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REVIEW

The New Updated Barcelona Clinic Liver Cancer Staging System: Roles of Trans-arterial Chemoembolization and Homework to Interventional Radiologists

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Abstract:
Barcelona Clinic Liver Cancer staging system, which has been identified as the most commonly used staging system in patients with hepatocellular carcinoma, was initially published in 1999, and it was updated in 2022. This new Barcelona Clinic Liver Cancer staging shows more flexible strategies for the treatment of hepatocellular carcinoma based on each stage. Although the roles of trans-arterial chemoembolization were limited in intermediate stage (Barcelona Clinic Liver Cancer-B) patients in the previous version, its roles have been expanded in the new version of Barcelona Clinic Liver Cancer staging system. In this manuscript, we introduce how trans-arterial chemoembolization is incorporated in a new Barcelona Clinic Liver Cancer staging system and explore the new role of trans-arterial chemoembolization and what interventional radiologists seek for in a near future.

Keywords:
hepatocellular carcinoma, trans-arterial chemoembolization, Barcelona Clinic Liver Cancer staging system, interventional radiologists

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Introduction

Barcelona Clinic Liver Cancer (BCLC) staging system has been updated in 2022 [1]. This update reflects the concept of treatment stage migration. New treatment strategies are fabricated by expert clinical decision-making by a tumor board, factors reflecting patients and tumor's characteristics, and technical availability. Although trans-arterial chemoembolization (TACE) used to be a standard treatment in BCLC-B patients in the previous staging system, it is flexibly incorporated in each stage from BCLC-0 to BCLC-B. This manuscript shows how TACE is incorporated in the new BCLC staging system and explores the new role of TACE and interventional radiologists for patients with hepatocellular carcinoma (HCC).

Very Early Stage (BCLC-0)

BCLC-0 is defined as a solitary HCC smaller than 2 cm without vascular invasion or extrahepatic spread in patients with preserved liver function and no symptoms related to cancer. Although ablation is considered the preferred treatment option, if it is not feasible for anatomical or technical reason, resection should be considered first, followed by TACE.

Expected survival after first treatment option is over 5 years.

Early Stage (BCLC-A)

BCLC-A is defined as solitary HCC irrespective of size or as 3 or fewer HCCs 3 cm or smaller, without vascular invasion, extrahepatic spread, or cancer-related symptoms (PS-0).

In BCLC-A, curative treatments such as ablation, resection, and liver transplantation (LT) are recommended as the first treatment option. It is noteworthy that the updated BCLC staging system does not recommend resection for patients with 2 or 3 HCC nodules within Milan criteria. It throws a question whether outcomes after surgery or ablation are better than that offered by TACE, thus advocating prospective data collection [2, 3].

Another interesting point is that this staging system does not recommend TACE in tumors exceeding 8 to 10 cm, as it

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has been reported that worse outcomes are associated after TACE [4, 5].

Expected survival after first treatment option is over 5 years.

Intermediate Stage (BCLC-B)

BCLC-B is defined as multifocal HCC (beyond BCLC-A criteria) with preserved liver function, no symptoms related to cancer (PS 0), and no vascular invasion or extrahepatic spread. In 2022 BCLC staging system, this stage was divided into three subgroups.

The first subgroup includes patients with HCC who could be candidates for LT if they meet the "Extended Liver Transplant criteria" according to the criteria of the institution [6].

The second subgroup is filled with candidates for TACE. They are not LT candidates and have well-preserved liver profile. The new BCLC staging system has mentioned about conventional TACE using lipiodol and drug-eluting bead (DEB) TACE using microsphere, describing that response rates and survival are not different between the two techniques [7, 8]. The staging system suggests for each team to define its preference.

The third subgroup comprises patients with diffuse, infiltrative, extensive HCC liver involvement. TACE is considered not beneficial for them; moreover, systemic therapy should be the recommended option, although there is no strict cut-off for when this is the case.

Expected survival is over 5 years after LT, over 2.5 years after TACE, and over 2 years after systemic treatment.

Advanced Stage (BCLC-C)

This stage includes patients with vascular invasion or extrahepatic spread with relatively preserved PS less than 2 and preserved liver function. BCLC staging system recommends BCLC-C patients to receive systemic therapy.

Expected survival is over 2 years.

Discussion

Very early and early stage (BCLC-0 and BCLC-A)

TACE is applied not only in patients with BCLC-B diseases but also those with BCLC-0 or BCLC-A diseases when curative treatments such as surgery, ablation, or LT are not feasible or deemed to fail.

Although expected survival after curative treatments is over 5 years, there have been few survival data after TACE in these patients prospectively collected. According to the data from Liver Cancer Study Group of Japan, the 5-year survival rate is 47.8% in patients with HCC of 2 cm or smaller [9]. Recent development of catheter and guidewire has enabled superselective catheterization and guidance software, which automatically detects tumor-feeding arteries [10]. Miyayama et al. performed superselective conventional TACE using guidance software in 175 patients who had 3 or fewer HCCs smaller than 3 cm. Their 5-year overall rates were as high as 64.8%.

It is noteworthy that this new staging system does not recommend resection in BCLC-A patients with 2 or 3 HCCs; moreover, this system advocates the necessity to collect prospective data after surgery and TACE in such patients. If survival benefit (>5 years) could be shown after TACE, the role of TACE would then be expanded.

This new staging system also gives warning in terms of utilizing TACE among patients with large HCCs as it may only worsen outcomes. However, safety and good initial clinical outcomes have been reported in patients with large HCCs after conventional TACE and DEB-TACE in retrospective studies [11, 12]. Miyayama et al. performed conventional TACE in 25 patients with HCCs larger than 10 cm in a maximum diameter [12]. The 5-year survival rate was 23.1% in all patients and 38.9% in 16 patients with 3 or fewer HCC nodules. Bile duct complications requiring additional interventions were noted to develop in two patients (8%). Hidaka et al. performed bland embolization followed by conventional TACE in 21 patients with HCCs larger than 10 cm [13]. Complete response was 38.1%, whereas partial response rate was 57.1% with a 5-year survival rate of 25.0%. Severe adverse events developed in two patients (9.5%), and acute cholecystitis and tumor rupture were found to develop in each one patient. One prospective phase II clinical trial featuring bland embolization using microsphere in patients with large (5.1 cm to 10 cm) HCCs (UMIN000021457) is ongoing in Japan.

Intermediate stage (BCLC-B)

As has been well known, the magnitude of tumor burden is quite heterogeneous; in fact, there have been many attempts to divide BCLC-B into subgroups. In fact, BCLC-B was divided into three subgroups: one is candidates for LT, the second is candidate for TACE, and the third are candidates for systemic therapy. But there is no clear cut-off between each subgroup. Subgrouping has been attempted in combining tumor burden, liver profile, and performance status. Indexes reflecting tumor burden were as follows: up to 7 criterion, up to 11 criterion, and 4 tumors of <7 cm, and so on [14-16]. Indexes reflecting liver profile were Child-Pugh score and grade, and albumin-bilirubin (ALBI) score, and so on. These indexes still help to find and stratify patients who benefit from TACE. The median survival time was 40.5 months in Child-Pugh score 5 or 6 patients with HCCs within 4 of 7 cm criterion (B1), 13 months in Child-Pugh score 9 patients regardless of tumor burden (B3), and 28.1 months in patients other than B1 and B3 (B2) [16].

When and to whom systemic therapy is applied remains to be controversial. The definition of TACE failure and refractoriness was introduced to find patients who do not benefit from TACE [17].

As described in the staging system, ongoing trials comparing TACE vs. systemic therapy for BCLC-B patients have detailed inclusion and exclusion criteria and may pro-

duce very useful information that will guide clinical practice.

New treatment concept is a combination of TACE and systemic therapy. TACE combined with lenvatinib has shown promising outcomes in 62 patients with unresectable HCCs in a prospective phase II clinical trial [18]. Moreover, 24 (38.7%, 24/62) patients were found to have BCLC-A disease, 35 patients (56.5%, 35/62) with BCLC-B disease, and 3 patients with BCLC-C disease (4.8%, 3/62). The estimated progression-free survival, time to untreatable progression, and overall survival were more than 2 years, and objective response rate was 88.7% (90% CI 79.8%-94.6%). The complete response rate was as high as 66.1%.

Advanced stage (BCLC-C)

The combination of atezolizumab and bevacizumab has been considered as the first-line treatment in patients with BCLC-C disease.

Trans-arterial radioembolization was expected to be as effective as sorafenib in patients with liver-only involvement [19]. However, prospective phase III trials comparing it with sorafenib or combination of it and sorafenib vs. sorafenib alone failed to show its superiority [20, 21].

One prospective phase II clinical trial featuring combination therapy of sorafenib and conventional TACE showed good clinical outcomes in patients with BCLC-C disease [22]. Not only liver-only involvement but also extrahepatic metastasis patients were included. Objective response rate was 77.4% with median overall survival of 17.3 months. The role of TACE combined with systemic therapy should be confirmed not only in patients with liver-only involvement but also those with intrahepatic lesion and extrahepatic metastasis in future studies.

Summary

The new BCLC staging system was published in 2022, which gives a flexible treatment choice for HCC patients and gives interventional radiologist opportunity to play an important role in the treatment of HCC. It is noteworthy that this new version BCLC staging system has shown not only a new treatment strategy but also raise some questions to be solved in a near future. a) Clinical efficacy of TACE in BCLC-A patients with 2 or 3 HCC nodules. b) Clinical efficacy and safety of TACE or bland embolization in patients with large HCC. c) Clinical utility of combination of systemic therapy and TACE in BCLC-C patients with both liver lesion and extrahepatic metastasis. We IRs have to be ready to solve questions this staging system raised until the next update of BCLC staging system.

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2. Drafting of the work and final approval of the version to be published; KY, HT.

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