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Anti-Tumour Treatment

Updated use of TACE for hepatocellular carcinoma treatment: How and when to use it based on clinical evidence

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ABSTRACT

Hepatocellular carcinoma (HCC) is the most common primary liver cancer, representing the sixth leading cause of cancer and the third leading cause of cancer-related mortality. Patient stratification and treatment allocation are based on tumor stage, liver function, and performance status. According to the Barcelona Clinic Liver Cancer (BCLC) staging system, transarterial chemoembolization (TACE) is the first-line treatment for patients with intermediate stage HCC, including those with large or multinodular HCC, well-preserved liver function, and no cancer-related symptoms or evidence of vascular invasion or extrahepatic spread. Two TACE techniques have been used since 2004, conventional TACE (cTACE) and TACE with drug-eluting beads (DEB-TACE). cTACE was evidenced first to treat intermediate stage HCC patients. It combines the transcatheter delivery of chemotherapy using Lipiodol-based emulsion plus an embolizing agent to achieve strong cytotoxic and ischemic effects. Drug-eluting beads (DEBs) were developed in order to slowly release chemotherapeutic agents, and to increase ischemia intensity and duration. Recent advances allow TACE treatment of both early stage patients (i.e. those with a solitary nodule or up to 3 nodules under 3 cm) and some advanced stage patients. Here we review recent clinical evidence related to TACE treatment of patients with early, intermediate, and advanced stage HCC. Based on the 2014 TACE algorithm of Raoul et al., this international expert panel proposes an updated TACE algorithm and provides insights into TACE use for patients at any HCC stage.

Introduction

Hepatocellular carcinoma (HCC) is mainly associated with chronic liver disease. Indeed, its incidence is highest in Asia and Sub-Saharan Africa, where chronic hepatitis B virus infection is endemic. Until recently, the hepatitis C virus was the leading cause of HCC, but non-alcoholic fatty liver disease (NAFLD) is now emerging as a major risk factor for HCC, especially in Western countries [1–3]. Obesity and metabolic disorders represent the most important risk factors for HCC and currently account for 36.6% of HCC cases in the US. This percentage is expected to increase to 40% to 50% by 2030 [2].

The Barcelona Clinic Liver Cancer (BCLC) staging system is commonly used in Western countries for HCC management. Following the BCLC system and based on the most robust scientific evidence, prognosis is based on factors related to tumor burden (lesion number and size, the presence of vascular invasion, and extrahepatic spread); on liver function (Child-Pugh status); on the presence of cancer-related symptoms (ECOG-performance status); and on treatment allocation (i.e. resection, liver transplantation, ablation, transarterial chemoembolization, systemic therapy, or best supportive care) [4,5]. According to the BCLC system, transarterial chemoembolization (TACE) is the first-line treatment for intermediate stage disease, which includes asymptomatic patients with limited unresectable multinodular lesions, without vascular invasion or extrahepatic spread and who have well-preserved liver function. The BCLC system also incorporates the treatment migration concept in that TACE should be used in patients with

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early stage HCC in whom the recommended treatments are not feasible or have failed. The use of TACE is also supported by other staging systems, such as the Japanese Integrated Staging (JIS) scoring system [6], the Chinese University Prognostic Index (CUPI) [7], and the Hong Kong Liver Cancer (HKLC) staging system [8], all of which have been validated in Eastern Asian populations.

There are two TACE techniques, namely conventional TACE (cTACE), which uses Lipiodol, and TACE with drug-eluting beads (DEB-TACE). Notably, TACE is a well-established treatment for patients with intermediate stage HCC [4,9–11]. Accordingly, the goal of this review article is to summarize the most recent data from studies that compared the efficacy and safety of cTACE and DEB-TACE, including emerging data from studies that used TACE to treat patients with early and advanced stage HCC. As a multidisciplinary group of experts in the treatment of HCC, we aimed to identify factors that predict survival after TACE as well as potential new indications that could be treated by TACE in the near future. Based on our own clinical experience with TACE as well as on published data, we propose an updated algorithm for TACE with the hope that it will provide some guidance for treatment decisions.

Clinical-based evidence of TACE efficacy and safety

TACE treatment aims to induce tumor necrosis and is based on the observation that HCC has predominantly arterial vascularization compared with the surrounding liver parenchyma. This approach results in a cytotoxic effect combined with ischemia in tumor tissue.

Conventional TACE (cTACE): Clinical evidence and technical standardization

cTACE treatment involves the intra-arterial injection of a cytotoxic drug, such as doxorubicin, epirubicin, idarubicin, mitomycin C, or cisplatin, that is emulsified in the oily radio-opaque agent Lipiodol (Lipiodol® Ultra-Fluid, Guerbet). This is followed by intra-arterial injection of an embolic agent, such as gelatin sponge, polyvinyl alcohol particles, or microspheres. During cTACE, Lipiodol carries and delivers chemotherapy to the tumor [12,13] and causes embolization of the tumor microcirculation [14]. Moreover, intratumoral retention of Lipiodol as detected on post-procedure CT-scan predicts overall survival [15,16].

Randomized controlled trials (RCTs) and meta-analyses have demonstrated the superiority of cTACE over best supportive care (BSC) for intermediate stage HCC. In 2002, Llovet et al. reported that the mean survival was significantly longer with cTACE (28.6 months) than with BSC (17.9 months; P = 0.009) [17]. Another RCT confirmed that cTACE has a benefit over BSC in terms of survival rate (57% vs. 32% at 1 year; 31% vs. 11% at 2 years; 26% vs. 3% at 3 years, respectively, P = 0.002) [18]. The superiority of cTACE over BSC was confirmed by a meta-analysis that found higher 2-year overall survival with cTACE (OR 0.53; 95% CI 0.32–0.89; P = 0.017) [19]: the median overall survival was 20 months for cTACE versus 16 months for BSC. Based on these data, cTACE was recognized in 2012 as the gold standard treatment for intermediate stage HCC with the highest grade of recommendation (1A) [20]. A recent systematic review of cTACE efficacy that included a total of 10,108 HCC patients found that the median overall survival was 19.4 months and that the 5-year survival rate was 32.4% [21], confirming historical data from RCTs and meta-analyses.

For 30 years, cTACE has been referenced in many publications with various levels of details for the method of preparation and administration. In 2016, a worldwide expert panel published consensus technical recommendations in order to encourage cTACE standardization [22]. The consensus endorsements are summarized in Table 1.

DEB-TACE: Clinical evidence of efficacy

Drug-eluting beads (DEBs) are non-resorbable embolic microspheres that can be loaded with cytotoxic agents. They were developed to achieve more sustained drug release with concomitant embolization. Commercialized DEBs are composed of various hydrophilic ionic polymers that can bind to anthracycline drugs via an ion exchange mechanism. Up to 37.5 mg of doxorubicin per mL of microspheres can be loaded in 30 min to 2 h. Several microsphere diameters are available, ranging from 40 μm to 900 μm [23,24]. An *in vitro* analysis showed that there are important differences in doxorubicin loading and release depending on the type and the size of the microspheres [25,26]. Interestingly, in two separate *in vitro* experiments, only 30% of the doxorubicin was released from the microspheres [26,27]. Doxorubicin, which was loaded onto DC Bead® (100–300 μm) (BTG), was detected 1.2 mm away from the occluded vessel in explanted HCC livers [28]. The tissue concentration of doxorubicin decreased from 5 μmol/L 8 h after DEB-TACE to 0.65 μmol/L at 1 month. The authors concluded that in these conditions, DEB-TACE provides sustained drug delivery for a 1-month period.

The first phase II trial of DEB-TACE, which evaluated DC Bead® (500–700 μm) (BTG), reported that the DEB-TACE group had a lower plasma doxorubicin C_{max} and Area Under the Curve (AUC) for up to 7 days compared to the cTACE group [29]. Because of some methodological challenges, including differences in treatment selectivity, a lack of technical TACE reproducibility, and variable AUC values in the DEB-TACE group, an additional comparative pharmacokinetic study is still needed to draw robust conclusions.

In 2012, two retrospective studies evaluated DEB-TACE using 100–300 μm and/or 300–500 μm microspheres with an intended doxorubicin dose of 150 mg in selected BCLC-A or -B patients [30,31]. The median overall survival in the two groups was 43.8 months and 48 months, respectively. Although there was no comparative evaluation of different sizes of DC-Bead®, the 100–300 μm beads became the most frequently used microspheres. Smaller DC Bead M1® (70–150 μm) (BTG) were evaluated in recent prospective and retrospective studies and showed an objective response rate that ranged from 77% to 93% [32–34] with variable serious adverse event (AE) rates.

HepaSphere® microspheres (Merit Medical) are another type of commercialized microsphere that have a dry diameter of 30–60 μm and that expand in diameter according to the suspension protocol: 166–242 μm in diameter in saline and 145–213 μm in doxorubicin solution [35]. In 2014, a Greek study of 45 patients treated with HepaSphere® (30–60 μm) reported an objective response rate of 68.9% with no serious AEs [36].

Very recently, the MIRACLE I pilot study showed that Embozene TANDEM® 75 μm microspheres (Boston Scientific) loaded with 150 mg of doxorubicin provided good local tumor control (95%) in a small cohort of patients who mainly had unilobar disease [37]. Aliberti et al. suggested that TACE with LifePearl® microspheres (Terumo) loaded with doxorubicin is efficient and safe for the treatment of unresectable primary liver cancer [38].

Currently, in the absence of RCTs that compare different DEB devices, no definitive indication can be recommended as to which DEBs should be used.

Choosing between cTACE and DEB-TACE: Tumor response and survival

In the PRECISION V multicenter RCT phase II trial, DEB-TACE (DC Bead® 300–500 μm followed by DC Bead® 500–700 μm) failed to show superiority over cTACE for the primary endpoint, which was tumor response on MRI 6 months after the procedure (P = 0.11) [39]. Notably, 27.8% of cTACE patients did not receive an embolic agent during the procedure.

The PRECISION ITALIA STUDY GROUP phase III trial planned to enroll 214 patients to demonstrate the superiority of DEB-TACE using

Table 1
Summary of technical recommendations from experts on how to perform reproducible cTACE. Adapted from de Baere et al. [22].

Item	Recommendations for reproducible cTACE
Patient selection	Pay particular attention to underlying liver disease and Performance Status (PS)
Pre-procedure imaging	Perform multiphasic computed tomography (CT) or dynamic contrast-enhanced-magnetic resonance imaging (MRI) of the liver before treatment allocation
Patient preparation	Discuss systematic antiemetic treatment, intravenous hydration, and pain killer use as well as antibiotic prophylaxis according to the risk of liver abscess
Per-procedure imaging	Use cone beam (CB)-CT for tumor visualization, targeting, and assessment of treatment completion
Chemotherapy	Use doxorubicin 50–75 mg/m^2 body surface area or cisplatin 50–100 mg/m^2
Lipiodol emulsion	Prepare water-in-oil emulsion (aqueous chemotherapy droplets in internal phase and Lipiodol in continuous external phase) to improve tumor deposit. The water-in-oil emulsion is obtained by mixing one volume of drug solution with two to three volumes of Lipiodol by pushing the drug syringe into the syringe containing Lipiodol
Embolizing agent	Gelatin sponge is commonly used. If used, the size of calibrated microspheres should be 100–300 μm in order to ensure distal occlusion with preservation of feeding segmental arteries
Selectivity	Superselective cTACE, using microcatheter when treating a single tumor or low number of tumors
Endpoint	Lipiodol opacification of the small arterioportal sinusoids should be used as a predictive factor for tumor response, tumor necrosis, and local recurrence
Response evaluation	Assess tumor viability using the mRECIST criteria
cTACE regimen	Perform at least two cTACE procedures 2–8 weeks apart before stopping due to a lack of response

DC Beads® versus cTACE on survival [40]. The trial was stopped for futility after 177 patients were enrolled, 89 in the DEB-TACE group and 88 in the cTACE group. No difference was found in tumor response, and the median time-to-progression was 9 months in both arms. The 1- and 2-year survival rates were 86.2% and 56.8%, respectively, after DEB-TACE, and 83.5% and 55.4%, respectively, after cTACE (P = 0.949). Although the heterogeneity in patient selection makes it difficult to draw definitive conclusions, the most comprehensive updated meta-analysis of 4 RCTs and 8 observational studies, which included 1449 patients, confirmed the non-superiority of DEB-TACE over cTACE in terms of tumor response and survival [41].

Choosing between cTACE and DEB-TACE: Safety

The most frequent AEs for both DEB-TACE and cTACE are typical of post-embolization syndrome, which is characterized by pain, fever, nausea, and vomiting. Notably, systemic doxorubicin-related complications are rare. Indeed, a recent systematic review from 217 articles published between 1980 and 2013 showed that post-embolization syndrome (fever, abdominal pain, and ileus) was the most common treatment-related AE, occurring in 47.7% of patients treated with cTACE [21]. There was a transient liver enzyme increase in 52% of patients, and the overall post-procedure mortality rate was 0.6% [21].

RCTs have failed to find any difference between DEB-TACE and cTACE in terms of safety endpoints. In the PRECISION V study, there was no significant difference (P = 0.86) in DEB-TACE and cTACE in the primary endpoint of serious AEs within 30 days of the procedure (20.4% and 19.4% after DEB-TACE and cTACE, respectively); however, more than 25% of cTACE patients did not have embolization [39]. Similarly, a recent meta-analysis found no statistically significant difference in AEs (OR 0.85, 95% CI 0.60–1.20, P = 0.36) [41]. In the PRECISION ITALIA STUDY GROUP trial, post-procedural pain was less frequent in the DEB-TACE arm [40].

Interestingly, other studies have provided safety data after longer follow-up periods to compare the liver and biliary injury rates between TACE techniques. In 2012, a large retrospective study of HCC (n = 88) and liver metastases from neuroendocrine tumors (NETs) (n = 120) that were treated either by cTACE or DEB-TACE demonstrated that liver/biliary injury at follow-up imaging was associated with DEB-TACE (OR 6.63; P < 0.001) irrespective of tumor type [42]. In the same study, biloma/parenchymal infarct was also strongly associated with DEB-TACE (OR 9.78; P = 0.002) and with NETs (OR 8.13; P = 0.04). In the cirrhotic HCC group, at least one liver/biliary injury was observed after 30.4% of DEB-TACE sessions versus after 4.2% of cTACE sessions (P < 0.001). The authors recommended caution when using DEB-TACE in non-cirrhotic patients [42].

Very recently, a retrospective study compared TACE-related hepatic toxicities 3 months after cTACE and DEB-TACE in 151 patients with intermediate stage HCC [43]. Biliary injuries and intrahepatic biloma incidence at follow-up imaging was significantly higher following DEB-TACE (P < 0.001). DEB-TACE was associated with a significantly increased risk of hepatic damage (OR 3.13, 95% CI 1.74–5.63, P < 0.001) and biliary injuries (OR 4.53, 95% CI 2.37–8.67, P < 0.001). However, the clinical impact of these biliary injuries, which were identified by imaging at follow-up, is unknown.

A recent retrospective study compared the incidence and predictors of hepatic arterial damage after a single DEB-TACE treatment (54 patients) versus a single cTACE treatment (54 patients) [44]. The incidence was significantly higher after DEB-TACE when analyzed per branch (OR 6.36; P < 0.001) and per patient (OR 3.15; P = 0.005), with doxorubicin dose as a possible risk factor.

Lastly, a recent meta-analysis that pooled 9 studies and that included 1026 HCC patients reported severe AEs rate with no statistical difference between cTACE and DEB-TACE groups (OR 0.85, 0.60–1.20, P = 0.36) [41].

Thus, despite the appealing premise of DEB-TACE and several comparative studies and meta-analysis, the superiority of DEB-TACE over cTACE has never been demonstrated in terms of patient survival, tumor response, and safety. Efforts are still needed to standardize both techniques.

Choosing between cTACE and DEB-TACE: Cost

Comparison in costs and cost-effectiveness between DEB-TACE and cTACE are not easy. A recent Italian meta-analysis has been performed from the healthcare provider point of view [45] following a Markov simulation model from the first TACE until death. This simulation was based on a meta-analysis mixing randomized controlled trials and prospective and retrospective series of DEB-TACE, including 1860 patients. Despite longer (p = 0.001) in-hospital stay after cTACE, due to more frequent post-embolisation syndrome, global costs were non significantly lower with cTACE than with DEB-TACE.

How to assess tumor response?

Ideally, tumor response should discriminate between patients who have benefitted from treatment and those who have not. Regrettably, the conventional criteria, which are based on tumor diameter shrinkage, such as Response Evaluation Criteria In Solid Tumor (RECIST) criteria, underestimate response and do not predict the survival of HCC patients undergoing molecular targeted therapies and locoregional treatments [46]. Accordingly, modified RECIST (mRECIST) criteria that assess contrast-enhancement have been developed to measure the reduction in viable tumor burden [47–49]. These criteria

are predictive for survival if they are measured at least 3 months after TACE [50]. However, even reduction in viable tumor burden in dynamic imaging studies remains a surrogate marker for evaluating the response rate [51], it cannot replace overall survival as the reference endpoint for the assessment of treatment efficacy.

The dense tumor staining due to Lipiodol accumulation in tumors on CT scan and the lack of residual enhancement on MRI after cTACE are associated with greater extent of tumor necrosis [52]. It was recently demonstrated that Lipiodol deposition, as an early radiological marker, is helpful in survival prognosis for patients with large HCC lesions [53]. Because long-lasting, complete Lipiodol tumor deposition is considered to indicate tumor necrosis, a lack of deposition or partial deposition suggests that tumor feeders may have been missed or that Lipiodol uptake in the tumor was low. In these cases, the patient can be scheduled for repeat TACE without waiting for delayed follow-up imaging. After DEB-TACE, tumor response can be assessed using both dynamic CT and MRI.

Deciding to initiate, stop, or repeat TACE (Table 2)

The Selection for TrAnsarterial chemoembolization TrEatment (STATE) [54] and the Hepatoma arterial-embolisation prognostic (HAP) [55] scores were developed to improve patient selection for the first TACE treatment. Moreover, the Assessment for Retreatment with TACE (ART) score [56] and the ABCR (α-fetoprotein, Barcelona Clinic Liver Cancer, Child-Pugh, and Response) score [57] were developed in order to identify patients who may or who may not benefit from repeated TACE.

The STATE score includes the serum albumin level, tumor load, and C-reactive protein (CRP) level [54]; the HAP score was based on 4 parameters (albumin, bilirubin, AFP and tumor size). The ART score includes serum AST increase > 25% after the first TACE, an increase in the Child-Pugh score of 1 or ≥2 points after the first TACE, and the absence of radiological tumor response [56]. The START strategy combines the STATE score and the ART score and aims to improve both patient selection for the initial treatment and patient suitability for retreatment [54].

ABCR score calculation includes an AFP level ≥200 ng/mL at baseline, the BCLC stage at baseline, an increase in Child-Pugh score of ≥2 points from baseline after the 1st TACE session, and radiologic response after the first TACE session [57].

The STATE score was validated in an external cohort of 228 HCC patients [58], and the HAP score in an international cohort of 3030 patients [59], but other studies have demonstrated that the STATE, ART, and ABCR scores just identify patients who are not good candidates for TACE [60–64]. Thus far, these scores have shown limited predictive value and cannot be used to make clear-cut clinical decisions.

Because the predictive value of these scores has not been demonstrated, they can only serve as one component in the decision-making process. To date, tumor burden, BCLC stage at baseline, Child-Pugh score, and radiologic response are considered the most predictive factors for TACE retreatment decision-making and for consideration of alternative therapy after two TACE treatments.

In practice, TACE should not be repeated when substantial necrosis is not achieved after two TACE treatments or when there is progression or liver function impairment, worsening of performance status (PS), or the appearance of portal vein tumor thrombosis or extrahepatic metastases [10].

TACE: Outside of intermediate stage

Early stage disease

The current EASL guidelines recommend TACE for patients with intermediate stage disease, i.e. with multinodular asymptomatic tumors without vascular invasion or extrahepatic spread [9]. However, patients with earlier stage disease who cannot benefit from the recommended option can receive TACE according to the treatment stage migration concept [9]. Several authors have reported a high response rate and very good outcomes in patients with early stage disease who are unsuitable for surgery or for percutaneous ablation who were treated with TACE [30,31,64–67]. In some series, the number of patients treated with TACE included more than 40% of cases with solitary nodules, most with early stage disease [64,68].

The role of TACE as neoadjuvant therapy prior to liver transplantation (LT) is widely accepted, either as a bridge between treatments while the patient is on the waiting list or to downstage tumor burden to accepted criteria for transplantation [9]. The waiting time to LT varies in different regions, but in most areas, treatment is mandatory while on the waiting list. Studies have found that cTACE is associated with waitlist dropout rates of 3–13% [69–71], which is lower than expected based on historical data [72].

Table 2
Parameters used to calculate STATE, HAP, ART, and ABCR scores.

	To decide for 1st TACE		To decide for reTACE	
	STATE [54]	HAP [55]	ART [56]	ABCR [57]
	Baseline (before 1st TACE)			
Albumin	In g/L as score points	< 36 g/dL (1 point)		
Bilirubin		> 37 μmol/L (1 point)		
Tumor load	Beyond up-to-seven criteria (−12 points)	Max tumor diameter > 7 cm (1 point)		
CRP	≥1 mg/dL (−12 points)			
BCLC stage				A (0 point) B (2 points) C (3 points)
AFP		> 400 ng/mL (1 point)		≥200 ng/mL (1 point)
			After 1st TACE	
Child-Pugh score			1-point increase (1.5 point) ≥2-point increase (3 points)	≥2-point increase (2 points)
Radiologic tumor response			No (1 point)	Yes (-3 points)
AST			> 25% increase (4 points)	
Score range	*Depends on serum albumin level (range greater than ART)*	*From 0 to 4*	*From 0 to 8*	*From −3 to +6*

BCLC: Barcelona Clinic of Liver Cancer; AFP: alpha-foeto-protein; CRP: C-reative protein.
STATE: **s**election for **t**rans**a**rterial chemoembolization **t**r**e**atment; HAP: **h**epatoma **a**rterial-embolisation **p**rognostic; ART: **A**ssessment for **Re**t**r**eatment; ABCR: **A**lpha-foeto Protein, **B**CLC, **C**hild-Pugh, **R**esponse.

Moreover, cTACE has been shown to reduce HCC recurrence after LT and to improve post-transplant overall survival, especially when the period on the waiting list exceeds 6–12 months [73]. An analysis of the largest available series indicates that complete necrosis ranges between 27% and 57% in patients within the Milan criteria [73]. Although adequate tumor response and efficacy in maintaining the patient within the Milan criteria were reported after DEB-TACE treatment [74,75], DEB-TACE has not been widely studied as bridging therapy, and the available evidence is not as good as for cTACE.

Advanced stage disease

According to the 2018 EASL Clinical Practice Guidelines, advanced BCLC (stage C) represents a subgroup of HCC patients with cancer symptoms and/or vascular invasion or extrahepatic spread, with preserved liver function and PS 1–2 [9]. Based on the SHARP trial, sorafenib is the standard-of-care for this patient subgroup [76]. Recently, lenvatinib was demonstrated to be non-inferior to sorafenib: the median survival did not differ significantly between the two groups (13.6 and 12.3 months for lenvatinib and sorafenib, respectively), and they had similar AE rates [77]. As second-line therapy, regorafenib [78] demonstrated a survival benefit after sorafenib in patients who tolerated sorafenib, and cabozantinib [79] and ramucirumab (the REACH trial) [80] also showed positive results.

Both the EASL and AASLD Guidelines stand against the use of TACE in patients with portal vein tumor thrombosis (PVTT). In the first trial to demonstrate the efficacy of cTACE versus BSC [17], patients with PVTT were excluded. In the second trial [18], multi-parametric assessment revealed that two prognostic factors were statistically significant: treatment (TACE vs BSC; RR of 0.49) and the presence of PVTT (RR of death of 2.71; CI95: 1.38–5.32). The latter can be related either to an increased risk of liver failure after arterial obstruction or to a specific patient pattern of aggressive disease that does not respond to locoregional treatment.

Nevertheless, some authors have proposed expanding the scope of indications for TACE beyond BCLC-B in some patients with advanced HCC due to PVTT. The rationale is that the formation of collateral vessels around the portal vein along with good liver function may allow TACE to be tolerated in selected cases, with this so-called Quasi-C subgroup population being defined by segmental or sub-segmental PVTT [81]. However, a large Japanese study (n = 655) found that even for HCC patients who had a portal thrombus distal to but not involving the second order branch (VP1 in the Japanese classification), the median overall survival was poorer (18.6 months) than in patients without PVTT (28.2 months) [59].

Strikingly, the BRIDGE study, an international large-scale and longitudinal cohort study that included 18,031 patients in 14 countries, documented the HCC patient experience in real-world clinical practice and found that TACE was the first-line treatment for nearly 50% of the BCLC-C stage HCC patient [82]. The survival benefit of cTACE over BSC has been described in two prospective non-randomized trials [83,84] and in one meta-analysis [85] of advanced HCC patients with PVTT. The survival benefits for the different degrees of PVTT were reported as follows for cTACE and BSC, respectively: type I, 19 months vs. 4 months ($P = 0.001$); type II, 11 months vs. 1.4 months ($P < 0.001$); type III, 7.1 months vs. 1.3 months ($P < 0.001$), and type IV, 4 months vs. 1 month ($P = 0.005$) [83]. Finally, in a large cohort of 164 patients with PVTT, cTACE significantly improved survival compared to BSC, both in patients with PVTT in the segmental branches ($P = 0.002$) and in patients with PVTT in the first order branches or in the main trunk of the portal vein ($P = 0.002$) [84]. However, the prognosis was poor in both arms.

Few studies have shown that DEB-TACE is a feasible treatment for HCC patients with advanced stage disease. A retrospective series of 80 patients with advanced stage HCC showed that DEB-TACE is feasible, with no 30-day mortality and median progression-free survival and overall survival of 5.1 months and 13.3 months, respectively [86].

Thus, in most cases, TACE is not recommended for advanced stage HCC. The question of which therapeutic option is best for the specific subset of patients with advanced disease, i.e. with 'Quasi-C' (segmental PVTT, Child-Pugh A, acceptable PS) is still open. RCTs comparing TACE to sorafenib as first-line treatment are still needed to assess the potential role of this technique for patients with advanced disease who are intolerant of or unsuitable for systemic therapy.

The burning question is regarding the definition of advanced HCC just only because impaired PS despite absence of vascular invasion or extrahepatic spread. Notably, according to the BCLC classification, PS is based on tumor-induced modifications, and some authors have suggested that the distinction between PS 0 and PS 1 can be challenging. Reassignment has been described as enhancing the prognostic capability of the BCLC classification [87].

Combined treatments

Combining TACE with local ablation

Surgical resection (SR) and LT are considered standard curative therapies for HCC. When surgery is not possible, percutaneous ablation (radiofrequency ablation, RFA, or microwave ablation, MWA) is usually considered to be a suitable alternative [88–91].

In 2012, an RCT in patients with solitary recurrent HCC lesions up to 5 cm in diameter demonstrated the superiority of combined treatment (first cTACE and then RFA) over RFA alone [92]. The 1-, 3-, and 5-year overall survival rates were 94%, 69%, and 46%, respectively, for combined treatment and 82%, 47%, and 36% for RFA alone ($P = 0.037$). The corresponding recurrence-free survival rates were 80%, 45%, and 40% for combined treatment and 64%, 18%, and 18% for RFA alone ($P = 0.005$). In 2013, the same authors reported the results of an RCT conducted in 189 Chinese patients who had solitary HCC lesions that were less than 7 cm or who had a maximum of 3 lesions that were less than 3 cm [93]. Patients undergoing combined cTACE + RFA treatment had significantly better overall survival and recurrence-free survival than patients treated with RFA alone (HR 0.525; $P = 0.002$; HR 0.575; $P = 0.009$, respectively).

Combined TACE + RFA may also be a good option if there is a risk of surgical complications or if the tumor location makes the tumor difficult or impossible to resect. Indeed, a recent retrospective Korean study in patients with solitary 2- to 3-cm lesions did not find any significant differences in long-term therapeutic outcomes (local tumor progression, intrahepatic distant recurrence, disease-free survival, or overall survival) between combined cTACE + RFA versus surgical resection alone [94].

Unfortunately, up to now no trial had compared cTACE vs cTACE + RFA to destroy residual viable tissues; this combination deserves to go further.

Combining TACE with systemic therapy

TACE can cause acute hypoxia, leading to the upregulation of VEGF, which might contribute to tumor revascularization and local recurrence. Thus, the rationale for combining TACE with systemic therapy was that combining TACE with tyrosine kinase inhibitors would inhibit both revascularization and tumor (re)proliferation. The combination of TACE plus anti-angiogenic drugs was expected to extend the period during which TACE controls tumor progression and improves the survival of patients with intermediate stage disease.

Two phase II/phase III RCTs, the SPACE trial [95] and the TACE 2 trial [96], compared the combination of TACE + sorafenib to TACE alone. Two other RCTs compared TACE to a combination of TACE + antiangiogenic drugs: brivanib in the BRISK-TA study [97] and orantinib in the ORIENTAL study [98]. Unfortunately, all four trials failed to demonstrate any clinical benefit from combined therapy. Recently,

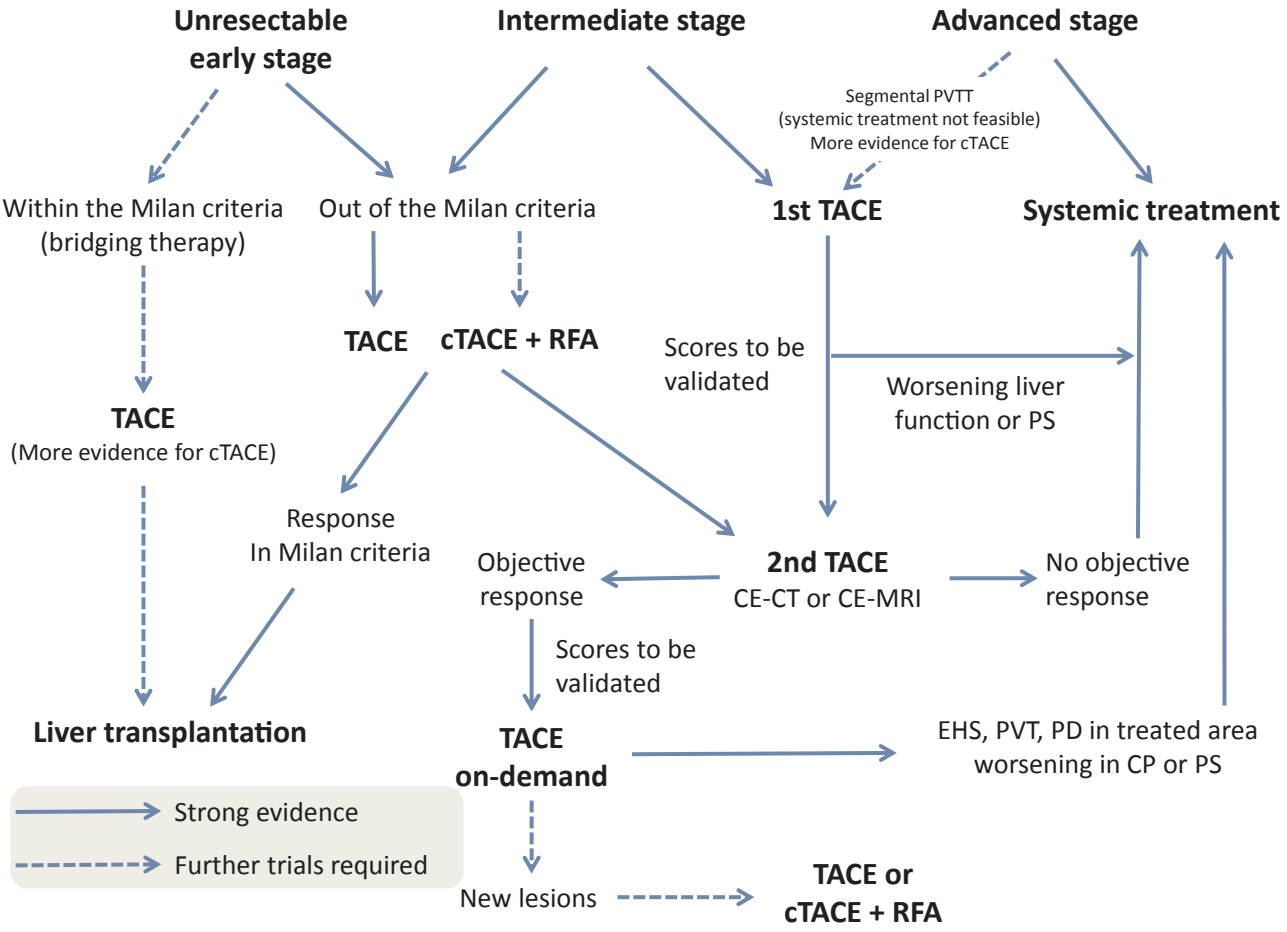

Fig. 1. An updated algorithm decision tree for TACE in managing early, intermediate, and advanced stage HCC. TACE = transarterial chemoembolization; Seg PVTT: segmental portal vein tumor thrombosis; RF: radio-frequency; CE-CT = contrast enhanced computed tomography; CE-MRI = contrast enhanced magnetic resonance imaging; CP = Child-Pugh; cTACE = conventional transarterial chemoembolization; EHS = extrahepatic spread; OR = Objective Response; PD = Progressive Disease; PS = performans status; PVT = portal vein tumor thrombosis.

Kudo et al. suggested potential reasons for these repeated failures, including drug efficacy, drug management (regimen duration, dose, AEs), and methodological issues (endpoint selection) [99]. During 2018 ASCO meeting, a randomized phase II trial – called TACTICS trial - comparing cTACE plus sorafenib (initiated 3 weeks before the first cTACE) with cTACE alone in 156 patients reported a major improvement in PFS based on a new definition of untreatable progression [100]; but these results did not allow to revise previous conclusions about combinations.

Summary and expert opinion

Since 2011, clinical evidence has supported TACE as the first-line treatment for intermediate stage HCC patients, and there has been no demonstrated difference in efficacy (tumor response and overall survival) between cTACE and DEB-TACE. Based on recent EASL guidelines [9], either technique can be utilized, with the choice left to the physician knowing that (1) a higher risk of hepatic and biliary injuries after DEB-TACE than after cTACE was reported in two retrospective studies [42,43], (2) less post-procedural pain after DEB-TACE was reported in the PRECISION ITALIA STUDY GROUP trial [40].

The BRIDGE study reported that TACE is used to treat nearly 50% of patients from stage 0 to stage D HCC in daily practice [84]. Moreover, the large GIDEON study showed that cTACE and DEB-TACE comprise 74% and 16% of TACE procedures overall, respectively [101]. Recent clinical studies demonstrated that TACE should be considered a therapeutic option outside of intermediate stage HCC i.e. those with early-stage disease and eventually selected patients with advanced-stage disease. The updated treatment algorithm illustrates the following extended potential indications for TACE (Fig. 1):

- Early stage disease (as bridging therapy for LT),
- Early stage disease involving unresectable single lesions up to 7 cm in diameter or 3 lesions up to 3 cm in diameter; these can be treated with cTACE in sequential combination with local ablation,
- Recurrent intrahepatic lesions up to 3 cm in diameter can be treated with TACE (cTACE or DEB-TACE) alone or with cTACE in sequential combination with RFA,
- Advanced stage – Quasi C patients with PS 0, CP-A, and with segmental PVTT. So far, cTACE efficacy and tolerance is much more evidenced than DEB-TACE and its potential efficacy might be explored when sorafenib is not feasible.

Despite intense clinical research on the development of new scoring systems for patient selection for the first TACE treatment and for TACE retreatment (STATE, ART, ABCR, and START scores), no scoring system has been validated for use in routine practice at different centers and in different patient populations. Therefore, the decision about TACE retreatment remains at the discretion of the tumor board.

Although TACE is considered a well-established treatment for patients with intermediate stage B HCC, additional clinical studies are needed to further change or refine guidelines and to potentially adjust

current contra-indications in the next international guidelines, especially for the treatment of early stage and locally advanced HCC.

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