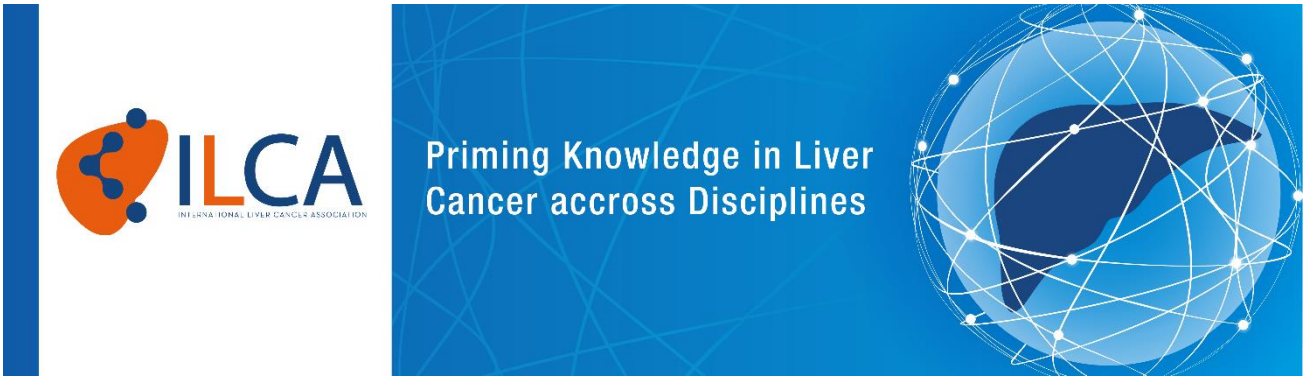

2023 International Liver Cancer Association consensus statements on treatment of liver cancer with TACE – summary document

Part A – How to select HCC patients for first-line treatment with TACE?

A-1. TACE should be considered as the first-line liver-directed treatment for patients with BCLC intermediate-stage HCC who are suitable for liver-directed therapy.

A-2. For patients with BCLC intermediate-stage HCC, the decision on TACE versus other locoregional or systemic therapy should be made in a multidisciplinary team setting.

A-3. Patients with BCLC early-stage HCC may receive TACE when surgery or local ablation is not feasible.

Rationale/Elaboration

- Beneficial clinical outcomes of TACE in unresectable hepatocellular carcinoma (HCC) are supported by two positive randomised controlled trials (RCTs) and several meta-analyses.[1–6]
- European/North American guidance endorses the use of TACE in this population,[7-11], and a multidisciplinary team (MDT) approach to treatment is endorsed by various expert groups.10, 12-15[9,11–14]
- It is appreciated that some intermediate-stage HCC is considered resectable by some MDTs. In that case, resection could be considered over TACE.16[15]
- Other treatment options including yttrium-90 transarterial radioembolisation (TARE)17-21[16–20] or hepatic arterial infusion chemotherapy (HAIC) may be considered as alternatives to TACE according to the local practice.22[21] Studies suggest that overall survival after TARE is similar to TACE but TARE appears to induce significantly longer time to progression. 22The administration of TACE to earlier-stage HCC patients (e.g. BCLC A) has been documented in both observational studies and in RCTs,24-29[22–27] and both ESMO and AASLD guidelines include TACE as an option for BCLC A patients if resection is not feasible.7,11[7,10]

A-4. The administration of TACE in HCC with Vp3 and Vp4 vascular invasion is discouraged.

Rationale/Elaboration

- In some regions (predominantly Asia), TACE has been used to treat patients with Vp1 and Vp2 vascular invasion.30-32[28–30]
- However, given the limited efficacy of TACE in patients with Vp3 and Vp4, and increasing availability of systemic therapies, TACE should be reserved for patients with more focal disease that is amenable to selective TACE.33,34[31,32]

A-5. Hepatic function is an important consideration for starting TACE treatment. Preferably, TACE should be commenced in patients with preserved hepatic function.

Rationale/Elaboration

- Worse hepatic function, e.g., albumin-bilirubin (ALBI) Grade 2 or Child-Pugh B, is a poor prognostic factor for OS,35,36[33,34] and patients with hepatic dysfunction after TACE have limited options for subsequent systemic therapy.35-37[33–35]
- The optimal cut-off of hepatic function remains unclear.38-40[36–38]

A-6. For intermediate-stage HCC, TACE-unsuitability is defined as clinical conditions (e.g., liver dysfunction) that prevent survival benefit from TACE or conditions in which TACE is harmful.

Rationale/Elaboration

- Technical feasibility of TACE does not equal clinical benefits from TACE. Evidence from a prospective study, the latest BCLC stage and the APPLE consensus indicate intermediate-stage patients with extensive intrahepatic disease burden should be considered for systemic therapy, rather than TACE.33,41,42[31,39,40]

A-7. Other conditions that may increase the risk of TACE include:

i. Bile duct obstruction or active cholangitis.
ii. Untreatable intrahepatic arterio-venous fistula.
iii. Compromised liver function (Child-Pugh B8 or above).
iv. Renal insufficiency.
v. Poor performance status of 2 or above.

Rationale/Elaboration

- These conditions have been proposed previously as contraindications to TACE by multiple publications and guidelines, and are widely applied as such in real-world practice.8, 38, 40, 43[8,36,38,41]
- Other high-risk criteria may also contraindicate patients;44[42] therefore, the decision to proceed or not with TACE should be guided by the clinical judgement of the MDT and individualised to the patient.

Part B – How to administer TACE

B-1. TACE should be administered using a 3D-angiography obtained either with rotational flat panel detector system (CBCT) or a multi-detector computed tomography (MDCT) combined with angiography system.

Rationale/Elaboration

- The ideal imaging modalities for TACE administration are C-arm cone-beam computed tomography (CBCT) or multi-detector computed tomography (MDCT) combined with angiography; these are the 'gold standard' for imaging during TACE.45-55[43–53]

B-2. In cases of major arterio-portal or hepatic-venous shunting, embolisation of the shunt should be performed before proceeding with TACE.

Rationale/Elaboration

- The presence of arterio-portal or arterio-venous (AV) shunts may lead to diversion of TACE emulsion away from the targeted region and ineffective concentration of therapy in the tumour.56[54] This can be counteracted by embolization of shunts.57[55]

B-3. TACE should be administered super-selectively whenever possible.

B-4. Conventional TACE (c-TACE) should ideally cover the whole tumour plus, where possible, the peritumoural margin.

B-5. In general, following super-selective TACE, complete embolisation of the feeding artery should be confirmed.

Rationale/Elaboration

- Recent guidelines support TACE for patients where highly-selective access to the tumour is feasible.8,9 11[8,10]
- HCC with tumour diameter ≤7 cm, a number of lesions ≤5, and fewer than 2 segments involved are commonly reported as the best candidates for super-selective TACE (ss-TACE).58,59[56,57]
- TACE delivery should ensure a safety margin around the tumour is achieved.60,61[58,59]
- Complete embolisation of the feeding artery should be confirmed to avoid embolic material flowing into the portal and hepatic veins when the balloon is released; better embolization is associated with better outcomes.62,63[60,61]

B-6. For c-TACE, water-in-oil emulsion with Lipiodol should be used as a drug carrier with focus on ensuring:

i. The drug-aqueous solution to Lipiodol ratio should be in the range of 1:2 to 1:4
ii. The density and stability of drug/Lipiodol emulsion

Rationale/Elaboration

- *In vitro* studies showed that an aqueous-to-oil ratio of 1:2 to 1:4 displays a prolonged drug release profile.64[62]

- Non-ionic contrast medium for preparation of drug aqueous solution will increase the density of the drug solution and thus favours stability of the drug/Lipiodol emulsion by lowering the sedimentation process induced by gravity.65[63]

B-7. For c-TACE, particulate embolisation must finalise the TACE procedure after injection of the drug/Lipiodol mixture.

Rationale/Elaboration

- Once the Lipiodol emulsion is administered, c-TACE is frequently finalised by particulate embolisation.66-68[64–66]

- Gelatin sponge particles are one of the most commonly used embolic materials2,3,69,70[2,3,67,68]

- Gelatin sponge embolisation performed after delivering the Lipiodol/drug emulsion should provide complete stasis up to the catheter tip.67[65]

B-8. TACE remains the most commonly performed procedure globally, but TAE is an acceptable alternative.

Rationale/Elaboration

- Although TACE is widely-recommended modality in treatment of intermediate HCC,10,71[9,69] transcatheter arterial embolisation (TAE) is an acceptable alternative.

- There is no firm evidence showing TACE produces better outcomes than TAE,72[70] and TAE can achieve good outcomes using only embolisation particles.73[71]

B-9. Prophylactic antibiotic is not a routine requirement but may be considered in patients with high risk of infection.

Rationale/Elaboration

- Data on the efficacy of prophylactic antibiotics are conflicting74-76[72–74]
- The risk of infection is generally low, but may be increased by underlying risk factors e.g. diabetes, bilioenteric anastomosis76,77[74,75]

Part C – Monitoring of patients during TACE

C-1. Hepatic function should be monitored before each TACE to prevent liver deterioration.

Rationale/Elaboration

- Repeated TACE can lead to increasing deterioration of the liver over time.35,37,78-83[33,35,76–81]
- Preserved liver function is key to deriving optimal benefit from systemic therapies: further deterioration of hepatic function decreases efficacy of and may jeopardize eligibility for systemic therapies.35,36,82[33,34,80]
- Post-TACE hepatic decompensation may be predicted by lower baseline serum albumin and higher tumour burden, including elevated alpha-fetoprotein, larger tumour size, and more nodules.84,85[82,83] and scores including ALBI, Child-Pugh, and HAP should be used to monitor liver function.35,36,86-88[33,34,84–86]

C-2. After each procedure, the response to TACE should be assessed with dynamic contrast enhanced imaging preferably at a timeframe of

i. More than 4 weeks after the first procedure
ii. Between 6 to 10 weeks after subsequent procedures.

Rationale/Elaboration

- Computed tomography (CT) or MRI is generally recommended at 4 weeks post c-TACE so that Lipiodol can get localised within the tumour.89,90[87,88]
- European Conference on Interventional Oncology and the European Society of Oncologic Imaging recommend magnetic resonance imaging (MRI) of the liver as the first preference, and CT scan as the second preference.91[89]

C-3. When classification of tumour response is needed, mRECIST criteria are preferred. For atypical HCC lesions with heterogeneous or infiltrative areas of tumour RECIST 1.1 will be more appropriate.

Rationale/Elaboration

- Radiological evaluation of tumour response can performed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 or modified RECIST (mRECIST) (Table 2).92-94[90–92]
- The use of RECIST 1.1 or mRECIST varies from centre to centre; mRECIST is a stricter set of criteria that avoids the reviewer subjectivity of RECIST 1.1; a key difference in mRECIST vs. RECIST 1.1 is that the target lesion is measured not in the whole lesion, but only in the viable tumour (defined by hepatic arterial phase imaging).92,94[90,92]
- However, the additional steps required by mRECIST are not always performed in routine clinical practice. Therefore, although evaluation by mRECIST is preferable, the decision to implement it is to be decided locally by the MDT.

C-4. TACE should be administered on an on-demand basis when dynamic contrast enhanced image shows viable tumour without fulfilling the stopping criteria of TACE.

Rationale/Elaboration

- The ORR decreases with additional TACE sessions, while TACE continues to induce hepatic damage.95,96[93,94]
- Compared to TACE administered on an aggressive fixed schedule, TACE 'on-demand' may have a lower incidence of adverse events and shorter hospitalisation duration for the overall treatment, and can improve quality-of-life.40,97[38,95]

Part D. When to stop TACE

D-1. TACE should be stopped if any one of the following conditions are met:

i. There is evidence of TACE refractoriness, referring to patients who do not achieve the mRECIST CR or PR in the treated tumour territory after no more than two treatments, who are unlikely to benefit from further TACE.
ii. The patient progresses to BCLC C stage.
iii. Evidence of persistent post-treatment liver impairment or liver failure.
iv. The patient becomes TACE-unsuitable as per definition of Statement A6.

Rationale/Elaboration

- The criteria for stopping TACE are aligned with previously-published expert recommendations.38,98,99[36,96,97]
- TACE benefits for refractory patients decrease upon further administration of TACE.95,96[93,94]
- TACE-refractory patients have improved OS and response under systemic therapies compared to additional TACE sessions.37,100,101[35,98,99]
- A number of approaches to identifying TACE-refractory patients have been reported. E.g., lesion morphology-based criteria,102-104[100–102] up-to-7 criteria105-106[103,104] hepatoma arterial-embolisation prognostic (HAP) score,107-109[105–107] ALBI Grade,88,110,111[86,108,109] and ART (assessment for re-treatment with TACE) and STATE (Selection for TrAnsarterial chemoembolisation TrEatment) scores 112-114[110–112]

D-2. Patients meeting the TACE stopping criteria or the TACE unsuitable criteria should preferably be discussed in the MDT and considered for commencement of systemic therapy.

Rationale/Elaboration

- There is a growing armamentarium for first- and second-line systemic treatment of HCC, notably 1st line choices (atezolizumab and bevacizumab, tremelimumab and durvaluman, lenvatinib, sorafenib) and 2nd line choices following sorafenib failure (regoarafenib, cabozantinib, nivoluman and

ipilimumab, ramucirumab). The choice depends on local practice and decision of individual clinicians. .115-139[113–137]

- Retrospective studies have shown OS is extended by 10–12 months when TACE-refractory patients are switched to systemic therapy (vs. continued TACE or switching from TACE to HAIC).37,100[35,98]
- The MDT should ensure a timely stop to TACE as soon as the criteria are met because patients with optimal hepatic function derive more benefit from systemic therapy.140[138]

PART E. Use of TACE for specific indications

Transplantation

E-1. TACE can be used as a bridge to transplant in patients listed for liver transplantation.

Rationale/Elaboration

- TACE is a widely-used strategy reduce the risk of HCC progression and subsequent dropout of eligible patients awaiting liver transplantation141-147[139–145]

E-2. TACE could be used to downstage for liver transplantation in patients beyond transplant eligibility criteria.

Rationale/Elaboration

- Downstaging of disease with TACE, may allow transplantation in patients who are beyond eligibility at diagnosis.145,148[143,146]
- Although all patients beyond eligibility criteria should be considered for downstaging, the MDT should be aware of the limitations, e.g. patients with macrovascular invasion and extrahepatic disease should not be considered for liver transplant,149[147] patients with Child Pugh class B or C and Alpha-1-fetoprotein (AFP)>1000 are unlikely to benefit from downstaging.150[148]

Addition of systemic therapy

E-3. TACE should not be combined with systemic therapies outside of a clinical trial.

Rationale/Elaboration

- Following the expanding options for systemic treatment of HCC, numerous trials have evaluated the effects of combining them with TACE, with some reporting encouraging results e.g. TACTICS and LAUNCH151,152[149,150]
- However, other studies do not support combining TACE with systemic therapy.153-157[151–155]
- Numerous phase 3 clinical trials of TACE plus other systemic treatments are ongoing, but current American and European guidelines do not recommend TACE combined with systemic treatment due

to a lack of evidence.14,158[13,156]Note as on 8 Dec 2023: the committee is aware of the coming EMERALD-1 data to be presented in early 2024. This statement may be modified in 2024 according to the latest results

**This section may be updated based on latest evidence*

Biomarkers for monitoring and prognosis of TACE patients

E-4. There is a lack of well-established or validated biomarkers for clinical application in TACE patients. AFP response is a more robust prognostic and monitoring marker.

Rationale/Elaboration

- AFP and fucosylated AFP (AFP-L3) can be used as prognostic markers for survival outcomes in BCLC intermediate stage patients undergoing TACE.162-169[160–167]
- Development of various other biomarkers associated with TACE response have been investigated.17-[168]

Clinical trial recommendations.

E-5. For multi-centred clinical trial using c-TACE, the chemotherapy regimen should be narrowed to cisplatin or doxorubicin to minimise heterogeneity.

E-6. For multi-centred clinical trials using DEB-TACE, anthracyclines should be used as the reference drug to minimise heterogeneity.

Rationale/Elaboration

- There is no consensus on the optimum anticancer drug(s) to administer via TACE,171[169] and thus a number of drugs or regimens are used for c-TACE.
- To reduce the heterogeneity noted in clinical studies of TACE the committee suggests that studies of c-TACE should use cisplatin or doxorubicin as a reference and studies of DEB-TACE use anthracyclines.

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