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**Transarterial chemoembolization: Evidences from the literature and applications in hepatocellular carcinoma patients**

Facciorusso A *et al*. TACE in HCC patients

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**Abstract**

Transarterial chemoembolization (TACE) is the current standard of care for patients with large or multinodular hepatocellular carcinoma (HCC), preserved liver function, absence of cancer-related symptoms and no evidence of vascular invasion or extrahepatic spread (*i.e.*, those classified as intermediate stage according to the Barcelona Clinic Liver Cancer staging system). The rationale for TACE is that the intra-arterial injection of a chemotherapeutic drug such as doxorubicin or cisplatin followed by embolization of the blood vessel will result in a strong cytotoxic effect enhanced by ischemia. However, TACE is a very heterogeneous operative technique and varies in terms of chemotherapeutic agents, treatment devices and schedule. In order to overcome the major drawbacks of conventional TACE (cTACE), non-resorbable drug-eluting beads (DEBs) loaded with cytotoxic drugs have been developed. DEBs are able to slowly release the drug upon injection and increase the intensity and duration of ischemia while enhancing the drug delivery to the tumor. Unfortunately, despite the theoretical advantages of this new device and the promising results of the pivotal studies, definitive data in favor of its superiority over cTACE are still lacking. The recommendation for TACE as the standard-of-care for intermediate-stage HCC is based on the demonstration of improved survival compared with best supportive care or suboptimal therapies in a meta-analysis of six randomized controlled trials, but other therapeutic options (namely, surgery and radioembolization) proved competitive in selected subsets of intermediate HCC patients. Other potential fields of application of TACE in hepato-oncology are the pre-transplant setting (as downstaging/bridging treatment) and the early stage (in patients unsuitable to curative therapy). The potential of TACE in selected advanced patients with segmental portal vein thrombosis and preserved liver function deserves further reports.

**Key words:** Transarterial chemoembolization; Loco-regional treatment; Hepatocellular carcinoma; Liver cancer; Hepatocarcinoma; Radiofrequency ablation

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**Core tip:** Transarterial chemoembolization (TACE) represents the standard of care for patients with large or multinodular hepatocellular carcinoma (HCC). However, TACE is a heterogeneous technique varying in terms of chemotherapeutic agents, devices and schedule. In order to overcome these drawbacks of conventional TACE (cTACE), drug-eluting beads have been developed. Unfortunately, despite its theoretical advantages, definitive data in favor of its superiority over cTACE are still lacking. TACE represents the standard-of-care for intermediate-stage HCC, in competition with other therapeutic options (surgery and radioembolization). Other fields of application are the pre-transplant setting and the early stage (in patients unsuitable to curative therapy).

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**INTRODUCTION**

Transarterial chemoembolization (TACE) is the current standard of care for patients with large or multinodular hepatocellular carcinoma (HCC), preserved liver function, absence of cancer-related symptoms, and no evidence of vascular invasion or extrahepatic spread [*i.e.*, those classified as intermediate stage according to the Barcelona Clinic Liver Cancer (BCLC) staging system][1,2]. Furthermore, in clinical practice, many patients in the early stage (*i.e.*, single nodule or up to 3 nodules under 3 cm) carrying contraindications to curative approaches – liver resection, liver transplantation (LT) or radiofrequency ablation (RFA) – are treated with TACE.

The rationale for TACE is that the intra-arterial injection of a chemotherapeutic drug such as doxorubicin or cisplatin followed by embolization of the blood vessel will result in a strong cytotoxic effect enhanced by ischemia[3]. The embolization end point is usually defined as stasis in the second- or third-order branches of the lobar hepatic artery and injection should be continued until near stasis is observed in the artery directly feeding the tumor (*i.e.*, the contrast column should clear within 2-5 heartbeats)[4].

TACE is a very heterogeneous operative technique and varies in terms of chemotherapeutic agents, treatment devices and schedule. Such heterogeneity explains the great range in terms of efficacy outcomes: a recent systematic review reported mean overall survival (OS) times of 3.422 up to more than 40 mo, with a median of 16.5 mo[5]. The best outcomes in terms of OS reported so far are 48 mo in a series published by the Barcelona group[6].

**INDICATIONS**

Patients should present a relatively well preserved liver function, defined as Child–Pugh (CP) ≤ B7 stage without ascites according to European Association for the Study of the Liver (EASL) guidelines[2] or only CP A according to the more conservative American Association for the Study of Liver Diseases (AASLD) guidelines[1].

Absolute contraindications to TACE are generally related to decompensated cirrhosis or impaired portal blood flow[1,2]. Other absolute contraindication, supported by the expert opinion, is represented by extensive tumors massively replacing both entire lobes, whereas a tumor size ≥ 10 cm, the bile-duct occlusion and untreated varices at high risk of bleeding constitute relative contraindication rather than absolute ones[5]. Main absolute and relative contraindications to TACE are reported in Table 1.

Although the adverse events associated with TACE are generally transient and easily manageable, they are very common with 35%[7] to 100%[8] of treated patients experiencing post-embolization syndrome (defined by the occurrence of abdominal pain, fever and nausea). Treatment-related deaths are expected in less than 2% of cases if proper selection of candidates is in place[9].

Therefore, TACE appears as a safe treatment in selected candidates, as defined by current guidelines.

**TREATMENT SCHEDULE**

Current evidence suggests that one cycle of TACE may not be sufficient for effective treatment of intermediate-stage HCC. On the other hand, there is evidence suggesting that repeating TACE prolongs survival; however, current guidelines do not specify the criteria for treatment repetition. In particular, it should be noted that in bilobar tumors, the two hepatic lobes usually have to be treated in separate treatment sessions 2-4 wk apart.

There are no solid data to suggest that “on-demand” TACE (*i.e.*, number of sessions on the basis of tumor response after each TACE cycle) is more or less effective than scheduled TACE (pre-defined number of sessions regardless of “at interim” response or safety evaluations) for improving patient survival. In fact, although scheduled strategy is more concordant with the general principle of oncologic therapy, which uses standard chemotherapeutic sessions based on the cell cycle, however, there is evidence suggesting that the repetition of TACE with an aggressive schedule increases the incidence of adverse events[10]. Therefore, the experts in the field propose the on-demand repetition with longer intervals between treatments, rather than a regular predefined schedule[5,11]. This has been recently confirmed by Terzi *et al*[12] in a series of 151 patients treated with on-demand conventional TACE (cTACE). In their analysis, a second TACE course was administered to 65% of patients who experienced a recurrence after the complete response (CR) and to only 41% of patients non responder to the first course. Therefore, the results of this study demonstrate that only approximately half of the patients with incomplete response or recurrences were eligible for repeated TACE, mainly because of tumor burden growth and liver function impairment[12]. These findings stand for an on-demand strategy to be “tailored” according to individual patients’ characteristics.

**REPEATED TACE: IS IT POSSIBLE A SCORE FOR ALL SEASONS?**

What remains to be definitively established is the maximum number of repeated TACE procedures that should be administered before switching to another therapeutic option or stopping treatment. Applying TACE procedures up to 3 to 4 times per year[11] and switching in absence of response to at least 2 sessions[5] has been recommended in absence of definitive evidence of an optimal retreatment strategy because more intensive regimens might induce liver failure in an unacceptable proportion of patients. A review of cohort and randomized controlled trials (RCTs) reported a mean number of TACE courses of 2.5 ± 1.5 per patient[13], but in the common clinical practice an even greater number of repeated sessions is undertaken.

To help the hepatologists to select appropriate candidates for starting or repeating TACE, several prognostic indices were introduced in the past, but none of them were universally accepted since they resulted difficult to implement or insufficiently discriminatory[14,15]. More recently, a number of other scores and nomograms have been proposed, particularly: the hepatoma arterial-embolization prognostic (HAP) score published by Kadalayil *et al*[16] in 2013, based on albumin, bilirubin, alpha-fetoprotein (AFP) and tumour size; the assessment for retreatment with TACE (ART) score proposed by Sieghart *et al*[17] in 2013, considering aspartate transaminase (AST) and CP increase after the first session together with tumor response; the ABCR score published by Adhoute *et al*[18] in 2014 on the basis of AFP and BCLC stage at baseline together with CP increase and tumor response after TACE; the inflammation based index (IBI) score, that combines C-reactive protein (CRP) and serum albumin, proposed by Pinato *et al*[19] and applied to TACE patients in 2015. Other proposed scores and nomograms are reported in Table 2[20-22].

Unfortunately, none of these new prognostic systems have been unequivocally confirmed in clinical practice[23-26]. In fact, all these efforts, although properly conducted, suffer from overfitting: a phenomenon occurring when a model maximizes its performance on some set of data but its predictive performance is not confirmed elsewhere due to random fluctuations of patients’ characteristics in different clinical and demographical backgrounds. The very fact that so different scores keep on being proposed confirms and gives proof of this concept. When a model is built, as in the case of the aforementioned studies, the score is tested in a different but “plausibly related” cohort and that is called external validation; unfortunately, external validation has been found to show sufficient power to detect clinically important changes in performance only when substantial sample sizes are available, that is not common in clinical research[27]. With smaller series, as in the case of most of the above reported papers, the sole external validation may lead to an overestimation of the performance of the model. In attendance of larger multicenter series and more reliable statistical tools (for instance bootstrap sampling or internal validation)[28], an unequivocally accepted prognostic system able to guide the decision of TACE repetition remains an unmet need. The detailed list of the proposed scoring systems for HCC patients undergoing TACE is reported in Table 2.

**USEFULNESS OF DRUG INJECTION**

Robust data in favor of a clear superiority of conventional TACE over transarterial embolization (TAE) are lacking[29]. A RCT comparing cTACE, TAE and best supportive care (BSC) was prematurely terminated due to the superiority of cTACE over BSC (see below)[30]. Unfortunately, this prevented the possibility to verify the efficacy of TAE, which could be hypothesized based on the trend observed in OS[30]. Similarly, no difference in terms of survival rates was reported between cisplatin-based TACE and TAE in a small Chinese RCT[31]. On the other hand, the added value of the chemotherapeutic agent (doxorubicin) in drug-eluting bead (DEB)-TACE over bland TAE has been recently demonstrated in a Greek RCT, which found an increase in time to progression (TTP) from 36.2 ± 9 wk up to 42.4 ± 9.5 wk (*P* = 0.008) in DEB-TACE patients[32]. Another investigation assessed the degree of necrosis in explanted livers after epirubicin DEB-TACE versus TAE and found tripled complete necrosis rates (77% *vs* 27% of lesions) in the DEB-TACE group[33].

There is no consensus on the optimal chemotherapeutic agent to use in TACE. Worldwide, the most popular anticancer drug injected is doxorubicin. In cTACE, the dose of doxorubicin typically ranges from 30 to 75 mg/m2 (to a maximum of 150 mg) mixed with 5 to 20 mL of lipiodol, followed by mechanical embolization with an embolic agent, as Gelfoam[4]. In DEB-TACE, the planned dose of doxorubicin should depend on the extent of the liver tumor burden: as a general rule, for disease within the Milan criteria each single treatment should include a planned dose of up to 75 mg doxorubicin loaded into one vial of DC Bead, whereas for disease beyond the Milan criteria, the dose should be of up to 150 mg loaded into two vials of DC Bead[4].

**DEB-TACE *VS* CTACE**

Ideally, the injected chemotherapeutic should be retained in the tumor and be gradually released to avoid systemic toxicity. However, even if suspended in lipiodol as in the case of cTACE, its selective injection is associated to significant passage into the systemic circulation. Other important limitation of conventional TACE has been the lack of standardization of the technique. In fact, the emulsification of the drug and lipiodol is prepared extemporaneously and hence is operator-dependent (not standardized) and is unstable. Therefore, to overcome the major drawbacks of cTACE, non-resorbable embolic microspheres loaded with cytotoxic drugs (DEBs) have been developed. In fact, DEBs are able to slowly release the drug upon injection and increase the intensity and duration of ischemia while enhancing the drug delivery to the tumor[4].

The first report on the efficacy of DEB-TACE was the phase II study by Varela *et al*[34]. In this pivotal paper, 27 Child-Pugh A HCC patients received two DEB-TACE (500-700 µm particles) sessions at 2-mo intervals: objective response rate (ORR) was 66.6% (whereof 26% were complete responses). Serial blood samples were obtained in 13 patients to determine doxorubicin maximal concentration (Cmax) and area under the curve (AUC), which resulted significantly lower in DEB-TACE patients as compared to an historical cohort of cTACE patients (*P* = 0.00002 and *P* = 0.001, respectively). Furthermore, DEB-TACE was well tolerated with only two cases of severe adverse events (namely, liver abscesses)[34]. These results were confirmed by Poon *et al*[35], who used the highest dose possible of doxorubicin (150 mg). In both studies, none of treated patients presented doxorubicin-related systemic toxicity (alopecia, bone marrow toxicity, dyspnea or pulmonary embolism)[34,35].

In light of successive clinical and in-animal studies[36,37], use of 100–300 µm beads is actually recommended, based on the demonstration that such small particles are delivered inside the tumor or in close proximity to the tumor margins and thus are ideal for drug delivery or precise embolization[4].

Despite the promising results of these preliminary studies and the aforementioned theoretical advantages of DEB-TACE, a clear superiority of one technique over the other is still lacking.

The comparison between cTACE and DEBs has been object of 12 studies (whereof 4 RCTs)[38-49] and 3 recent meta-analyses[50-52] (Table 3). In the most recent meta-analysis, a significantly better objective tumor response rate was found for DEB-TACE than for conventional TACE [odds ratio (OR) = 1.84, 95%CI: 1.02-3.33; *P* = 0.04], but Mantel-Haenzel OR for 3-year survival (reported in 4 studies) was non significant (0.77, CI: 0.55-1.06, *P* = 0.11)[50]. With regard to toxicity, either overall and severe adverse events were similar in both groups, with post-embolization syndrome occurring most commonly[50,51].

Although a clear superiority of DEB-TACE is still lacking, new micro-particles have been recently introduced in the clinical practice. As previously mentioned, small diameter beads have been shown to inflict pan-necrosis of the target lesion since smaller bead diameters achieve a more distal embolization, thus also obstructing collateral channels[35-37]. Therefore, smaller particles have been recently tested with promising results[53-55], but broader cohort studies and RCTs are warranted to validate such findings.

**APPLICATIONS OF TACE IN HEPATO-ONCOLOGY**

***Intermediate stage***

The recommendation for TACE as the standard-of-care for intermediate-stage HCC is based on the demonstration of improved survival compared with best supportive care or suboptimal therapies in a meta-analysis of six RCTs[56]. However, there was considerable heterogeneity between the individual study designs (including patient populations and TACE technique) as well as the study results, with only two[30,57] of the six individual studies that reported 2-year survival rates showing a statistically significant improvement compared with conservative management (relative risk of death after 2 years: 0.53, *P* = 0.017). Results from other two meta-analyses confirmed that TACE improved survival outcomes compared with conservative management, however, both meta-analyses also concluded that there were other treatment options (such as TAE or ethanol injection) as effective as, if not superior to, TACE for the treatment of unresectable HCC[58,59]. Furthermore, intermediate-stage HCC includes a heterogeneous population of patients varying widely in terms of tumour burden, liver function and disease etiology[11]. In fact, it should be noted that the previously mentioned studies included patients with HCC described as ‘‘unresectable” rather than those with HCC classified as intermediate according to the BCLC schema.

Overall, the expected survival for untreated intermediate HCC is 16 months, whereas after TACE increased up to 20 in the first studies[56]. However, these studies compared TACE to BSC and not to other treatment modalities such as surgery. Several reports on expanding criteria for resection in HCC have been published in the last years. In fact, two retrospective studies[60,61] and, above all, a RCT[62] explored the comparative effectiveness of surgery (partial hepatectomy) with respect to cTACE for intermediate patients. In the Chinese RCT, median survival was 41 mo (range 1-50 mo) after surgery *vs* only 14 mo (range 5-47 mo) after TACE (*P* < 0.001). However, it should be noticed that in both study groups, median tumor size was beyond 7 cm, a value representing a suboptimal indication to TACE[62].This may explain the relatively poor outcomes observed in TACE patients, that resulted very far from the most recent studies in the field[6,63].

On the other hand, besides the attempt to expand criteria for radical treatments, also the recently developed new loco-regional techniques have challenged the assumption of TACE as standard of care for BCLC B patients. Transarterial radioembolization (TARE) with yttrium 90 has gained increasing attention for intermediate and advanced patients in the last years[64-66]. Salem et al. retrospectively compared data from 245 patients (122 who received chemoembolization and 123 who received radioembolization) and reported longer TTP following radioembolization than chemoembolization (13.3 mo *vs* 9.4 mo, *P* = 0.047) but similar median OS (17.5 mo *vs* 17.2 mo, *P* = 0.42) in BCLC B patients[67]. Therefore, in this landmark paper by the Chicago group, TARE resulted in longer time-to-progression and less toxicity than chemoembolization[67]. Post-hoc analyses of sample size indicated that a randomized study with > 1000 patients would be required to establish equivalence of survival times between patients given the different therapies, a cohort not easy to collect in the clinical practice[67,68]. Other retrospective reports and a small RCTs confirmed the non significant superiority of one technique over the other[69-71].

In conclusion, in absence of further solid data provided by large RCTs, TACE remains the standard of care for intermediate HCC patients, with surgery and TARE as competitive options in case of compensated cirrhosis (CP A) or more advanced tumor burden, respectively.

***Early stage***

The EASL and AASLD guidelines recommend that the first option for HCC patients within Milan criteria should be hepatic resection or LT[1,2]. Nevertheless, some patients may be poor surgical candidates and the alternative is a variety of loco-regional ablation techniques. Of these, RFA is considered the treatment of choice for these patients, recently reported to be as effective for small HCCs (BCLC 0) as surgical resection[72-74]. However, some tumors with a subcapsular or dome location and tumors adjacent to intestinal loops or the main bile duct may be unsuitable for RFA and in such cases TACE can be used as therapy. Recently, Hsu *et al*[75] investigated the clinical outcomes of Milan-in HCC patients undergoing RFA (*n* = 315) or cTACE (*n* = 215). In the univariate survival analysis, the RFA group had a significantly better long-term survival than the TACE group (the 1-, 3-, and 5-year survival rates were 93%, 89%, and 72% for RFA, and 63%, 55%, and 43 % for TACE, *P* = 0.048), but after propensity-score matching (selecting 101 patients from each treatment arm) such a difference was lost (1-, 3-, and 5-year survival rates were 85%, 60%, and 41% for RFA, and 86%, 55%, and 36% for TACE; *P* = 0.476)[75]. However, patients undergoing TACE had a significantly higher cumulative recurrence rate than patients undergoing RFA (*P* = 0.023), hence, this study indicates that TACE and RFA lead to comparable long-term survival but differ in recurrence rate for HCC patients within the Milan criteria[75]. In subgroup analysis, patients with a smaller total tumor volume (< 11 cm3, equivalent to a single nodule 2.8 cm in diameter) were found likely to benefit more from RFA with respect to TACE[75]. A probable reason for these results is that RFA has a less satisfactory effect on medium tumors (3.1-5 cm in diameter) and multiple tumors[76-78].

Following the conclusions of this paper, Kim *et al*[79] have recently compared the two treatments in 287 very early (BCLC 0) HCC patients (122 and 165 patients treated with cTACE and RFA, respectively). In this study, RFA and TACE did not differ significantly in terms of mean survival (80.0 ± 2.3 mo and 72.1 ± 3.2 mo, respectively; *P* = 0.079), but objective response rate (100 % and 95.9 % in the RFA and TACE group, respectively; *P* = 0.013) and median TTP were significantly in favor of RFA (27.0 ± 3.8 mo after RFA and 18.0 ± 2.9 mo after TACE; *P* = 0.034) [79]. Therefore, although the study by Kim *et al*[79] does not strongly support the superiority of RFA over TACE as no statistically significant difference was noted in terms of OS, however, RFA led to better tumor responses and was associated with delayed tumor progression compared with TACE.

The aforementioned study suggests RFA as first-line treatment for unresectable early/very early HCC patients, whereas TACE may be considered a viable alternative when RFA is not feasible.

***Downstaging/Bridging***

TACE is the most used treatment for patients in waiting list for LT[80].

The aims of bridging treatments include decreasing the waiting list dropout rate before transplantation, reducing HCC recurrence after LT and improving post-transplant overall survival.

TACE has been extensively used in the past as a bridging treatment to LT and a number of studies have shown that it is an effective therapy in terms of adequate tumor necrosis achievement at explant analysis with complete tumor necrosis rates ranging between 27% and 57% in patients within Milan criteria[81,82].

These results are certainly of interest, considering that RFA leads to superior complete necrosis rates (between 50% and 78%) in single HCCs up to 3 cm, but significantly poorer outcomes in larger or multiple neoplasms (necrosis rate between 13% and 43%)[83-85].

The effectiveness of TARE has recently been evaluated by Riaz *et al*[86], who studied 38 nodules in 35 patients treated with radioembolization before LT. In this study, at explant analysis, 23 of the 38 target lesions (61%) showed complete tumor necrosis; in particular, complete tumor ablation was detected in 89%, 65%, and 33% of lesions smaller than 3 cm, between 3 and 5 cm, and larger than 5 cm, respectively[86]. The same Group retrospectively compared effectiveness of TACE and TARE in T3 HCC patients (*i.e.*, beyond conventional criteria): down-staging rate was 58% after TARE *vs* 31% after TACE (*P* < 0.05) [87].

In conclusion, no definitive recommendation can be made for one type of loco-regional therapy over others in the pre-transplant setting. However, on the basis of the aforementioned studies, RFA could be considered as the first-line treatment for single lesions up to 3 cm, in which complete tumor necrosis has been shown in more than 50% of cases at explant analysis[83-85]. TACE should be preferred for treating lesions > 3 cm because its effectiveness appears to be better in well-vascularized tumors with large feeding arteries.

***Advanced stage***

Advanced HCC (*i.e.*, BCLC stage C) is characterized by an Eastern Cooperative Oncology Group (ECOG) performance status of 1-2 and/or the presence of portal vein thrombosis (PVT) or extrahepatic metastases. According to current guidelines, advanced HCC patients can only receive sorafenib while it is generally accepted that TACE is not recommended in cases of macroscopic portal vein invasion because of the potentially increased risk of liver failure[1,2]. Recently, however, some prospective controlled trials have shown the survival benefit of TACE over BSC in advanced HCC patients with PVT[88,89]. Therefore, the clear effects and safety of TACE in these patients remain controversial. A recent meta-analysis of 8 studies (whereof 3 prospective) has summarized the published results on this regard: TACE resulted potentially suitable and safe for advanced HCC patients with PVT with a low rate of fatal complications[90]. Furthermore, for selected patients (those with established collateral circulation and good liver function), TACE treatment prolonged survival[90]. However, the results of this meta-analysis should be interpreted with caution because all the included studies were conducted in Asia (hence, it is uncertain the applicability of these findings to Western settings) and patients with better liver function tended to be selected into the TACE group, whereas those decompensated tended to be treated with BSC. Moreover, sorafenib, and not BSC, is the reference standard treatment for advanced-stage HCC, hence, direct comparisons between the two therapies are needed.

The only head-to-head comparison between the two treatments published so far, is a retrospective European study delivered by the Vienna group[91]. By the way, even in this well written paper, an underlying selection bias can be detected, as thrombosis of the main trunk of portal vein (well-known as at poorer prognosis) was more frequently present in the sorafenib group than in the TACE group (25% *vs* 3%). Median TTP was similar between the two treatment groups (*P* = 0.737) as well as median OS (9.2 mo, 95%CI: 6.1-12.3 mo after TACE *vs* 7.4 mo, 95%CI: 5.6-9.2 mo in patients treated with sorafenib, *P* = 0.377)[91]. Interestingly, in the Austrian study, TACE achieved promising outcomes (median OS of 14 mo) in selected advanced patients (CP A and segmental PVT), a result confirmed in other retrospective reports[92]. However, in the TACE group, 13 patients experienced severe adverse events and 4 treatment-related deaths, thus pointing out serious concerns on the safety of TACE in this setting[91].

Therefore, TACE might be a reasonable alternative for selected advanced patients (segmental PVT and CP A) who do not have access or are intolerant/unsuitable to sorafenib or TARE, but the particular attention to be paid to the safety profile restricts this therapeutic opportunity to highly-experienced Centers.

***Combined regimens***

A meta-analysis of 10 randomized trials and 18 observational studies including 2497 patients showed that the combination of TACE with other treatments, such as ethanol injection, external radiotherapy and high-intensity focused ultrasound (HIFU), result in better survival outcomes and similar side effects than TACE alone[93]. However, for each combination, the number of studies were mostly inadequate to provide a definitive recommendation, thus further well-organized randomized trials are needed to confirm these findings.

TACE is associated with local and systemic increase in vascular endothelial growth factor (VEGF), since embolization interrupts blood supply to the tumor, inducing hypoxia and necrosis[94].These observations suggest that an antiangiogenetic agent (namely, sorafenib) may counteract TACE-induced angiogenesis, thus improving the post-procedural outcomes[95,96]. Two important RCTs have explored the feasibility and the efficacy of the combined regimen, without finding any definitive evidence in favor of the association of sorafenib with TACE[97,98]. However, since other smaller RCTs and retrospective studies provided discordant results, combined regimens between antiangiogenetic agents and TACE remain an interesting field of research in hepato-oncology[99-102].

**CONCLUSION**

TACE covers a broad spectrum of therapeutic indications in hepato-oncology and, if the proper selection of candidates is followed, represents a safe and effective treatment. Further studies are needed to correctly expand treatment indications and define the more appropriate combined regimens with other loco-regional therapies or systemic drugs.

**REFERENCES**

1 **Bruix J**, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology* 2011; **53**: 1020-1022 [PMID: 21374666 DOI: 10.1002/hep.24199]

2 [European Association For The Study Of The Liver](http://www.ncbi.nlm.nih.gov/pubmed/?term=European%20Association%20For%20The%20Study%20Of%20The%20Liver%5BCorporate%20Author%5D)1; [European Organisation For Research And Treatment Of Cancer](http://www.ncbi.nlm.nih.gov/pubmed/?term=European%20Organisation%20For%20Research%20And%20Treatment%20Of%20Cancer%5BCorporate%20Author%5D). EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012; **56**: 908-943 [PMID: 22424438 DOI: 10.1016/j.jhep.2011.12.001]

3 **Lencioni R**, Petruzzi P, Crocetti L. Chemoembolization of hepatocellular carcinoma. *Semin Intervent Radiol* 2013; **30**: 3-11 [PMID: 24436512 DOI: 10.1055/s-0033-1333648]

4 **Lencioni R**, de Baere T, Burrel M, Caridi JG, Lammer J, Malagari K, Martin RC, O'Grady E, Real MI, Vogl TJ, Watkinson A, Geschwind JF. Transcatheter treatment of hepatocellular carcinoma with Doxorubicin-loaded DC Bead (DEBDOX): technical recommendations. *Cardiovasc Intervent Radiol* 2012; **35**: 980-985 [PMID: 22009576]

5 **Raoul JL**, Sangro B, Forner A, Mazzaferro V, Piscaglia F, Bolondi L, Lencioni R. Evolving strategies for the management of intermediate-stage hepatocellular carcinoma: available evidence and expert opinion on the use of transarterial chemoembolization. *Cancer Treat Rev* 2011; **37**: 212-220 [PMID: 20724077 DOI: 10.1016/j.ctrv.2010.07.006]

6 **Burrel M**, Reig M, Forner A, Barrufet M, de Lope CR, Tremosini S, Ayuso C, Llovet JM, Real MI, Bruix J. Survival of patients with hepatocellular carcinoma treated by transarterial chemoembolisation (TACE) using Drug Eluting Beads. Implications for clinical practice and trial design. *J Hepatol* 2012; **56:** 1330-1335 [PMID: 22314428 DOI: 10.1016/j.jhep.2012.01.008]

7 **Bruix J**, Llovet JM, Castells A, Montañá X, Brú C, Ayuso MC, Vilana R, Rodés J. Transarterial embolization versus symptomatic treatment in patients with advanced hepatocellular carcinoma: results of a randomized, controlled trial in a single institution. *Hepatology* 1998; **27**: 1578-1583 [PMID: 9620330]

8 **Bayraktar Y**, Balkanci F, Kayhan B, Uzunalimoglu B, Gokoz A, Ozisik Y, Gurakar A, Van Thiel DH, Firat D. A comparison of chemoembolization with conventional chemotherapy and symptomatic treatment in cirrhotic patients with hepatocellular carcinoma. *Hepatogastroenterology* 1996; **43:** 681-687 [PMID: 8799415]

9 **Lencioni R**. Chemoembolization for hepatocellular carcinoma. *Semin Oncol* 2012; **39**: 503-509 [PMID: 22846867 DOI: 10.1053/j.seminoncol.2012.05.004]

10 **Ernst O,** Sergent G, Mizrahi D, Delemazure O, Paris JC, L'Herminé C. Treatment of hepatocellular carcinoma by transcatheter arterial chemoembolization: comparison of planned periodic chemoembolization and chemoembolization based on tumor response. *AJR Am J Roentgenol* 1999; **172:** 59-64 [PMID: 9888740]

11 **Bolondi L**, Burroughs A, Dufour JF, Galle PR, Mazzaferro V, Piscaglia F, Raoul JL, Sangro B. Heterogeneity of patients with intermediate (BCLC B) Hepatocellular Carcinoma: proposal for a subclassification to facilitate treatment decisions. *Semin Liver Dis* 2012; **32**: 348-359 [PMID: 23397536 DOI: 10.1055/s-0032-1329906]

12 **Terzi E**, Golfieri R, Piscaglia F, Galassi M, Dazzi A, Leoni S, Giampalma E, Renzulli M, Bolondi L. Response rate and clinical outcome of HCC after first and repeated cTACE performed "on demand". *J Hepatol* 2012; **57**: 1258-1267 [PMID: 22871502 DOI: 10.1016/j.jhep.2012.07.025]

13 **Forner A**, Ayuso C, Varela M, Rimola J, Hessheimer AJ, de Lope CR, Reig M, Bianchi L, Llovet JM, Bruix J. Evaluation of tumor response after locoregional therapies in hepatocellular carcinoma: are response evaluation criteria in solid tumors reliable? *Cancer* 2009; **115**: 616-623 [PMID: 19117042 DOI: 10.1002/cncr.24050]

14 **Dumortier J**, Chapuis F, Borson O, Davril B, Scoazec JY, Poncet G, Henry L, Boillot O, Mion F, Berger F, Partensky C, Paliard P, Valette PJ. Unresectable hepatocellular carcinoma: survival and prognostic factors after lipiodol chemoembolisation in 89 patients. *Dig Liver Dis* 2006; **38**: 125-133 [PMID: 16389002]

15 **Lladó L**, Virgili J, Figueras J, Valls C, Dominguez J, Rafecas A, Torras J, Fabregat J, Guardiola J, Jaurrieta E. A prognostic index of the survival of patients with unresectable hepatocellular carcinoma after transcatheter arterial chemoembolization. *Cancer* 2000; **88**: 50-57 [PMID: 10618605]

16 **Kadalayil L**, Benini R, Pallan L, O'Beirne J, Marelli L, Yu D, Hackshaw A, Fox R, Johnson P, Burroughs AK, Palmer DH, Meyer T. A simple prognostic scoring system for patients receiving transarterial embolisation for hepatocellular cancer. *Ann Oncol* 2013; **24**: 2565-2570 [PMID: 23857958 DOI: 10.1093/annonc/mdt247]

17 **Sieghart W**, Hucke F, Pinter M, Graziadei I, Vogel W, Müller C, Heinzl H, Trauner M, Peck-Radosavljevic M. The ART of decision making: retreatment with transarterial chemoembolization in patients with hepatocellular carcinoma. *Hepatology* 2013; **57**: 2261-2273 [PMID: 23316013 DOI: 10.1002/hep.26256]

18 **Adhoute X**, Penaranda G, Naude S, Raoul JL, Perrier H, Bayle O, Monnet O, Beaurain P, Bazin C, Pol B, Folgoc GL, Castellani P, Bronowicki JP, Bourlière M. Retreatment with TACE: the ABCR SCORE, an aid to the decision-making process. *J Hepatol* 2015; **62**: 855-862 [PMID: 25463541 DOI: 10.1016/j.jhep.2014.11.014]

19 **Pinato DJ**, Karamanakos G, Arizumi T, Adjogatse D, Kim YW, Stebbing J, Kudo M, Jang JW, Sharma R. Dynamic changes of the inflammation-based index predict mortality following chemoembolisation for hepatocellular carcinoma: a prospective study. *Aliment Pharmacol Ther* 2014; **40**: 1270-1281 [PMID: 25327965 DOI: 10.1111/apt.12992]

20 **Hucke F,** Pinter M, Graziadei I, Bota S, Vogel W, Müller C, Heinzl H, Waneck F, Trauner M, Peck-Radosavljevic M, Sieghart W. How to STATE suitability and START transarterial chemoembolization in patients with intermediate stage hepatocellular carcinoma. *J Hepatol* 2014; **61:** 1287-96 [DOI: 10.1016/j.jhep.2014.07.002]

21 **Xu L**, Peng ZW, Chen MS, Shi M, Zhang YJ, Guo RP, Lin XJ, Lau WY. Prognostic nomogram for patients with unresectable hepatocellular carcinoma after transcatheter arterial chemoembolization. *J Hepatol* 2015; **63**: 122-130 [PMID: 25725438 DOI: 10.1016/j.jhep.2015.02.034]

22 **Sciarra A**, Ronot M, Di Tommaso L, Raschioni C, Castera L, Belghiti J, Bedossa P, Vilgrain V, Roncalli M, Paradis V. TRIP: a pathological score for transarterial chemoembolization resistance individualized prediction in hepatocellular carcinoma. *Liver Int* 2015; In press [PMID: 25865109 DOI: 10.1111/liv.12844]

23 **Kudo M**, Arizumi T, Ueshima K. Assessment for retreatment (ART) score for repeated transarterial chemoembolization in patients with hepatocellular carcinoma. *Hepatology* 2014; **59**: 2424-2425 [PMID: 24114720 DOI: 10.1002/hep.26760]

24 **Terzi E**, Terenzi L, Venerandi L, Croci L, Renzulli M, Mosconi C, Allegretti G, Granito A, Golfieri R, Bolondi L, Piscaglia F. The ART score is not effective to select patients for transarterial chemoembolization retreatment in an Italian series. *Dig Dis* 2014; **32**: 711-716 [PMID: 25376288 DOI: 10.1159/000368007]

25 **Facciorusso A**, Muscatiello N, Barone M. Letter: prognostic scoring systems for hepatocellular carcinoma patients--the jury is still out. *Aliment Pharmacol Ther* 2015; **41**: 596-597 [PMID: 25659216 DOI: 10.1111/apt.13078]

26 **Facciorusso A**, Bhoori S, Sposito C, Mazzaferro V. Repeated transarterial chemoembolization: An overfitting effort? *J Hepatol* 2015; **62**: 1440-1442 [PMID: 25678386 DOI: 10.1016/j.jhep.2015.01.033]

27 **Steyerberg EW**, Bleeker SE, Moll HA, Grobbee DE, Moons KG. Internal and external validation of predictive models: a simulation study of bias and precision in small samples. *J Clin Epidemiol* 2003; **56**: 441-447 [PMID: 12812818]

28 **Altman DG**, Andersen PK. Bootstrap investigation of the stability of a Cox regression model. *Stat Med* 1989; **8**: 771-783 [PMID: 2672226]

29 **Tsochatzis EA**, Fatourou E, O'Beirne J, Meyer T, Burroughs AK. Transarterial chemoembolization and bland embolization for hepatocellular carcinoma. *World J Gastroenterol* 2014; **20**: 3069-3077 [PMID: 24695579 DOI: 10.3748/wjg.v20.i12.3069]

30 **Llovet JM**, Real MI, Montaña X, Planas R, Coll S, Aponte J, Ayuso C, Sala M, Muchart J, Solà R, Rodés J, Bruix J. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002; **359**: 1734-1739 [PMID: 12049862]

31 **Chang JM**, Tzeng WS, Pan HB, Yang CF, Lai KH. Transcatheter arterial embolization with or without cisplatin treatment of hepatocellular carcinoma. A randomized controlled study. *Cancer* 1994; **74**: 2449-2453 [PMID: 7922999]

32 **Malagari K**, Pomoni M, Kelekis A, Pomoni A, Dourakis S, Spyridopoulos T, Moschouris H, Emmanouil E, Rizos S, Kelekis D. Prospective randomized comparison of chemoembolization with doxorubicin-eluting beads and bland embolization with BeadBlock for hepatocellular carcinoma. *Cardiovasc Intervent Radiol* 2010; **33**: 541-551 [PMID: 19937027 DOI: 10.1007/s00270-009-9750-0]

33 **Nicolini A**, Martinetti L, Crespi S, Maggioni M, Sangiovanni A. Transarterial chemoembolization with epirubicin-eluting beads versus transarterial embolization before liver transplantation for hepatocellular carcinoma. *J Vasc Interv Radiol* 2010; **21**: 327-332 [PMID: 20097098 DOI: 10.1016/j.jvir.2009.10.038]

34 **Varela M**, Real MI, Burrel M, Forner A, Sala M, Brunet M, Ayuso C, Castells L, Montañá X, Llovet JM, Bruix J. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. *J Hepatol* 2007; **46**: 474-481 [PMID: 17239480]

35 **Poon RT**, Tso WK, Pang RW, Ng KK, Woo R, Tai KS, Fan ST. A phase I/II trial of chemoembolization for hepatocellular carcinoma using a novel intra-arterial drug-eluting bead. *Clin Gastroenterol Hepatol* 2007; **5**: 1100-1108 [PMID: 17627902]

36 **Lee KH**, Liapi E, Ventura VP, Buijs M, Vossen JA, Vali M, Geschwind JF. Evaluation of different calibrated spherical polyvinyl alcohol microspheres in transcatheter arterial chemoembolization: VX2 tumor model in rabbit liver. *J Vasc Interv Radiol* 2008; **19**: 1065-1069 [PMID: 18589321 DOI: 10.1016/j.jvir.2008.02.023]

37 **Lewis AL**, Taylor RR, Hall B, Gonzalez MV, Willis SL, Stratford PW. Pharmacokinetic and safety study of doxorubicin-eluting beads in a porcine model of hepatic arterial embolization. *J Vasc Interv Radiol* 2006; **17**: 1335-1343 [PMID: 16923981]

38 **Nicolini D**, Svegliati-Baroni G, Candelari R, Mincarelli C, Mandolesi A, Bearzi I, Mocchegiani F, Vecchi A, Montalti R, Benedetti A, Risaliti A, Vivarelli M. Doxorubicin-eluting bead vs conventional transcatheter arterial chemoembolization for hepatocellular carcinoma before liver transplantation. *World J Gastroenterol* 2013; **19**: 5622-5632 [PMID: 24039354 DOI: 10.3748/wjg.v19.i34.5622]

39 **Frenette CT**, Osorio RC, Stark J, Fok B, Boktour MR, Guy J, Rhee J, Osorio RW. Conventional TACE and drug-eluting bead TACE as locoregional therapy before orthotopic liver transplantation: comparison of explant pathologic response. *Transplantation* 2014; **98**: 781-787 [PMID: 24825513 DOI: 10.1097/TP.0000000000000121]

40 **Song MJ**, Chun HJ, Song do S, Kim HY, Yoo SH, Park CH, Bae SH, Choi JY, Chang UI, Yang JM, Lee HG, Yoon SK. Comparative study between doxorubicin-eluting beads and conventional transarterial chemoembolization for treatment of hepatocellular carcinoma. *J Hepatol* 2012; **57**: 1244-1250 [PMID: 22824821 DOI: 10.1016/j.jhep.2012.07.017]

41 **Sacco R**, Bargellini I, Bertini M, Bozzi E, Romano A, Petruzzi P, Tumino E, Ginanni B, Federici G, Cioni R, Metrangolo S, Bertoni M, Bresci G, Parisi G, Altomare E, Capria A, Bartolozzi C. Conventional versus doxorubicin-eluting bead transarterial chemoembolization for hepatocellular carcinoma. *J Vasc Interv Radiol* 2011; **22**: 1545-1552 [PMID: 21849247 DOI: 10.1016/j.jvir.2011.07.002]

42 **van Malenstein H**, Maleux G, Vandecaveye V, Heye S, Laleman W, van Pelt J, Vaninbroukx J, Nevens F, Verslype C. A randomized phase II study of drug-eluting beads versus transarterial chemoembolization for unresectable hepatocellular carcinoma. *Onkologie* 2011; **34**: 368-376 [PMID: 21734423 DOI: 10.1159/000329602]

43 **Lammer J**, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, Pitton M, Sergent G, Pfammatter T, Terraz S, Benhamou Y, Avajon Y, Gruenberger T, Pomoni M, Langenberger H, Schuchmann M, Dumortier J, Mueller C, Chevallier P, Lencioni R. 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**: 41-52 [PMID: 19908093 DOI: 10.1007/s00270-009-9711-7]

44 **Golfieri R**, Giampalma E, Renzulli M, Cioni R, Bargellini I, Bartolozzi C, Breatta AD, Gandini G, Nani R, Gasparini D, Cucchetti A, Bolondi L, Trevisani F. Randomised controlled trial of doxorubicin-eluting beads vs conventional chemoembolisation for hepatocellular carcinoma. *Br J Cancer* 2014; **111**: 255-264 [PMID: 24937669 DOI: 10.1038/bjc.2014.199]

45 **Ferrer Puchol MD**, la Parra C, Esteban E, Vaño M, Forment M, Vera A, Cosín O. [Comparison of doxorubicin-eluting bead transarterial chemoembolization (DEB-TACE) with conventional transarterial chemoembolization (TACE) for the treatment of hepatocellular carcinoma]. *Radiologia* 2011; **53**: 246-253 [PMID: 21295802 DOI: 10.1016/j.rx.2010.07.010]

46 **Dhanasekaran R**, Kooby DA, Staley CA, Kauh JS, Khanna V, Kim HS. Comparison of conventional transarterial chemoembolization (TACE) and chemoembolization with doxorubicin drug eluting beads (DEB) for unresectable hepatocelluar carcinoma (HCC). *J Surg Oncol* 2010; **101**: 476-480 [PMID: 20213741 DOI: 10.1002/jso.21522]

47 **Wiggermann P**, Sieron D, Brosche C, Brauer T, Scheer F, Platzek I, Wawrzynek W, Stroszczynski C. Transarterial Chemoembolization of Child-A hepatocellular carcinoma: drug-eluting bead TACE (DEB TACE) vs. TACE with cisplatin/lipiodol (cTACE). *Med Sci Monit* 2011; **17**: CR189-CR195 [PMID: 21455104]

48 **Recchia F**, Passalacqua G, Filauri P, Doddi M, Boscarato P, Candeloro G, Necozione S, Desideri G, Rea S. Chemoembolization of unresectable hepatocellular carcinoma: Decreased toxicity with slow-release doxorubicin‑eluting beads compared with lipiodol. *Oncol Rep* 2012; **27**: 1377-1383 [PMID: 22294036 DOI: 10.3892/or.2012.1651]

49 **Megías Vericat JE**, García Marcos R, López Briz E, Gómez Muñoz F, Ramos Ruiz J, Martínez Rodrigo JJ, Poveda Andrés JL. Trans-arterial Chemoembolization with Doxorubicin-eluting Particles versus Conventional Trans-arterial Chemoembolization in Unresectable Hepatocellular Carcinoma: a Study of Effectiveness, Safety and Costs. *Radiologia* 2015; In press [PMID: 25857250 DOI: 10.1016/j.rx.2015.01.008]

50 **Huang K**, Zhou Q, Wang R, Cheng D, Ma Y. Doxorubicin-eluting beads versus conventional transarterial chemoembolization for the treatment of hepatocellular carcinoma. *J Gastroenterol Hepatol* 2014; **29**: 920-925 [PMID: 24224722 DOI: 10.1111/jgh.12439]

51 **Han S**, Zhang X, Zou L, Lu C, Zhang J, Li J, Li M. Does drug-eluting bead transcatheter arterial chemoembolization improve the management of patients with hepatocellular carcinoma? A meta-analysis. *PLoS One* 2014; **9**: e102686 [PMID: 25083860 DOI: 10.1371/journal.pone.0102686]

52 **Xie ZB**, Wang XB, Peng YC, Zhu SL, Ma L, Xiang BD, Gong WF, Chen J, You XM, Jiang JH, Li LQ, Zhong JH. Systematic review comparing the safety and efficacy of conventional and drug-eluting bead transarterial chemoembolization for inoperable hepatocellular carcinoma. *Hepatol Res* 2015; **45**: 190-200 [PMID: 25388603 DOI: 10.1111/hepr.12450]

53 **Malagari K**, Pomoni M, Moschouris H, Kelekis A, Charokopakis A, Bouma E, Spyridopoulos T, Chatziioannou A, Sotirchos V, Karampelas T, Tamvakopoulos C, Filippiadis D, Karagiannis E, Marinis A, Koskinas J, Kelekis DA. Chemoembolization of hepatocellular carcinoma with HepaSphere 30-60 μm. Safety and efficacy study. *Cardiovasc Intervent Radiol* 2014; **37**: 165-175 [PMID: 24263774 DOI: 10.1007/s00270-013-0777-x]

54 **Spreafico C**, Cascella T, Facciorusso A, Sposito C, Rodolfo L, Morosi C, Civelli EM, Vaiani M, Bhoori S, Pellegrinelli A, Marchianò A, Mazzaferro V. Transarterial chemoembolization for hepatocellular carcinoma with a new generation of beads: clinical-radiological outcomes and safety profile. *Cardiovasc Intervent Radiol* 2015; **38**: 129-134 [PMID: 24870698 DOI: 10.1007/s00270-014-0907-0]

55 **Deipolyi AR**, Oklu R, Al-Ansari S, Zhu AX, Goyal L, Ganguli S. Safety and efficacy of 70-150 μm and 100-300 μm drug-eluting bead transarterial chemoembolization for hepatocellular carcinoma. *J Vasc Interv Radiol* 2015; **26**: 516-522 [PMID: 25704226 DOI: 10.1016/j.jvir.2014.12.020]

56 **Llovet JM**, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. *Hepatology* 2003; **37**: 429-442 [PMID: 12540794]

57 **Lo CM**, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, Fan ST, Wong J. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology* 2002; **35**: 1164-1171 [PMID: 11981766]

58 **Cammà C**, Schepis F, Orlando A, Albanese M, Shahied L, Trevisani F, Andreone P, Craxì A, Cottone M. Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials. *Radiology* 2002; **224**: 47-54 [PMID: 12091661]

59 **Befeler AS**. Chemoembolization and bland embolization: a critical appraisal. *Clin Liver Dis* 2005; **9**: 287-300, vii [PMID: 15831274]

60 **Zhong JH**, Xiang BD, Gong WF, Ke Y, Mo QG, Ma L, Liu X, Li LQ. Comparison of long-term survival of patients with BCLC stage B hepatocellular carcinoma after liver resection or transarterial chemoembolization. *PLoS One* 2013; **8**: e68193 [PMID: 23874536 DOI: 10.1371/journal.pone.0068193]

61 **Choi SH**, Choi GH, Kim SU, Park JY, Joo DJ, Ju MK, Kim MS, Choi JS, Han KH, Kim SI. Role of surgical resection for multiple hepatocellular carcinomas. *World J Gastroenterol* 2013; **19**: 366-374 [PMID: 23372359 DOI: 10.3748/wjg.v19.i3.366]

62 **Yin L**, Li H, Li AJ, Lau WY, Pan ZY, Lai EC, Wu MC, Zhou WP. Partial hepatectomy vs. transcatheter arterial chemoembolization for resectable multiple hepatocellular carcinoma beyond Milan Criteria: a RCT. *J Hepatol* 2014; **61**: 82-88 [PMID: 24650695 DOI: 10.1016/j.jhep.2014.03.012]

63 **Malagari K**, Pomoni M, Moschouris H, Bouma E, Koskinas J, Stefaniotou A, Marinis A, Kelekis A, Alexopoulou E, Chatziioannou A, Chatzimichael K, Dourakis S, Kelekis N, Rizos S, Kelekis D. Chemoembolization with doxorubicin-eluting beads for unresectable hepatocellular carcinoma: five-year survival analysis. *Cardiovasc Intervent Radiol* 2012; **35**: 1119-1128 [PMID: 22614031]

64 **Salem R**, Lewandowski RJ, Mulcahy MF, Riaz A, Ryu RK, Ibrahim S, Atassi B, Baker T, Gates V, Miller FH, Sato KT, Wang E, Gupta R, Benson AB, Newman SB, Omary RA, Abecassis M, Kulik L. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. *Gastroenterology* 2010; **138**: 52-64 [PMID: 19766639 DOI: 10.1053/j.gastro.2009.09.006]

65 **Mazzaferro V**, Sposito C, Bhoori S, Romito R, Chiesa C, Morosi C, Maccauro M, Marchianò A, Bongini M, Lanocita R, Civelli E, Bombardieri E, Camerini T, Spreafico C. Yttrium-90 radioembolization for intermediate-advanced hepatocellular carcinoma: a phase 2 study. *Hepatology* 2013; **57**: 1826-1837 [PMID: 22911442 DOI: 10.1002/hep.26014]

66 **Sangro B**, Carpanese L, Cianni R, Golfieri R, Gasparini D, Ezziddin S, Paprottka PM, Fiore F, Van Buskirk M, Bilbao JI, Ettorre GM, Salvatori R, Giampalma E, Geatti O, Wilhelm K, Hoffmann RT, Izzo F, Iñarrairaegui M, Maini CL, Urigo C, Cappelli A, Vit A, Ahmadzadehfar H, Jakobs TF, Lastoria S. Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. *Hepatology* 2011; **54**: 868-878 [PMID: 21618574 DOI: 10.1002/hep.24451]

67 **Salem R**, Lewandowski RJ, Kulik L, Wang E, Riaz A, Ryu RK, Sato KT, Gupta R, Nikolaidis P, Miller FH, Yaghmai V, Ibrahim SM, Senthilnathan S, Baker T, Gates VL, Atassi B, Newman S, Memon K, Chen R, Vogelzang RL, Nemcek AA, Resnick SA, Chrisman HB, Carr J, Omary RA, Abecassis M, Benson AB, Mulcahy MF. Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma. *Gastroenterology* 2011; **140**: 497-507.e2 [PMID: 21044630 DOI: 10.1053/j.gastro.2010.10.049]

68 **Salem R**, Mazzaferro V, Sangro B. Yttrium 90 radioembolization for the treatment of hepatocellular carcinoma: biological lessons, current challenges, and clinical perspectives. *Hepatology* 2013; **58**: 2188-2197 [PMID: 23512791 DOI: 10.1002/hep.26382]

69 **Moreno-Luna LE**, Yang JD, Sanchez W, Paz-Fumagalli R, Harnois DM, Mettler TA, Gansen DN, de Groen PC, Lazaridis KN, Narayanan Menon KV, Larusso NF, Alberts SR, Gores GJ, Fleming CJ, Slettedahl SW, Harmsen WS, Therneau TM, Wiseman GA, Andrews JC, Roberts LR. Efficacy and safety of transarterial radioembolization versus chemoembolization in patients with hepatocellular carcinoma. *Cardiovasc Intervent Radiol* 2013; **36**: 714-723 [PMID: 23093355 DOI: 10.1007/s00270-012-0481-2]

70 **El Fouly A**, Ertle J, El Dorry A, Shaker MK, Dechêne A, Abdella H, Mueller S, Barakat E, Lauenstein T, Bockisch A, Gerken G, Schlaak JF. In intermediate stage hepatocellular carcinoma: radioembolization with yttrium 90 or chemoembolization? *Liver Int* 2015; **35**: 627-635 [PMID: 25040497 DOI: 10.1111/liv.12637]

71 **Pitton MB**, Kloeckner R, Ruckes C, Wirth GM, Eichhorn W, Wörns MA, Weinmann A, Schreckenberger M, Galle PR, Otto G, Dueber C. Randomized comparison of selective internal radiotherapy (SIRT) versus drug-eluting bead transarterial chemoembolization (DEB-TACE) for the treatment of hepatocellular carcinoma. *Cardiovasc Intervent Radiol* 2015; **38**: 352-360 [PMID: 25373796 DOI: 10.1007/s00270-014-1012-0]

72 **Pompili M**, Saviano A, de Matthaeis N, Cucchetti A, Ardito F, Federico B, Brunello F, Pinna AD, Giorgio A, Giulini SM, De Sio I, Torzilli G, Fornari F, Capussotti L, Guglielmi A, Piscaglia F, Aldrighetti L, Caturelli E, Calise F, Nuzzo G, Rapaccini GL, Giuliante F. Long-term effectiveness of resection and radiofrequency ablation for single hepatocellular carcinoma ≤3 cm. Results of a multicenter Italian survey. *J Hepatol* 2013; **59**: 89-97 [PMID: 23523578 DOI: 10.1016/j.jhep.2013.03.009]

73 **Feng K**, Yan J, Li X, Xia F, Ma K, Wang S, Bie P, Dong J. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. *J Hepatol* 2012; **57**: 794-802 [PMID: 22634125 DOI: 10.1016/j.jhep.2012.05.007]

74 **Facciorusso A**, Del Prete V, Antonino M, Neve V, Crucinio N, Di Leo A, Carr BI, Barone M. Serum ferritin as a new prognostic factor in hepatocellular carcinoma patients treated with radiofrequency ablation. *J Gastroenterol Hepatol* 2014; **29**: 1905-1910 [PMID: 24731153 DOI: 10.1111/jgh.12618]

75 **Hsu CY**, Huang YH, Chiou YY, Su CW, Lin HC, Lee RC, Chiang JH, Huo TI, Lee FY, Lee SD. Comparison of radiofrequency ablation and transarterial chemoembolization for hepatocellular carcinoma within the Milan criteria: a propensity score analysis. *Liver Transpl* 2011; **17**: 556-566 [PMID: 21506244 DOI: 10.1002/lt.22273]

76 **N'Kontchou G**, Mahamoudi A, Aout M, Ganne-Carrié N, Grando V, Coderc E, Vicaut E, Trinchet JC, Sellier N, Beaugrand M, Seror O. Radiofrequency ablation of hepatocellular carcinoma: long-term results and prognostic factors in 235 Western patients with cirrhosis. *Hepatology* 2009; **50**: 1475-1483 [PMID: 19731239 DOI: 10.1002/hep.23181]

77 **Lencioni R**, Cioni D, Crocetti L, Franchini C, Pina CD, Lera J, Bartolozzi C. Early-stage hepatocellular carcinoma in patients with cirrhosis: long-term results of percutaneous image-guided radiofrequency ablation. *Radiology* 2005; **234**: 961-967 [PMID: 15665226]

78 **Facciorusso A**, Del Prete V, Antonino M, Crucinio N, Neve V, Di Leo A, Carr BI, Barone M. Post-recurrence survival in hepatocellular carcinoma after percutaneous radiofrequency ablation. *Dig Liver Dis* 2014; **46**: 1014-1019 [PMID: 25085684 DOI: 10.1016/j.dld.2014.07.012]

79 **Kim JW**, Kim JH, Sung KB, Ko HK, Shin JH, Kim PN, Choi HK, Ko GY, Yoon HK, Chun SY, Gwon DI. Transarterial chemoembolization vs. radiofrequency ablation for the treatment of single hepatocellular carcinoma 2 cm or smaller. *Am J Gastroenterol* 2014; **109**: 1234-1240 [PMID: 24935276 DOI: 10.1038/ajg.2014.152]

80 **Clavien PA**, Lesurtel M, Bossuyt PM, Gores GJ, Langer B, Perrier A. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. *Lancet Oncol* 2012; **13**: e11-e22 [PMID: 22047762 DOI: 10.1016/S1470-2045(11)70175-9]

81 **Majno PE**, Adam R, Bismuth H, Castaing D, Ariche A, Krissat J, Perrin H, Azoulay D. Influence of preoperative transarterial lipiodol chemoembolization on resection and transplantation for hepatocellular carcinoma in patients with cirrhosis. *Ann Surg* 1997; **226**: 688-701; discussion 701-3 [PMID: 9409568]

82 **Golfieri R**, Cappelli A, Cucchetti A, Piscaglia F, Carpenzano M, Peri E, Ravaioli M, D'Errico-Grigioni A, Pinna AD, Bolondi L. Efficacy of selective transarterial chemoembolization in inducing tumor necrosis in small (& lt; 5 cm) hepatocellular carcinomas. *Hepatology* 2011; **53**: 1580-1589 [PMID: 21351114 DOI: 10.1002/hep.24246]

83 **Mazzaferro V**, Battiston C, Perrone S, Pulvirenti A, Regalia E, Romito R, Sarli D, Schiavo M, Garbagnati F, Marchianò A, Spreafico C, Camerini T, Mariani L, Miceli R, Andreola S. Radiofrequency ablation of small hepatocellular carcinoma in cirrhotic patients awaiting liver transplantation: a prospective study. *Ann Surg* 2004; **240**: 900-909 [PMID: 15492574]

84 **Lu DS**, Yu NC, Raman SS, Lassman C, Tong MJ, Britten C, Durazo F, Saab S, Han S, Finn R, Hiatt JR, Busuttil RW. Percutaneous radiofrequency ablation of hepatocellular carcinoma as a bridge to liver transplantation. *Hepatology* 2005; **41**: 1130-1137 [PMID: 15841454]

85 **Pompili M**, Mirante VG, Rondinara G, Fassati LR, Piscaglia F, Agnes S, Covino M, Ravaioli M, Fagiuoli S, Gasbarrini G, Rapaccini GL. Percutaneous ablation procedures in cirrhotic patients with hepatocellular carcinoma submitted to liver transplantation: Assessment of efficacy at explant analysis and of safety for tumor recurrence. *Liver Transpl* 2005; **11**: 1117-1126 [PMID: 16123960]

86 **Riaz A**, Kulik L, Lewandowski RJ, Ryu RK, Giakoumis Spear G, Mulcahy MF, Abecassis M, Baker T, Gates V, Nayar R, Miller FH, Sato KT, Omary RA, Salem R. Radiologic-pathologic correlation of hepatocellular carcinoma treated with internal radiation using yttrium-90 microspheres. *Hepatology* 2009; **49**: 1185-1193 [PMID: 19133645 DOI: 10.1002/hep.22747]

87 **Lewandowski RJ**, Kulik LM, Riaz A, Senthilnathan S, Mulcahy MF, Ryu RK, Ibrahim SM, Sato KT, Baker T, Miller FH, Omary R, Abecassis M, Salem R. A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization. *Am J Transplant* 2009; **9**: 1920-1928 [PMID: 19552767 DOI: 10.1111/j.1600-6143.2009.02695.x]

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

89 **Niu ZJ**, Ma YL, Kang P, Ou SQ, Meng ZB, Li ZK, Qi F, Zhao C. Transarterial chemoembolization compared with conservative treatment for advanced hepatocellular carcinoma with portal vein tumor thrombus: using a new classification. *Med Oncol* 2012; **29**: 2992-2997 [PMID: 22200992 DOI: 10.1007/s12032-011-0145-0]

90 **Xue TC**, Xie XY, Zhang L, Yin X, Zhang BH, Ren ZG. Transarterial chemoembolization for hepatocellular carcinoma with portal vein tumor thrombus: a meta-analysis. *BMC Gastroenterol* 2013; **13**: 60 [PMID: 23566041 DOI: 10.1186/1471-230X-13-60]

91 **Pinter M**, Hucke F, Graziadei I, Vogel W, Maieron A, Königsberg R, Stauber R, Grünberger B, Müller C, Kölblinger C, Peck-Radosavljevic M, Sieghart W. Advanced-stage hepatocellular carcinoma: transarterial chemoembolization versus sorafenib. *Radiology* 2012; **263**: 590-599 [PMID: 22438359 DOI: 10.1148/radiol.12111550]

92 **Kalva SP**, Pectasides M, Liu R, Rachamreddy N, Surakanti S, Yeddula K, Ganguli S, Wicky S, Blaszkowsky LS, Zhu AX. Safety and effectiveness of chemoembolization with drug-eluting beads for advanced-stage hepatocellular carcinoma. *Cardiovasc Intervent Radiol* 2014; **37**: 381-387 [PMID: 23754191 DOI: 10.1007/s00270-013-0654-7]

93 **Liao M**, Huang J, Zhang T, Wu H. Transarterial chemoembolization in combination with local therapies for hepatocellular carcinoma: a meta-analysis. *PLoS One* 2013; **8**: e68453 [PMID: 23844203 DOI: 10.1371/journal.pone.0068453]

94 **Weintraub JL**, Salem R. Treatment of hepatocellular carcinoma combining sorafenib and transarterial locoregional therapy: state of the science. *J Vasc Interv Radiol* 2013; **24**: 1123-1134 [PMID: 23562168 DOI: 10.1016/j.jvir.2013.01.494]

95 **Facciorusso A**, Licinio R, Carr BI, Di Leo A, Barone M. MEK 1/2 inhibitors in the treatment of hepatocellular carcinoma. *Expert Rev Gastroenterol Hepatol* 2015; **9**: 993-1003 [PMID: 25915713 DOI: 10.1586/17474124.2015.1040763]

96 **Facciorusso A**, Antonino M, Del Prete V, Neve V, Scavo MP, Barone M. Are hematopoietic stem cells involved in hepatocarcinogenesis? *Hepatobiliary Surg Nutr* 2014; **3**: 199-206 [PMID: 25202697 DOI: 10.3978/j.issn.2304-3881.2014.06.02]

97 **Kudo M**, Imanaka K, Chida N, Nakachi K, Tak WY, Takayama T, Yoon JH, Hori T, Kumada H, Hayashi N, Kaneko S, Tsubouchi H, Suh DJ, Furuse J, Okusaka T, Tanaka K, Matsui O, Wada M, Yamaguchi I, Ohya T, Meinhardt G, Okita K. Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma. *Eur J Cancer* 2011; **47**: 2117-2127 [PMID: 21664811 DOI: 10.1016/j.ejca.2011.05.007]

98 **Lencioni R,** Llovet JM, Han G, Tak WJ, Yang J, Leberre MA, Niu W, Nicholson K, Meinhardt G, Bruix J. Sorafenib or placebo in combination with transarterial chemoembolization (TACE) with doxorubicin-eluting beads (DEBDOX) for intermediate-stage hepatocellular carcinoma (HCC): Phase II, randomized, double-blind SPACE trial. *J Clin Oncol* 2012 (suppl 4; abstr LBA154^)

99 **Sansonno D**, Lauletta G, Russi S, Conteduca V, Sansonno L, Dammacco F. Transarterial chemoembolization plus sorafenib: a sequential therapeutic scheme for HCV-related intermediate-stage hepatocellular carcinoma: a randomized clinical trial. *Oncologist* 2012; **17**: 359-366 [PMID: 22334456 DOI: 10.1634/theoncologist.2011-0313]

100 **Erhardt A**, Kolligs F, Dollinger M, Schott E, Wege H, Bitzer M, Gog C, Lammert F, Schuchmann M, Walter C, Blondin D, Ohmann C, Häussinger D. TACE plus sorafenib for the treatment of hepatocellular carcinoma: results of the multicenter, phase II SOCRATES trial. *Cancer Chemother Pharmacol* 2014; **74**: 947-954 [PMID: 25173458 DOI: 10.1007/s00280-014-2568-8]

101 **Chao Y**, Chung YH, Han G, Yoon JH, Yang J, Wang J, Shao GL, Kim BI, Lee TY. The combination of transcatheter arterial chemoembolization and sorafenib is well tolerated and effective in Asian patients with hepatocellular carcinoma: final results of the START trial. *Int J Cancer* 2015; **136**: 1458-1467 [PMID: 25099027 DOI: 10.1002/ijc.29126]

102 **Zhang L**, Hu P, Chen X, Bie P. Transarterial chemoembolization (TACE) plus sorafenib versus TACE for intermediate or advanced stage hepatocellular carcinoma: a meta-analysis. *PLoS One* 2014; **9**: e100305 [PMID: 24945380 DOI: 10.1371/journal.pone.0100305]

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**Table 1 Absolute and relative contraindications to transarterial chemoembolization**

|  |
| --- |
| Absolute contraindications |
| Decompensated cirrhosis (Child-Pugh ≥ B8)  Extensive tumor with massive replacement of both entire lobes  Severely reduced portal vein flow  Technical impediments to hepatic intra-arterial treatment |
| Relative contraindications |
| Kidney failure  Severe cardiopulmonary comorbidities  Tumor size ≥ 10 cm  Untreated varices at high risk of bleeding  Bile-duct occlusion |

**Table 2 Proposed scoring systems for hepatocellular carcinoma patients undergoing transarterial chemoembolization**

|  |  |  |
| --- | --- | --- |
| **Score** | **Variables considered** | **Aim** |
| Lladò[15] | AFP (> 400 UI/L), tumor size (> 50%) and CP score | Treatment selection |
| Kadalayil[16] | Albumin < 3.6 g/L, bilirubin > 17 μmol/L, AFP > 400 ng/mL and dominant tumor size > 7 cm | Treatment selection |
| Sieghart[17] | Increase of AST by > 25% and of CP score from baseline, tumor response | Treatment repetition |
| Adhoute[18] | BCLC, AFP (> 200 ng/mL), increase in CP score by ≥ 2 from baseline and tumor response | Treatment repetition |
| Pinato[19] | Normalization of CRP and serum albumin after TACE | Treatment repetition |
| Hucke[20] | Albumin level, tumour burden (reference: up-to-7 criteria) and CRP(≥ 1 mg/dL) | Treatment selection |
| Xu[21] | PVT, tumor number, tumor capsule, AFP, AST and ICR | Treatment selection |
| Sciarra[22] | CD34 and VEGF staining1 | Treatment selection |

1Assessed in tumor biopsy. AFP: Alpha-fetoprotein; CP: Child-Pugh; AST: Aspartate transaminase; BCLC: Barcelona Clinic Liver Cancer; CRP: C-reactive protein; TACE: Transarterial chemoembolization; PVT: Portal vein thrombosis; ICR: Indocyanin retention test; VEGF: Vascular endothelial growth factor.

**Table 3 Studies comparing conventional and drug-eluting beads transarterial chemoembolization in hepatocellular carcinoma patients**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Study | Arm | Drug | Sample size | Study design | Region |
| Nicolini 2013[38]1 | DEB-TACE  cTACE | Doxorubicin  Epirubicin | 22  16 | R | Italy |
| Frenette 2014[39]1 | DEB-TACE  cTACE | Doxorubicin  Doxorubicin | 35  76 | R | United States |
| Song 2012[40] | DEB-TACE  cTACE | Doxorubicin  Doxorubicin or Epirubicin/Cisplatin | 60  69 | R | South Korea |
| Sacco 2011[41] | DEB-TACE  cTACE | Doxorubicin  Doxorubicin | 33  34 | RCT | Italy |
| Van Malenstein 2011[42] | DEB-TACE  cTACE | Doxorubicin  Doxorubicin | 16  14 | RCT | Belgium |
| Lammer 2010[43] | DEB-TACE  cTACE | Doxorubicin  Doxorubicin | 93  108 | RCT | Europe |
| Golfieri 2014[44] | DEB-TACE  cTACE | Doxorubicin  Epirubicin | 89  88 | RCT | Italy |
| Ferrer 2011[45] | DEB-TACE  cTACE | Doxorubicin  Doxorubicin | 47  25 | P | Spain |
| Dhanasekaran 2010[46] | DEB-TACE  cTACE | Doxorubicin  Doxorubicin/Cisplatin/Mytomicin-C | 45  26 | R | United States |
| Wiggermann 2011[47] | DEB-TACE  cTACE | Epirubicin  Cisplatin | 22  22 | R | Germany |
| Recchia 2012[48] | DEB-TACE  cTACE | Doxorubicin  Doxorubicin | 35  70 | P | Italy |
| Megìas Vericat 2015[49] | DEB-TACE  cTACE | Doxorubicin  DOxorubicin | 30  30 | R | Spain |
|  | | | | | |

1Study conducted on transplanted patients. DEB-TACE: Drug-eluting beads transarterial chemoembolization; cTACE: Conventional transarterial chemoembolization; R: Retrospective; RCT: Randomizes controlled trial; P: Prospective; CP: Child-Pugh; BCLC: Barcelona Clinic Liver Cancer; NA: Not available.