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REVIEW ARTICLE

Systematic review of catheter-based intra-arterial therapies in hepatocellular carcinoma: state of the art and future directions

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ABSTRACT

Intra-arterial therapies (IATs) play a pivotal role in the management of patients with primary and secondary liver malignancies. The unique advantages of these treatments are their ability to selectively deliver a high dose of anticancer treatment while preserving healthy liver tissue. The proven efficacy of these catheter-based locoregional therapies in a highly systemic chemoresistant cancer such as hepatocellular carcinoma (HCC), along with the minimally invasive nature of these treatments, quickly yielded wide acceptance in the medical community and revolutionized the field of Interventional Oncology. In this article, we describe the clinical rationale and background of catheter-based IATs. We provide an overview of clinical achievements of these treatments alone and in combination with sorafenib in patients with HCC.

Hepatocellular carcinoma (HCC) is the fifth most common malignancy in males and the seventh in females.[1] This disease carries a dismal prognosis, corresponding to the third most common cancer-related death worldwide.[2] The incidence of HCC is rising worldwide and has almost tripled in the last three decades in the USA.[3] About 80% of patients with HCC are diagnosed with disease that is not amenable to liver transplantation or surgical resection.[4] Thus, a majority of patients with unresectable HCC are referred for image-guided locoregional therapies. These interventional treatments include catheter-based techniques [transarterial chemoembolization (TACE), drug-eluting beads TACE (DEBs-TACE), transarterial embolization (TAE), radioembolization using yttrium-90 (Y^{90})] and percutaneous thermal (radiofrequency, microwave and laser ablation or cryoablation) and chemical (such as percutaneous ethanol injection) techniques. More recently, techniques such as irreversible electroporation and high-intensity focused ultrasound have been developed.

Although being part of the armamentarium of Interventional Oncology, percutaneous locoregional ablative therapies and their combination with catheter-based intra-arterial therapies (IATs), as well as the role of the latter in the downstaging and bridging of patients with HCC to surgical resection and liver transplantation, will not be discussed because of space limitations. The aim of this article is to describe the clinical rationale and background of catheter-based IATs in patients with HCC. An overview of clinical achievements of these treatments alone and in combination with sorafenib will be discussed.

CLINICAL RATIONALE

As opposed to most other organs, the liver has a dual vascular supply *via* the portal vein and the hepatic artery. Interestingly, liver malignancies are predominantly vascularized by the hepatic artery, while non-tumoral liver parenchyma is supplied mostly by the portal vein.[5] This pathophysiological particularity provides a unique advantage for catheter-based therapies. In TACE, the embolization of the vascular supply to the tumour causes ischaemic tumour necrosis and prevents rapid washout of the chemotherapeutic drug allowing for better locoregional diffusion of the payload into targeted tumour tissues. This allows the locoregional infusion to reach a therapeutic drug concentration that could otherwise not be achieved by a systemic delivery, thus maximizing anticancer drug efficacy while minimizing systemic toxicity. In TAE, only bland embolization is performed (*i.e.* no chemotherapeutic drug is delivered). In radioembolization, liver-directed catheter-infused Y^{90}-loaded microspheres can deliver

tumoricidal radiation doses while sparing healthy liver tissue and surrounding structures.

PATIENT SELECTION

The best available treatment for every HCC patient should always be decided in consensus by a multidisciplinary team. IATs can be used to downstage lesions to surgical treatment, as a bridge to surgical tumour resection or liver transplantation, and for palliative treatment of patients with unresectable HCC. Specifically, TACE has been included in the official treatment guidelines for the management of HCC.[6] According to the Barcelona Clinic Liver Cancer (BCLC) staging system, the most widely used treatment algorithm for HCC in Western countries, TACE can be applied as a palliative therapy in patients with intermediate-stage disease.[6] Not all patients with unresectable HCC can benefit from TACE. The best candidates have preserved liver function, adequate performance status [according to Eastern Cooperative Oncology Group (ECOG) performance status], asymptomatic and liver-limited multinodular disease without tumour vascular invasion.[6–8] Liver function, assessed by the Child–Pugh classification, plays a pivotal role in patient selection. Ideal candidates are Child–Pugh A, but patients with up to Child–Pugh B7 without ascites can be considered for therapy.[6] The presence of main or branch portal vein thrombosis (PVT) with or without tumour invasion decreasing significantly the blood flow (*e.g.* hepatofugal blood flow on ultrasound) is a contraindication to TACE due to the risk of ischaemic liver necrosis.[9] However, TACE can be performed safely in selected patients with PVT.[10–12] Selection criteria for TAE are similar to TACE. Until recently, there were no defined recommendations for the use of radioembolization in patients with HCC. Potential indications for radioembolization include patients with intermediate-stage disease who are poor candidates for TACE, patients with large solitary tumours invading segmental or lobar branches of the portal vein and patients with progressive disease after TACE.[13] The most important contraindications to all IATs are similar and are summarized in Table 1.

BACKGROUND AND CLINICAL EVIDENCE

Transarterial chemoembolization

The 1970s was the decade that brought the advent of catheter-based arterial embolization techniques. Indications such as control of haemorrhage and palliation of local symptoms like pain in cancer patients quickly expanded to include bridge therapy to surgery and cancer treatment, notably renal cancer, using embolic agents such as Gelfoam® and coils.[14–18] In the late 1970s–early 1980s, studies began to evaluate the combination of an anticancer drug (mitomycin C or doxorubicin) followed by an embolic agent (gelatin-based agent; Gelfoam) in unresectable HCC.[19,20] Hence, the concept of "chemoembolization" was introduced. Nakamura et al[21] compared this combination therapy to the infusion of an emulsion composed of a chemotherapeutic drug and an oily contrast medium (Lipiodol®; Laboratoire Guerbet, Aulnay-sous-Bois, France) followed by Gelfoam embolization and demonstrated a survival benefit for the latter. This work along with others established the use of Lipiodol in TACE [known as conventional TACE (cTACE)]. Lipiodol combines unique properties of a drug carrier and an embolic agent. Moreover, this poppy seed oil-based chemical is a radio-opaque contrast agent that accumulates preferentially in hepatic malignancies and persists in tumour nodules for weeks.[22–24] Lipiodol has been widely used as a suspension medium for chemotherapeutic agents in cTACE. Because no universally accepted protocol exists, several regimens of cTACE have been used. Doxorubicin is the most commonly administered drug worldwide. In the USA, a combination of doxorubicin, mitomycin C and cisplatin (currently not administered due to shortage) is utilized (Figure 1).[25] This combination

Table 1. Main contraindications to TACE and radioembolization

Relative contraindications	Absolute contraindications
• Diffuse tumour burden involving >50% of the liver	• Eastern Cooperative Oncology Group performance status >2
• Segmental or branch PVT[a]	• Severely reduced portal flow by branch or main PVT (*e.g.* hepatofugal blood flow)[a]
• Extrahepatic metastases	• Active systemic infection
• Ascites	• Uncorrectable bleeding disorder
• Serum bilirubin >3 mg dl^{-1}	• Uncorrectable contrast media sensitivity
• High serum levels of lactate dehydrogenase (>425 U l^{-1})	• Leukopenia (white blood cell count <1000 μl^{-1})
• High serum levels of aspartate aminotransferase and alanine aminotransferase (>5 × upper limit of normal)	• Renal insufficiency (serum creatinine >2 mg dl^{-1}, glomerular filtration rate <30 ml min^{-1})
• Biliary obstruction	• Hepatic encephalopathy
• Severe thrombocytopaenia (<50,000 μl^{-1})	• Excessive hepatopulmonary shunting[b]
• Recent variceal bleeding	• Tc^{99m}-MAA scan showing gastrointestinal deposition technically not correctable[b]
• Intractable arteriovenous fistula	
• Right-to-left cardiopulmonary shunting	
• Prior hepatic radiotherapy[b]	

PVT, portal venous thrombosis; TACE, transarterial embolization; Tc^{99m}-MAA, technetium-99m—macroaggregate albumin.
[a]Specific to TACE.
[b]Specific to radioembolization.

has been recently shown to have a higher response rate and less tumour progression compared to doxorubicin alone.[26] There is evidence showing that chemoembolization followed by bland embolization achieves better local response and survival compared to chemoembolization alone.[27,28] Several different types of embolization material delivered after the infusion of the Lipiodol/anticancer drug emulsion have been used and they include temporary materials such as absorbable gelatin (Gelfoam; Pfizer Inc., New York, NY) and degradable starch microspheres (Spherex; Pharmacia AB, Stockholm, Sweden) or permanent materials such as polyvinyl alcohol (PVA) particles (Contour SE; Boston Scientific, Marlborough, MA) PVA hydrogel beads (Bead Block™; Biocompatibles UK Ltd, Farnham, UK), polyphosphazene-coated polyacrylate microspheres (Embozene® Microspheres; CelaNova Bio-Sciences, Peachtree, GA) and trisacryl gelatin microspheres (Embosphere® Microspheres; Merit Medical Systems, Inc., South Jordan, UT).[29,30] cTACE is performed on demand allowing for a personalized patient-centred approach and better safety profile compared to fixed interval treatment. cTACE is safe and well tolerated with a favourable long-term toxicity profile.[31] While no consensus exists about the number of cTACE procedures to achieve satisfactory target lesion treatment, at least two sessions of chemoembolization should be performed before further treatment is abandoned or alternative therapies are considered.[32] Patients are typically followed up 6 weeks after the procedure for clinical, blood work and cross-sectional imaging evaluation.

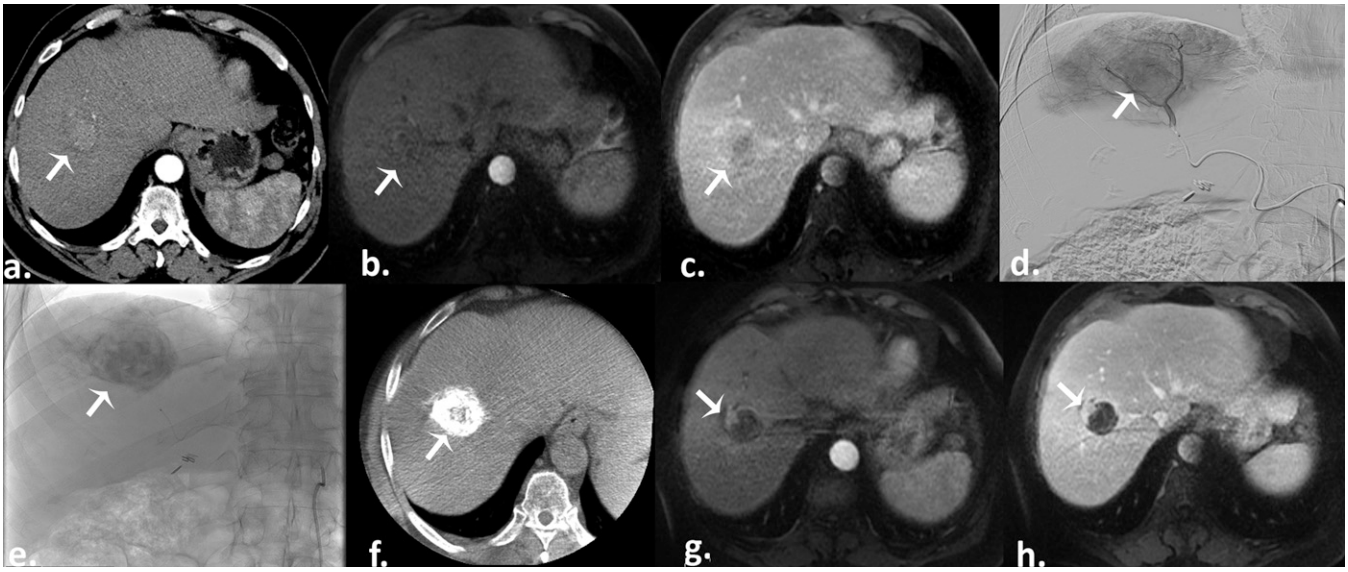
The lack of consensus and uniformly adopted protocols together with heterogeneous study cohorts casted doubt on the benefit of cTACE in patients with unresectable HCC. Four randomized controlled trials (RCTs) failed to show any survival benefit of cTACE *vs* symptomatic treatment[33–35] or tamoxifen,[36] and two systematic reviews[37,38] highlighted discrepant data. 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.[7,8] These two landmark studies along with a systematic review of RCTs[39] led to the inclusion of cTACE into the official treatment guidelines for HCC.[6,40,41] cTACE is endorsed by the American Association for the Study of the Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL).[6,40,41] Upon the introduction of cTACE, the median overall survival (OS) for intermediate stage HCC patients (according to the BCLC classification) increased from approximately 16 to 20 months, propelling this treatment modality as the standard of care.[6,39]

The presence of portal invasion is a common feature in HCC patients. This classifies a patient as advanced stage according to the BCLC classification and no IAT is recommended. Selected patients with PVT treated with cTACE have shown a potential

Key points of conventional TACE

- cTACE is safe and effective in properly selected patients
- Preserved liver function is essential as survival benefit has only been shown for patients with Child–Pugh A or B7 without ascites
- Ideal patient profile: preserved liver function, adequate ECOG performance status, asymptomatic multinodular liver disease without macrovascular tumour invasion and extrahepatic disease
- cTACE constitutes the standard of care for intermediate-stage (BCLC B) HCC patient (Level I evidence)

Figure 1. Conventional transarterial chemoembolization in a 68-year-old male with a history of hepatitis C cirrhosis recently diagnosed with hepatocellular carcinoma (HCC). (a) Pretreatment arterial phase CT scan reveals a hyperenhancing right hepatic lobe mass consistent with HCC (arrow). (b) Pretreatment arterial phase T_1 weighted gradient-echo MR scan demonstrates the lesion, with subsequent washout on the portal venous phase (c) (arrows). (d) Selective digital subtraction angiography demonstrates tumour blush (arrow). Postembolization single-snap shot (e) and cone beam CT (f) show an excellent Lipiodol® deposition into the tumour (arrows). Arterial (g) and portal venous (h) phases T_1 weighted gradient-echo MR images obtained 1 month after therapy demonstrate a good result (partial response) with small residual viable tumour (arrows).



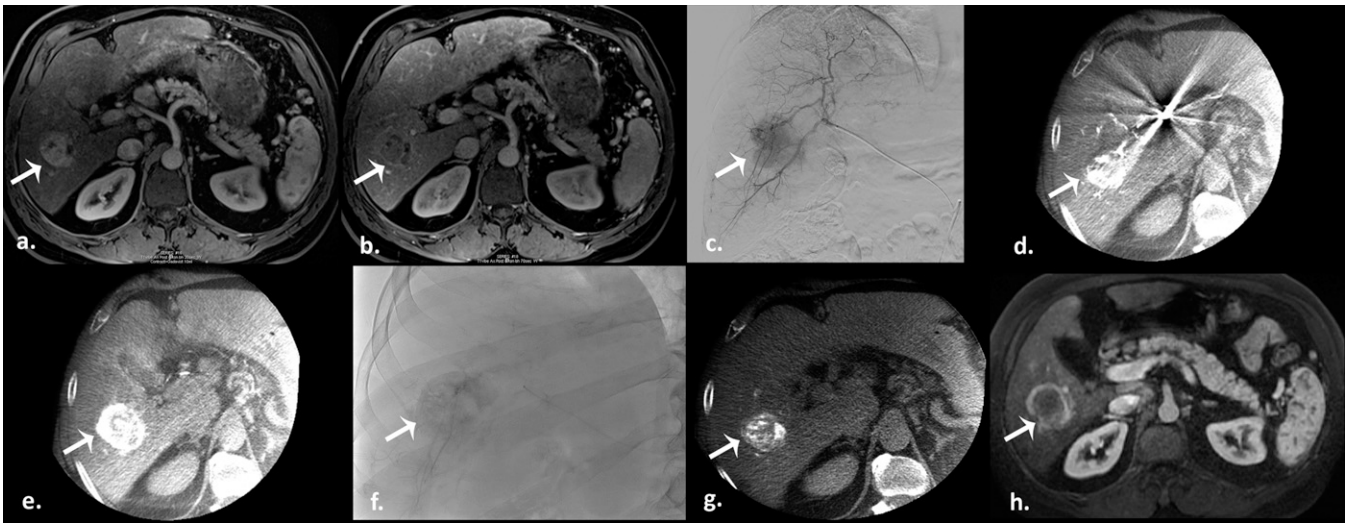
benefit in survival compared to best supportive care.[10–12] However, it should be noted that this evidence is only based on non-controlled studies.

Drug-eluting beads transarterial chemoembolization

Microparticulate drug delivery systems have come a long way. Ehrlich's "magic bullet" concept dating from the beginning of the 20th century,[42] with the goal of improved drug efficacy while reducing related side effects, has led to important investigations in the field of drug delivery. In 1987, the ideal characteristics of drug-eluting microspheres were described:[43] appropriate-sized beads containing a variety of anticancer drugs are used as vehicles for the locoregional delivery *via* the arterial system of an organ harboring cancer, to cause tumour infarction through an embolic effect and providing an ideal setting for a controlled and sustained drug release with decreased systemic exposure. The following two decades saw the refinement and further development of DEBs which resulted in a promising alternative to conventional Lipiodol-based regimens. Several DEB systems have been tested such as DC Bead (Biocompatibles UK Ltd) and HepaSphere™/QuadraSphere® microspheres (Merit Medical Systems, Inc.). The DC Beads are PVA-based microspheres and range from 75 to 900 μm in size, while the HepaSphere microspheres are superabsorbent polymer based and range from 120 to 800 μm in size. Both systems can be efficiently loaded with doxorubicin (and irinotecan),[44] and preclinical studies have shown safe pharmacokinetic profiles with sustained drug release and antitumour efficacy.[45–47] In clinical practice, DEB-TACE has the same indications and contraindications as cTACE. The best candidates for DEB-TACE have a disease that can be selectively targeted. To date, most of the clinical data about DEB-TACE have been generated with DC Bead. Therefore, doxorubicin-loaded HepaSphere microspheres have less clinical validation although similar results to DC Bead have been reported.[48,49] Major studies with DC Bead are presented here.

In 2007, Varela et al[50] published seminal data on the safety, pharmacokinetics and efficacy of DC Bead loaded with doxorubicin (DEBDOX; 500–700 μm) in selected patients ($n = 27$) with HCC (Child–Pugh A, BCLC B). The procedure was well tolerated with postembolization syndrome observed in 37% of patients after the first DEB-TACE, which dropped to 18% after the second. Two patients developed liver abscess. Importantly, peak plasma concentrations of doxorubicin were significantly lower compared to those measured in cTACE. Objective response was seen in two-thirds of the patients according to the EASL guidelines [*i.e.* tumour response is based on the assessment of enhancing portion of the target tumours (the product of bidimensional diameter of enhancing tissue)].[51] The same year, the results of a combined Phase I/II study in patients with HCC ($n = 15/n = 20$, respectively; 100% Child–Pugh A) were reported.[52] The Phase I trial, a dose-escalating study starting from 25 to 150 mg of doxorubicin, 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 tumours (mRECIST; tumour response is based on the assessment of the longest enhancing diameter of the target tumours). Six patients had treatment-related complications. In 2008, similar results were reported in an open-label, single-centre, single-arm study including 62 patients with unresectable HCC.[53] 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%. In the United States, the first prospective Phase II

Figure 2. Drug-eluting beads transarterial chemoembolization in a 55-year-old male with a history of nonalcoholic steatohepatitis. (a) Pretreatment arterial phase T_1 weighted gradient-echo MR scan demonstrates a hyperenhancing hepatocellular carcinoma in the right hepatic lobe, with subsequent washout on the portal venous phase (b) (arrows). (c) Selective digital subtraction angiography clearly demonstrates tumour blush (arrow). Intraprocedural pretreatment dual-phase cone beam CT (CBCT) in early (d) and late (e) arterial phases evidence the lesion (arrows). Postembolization single-snap shot (f) and CBCT (g) show an excellent contrast staining of the tumour (arrows). (h) Arterial phase T_1 weighted gradient-echo MR scan obtained 1 month after therapy demonstrate a good result (partial response) (arrow).



pilot study evaluating the safety and efficacy of DEBDOX (100–300 or 300–500 μm) was reported in 2009.[54] 20 patients (Child–Pugh A, 75%; BCLC C, 60%) underwent 34 DEB-TACE sessions. The safety profile was good with only 10% of grade III toxicities. Two patients died within 30 days after DEB-TACE but neither death could be attributed to the procedure. Objective response at 1 month was 60% (EASL) and disease control at 6 months was 95% (RECIST; tumour response is based on the assessment of the longest diameter of the target tumours). 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 (Figure 2). Recently, unparalleled outcomes were achieved in almost 300 HCC patients with early and intermediate stage disease [mean OS of 43.8 months[55] and median OS of 48.6 months (BCLC A: 54.2 months and BCLC B: 47.7 months)[56]]. Of note, these two works highlight the pivotal role and challenge of patient selection in HCC.

The safety and survival outcomes of DEB-TACE in patients with advanced stage HCC have recently been evaluated. Two retrospective works combining 201 patients (Child–Pugh A/B: 123/78, BCLC C: 100%, ECOG 0/1/2: 22/139/40) reported 19 patients with grade 3 toxicities.[57,58] Neither grade 4 toxicities nor 30-day mortality were observed. Similar median OS was obtained with 13.3[57] and 13.5 months,[58] respectively. These studies underscore the favourable toxicity profile of DEB-TACE with advanced disease and the reported encouraging outcomes need to be validated in well-conducted prospective trials.

The question about the safety and the size of available DEBDOX was addressed in a recent publication.[59] The use of small caliber beads (100–300 μm) in tumours of <6 cm was not associated with an increase in liver toxicity or complications when compared to larger beads (300–500 μm).[59] An ongoing prospective trial is evaluating the feasibility and safety of using 70–150 μm beads (LC-Bead M1) loaded with doxorubicin in patients with HCC and will certainly bring more data about the use of small-caliber microspheres (Figure 3).[60]

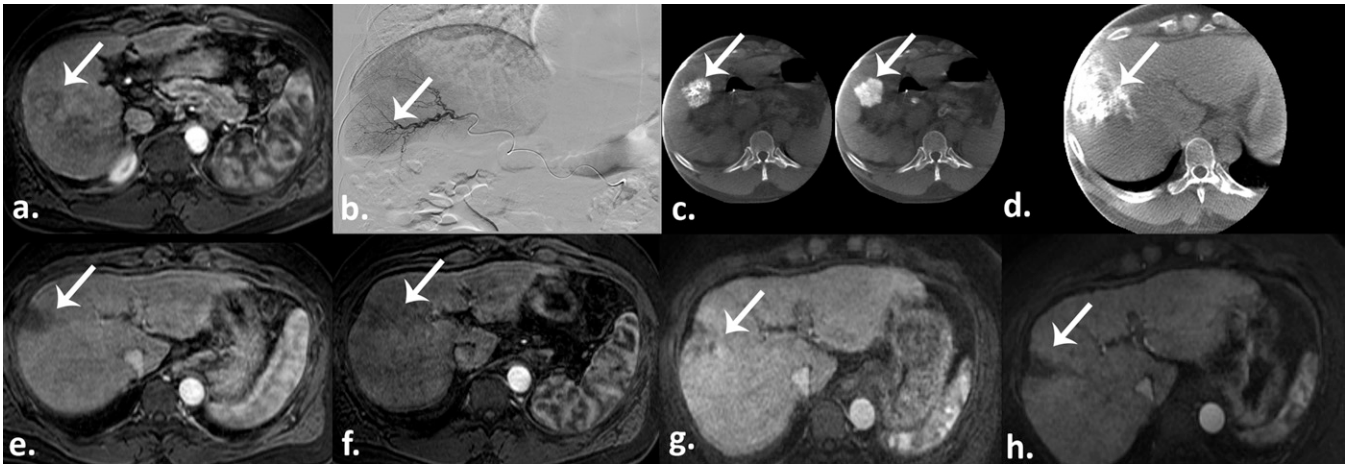
Drug-eluting beads transarterial chemoembolization vs conventional transarterial chemoembolization

A prospective randomized multicentre trial of 212 patients across Europe compared efficacy and safety of DEB-TACE using DEBDOX to cTACE.[61] Although response rates were higher in the DEB-TACE group, this study failed to show any statistically significant difference in efficacy compared to 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 of liver toxicity and doxorubicin-related adverse events, this trial confirmed the better tolerability profile of DEB-TACE over cTACE. In a retrospective study, Song et al[62] reported a better treatment response in patients who received DEBDOX *vs* cTACE with no

Key points of DEB-TACE

- DEB-TACE is safe and effective in properly selected patients
- Ideal patient profile: preserved liver function, adequate ECOG performance status, asymptomatic and selectively targetable liver disease (as opposed to lobar treatment), without macrovascular tumour invasion and extrahepatic disease
- DEB-TACE has a better toxicity profile compared to cTACE (Level I evidence)
- To date, DEB-TACE has not shown better survival compared to cTACE

Figure 3. Drug-eluting beads transarterial chemoembolization in a 48-year-old male with a history of alcohol abuse-related liver cirrhosis and hepatocellular carcinoma (HCC). (a) Pretreatment arterial phase T_1 weighted gradient-echo MR scan demonstrates a hyperenhancing HCC in segment six (arrow). (b) Selective digital subtraction angiography shows tumour blush (arrow). (c) Intraprocedural pretreatment dual-phase cone beam CT (CBCT) shows the hypervascularized lesion (arrows). (d) Postembolization intraprocedural CBCT shows an excellent contrast staining of the segment containing the tumour (arrow). Arterial phase T_1 weighted gradient-echo MR scans obtained 1 month (e), 3 months (f), 6 months (g), and 9 months (h) after therapy demonstrate chemoembosegmentectomy with complete response and no residual viable tumour (arrows).



differences in treatment-related liver toxicity. Longer time to progression (TTP) and better OS were also seen with DEB-DOX.[62] These promising results, however, need to be confirmed in a well-designed prospective RCT of properly selected HCC patients to fully establish the survival benefit of DEB-TACE over cTACE.

Transarterial embolization

Unlike TACE, TAE relies solely on the occlusion of the vascular supply to the tumour. Proponents of TAE believe that the ischaemic insult induced by embolization is sufficient to cause tumour cell death and that the adjunction of a chemotherapeutic agent contributes to unnecessary toxicity. In 1998, Bruix et al[63] reported the results of a prospective single centre RCT comparing TAE ($n = 40$) *vs* symptomatic treatment ($n = 40$) in patients with unresectable HCC. Distal TAE was performed using Gelfoam; in patients with unilobar disease, distal TAE was combined with proximal coiling ($n = 18$). Despite a marked antitumoral effect (partial response was observed in 55% of the patients in the TAE group), there was no benefit in survival compared to untreated patients. In 2008, the outcomes of 322 patients treated with 766 TAEs were reported in a single-armed single-institution retrospective study.[64] The median OS was 21 months (16–26 months). 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 escalated the need for an RCT. In 2010, an RCT comparing TAE (Bead Block, 100–300 and 300–500 μm) *vs* DEB-TACE (DC Bead, 100–300 and 300–500 μm) in 84 (43/41) patients with intermediate-stage HCC was published.[65] Patients were randomized by tumour size and treated every 2 months, up to three procedures. Complications were similar in both groups. DEB-TACE yielded a better local response with higher response rates at every time point of the study (6, 9 and 12 months) reaching statistical significance at 9 months. DEB-TACE had fewer recurrences at 9 and 12 months and longer TTP compared to TAE (10.6 ± 2.7 *vs* 9 ± 2.3 months, respectively).[65] Unfortunately, the short follow-up (12 months) precluded any definite conclusion about survival. The results of a Phase II study comparing TAE (Bead Block) *vs* DEB-TACE (LC Beads—150 mg doxorubicin) were recently presented (not yet published).[66] Study arms were composed of 51 and 50 patients (TAE and DEB-TACE, respectively). No difference in adverse events, response or disease control rate, PFS or OS [6.8 *vs* 8.9 months ($p = 0.59$) and 14 *vs* 16 months ($p = 0.7$) for TAE and DEB-TACE, respectively] were found between both groups.

Taken together, these results demonstrate that TAE has a clear antitumour effect. These findings suggest that the main trigger of cell death in TACE can also be attributed to the ischaemic insult provided by the embolization. However, the addition of cytotoxic drug is beneficial until proven otherwise based on the current clinical evidence. Thus, further investigations are needed to dispute the dominance of cytotoxic catheter-based therapies over bland embolization. TAE is currently not endorsed by the EASL or the AASLD.[6]

Key points of TAE

- TAE is safe and effective in properly selected patients
- Ideal patient profile: preserved liver function, adequate ECOG performance status, asymptomatic and selectively targetable liver disease (as opposed to lobar treatment), without macrovascular tumour invasion and extrahepatic disease
- Further studies are needed to evaluate TAE in comparison to other catheter-based therapies
- TAE is currently not included in the official treatment guidelines for HCC

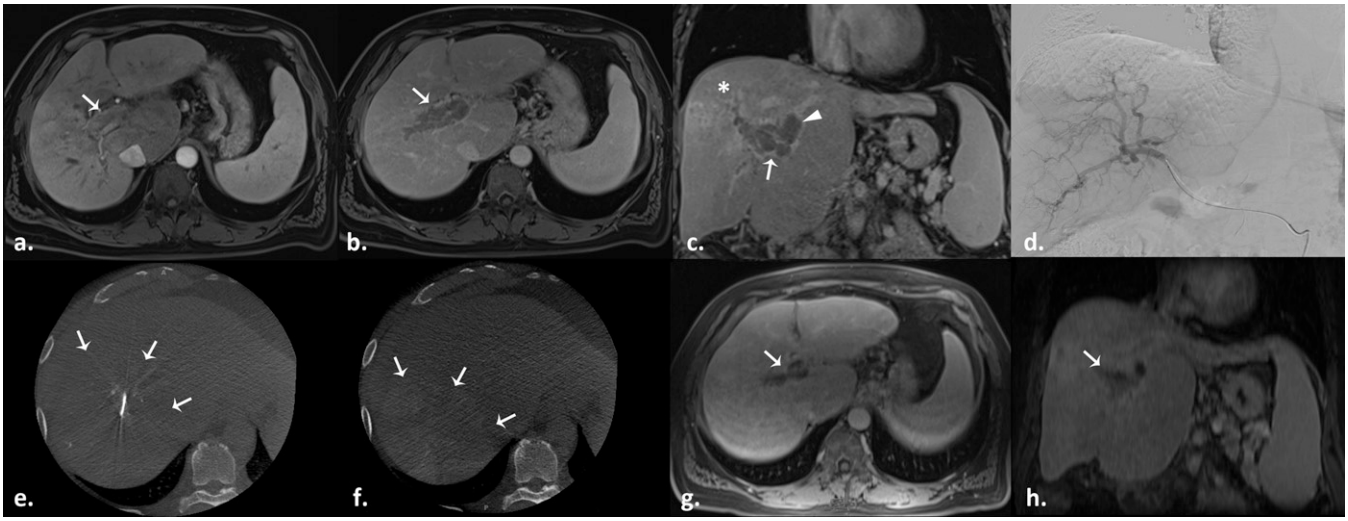
Radioembolization with yttrium-90

Radioembolization is the catheter-based intra-arterial infusion of microspheres labelled with a radioactive isotope. To date, Y^{90}, a pure beta-emitter, is the most widely used isotope in the locoregional treatment of liver malignancies. In contrast to TACE, the antitumour effect is mainly caused by the radiation while embolization is only a minor contributor.[67] Two types of microspheres are currently used. The first are resin-based (SIR-Spheres®; Sirtex Medical Ltd, North Sydney, Australia) with a diameter of 20–60 μm and an activity of 50 Bq per microsphere. The number of spheres per vial is $40–80 \times 10^6$. The second are glass-based (TheraSphere®; MDS Nordion, Ottawa, Canada) with a diameter of 20–30 μm and an activity of 2500 Bq per microsphere. The number of spheres per vial is $1.2–8 \times 10^6$.[68] Despite these particularities, both microsphere types have shown similar efficacy and outcomes.[69]

This technology, although already evaluated in the late 1950s–60s,[70–72] has matured into a palliative treatment option for patients with HCC over the last two decades. Salem and Thurston published a detailed and comprehensive literature review of seminal works of Y^{90} radioembolization in HCC patients, covering the late 1980s and mid 2000s.[73] In substance, these studies established the safety of this technique, the optimal tumoricidal dose calculation based on hepatic and tumour volumes, the role of the shunt study and the management of collaterals responsible for liver shunting. Many of the more recent and influential works are highlighted here.

In 2004–05, two important series established the safety and efficacy of Y^{90} radioembolization in HCC patients.[74,75] These landmark works have since been confirmed in two of the largest studies reported to date.[76,77] In 2010, Salem et al[76] published a single-centre, prospective study in 291 patients (Child–Pugh A/B/C, 131/152/8; BCLC A/B/C/D, 48/83/152/8; PVT, 125). Response rates according to EASL were 57%. The median follow-up was 30.9 months. Overall median TTP was 7.9 months. Median survival time for Child–Pugh/BCLC A compared to Child–Pugh/BCLC B patients was 17.2/26.9 and 7.7/17.2 months, respectively. Child–Pugh A patients with or without PVT had a median survival of 10.4 and 22.1 months, whereas Child–Pugh B patients with or without PVT had a median

Figure 4. Radioembolization with glass-based Y^{90} microspheres in a 62-year-old male with a history of haemachromatosis and right lobe infiltrative hepatocellular carcinoma with portal vein invasion. (a) Pretreatment arterial phase T_1 weighted gradient-echo MR image demonstrates an enhancing mass in the right portal vein consistent with tumour thrombus (arrow). Portal vein tumour thrombus washout is visible on the subsequent portal venous on axial (b) and coronal (c) views (arrows), as well as its extension into the left portal vein (c, arrowhead). The infiltrative tumour of the right hemi-liver is better appreciated on the coronal view (star). (d) Selective digital subtraction angiography fails to clearly demonstrate tumour blush. Intraprocedural pretreatment dual-phase cone beam CT in early (e) and late (f) arterial phases better evidence the lesion extension (arrows). Axial (g) and coronal (h) venous phase T_1 weighted gradient-echo MR images obtained 3 months after therapy demonstrate portal vein thrombus shrinkage (arrows).



survival of 5.6 and 14.8 months, respectively. Sangro et al[77] reported findings on a large multicentre retrospective study conducted in Europe. Here, 325 patients (Child–Pugh A/B, 268/57; BCLC A/B/C/D, 52/87/183/3; PVT, 76) were included. The median OS of the cohort was 12.8 months and depended on the BCLC class (BCLC A, 24.4 months; BCLC B, 16.9 months; BCLC C, 10.0 months) reflecting liver function and tumour burden. The presence of PVT was identified as a negative predictive factor of survival (10 months with PVT *vs* 15.3 months without PVT).

Patients with HCC invading the portal vein constitute a common indication for Y^{90} radioembolization. Indeed, the apprehensiveness of decreasing the arterial blood supply by TACE in the setting of portal vein invasion provides an appealing rationale for the use of Y^{90} radioembolization. In 2008, Kulik et al[78] evaluated the safety and efficacy of Y^{90} in the presence ($n = 37$) and absence ($n = 71$) of PVT. Cirrhosis and PVT had higher adverse event rates. However, there were no clinically significant differences in bilirubin toxicities when stratifying by PVT status. Moreover, the risk of hepatic encephalopathy and liver failure was not increased by the presence of PVT. Objective response was reported in 70%. Survival data were hampered by a short follow-up (6 months). Importantly, this study established the safety profile of Y^{90} radioembolization in PVT and further supported the notion of the microembolic (compared to macroembolic for TACE) component of this liver-directed brachytherapy (Figure 4). In 2010, Hilgard et al[79] reported the results of a prospective, single-centre observational study designed to validate safety and antitumour effect of Y^{90} in advanced stage HCC patients who were not candidates for TACE or other locoregional treatments. 108 patients (Child–Pugh A/B, 84/24; BCLC A/B/C, 2/51/55; PVT, 33) underwent 159 Y^{90} sessions. The most frequent adverse events were transient fatigue and abdominal pain. Objective response at 90 days was 40%. For the entire cohort, the median TTP was 10 months and median survival time was 16.4 months (Child–Pugh A/B, 17.2/6 months; no PVT/PVT, 16.4/10 months).

Taken together, these encouraging outcomes underline the increasing role of Y^{90} radioembolization in the treatment of HCC, especially in patients with locally advanced tumour with or without PVT with preserved liver function (Child–Pugh A) or impaired liver function (Child–Pugh B) without PVT.

Key points of Y^{90} radioembolization

- Y^{90} radioembolization is safe, particularly in the setting of portal venous invasion, in properly selected patients
- Patients with intermediate-stage disease (BCLC B) who are poor candidates for TACE, patients with large solitary tumours invading the portal vein or patients with progressive disease after TACE are considered good candidates
- Y^{90} radioembolization achieved strong anticancer efficacy but did not demonstrate survival benefit over TACE
- There are no RCTs comparing Y^{90} radioembolization with other IATs
- Y^{90} radioembolization is currently not endorsed by the AASLD or EASL

Y^{90} vs *conventional transarterial chemoembolization*

In 2011, Salem et al[80] published a comparative study of the efficacy of Y^{90} radioembolization *vs* cTACE. Patients were balanced for Child–Pugh class, BCLC and United Network for Organ Sharing systems. Both therapies showed a similar response rate. Y^{90} radioembolization demonstrated a longer TTP compared to cTACE (13.3 *vs* 8.4 months, respectively, $p = 0.046$). However, no difference in median OS was observed (20.5 months for Y^{90} *vs* 17.4 months for cTACE; $p = 0.232$). Patients with intermediate-stage disease had a similar survival whether treated by cTACE (17.5 months) or Y^{90} radioembolization (17.2 months; $p = 0.42$).

Despite convincing and compelling data supporting the safety and efficacy of Y^{90}, the evidence, to date, is derived solely from retrospective and prospective non-controlled studies. As such, the AASLD and EASL have not endorsed radioembolization as a standard of care. A head-to-head comparison of Y^{90} to cTACE is a real challenge because similarities in survival outcomes require a large patient cohort (>1000) to demonstrate equivalence.[80] However, many clinical studies are under way. Among them, a multicentre randomized Phase II trial (PREMIERE: Prospective Randomized Trial of Radioembolization and Chemoembolization in Hepatocellular Carcinoma[81]) comparing Y^{90} to cTACE is very much expected.

ANTIANGIOGENIC THERAPY

Unequivocal evidence has demonstrated that hypoxia present in the tumour microenvironment triggers the accumulation of hypoxia-inducible factor one and the subsequent overexpression of the pro-angiogenic vascular endothelial growth factor (VEGF) gene.[82,83] Thus, targeting molecular mechanisms of angiogenesis has been the subject of intense research. However, no anti-angiogenic drug that entered Phase III trials showed significant benefits with one exception, sorafenib, an oral multikinase inhibitor of VEGF receptors (1–3), Raf-1, platelet-derived growth factor receptor β, B-Raf and c-Kit. Indeed, between 2005 and 2007, two Phase III, multicentre, double-blinded, placebo-controlled trials independently demonstrated a survival benefit of sorafenib over supportive treatment.[84,85] In the Western series,[84] the median OS was 10.7 months in the sorafenib group and 7.9 months in the placebo group ($p < 0.001$), whereas in the Asian series,[85] the median OS was 6.5 months for the sorafenib group and 4.2 months for the placebo group ($p = 0.014$). In a notoriously systemic chemoresistant cancer such as HCC, these positive results, although modest, earned wide acceptance. Sorafenib became the standard of care and changed the landscape of advanced disease in HCC. Major works with sorafenib combined various IATs are presented here.

Conventional transarterial chemoembolization and sorafenib

The interim results of the START (Study in Asia of the Combination of TACE with sorafenib in HCC Patients) trial were recently published.[86] This prospective Phase II, open label study evaluates the safety and efficacy of the combination of cTACE (Lipiodol/doxorubicin followed by Gelfoam embolization) and sorafenib in patients from the Asia-Pacific region with intermediate-stage HCC. Sorafenib (400 mg twice daily) was given on an interrupted treatment schedule starting 4–7 days after cTACE, with cTACE sessions being performed on demand. Patients who were not candidates for additional cTACE procedures continued on sorafenib monotherapy until unacceptable toxicity or disease progression occurred. A majority of the 147 patients experienced gastrointestinal (62.6%) or skin (57.8%) adverse events, most being mild to moderate. Objective response according to mRECIST was seen in 52.4% of patients. PFS and TTP were 9 and 9.3 months, respectively. This study confirmed the safety profile of the combination therapy using an interrupted sorafenib protocol.[87]

In 2013, a propensity score analysis was performed to investigate outcomes of the combination of cTACE (Lipiodol/Cisplatin + Gelfoam) with sorafenib ($n = 164$) and sorafenib alone ($n = 191$) in a retrospective cohort study with advanced-stage HCC (BCLC C).[88] All patients received sorafenib therapy for at least 5 weeks. The median TTP in the combination group was significantly longer compared to the sorafenib group (2.7 *vs* 2.1 months, respectively; $p = 0.011$). Importantly, however, there was no benefit in survival (9.1 *vs* 6.7 months; $p = 0.21$).

Drug-eluting bead-transarterial chemoembolization and sorafenib

In 2011, a Phase II prospective single-centre study evaluated DEB-TACE (LC Beads, 100–300 μm; doxorubicin) in combination with sorafenib in 35 patients (Child–Pugh A/B, 31/4; BCLC B/C, 12/23; PVT, 11).[89] Patients were treated on a 6-week cycle regimen, in which one cycle consisted of 400 mg of sorafenib twice daily, initiated 1 week before DEB-TACE and administered continuously to obtain synergistic effects. The primary end points were safety and toxicity, while efficacy was the secondary end point. The median number of cycles per patient was two (range, 1–5). Most patients experienced at least one grade 3–4 toxicity; however, most toxicities were grade minor, 83% grade 1–2 and 17% grade 3–4. Objective response was observed in 58% (EASL). This study not only demonstrated the safety profile of sorafenib combined with DEB-TACE but also established the feasibility and tolerability of the continuous administration of sorafenib.

A Phase II, multicentre, international, randomized, double-blinded trial [the sorafenib or placebo in combination with TACE with doxorubicin-eluting beads (DEBDOX) for intermediate-stage HCC—(SPACE)—trial][90] was conducted in patients with intermediate-stage HCC to evaluate whether sorafenib with DEB-TACE has an impact on disease progression compared to DEB-TACE alone (completed, unpublished trial). 307 patients were randomized to receive sorafenib 400 mg twice daily or matching placebo continuously until progression. All patients underwent DEB-TACE 3–7 days after the first dose of the study drug, on Day 1 (±4 days) of months 3, 7 and 13, and every 6 months thereafter. The median TTP was 169 days for the sorafenib group *vs* 166 days for the placebo group. Although the hazard ratios seemed to favour the combination treatment over the placebo arm, there was no statistically significant benefit in TTP or survival for the combination therapy compared to DEB-TACE alone.

Overall, the combination of sorafenib and cTACE or DEB-TACE has shown to be safe and well tolerated. However, results regarding efficacy and benefit in OS have yet to be confirmed. As such, multiple studies have been designed to investigate the combination of cTACE or DEB-TACE with systemic antiangiogenic therapy; of particular importance are two Phase III randomized, double-blinded trials.[91,92]

Y^{90} and sorafenib

Y^{90} radioembolization is gaining acceptance in patients with more advanced intermediate-stage and early advanced-stage HCC patients, in part due to fewer procedure-related toxicities and better quality of life compared to TACE.[93] Given this favourable profile, the combination of Y^{90} with sorafenib is appealing. Although data about this combination therapy are scarce, most trials being at an early stage or have yet to start, some results were made available recently.

An open-label, multicentre, single-arm, Phase II study conducted in the Asia–Pacific region evaluated the safety and efficacy of sequential treatment with radioembolization and sorafenib.[94] Sorafenib (400 mg twice daily) was initiated 14 days after Y^{90} and given continuously until tumour progression or drug-related adverse events in 29 patients (Child–Pugh A/B, 20/9; BCLC B/C, 11/18; PVT, 8). The median daily dose of sorafenib was 600 mg (range, 127–791 mg). A majority of patients (28/29) experienced ≥grade 1 toxicity, while ≥grade 3 toxicity was observed in 15 patients (52%). Objective response (RECIST) was seen in 25%. Median TTP was 15.2 and 9.0 months for BCLC B and C patients, respectively. Median OS for BCLC B and C patients was 20.3 and 8.6 months, respectively. It was concluded that the sequential treatment of Y^{90} and sorafenib is safe and potentially effective.

The safety interim analysis of the combination of Y^{90} radioembolization and sorafenib compared with sorafenib alone in patients with advanced-stage disease was recently published.[95] These preliminary results are part of a prospective, multicentre RCT currently being conducted in Europe.[96] Patients with good performance status and preserved liver function, who were not candidates for TACE or progressed after TACE, were included in the analysis. Eligible candidates ($n = 40$; 20 each arm) were further stratified by the presence or absence of PVT. Patients received sorafenib on Day 3 after the last Y^{90} procedure. Both treatment arms received sorafenib 200 mg twice daily for 1 week, then the dose was increased to 400 mg twice daily. The regimen was continuous until disease progression or the advent of intolerable drug-related toxicity. Dose and duration of sorafenib was similar between groups (median daily dose 614 mg over 8.5 months and 557 mg over 9.6 months in the combination and sorafenib groups, respectively). Two patients died, one in each arm, but neither event was considered to be treatment related. The incidence of total (196 *vs* 222) and grade ≥3 (43 *vs* 47) adverse events was similar in the combination *vs* sorafenib groups, respectively. It was concluded that radioembolization followed by sorafenib is as safe and well tolerated as sorafenib alone.

Taken together, these results underline the potential of combining Y^{90} radioembolization and sorafenib in patients with more advanced disease. Ongoing studies will certainly shed more light on the potential benefit of this combination treatment,[96,97] while other trials challenge the hegemony of sorafenib comparing Y^{90} radioembolization to the antiangiogenic therapy.[98–100]

FUTURE DIRECTIONS

Catheter-based IATs have achieved unparalleled results in the treatment of patients with HCC. Together with other treatment modalities in the field of Interventional Radiology, these minimally invasive therapies have led to the establishment of Interventional Oncology as the fourth pillar of cancer therapy. The future of catheter-based therapies is promising.

Patient selection

Published outcomes are predominantly impacted by major prognostic factors such as liver function, portal vein invasion, performance status, tumour burden and response to therapy. Thus, patient selection for IATs is fundamental. Intermediate-stage HCC encompasses a very heterogeneous group, which led to many difficulties when comparing trials.[101] Highly selected intermediate-stage HCC patients have been shown to reach exceptional outcomes.[56] Further studies implementing a discernible subpopulation of patients will certainly lead to a better identification of the ideal catheter-based therapy.

Many staging systems for patients with HCC have been developed.[102] While the BCLC staging system is the most widely used treatment algorithm in Western countries, no standard system has been uniformly adopted worldwide. A new classification was recently proposed, the Hong Kong Liver Cancer (HKLC) staging system.[103] This prognostic classification was retrospectively developed from 3856 patients with HCC. Four prognostic factors served as the backbone of the new system: ECOG performance status, Child–Pugh class, liver tumour status and presence of extrahepatic vascular invasion/metastasis. Importantly, the new system identified subsets of intermediate- and advanced-stage BCLC patients for whom a more aggressive treatment approach was recommended. This staging system may more accurately reflect contemporary treatment approaches that are typically seen in daily clinical practice. Indeed, whereas the BCLC system would preclude certain patients from some IATs, the HKLC system would not only allow but recommend such treatments. It is very clear that the number of IATs would dramatically increase should the HKLC staging system be universally adopted. With reported better outcomes compared to BCLC, this new system will certainly make headlines and challenge BCLC. The validity of HKLC should be tested, notably in Europe and North America where hepatitis C is the main trigger for HCC compared to hepatitis B in Asia (about 80% of the HKLC cohort had hepatitis B).

Sorafenib

The advent of sorafenib as the standard of care in advanced-stage HCC patients changed the landscape of BCLC C. Ongoing research evaluating this therapy alone or in combination with catheter-based treatment will certainly change the paradigm for this category of patients. Future investigations should focus on the ideal timing and type (sequential, interrupted *vs* continuous) of sorafenib administration. Moreover, the ideal subset of patients

for the combination therapy with sorafenib remains to be elucidated. While the toxicity profile of Y^{90} radioembolization and DEB-TACE has been shown to be more favourable than cTACE, and thus appears more attractive for a combination therapy with sorafenib, the ideal catheter-based therapy has yet to be determined.

Evaluation of treatment response

Evaluation of treatment response after IAT is a key component for patient management and is performed on a daily basis in clinical practice. The survival-based end points traditionally used in clinical studies have largely been replaced by radiologic objective response, which has been widely used and accepted as a surrogate end point. Baseline imaging is typically performed within 2–3 weeks prior to therapy, and follow-up imaging is performed 4–6 weeks after IAT. Most liver tumours exhibit heterogeneous pattern of necrosis after catheter-based treatments that challenge tumour response evaluation.[104] While conventional response criteria assessing anatomic (*i.e.* size-based) changes in the tumour (World Health Organization response criteria and RECIST) have shown their limitations compared to contrast enhancement-based criteria (EASL and mRECIST),[51,105,106] new response criteria using three dimensional (3D) quantitative approaches are already being evaluated and will certainly improve upon established guidelines.[107,108]

From bench to bedside

The field of catheter-based therapies will continue to grow. Understanding the molecular biology of cancer is crucial in the development of therapies. Thus, continued experimental research is fundamental and every effort should be carried out to translate basic scientific findings into therapeutic options for patients. Dynamic multiphase contrast-enhanced CT and MRI have achieved unparalleled accuracy in the diagnosis of HCC in the presence of a cirrhotic liver, relegating the role of the biopsy to a second level. However, collection of tissue samples should be favoured in future research to better understand liver cancer molecular biology and identify new molecular targets. A personalized medicine approach is likely to develop in the near future. Development of novel drugs such as agents targeting tumour metabolism or hypoxia, new drug delivery systems and interventional equipment is part of some of the exciting ongoing research. Innovative concepts such as imageable (*i.e.* radiopaque) beads[109] or beads loaded with antiangiogenic agents[110] are currently being investigated. Imaging modalities such as cone beam CT will be further refined allowing for a more comprehensive utilization of 3D imaging technology in the procedure room. Moreover, image fusion techniques and software identifying tumour-feeding arteries[111] will undoubtedly help treatment guidance and expand indications for therapy.

In conclusion, catheter-based IATs have revolutionized the treatment of HCC. Level I evidence of the benefit in survival of cTACE led to the recognition of catheter-based therapies in the management of patient with unresectable HCC. cTACE remains the standard of care in HCC patients with intermediate-stage disease (BCLC B). DEB-TACE has a decreased toxicity profile compared to cTACE (Level I evidence) with similar tumour response rates. However, no survival benefit of DEB-TACE over cTACE has been shown to date. Y^{90} is maturing as a serious treatment option for patients situated between intermediate and advanced stages. Sorafenib has revolutionized the systemic therapy of HCC and is indicated in advanced-stage disease with preserved liver function and in patients with progressing lesions despite locoregional treatments (Level I evidence).

CONFLICTS OF INTEREST

Jean-François Geschwind, MD, is a consultant for Biocompatibles/BTG, Bayer HealthCare, Guerbet, Nordion/BTG, Philips Healthcare and Jennerex.

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