached in either group.[52]

The GIDEON study is so far the only prospective registry that evaluated the impact of liver function in a large cohort of patients (>3,000) treated with TACE in conjunction with sorafenib.[83] In the final analysis, overall adverse events were similarly observed in both Child A and B patients, but a significant increase in serious adverse events was found in the Child B group. Patients with concomitant use of TACE and sorafenib achieved an OS of 22 months, in comparison to 10 months in nonconcomitant TACE patients, lending evidence, albeit indirectly, of improved outcomes of combination therapy. However, future RCTs are needed to determine with confidence the benefit of sorafenib in combination with both cTACE and DEB-TACE.

Radioembolization is also associated with a mild increase in angiogenic markers, suggesting a role for sorafenib in conjunction with radioembolization as well.[84] There does not seem to be additional adverse effects of radioembolization and sorafenib compared with sorafenib alone.[85,86] However, Vouche et al found that the addition of sorafenib did not augment radiological and pathological response to Y-90 therapy.[87] An area of ongoing investigation assessed whether radioembolization plus sorafenib is superior in advanced HCC (BCLC stage C) where sorafenib alone is the standard of care. Large RCTs comparing the efficacy of combining sorafenib and Y-90 therapy versus sorafenib alone, such as the SORAMIC study (NCT01126645), are in progress to elucidate this question.

## Future Horizons

With the development of new drugs, improvement of IAT drug delivery techniques, and knowledge of liver cancer biology, the future of IATs is promising. These therapies in combination with other treatment modalities such as ablation or systemic therapies may have great potential. TACE has been combined with RFA for the treatment of HCC and a recent meta-analysis demonstrated the benefits of this approach.[88] The combination of TACE with other strategies will continue to evolve.

Novel embolic materials are currently being developed and may improve efficacy of IATs. One approach currently under investigation is degradable starch microspheres (DSMs). Since the extended ischemia caused by permanent occlusion of blood flow, such as with Lipiodol or DEBs, may induce new tumor vessel growth via VEGF upregulation, only transient obstruction is desirable.[89] DSMs, such as EmboCept (PharmaCept, Berlin, Germany), achieve this through degradation by serum α-amylase, and have a half-life that ranges from 15 to 50 minutes.[90,91] Early studies show this is a safe and effective option, even achieving downstaging of disease in some patients.[92] Calibrated drug-eluting microspheres, such as Embozene TANDEM and Oncozene (Boston Scientific, Marlborough, MA), is another approach being developed. These microspheres are as small as 40 µm, and vary by less than 10 µm, maintaining their size after drug loading. In comparison, the smallest DC Bead M1 is 70 to 150 µm. Animal studies demonstrate that this allows for a larger number of small-size drug-eluting microspheres to penetrate deeply into the targeted tissue with more uniform drug coverage.[93,94]

The evaluation of treatment response after IAT is key for the continued improvement of current treatment. The survival-based endpoints traditionally used in clinical studies have largely been replaced by radiologic objective response as a surrogate endpoint. Most liver tumors exhibit heterogeneous pattern of necrosis after catheter-based treatments and sometimes make current response assessment criteria less conclusive.[95] While conventional response criteria assessing size-based changes in the tumor (World Health Organization response criteria and RECIST) have shown their limitations compared with contrast enhancement-based criteria (EASL and mRECIST),[96,97] new response criteria using three-dimensional (3D) quantitative approaches are being evaluated and may serve to improve treatment assessment.[98,99]

Understanding the molecular biology of cancer is crucial in the development of therapies. Thus, continued experimental research is fundamental and significant resources should go into translating basic scientific findings into

therapeutic options for patients. Dynamic multiphase contrast-enhanced CT and magnetic resonance imaging have achieved unparalleled accuracy in the diagnosis of HCC in the presence of a cirrhotic liver, supplanting biopsy in diagnosis. However, the collection of tissue samples in future research still has a role: to better understand liver cancer molecular biology and identify new molecular targets.

A personalized medicine approach is likely to develop in the near future. Nanotechnology has great potential to allow drugs to be attached to tumor specific cells, and promises to be a highly efficient method of drug delivery and gene therapy. In addition, new classes of drugs such as 3-bromopyruvate (which specifically targets tumor metabolism) delivered intra-arterially could be more potent than conventional chemotherapeutic agents, and is a very promising new approach.[100] Imaging modalities such as cone beam CT will be further refined allowing for a more comprehensive utilization of 3D imaging technology in the interventional suite. Moreover, image fusion techniques and software identifying tumor-feeding arteries[101] will undoubtedly make treatment more precise and further improve clinical outcomes for patients.

Intelligently conceived and designed clinical trials will be the cornerstone of IAT development and help broaden the application of established therapeutic modalities for the treatment of HCC. IAT should be expanded to both early-stage disease and more advanced stages, for which sorafenib is currently the only officially recommended treatment. These future studies will require higher quality and greater numbers of prospective RCTs with OS as the final endpoint.

## Conclusion

Over the past three decades, catheter-based embolotherapies have revolutionized the treatment of HCC. Level IA evidence for the existence of survival benefits from cTACE led to the recognition of catheter-based therapies in the management of patients with unresectable HCC and the incorporation of TACE into official staging systems and treatment guidelines. cTACE remains the standard of care in HCC patients with intermediate-stage disease (BCLC B), with increasingly broader indications in advanced-stage disease (BCLC C), for downstaging purposes and as a bridge to transplantation. The failure of currently available DEB technologies to fulfill the initial promise of better TACE outcomes through improved targeting has triggered a resurrection of the cTACE protocol throughout the western world. However, it may very well be that novel technologies such as smaller generations of radiopaque DEBs in combination with advanced intraprocedural cone-beam CT imaging will achieve the goal of substantially improving TACE therapy. Y-90 radioembolization has also proven to be a formidable competitor to TACE, but further study is needed to make definite conclusions of relative efficacy. As for the combination of locoregional and systemic therapies, sorafenib has achieved only marginal improvements over IAT alone and the available data appear to be inconclusive. Therefore, future rigorously designed, large-scale RCTs are needed to determine the optimal treatment algorithms for treatment of patients with HCC.

Grant Support
This study was funded by grant number NIH/NCI R01 CA206180.

## References

1 El-Serag HB. Hepatocellular carcinoma. N Engl J Med 2011; 365(12):1118–1127
2 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(05):E359–E386
3 El-Serag HB, Kanwal F. Epidemiology of hepatocellular carcinoma in the United States: where are we? Where do we go? Hepatology 2014;60(05):1767–1775
4 Arciero CA, Sigurdson ER. Liver-directed therapies for hepatocellular carcinoma. J Natl Compr Canc Netw 2006;4(08):768–774
5 Lewandowski RJ, Geschwind JF, Liapi E, Salem R. Transcatheter intraarterial therapies: rationale and overview. Radiology 2011; 259(03):641–657
6 Benson AB III, Abrams TA, Ben-Josef E, et al. NCCN clinical practice guidelines in oncology: hepatobiliary cancers. J Natl Compr Canc Netw 2009;7(04):350–391
7 Mannelli L, Kim S, Hajdu CH, Babb JS, Clark TW, Taouli B. Assessment of tumor necrosis of hepatocellular carcinoma after chemoembolization: diffusion-weighted and contrast-enhanced MRI with histopathologic correlation of the explanted liver. AJR Am J Roentgenol 2009;193(04):1044–1052
8 Sergio A, Cristofori C, Cardin R, et al. Transcatheter arterial chemoembolization (TACE) in hepatocellular carcinoma (HCC): the role of angiogenesis and invasiveness. Am J Gastroenterol 2008;103(04):914–921
9 Scartozzi M, Faloppi L, Bianconi M, et al. The role of LDH serum levels in predicting global outcome in HCC patients undergoing TACE: implications for clinical management. PLoS One 2012; 7(03):e32653
10 Llovet JM, Ricci S, Mazzaferro V, et al; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359(04):378–390
11 Cheng A-L, Kang Y-K, Chen Z, et al. 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(01):25–34
12 Yamada R, Nakatsuka H, Nakamura K, et al. Hepatic artery embolization in 32 patients with unresectable hepatoma. Osaka City Med J 1980;26(02):81–96
13 Idée JM, Guiu B. Use of Lipiodol as a drug-delivery system for transcatheter arterial chemoembolization of hepatocellular carcinoma: a review. Crit Rev Oncol Hematol 2013;88(03): 530–549
14 Yumoto Y, Jinno K, Tokuyama K, et al. Hepatocellular carcinoma detected by iodized oil. Radiology 1985;154(01):19–24
15 Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology 2011;53(03):1020–1022
16 Petruzzi NJ, Frangos AJ, Fenkel JM, et al. Single-center comparison of three chemoembolization regimens for hepatocellular carcinoma. J Vasc Interv Radiol 2013;24(02):266–273
17 Mouli SK, Hickey R, Thornburg B, et al. Single- versus triple-drug chemoembolization for hepatocellular carcinoma: comparing outcomes by toxicity, imaging response, and survival. J Vasc Interv Radiol 2016;27(09):1279–1287

18 Brown DB, Gould JE, Gervais DA, et al; Society of Interventional Radiology Technology Assessment Committee and the International Working Group on Image-Guided Tumor Ablation. Transcatheter therapy for hepatic malignancy: standardization of terminology and reporting criteria. J Vasc Interv Radiol 2009; 20(7, Suppl):S425–S434

19 Kim YJ, Lee HG, Park JM, et al. Polyvinyl alcohol embolization adjuvant to oily chemoembolization in advanced hepatocellular carcinoma with arterioportal shunts. Korean J Radiol 2007;8 (04):311–319

20 Laurent A, Beaujeux R, Wassef M, Rüfenacht D, Boschetti E, Merland JJ. Trisacryl gelatin microspheres for therapeutic embolization, I: development and in vitro evaluation. AJNR Am J Neuroradiol 1996;17(03):533–540

21 Pelletier G, Roche A, Ink O, et al. A randomized trial of hepatic arterial chemoembolization in patients with unresectable hepatocellular carcinoma. J Hepatol 1990;11(02):181–184

22 Cheng AL, Amarapurkar D, Chao Y, et al. Re-evaluating transarterial chemoembolization for the treatment of hepatocellular carcinoma: consensus recommendations and review by an International Expert Panel. Liver Int 2014;34(02):174–183

23 Yamashita Y, Torashima M, Oguni T, et al. Liver parenchymal changes after transcatheter arterial embolization therapy for hepatoma: CT evaluation. Abdom Imaging 1993;18(04): 352–356

24 Ernst O, Sergent G, Mizrahi D, Delemazure O, Paris JC, L'Herminé C. Treatment of hepatocellular carcinoma by transcatheter arterial chemoembolization: comparison of planned periodic chemoembolization and chemoembolization based on tumor response. AJR Am J Roentgenol 1999;172(01):59–64

25 Wang S-Y, Zhu W-H, Vargulick S, Lin SB, Meng Z-Q. Nausea and vomiting after transcatheter arterial chemoembolization for hepatocellular carcinoma: incidence and risk factor analysis. Asian Pac J Cancer Prev 2013;14(10):5995–6000

26 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(01):6–25

27 Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999;19(03): 329–338

28 Brown DB, Fundakowski CE, Lisker-Melman M, et al. Comparison of MELD and Child-Pugh scores to predict survival after chemoembolization for hepatocellular carcinoma. J Vasc Interv Radiol 2004;15(11):1209–1218

29 Madden MV, Krige JE, Bailey S, et al. Randomised trial of targeted chemotherapy with lipiodol and 5-epidoxorubicin compared with symptomatic treatment for hepatoma. Gut 1993;34(11): 1598–1600

30 Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire. A comparison of lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. N Engl J Med 1995;332(19):1256–1261

31 Llovet JM, Real MI, Montaña X, et al; Barcelona Liver Cancer Group. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002; 359(9319): 1734–1739

32 Lo C-M, Ngan H, Tso W-K, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002;35(05):1164–1171

33 Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. Hepatology 2003;37(02):429–442

34 European Association for the Study of the Liver; European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56(04):908–943

35 Kudo M, Han G, Finn RS, et al. Brivanib as adjuvant therapy to transarterial chemoembolization in patients with hepatocellular carcinoma: a randomized phase III trial. Hepatology 2014;60 (05):1697–1707

36 Kim KM, Kim JH, Park IS, et al. Reappraisal of repeated transarterial chemoembolization in the treatment of hepatocellular carcinoma with portal vein invasion. J Gastroenterol Hepatol 2009;
24(05):806–814

37 Luo J, Guo R-P, Lai ECH, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma with portal vein tumor thrombosis: a prospective comparative study. Ann Surg Oncol 2011;18(02):413–420

38 Chung GE, Lee J-H, Kim HY, et al. Transarterial chemoembolization can be safely performed in patients with hepatocellular carcinoma invading the main portal vein and may improve the overall survival. Radiology 2011;258(02):627–634

39 Gorodetski B, Chapiro J, Schernthaner R, et al. Advanced-stage hepatocellular carcinoma with portal vein thrombosis: conventional versus drug-eluting beads transcatheter arterial chemoembolization. Eur Radiol 2017;27(02):526–535

40 Zhao Y, Duran R, Chapiro J, et al. Transarterial chemoembolization for the treatment of advanced-stage hepatocellular carcinoma. J Gastrointest Surg 2016;20(12):2002–2009

41 Zhao Y, Wang WJ, Guan S, et al. Sorafenib combined with transarterial chemoembolization for the treatment of advanced hepatocellular carcinoma: a large-scale multicenter study of 222 patients. Ann Oncol 2013;24(07):1786–1792

42 Hong K, Khwaja A, Liapi E, Torbenson MS, Georgiades CS, Geschwind JF. New intra-arterial drug delivery system for the treatment of liver cancer: preclinical assessment in a rabbit model of liver cancer. Clin Cancer Res 2006;12(08):2563–2567

43 Lammer J, Malagari K, Vogl T, et al; 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 (01):41–52

44 Reyes DK, Vossen JA, Kamel IR, et al. Single-center phase II trial of transarterial chemoembolization with drug-eluting beads for patients with unresectable hepatocellular carcinoma: initial experience in the United States. Cancer J 2009; 15(06):526–532

45 Constantin M, Fundueanu G, Bortolotti F, Cortesi R, Ascenzi P, Menegatti E. Preparation and characterisation of poly(vinyl alcohol)/cyclodextrin microspheres as matrix for inclusion and separation of drugs. Int J Pharm 2004;285(1-2):87–96

46 Qian J, Truebenbach J, Graepler F, et al. Application of polylactide-co-glycolide-microspheres in the transarterial chemoembolization in an animal model of hepatocellular carcinoma. World J Gastroenterol 2003;9(01):94–98

47 Gonzalez MV, Tang Y, Phillips GJ, et al. Doxorubicin eluting beads-2: methods for evaluating drug elution and in-vitro:in-vivo correlation. J Mater Sci Mater Med 2008;19(02):767–775

48 Malagari K, Pomoni M, Spyridopoulos TN, et al. Safety profile of sequential transcatheter chemoembolization with DC Bead™: results of 237 hepatocellular carcinoma (HCC) patients. Cardiovasc Intervent Radiol 2011;34(04):774–785

49 Gholamrezanezhad A, Mirpour S, Geschwind JF, et al. Evaluation of 70-150-µm doxorubicin-eluting beads for transcatheter arterial chemoembolization in the rabbit liver VX2 tumour model. Eur Radiol 2016;26(10):3474–3482

50 Spreafico C, Cascella T, Facciorusso A, et al. Transarterial chemoembolization for hepatocellular carcinoma with a new generation of beads: clinical-radiological outcomes and safety profile. Cardiovasc Intervent Radiol 2015;38(01):129–134

51 Lewis AL, Gonzalez MV, Lloyd AW, et al. DC bead: in vitro characterization of a drug-delivery device for transarterial chemoembolization. J Vasc Interv Radiol 2006;17(2, Pt 1):335–342

52 Namur J, Citron SJ, Sellers MT, et al. Embolization of hepatocellular carcinoma with drug-eluting beads: doxorubicin tissue concentration and distribution in patient liver explants. J Hepatol 2011;55(06):1332–1338

53 Varela M, Real MI, Burrel M, et al. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. J Hepatol 2007;46(03):474–481

54 Poon RTP, Tso WK, Pang RWC, et al. A phase I/II trial of chemoembolization for hepatocellular carcinoma using a novel intra-arterial drug-eluting bead. Clin Gastroenterol Hepatol 2007; 5(09):1100–1108

55 Malagari K, Chatzimichael K, Alexopoulou E, et al. Transarterial chemoembolization of unresectable hepatocellular carcinoma with drug eluting beads: results of an open-label study of 62 patients. Cardiovasc Intervent Radiol 2008;31(02):269–280

56 Malagari K, Pomoni M, Moschouris H, et al. Chemoembolization with doxorubicin-eluting beads for unresectable hepatocellular carcinoma: five-year survival analysis. Cardiovasc Intervent Radiol 2012;35(05):1119–1128

57 Burrel M, Reig M, Forner A, et al. Survival of patients with hepatocellular carcinoma treated by transarterial chemoembolisation (TACE) using Drug Eluting Beads. Implications for clinical practice and trial design. J Hepatol 2012;56(06):1330–1335

58 Kalva SP, Pectasides M, Liu R, et al. Safety and effectiveness of chemoembolization with drug-eluting beads for advanced-stage hepatocellular carcinoma. Cardiovasc Intervent Radiol 2014; 37(02):381–387

59 Prajapati HJ, Dhanasekaran R, El-Rayes BF, et al. Safety and efficacy of doxorubicin drug-eluting bead transarterial chemoembolization in patients with advanced hepatocellular carcinoma. J Vasc Interv Radiol 2013;24(03):307–315

60 Grosso M, Vignali C, Quaretti P, et al. Transarterial chemoembolization for hepatocellular carcinoma with drug-eluting microspheres: preliminary results from an Italian multicentre study. Cardiovasc Intervent Radiol 2008;31(06):1141–1149

61 Malagari K, Pomoni M, Moschouris H, et al. Chemoembolization of hepatocellular carcinoma with HepaSphere 30-60 µm. Safety and efficacy study. Cardiovasc Intervent Radiol 2014;37(01): 165–175

62 Golfieri R, Giampalma E, Renzulli M, et al; Precision Italia Study Group. Randomised controlled trial of doxorubicin-eluting beads vs conventional chemoembolisation for hepatocellular carcinoma. Br J Cancer 2014;111(02):255–264

63 Song MJ, Chun HJ, Song DS, et al. Comparative study between doxorubicin-eluting beads and conventional transarterial chemoembolization for treatment of hepatocellular carcinoma. J Hepatol 2012;57(06):1244–1250

64 Zou JH, Zhang L, Ren ZG, Ye S-L. Efficacy and safety of cTACE versus DEB-TACE in patients with hepatocellular carcinoma: a meta-analysis. J Dig Dis 2016;17(08):510–517

65 Duran R, Sharma K, Dreher MR, et al. A novel inherently radiopaque bead for transarterial embolization to treat liver cancer - a pre-clinical study. Theranostics 2016;6(01):28–39

66 Levy EB, Krishnasamy VP, Lewis AL, et al. First human experience with directly image-able iodinated embolization microbeads. Cardiovasc Intervent Radiol 2016;39(08):1177–1186

67 Brown KT, Do RK, Gonen M, et al. Randomized trial of hepatic artery embolization for hepatocellular carcinoma using doxorubicin-eluting microspheres compared with embolization with microspheres alone. J Clin Oncol 2016;34(17):2046–2053

68 Maluccio MA, Covey AM, Porat LB, et al. Transcatheter arterial embolization with only particles for the treatment of unresectable hepatocellular carcinoma. J Vasc Interv Radiol 2008;19(06): 862–869

69 Bruix J, Llovet JM, Castells A, et al. Transarterial embolization versus symptomatic treatment in patients with advanced hepatocellular carcinoma: results of a randomized, controlled trial in a single institution. Hepatology 1998;27(06):1578–1583

70 Xie Z-B, Ma L, Wang X-B, et al. Transarterial embolization with or without chemotherapy for advanced hepatocellular carcinoma: a systematic review. Tumour Biol 2014;35(09):8451–8459

71 Malagari K, Pomoni M, Kelekis A, et al. Prospective randomized comparison of chemoembolization with doxorubicin-eluting beads and bland embolization with BeadBlock for hepatocellular carcinoma. Cardiovasc Intervent Radiol 2010;33(03):541–551

72 Atassi B, Bangash AK, Bahrani A, et al. Multimodality imaging following 90Y radioembolization: a comprehensive review and pictorial essay. Radiographics;28(01):81–99. doi:10.1148/rg.281065721

73 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(01):13–23. doi:10.1016/j.ijrobp.2006.11.060

74 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(09): 1121–30; quiz 1131. doi:10.1016/j.jvir.2009.05.030

75 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(08):1920–1928. doi:10.1111/j.1600-6143.2009.02695.x

76 Salem R, Gordon AC, Mouli S, et al. Y90 Radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology 2016;151(06):1155–1163.e2. doi:10.1053/j.gastro.2016.08.029

77 Pan L-H, Zhao C, Ma Y-L. Is Y90 radioembolization superior or comparable to transarterial chemoembolization for treating hepatocellular carcinoma? Gastroenterology 2017;152(06): 1627–1628. doi:10.1053/j.gastro.2016.10.048

78 Duran R, Deltenre P, Denys A. RE: Y90 radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology 2017;152(06):1625–1626. doi:10.1053/j.gastro.2016.09.069

79 Ludwig JM, Zhang D, Xing M, Kim HS. Meta-analysis: adjusted indirect comparison of drug-eluting bead transarterial chemoembolization versus 90Y-radioembolization for hepatocellular carcinoma. Eur Radiol 2017;27(05):2031–2041. doi:10.1007/s00330-016-4548-3

80 Kudo M, Imanaka K, Chida N, et al. Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma. Eur J Cancer 2011;47(14):2117–2127

81 Pawlik TM, Reyes DK, Cosgrove D, Kamel IR, Bhagat N, Geschwind J-FH. Phase II trial of sorafenib combined with concurrent transarterial chemoembolization with drug-eluting beads for hepatocellular carcinoma. J Clin Oncol 2011;29(30):3960–3967

82 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(05):1090–1098

83 Geschwind J-F, Kudo M, Marrero JA, et al. TACE treatment in patients with sorafenib-treated unresectable hepatocellular carcinoma in clinical practice: final analysis of GIDEON. Radiology 2016;279(02):630–640

84 Lewandowski RJ, Andreoli JM, Hickey R, et al. Angiogenic response following radioembolization: results from a randomized pilot study of Yttrium-90 with or without sorafenib. J Vasc Interv Radiol 2016;27(09):1329–1336. doi:10.1016/j.jvir.2016.03.043

85 Ricke J, Bulla K, Kolligs F, et al. Safety and toxicity of radioembolization plus sorafenib in advanced hepatocellular carcinoma: analysis of the European multicentre trial SORAMIC. Liver Int 2015;35(02):620–626. doi:10.1111/liv.12622

86 Chow PKH, Poon DYH, Khin M-W, et al. Multicenter phase II study of sequential radioembolization-sorafenib therapy for inoperable hepatocellular carcinoma. PLoS One 2014;9(03): e90909. doi:10.1371/journal.pone.0090909
87 Vouche M, Kulik L, Atassi R, et al. Radiological-pathological analysis of WHO, RECIST, EASL, mRECIST and DWI: imaging analysis from a prospective randomized trial of Y90 ± sorafenib. Hepatology 2013;58(05):1655–1666. doi:10.1002/hep.26487
88 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(08):7407–7413
89 Lencioni R. Management of hepatocellular carcinoma with transarterial chemoembolization in the era of systemic targeted therapy. Crit Rev Oncol Hematol 2012;83(02):216–224
90 Nishiofuku H, Tanaka T, Matsuoka M, et al. Transcatheter arterial chemoembolization using cisplatin powder mixed with degradable starch microspheres for colorectal liver metastases after FOLFOX failure: results of a phase I/II study. J Vasc Interv Radiol 2013;24(01):56–65
91 Pieper CC, Meyer C, Vollmar B, Hauenstein K, Schild HH, Wilhelm KE. Temporary arterial embolization of liver parenchyma with degradable starch microspheres (EmboCept®S) in a swine model. Cardiovasc Intervent Radiol 2015;38(02):435–441
92 Orlacchio A, Chegai F, Merolla S, et al. Downstaging disease in patients with hepatocellular carcinoma outside up-to-seven criteria: strategies using degradable starch microspheres transcatheter arterial chemo-embolization. World J Hepatol 2015;7 (12):1694–1700
93 Dreher MR, Sharma KV, Woods DL, et al. Radiopaque drug-eluting beads for transcatheter embolotherapy: experimental study of drug penetration and coverage in swine. J Vasc Interv Radiol 2012;23(02):257–64.e4
94 Bonomo G, Pedicini V, Monfardini L, et al. Bland embolization in patients with unresectable hepatocellular carcinoma using precise, tightly size-calibrated, anti-inflammatory microparticles: first clinical experience and one-year follow-up. Cardiovasc Intervent Radiol 2010;33(03):552–559
95 Gonzalez-Guindalini FD, Botelho MP, Harmath CB, et al. Assessment of liver tumor response to therapy: role of quantitative imaging. Radiographics 2013;33(06):1781–1800
96 Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 2010;30(01):52–60
97 Forner A, Ayuso C, Varela M, et al. Evaluation of tumor response after locoregional therapies in hepatocellular carcinoma: are response evaluation criteria in solid tumors reliable? Cancer 2009;115(03):616–623
98 Lin M, Pellerin O, Bhagat N, et al. Quantitative and volumetric European Association for the Study of the Liver and Response Evaluation Criteria in Solid Tumors measurements: feasibility of a semiautomated software method to assess tumor response after transcatheter arterial chemoembolization. J Vasc Interv Radiol 2012;23(12):1629–1637
99 Chapiro J, Wood LD, Lin M, et al. Radiologic-pathologic analysis of contrast-enhanced and diffusion-weighted MR imaging in patients with HCC after TACE: diagnostic accuracy of 3D quantitative image analysis. Radiology 2014;273(03):746–758
100 Ganapathy-Kanniappan S, Vali M, Kunjithapatham R, et al. 3-bromopyruvate: a new targeted antiglycolytic agent and a promise for cancer therapy. Curr Pharm Biotechnol 2010;11 (05):510–517
101 Miyayama S, Yamashiro M, Hashimoto M, et al. Identification of small hepatocellular carcinoma and tumor-feeding branches with cone-beam CT guidance technology during transcatheter arterial chemoembolization. J Vasc Interv Radiol 2013;24(04): 501–508