Review

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Transarterial chemoembolization: Modalities, indication, and patient selection

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Summary

Transarterial chemoembolization (TACE) is the standard of care for patients with intermediate stage hepatocellular carcinoma (BCLC B). Further improvement of the use of TACE was the subject of intense clinical research over the past years. The introduction of DEB-TACE brought more technical standardization and reduction of TACE related toxicity. The use of dynamic radiologic response evaluation criteria (EASL, mRECIST), uncovered the prognostic significance of objective tumor response. Finally, new approaches for better patient selection for initial and subsequent TACE treatment schedules will limit the use of TACE to some extent but have the potential to improve outcome for patients at risk for TACE-induced harm.

Introduction

Hepatocellular carcinoma (HCC), is the fifth most common cancer worldwide, and develops predominately in patients with liver cirrhosis [1]. The Barcelona Clinic Liver Cancer (BCLC) staging system [2,3] integrates tumor characteristics and performance status with liver function and links them to evidence based therapeutic options. It is the basis for the European [4] and the American [5] HCC management guidelines. Unfortunately HCC is commonly diagnosed only at intermediate (BCLC stage B) or advanced (BCLC stage C) tumor stages [6,7], where only palliative treatment options can be offered resulting in a limited overall survival (OS) of 11–20 months. Transarterial chemoembolization (TACE) is the recommended treatment modality for asymptomatic, large or multifocal HCC without macrovascular invasion or extrahepatic metastasis (intermediate HCC, BCLC stage B).

This narrative review provides a critical appraisal of the available data supporting TACE and recapitulates the recent advancements in the use of TACE in patients with intermediate stage HCC.

Key Points

- Conventional TACE is the standard of care for intermediate stage HCC
- DEB-TACE is equally effective as cTACE, but may provide a better safety profile due to less systemic absorption of chemotherapy
- Early radiologic response according to mRECIST after TACE-1 correlates with overall survival
- Patient selection for initial TACE and retreatment with TACE is key for optimal survival outcomes and may be guided by recently developed clinical scoring system

Conventional transarterial chemoembolization

Conventional transarterial chemoembolization (cTACE) using a mixture of a chemotherapeutic agent (e.g. doxorubicin or cisplatin) and lipiodol is the recommended standard of care for the treatment of intermediate stage HCC. The basis of this recommendation derived from a systematic review of randomized controlled trials [8] that tested TACE/bland arterial embolization (TAE) *vs.* best supportive care in patients with "unresectable HCC". Of note, only seven trials [7,9–14], all published between 1988 and 2002, met the inclusion criteria of this meta-analysis and only two trials reported positive results in terms of OS. Nevertheless, this systematic review found a significant improvement in 2-year survival favoring treatment (OR, 0.53; 95%CI, 0.32–0.89; $p = 0.017$). Subsequent sensitivity analysis confirmed the observed survival benefit for TACE performed with cisplatin

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or doxorubicin by analyzing 323 patients in four studies (OR, 0.42; 95%CI, 0.20–0.88) but not for TAE (OR, 0.59; 95%CI, 0.29–1.20) which failed to demonstrate significant benefit over best supportive care. While two other meta-analyses confirmed positive effects of TACE on OS (OR, 0.54; 95%CI: 0.33, 0.89; $p = 0.015$ and OR: 0.705 95%CI: 0.5, 0.99; $p = 0.0026$) compared to best supportive care, no superiority of TACE over TAE could be observed after analysis of available randomized head to head comparison trials and cohort studies, respectively [15,16] and two recent randomized controlled trials [17,18]. Given the lack of superiority of TAE over best supportive care virtually most current international guidelines [4,5,19] finally recommended TACE as the standard of care for intermediate stage HCC.

This recommendation has been recently challenged by a Cochrane review [20] which included trials published after 2002 and found no firm evidence to support or refute TACE or TAE for patients with unresectable HCC. However, this review was heavily criticized [21,22] as it included trials with inadequate patient selection and control arms, which has likely biased the results of this analysis.

Despite the fact, that the use of cTACE for the treatment of HCC is supported by 3 of 4 meta-analyses of randomized trials, some important limitations remain. One of the great problems of TACE is the huge heterogeneity of the TACE technique and schedules used in world wide clinical practice. Even the two positive randomized controlled trials [7,12] used very different technical approaches. The European study performed cTACE with the chemotherapeutic agent doxorubicin at dosages adjusted to bilirubin levels (<25.6 μmol/L: 75 mg/m^2; 25.6–51.3 μmol/L: 50 mg/m^2; 51.3–85.5 μmol/L: 25 mg/m^2) with a fixed schedule at baseline, 2 months and 6 months, while the Asian study performed cTACE with cisplatin (up to 30 mg/session), repeated every 2–3 month until disease progression, serious adverse events or hepatic decompensation. Further differences exist with regard to the selectivity of TACE (lobar *vs.* segmental *vs.* subsegmental embolization), which has been reported to be an important determinant of procedure tolerance and efficacy [23]. For all these factors no universal consensus exists and the resulting heterogeneity hinders the reliable comparison of results of different studies and complicates the conduction of high quality multicenter TACE trials.

TACE with drug eluting beads

The introduction of TACE with drug eluting beads (DEB-TACE) was primarily developed to enhance the delivery of the chemotherapeutic agent while minimizing systemic toxicity and to provide a standardized embolizing effect. DEBs are embolic microspheres loaded with a chemotherapeutic agent (mostly doxorubicin) with the ability of slow drug release, which should ensure high local and low systemic drug concentrations. Indeed, systemic levels of doxorubicin were significantly lower in patients receiving DEB-TACE compared to patients receiving cTACE with lipiodol [24]. The value of doxorubicin in this setting was investigated in a randomized, tumor size adjusted trial [17] testing DEB-TACE *vs.* bland embolization with non-loaded particles of the same diameter (BeadBlock-TAE). DEB-TACE was associated with better local response (CR: 26.8 *vs.* 14%), fewer recurrences (78.3% *vs.* 45.7%) at 12 months, and a longer TTP (42.4 ± 9.5 and 36.2 ± 9.0 weeks), than TAE with BeadBlock alone thus favoring the role of doxorubicin in the setting of TACE with microparticles, although no survival benefit was observed in this study [17]. Positive effects of doxorubicin loaded microparticles were further reported by another trial [25] showing higher rates of tumor necrosis with DEB-TACE compared to embolization with unloaded microparticles (Embosphere particles) of the same size, which was pathologically confirmed in explanted livers of HCC patients undergoing liver transplantation.

Efficacy and safety was evaluated by the randomized European Precision V phase-2 trial [26] testing DEB-TACE *vs.* cTACE in 212 patients with predominately intermediate stage HCC. Neither the primary efficacy endpoint (response at 6 months, $p = 0.11$) nor the primary safety endpoint (incidence of SAE within 30 days of the procedure, $p = 0.86$) were met in this study. However, a post hoc comparison showed a significant reduction in drug related systemic and liver toxicity in DEB-TACE group compared to the cTACE group. This better tolerability was probably responsible for better response rates of DEB-TACE at 6 months in a predefined post hoc subgroup analysis of patients with more advanced liver dysfunction (Child-Pugh B), higher tumor load (bilobular/recurrent disease) or less preserved performance status (ECOG 1). Whether this group of advanced patients should receive TACE at all is subject of repeated discussion in the scientific community, but generally discouraged by most international HCC treatment guidelines.

A potential impact of DEB-TACE on OS was further evaluated in a prospective 1:1 randomized controlled multicenter, head to head comparison trial of TACE with doxorubicin eluting beads (DEB-TACE) *vs.* cTACE using a mixture of lipiodol and epirubicin followed by occlusion of the feeding artery with gelatin sponge particles in patients with HCC [27]. This trial included 177 patients with a follow-up of at least 2 years. The study was terminated prematurely, because the second planned interim analysis revealed no significant differences between both techniques in terms of survival, radiologic response or adverse events with the exception of a significantly lower incidence of the post-embolization syndrome in the DEB-TACE group, which did not result in shorter hospital stays. Due to the equality of both TACE techniques and the higher costs of DEB-TACE the authors concluded that the routine use of DEB-TACE is debatable. However it should be noted that the maximum allowed dose of doxorubicin/epirubicin in this study was restricted to only 75 mg for both techniques. Additionally, the study predominantly included patients with low tumor load, as 46% of the population had early HCC (BCLC A) with only 11% of patients exceeding 3 nodules and only 20% with bilobular involvement and a median tumor size of only 2.6 cm. Hence, this study a priori precluded one of the major advantages of DEB-TACE namely to apply higher doxorubicin doses without increasing systemic toxicity in patients with higher tumor load as reported in the Precision V study. Therefore this study shows, that DEB-TACE is not superior to cTACE in patients with predominantly well preserved liver function and relatively low tumor load. This is important, as cTACE can obviously still be safely and effectively applied in this patient population at lower costs. Although a survival benefit still remains to be proven, DEB-TACE should be the technique of choice in the setting of clinical trials, due to its higher degree of technical standardization and the lower systemic absorption of doxorubicin with less doxorubicin toxicity. The latter facilitates potential combination trials with systemic therapies as it may reduce the risk of potential drug-drug interactions.

Critical appraisal of patient selection in randomized TACE trials

Patient selection seems to be a crucial point for the success of TACE. For many years, HCC was divided in surgical and non-surgical HCC until the BCLC group published a hallmark study [28] on the natural history of "non-surgical HCC" by analyzing untreated control groups of two randomized controlled trials. After pooling these cohorts, multivariate analysis revealed performance status >0, presence of constitutional syndrome (weight loss, malaise, loss of appetite), portal thrombosis, and extrahepatic spread as negative predictors for OS. The authors demonstrated that the absence of any risk factors was associated with significantly better prognosis and finally defined this condition as intermediate stage HCC (BCLC B). However, this definition was published after the conduction of all randomized controlled TACE trials that were included into meta-analyses of TACE [8,15,16]. Accordingly there is no randomized controlled trial that formally tested TACE *vs.* best supportive care in an a priori defined intermediate stage HCC cohort. Additionally, the positive randomized trials [7,12] had a very small sample size as compared to other fields of oncology, so little is known about potential benefits of TACE in certain clinical subgroups. Although the analysis of negative predictors of TACE in randomized controlled trials [29] confirmed that patients with clinical features defining advanced stage of disease (BCLC C), like presence of vascular invasion and performance status >0, respond worse with TACE than those without such features, this does not necessarily preclude any benefit compared to best supportive care. Taking a closer look to the two positive randomized trials published thus far [7,12], only one study [12] comprised enough patients to compare TACE *vs.* best supportive care depending on performance status or symptoms respectively, in a small sub-analysis. While performance status alone was not significant even upon univariate analysis, patients who received TACE and displayed symptoms did worse than patients without symptoms, but still significantly better than symptomatic patients who only received best supportive care [12]. These results suggest that the presence of performance status 1 which is defined as "restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work may not be synonymous with the presence (and significance) of cancer related symptoms, and provide the rationale for some experts in the field to discard presence of ECOG 1 as a general contraindication for TACE [30]. Similar discussions with even less evidence for reliable recommendations exist for patients with compensated Child-Pugh B cirrhosis (without ascites) and patients with restricted tumor load, but presence of segmental macrovascular invasion.

It should be reinforced, that a definitive survival benefit of TACE for these patient groups has never been demonstrated. Treatment stage migration is recommended here but at least cohort studies do not provide definitive proof [31] and randomized trials testing TACE *vs.* sorafenib in this subgroup of patients have never been conducted, leaving room for individual interdisciplinary decisions in this patient cohort in clinical practice.

Intermediate stage HCC comprises a heterogeneous patient population

The need to extend the indication for TACE could be questioned. All international guidelines acknowledge intermediate stage HCC as a target population for TACE. However, only 10–12% [7,32] of patients present in concordance with this definition at the time of first diagnosis. Regardless of this, TACE is overall the most common first line treatment for HCC world wide and currently almost half of all TACE treatments are performed in BCLC stage C [33]. Even when physicians follow the definition of intermediate stage HCC as selection criterion for TACE, patients will vary widely in terms of liver function and tumor load [34,35]. The phenomenal patient survival of recent DEB-TACE cohort studies (Fig. 1) [36–38] seems explainable by the more rigorous selection of good risk patients rather than therapeutic advancements. Indeed, these studies recruited presumably the ideal TACE candidates, characterized by low tumor load BCLC A or BCLC B slightly beyond Milan criteria and well preserved liver function (Child-Pugh A). These studies are important as they set a new reference standard for approaches aiming to extend indications for resection or liver transplantation that have been proposed for the treatment of intermediate stage HCC with tumor load slightly beyond the Milan criteria and well preserved liver function in some studies [39–41].

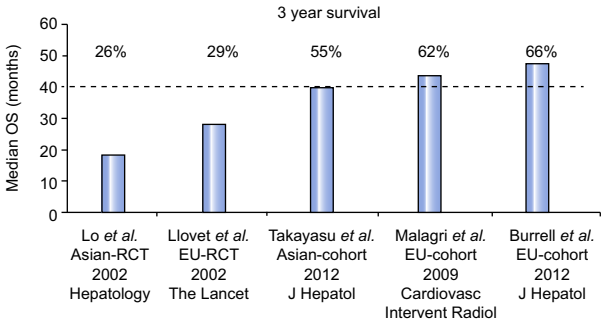

Fig. 1. Heterogeneous survival outcomes of HCC patients treated with TACE. Median OS and 3-year survival of the two positive randomized controlled trials [7,12] and recent prospective TACE cohort studies [35–37]. The observed heterogeneous results may at least in part be explained by differences in patient selection. OS, overall survival.

However, these studies provide no answer to the question of how to select and proceed with all the other patients. Patients that bear higher tumor load or less preserved liver function but still correspond to the definition of intermediate stage HCC. Although they may eventually benefit from TACE but are not initially subjected to stage migration treatment given to advanced stage patients. This is an important issue, maximal restriction of patient selection for TACE would otherwise only improve the results of the treatment modality per se but again would leave these more advanced patients within the intermediate stage without treatment options (with confirmed significant clinical benefit in randomized clinical trials) [42]. The HCC guidelines (EASL/EORTC) recommend "treatment stage migration" which is the switch to the next evidence based treatment option (within or the next BCLC stage) for patients considered "unsuitable" for or "refractory" to TACE. This would be systemic treatment with sorafenib, but this recommendation can, at best, be called pragmatic, as randomized data of sorafenib in intermediate stage HCC is scarce and shows no clear survival benefit (median OS: 14.5 *vs.* 11.4 months (HR: 0.72; 95%CI: 0.38–1.38)) [42]. This result is moderate in absolute numbers considering the fact that the SHARP trial only included patients with Child-Pugh A liver

Table 1. Absolute and relative contraindications for TACE [34,43].

Absolute contraindications
Factors related to liver cirrhosis: • Decompensated cirrhosis (Child-Pugh B, score >8), including jaundice, clinical hepatic encephalopathy, and refractory ascites and/or hepatorenal syndrome • Impaired portal-vein blood flow (portal-vein thrombus, hepatofugal blood flow)
Factors related to HCC • Extensive tumour involving the entirety of both lobes of the liver • Malignant portal vein thrombosis
Technical contraindication to hepatic intra-arterial treatment: • e.g., untreatable arteriovenous fistula
Impaired renal function • Creatinine ≥2 mg/dl or creatinine clearance <30 ml/min
Relative contraindications
Factors related to liver cirrhosis: • Untreated oesophageal varices at high risk of bleeding
Factors related to HCC: • Large tumour (>10 cm)
Others factors: • Severe comorbidities • Incompetent papilla with aerobilia (owing to biliary stenting or surgery) • Biliary dilatation

function. Looking at the data of molecular targeted agents in other tumor entities, which are approved for advanced colorectal cancer but failed in earlier disease stages [43], seems necessary to prove the validity of the stage migration concept in randomized trials of sorafenib or any new systemic treatment *vs.* TACE or best supportive care. The same is true for radioembolization, which is used in some centers for patients considered unsuitable or refractory to TACE.

Tools to refine the decision for the first TACE treatment

The exclusion of absolute contraindications should always be the first step in the assessment of patient suitability for TACE. Absolute and relative contraindications are generally well accepted [35,44], and include features of decompensated liver disease, extensive bilobular tumor load and impaired integrity of the portal vein due to (non)-malignant thrombosis or hepatofugal flow, as well as untreated large varices, huge tumor diameter, and severe co-morbidities (Table 1).

In clinical practice, decision making is most problematic in patients who lack clear contraindications for TACE but do not share all features of the ideal TACE candidate (ECOG 0, low tumor load, well preserved liver function). While better prognosis is not necessarily a surrogate marker for treatment benefit, it seems in turn important that tools to refine the decision for the first TACE treatment identify patients at risk of TACE related harm.

Recently, several groups have elaborated new concepts that may support treatment decisions in these difficult clinical situations. These concepts include empirical patient stratifications on one-end and outcome data-derived scores on the other end of the spectrum.

Bolondi *et al.* [34] proposed a subclassification of intermediate stage HCC (BCLC B). Based on liver function (Child-Pugh A5-B9), tumor load (within or beyond the "up to seven" criteria), the ECOG performance status, and the status of the portal vein, four sub-groups of intermediate stage HCC (BCLC B1-B4) were developed and linked with first and second-choice treatment options (Fig. 2A). The prognostic value of this subclassification was subsequently validated in an external cohort of patients [45] who received TACE for HCC. In this typical Asian cohort (73% HBV positive, 23% non-cirrhotic) patients corresponding to BCLC B1 (Child-Pugh A5-7, ECOG 0, within the "up to seven" criteria) and B2 (Child-Pugh A5-6, ECOG 0, beyond the "up to seven" criteria) had a median OS of 41 and 22 months, respectively. No survival difference (14.1 *vs.* 17.2) was observed between the subclasses B3 (Child-Pugh B7, ECOG 0, beyond the "up to seven" criteria) and B4 (Child-Pugh B8-9, ECOG 0-1, any tumor load). Thus the authors proposed a revised BCLC B subclassification and pooled the B3 and B4 subclasses for the prognostic assessment of potential TACE candidates (median OS for pooled BCLC B3/B4: 16.6 months). We reanalyzed our own patient cohort using the subclassification of intermediate stage HCC and confirmed the advantage of the revised subclassification with pooling of B3/B4 subclasses [46]. In summary, this subclassification confirmed that the subgroup of intermediate stage HCC patient with well preserved liver function and low tumor load (as defined by BCLC B1) represents the best candidates for TACE. However, the subclasses B2 and B3/4 still comprise of very heterogeneous patients and will need prospective evaluation of the optimal treatment strategy in these groups.

A data-driven approach was taken to establish the Hepatoma Arterial Embolization Prognostic score (HAP score) [47] to guide the initial selection of patients for the first TACE treatment (Fig. 2B). Patients were divided into four risk groups based on their HAP scores; HAP A, B, C and D (scores 0, 1, 2, and >2, respectively). The median survival for the groups A, B, C, and D was 27.6, 18.5, 9.0, and 3.6 months, respectively. Though a significant number of patients in this study corresponded to BCLC C (31%) or D (4%), this score was recently validated in a cohort of patients with intermediate stage HCC only [48] showing a median OS of 25.7, 18.5, 12.5, and 10 months for HAP groups A/B/C/D, respectively.

A

BCLC B subclassification

BCLC sub-stage	B1	B2	B3	B4
Child-Pugh score	5-6-7	5-6	7	8-9
Beyond Milan and within Up to 7	in	out	out	any
ECOG-PS	0	0	0	0-1
Portal vein thrombosis	no	no	no	no

B

HAP score

Albumin <36 g/dl	→ 1 point
AFP >400 ng/ml	→ 1 point
Bilirubin >17 μmol/L	→ 1 point
Max TU diameter >7 cm	→ 1 point

HAP A	0 point
HAP B	1 point
HAP C	2 points
HAP D	>2 points

C

STATE score

Albumin (mg/dl)
- 12 (if CRP ≥1)
- 12 (if up-to-seven out)

D

ART score

Absence of radiologic response	→ 1 point
AST increase >25%	→ 4 points
Child-Pugh increase: 1 point	→ 1.5 points
≥2 points	→ 3 points

Fig. 2. Overview about new clinical scoring systems to improve patient selection for TACE. (A) The BCLC B subclassification. (B) Hepatoma Arterial Embolization Prognostic score (HAP) score. (C) The Selection for Transarterial chemoembolization TrEatment (STATE) score may support the decision for the first TACE treatment, while (D) the Assessment for Retreatment with TACE (ART) score may guide the decision for retreatment with TACE. BCLC, Barcelona Clinic Liver stage; ECOG, Eastern Cooperative Oncology Group; PS, performance status; AFP, alpha-1-fetoprotein; CRP, C-reactive protein; AST, aspartate aminotransferase.

This suggests that patients in the HAP score groups A and B are most suitable for TACE.

Finally, the Selection for Transarterial chemoembolization TrEatment (STATE) score [48] was recently developed in a training-cohort (n = 131) by using a stepwise Cox regression model and validated in an external validation cohort (n = 146) (Fig. 2C). The STATE score differentiated 2 groups (<18, ⩾18 points) with distinct prognosis (median OS: 5.3 *vs.* 19.5 months; p <0.001) and a lower STATE score was associated with short-term harm and increased mortality after the first TACE. A STATE score of <18 points therefore reflects an absolute contraindication for TACE based on these predicted survival numbers.

Evaluating the success of TACE: the significance of radiologic tumor response

Radiologic response assessment plays the central role in the evaluation of treatment success following TACE and underwent several refinements during the past decade. These refinements acknowledged the fact that conventional bi-dimensional [49] or uni-dimensional [50] evaluation of the whole treated tumor lesion may not adequately cover therapeutic effects of interventional therapies, as treatment induced tumor necrosis is not immediately paralleled by tumor shrinkage [51]. This lack of correlation hinders early prognostic stratification, may lead to unnecessary overtreatment with TACE and generally precludes a response guided retreatment strategy with TACE if complete response is not achieved following the first TACE session.

For these reasons, a panel of experts proposed the bi-dimensional measurement of viable (contrast-enhanced) tumor tissue by triphasic radiologic imaging [52]. This modification was first acknowledged by an amendment to WHO criteria [52] in the EASL recommendations for HCC management 2002 and subsequently endorsed by the AASLD practice guidelines for HCC management 2005 [53]. Replacement of WHO criteria by RECIST (V1.0) [54] as standard response evaluation method in clinical oncology further prompted the proposal of modified RECIST criteria [55,56]. Modified RECIST kept the concept of measuring the viable part of residual tumor tissue, but recommended the uni-dimensional assessment of the longest viable tumor diameter and the numeric definitions of response according to RECIST.

Indeed, determination of objective treatment response following TACE by measuring residual viable tumor tissue was proven to be a surrogate marker of OS. Gillmore *et al.* [57] used RECIST, mRECIST and EASL response criteria to analyze the treatment response in 83 patients after a median time of 64 days after the first transarterial-(chemo) embolization. Overall response rates were 57% and 58% respectively if EASL or mRECIST criteria were applied, while only 6 patients were identified with objective response according to conventional RECIST (1.1). Of note, only the presence of objective response (complete or partial) according to EASL or mRECIST was independently associated with OS, while objective response according to conventional RECIST criteria was not. Similar results were also observed in other studies [58–61] and did not depend on the maximum number of measured lesions in the liver [61,62]. Measurement of up to 5 target lesions, following the original 1.0 RECIST guideline, was as efficacious as measurement of up to 2 target lesions, according to the revised 1.1 RECIST recommendations [63]. Whether further reduction of evaluation efforts to only target index lesion measurement of the largest nodule is a feasible concept [64] needs to be evaluated in further studies.

Significance of radiologic response in the context of retreatment and follow-up

Before the implementation of EASL criteria, most studies, including the two positive randomized controlled trials testing TACE *vs.* best supportive care, were performed with a fixed predefined TACE schedule with varying time points of response assessment [7,12]. The rationale for a fixed TACE schedule was to maximize dose intensity similar to systemic chemotherapeutic schedules and reinforced by the fact that complete response according to conventional response evaluation criteria was a relatively rare event after a single TACE session as outlined above. However a fixed treatment strategy leads to aggressive retreatment schedules, which may have a deleterious effect on liver function [35]. The opportunity to follow a response guided retreatment (treatment on demand) strategy in patients at need for more than one TACE session for adequate treatment success is therefore another important advantage of radiologic response evaluation based on contrast-enhanced viable tumor tissue. Although there is no randomized controlled trial showing superiority of one strategy over the other, it seems reasonable to include assessment of residual viable tumor tissue into retreatment decisions.

In this context it is noteworthy that achievement of objective response (complete or (CR) partial response (PR)) as "best response" following TACE might be an important treatment goal.

Shim *et al.* [60] demonstrated a clear prognostic difference between CR (HR: 1), PR (HR: 2.75, p <0.001), stable disease (SD) (HR: 6.32, p <0.001) and progressive disease (PD) (HR: 16.06, p <0.001). Importantly, a lack of objective response according to EASL or mRECIST criteria after the first TACE session should not automatically abandon further TACE treatments. Georgiades *et al.* [65] showed that 47% of patients who did not respond to the first TACE session showed objective response after second TACE procedure. Additionally, these patients showed a similar OS as patients who responded to the initial TACE treatment and a significantly better survival compared to patients who neither responded to the first nor to the second TACE session. Choi *et al.* [66] evaluated the significance of "best radiologic response" in 332 patients with multifocal intermediate stage HCC and well preserved liver function treated with cTACE in further detail. Of 112 patients (33.7%) who achieved PR according to mRECIST after the first TACE session, 71 (63.4%) patients could ultimately achieve CR with repeated TACE treatments while the others maintained PR. Of 126 (38%) with SD after the first TACE, 102 (80%) patients finally achieved PR while the rest maintained SD. In summary, the objective response rate could be overall increased from 53% (after TACE-1) to 83.7% with subsequent TACE cycles. A median of 2 (1-6) TACE cycles was performed prior to achievement of "best response" and only 26.5% of patients received $\geqslant$3 sessions.

Best OS was observed for patients with initial objective response, which was better than for patients with objective response in subsequent TACE sessions and worst for patients who showed persistent non-response. Of note, a difference in survival was also observed between patients with initial or subsequent CR, which was also in any case significantly better than for patients with PR as best response. However, some caution should be applied in interpreting the data on the best response concept since it carries some risk of guarantee time bias [67].

Additionally, the likelihood to achieve objective response, especially CR as best response following TACE significantly depends on treatment, tumor number [66] and tumor size [66,68] with radiologic CR rates of up to 77% in tumors <2 cm in size but only 25% in tumors with diameters of >5 cm after the first TACE [68]. Similar size dependent differences in radiologic response also apply to repeated TACE sessions. While retreatment with TACE-2 and TACE-3 shows a CR rate of 55% and 40% respectively in lesions <5 cm with previous PR, CR rates are 25% and 0% in a tumor >5 cm and previous PR [68]. Based on this data and with regard to the prognostic importance of achieving CR, Golfieri *et al.* [68] proposed the consideration of tumor size besides radiologic response for retreatment decisions.

Once complete radiologic response is achieved, overall 72% will suffer tumor recurrence after a median of 8.5 months of which 31% will present as local, 40% as distant intrahepatic and 27% a mixed (local and distant intrahepatic) relapse of disease [69] and again, tumors >5 cm showed a significantly shorter time to recurrence (6 months, p <0.05) [68]. This fits to radiologic-pathologic correlation studies showing that despite overall acceptable agreement (67.4%) between radiologic response assessed by CT and necrosis upon pathologic analysis, mRECIST tends to overestimate response in about 22% of all patients, especially in those bearing larger tumors [70]. Besides tumor number and size, also treatment selectivity (selective/superselective *vs.* lobar) selective/superselective TACE [71] (p = 0.049) was an independent predictor for complete pathological necrosis.

Finally, not every kind of radiologic progression is a reason to refute further TACE treatments. In this context, Kim *et al.* [72] invented the term "tumor stage progression" which describes the occurrence of new vascular invasion or extrahepatic spread and analyzed its prognostic significance in 264 Korean patients with intermediate stage HCC. The authors demonstrated that patients with treatable progression (new lesion or growth of existing lesion) had similar survival compared to those without progression (36.6 *vs.* 35.8 months, respectively), while patients who suffered from simultaneous PD and stage progression at the same time had the worst prognosis (median OS 12.0, 95%CI: 8.3–15.7 months). Over time, stage progression developed more likely in the presence of higher tumor load (Tu-number $\geqslant$4, tumor size $\geqslant$5 cm), higher serum AFP ($\geqslant$200 ng/ml), or partial lipiodol uptake and if radiologic progression (new lesion or growth of existing lesion) occurred.

Retreatment algorithms for patients who need multiple TACE sessions

TACE may become a double-edged sword independent from the presence of objective radiologic response if deterioration of liver function is caused by the intervention, which may obviate any kind of further treatment and trigger liver related death [35]. For this reason, the best treatment strategy achieves objective response (ideally complete response), while preserving liver function at the same time. Importantly, this principle applies to every TACE treatment especially in the context of repeated, multiple TACE sessions, which may be necessary due to a lack of adequate radiologic response after the previous intervention. Thus, retreatment decisions should not only be taken based on target lesion response or presence or absence of overall disease progression but also on changes in liver function following TACE.

Virtually all published retreatment algorithms suggest to perform two TACE sessions in absence of liver deterioration or major complications before discarding TACE as not effective. Based on the prognostic value of (best) radiologic response mentioned above, most authors consider absence of objective radiologic response after two TACE cycles as a sign for TACE failure [30,44,73], and only some [35] would also accept SD as treatment success similar to other fields in oncology, especially in patients with higher tumor load. Superselective TACE is advocated by all guidelines as the method of choice to minimize liver damage, but the term seems to be poorly defined and its application is difficult to monitor. Clearly, some of the heterogeneity in patient outcome (Fig. 1) and local practice is attributable to technical variability, specific to geographic regions or even individual centers [7,12,35–38,73].

Deterioration of liver function following TACE has been either not specified [35,72] or very strictly defined [44,74] as a criteria of TACE failure by several expert groups. The BCLC group invented the term "untreatable progression" [44,74,75] which is present in case of either impairment of liver function (presence of ascites of any grade; sustained Child-Pugh B liver function, including Child-Pugh B7), occurrence of BCLC stage progression (vascular invasion, extrahepatic spread or clinical progression to ECOG $\geqslant$2) or absence of objective radiologic response after two TACE sessions as mentioned above.

In contrast, radiologic progression (e.g. new intrahepatic lesions) may be an indication for retreatment if technically

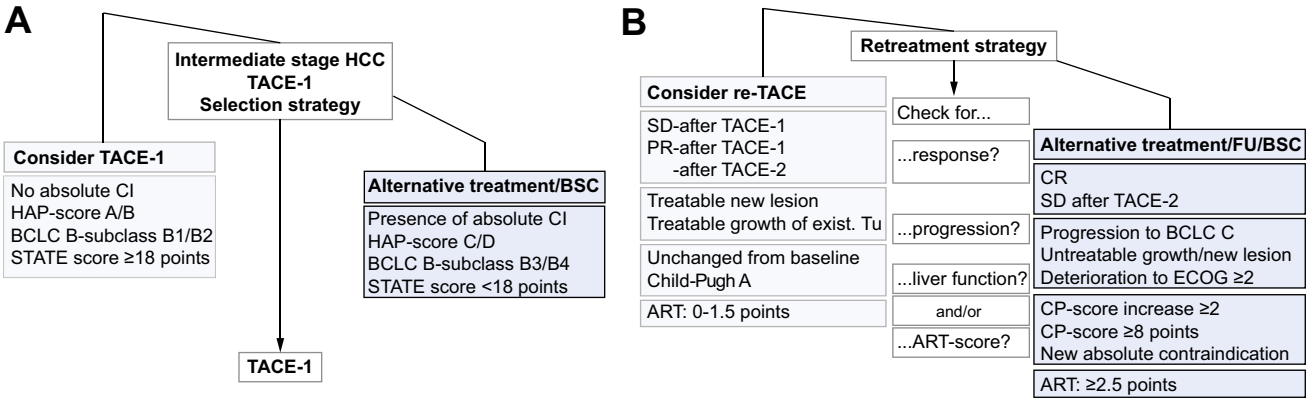

Fig. 3. The scale of decision making: how to select patients for (re)-treatment with TACE. Presence of any arguments contra-TACE (right) outweigh arguments pro-TACE (left) at (A) baseline (prior TACE-1) and (B) prior retreatment with TACE. CI, contraindication; HAP score, Hepatoma Arterial Embolization Prognostic score; STATE score, Selection for Transarterial chemoembolization TrEatment score; SD, stable disease; PR, partial response; CR, complete response; CP score, Child-Pugh score; ART score, Assessment for Retreatment with TACE-score.

feasible and justifiable regarding liver function [35,44] and in absence from tumor stage progression [43,70].

However, these definitions do not consider the significance of discrete subclinical changes of liver function following TACE. In this context the Assessment for Retreatment with TACE score (ART score) [76] was developed for patients undergoing repeated TACE sessions. The ART score integrates objective radiologic tumor response (present *vs.* absent), impairment of liver function (presence *vs.* absence of Child-Pugh score increase by 1 or $\geqslant$2 points) and liver damage (AST increase by 25% from pre-TACE-1, respectively) after the first TACE to predict patient survival if retreated with another TACE session (Fig. 2D). The ART score selected two distinct patient groups (0–1.5 *vs.* $\geqslant$2.5 points) with significantly different prognosis and identified patients who probably will not benefit from continued TACE sessions. These results were confirmed in an independent external validation cohort, at other time points (prior TACE-3 and 4) [77] and by other research groups [78]. Furthermore, sequential assessment of the ART score prior to each further TACE session reliably identified patients with dismal prognosis if retreated with TACE. In summary, the overall success of TACE depends on both optimal baseline selection and careful retreatment decisions. Compatibly, combination of baseline and retreatment scores like the START strategy (STATE and ART score) [48], may guide decision making for the more difficult to treat intermediate stage HCC patients. Fig. 3 gives an overview about variables and scores to support patient selection for the first TACE (Fig. 3A) and for retreatment with TACE (Fig. 3B) in clinical practice.

Conclusion and perspective

TACE remains the standard of care for the treatment of intermediate stage HCC. Despite several advancements in TACE technique, radiologic response evaluation and patient selection for TACE, there is room for improvement concerning therapeutic efficacy. This may be achieved by clinical trials testing the combination of TACE and other treatments in well-selected patients. Intermediate stage HCC patients with lower tumor load may be candidates for trials evaluating TACE plus local ablative approaches like radiofrequency or microwave ablation. Intermediate stage patients with higher tumor load may be candidates for combination trials with systemic therapies, although it has to be outlined, that recent results of such studies were disappointing [75,79]. Prospective validation of more inclusive selection tools for repeat TACE cycles might enlarge the pool of patients benefiting from TACE without putting patients at risk for TACE-induced liver damage. Finally, the best alternative treatment for patients unsuitable for or refractory to TACE should be determined in randomized clinical trials.

Conflict of interest

The authors who have taken part in this study declared that they do not have any conflict of interest with respect to this manuscript. W. Sieghart received speaker and consulting fees and research grants from Bayer Schering Pharma; M. Peck-Radosavljevic received speakers and consulting fees and research grants from Bayer Schering Pharma, Lilly Pharma and Boehringer Ingelheim.

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