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Transarterial chemoembolization in hepatocellular carcinoma treatment: Barcelona clinic liver cancer staging system

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Abstract

Hepatocellular carcinoma (HCC), the fifth most common

cancer that predominantly occurs in liver cirrhosis patients, requires staging systems to design treatments. The barcelona clinic liver cancer staging system (BCLC) is the most commonly used HCC management guideline. For BCLC stage B (intermediate HCC), transarterial chemoembolization (TACE) is the standard treatment. Many studies support the use of TACE in early and advanced HCC patients. For BCLC stage 0 (very early HCC), TACE could be an alternative for patients unsuitable for radiofrequency ablation (RFA) or hepatic resection. In patients with BCLC stage A, TACE plus RFA provides better local tumor control than RFA alone. TACE can serve as bridge therapy for patients awaiting liver transplantation. For patients with BCLC B, TACE provides survival benefits compared with supportive care options. However, because of the substantial heterogeneity in the patient population with this stage, a better patient stratification system is needed to select the best candidates for TACE. Sorafenib represents the first line treatment in patients with BCLC C stage HCC. Sorafenib plus TACE has shown a demonstrable effect in delaying tumor progression. Additionally, TACE plus radiotherapy has yielded better survival in patients with HCC and portal venous thrombosis. Considering these observations together, TACE clearly has a critical role in the treatment of HCC as a stand-alone or combination therapy in each stage of HCC. Diverse treatment modalities should be used for patients with HCC and a better patient stratification system should be developed to select the best candidates for TACE.

Key words: Hepatocellular carcinoma; Transarterial chemoembolization; Sorafenib; Radiofrequency ablation; Hepatic resection; Liver transplantation

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Core tip: This article describes the role of transarterial

chemoembolization (TACE) in the treatment of hepatocellular carcinoma (HCC) according to the barcelona clinic liver cancer (BCLC) staging system. Notably, TACE is the treatment of choice in the treatment of intermediate HCC (BCLC stage B). However, in clinical practice, TACE has been used as an alternative or combination therapy in patients with early or advanced HCC. Therefore, diverse treatment modalities, including TACE, should be considered for the best interests of patients with HCC.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common type of cancer worldwide, predominantly occurs in patients with liver cirrhosis, and its rate of incidence is increasing^[1,2]. HCC is a unique type of tumor because in addition to the extent of the tumor, the underlying liver function affects the prognosis^[3]. The barcelona clinic liver cancer (BCLC) staging system is the most widely accepted model worldwide as it integrates both tumor characteristics and general health status with hepatic function to provide a clinical algorithm to help guide treatment decision-making according to disease stages^[4-6]. Notably, the BCLC staging system stipulates that transarterial chemoembolization (TACE) is the standard of care for patients with intermediate HCC. A growing body of evidence supports the use of TACE for patients with early and advanced HCC. This narrative review offers a critical appraisal of the available data regarding the role of TACE in the treatment of HCC based on the BCLC staging system.

BCLC STAGING SYSTEM

Recently, diverse HCC staging systems have been proposed, including TNM staging, the Cancer of the Liver Italian Program (CLIP), the Chinese University Prognostic Index (CUPI), the Japanese Integrated Staging (JIS) system, and the BCLC staging and treatment strategy^[7-10]. Among these systems, only BCLC staging has been externally validated and allocates management choices to the following five different disease categories: very early, early, intermediate, advanced, and terminal. Importantly, liver expert groups (EASL and AASLD) generally agree that the BCLC system is preferred for HCC staging because it helps to predict survival outcomes and plan treatment options, and it is likely to be

updated to reflect the latest molecular research to enhance prognostic and stage-specific management strategies^[11,12]. We summarize the BCLC staging system and treatment strategies for each disease stage in Figure 1.

BCLC STAGING SYSTEM AND TACE

According to the BCLC system, TACE is the standard of care for both intermediate HCC. As described in the BCLC guidelines, this stratum of patients shows a survival benefit from TACE, which will be discussed later. However, in clinical practice, TACE has been widely used for different stages of HCC that extend beyond those recommended in the BCLC system (early or even advanced HCC). Irrespective of the heterogeneity in TACE techniques, chemotherapeutic agents, and treatment intervals, the term "conventional TACE" generally refers to the use of Lipiodol as an embolic material. For conventional TACE, various anticancer drugs are vigorously mixed with Lipiodol, which functions as a microvessel embolic agent, a chemotherapeutic agent carrier, and an augments of antitumor effects by promoting efflux into the portal vein^[13]. As an alternative to conventional Lipiodol-based regimens, non-resorbable microspheres loaded with cytotoxic drugs can be administered intra-arterially to HCC patients. These particles are termed "drug-eluting beads" and were developed to sequester doxorubicin from solution and release it in a sustained manner. It has been reported that the amount of chemotherapeutic agents that reach systemic circulation compared with Lipiodol-based TACE can be substantially reduced, thus sharply increasing the local drug concentration^[14].

The phase II PRECISION V trial compared doxorubicin-loaded DEBs with conventional TACE and demonstrated a significant reduction in liver toxicity and drug-related adverse events. However, to date, no prospective study has yet reported a significant difference in clinical efficacy between Lipiodol-based TACE and DEB TACE^[15].

Herein, we review the clinical implications of conventional TACE in each BCLC category.

VERY EARLY STAGE HCC OR STAGE 0 (PST 0, CHILD-PUGH A)

This stage refers to patients with a single tumor ≤ 2 cm or *in situ*. The American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) recommend that hepatic resection (HR) or liver transplantation (LT) should be the first option in BCLC 0 patients^[11,12]. However, various risks, such as insufficient liver function, major blood loss, further injury to the normal parenchyma, and a shortage of liver donors, can prevent some patients from undergoing HR or LT^[16,17].

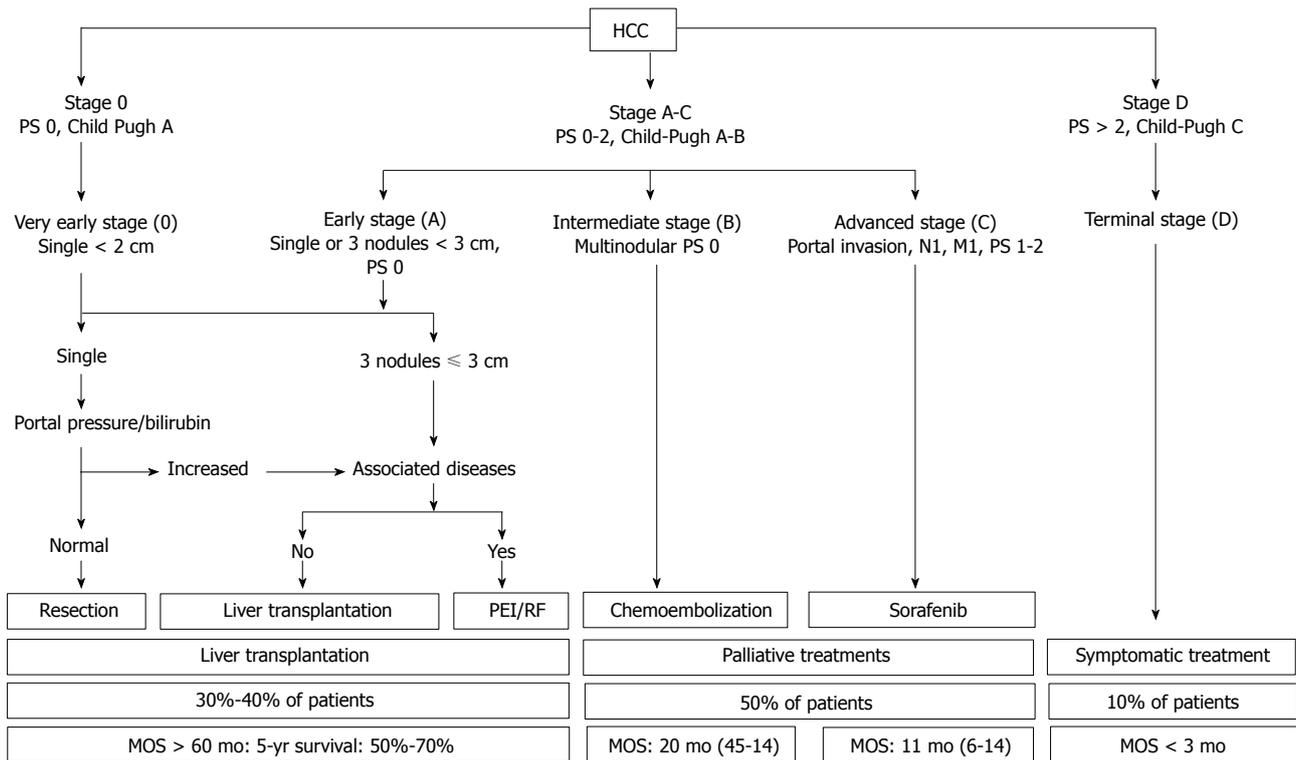


Figure 1 Updated barcelona clinic liver cancer staging system and treatment strategy.

In stage 0 patients who are not suitable for HR or LT, diverse logoregional ablation techniques have been employed. Among these patients, radiofrequency ablation (RFA) is recognized to be the modality of choice. Recently, RFA was shown to be as effective as HR for small HCCs in terms of overall survival, and some investigators suggest that RFA may be the first option for patients with a single HCC that is 2 cm or smaller, even when they can be surgically resected^[18-20]. However, in patients with HCCs with a subcapsular or dome location or HCCs adjacent to the main bile duct or bowel loop, RFA may not be technically feasible because of the associated risks that include bowel perforation, major bleeding, and bile leakage^[21].

Notably, TACE was previously only considered in this group of patients when HR, RFA, and LT were all not possible for various reasons. Kim *et al.*^[22] recently compared the effectiveness of TACE and RFA for stage 0 HCC, and reported no statistically significant difference in overall survival between the two groups, although RFA showed a better tumor response and delayed tumor progression. TACE may be considered a viable alternative treatment to RFA for treating single HCCs that are 2 cm or smaller when RFA is not feasible.

EARLY STAGE HCC OR STAGE A (≤ 3 NODULES, ≤ 3 CM EACH, PS 0)

This stage includes patients with a single HCC or up

to three nodules < 3 cm. Currently, if patients have well-preserved liver function without major vascular or lymphatic invasion, HR is considered to be the standard of care for early HCCs^[12]. Unfortunately, in this stage, many patients do not satisfy the BCLC criteria for HR because HCC usually occurs in liver cirrhosis. As mentioned above, RFA has been found to be equally safe and effective as a first-line treatment for a single HCC up to 5 cm in diameter^[23]. However, the local tumor progression rate, an important prognostic factor for RFA-treated HCC, was reported to sharply increase for tumors that exceeded 3 cm in size^[24,25]. Notably, it is rarely possible to achieve complete ablation for tumors larger than 5 cm because of limitations for the ablation zone^[26,27]. Kim *et al.*^[28] compared the effectiveness and safety of combined RFA and TACE to RFA alone in the treatment of mid-sized HCC (3-5 cm). In the combined therapy group, the long-term local tumor progression rates were lower than those of the RFA alone group (1-, 3-, 5-, and 7-year LTP rate: 9%, 40%, 55%, and 66% vs 45%, 76%, 86%, and 89%, respectively; all *P* < 0.001). The observed advantages appear to be attributed to reduced heat-sink effects by occluding the arterial flow and allowing for more microscopic satellite tumor control^[29-31].

Because the BCLC staging system categorizes solitary HCC as an early stage disease irrespective of tumor size, large single HCCs (> 5 cm) without vascular invasion also belong to the BCLC A stage. Jin *et al.*^[32] compared the outcomes of HR and TACE for solitary large HCC. They reported that HR offered a significantly better 5-year survival rate in the surgical

Table 1 Subclassification system for intermediate hepatocellular carcinoma proposed by Bolondi *et al.*^[43]

BCLC substage	B1	B2	B3	B4
Child-Pugh Score	5-6-7	5-6	7	8-9
Beyond Milan and Within Ut-7	In	Out	Out	Any
ECOG-PS	0	0	0	0-1
PVT	No	No	No	No
1 st option	TACE	TACE or TARE		BSC
Alternative	LT, TACE + ablation	SOR	Research trials TACE, SOR	LT

TACE: Transarterial chemoembolization; LT: Liver transplantation.

group than in the TACE group (65% vs 17%, $P < 0.01$) irrespective of tumor size. In the study of Zhu *et al.*^[33], the propensity score matched findings also demonstrated a better 5-year survival rate in the surgical group than in the TACE group with propensity score matching (41.3% vs 18.5%, $P = 0.007$). Recently, Lee *et al.*^[34] conducted the largest study (159 total patients: 91 patients for HR and 68 patients for TACE) to date that compared long-term survival after HR and TACE as the initial treatment for large solitary HCC (> 5 cm), which yielded contradicting results. The 5-year overall survival rates of HR and TACE were 66% and 50%, respectively, and TTP was longer in the HR group. After propensity score matching (58 pairs), the overall survival of TACE patients was comparable to that of HR patients, and TTP remained significantly longer in patients treated with HR. The difference in overall survival between the two groups might result from differences in baseline patient characteristics rather than the treatment modality. They concluded that TACE could be considered as an alternative initial treatment for large solitary HCCs if HR is not feasible, particularly in patients with clinically presumed portal hypertension. A large, randomized, controlled study is warranted to compare the long-term outcomes of HR and TACE in the treatment of large solitary HCCs.

The Milan criteria (one lesion ≤ 5 cm in diameter or up to 3 lesions ≤ 3 cm) can be applied as a basis for selecting patients with cirrhosis and HCC for LT. However, liver transplant candidates greatly outnumber liver donors. It has been suggested that TACE can be used to downstage a tumor within the Milan criteria before transplantation^[35-39]. Additionally, TACE can be used as a bridge to LT in cirrhotic patients with HCC within the Milan criteria^[40].

STAGE B (INTERMEDIATE HCC)

The intermediate stage constitutes asymptomatic, large, or multifocal HCCs without evidence of vascular invasion or extrahepatic metastasis. TACE is the recommended treatment modality for this stratum of patients^[4]. This recommendation is based on a meta-analysis of seven trials, which demonstrated that

TACE showed a significant improvement in 2-year survival compared with best supportive care (OR = 0.53; 95%CI: 0.32-0.89; $P = 0.017$)^[41]. However, patients enrolled in these studies were not categorized according to the BCLC staging system and many patients with early HCCs were included. Furthermore, many patients had compensated liver function (Child-Pugh A) and, thus, the role of TACE in HCC patients with Child-Pugh class B is relatively insufficient. Similarly, one of the great problems of BCLC stage B is the enormous heterogeneity of the population in tumor load, age, liver function, and potential comorbidities. However, no subgroup stratification exists for this stage, making it difficult to provide optimal treatment strategies^[42]. Therefore, in clinical practice, TACE is often used outside of the current treatment guidelines.

Recently, several groups have proposed patient stratification systems. Bolondi *et al.*^[43] proposed a subclassification system of intermediate HCC based on key parameters related to tumor burden and liver function. The key parameters in such four-subgroup systems included the Child-Pugh score, tumor load (within or beyond the up-to-seven criteria), the ECOG performance and portal venous thrombosis, and the first and alternative treatment options were assigned to each category (Table 1). Ha *et al.*^[44] evaluated the usefulness of such subclassifications. In their study, patients belonging to the B1 and B2 subclasses had a median overall survival of 41 or 22 months, respectively. They did not observe any survival difference between the B3 and B4 groups (14.1 mo vs 17.2 mo, $P = 0.48$) and proposed a modified subclassification system by merging the B3 and B4 patients to facilitate per-subclass-based treatment options (median OS: 16.6 mo).

COMBINATION STRATEGIES

TACE + RFA

Despite the established survival benefit of TACE in patients with intermediate HCC, and as TACE is a palliative treatment that does not result in complete tumor necrosis, tumor recurrence after TACE is common. Additionally, repeat TACE might damage liver function and adversely affect patient survival. Nevertheless, RFA is known to provide better local control of disease than TACE and can achieve complete necrosis for small HCCs. However, the effectiveness of RFA in patients with intermediate or large HCC is unsatisfactory, with a relatively low complete necrosis rate that ranges from 29% to 70%, even if an overlapping technique or repeated procedures are used. However, Tanaka *et al.*^[45] investigated the long-term effects of combination therapy for intermediate HCC. A total of 58 patients with BCLC stage B (single nodule > 5 cm or measuring more than 30 mm in diameter or two to three nodules, each measuring more than 30 mm in diameter, or more than three nodules, no vascular invasion, and no extrahepatic

metastasis) were included in that study. They reported that the 1-, 2-, 3- and 5-year overall survival rates of the combination therapy group (91%, 65%, 53%, and 27%, respectively) were significantly better than those of the supportive care group (42%, 8%, 8%, and 0%, respectively). The overall survival rates for the combination therapy group tended to be higher than those of patients treated with TACE alone in previous studies (1-, 2-, and 3-year survival rates of 75%, 50%, and 29%, respectively). Although a large-scale randomized controlled trial will be required to compare those results with TACE alone, TACE combined with RFA seems to be a safe and effective treatment strategy for patients with intermediate HCC.

Systemic treatment with sorafenib

Sorafenib, an oral multikinase tyrosine inhibitor, is the treatment of choice in BCLC C patients. However, a subanalysis of the SHARP trial revealed that sorafenib was safe and effective, irrespective of whether patients were either BCLC stage B or C (median OS: 14.5 mo in BCLC B stage vs 9.7 mo in BCLC C)^[46]. Some investigators demonstrated that sorafenib may provide benefits for patients with BCLC B HCC who are ineligible for or have progressed after TACE^[46,47]. Furthermore, it is suggested that patients who do not meet the allocated treatment criteria within a stage should be offered the next most suitable treatment within the same or next stage^[11]. Patients with intermediate HCC who do not respond to TACE may benefit from sorafenib. Sorafenib will be discussed more thoroughly in the following section on the BCLC C stage.

STAGE C (ADVANCED HCC)

Emergence of sorafenib

This category applies to patients who have symptoms and/or vascular invasion or extrahepatic spread. No effective systemic chemotherapy exists for advanced HCC, and systemic chemotherapy might even adversely affect patient survival^[46]. In this context, sorafenib, an oral multikinase inhibitor with antiproliferative and antiangiogenic effects, has emerged as a promising drug for advanced HCC interventions. The SHARP trial reported an improved median overall survival without significant drug toxicity in patients treated with sorafenib (10.7 mo in the sorafenib group vs 7.9 mo in the placebo group; HR = 0.69; 95%CI: 0.55-0.87; $P < 0.001$), and this improvement in survival was also identified in the Asian-Pacific population (6.5 mo in the sorafenib group vs 4.2 mo in the placebo group; HR = 0.68; 95%CI: 0.50-0.93; $P = 0.014$)^[48,49]. Subsequently, sorafenib has been considered as the standard of care for BCLC stage C HCC.

TACE and its combination with sorafenib

As demonstrated by the aforementioned previous

studies, the survival benefit observed after sorafenib treatment is limited to less than 3 mo, which highlights the need for better treatment strategies. Under these circumstances, several investigators have reported that TACE has the potential to benefit this group of patients^[50-55]. Chung *et al.*^[56] compared the efficacy and safety of TACE in patients with HCC who initially presented with main portal vein invasion. They showed that repeated TACE showed significant survival benefits compared with supportive care in both Child-Pugh class A (median OS: 7.4 mo vs 2.6 mo) and B (median OS: 2.8 mo vs 1.9 mo). Furthermore, irrespective of the use of sorafenib, the use of TACE to control intrahepatic HCC has been found to offer survival benefits compared with conservative management in patients with HCC and extrahepatic spread^[57].

TACE-induced hypoxia in surviving tumor cells results in the release of angiogenic growth factors, which contribute to tumor recurrence or metastases and a worse outcome^[58,59]. Sorafenib inhibits tumor cell proliferation by blocking the Raf-MEK-ERK signaling pathway at the Raf kinase level, and exerts an anti-angiogenic effect by blocking vascular endothelial growth factor receptor-2 and -3 and platelet-derived growth factor receptor tyrosine kinase^[60]. Therefore, in theory a combination of TACE with sorafenib might provide a benefit for patients with HCC. Choi *et al.*^[61] studied the time to progression and overall survival in patients with advanced HCC who were treated with sorafenib plus TACE versus sorafenib alone. They reported that the median TTP and OS in the combined group were longer than those in the monotherapy group (TTP: 2.5 mo vs 2.1 mo, $P = 0.008$; OS: 8.9 mo vs 5.9 mo, $P = 0.009$). Therefore, the addition of TACE to established sorafenib therapy has a demonstrable effect in delaying tumor progression in patients with advanced HCC, although the survival benefit is uncertain.

TACE plus radiotherapy

TACE combined with radiotherapy has resulted in improved outcomes for patients with HCC and portal vein thrombosis^[62-70]. The rationale for this combined treatment is that reducing PVT with RT can delay intravascular tumor growth and the deterioration of liver function by preserving adequate portal flow, as well as by facilitating subsequent treatment of the primary tumor^[66,67]. Recently, Kim *et al.*^[71] compared the efficacy of TACE with or without RT vs sorafenib for advanced HCC with PVT. In this single center study, patients were divided into three different pairs (TACE vs TACE + RT, TACE vs sorafenib, and TACE + RT vs sorafenib). By propensity score matched analysis, the TACE + RT group had a longer median time to progression and overall survival than the TACE-alone [102 pairs; TTP 8.7 mo vs 3.6 mo ($P < 0.01$); OS, 11.4 mo vs 7.4 mo ($P = 0.023$)] and sorafenib groups [30 pairs; TTP, 3.4 mo vs 1.8 mo ($P < 0.01$); OS, 5.9 mo vs 4.4 mo ($P = 0.03$)]. Although these findings

Table 2 Potential role of transarterial chemoembolization in the treatment of hepatocellular carcinoma

Stage	Potential role of TACE
BCLC 0	TACE may be considered a viable alternative treatment to RFA for treating single HCCs measuring 2 cm or smaller when RFA is not feasible
BCLC A	1: The combination of TACE and RFA is safe and provides better local tumor control than RFA alone in the treatment of medium sized HCC (3-5 cm) 2: For a large solitary HCC (> 5 cm), HR provides better overall survival than HCC, but TACE could be considered as an alternative initial treatment when HR is not feasible 3: TACE can be used to downstage the tumor within the Milan criteria before LT or serve as a bridge to LT
BCLC B	1: TACE is the standard of care for this stratum of patients 2: Combination with other therapies such as RFA and sorafenib may provide better patient survival or local tumor control
BCLC C	1: Repeated TACE showed significant survival benefits in patients with advanced HCC compared with supportive care 2: Sorafenib plus TACE has a demonstrable effect in delaying tumor progression 3: Combination with radiotherapy has resulted in better survival in patients with HCC and PVT

TACE: Transarterial chemoembolization; RFA: Radiofrequency ablation; HCC: Hepatocellular carcinoma; HR: Hepatic resection; LT: Liver transplantation.

need to be verified with future randomized controlled trials, concurrent treatment with TACE and RT could represent an alternative option to the current standard sorafenib therapy for the treatment of HCC with PVT.

CONCLUSION

The BCLC staging system has served as the backbone of HCC treatment strategies as it stratifies patients according to outcomes and allocates treatments. Notably, despite the substantial heterogeneity of the HCC patient population with BCLC stage B, TACE has played a key role in the treatment of intermediate HCC. Additionally, as discussed in this review, TACE has been used as an alternative or combination therapy in patients with early or advanced HCC (Table 2). Therefore, diverse treatment modalities should be utilized for the best interest of patients with HCC. In future studies, we should also develop a better patient stratification system to select suitable candidates for TACE and identify the best alternative treatment for patients who are refractory to TACE.

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