Review Article

Role of Transarterial Chemoembolization in the Treatment of Hepatocellular Carcinoma

Bin-Yan Zhong[1#], Zhi-Cheng Jin[2#], Jian-Jian Chen[2], Hai-Dong Zhu[2*] and Xiao-Li Zhu[1*]

[1]Department of Interventional Radiology, the First Affiliated Hospital of Soochow University, Suzhou, Jiangsu, China; [2]Center of Interventional Radiology & Vascular Surgery, Department of Radiology, Zhongda Hospital, Medical School, Southeast University, Nanjing, Jiangsu, China

Abstract

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide. According to the Barcelona Clinic Liver Cancer (BCLC) staging system, transarterial chemoembolization (TACE) is the first-line recommendation for intermediate-stage HCC. In real-world clinical practice, TACE also plays an important role in early- and advanced-stage HCC. This review article by the experts from Chinese Liver Cancer Clinical Study Alliance (CHANCE) summarizes the available clinical evidence pertaining to the current application of TACE in patients with early-, intermediate-, and advanced-stage HCC. In addition, combination of TACE with other treatment modalities, especially immunotherapy, is reviewed.

Introduction

With increasing incidence and mortality, hepatocellular carcinoma (HCC) is one of the most common and fatal cancers worldwide.[1,2] Approximately 72% of all new cases of HCC are diagnosed in Asia and Western countries are also experiencinmg an increasing trend of incidence.[3] HCC mainly occurs against a background of chronic liver disease caused by hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, alcohol abuse. or metabolic disorders.[2] The Barcelona Clinic Liver Cancer (BCLC) staging system is commonly applied as the staging and treatment recommendation system for HCC.[4,5] Despite improved surveillance programs, approximately 80% of patients with HCC have intermediate- or advanced-stage disease at the time of diagnosis, which is the main cause of dismal long-term prognosis.[2]

According to the BCLC staging system, transarterial chemoembolization (TACE) is the first-line treatment option for intermediate-stage HCC. The BCLC staging system also introduces the concept of treatment stage migration, which means that TACE should be considered and recommended for patients with early-stage HCC in whom the recommended first-line treatment choices have failed or are not feasible.[4] In addition, the BRIDGE study demonstrated that TACE is most widely applied not only for intermediate but also for advanced HCC in clinical practice.[6] The application of TACE for intermediate and locally advanced HCC is also recommended by the China liver cancer (CNLC), Japan Society of Hepatology (JSH), Asia Pacific Association for the Study of the Liver (APASL), and Hong Kong Liver Cancer (HKLC) staging systems (Fig. 1).[7–10] Reported by the experts from Chinese Liver Cancer Clinical Study Alliance (CHANCE), the goal of this review article is to summarize the most recent data and evidence from studies and guidelines regarding the application of TACE for the management of HCC especially in the era of immunotherapy.

TACE for intermediate HCC

Patient selection

The BCLC staging system defines intermediate HCC as presence of multifocal nodules (>3 nodules or a maximum nodule diameter of >3 cm), preserved liver function, no cancer-related symptoms, i.e. Eastern Cooperative Oncology Group (ECOG) 0, and no macrovascular invasion or extrahepatic
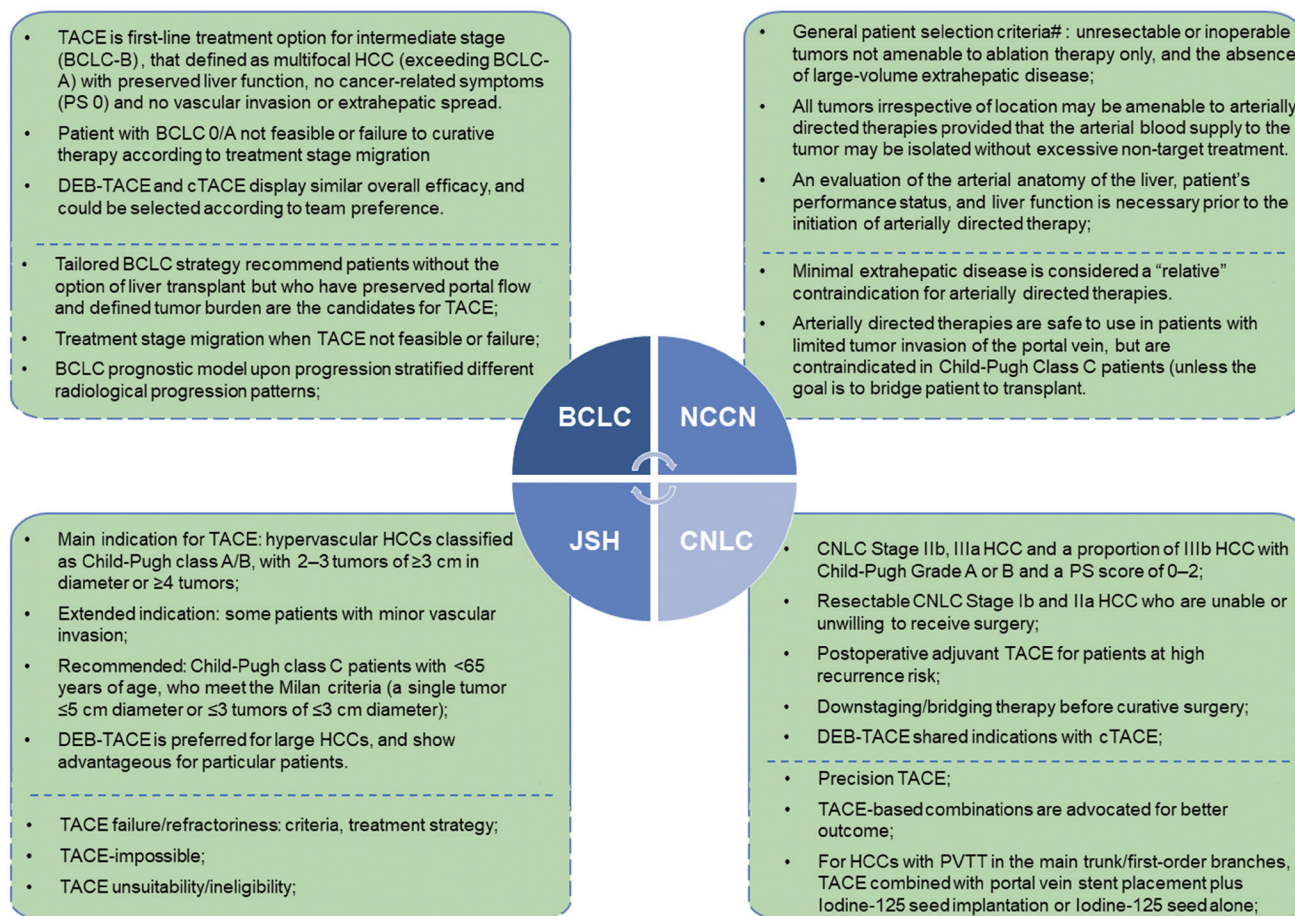
Fig. 1. Summary and comparison of the recommendations of TACE for HCC in different guidelines. BCLC, Barcelona Clinic Liver Cancer; CNLC, China liver cancer; cTACE, conventional transarterial chemoembolization; DEB-TACE, drug-eluting bead transarterial chemoembolization; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; JSH, Japan Society of Hepatology; NCCN, National Comprehensive Cancer Network; PVTT, portal vein tumor thrombosis; TACE, transarterial chemoembolization.

spread.[4] The recently updated BCLC staging system stratifies patients with intermediate-stage (BCLC-B) into three groups according to tumor burden and liver function.[4] TACE is recommended as the first-line choice for the second subgroup, i.e. patients without the option for liver transplantation but who have preserved portal flow and in whom selective access to feeding tumor arteries is feasible.[4] Notably, the updated BCLC staging system recommends that intermediate-stage HCCs with diffuse, infiltrative, extensive liver involvement do not benefit from TACE, and systemic therapy is the recommended first-line choice for these patients. The treatment recommendations of the European Association for the Study of the Liver (EASL), the American Association for the Study of Liver Diseases (AASLD), the APASL, and the JSH for intermediate-stage HCC are similar. All recommend TACE as first-line choice for all BCLC-B patients.[8,9,11,12] The CNLC staging system recommends TACE as first-line choice for intermediate HCC with more than three lesions, which is different from the other recommendations mentioned above.[7] Figure 2 shows a typical case of TACE treatment for patients with HCC.

The major contraindications for TACE in patients with intermediate-stage HCC in the guidelines include decompensated cirrhosis (jaundice, refractory ascites, overt hepatic encephalopathy, and hepatorenal syndrome), extensive tumor involving both liver lobes, renal insufficiency (creatinine ≥2 mg/dL or creatinine clearance <30 mL/min), serious coagulation dysfunction that is not amenable to treatment, technical contraindications such as untreatable arteriovenous fistula, presence of cachexia or multiple organ failure, and distal extensive metastasis with an expected survival <3 months.

TACE techniques

Two major techniques for performing TACE are widely adopted worldwide, which are conventional TACE (cTACE) and drug-eluting beads TACE (DEB-TACE). Conventional TACE, also known as lipiodol TACE, was developed in the early 1980s in Japan. It was subsequently established as the standard treatment based on the results of two randomized controlled trials (RCTs) that showed a significant survival benefit.[13,14] During cTACE, emulsion mixtures of lipiodol and cytotoxic drugs such as doxorubicin, epirubicin, or cisplatin are delivered to the tumor-feeding arteries, followed by administration with gelatin sponge or particles. DEB-TACE, which entails the delivery of microspheres charged with cytotoxic drugs, can achieve sustained drug release into the surrounding tissues over time and embolization. To date, data from several clinical trials suggest that DEB-TACE shows comparable efficacy to cTACE and has
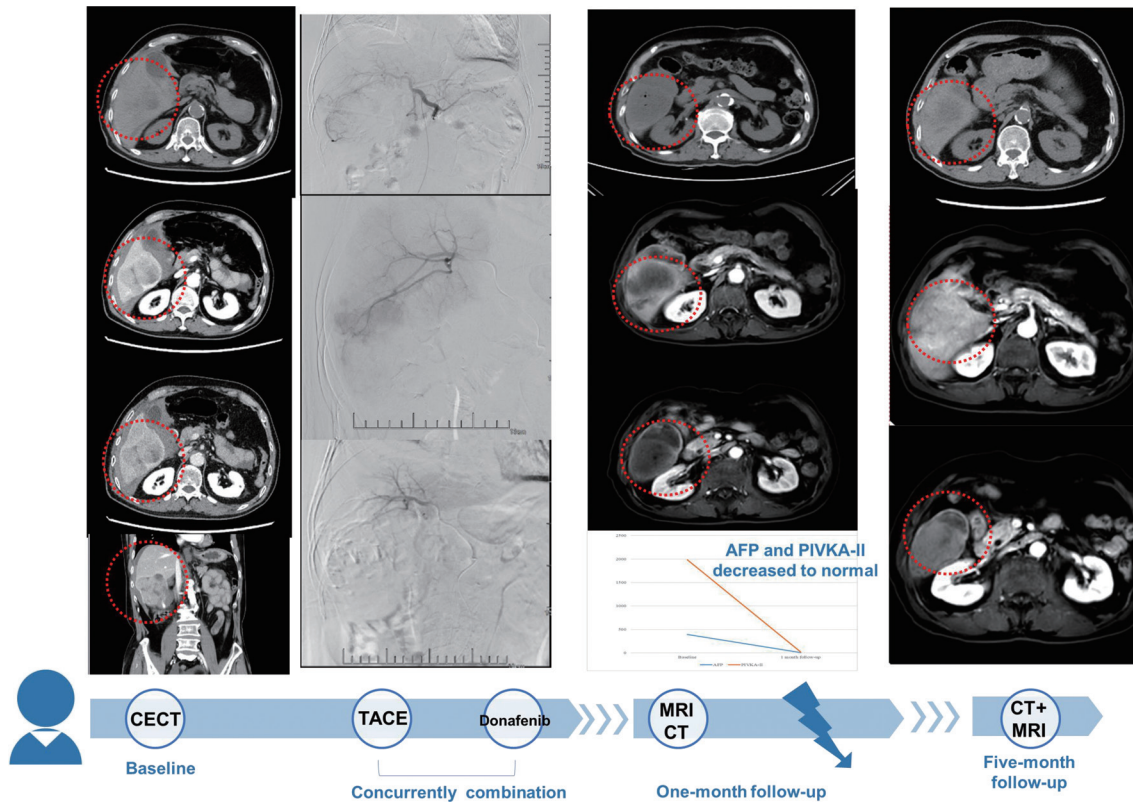
Fig. 2. Images obtained in patients with HCC treated with TACE. A 73-year-old man had a history of chronic hepatitis B ≥20 years. The baseline CT showed a huge intrahepatic lesion without peritumoral star lesions or vascular invasion (red dotted circle). There is no extrahepatic spread. The patient was treated with DEB-TACE combined with oral donafenib (0.2 g). The 1- and 5-month follow-up MRI after DEB-TACE showed that the patient achieved a continued complete response. The patient is still being followed-up. CT, computed tomography; DEB-TACE, drug-eluting bead transarterial chemoembolization; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; TACE, transarterial chemoembolization.

relatively fewer cytotoxic drug-related adverse events.[15,16] Use of multifunction embolization microspheres has also been explored *in vivo,* and *in vitro* experiments, and in clinical trials. They are designed to be biodegradable, are visible by imaging, and can load different therapeutic agents.[17–19]

Balloon-occluded TACE (B-TACE) was first introduced in 2009 and uses a balloon microcatheter inflated within the tumor-feeding arteries. The theoretical basis of B-TACE is the hemodynamic changes caused by the balloon inflation that further results in the accumulation of dense lipiodol emulsion in the HCC nodule. Transarterial embolization, also called bland embolization, refers to transarterial administration of an embolic agent without additional chemotherapy, and is aimed at occluding small feeding arteries and inducing tumor ischemia and necrosis. In addition, TACE combined with bicarbonate infusion was reported to enhance the anticancer activity by targeting intratumoral lactic acidosis.[20]

Response assessment and treatment outcomes

Conventional evaluation of outcomes with the Response Evaluation Criteria In Solid Tumors (RECIST) criteria, which are based on tumor diameter shrinkage, tends to underestimate tumor response. Currently, the most widely accepted and applied evaluation of tumor response are the modified RECIST (mRECIST) criteria which are rules based on using contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) to measure the reduction in viable tumor burden.[21] The AASLD recommends progression-free survival (PFS) as a potential surrogate endpoint instead of overall survival (OS) for TACE-related trials.[22] Several ongoing trials of TACE combined with systemic therapy also use PFS as the primary endpoint or co-primary endpoint with OS (Table 1). Novel response assessment and prediction approach such as radiomics, glycans, and glycosylation, has also been applied for patients treated with a combination of TACE with other treatments; however, its applicability in clinical practice needs further exploration and discussion.[23–25]

Two milestone RCTs reported 1-year survival probabilities of 75% and 57%.[14] A systematic review of 14 RCTs also found that TACE improved the survival of patients with unresectable HCC.[26] Arterial embolization improved 2-year survival compared with controls. In addition, treatment induced objective responses in 35% of patients. Notably, all included RCTs in the systematic review were published between 1988 and 2002. Another systematic review of the treatment efficacy and safety of lipiodol TACE for HCC was published in 2016.[27] It included 10,108 patients in 101 studies, and the results showed a median OS of 19.4 months, without any new unexpected safety concerns. Figure 3 shows the results of reported objective response rate (ORR) of TACE for intermediate-stage HCC. Table 2 shows reported outcomes of RCTs for TACE in the treatment of HCC.[13–16,28–40]

Repeat TACE and TACE failure/refractory

Considering its palliative nature, repeat TACE is often re-

Table 1. Ongoing randomized controlled trials of TACE combined with immunotherapy

Trial (NCT number)	Enrollment	Population under study (BCLC stage)	Therapies under comparison	Primary endpoint(s)
EMERALD-1 (NCT03778957)	710	Candidates for first TACE (BCLC-B)	TACE plus durvalumab plus bevacizumab vs. TACE plus durvalumab vs. TACE plus placebo	PFS for placebo vs. combination
CHECKMATE-74W (NCT04340193)	765	Candidates for first TACE (BCLC-B)	TACE plus nivolumab plus ipilimumab vs. TACE plus nivolumab vs. TACE	OS and TTTP
LEAP-012 (NCT04246177)	950	Candidates for first TACE (BCLC-B)	TACE plus pembrolizumab plus lenvatinib vs. TACE plus oral placebo plus IV placebo	OS and PFS
TACE-3 (NCT04268888)	522	Candidates for first TACE (BCLC-B)	DEB-TACE plus nivolumab vs. DEB-TACE	OS (TTTP for the phase II portion)
RENOTACE (NCT04777851)	496	Candidates for first TACE (BCLC-B)	Regorafenib plus nivolumab vs. TACE	PFS
ABC-HCC (NCT04803994)	434	Candidates for first TACE (BCLC-B)	Atezolizumab plus bevacizumab vs. TACE	Time to failure of treatment

BCLC, Barcelona Clinic Liver Cancer; DEB-TACE, drug-eluting beads transarterial chemoembolization; OS, overall survival; PFS, progression-free survival; TACE, transarterial chemoembolization; TTTP, time to TACE progression.

quired to achieve better tumor control and long-term prognosis. Several previous studies have found that repeat TACE conferred a survival benefit.[41] Nevertheless, repeat TACE was associated with increased side effects and impaired liver function. Therefore, the potential treatment benefits must be carefully weighed against the side effects of repeat TACE. Currently, on-demand mode and scheduled mode are the two major modes of repeat TACE in clinical practice. For on-demand mode, repeat TACE is considered only if a viable tumor or local and/or distant intrahepatic recurrence is observed during routine follow-up.[11] Notably, the concept of viable tumor has not yet been accurately defined. For scheduled mode, repeat TACE is performed at fixed intervals regardless of the tumor response after previous TACE.

According to the EASL, TACE should not be repeated if substantial necrosis is not achieved after two rounds of treatment or when follow-up treatment fails to induce marked necrosis at sites that have progressed after an initial tumor response, or if there is occurrence of untreatable progression defined as tumor progression associated with
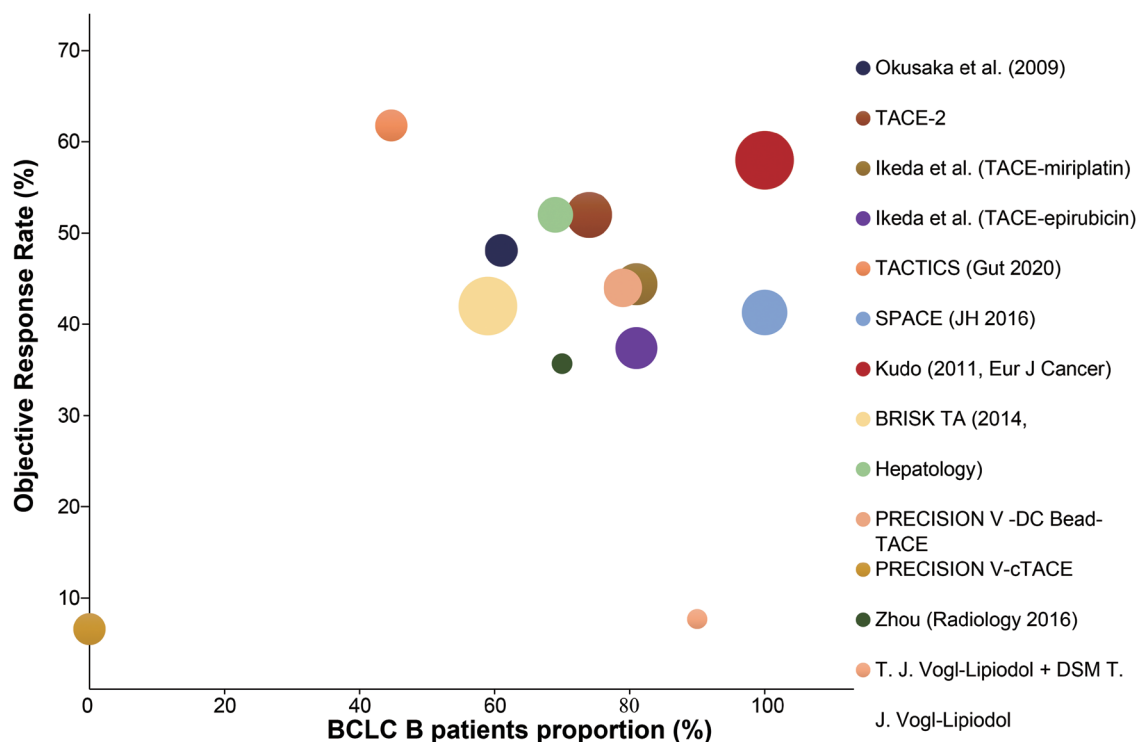

Fig. 3. Results of reported objective response rate of TACE for intermediate HCC. BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; ORR, objective response rate; TACE, transarterial chemoembolizarion.

Table 2. Reported outcomes of randomized controlled trials for TACE in HCC

Trial (year)	Arms	BCLC stage	End point(s)	Outcome(s)
Llovet et al. (2002)[13]	TAE (n=37)/cTACE (n=40) vs. symptomatic treatment (n=35)	N/A	OS	25.3/28.7 months vs. 17.9 months; p=0.009 (cTACE vs. symptomatic treatment)
Lo et al. (2002)[14]	cTACE (n=40) vs. symptomatic treatment (n=39)	N/A	survival	1-year, 2-year, and 3-year survival rates: 57%, 31%, and 26% vs. 32%, 11%, and 3%; p=0.005
Okusaka et al. (2009)[28]	TAI (n=82) vs. cTACE (n=79)	N/A	OS	22.3 months vs. 21.2 months; p=0.383
Lammer et al. (2010) (PRECISION V trial)[15]	DEB-TACE (n=93) vs. cTACE (n=108)	A/B	6-month ORR	51.6% vs. 43.5%; p=0.11
Kudo et al. (2011) (POST-TACE trial)[29]	cTACE (responders) plus sorafenib (n=229) vs. cTACE plus placebo (n=229)	N/A	TTP	5.4 months vs. 3.7 months; p=0.252
Yu et al. (2014)[30]	TEA (n=49) vs. cTACE (n=49)	A/B/C	OS	24.3 months vs. 20.1 months; p=0.513
Golfieri et al. (2014) (PRECISION ITALIA trial)[16]	DEB-TACE (n=89) vs. cTACE (n=88)	A/B/C	2-year survival rate	56.8% vs. 55.4%; p=0.949
Kudo et al. (2014) (BRISK-TA trial)[31]	cTACE or DEB-TACE plus brivanib (n=249) vs. cTACE plus placebo (n=253)	A/B/C/D	OS	26.4 months vs. 26.1 months; p=0.53
Lencioni et al. (2016) (SPACE trial)[32]	DEB-TACE plus sorafenib (n=154) vs DEB-TACE plus placebo (n=153)	B	TTP	5.6 months vs. 5.5 months; P=0.072
Meyer et al. (2017) (TACE 2 trial)[33]	DEB-TACE plus sorafenib (n=157) vs DEB-TACE plus placebo (n=156)	A/B	PFS	7.8 months vs. 7.7 months; p=0.85
Ikeda et al. (2018)[34]	cTACE with miriplatin (n=129) vs. cTACE with epirubicin (n=128)	N/A	OS	36.5 months vs. 37.1 months; p=0.946
Kudo et al. (2018) (ORIENTAL trial)[35]	cTACE plus orantinib (n=445) vs. cTACE plus placebo (n=444)	A/B/C	OS	31.1 months vs. 32.3 months; p=0.435
Park et al. (2019) (STAH trial)[36]	cTACE plus sorafenib (n=170) vs. sorafenib (n=169)	A/B/C	OS	12.8 months vs. 10.8 months; p=0.290
Ikeda et al. (2020) (JIVROSG-1302 PRESIDENT trial)[37]	DEB-TACE (n=99) vs. cTACE (n=101)	A/B/C	3-month CR rate	27.6% vs. 75.2%; p<0.0001
Kudo et al. (2021) (TACTICS trial)[38]	cTACE plus sorafenib (n=80) vs. cTACE (n=76)	A/B/C	PFS; OS	25.2 months vs. 13.5 months; p=0.006; 36.2 months vs. 30.8 months; p=0.40
Zhu et al. (2022)[39]	cTACE with dicycloplatin (n=22, A1) vs. cTACE with dicycloplatin plus epirubicin (n=25, A2) vs. cTACE with epirubicin (n=24, B)	A/B	ORR	50.0% vs. 44.0% vs. 29.17%; p=0.093 (A1 vs. B); P=0.338 (A2 vs. B)
Peng et al. (2022) (LAUNCH trial)[40]	lenvatinib plus cTACE/DEB-TACE (n=170) vs. lenvatinib (n=168)	C	OS	17.8 months vs. 11.5 months; p<0.001

BCLC, Barcelona Clinic Liver Cancer; cTACE, conventional transarterial chemoembolization; DEB-TACE, drug-eluting beads transarterial chemoembolization; HCC, hepatocellular carcinoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TACE, transarterial chemoembolization; TAE, transarterial embolization; TAI, transarterial infusion chemotherapy; TEA; transarterial ethanol ablation; TTP, time to tumor progression.

a clinical profile that prevents re-treatment.[11] Notably, the JSH indicates that new occurrence of intrahepatic lesion(s) is a natural process of liver disease, and that it should not be regarded as disease progression. Therefore, TACE should not be stopped if new intrahepatic lesion(s) occurs.[8] Both the AASLD and CNLC provide no detailed recommendation for the optimal time to stop TACE.[7,12] Several prognostic models or scores have been used to help stratify patients who are more likely to benefit from initial or repeat TACE. However, none of these models have been strongly recommended by the guidelines.[42,43]

The concept of TACE failure/refractory was introduced in order to avoid ineffective repeat TACE.[44–46] The definition of the JSH-Liver Cancer Study Group of Japan (LCS-GJ) and updated in 2014 is most widely used in clinical practice and clinical trials.[44] Nevertheless, the objectivity

and rationality of such definition is debated. Without high-level evidence support, the concept suggests switching to systemic agent monotherapy if TACE failure/refractoriness occurs. In contrast, a recently published article reviewing the current evidence on subsequent treatment after TACE failure/refractoriness concluded that not only sorafenib, but also other therapies such as TACE with drug-eluting beads, hepatic arterial infusion chemotherapy, ablation, and TACE combined with systemic therapies are potentially useful as subsequent treatment after TACE failure/refractoriness.[47] In addition, a nationwide online survey by the Chinese College of Interventionalists (CCI) in 2020 found an obvious difference in the recognition of TACE failure/refractoriness among Chinese clinicians based on existing definitions.[48] Recently, an expert consensus on TACE refractoriness and subsequent therapies in HCC was published by the CCI.[49] The CCI definition of TACE refractoriness is progression of the treated tumor(s) (progression disease according to mRECIST criteria seen on contrast-enhanced CT/MRI at 1–3 months after the latest TACE) compared with baseline after three or more consecutive standardized and precision TACE sessions.

TACE for HCC beyond intermediate-stage

Early and very early HCC

Early-stage HCC (BCLC A) is defined as solitary HCC irrespective of tumor size or as a multifocal HCC with up to three nodules (none >3 cm), preserved liver function, no cancer-related symptoms (ECOG 0), and no macrovascular invasion or extrahepatic spread. Very early HCC (BCLC 0) is a solitary HCC ≤2 cm.[4] For that stage, curative approaches include liver transplantation (LT), surgical resection, or local ablation, and are generally recommended based on individual profiles. However, some patients refuse surgery or are unsuitable for surgery because of factors such as old age, hepatic dysfunction, and severe comorbidities. Moreover, the shortage of liver donors poses a challenge to transplantation, and ablation is not feasible for tumors with subcapsular, dome, or other high-risk locations.[50,51]

According to the treatment stage migration strategy, TACE treatment should be considered for these patients who are not candidates for any of the mentioned approaches.[4] Several studies have reported that TACE was an effective alternative treatment that achieved long-term survival benefits in BCLC 0/A HCC patients for whom curative treatment was not feasible.[52–55] TACE is recommended as the first-line downstaging treatment for LT to reduce tumor burden and allow patients to meet acceptable transplantation criteria.[11,50] TACE is often chosen as a bridge therapy before LT and is associated with a decrease in the dropout rate for patients awaiting LT, especially when the anticipated waiting time exceeds six months.[50,56,57]

Advanced HCC

Advanced-stage stage HCC includes patients with vascular invasion or extrahepatic spread, preserved liver function, and ECOG performance score 1–2. Systemic therapy is recommended for those patients.[4] Recently, immunotherapy-based combination protocols, such as atezolizumab plus bevacizumab, have become the first-line therapeutics for advanced-stage HCC after several trials demonstrated favorable results over sorafenib.[58,59] Sorafenib or lenvatinib can still be considered for patients in whom immune checkpoint inhibitors are contraindicated.

The majority of guidelines do not recommend the use of TACE in advanced HCC patients; the only exception is the CNLC which recommends TACE as the first-line choice for patients with macrovascular invasion.[7,11,12] However, the HCC BRIDGE study, a global large-scale, longitudinal cohort study that retrospectively included 18,031 patients in 14 countries and treated between January 2005 and September 2012, documented the real-life clinical management of HCC patients and found that TACE was the first-line treatment in nearly 50% patients with BCLC-C stage HCC.[6] Previous studies demonstrated that TACE confered survival benefits over the best supportive care in patients with portal vein tumor thrombus.[60,61] With the advent of the era of immunotherapy-based combination treatments, TACE may provide a potential synergistic anti-tumor effect when administered in combination with molecular and immune therapies.[62]

TACE combined with other treatments

Combination with ablation

Percutaneous ablation through radiofrequency ablation (RFA) or microwave ablation (MWA) is recommended as the first treatment option for BCLC 0/A stage HCC patients who are not potential candidates for liver transplantation and surgical resection.[4,11,12] RFA was shown to provide the same survival benefit in cases of HCC ≤2–3 cm compared with surgical resection, while MWA was shown to achieve more extensive tumor necrosis than RFA and was an effective method for treating HCC lesions ≤5 cm. Other ablative techniques, such as cryoablation, and irreversible electroporation are currently under investigation.

Several studies have explored the synergistic cytotoxic effects of the combination of TACE and ablation in selected populations of early- or intermediate-stage HCC. An RCT by Peng *et al*.[63] compared the efficacy of TACE combined with RFA versus RFA alone in patients with solitary HCC ≤7 cm, or multinodular HCC within the Milan criteria. Patients treated with TACE plus RFA treatment had significantly better OS and recurrence-free survival than patients treated with RFA alone [hazard ratio (HR), 0.525; p=0.002 and HR, 0.575; p=0.009], respectively. The long-term survival outcomes were updated after approximately 6 years of follow-up, suggesting that TACE with RFA may be a better first-line treatment than RFA alone for patients with early-stage HCC.[64] However, subgroup analysis demonstrated that HCC patients with tumor size ≤3 cm may not benefit as much from combination treatment when compared with those who had tumor size >3 cm. The results are in line with two previous meta-analyses that demonstrated greater effectiveness of TACE-RFA in patients with higher tumor burden.[65,66] Another meta-analysis of data from eight retrospective studies and one RCT compared the survival outcomes and safety profile between TACE combined with RFA and surgical resection in patients with early-stage HCC.[67] There were no significant differences between 1-, 3-, and 5-year OS and 1-year disease-free survival in the two groups regardless of matched data or unadjusted pooled data. Differences in 3- and 5-year disease-free survival in the propensity-matched cohort were not significant. Sequential TACE-RFA combination therapy also showed good efficacy in patients with recurrent early-stage HCC, and can be recommended for patients with tumors measuring 3–5 cm or in those who develop tumor recurrence 1 year or less after the initial treatment.[68] The combination of TACE with other ablative techniques was also shown to achieve better outcomes than monotherapy in selected populations.[69,70]
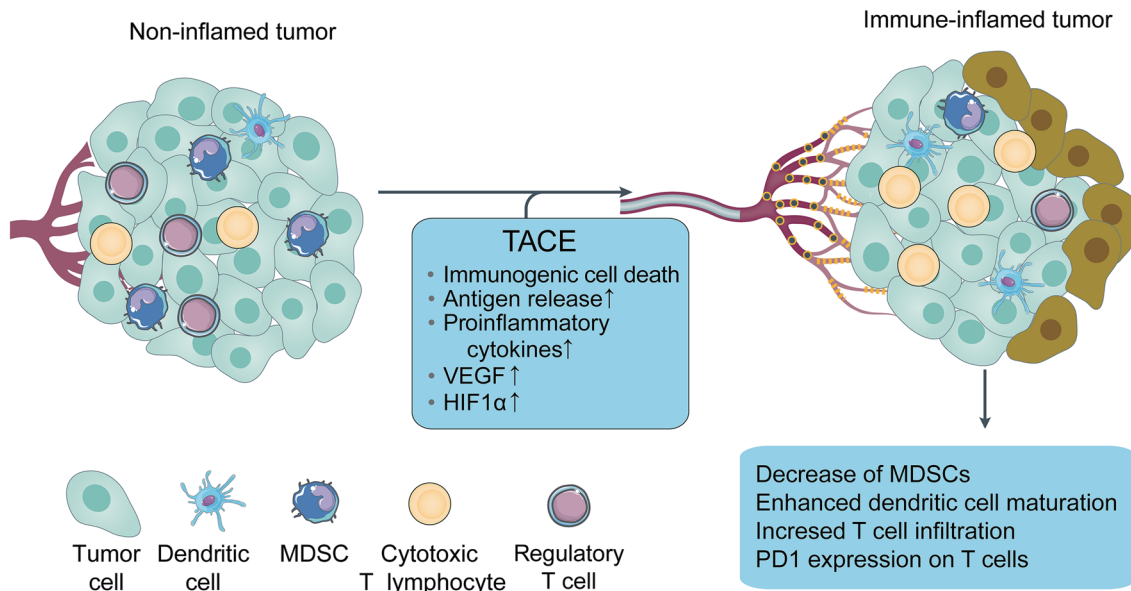
Fig. 4. Possible mechanisms by which TACE and combination therapies provide benefit in HCC treatment. HCC, hepatocellular carcinoma; HIF1α, hypoxia inducible factor-1 α; MDSC, myeloid-derived suppressor cell; PD1, programmed death 1; TACE, transarterial chemoembolization; VEGF, vascular endothelial growth factor.

Combination with molecular targeted agents

By embolizing tumor-feeding arteries, TACE leads to acute hypoxia, resulting in an increase in vascular endothelial growth factor (VEGF).[71] Thus, the combination of tyrosine kinase inhibitors (TKIs) targeting on VEGF with TACE to decrease TACE-induced angiogenesis may potentially improve treatment efficacy of TACE due to the synergistic action (Fig. 4).[62] Several phase II/III RCTs have investigated the treatment efficacy and safety of TACE combined with TKIs versus TACE monotherapy for intermediate-stage HCC.[31–33,35] The SPACE and TACE-2 trials compared TACE plus sorafenib to TACE monotherapy.[32,33] Two other RCTs compared TACE plus brivanib (BRISK-TA study) or orantinib (ORIENTAL study) to TACE monotherapy.[31,35] Unfortunately, none of the four trials found any significant treatment benefit from TACE combined with TKIs.

Recently, the phase II TACTICS trial comparing TACE plus sorafenib versus TACE monotherapy for intermediate HCC, demonstrated significant improvement in PFS based on a new definition of untreatable progression.[72] Median PFS was 25.2 months in the combination group and 13.5 months in the TACE monotherapy group (p=0.006). Different from previous trials, in the TACTICS trial, sorafenib administration was initiated 3 weeks before the first TACE. Notably, the updated data showed that another co-primary endpoint, OS, was comparable, without a significant difference between the two groups.[38]

More recently, the primary analysis of TACTICS-L trial, which was a single-arm trial investigating the efficacy and safety of TACE plus lenvatinib for intermediate HCC, reported a promising outcome. A total of 62 patients were included, and lenvatinib was initiated 14–21 days prior to first TACE. The median PFS following the per Response Evaluation Criteria in Cancer of the Liver (RECICL) criteria was 24.4 months. The ORR evaluated using the RECICL was 79.0%, including a 53.2% complete response (CR).

Combination with immunotherapy

The successful prospective trials of anti-programmed death 1 (PD-1) and anti-programmed death ligand 1 (PD-L1) agents for advanced HCC heralded the era of immunotherapy for HCC.[73] Despite negative results of two phase III RCTs focusing on anti-PD-1 agent monotherapy for advanced HCC, several subsequent RCTs have demonstrated the advantage of a new strategy of combination of anti-PD-(L)1 and anti-VEGF or TKI agents over sorafenib for advanced HCC.[58,59] It is now recommended as the preferred first-line choice for advanced HCC.[4] TACE serves the function of transforming the immunosuppressive cold tumor to a hot tumor for HCC (Fig. 4). In detail, TACE results in necrosis of the tumor tissue as well as induces a hypoxic microenvironment, which increases the expression of PD-L1 on the surface of immune cells and tumor cells, reduces the release of immunosuppressive factors, and attenuates the inhibition to immune function. Therefore, the combination of TACE with anti-PD-(L)1 and molecular targeted therapies provides a potential synergistic anti-tumor effect. To date, only a few retrospective studies with small sample size have been reported on that topic.[74,75] Several RCTs investigating the efficacy and safety of TACE combined with anti-PD-(L)1 and anti-VEGF or TKI agents for unresectable HCC are currently underway (Table 1).

To promote comprehensive treatment of liver cancer by multidisciplinary team, Chinese Liver Cancer Clinical Study Alliance (CHANCE) national registry platform sponsored by CCI was launched in April 20, 2021 in Nanjing, China. In addition, a nationwide, multicenter, retrospective study, the CHANCE 001 study, was then carried out. The study (NCT 04975932) included more than 800 HCC patients treated at 59 academic hospitals in China with either TACE plus anti-PD-(L)1 and molecular targeted therapies or TACE monotherapy. Details on this study will be reported soon.

Combination with other local treatments

Several studies focusing on the combination of TACE plus radiotherapy have reported promising results in intermediate-stage HCC patients, as well as advanced-stage HCC with portal vein tumor thrombosis (PVTT). A meta-analysis of 25

trials (11 RCTs and 14 non-RCTs) including 2,577 patients evaluated the efficacy and safety of TACE plus radiotherapy versus TACE alone for unresectable HCC.[76] Patients receiving TACE plus radiotherapy had significantly better 1-, 2-, 3-, 4-, and 5-year survival and overall response. However, combination treatment was associated with a greater incidence of gastrointestinal and hepatobiliary complications that were easily managed and treated. Interestingly, a subgroup analysis found that TACE plus radiotherapy showed a tendency for increased survival in patients with PVTT compared with those without PVTT, although the trend was not significant. Yoon *et al*. conducted an RCT in HCC patients with macrovascular invasion to explore whether first-line combined TACE plus radiotherapy treatment can improve survival compared with sorafenib. TACE combined with radiotherapy was associated with significantly improved PFS, ORR, time to progression, and OS; therefore, it represents a viable, well-tolerated alternative to systemic therapies.

Iodine-125 implantation, as a type of local brachytherapy, provides a long-term cytocidal effect at a low dose and minimal damage to normal tissue. Two retrospective matched-cohort studies revealed that TACE plus iodine-125 implantation improved survival in patients with early- and intermediate-stage HCC.[77,78] For patients with malignant portal vein tumor thrombosis, iodine-125 seed implantation, integrated iodine-125 seed implantation, endovascular iodine-125 seed strands with/without portal vein stent placement, or self-expandable iodine-125 seed loaded irradiation stent combined with TACE may represent a safe and effective treatment modalities.[79–82]

Adverse events (AEs) of TACE

AEs or side effects of TACE for HCC are mainly intraoperative and postoperative. The former mainly includes allergic reactions, intraoperative bleeding, and biliary cardiac reflex. The latter mainly includes postembolization syndrome (PES) liver abscess, upper gastrointestinal bleeding, liver and renal failure, myelosuppression, and ectopic embolism.[83] A systematic review including 217 selected studies showed that a total of 21,461 AEs were reported in 15,351 patients who underwent at least 27,497 treatment sessions of lipiodol TACE.[27] The most frequent AE was PES (47.7%) including fever, vomiting, liver enzyme abnormalities, abdominal pain, and nausea.[27]

Comparison with transarterial radioembolization (TARE)

TARE is a modality for selective internal radiation therapy. It is performed by injecting radioactive microspheres loaded with yttrium-90 (Y90, a β-emitting isotope) into the arteries feeding the lesion(s). TARE has recently been recommended as a choice for early-stage HCC by the BCLC, whereas it has also been largely explored in intermediate and advanced HCC.[4,84,85] TARE has been shown to confer similar survival duration compared with TACE.[86] However, TARE was associated with significantly increased time to progression compared with TACE (>26 months versus 6.8 months).[86] To date, no phase III RCTs have reported the comparative efficacy and safety of TARE versus TACE.

Precision TACE

Despite its widely application, standardization of TACE in clinical practice is hard to achieve. Lencioni *et al.*[27] report-

ed a systematic review including 10 108 patients with HCC treated with conventional TACE between 1980 and 2013 worldwide. The results showed considerable variability in the treatment efficacy of TACE between countries and time periods. The concept of precision TACE was introduced to maximize the standardization of TACE. Briefly, precision TACE requires physicians to perform TACE based on patient-specific condition, careful pretreatment preparation, accurate implementation, close follow-up, and whole-process management.

Perspective

TACE has an important role in the treatment of all stages of HCC. The indications for TACE have expanded, ranging from a curative approach for patients with early-stage HCC to palliative treatment for patients with advanced-stage HCC. Owing to limited evidence, TACE is recommended as the first-line choice mainly for intermediate-stage HCC by several guidelines. Further work is warranted to provide more evidence to support the indications and recommendations for TACE in patients with HCC. Besides, in the era of immunotherapy, TACE administrated in combination with immunotherapy-based systemic therapy offers a new paradigm for the treatment of unresectable HCC.

Funding

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Review concept and design (XLZ, HDZ), drafting of the manuscript (BYZ, ZCJ), literature search (BYZ, ZCJ, JJC), and administrative, technical, or material support, study supervision (XLZ, HDZ).

References

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al*. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71(3):209–249. doi:10.3322/caac.21660, PMID:33538338.
[2] Villanueva A. Hepatocellular Carcinoma. N Engl J Med 2019;380(15):1450–1462. doi:10.1056/NEJMra1713263, PMID:30970190.
[3] Llovet JM, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S, *et al*. Hepatocellular carcinoma. Nat Rev Dis Primers 2021;7(1):6. doi:10.1038/s41572-020-00240-3, PMID:33479224.
[4] Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, *et al*. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol 2022;76(3):681–693. doi:10.1016/j.jhep.2021.11.018, PMID:34801630.
[5] Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet 2018;391(10127):1301–1314. doi:10.1016/S0140-6736(18)30010-2, PMID:29307467.
[6] Park JW, Chen M, Colombo M, Roberts LR, Schwartz M, Chen PJ, *et al*. Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study. Liver Int 2015;35(9):2155–2166. doi:10.1111/liv.12818, PMID:25752327.
[7] Zhou J, Sun H, Wang Z, Cong W, Wang J, Zeng M, *et al*. Guidelines for the Diagnosis and Treatment of Hepatocellular Carcinoma (2019 Edition). Liver

Cancer 2020;9(6):682–720. doi:10.1159/000509424, PMID:33442540.

[8] Kudo M, Kawamura Y, Hasegawa K, Tateishi R, Kariyama K, Shiina S, *et al*. Management of Hepatocellular Carcinoma in Japan: JSH Consensus Statements and Recommendations 2021 Update. Liver Cancer 2021;10(3):181–223. doi:10.1159/000514174, PMID:34239808.

[9] Omata M, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, *et al*. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int 2017;11(4):317–370. doi:10.1007/s12072-017-9799-9, PMID:28620797.

[10] Yau T, Tang VY, Yao TJ, Fan ST, Lo CM, Poon RT. Development of Hong Kong Liver Cancer staging system with treatment stratification for patients with hepatocellular carcinoma. Gastroenterology 2014;146(7):1691–700.e3. doi:10.1053/j.gastro.2014.02.032, PMID:24583061.

[11] European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018;69(1):182–236. doi:10.1016/j.jhep.2018.03.019, PMID:29628281.

[12] Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, *et al*. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology 2018;67(1):358–380. doi:10.1002/hep.29086.

[13] Llovet JM, Real MI, Montaña X, Planas R, Coll S, Aponte J, *et al*. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002;359(9319):1734–1739. doi:10.1016/S0140-6736(02)08649-X, PMID:12049862.

[14] Lo CM, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, *et al*. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002;35(5):1164–1171. doi:10.1053/jhep.2002.33156, PMID:11981766.

[15] Lammer J, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, *et al*. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Intervent Radiol 2010;33(1):41–52. doi:10.1007/s00270-009-9711-7, PMID:19908093.

[16] Golfieri R, Giampalma E, Renzulli M, Cioni R, Bargellini I, Bartolozzi C, *et al*. Randomised controlled trial of doxorubicin-eluting beads vs conventional chemoembolisation for hepatocellular carcinoma. Br J Cancer 2014;111(2):255–264. doi:10.1038/bjc.2014.199, PMID:24937669.

[17] Vogl TJ, Langenbach MC, Hammerstingl R, Albrecht MH, Chatterjee AR, Gruber-Rouh T. Evaluation of two different transarterial chemoembolization protocols using Lipiodol and degradable starch microspheres in therapy of hepatocellular carcinoma: a prospective trial. Hepatol Int 2021;15(3):685–694. doi:10.1007/s12072-021-10193-8, PMID:34043158.

[18] Kunliang L, Zhicheng J, Xiaolong H, Dan Y, Yu Z, Haidong Z, *et al*. A biodegradable multifunctional porous microsphere composed of carrageenan for promoting imageable trans-arterial chemoembolization. Int J Biol Macromol 2020;142:866–878. doi:10.1016/j.ijbiomac.2019.10.026, PMID:31622716.

[19] Guiu B, Chevallier P, Assenat E, Barbier E, Merle P, Bouvier A, *et al*. Idarubicin-loaded Beads for Chemoembolization of Hepatocellular Carcinoma: The IDASPHERE II Single-Arm Phase II Trial. Radiology 2019;291(3):801–808. doi:10.1148/radiol.2019182399, PMID:31038408.

[20] Chao M, Wu H, Jin K, Li B, Wu J, Zhang G, *et al*. A nonrandomized cohort and a randomized study of local control of large hepatocarcinoma by targeting intratumoral lactic acidosis. Elife 2016;5:e15691. doi:10.7554/eLife.15691, PMID:27481188.

[21] Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 2010;30(1):52–60. doi:10.1055/s-0030-1247132, PMID:20175033.

[22] Llovet JM, Villanueva A, Marrero JA, Schwartz M, Meyer T, Galle PR, *et al*. Trial Design and Endpoints in Hepatocellular Carcinoma: AASLD Consensus Conference. Hepatology 2021;73(Suppl 1):158–191. doi:10.1002/hep.31327, PMID:32430997.

[23] Jin Z, Chen L, Zhong B, Zhou H, Zhu H, Zhou H, *et al*. Machine-learning analysis of contrast-enhanced computed tomography radiomics predicts patients with hepatocellular carcinoma who are unsuitable for initial transarterial chemoembolization monotherapy: A multicenter study. Transl Oncol 2021;14(4):101034. doi:10.1016/j.tranon.2021.101034, PMID:33567388.

[24] Meng XP, Wang YC, Ju S, Lu CQ, Zhong BY, Ni CF, *et al*. Radiomics Analysis on Multiphase Contrast-Enhanced CT: A Survival Prediction Tool in Patients With Hepatocellular Carcinoma Undergoing Transarterial Chemoembolization. Front Oncol 2020;10:1196. doi:10.3389/fonc.2020.01196, PMID:32850345.

[25] Gao G, Li C, Fan W, Zhang M, Li X, Chen W, *et al*. Brilliant glycans and glycosylation: Seq and ye shall find. Int J Biol Macromol 2021;189:279–291. doi:10.1016/j.ijbiomac.2021.08.054, PMID:34389387.

[26] Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. Hepatology 2003;37(2):429–442. doi:10.1053/jhep.2003.50047, PMID:12540794.

[27] Lencioni R, de Baere T, Soulen MC, Rilling WS, Geschwind JF. Lipiodol transarterial chemoembolization for hepatocellular carcinoma: A systematic review of efficacy and safety data. Hepatology 2016;64(1):106–116. doi:10.1002/hep.28453, PMID:26765068.

[28] Okusaka T, Kasugai H, Shioyama Y, Tanaka K, Kudo M, Saisho H, *et al*. Transarterial chemotherapy alone versus transarterial chemoembolization for hepatocellular carcinoma: a randomized phase III trial. J Hepatol 2009;51(6):1030–1036. doi:10.1016/j.jhep.2009.09.004, PMID:19864035.

[29] Kudo M, Imanaka K, Chida N, Nakachi K, Tak WY, Takayama T, *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. doi:10.1016/j.ejca.2011.05.007, PMID:21664811.

[30] Yu SC, Hui JW, Hui EP, Chan SL, Lee KF, Mo F, *et al*. Unresectable hepatocellular carcinoma: randomized controlled trial of transarterial ethanol ablation versus transcatheter arterial chemoembolization. Radiology 2014;270(2):607–620. doi:10.1148/radiol.13130498, PMID:24126369.

[31] Kudo M, Han G, Finn RS, Poon RT, Blanc JF, Yan L, *et al*. Brivanib as adjuvant therapy to transarterial chemoembolization in patients with hepatocellular carcinoma: A randomized phase III trial. Hepatology 2014;60(5):1697–1707. doi:10.1002/hep.27290, PMID:24996197.

[32] Lencioni R, Llovet JM, Han G, Tak WY, Yang J, Guglielmi A, *et al*. Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: The SPACE trial. J Hepatol 2016;64(5):1090–1098. doi:10.1016/j.jhep.2016.01.012, PMID:26809111.

[33] Meyer T, Fox R, Ma YT, Ross PJ, James MW, Sturgess R, *et al*. Sorafenib in combination with transarterial chemoembolisation in patients with unresectable hepatocellular carcinoma (TACE 2): a randomised placebo-controlled, double-blind, phase 3 trial. Lancet Gastroenterol Hepatol 2017;2(8):565–575. doi:10.1016/S2468-1253(17)30156-5, PMID:28648803.

[34] Ikeda M, Kudo M, Aikata H, Nagamatsu H, Ishii H, Yokosuka O, *et al*. Transarterial chemoembolization with miriplatin vs. epirubicin for unresectable hepatocellular carcinoma: a phase III randomized trial. J Gastroenterol 2018;53(2):281–290. doi:10.1007/s00535-017-1374-6, PMID:28766016.

[35] Kudo M, Cheng AL, Park JW, Park JH, Liang PC, Hidaka H, *et al*. Orantinib versus placebo combined with transcatheter arterial chemoembolisation in patients with unresectable hepatocellular carcinoma (ORIENTAL): a randomised, double-blind, placebo-controlled, multicentre, phase 3 study. Lancet Gastroenterol Hepatol 2018;3(1):37–46. doi:10.1016/S2468-1253(17)30290-X, PMID:28988687.

[36] Park JW, Kim YJ, Kim DY, Bae SH, Paik SW, Lee YJ, *et al*. Sorafenib with or without concurrent transarterial chemoembolization in patients with advanced hepatocellular carcinoma: The phase III STAH trial. J Hepatol 2019;70(4):684–691. doi:10.1016/j.jhep.2018.11.029, PMID:30529387.

[37] Ikeda M, Arai Y, Inaba Y, Tanaka T, Sugawara S, Kodama Y, *et al*. Conventional or Drug-Eluting Beads? Randomized Controlled Study of Chemoembolization for Hepatocellular Carcinoma: JIVROSG-1302. Liver Cancer 2022;11:440–450. doi:10.1159/000525500.

[38] Kudo M, Ueshima K, Ikeda M, Torimura T, Tanabe N, Aikata H, *et al*. Final Results of TACTICS: A Randomized, Prospective Trial Comparing Transarterial Chemoembolization Plus Sorafenib to Transarterial Chemoembolization Alone in Patients with Unresectable Hepatocellular Carcinoma. Liver Cancer 2022;11(4):354–367. doi:10.1159/000522547, PMID:35978604.

[39] Zhu HD, Li X, Ji JS, Huang M, Shao GL, Lu J, *et al*. TACE with dicycloplatin in patients with unresectable hepatocellular carcinoma: a multicenter randomized phase II trial. Eur Radiol 2022. doi:10.1007/s00330-022-08848-7, PMID:35776182.

[40] Peng Z, Fan W, Zhu B, Wang G, Sun J, Xiao C, *et al*. Lenvatinib Combined With Transarterial Chemoembolization as First-Line Treatment for Advanced Hepatocellular Carcinoma: A Phase III, Randomized Clinical Trial (LAUNCH). J Clin Oncol 2022;doi:10.1200/JCO.22.00392, PMID:35921605.

[41] Terzi E, Golfieri R, Piscaglia F, Galassi M, Dazzi A, Leoni S, *et al*. Response rate and clinical outcome of HCC after first and repeated cTACE performed "on demand". J Hepatol 2012;57(6):1258–1267. doi:10.1016/j.jhep.2012.07.025, PMID:22871502.

[42] Sieghart W, Hucke F, Pinter M, Graziadei I, Vogel W, Müller C, *et al*. The ART of decision making: retreatment with transarterial chemoembolization in patients with hepatocellular carcinoma. Hepatology 2013;57(6):2261–2273. doi:10.1002/hep.26256, PMID:23316013.

[43] Adhoute X, Penaranda G, Naude S, Raoul JL, Perrier H, Bayle O, *et al*. Retreatment with TACE: the ABCR SCORE, an aid to the decision-making process. J Hepatol 2015;62(4):855–862. doi:10.1016/j.jhep.2014.11.014, PMID:25463541.

[44] Kudo M, Matsui O, Izumi N, Kadoya M, Okusaka T, Miyayama S, *et al*. Transarterial chemoembolization failure/refractoriness: JSH-LCSGJ criteria 2014 update. Oncology 2014;87(Suppl 1):22–31. doi:10.1159/000368142, PMID:25427730.

[45] Park JW, Amarapurkar D, Chao Y, Chen PJ, Geschwind JF, Goh KL, *et al*. Consensus recommendations and review by an International Expert Panel on Interventions in Hepatocellular Carcinoma (EPOIHCC). Liver Int 2013;33(3):327–337. doi:10.1111/liv.12083, PMID:23331661.

[46] Raoul JL, Gilabert M, Piana G. How to define transarterial chemoembolization failure or refractoriness: a European perspective. Liver Cancer 2014;3(2):119–124. doi:10.1159/000343867, PMID:24945002.

[47] Zhang S, Wang WS, Zhong BY, Ni CF. Subsequent treatment after transarterial chemoembolization failure/refractoriness: a review based on published evidence. J Clin Transl Hepatol 2022;10(4):740–747. doi:10.14218/JCTH.2021.00336.

[48] Zhong BY, Wang WS, Zhang S, Zhu HD, Zhang L, Shen J, *et al*. Re-evaluating Transarterial Chemoembolization Failure/Refractoriness: A Survey by Chinese College of Interventionalists. J Clin Transl Hepatol 2021;9(4):521–527. doi:10.14218/JCTH.2021.00049, PMID:34447681.

[49] Clinical Guidelines Committee of Chinese College of Interventionalists. Expert consensus on transarterial chemoembolization refractoriness and subsequent therapies in hepatocellular carcinoma. Zhonghua Nei Ke Za Zhi 2022;61(8):860–866. doi:10.3760/cma.j.cn112138-20220615-00452, PMID:35922209.

[50] Mehta N, Bhangui P, Yao FY, Mazzaferro V, Toso C, Akamatsu N, *et al*. Liver Transplantation for Hepatocellular Carcinoma. Working Group Report from the ILTS Transplant Oncology Consensus Conference. Transplantation 2020;104(6):1136–1142. doi:10.1097/TP.0000000000003174,

PMID:32217938.

[51] Nault JC, Sutter O, Nahon P, Ganne-Carrié N, Séror O. Percutaneous treatment of hepatocellular carcinoma: State of the art and innovations. J Hepatol 2018;68(4):783–797. doi:10.1016/j.jhep.2017.10.004, PMID: 29031662.

[52] Kim JW, Kim JH, Sung KB, Ko HK, Shin JH, Kim PN, *et al*. Transarterial chemoembolization vs. radiofrequency ablation for the treatment of single hepatocellular carcinoma 2 cm or smaller. Am J Gastroenterol 2014;109(8):1234–1240. doi:10.1038/ajg.2014.152, PMID:24935276.

[53] Yun BY, Lee HW, Min IK, Kim SU, Park JY, Kim DY, *et al*. Prognosis of Early-Stage Hepatocellular Carcinoma: Comparison between Trans-Arterial Chemoembolization and Radiofrequency Ablation. Cancers (Basel) 2020;12(9):E2527. doi:10.3390/cancers12092527, PMID:32899584.

[54] Golfieri R, Cappelli A, Cucchetti A, Piscaglia F, Carpenzano M, Peri E, *et al*. Efficacy of selective transarterial chemoembolization in inducing tumor necrosis in small (<5 cm) hepatocellular carcinomas. Hepatology 2011;53(5):1580–1589. doi:10.1002/hep.24246, PMID:21351114.

[55] Yang HJ, Lee JH, Lee DH, Yu SJ, Kim YJ, Yoon JH, *et al*. Small single-nodule hepatocellular carcinoma: comparison of transarterial chemoembolization, radiofrequency ablation, and hepatic resection by using inverse probability weighting. Radiology 2014;271(3):909–918. doi:10.1148/radiol.13131760, PMID:24520944.

[56] De Luna W, Sze DY, Ahmed A, Ha BY, Ayoub W, Keeffe EB, *et al*. Transarterial chemoinfusion for hepatocellular carcinoma as downstaging therapy and a bridge toward liver transplantation. Am J Transplant 2009;9(5):1158–1168. doi:10.1111/j.1600-6143.2009.02576.x, PMID:19344435.

[57] Yao FY, Fidelman N. Reassessing the boundaries of liver transplantation for hepatocellular carcinoma: Where do we stand with tumor down-staging? Hepatology 2016;63(3):1014–1025. doi:10.1002/hep.28139, PMID: 26560491.

[58] Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, *et al*. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med 2020;382(20):1894–1905. doi:10.1056/NEJMoa1915745, PMID:32402160.

[59] Ren Z, Xu J, Bai Y, Xu A, Cang S, Du C, *et al*. Sintilimab plus a bevacizumab biosimilar (IBI305) versus sorafenib in unresectable hepatocellular carcinoma (ORIENT-32): a randomised, open-label, phase 2-3 study. Lancet Oncol 2021;22(7):977–990. doi:10.1016/S1470-2045(21)00252-7, PMID:34143971.

[60] Niu ZJ, Ma YL, Kang P, Ou SQ, Meng ZB, Li ZK, *et al*. Transarterial chemoembolization compared with conservative treatment for advanced hepatocellular carcinoma with portal vein tumor thrombus: using a new classification. Med Oncol 2012;29(4):2992–2997. doi:10.1007/s12032-011-0145-0, PMID:22200992.

[61] Luo J, Guo RP, Lai EC, Zhang YJ, Lau WY, Chen MS, *et al*. Transarterial chemoembolization for unresectable hepatocellular carcinoma with portal vein tumor thrombosis: a prospective comparative study. Ann Surg Oncol 2011;18(2):413–420. doi:10.1245/s10434-010-1321-8, PMID:20839057.

[62] Llovet JM, De Baere T, Kulik L, Haber PK, Greten TF, Meyer T, *et al*. Locoregional therapies in the era of molecular and immune treatments for hepatocellular carcinoma. Nat Rev Gastroenterol Hepatol 2021;18(5):293–313. doi:10.1038/s41575-020-00395-0, PMID:33510460.

[63] Peng ZW, Zhang YJ, Chen MS, Xu L, Liang HH, Lin XJ, *et al*. Radiofrequency ablation with or without transcatheter arterial chemoembolization in the treatment of hepatocellular carcinoma: a prospective randomized trial. J Clin Oncol 2013;31(4):426–432. doi:10.1200/JCO.2012.42.9936, PMID:23269991.

[64] Zhang YJ, Chen MS, Chen Y, Lau WY, Peng Z. Long-term Outcomes of Transcatheter Arterial Chemoembolization Combined With Radiofrequency Ablation as an Initial Treatment for Early-Stage Hepatocellular Carcinoma. JAMA Netw Open 2021;4(9):e2126992. doi:10.1001/jamanetworkopen.2021.26992, PMID:34570206.

[65] Ni JY, Liu SS, Xu LF, Sun HL, Chen YT. Meta-analysis of radiofrequency ablation in combination with transarterial chemoembolization for hepatocellular carcinoma. World J Gastroenterol 2013;19(24):3872–3882. doi:10.3748/wjg.v19.i24.3872, PMID:23840128.

[66] Chen QW, Ying HF, Gao S, Shen YH, Meng ZQ, Chen H, *et al*. Radiofrequency ablation plus chemoembolization versus radiofrequency ablation alone for hepatocellular carcinoma: A systematic review and meta-analysis. Clin Res Hepatol Gastroenterol 2016;40(3):309–314. doi:10.1016/j.clinre.2015.07.008, PMID:26428660.

[67] Gui CH, Baey S, D'cruz RT, Shelat VG. Trans-arterial chemoembolization + radiofrequency ablation versus surgical resection in hepatocellular carcinoma - A meta-analysis. Eur J Surg Oncol 2020;46(5):763–771. doi:10.1016/j.ejso.2020.01.004, PMID:31937433.

[68] Peng ZW, Zhang YJ, Liang HH, Lin XJ, Guo RP, Chen MS. Recurrent hepatocellular carcinoma treated with sequential transcatheter arterial chemoembolization and RF ablation versus RF ablation alone: a prospective randomized trial. Radiology 2012;262(2):689–700. doi:10.1148/radiol.11110637, PMID:22157201.

[69] Keshavarz P, Raman SS. Comparison of combined transarterial chemoembolization and ablations in patients with hepatocellular carcinoma: a systematic review and meta-analysis. Abdom Radiol (NY) 2022;47(3):1009–1023. doi:10.1007/s00261-021-03368-2, PMID:34982183.

[70] Shi F, Lian S, Mai Q, Mo Z, Zhuang W, Cui W, *et al*. Microwave ablation after downstaging of hepatocellular carcinoma: outcome was similar to tumor within Milan criteria. Eur Radiol 2020;30(5):2454–2462. doi:10.1007/s00330-019-06604-y, PMID:32002636.

[71] Carmeliet P, Jain RK. Angiogenesis in cancer and other diseases. Nature 2000;407(6801):249–257. doi:10.1038/35025220, PMID:11001068.

[72] Kudo M, Ueshima K, Ikeda M, Torimura T, Tanabe N, Aikata H, *et al*. Randomised, multicentre prospective trial of transarterial chemoembolisation (TACE) plus sorafenib as compared with TACE alone in patients with hepatocellular carcinoma: TACTICS trial. Gut 2020;69(8):1492–1501. doi:10.1136/gutjnl-2019-318934, PMID:31801872.

[73] Llovet JM, Castet F, Heikenwalder M, Maini MK, Mazzaferro V, Pinato DJ, *et al*. Immunotherapies for hepatocellular carcinoma. Nat Rev Clin Oncol 2022;19(3):151–172. doi:10.1038/s41571-021-00573-2, PMID:347 64464.

[74] Yang F, Xu GL, Huang JT, Yin Y, Xiang W, Zhong BY, *et al*. Transarterial Chemoembolization Combined With Immune Checkpoint Inhibitors and Tyrosine Kinase Inhibitors for Unresectable Hepatocellular Carcinoma: Efficacy and Systemic Immune Response. Front Immunol 2022;13:847601. doi:10.3389/fimmu.2022.847601, PMID:35300339.

[75] Marinelli B, Cedillo M, Pasik SD, Charles D, Murthy S, Patel RS, *et al*. Safety and Efficacy of Locoregional Treatment during Immunotherapy with Nivolumab for Hepatocellular Carcinoma: A Retrospective Study of 41 Interventions in 29 Patients. J Vasc Interv Radiol 2020;31(11):1729–1738. e1. doi:10.1016/j.jvir.2020.07.009, PMID:33012649.

[76] Huo YR, Eslick GD. Transcatheter Arterial Chemoembolization Plus Radiotherapy Compared With Chemoembolization Alone for Hepatocellular Carcinoma: A Systematic Review and Meta-analysis. JAMA Oncol 2015;1(6):756–765. doi:10.1001/jamaoncol.2015.2189, PMID:26182200.

[77] Li M, He J, Pan M, Yu Y, Pan Z, Xu B, *et al*. Iodine-125 implantation plus transarterial chemoembolization for the treatment of hepatocellular carcinoma of 3-5cm: A propensity score matching study. Dig Liver Dis 2016;48(9):1082–1087. doi:10.1016/j.dld.2016.06.007, PMID:27365224.

[78] Chen L, Kan X, Sun T, Ren Y, Cao Y, Yan L, *et al*. Transarterial chemoembolization combined with iodine 125 seeds versus transarterial chemoembolization combined with radiofrequency ablation in the treatment of early- and intermediate-stage hepatocellular carcinoma. BMC Gastroenterol 2020;20(1):205. doi:10.1186/s12876-020-01355-3, PMID:32600349.

[79] Luo JJ, Zhang ZH, Liu QX, Zhang W, Wang JH, Yan ZP. Endovascular brachytherapy combined with stent placement and TACE for treatment of HCC with main portal vein tumor thrombus. Hepatol Int 2016;10(1):185–195. doi:10.1007/s12072-015-9663-8, PMID:26341514.

[80] Yang M, Fang Z, Yan Z, Luo J, Liu L, Zhang W, *et al*. Transarterial chemoembolisation (TACE) combined with endovascular implantation of an iodine-125 seed strand for the treatment of hepatocellular carcinoma with portal vein tumour thrombosis versus TACE alone: a two-arm, randomised clinical trial. J Cancer Res Clin Oncol 2014;140(2):211–219. doi:10.1007/s00432-013-1568-0, PMID:24374800.

[81] Lu J, Guo JH, Zhu HD, Zhu GY, Chen L, Teng GJ. Safety and Efficacy of Irradiation Stent Placement for Malignant Portal Vein Thrombus Combined with Transarterial Chemoembolization for Hepatocellular Carcinoma: A Single-Center Experience. J Vasc Interv Radiol 2017;28(6):786–794.e3. doi:10.1016/j.jvir.2017.02.014, PMID:28396192.

[82] Wang W, Wang C, Shen J, Ren B, Yin Y, Yang J, *et al*. Integrated I-125 Seed Implantation Combined with Transarterial Chemoembolization for Treatment of Hepatocellular Carcinoma with Main Portal Vein Tumor Thrombus. Cardiovasc Intervent Radiol 2021;44(10):1570–1578. doi:10.1007/s00270-021-02887-1, PMID:34117503.

[83] Clinical Guidelines Committee of Chinese Interventionalists College. Chinese clinical practice guidelines for transarterial chemoembolization of hepatocellular carcinoma. Zhonghua Nei Ke Za Zhi 2021;60(7):599–614. doi:10.3760/cma.j.cn112137-20210425-00991, PMID:34619836.

[84] Vilgrain V, Pereira H, Assenat E, Guiu B, Ilonca AD, Pageaux GP, *et al*. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. Lancet Oncol 2017;18(12):1624–1636. doi:10.1016/S1470-2045(17)30683-6, PMID:29107679.

[85] Chow PKH, Gandhi M, Tan SB, Khin MW, Khasbazar A, Ong J, *et al*. SIRveNIB: Selective Internal Radiation Therapy Versus Sorafenib in Asia-Pacific Patients With Hepatocellular Carcinoma. J Clin Oncol 2018;36(19):1913–1921. doi:10.1200/JCO.2017.76.0892, PMID:29498924.

[86] Salem R, Gordon AC, Mouli S, Hickey R, Kallini J, Gabr A, *et al*. Y90 Radioembolization Significantly Prolongs Time to Progression Compared With Chemoembolization in Patients With Hepatocellular Carcinoma. Gastroenterology 2016;151(6):1155–1163.e2. doi:10.1053/j.gastro.2016.08.029, PMID:27575820.