ISSN 1948-9366 (online)

# World Journal of

# *Gastrointestinal Surgery*

*World J Gastrointest Surg* 2022 June 27; 14(6): 528-631

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Surgery

Contents

Monthly Volume 14 Number 6 June 27, 2022

*World Journal of Gastrointestinal Surgery*

**Monthly Volume 14 Number 6 June 27, 2022**

## Contents

### LETTER TO THE EDITOR

*World Journal of Gastrointestinal Surgery*

**Monthly Volume 14 Number 6 June 27, 2022**

# Contents

## ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Surgery*, Arun Prasad, FACS, FRCS (Ed), FRCS (Gen Surg), MBBS, Adjunct Professor, Doctor, Professor, Surgeon, Department of Minimal Access, Thoracoscopic, Bariatric and Robotic Surgery, Apollo Hospital, New Delhi 110044, India. surgerytimes@gmail.com

## AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS*, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

*WJGS* mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc*.

## INDEXING/ABSTRACTING

The *WJGS* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for *WJGS* as 2.505; IF without journal self cites: 2.473; 5-year IF: 3.099; Journal Citation Indicator: 0.49; Ranking: 104 among 211 journals in surgery; Quartile category: Q2; Ranking: 81 among 93 journals in gastroenterology and hepatology; and Quartile category: Q4.

## RESPONSIBLE EDITORS FOR THIS ISSUE



**NAME OF JOURNAL**

*World Journal of Gastrointestinal Surgery*

**ISSN**

ISSN 1948-9366 (online)

**LAUNCH DATE**

November 30, 2009

**FREQUENCY**

Monthly

**EDITORS-IN-CHIEF**

Peter Schemmer

**EDITORIAL BOARD MEMBERS**

https://www.wjgnet.com/1948-9366/editorialboard.htm

**PUBLICATION DATE**

June 27, 2022



**INSTRUCTIONS TO AUTHORS**

https://www.wjgnet.com/bpg/gerinfo/204

**GUIDELINES FOR ETHICS DOCUMENTS**

https://www.wjgnet.com/bpg/GerInfo/287

**GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH**

https://www.wjgnet.com/bpg/gerinfo/240

**PUBLICATION ETHICS**

https://www.wjgnet.com/bpg/GerInfo/288

**PUBLICATION MISCONDUCT**

https://www.wjgnet.com/bpg/gerinfo/208

**ARTICLE PROCESSING CHARGE**

https://www.wjgnet.com/bpg/gerinfo/242

**STEPS FOR SUBMITTING MANUSCRIPTS**

https://www.wjgnet.com/bpg/GerInfo/239

**ONLINE SUBMISSION**

https://www.f6publishing.com

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 June 27; 14(6): 528-537

DOI: 10.4240/wjgs.v14.i6.528

ISSN 1948-9366 (online)

*MINIREVIEWS*

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

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

**Specialty type:** Oncology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Elshimi E, Egypt; Kumar SKY, India
**A-Editor:** Chan KM, Taiwan

**Received:** December 13, 2021
**Peer-review started:** December 13, 2021
**First decision:** January 27, 2022
**Revised:** February 8, 2022
**Accepted:** June 4, 2022
**Article in press:** June 4, 2022
**Published online:** June 27, 2022

**Shen Zhang, Bin-Yan Zhong, Lei Zhang, Wan-Sheng Wang, Cai-Fang Ni,** Department of Interventional Radiology, The First Affiliated Hospital of Soochow University, Suzhou 215006, Jiangsu Province, China

**Corresponding author:** Cai-Fang Ni, MD, PhD, Chief Doctor, Department of Interventional Radiology, The First Affiliated Hospital of Soochow University, No. 899 Pinghai Road, Suzhou 215006, Jiangsu Province, China. szncf@suda.edu.cn

## 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 TAEC failure/refractoriness is also put forward.

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



**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.

**Citation:** Zhang S, Zhong BY, Zhang L, Wang WS, Ni CF. Transarterial chemoembolization failure/refractoriness: A scientific concept or pseudo-proposition. *World J Gastrointest Surg* 2022; 14(6): 528-537
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i6/528.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i6.528

## 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 microenvironment 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

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

| Guidelines/articles | Contents |
|---|---|
| JSH-LCSGJ 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-LCSGJ: JSH-Liver Cancer Study Group of Japan; TACE: Transarterial chemoembolization; CT: Computed tomography; MRI: Magnetic resonance imaging.

migration[2,4,16,26]. 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 ($^{125}$I) 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-1α, 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 untypical 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 attribute 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[48]. 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 $^{125}$I 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 investigated, 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.



**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

## REFERENCES

1 **Heimbach JK**, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, Zhu AX, Murad MH, Marrero JA. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology* 2018; **67**: 358-380 [PMID: 28130846 DOI: 10.1002/hep.29086]
2 **Kokudo N**, Takemura N, Hasegawa K, Takayama T, Kubo S, Shimada M, Nagano H, Hatano E, Izumi N, Kaneko S, Kudo M, Iijima H, Genda T, Tateishi R, Torimura T, Igaki H, Kobayashi S, Sakurai H, Murakami T, Watadani T, Matsuyama Y. Clinical practice guidelines for hepatocellular carcinoma: The Japan Society of Hepatology 2017 (4th JSH-HCC guidelines) 2019 update. *Hepatol Res* 2019; **49**: 1109-1113 [PMID: 31336394 DOI: 10.1111/hepr.13411]
3 **European Association for the Study of the Liver**. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol* 2018; **69**: 182-236 [PMID: 29628281 DOI: 10.1016/j.jhep.2018.03.019]
4 **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]
5 **Kudo M**, Ueshima K, Chan S, Minami T, Chishina H, Aoki T, Takita M, Hagiwara S, Minami Y, Ida H, Takenaka M,

Sakurai T, Watanabe T, Morita M, Ogawa C, Wada Y, Ikeda M, Ishii H, Izumi N, Nishida N. Lenvatinib as an Initial Treatment in Patients with Intermediate-Stage Hepatocellular Carcinoma Beyond Up-To-Seven Criteria and Child-Pugh A Liver Function: A Proof-Of-Concept Study. *Cancers (Basel)* 2019; **11** [PMID: 31370183 DOI: 10.3390/cancers11081084]

6 **Kudo M**, Matsui O, Izumi N, Kadoya M, Okusaka T, Miyayama S, Yamakado K, Tsuchiya K, Ueshima K, Hiraoka A, Ikeda M, Ogasawara S, Yamashita T, Minami T; Liver Cancer Study Group of Japan. Transarterial chemoembolization failure/refractoriness: JSH-LCSGJ criteria 2014 update. *Oncology* 2014; **87** Suppl 1: 22-31 [PMID: 25427730 DOI: 10.1159/000368142]

7 **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]

8 **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]

9 **Arizumi T**, Ueshima K, Minami T, Kono M, Chishina H, Takita M, Kitai S, Inoue T, Yada N, Hagiwara S, Minami Y, Sakurai T, Nishida N, Kudo M. Effectiveness of Sorafenib in Patients with Transcatheter Arterial Chemoembolization (TACE) Refractory and Intermediate-Stage Hepatocellular Carcinoma. *Liver Cancer* 2015; **4**: 253-262 [PMID: 26734579 DOI: 10.1159/000367743]

10 **Ogasawara S**, Chiba T, Ooka Y, Kanogawa N, Motoyama T, Suzuki E, Tawada A, Kanai F, Yoshikawa M, Yokosuka O. Efficacy of sorafenib in intermediate-stage hepatocellular carcinoma patients refractory to transarterial chemoembolization. *Oncology* 2014; **87**: 330-341 [PMID: 25227534 DOI: 10.1159/000365993]

11 **Kudo M**, Izumi N, Kokudo N, Matsui O, Sakamoto M, Nakashima O, Kojiro M, Makuuchi M; HCC Expert Panel of Japan Society of Hepatology. Management of hepatocellular carcinoma in Japan: Consensus-Based Clinical Practice Guidelines proposed by the Japan Society of Hepatology (JSH) 2010 updated version. *Dig Dis* 2011; **29**: 339-364 [PMID: 21829027 DOI: 10.1159/000327577]

12 **Kim HY**, Park JW, Joo J, Jung SJ, An S, Woo SM, Kim HB, Koh YH, Lee WJ, Kim CM. Severity and timing of progression predict refractoriness to transarterial chemoembolization in hepatocellular carcinoma. *J Gastroenterol Hepatol* 2012; **27**: 1051-1056 [PMID: 22098152 DOI: 10.1111/j.1440-1746.2011.06963.x]

13 **Park JW**, Amarapurkar D, Chao Y, Chen PJ, Geschwind JF, Goh KL, Han KH, Kudo M, Lee HC, Lee RC, Lesmana LA, Lim HY, Paik SW, Poon RT, Tan CK, Tanwandee T, Teng G, Cheng AL. Consensus recommendations and review by an International Expert Panel on Interventions in Hepatocellular Carcinoma (EPOIHCC). *Liver Int* 2013; **33**: 327-337 [PMID: 23331661 DOI: 10.1111/liv.12083]

14 **Raoul JL**, Gilabert M, Piana G. How to define transarterial chemoembolization failure or refractoriness: a European perspective. *Liver Cancer* 2014; **3**: 119-124 [PMID: 24945002 DOI: 10.1159/000343867]

15 **Lin PT**, Teng W, Jeng WJ, Hsieh YC, Hung CF, Huang CH, Lui KW, Chen YC, Lin CC, Lin CY, Sheen IS, Lin SM. Add-on sorafenib is beneficial for hepatocellular carcinoma patients with transarterial chemoembolization refractoriness: a real-world experience. *Eur J Gastroenterol Hepatol* 2020; **32**: 1192-1199 [PMID: 31851084 DOI: 10.1097/MEG.0000000000001637]

16 **Kudo M**, Ueshima K, Ikeda M, Torimura T, Tanabe N, Aikata H, Izumi N, Yamasaki T, Nojiri S, Hino K, Tsumura H, Kuzuya T, Isoda N, Yasui K, Aino H, Ido A, Kawabe N, Nakao K, Wada Y, Yokosuka O, Yoshimura K, Okusaka T, Furuse J, Kokudo N, Okita K, Johnson PJ, Arai Y; TACTICS study group. Randomised, multicentre prospective trial of transarterial chemoembolisation (TACE) plus sorafenib as compared with TACE alone in patients with hepatocellular carcinoma: TACTICS trial. *Gut* 2020; **69**: 1492-1501 [PMID: 31801872 DOI: 10.1136/gutjnl-2019-318934]

17 **Chen S**, Shi M, Shen L, Qi H, Wan W, Cao F, Xie L, Wu Y, Chen G, Mo J, Zhu G, Ye D, Zhang Y, Feng Z, Xu L, Fan W. Microwave ablation versus sorafenib for intermediate-Stage Hepatocellular carcinoma with transcatheter arterial chemoembolization refractoriness: a propensity score matching analysis. *Int J Hyperthermia* 2020; **37**: 384-391 [PMID: 32323585 DOI: 10.1080/02656736.2020.1752400]

18 **Yoshimitsu K**. Transarterial chemoembolization using iodized oil for unresectable hepatocellular carcinoma: perspective from multistep hepatocarcinogenesis. *Hepat Med* 2014; **6**: 89-94 [PMID: 25114603 DOI: 10.2147/hmer.s31440]

19 **International Consensus Group for Hepatocellular NeoplasiaThe International Consensus Group for Hepatocellular Neoplasia**. Pathologic diagnosis of early hepatocellular carcinoma: a report of the international consensus group for hepatocellular neoplasia. *Hepatology* 2009; **49**: 658-664 [PMID: 19177576 DOI: 10.1002/hep.22709]

20 **Miyayama S**, Matsui O, Zen Y, Yamashiro M, Hattori Y, Orito N, Matsui K, Tsuji K, Yoshida M, Sudo Y. Portal blood supply to locally progressed hepatocellular carcinoma after transcatheter arterial chemoembolization: Observation on CT during arterial portography. *Hepatol Res* 2011; **41**: 853-866 [PMID: 21699636 DOI: 10.1111/j.1872-034X.2011.00836.x]

21 **Park H**, Park JY. Clinical significance of AFP and PIVKA-II responses for monitoring treatment outcomes and predicting prognosis in patients with hepatocellular carcinoma. *Biomed Res Int* 2013; **2013**: 310427 [PMID: 24455683 DOI: 10.1155/2013/310427]

22 **Kojiro M**, Sugihara S, Kakizoe S, Nakashima O, Kiyomatsu K. Hepatocellular carcinoma with sarcomatous change: a special reference to the relationship with anticancer therapy. *Cancer Chemother Pharmacol* 1989; **23** Suppl: S4-S8 [PMID: 2466583 DOI: 10.1007/BF00647229]

23 **Zen C**, Zen Y, Mitry RR, Corbeil D, Karbanová J, O'Grady J, Karani J, Kane P, Heaton N, Portmann BC, Quaglia A. Mixed phenotype hepatocellular carcinoma after transarterial chemoembolization and liver transplantation. *Liver Transpl* 2011; **17**: 943-954 [PMID: 21491582 DOI: 10.1002/lt.22314]

24 **Tezuka M**, Hayashi K, Kubota K, Sekine S, Okada Y, Ina H, Irie T. Growth rate of locally recurrent hepatocellular carcinoma after transcatheter arterial chemoembolization: comparing the growth rate of locally recurrent tumor with that of primary hepatocellular carcinoma. *Dig Dis Sci* 2007; **52**: 783-788 [PMID: 17268830 DOI: 10.1007/s10620-006-9537-y]

25 **Georgiades C**, Geschwind JF, Harrison N, Hines-Peralta A, Liapi E, Hong K, Wu Z, Kamel I, Frangakis C. Lack of response after initial chemoembolization for hepatocellular carcinoma: does it predict failure of subsequent treatment? *Radiology* 2012; **265**: 115-123 [PMID: 22891361 DOI: 10.1148/radiol.12112264]

26 **Reig M**, Forner A, Rimola J, Ferrer-Fabrega J, Burrel M, Garcia-Criado A, Kelley RK, Galle PR, Mazzaferro V, Salem R, Sangro B, Singal AG, Vogel A, Fuster J, Ayuso C, Bruix J. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. *J Hepatol* 2021 [DOI: 10.1016/j.jhep.2021.11.018]

27 **Chen S**, Peng Z, Zhang Y, Chen M, Li J, Guo R, Li B, Mei J, Feng S, Kuang M. Lack of Response to Transarterial Chemoembolization for Intermediate-Stage Hepatocellular Carcinoma: Abandon or Repeat? *Radiology* 2021; **298**: 680-692 [PMID: 33464183 DOI: 10.1148/radiol.2021202289]

28 **Llovet JM**, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**: 378-390 [PMID: 18650514 DOI: 10.1056/NEJMoa0708857]

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

30 **Bekki Y**, Marti J, Toshima T, Lewis S, Kamath A, Argiriadi P, Simpson W, Facciuto L, Patel RS, Gunasekaran G, Kim E, Schiano TD, Facciuto ME. A comparative study of portal vein embolization versus radiation lobectomy with Yttrium-90 micropheres in preparation for liver resection for initially unresectable hepatocellular carcinoma. *Surgery* 2021; **169**: 1044-1051 [PMID: 33648768 DOI: 10.1016/j.surg.2020.12.012]

31 **Klompenhouwer EG**, Dresen RC, Verslype C, Laenen A, De Hertogh G, Deroose CM, Bonne L, Vandevaveye V, Maleux G. Safety and Efficacy of Transarterial Radioembolisation in Patients with Intermediate or Advanced Stage Hepatocellular Carcinoma Refractory to Chemoembolisation. *Cardiovasc Intervent Radiol* 2017; **40**: 1882-1890 [PMID: 28685382 DOI: 10.1007/s00270-017-1739-5]

32 **Duan F**, Bai YH, Cui L, Li XH, Yan JY, Wang MQ. Simultaneous transarterial chemoembolization and radiofrequency ablation for large hepatocellular carcinoma. *World J Gastrointest Oncol* 2020; **12**: 92-100 [PMID: 31966917 DOI: 10.4251/wjgo.v12.i1.92]

33 **Wu J**, Li A, Yang J, Lu Y, Li J. Efficacy and safety of TACE in combination with sorafenib for the treatment of TACE-refractory advanced hepatocellular carcinoma in Chinese patients: a retrospective study. *Onco Targets Ther* 2017; **10**: 2761-2768 [PMID: 28603426 DOI: 10.2147/OTT.S131022]

34 **Forner A**, Reig M, Bruix J. Hepatocellular carcinoma. *Lancet* 2018; **391**: 1301-1314 [PMID: 29307467 DOI: 10.1016/s0140-6736(18)30010-2]

35 **Kudo M**, Kubo S, Takayasu K, Sakamoto M, Tanaka M, Ikai I, Furuse J, Nakamura K, Makuuchi M; Liver Cancer Study Group of Japan (Committee for Response Evaluation Criteria in Cancer of the Liver, Liver Cancer Study Group of Japan). Response Evaluation Criteria in Cancer of the Liver (RECICL) proposed by the Liver Cancer Study Group of Japan (2009 Revised Version). *Hepatol Res* 2010; **40**: 686-692 [PMID: 20633194 DOI: 10.1111/j.1872-034X.2010.00674.x]

36 **Okusaka T**, Okada S, Ueno H, Ikeda M, Shimada K, Yamamoto J, Kosuge T, Yamasaki S, Fukushima N, Sakamoto M. Satellite lesions in patients with small hepatocellular carcinoma with reference to clinicopathologic features. *Cancer* 2002; **95**: 1931-1937 [PMID: 12404287 DOI: 10.1002/cncr.10892]

37 **Kudo M**. Multistep human hepatocarcinogenesis: correlation of imaging with pathology. *J Gastroenterol* 2009; **44** Suppl 19: 112-118 [PMID: 19148804 DOI: 10.1007/s00535-008-2274-6]

38 **Lauwers GY**, Terris B, Balis UJ, Batts KP, Regimbeau JM, Chang Y, Graeme-Cook F, Yamabe H, Ikai I, Cleary KR, Fujita S, Flejou JF, Zukerberg LR, Nagorney DM, Belghiti J, Yamaoka Y, Vauthey JN; International Cooperative Study Group on Hepatocellular Carcinoma. Prognostic histologic indicators of curatively resected hepatocellular carcinomas: a multi-institutional analysis of 425 patients with definition of a histologic prognostic index. *Am J Surg Pathol* 2002; **26**: 25-34 [PMID: 11756766 DOI: 10.1097/00000478-200201000-00003]

39 **Raoul JL**, Forner A, Bolondi L, Cheung TT, Kloeckner R, de Baere T. Updated use of TACE for hepatocellular carcinoma treatment: How and when to use it based on clinical evidence. *Cancer Treat Rev* 2019; **72**: 28-36 [PMID: 30447470 DOI: 10.1016/j.ctrv.2018.11.002]

40 **Miyayama S**. Ultraselective conventional transarterial chemoembolization: When and how? *Clin Mol Hepatol* 2019; **25**: 344-353 [PMID: 31022779 DOI: 10.3350/cmh.2019.0016]

41 **Park C**, Chu HH, Kim JH, Kim SY, Alrashidi I, Gwon DI, Yoon HK, Kim N. Clinical Significance of the Initial and Best Responses after Chemoembolization in the Treatment of Intermediate-Stage Hepatocellular Carcinoma with Preserved Liver Function. *J Vasc Interv Radiol* 2020; **31**: 1998-2006.e1 [PMID: 32988715 DOI: 10.1016/j.jvir.2020.04.017]

42 **Kudo M**, Cheng AL, Park JW, Park JH, Liang PC, Hidaka H, Izumi N, Heo J, Lee YJ, Sheen IS, Chiu CF, Arioka H, Morita S, Arai Y. Orantinib versus placebo combined with transcatheter arterial chemoembolisation in patients with unresectable hepatocellular carcinoma (ORIENTAL): a randomised, double-blind, placebo-controlled, multicentre, phase 3 study. *Lancet Gastroenterol Hepatol* 2018; **3**: 37-46 [PMID: 28988687 DOI: 10.1016/S2468-1253(17)30290-X]

43 **Kloeckner R**, Pitton MB, Dueber C, Schmidtmann I, Galle PR, Koch S, Wörns MA, Weinmann A. Validation of Clinical Scoring Systems ART and ABCR after Transarterial Chemoembolization of Hepatocellular Carcinoma. *J Vasc Interv Radiol* 2017; **28**: 94-102 [PMID: 27562621 DOI: 10.1016/j.jvir.2016.06.012]

44 **Nakazawa T**, Hidaka H, Takada J, Okuwaki Y, Tanaka Y, Watanabe M, Shibuya A, Minamino T, Kokubu S, Koizumi W. Early increase in α-fetoprotein for predicting unfavorable clinical outcomes in patients with advanced hepatocellular carcinoma treated with sorafenib. *Eur J Gastroenterol Hepatol* 2013; **25**: 683-689 [PMID: 23395995 DOI: 10.1097/MEG.0b013e32835d913b]

45 **Hiraoka A**, Ishimaru Y, Kawasaki H, Aibiki T, Okudaira T, Toshimori A, Kawamura T, Yamago H, Nakahara H, Suga Y, Azemoto N, Miyata H, Miyamoto Y, Ninomiya T, Hirooka M, Abe M, Matsuura B, Hiasa Y, Michitaka K. Tumor Markers AFP, AFP-L3, and DCP in Hepatocellular Carcinoma Refractory to Transcatheter Arterial Chemoembolization. *Oncology* 2015; **89**: 167-174 [PMID: 25999038 DOI: 10.1159/000381808]

46 **Arai T**, Kobayashi A, Ohya A, Takahashi M, Yokoyama T, Shimizu A, Motoyama H, Furusawa N, Notake T, Kitagawa N, Sakai H, Imamura H, Kadoya M, Miyagawa S. Assessment of treatment outcomes based on tumor marker trends in patients with recurrent hepatocellular carcinoma undergoing trans-catheter arterial chemo-embolization. *Int J Clin Oncol* 2014; **19**:

871-879 [PMID: 24218280 DOI: 10.1007/s10147-013-0634-6]
47 **Zhu AX**, Kang YK, Yen CJ, Finn RS, Galle PR, Llovet JM, Assenat E, Brandi G, Pracht M, Lim HY, Rau KM, Motomura K, Ohno I, Merle P, Daniele B, Shin DB, Gerken G, Borg C, Hiriart JB, Okusaka T, Morimoto M, Hsu Y, Abada PB, Kudo M; REACH-2 study investigators. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2019; **20**: 282-296 [PMID: 30665869 DOI: 10.1016/S1470-2045(18)30937-9]
48 **Lee JS**, Kim BK, Kim SU, Park JY, Ahn SH, Seong JS, Han KH, Kim DY. A survey on transarterial chemoembolization refractoriness and a real-world treatment pattern for hepatocellular carcinoma in Korea. *Clin Mol Hepatol* 2020; **26**: 24-32 [PMID: 31104456 DOI: 10.3350/cmh.2018.0065]
49 **Park JW**, Chen M, Colombo M, Roberts LR, Schwartz M, Chen PJ, Kudo M, Johnson P, Wagner S, Orsini LS, Sherman M. Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study. *Liver Int* 2015; **35**: 2155-2166 [PMID: 25752327 DOI: 10.1111/liv.12818]
50 **Cheng AL**, Guan Z, Chen Z, Tsao CJ, Qin S, Kim JS, Yang TS, Tak WY, Pan H, Yu S, Xu J, Fang F, Zou J, Lentini G, Voliotis D, Kang YK. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma according to baseline status: subset analyses of the phase III Sorafenib Asia-Pacific trial. *Eur J Cancer* 2012; **48**: 1452-1465 [PMID: 22240282 DOI: 10.1016/j.ejca.2011.12.006]
51 **Cheng AL**, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, Xu J, Sun Y, Liang H, Liu J, Wang J, Tak WY, Pan H, Burock K, Zou J, Voliotis D, Guan Z. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; **10**: 25-34 [PMID: 19095497 DOI: 10.1016/S1470-2045(08)70285-7]
52 **Bruix J**, Raoul JL, Sherman M, Mazzaferro V, Bolondi L, Craxi A, Galle PR, Santoro A, Beaugrand M, Sangiovanni A, Porta C, Gerken G, Marrero JA, Nadel A, Shan M, Moscovici M, Voliotis D, Llovet JM. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. *J Hepatol* 2012; **57**: 821-829 [PMID: 22727733 DOI: 10.1016/j.jhep.2012.06.014]
53 **Kirstein MM**, Voigtländer T, Schweitzer N, Hinrichs JB, Marquardt J, Wörns MA, Kloeckner R, Fründt TW, Ittrich H, Wacker F, Rodt T, Manns MP, Wege H, Weinmann A, Vogel A. Transarterial chemoembolization versus sorafenib in patients with hepatocellular carcinoma and extrahepatic disease. *United European Gastroenterol J* 2018; **6**: 238-246 [PMID: 29511553 DOI: 10.1177/2050640617716597]
54 **Li QJ**, He MK, Chen HW, Fang WQ, Zhou YM, Xu L, Wei W, Zhang YJ, Guo Y, Guo RP, Chen MS, Shi M. Hepatic Arterial Infusion of Oxaliplatin, Fluorouracil, and Leucovorin Versus Transarterial Chemoembolization for Large Hepatocellular Carcinoma: A Randomized Phase III Trial. *J Clin Oncol* 2022; **40**: 150-160 [PMID: 34648352 DOI: 10.1200/JCO.21.00608]
55 **Choi GH**, Shim JH, Kim MJ, Ryu MH, Ryoo BY, Kang YK, Shin YM, Kim KM, Lim YS, Lee HC. Sorafenib alone versus sorafenib combined with transarterial chemoembolization for advanced-stage hepatocellular carcinoma: results of propensity score analyses. *Radiology* 2013; **269**: 603-611 [PMID: 23864102 DOI: 10.1148/radiol.13130150]
56 **Kim JH**, Shim JH, Yoon HK, Ko HK, Kim JW, Gwon DI. Chemoembolization related to good survival for selected patients with hepatocellular carcinoma invading segmental portal vein. *Liver Int* 2018; **38**: 1646-1654 [PMID: 29436101 DOI: 10.1111/liv.13719]
57 **Cheng S**, Chen M, Cai J, Sun J, Guo R, Bi X, Lau WY, Wu M. Chinese Expert Consensus on Multidisciplinary Diagnosis and Treatment of Hepatocellular Carcinoma with Portal Vein Tumor Thrombus (2018 Edition). *Liver Cancer* 2020; **9**: 28-40 [PMID: 32071907 DOI: 10.1159/000503685]
58 **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]
59 **Silva JP**, Berger NG, Tsai S, Christians KK, Clarke CN, Mogal H, White S, Rilling W, Gamblin TC. Transarterial chemoembolization in hepatocellular carcinoma with portal vein tumor thrombosis: a systematic review and meta-analysis. *HPB (Oxford)* 2017; **19**: 659-666 [PMID: 28552299 DOI: 10.1016/j.hpb.2017.04.016]
60 **Lu J**, Guo JH, Zhu HD, Zhu GY, Chen L, Teng GJ. Safety and Efficacy of Irradiation Stent Placement for Malignant Portal Vein Thrombus Combined with Transarterial Chemoembolization for Hepatocellular Carcinoma: A Single-Center Experience. *J Vasc Interv Radiol* 2017; **28**: 786-794.e3 [PMID: 28396192 DOI: 10.1016/j.jvir.2017.02.014]
61 **Wang W**, Wang C, Shen J, Ren B, Yin Y, Yang J, Tang H, Zhu X, Ni C. Integrated I-125 Seed Implantation Combined with Transarterial Chemoembolization for Treatment of Hepatocellular Carcinoma with Main Portal Vein Tumor Thrombus. *Cardiovasc Intervent Radiol* 2021; **44**: 1570-1578 [PMID: 34117503 DOI: 10.1007/s00270-021-02887-1]
62 **Ding X**, Sun W, Li W, Shen Y, Guo X, Teng Y, Liu X, Zheng L, Chen J. Transarterial chemoembolization plus lenvatinib versus transarterial chemoembolization plus sorafenib as first-line treatment for hepatocellular carcinoma with portal vein tumor thrombus: A prospective randomized study. *Cancer* 2021; **127**: 3782-3793 [PMID: 34237154 DOI: 10.1002/cncr.33677]
63 **Kok VC**, Chen YC, Chen YY, Su YC, Ku MC, Kuo JT, Yoshida GJ. Sorafenib with Transarterial Chemoembolization Achieves Improved Survival vs. Sorafenib Alone in Advanced Hepatocellular Carcinoma: A Nationwide Population-Based Cohort Study. *Cancers (Basel)* 2019; **11** [PMID: 31311148 DOI: 10.3390/cancers11070985]
64 **Wang W**, Shen J, Wang C, Ren B, Zhu X, Ni C. Safety and Feasibility of Helical I-125 Seed Implants Combined with Transcatheter Arterial Chemoembolization in Hepatocellular Carcinomas with Main Portal Vein Tumor Thrombus. *Cardiovasc Intervent Radiol* 2019; **42**: 1420-1428 [PMID: 31187228 DOI: 10.1007/s00270-019-02256-z]
65 **Galle PR**, Finn RS, Qin S, Ikeda M, Zhu AX, Kim TY, Kudo M, Breder V, Merle P, Kaseb A, Li D, Mulla S, Verret W, Xu DZ, Hernandez S, Ding B, Liu J, Huang C, Lim HY, Cheng AL, Ducreux M. Patient-reported outcomes with atezolizumab plus bevacizumab versus sorafenib in patients with unresectable hepatocellular carcinoma (IMbrave150): an open-label, randomised, phase 3 trial. *Lancet Oncol* 2021; **22**: 991-1001 [PMID: 34051880 DOI: 10.1016/S1470-2045(21)00151-0]
66 **Kim J**, Sinn DH, Choi MS, Kang W, Gwak GY, Paik YH, Lee JH, Koh KC, Paik SW. Hepatocellular carcinoma with

extrahepatic metastasis: Are there still candidates for transarterial chemoembolization as an initial treatment? *PLoS One* 2019; **14**: e0213547 [PMID: 30845192 DOI: 10.1371/journal.pone.0213547]

67 **Zhong BY**, Wang WS, Zhang S, Zhu HD, Zhang L, Shen J, Zhu XL, Teng GJ, Ni CF. Re-evaluating Transarterial Chemoembolization Failure/Refractoriness: A Survey by Chinese College of Interventionalists. *J Clin Transl Hepatol* 2021; **9**: 521-527 [PMID: 34447681 DOI: 10.14218/JCTH.2021.00049]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
**Telephone:** +1-925-3991568
**E-mail:** bpgoffice@wjgnet.com
**Help Desk:** https://www.f6publishing.com/helpdesk
https://www.wjgnet.com