Transarterial chemoembolization failure/refractoriness: A scientific concept or pseudo-proposition

Shen Zhang, Bin-Yan Zhong, Lei Zhang, Wan-Sheng Wang, Cai-Fang Ni

Abstract

Multi-session transarterial chemoembolization (TACE) is usually needed for the treatment of intermediate-stage hepatocellular carcinoma (HCC), but it may not always have a positive influence on prognosis due to high heterogeneity of HCC. To avoid ineffective repeated TACE, the concept of TACE failure/refractoriness has been proposed by several organizations and is being addressed using tyrosine kinase inhibitors. The concept of TACE failure/refractoriness is controversial due to ambiguous definitions and low evidence-based data. To date, only a few studies have examined the rationality concerning the definition of TACE failure/refractoriness, although the concept has been introduced and applied in many TACE-related clinical trials. This review focuses on some of the issues related to different versions of TACE failure/refractoriness, the rationality of related definitions, and the feasibility of continuing TACE after so-called failure/refractoriness based on published evidence. A suggestion to re-define TACE failure/refractoriness is also put forward.

Key Words: Hepatocellular carcinoma; Transarterial chemoembolization; Failure; Refractoriness

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Core Tip: The definitions in the current concept of transarterial chemoembolization (TACE) failure/refractoriness are not capable of guiding clinical practice. A persistent viable tumor lesion is a well-accepted item of TACE failure/refractoriness, but that is not the case when it comes to new lesions, portal vein tumor thrombosis or extrahepatic spread. Patients with recurrent hepatocellular carcinoma after TACE constitute a heterogenous group and the treatment modalities need to be individualized.
INTRODUCTION

According to the Barcelona Clinic Liver Cancer (BCLC) staging system, transarterial chemoembolization (TACE) is the standard approach for patients with intermediate stage (BCLC-B) hepatocellular carcinoma (HCC)[1-3]. Nevertheless, the overall prognosis for patients undergoing TACE varies considerably due to the high heterogeneity of BCLC-B stage HCC[4]. In addition, repeated TACE courses are associated with an increase in angiogenesis and embolization-related liver damage, all of which may negate the benefits achieved in the tumor or even adversely affect overall survival (OS)[4-6]. Thus, many investigations have been carried out in order to identify a turning point where subsequent repeated TACE is not any more beneficial than alternative treatments or best supportive care for patients[7,8]. With the clinical application of tyrosine kinase inhibitors (TKIs), some scholars have proposed a new treatment paradigm where patients with intermediate stage HCC should switch to TKIs monotherapy when tumor progression occurs after TACE procedures[9,10], and as a consequence, the concept of TACE failure/refractoriness was introduced and proposed.

REVIEW OF DIFFERENT DEFINITIONS OF TACE FAILURE/REFRACTORINESS

The concept of TACE failure/refractoriness was initially proposed by the Japan Society of Hepatology (JHS) in 2010[11] and revised by the JSH-Liver Cancer Study Group of Japan (LCSGJ) in 2014 (Table 1) during a consensus meeting[6]. According to the definition, persistent viable treated lesions, consecutive emergence of new intrahepatic tumors and disease stage progression as well as continuous elevation of tumor markers were scenarios for terminating repeated TACE. However, Korean scholars did not take the same view and they concluded that 3 conditions, namely 3 or more TACE procedures within 6 mo, advancing to portal vein tumor thrombosis (PVTT) and extrahepatic spread (EHS) was TACE failure/refractoriness[12]. These suggestions were also supported by the International Association for the Study of the Liver (Table 1)[13]. Notably, the concept from Europeans seems to be more reliable in clinical practice (Table 1)[14]. They suggested that the determination of TACE failure/refractoriness should be in line with the indications of TACE. If stable disease (SD) of HCC is achieved when TACE is used as a palliative therapy it is regarded as effective. Conversely, when TACE acts as a curative treatment, the outcome of SD or progressive disease is identified as TACE failure/refractoriness. Currently, the concept of TACE failure/refractoriness has been widely introduced, especially in clinical trials for HCC[5,9,10,15,16]. However, these concepts require further discussion due to low evidence-based data. This article attempts to provide a comprehensive understanding concerning the omissions in the current definitions based on published evidence.

COMPREHENSIVE ANALYSES OF THE ENDPOINTS FOR TACE IN TACE FAILURE/REFRACTORINESS

Persistent viable targeted lesion(s) after consecutive treatments

When insufficient response in intrahepatic tumor occurs after multi-session TACE, it is sensible to define TACE failure/refractoriness and to stop TACE. The peripheral region as well as the capsular region of HCC nodules may be nourished by both the hepatic artery and portal vein and, as a result, substantial tumor necrosis by arterial embolization is not always guaranteed[17-19]. It has been reported that nourishing vessels of residual tumors may change from the hepatic artery to the portal vein after repeated TACE[20]. In addition, repeated chemoembolization increases pressure in the tumor micro-environment and may lead to phenotypic variation in surviving tumor cells, which tend to be more malignant and chemoembolization-resistant[21-23]. It has been reported that locally recurrent HCC after TACE has a significantly shorter doubling time than primary HCC nodules[24].

The number of TACE sessions performed before abandoning TACE in the case of insufficient tumor necrosis is a crucial issue. Georgiades et al[25] reported that 47% of non-responders to the first TACE ultimately achieved partial response (PR) or complete response (CR) after the second procedure, and median OS between patients who achieved response at the first or the second chemoembolization was comparable. Some experts suggested that if target nodule(s) show no response after at least two consecutive sessions of TACE, it is reasonable to define TACE-failure and trigger treatment stage
Depending on the purpose of TACE, if TACE is used as palliative therapy, stable lesions can be regarded as effective.

### Table 1 Different concepts of transarterial chemoembolization failure/refractoriness

| Guidelines/articles | Contents |
|---------------------|----------|
| JSH-LCSG criteria 2014 [6] | (1) Intrahepatic lesion: Two or more consecutive insufficient responses of the treated tumor (viable lesion > 50%) even after changing the chemotherapeutic agents and/or reanalysis of the feeding artery seen on response evaluation CT/MRI at 1-3 mo after having adequately performed selective TACE; two or more consecutive progressions in the liver (tumor number increases as compared with tumor number before the previous TACE procedure) even after having changed the chemotherapeutic agents and/or reanalysis of the feeding artery seen on response evaluation CT/MRI at 1-3 mo after having adequately performed selective TACE; (2) Continuous elevation of tumor markers immediately after TACE even though a slight transient decrease is observed; (3) Appearance of vascular invasion; and (4) Appearance of extrahepatic spread |
| International Association for the Study of the Liver [13] | No response after 3 or more TACE procedures within a 6 mo period, to the same area. |
| Europe [14] | Depending on the purpose of TACE, if TACE is used as palliative therapy, stable lesions can be regarded as effective. Conversely, if TACE is used as a curative therapy, stable lesions are considered TACE-failure |

JSH-LCSG: JSH-Liver Cancer Study Group of Japan; TACE: Transarterial chemoembolization; CT: Computed tomography; MRI: Magnetic resonance imaging.

Based on a large cohort study of 4154 patients with HCC, Chen et al [27] found that HCC nodules became insensitive to chemoembolization after 3 sessions of TACE, with an objective response rate (ORR) < 10%. Furthermore, patients with tumors eventually attaining CR or PR within the first 3 TACE sessions had a longer median OS than those who did not (43.4 mo vs 16.6 mo, P < 0.001). As a consequence, three sessions were recommended before abandoning TACE.

However, residual tumors with persistent viability may not be an absolute indication for systemic monotherapy owing to the unsatisfactory anti-tumor effect [28]. Other locoregional interventional methods, with curative potential, are preferred options once tumor size meets the indications. Chen et al [17] reported that subsequent microwave ablation (MWA) yielded a better survival time than sorafenib in patients with incomplete remission of targeted lesions after multiple sessions of TACE, with a longer progression-free survival (PFS) time (9.0 mo vs 2.8 mo, P = 0.006) and OS (not reached vs 16.6 mo, P = 0.001). In addition, Yttrium-90 radioembolization and Iodine-125 (125I) seed brachytherapy have been adopted to control target lesions [29-31]. TACE combined with systemic therapy or loco-regional therapy revealed favorable outcomes and good tolerance [15,31,32].

**New intrahepatic lesion(s) appearing after consecutive treatments**

Vascular endothelial growth factor (VEGF), which is regulated by hypoxia-inducible factor-1a, has been demonstrated to be the most important element in neovascularization [33]. Substantial evidence has been elucidated on the intrinsic connection between the transient upregulation of VEGF after TACE and intrahepatic metastasis. Tumor recurrences are frequently reported after TACE, whereas it is arbitrary to describe this scenario as an absolute contraindication to repeated TACE [34,35]. First, TACE is traditionally recognized as a palliative, loco-regional therapy and it is unreasonable to define the occurrence of new lesions outside treated areas as disease progression [4,27,35]. Second, frequent intrahepatic metastasis is the inherent nature of HCC and it occurs in the very early-stage. A clinicopathologic study found that nearly 19% of small HCC patients (solitary nodule with a diameter no more than 3 cm) had satellite lesions, located 2 cm or less from the main tumor and were 1 mm to 5 mm in diameter [36]. Although these undetectable and atypical micro-metastases are too small to be diagnosed as tumors according to the European Association for the Study of the Liver (EASL) [3], they possess enormous potential to develop into typical tumor lesions and appear as local recurrence or intrahepatic metastases [37]. In addition, the malignancy of HCC is positively associated with tumor size. It has been reported that approximately 51.3% of HCC nodules (with an average size of 5 cm) had microvascular invasion (MVI) and 42.4% of the nuclei were severely atypical [38]. For patients with intermediate- or advanced-stage HCC, early tumor progression after locoregional therapy was almost inevitable due to heavy tumor burden and frequent MVI [15,32,39]. Combination therapy was expected to delay tumor recurrence [16]. Even the supporters of TACE failure/refractoriness are ambivalent on the issue of whether new lesion(s) after TACE is a condition of TACE failure/refractoriness [6,16,35]. In the TACTICS trial, the first randomized control trial (RCT) demonstrating the superiority of TACE plus sorafenib compared to TACE monotherapy in unresectable HCC, “TACE failure/refractoriness” was one of the major endpoints for TACE treatment. However, the study simultaneously emphasized that multicentric occurrence and intrahepatic recurrence/metastases were the unique biological features of HCC [35], and therefore it was reasonable to perform demand TACE to control new tumor lesions [40]. To date, there is still no convincing evidence to conclude that new intrahepatic tumor lesions contribute to the biological features of HCC, whereas consecutive intrahepatic metastasis should be defined as TACE failure/refractoriness.
On-demand TACE for new intrahepatic lesions is safe and efficient in selected patients[12,41]. In a large cohort study, 264 patients with intermediate-stage HCC underwent TACE with “on demand” mode (range: 1-13 times; mean: 3 times)[12]. During the follow-up, patients experiencing intrahepatic metastasis or a total target tumor diameter increase of 20% were defined as having progressive disease (PD), while those having PVTT invasion or EHS were defined as having stage progression (SP). The results showed that median OS was comparable between patients in the PD (-) and SP (-) group (36.6 mo) and in the PD (+) and SP (-) group (35.5 mo). However, evidence from these studies only supports the feasibility of repeated TACE in new lesions, but by no means indicates that TACE can be implemented unrestrainedly. Liver function deterioration and hypoxia-induced pressure on residual HCCs have a great influence on patients’ survival. Additional systemic therapies including TKIs may prolong the interval between two TACE sessions and hamper intrahepatic micro-metastases[16,42]. Hence, the treatment decision has to be individualized according to expert evaluation. Several nomograms have been established to identify patients who may benefit from repeated TACE, but the rationality of these nomograms is still controversial[7,8,43].

**Continuous elevation of tumor markers**

On-schedule tumor marker assessment is a crucial adjuvant method for evaluating tumor response and monitoring tumor recurrence. A sudden increase in α-fetoprotein (AFP), AFP-L3 and/or des-gamma-carboxy prothrombin after treatment was thought to show tumor progression or greater malignancy of the tumor[44,45]. However, that does not indicate a definitive correlation with TACE failure/refractoriness. On the one hand, a well-designed control study is expected to clarify the superiority of TKIs to TACE in patients who experienced tumor marker flare after TACE. Although previous evidence has shown that rapid reductions in tumor markers were positive predictors of TACE and vice versa[46], subsequent treatments to deal with elevated tumor markers were not explored and recommended. Up to now, all TKIs targeting HCC, except ramucirumab which demonstrated apparent benefits in patients with AFP ≥ 400 ng/mL, are not designed for the biomarker-selected population[47]. On the other hand, the significance of the tumor marker trends has not yet been fully elucidated in the management of HCC and the relationship between different tumor markers and morphological changes is unclear[21,46]. As shown by the EASL clinical practice guideline, the use of changes in serum biomarker levels for assessment of response (i.e., AFP levels) is under investigation[3]. Hence, when tumor markers are increased after TACE, subsequent treatment should be codetermined by tumor burden, liver function and tumor response to previous TACE, rather than abandoning TACE blindly[3,48]. Furthermore, “continuous elevation” is a vague definition and an immature quantification of “elevation” brings many factors into the clinical decision. Ogasawara et al[10] suggested an increase in the level of AFP of 20% from baseline as a cut-off value. However, other researchers have different opinions[8,45].

**Appearance of vascular invasion or extrahepatic spread**

Neither the EASL nor the American Association for the Study of Liver Disease guidelines recommend TACE for the treatment of HCC with PVTT or EHS[1,3]. However, according to the BRIDGE study that documented real-world clinical practice in HCC, TACE was still the most frequent first treatment in advanced-stage HCC[49]. A national questionnaire conducted in Korea also indicated that nearly half of clinicians would not abandon TACE in the case of PVTT or EHS due to the heterogeneity of HCC[50]. Outcomes from the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) and Oriental clinical trials and the corresponding subgroup analyses showed a marginal improvement for sorafenib over placebo in terms of PVTT with/without EHS[28,50-52]. Lenvatinib exhibited a promising short-term anti-tumor effect compared with sorafenib in patients suffering PVTT with/without EHS [Hazard ratio (HR): 0.64; 95% confidence interval (CI): 0.54-0.77], while the long-term prognosis was undefined (HR: 0.87; 95% CI: 0.73-1.04). It is worth stressing that although the BCLC stage system recommends systemic therapy as the initial treatment for advanced-stage HCC, a special profile of an individual patient may induce a different option in clinical practice[48,49,53-55].

**Vascular invasion**

With the development of embolization techniques, TACE has been safely and effectively performed in some patients with adequate collateral pathways around the occluded portal vein[15,48,55-58]. These advanced stage populations were defined as “Quasi-C” patients (segmental PVTT, Child-Pugh A, and acceptable performance status). A meta-analysis showed that TACE conferred a longer OS in patients with branch PVTT than those with main trunk PVTT (11 mo vs 5 mo, $P < 0.001$)[59]. Significantly, for PVTT invading the main trunk, initial portal vein re-canalization using irradiation and a stent with subsequent selective TACE was effective in hampering disease progression, with a median stent patency of 8 mo and median OS of 12.5 mo[60]. Wang et al[61] introduced modified 121I seed brachytherapy to treat main trunk PVTT and exhibited favorable outcomes when combined with TACE (median OS: 9.8 mo). In addition, combination therapy of TACE and TKIs demonstrated better results for selected patients with PVTT[62]. According to a large cohort study, compared with sorafenib monotherapy, TACE combined with sorafenib showed a trend towards significant risk reduction in patients $(n = 1136)$ with vascular invasion (HR: 0.78; 95%CI: 0.59-1.02)[63]. Recently, a RCT conducted
by Ding et al[62] reported that TACE plus lenvatinib had a more favorable efficacy vs TACE plus sorafenib in patients with PVTT, especially those with Vp1-3 type (HR: 0.12; 95%CI: 0.03-0.42, P < 0.01) or heavy tumor burden (HR: 0.30; 95%CI: 0.15-0.61, P < 0.01). It should be emphasized that PVTT is a complex system and the optimal treatment strategy is individual rather than univocal. For patients whose tumor thrombus involves a segment of the portal vein or above, surgery is a potential option once tumor burden is downstaged to the Milan criteria in the liver; for patients who miss curative treatment, TACE, TKIs and other modalities may play a complementary role in controlling disease progression[57]. So far, many novel treatment strategies for PVTT have been investigated and have yielded exciting results, providing patients with more treatment options[30,57,60,64,65].

**Extrahepatic spread**

Subgroup analysis from the SHARP clinical trial revealed that sorafenib only conferred an additional survival time of 0.6 mo compared with placebo[52]. Due to the fact that more than two-thirds of patients with EHS died of intrahepatic tumor progression rather than extrahepatic disease, aggressive treatment targeting intrahepatic disease might be beneficial in selected patients with EHS[15,53,63]. The results from Kirstein et al[53] suggested that TACE was not inferior to sorafenib in patients with limited EHS of HCC, with a median OS of 8.8 mo vs 7.0 mo for sorafenib vs TACE (P = 0.312) before propensity score matching (PSM) analysis and 4.0 mo vs 8.0 mo after PSM (P = 0.613). In another large cohort study of 186 patients with EHS, TACE appeared to be more beneficial in patients aged below 60 years (HR: 0.58, 95%CI: 0.37-0.91, P = 0.017) or complicated with PVTT (HR: 0.44, 95%CI: 0.25-0.79, P < 0.001)[66]. Choi et al[55] compared combination treatment (TACE plus sorafenib) with sorafenib alone in advanced stage patients. The combination group demonstrated a more significant survival benefit than monotherapy both in time to progression (2.7 mo vs 2.1 mo, P = 0.011) and median OS (8.9 mo vs 5.9 mo; P = 0.009).

Subgroup analysis revealed that combination therapy was more efficacious in patients who had good liver function and EHS. Hence, although systemic therapy is recommended as the first choice for patients with EHS, TACE may still be a potential alternative in selected patients.

**SUGGESTIONS TO DEFINE TACE FAILURE/REFRACTORINESS**

For patients with intermediate-stage HCC, multidisciplinary treatment is compulsory to overcome the vast heterogeneity in HCC and different treatment modalities are cooperators rather than competitors. The term “failure” or “refractoriness” was initially derived from systemic chemotherapy in oncology where the current chemotherapeutic strategy failed to prevent overall tumor progression including tumor recurrences and new lesions. TACE is only a locoregional therapy but disease progression of HCC involves intrahepatic areas and extrahepatic tissues. In the absence of prospective well-designed studies, a persuasive definition of TACE failure/refractoriness should largely rely on the nature of the treatment, that is, a locoregional therapy. In 2020, a nationwide online survey of 257 clinicians in 184 hospitals was conducted to recognize TACE failure/refractoriness among clinicians treating HCC in China[67]. The survey showed that 89.1% (n = 229) of participants deemed TACE as a palliative therapy although sometimes could be a curative modality. While the outcome of TACE was full of variation (n = 244), almost all the participants (n = 252) would still choose TACE as the first choice for intermediate-stage HCC. In terms of TACE failure/refractoriness, nearly three-quarters (n = 199) acknowledged the rationality of the concept, whereas 91.4% (n = 235) of the respondents did not agree with the current definitions. A clear majority of clinicians would perform TACE combined with therapy in patients with segmental PVTT (n = 242) or EHS (n = 253) if liver function was well preserved. In addition, only 42 (16.3%) respondents unequivocally stated that new intrahepatic tumor lesions were an indication of TACE failure/refractoriness; and 36.6% (n = 94) gave an equivocal answer. Among the remaining 121 respondents who answered “No” to the question, most preferred combination therapy, including TACE (n = 80) and ablation (n = 80), to control new lesions. Additionally, 166 (64.6%) participants agreed that repeated TACE can be performed if tumor necrosis was insufficient and feeding arteries were available. Whereas, 150 participants (58.4%) believed that repeated TACE on pre-treated lesions should be limited to 3 times. Notably, 98.1% (n = 252) of the respondents expressed a strong desire for the improvement of TACE, including preferable embolization agents, chemotherapeutic drugs followed by embolization technique and more advanced microcatheters. Based on the above discussion and evidence, if intrahepatic targeted lesions are well controlled by appropriate TACE regimens, TACE should not be indiscriminately abandoned in the context of disease progression including new lesions, PVTT and EHS. However, if three consecutive insufficient tumor responses in targeted lesions occur, TACE should not be repeated and TACE failure/refractoriness proposed.

**FUTURE OF TACE FAILURE/REFRACTORINESS**

Treatment modalities for unresectable HCC have undergone profound changes and TACE faces
unprecedented challenges, where novel treatment strategies may substitute for TACE as the first
treatment option in selected patients with intermediate-stage HCC (ABC-HCC, NCT04803994;
RENOTACE, NCT04777851). As a consequence, the concept of TACE failure/refractoriness may be
expanded or re-defined as other proposals, for example, TACE unsuitability and TACE impossible.
However, such concepts should not be overemphasized before substantial evidence is published, as the
management of unresectable HCC is no longer the conversion between various monotherapies in the
era of comprehensive therapy. The evolution of TACE will continue and many options are being invest-
igated, including new embolic or chemotherapeutic agents in order to ensure complete tumor necrosis,
and combination treatments with newly-developed immune checkpoint inhibitors (LEAP-012,
NCT04246177; EMERALD-1, NCT03778957; CheckMate74W, NCT04340193; IMMUTACE,
NCT03572582). In the near future, the outcomes of these RCTs may re-position the role of TACE in the
management of HCC.

CONCLUSION

TACE failure/refractoriness is a scientific proposal for HCC but certain definitions in current concepts
are debatable. Tumor progression after TACE is due to high heterogeneity and therefore subsequent
treatment is an individual profile rather than a univocal recommendation. We put forward new
opinions concerning TACE failure/refractoriness which might be more reasonable in clinical practice.

FOOTNOTES

Author contributions: Zhang S and Zhong BY contributed equally to drafting the manuscript; Zhang L polished
the vocabulary and the grammar; Wang WS and Ni CF shared responsibility for the study concept and design; all
authors contributed to reviewing and criticizing revision of the manuscript and approving the final version of the
manuscript.

Supported by the National Natural Science Foundation of China, No. 81901847; Natural Science Foundation of
Jiangsu Province, No. BK20190177; and the Suzhou Science and Technology Youth Plan, No. KJXW2018003.

Conflict-of-interest statement: There are no conflicts of interest to report.

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Country/Territory of origin: China

ORCID number: Shen Zhang 0000-0001-7363-351X; Bin-Yan Zhong 0000-0001-9716-1211; Lei Zhang 0000-0002-2564-
3948; Wan-Sheng Wang 0000-0001-9539-4425; Cai-Fang Ni 0000-0003-2693-367X.

S-Editor: Chen YL
L-Editor: Webster JR
P-Editor: Chen YL

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