

Treatment Strategies of Intermediate-Stage Hepatocellular Carcinomas in Japan (Barcelona Clinic Liver Cancer Stage B)

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Key Words

Hepatocellular carcinoma · Intermediate stage · Chemoembolization · Child-Pugh score · Prognosis

Abstract

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world, and it shows increasing incidence worldwide. The Barcelona Clinic Liver Cancer (BCLC) staging system has become widely accepted in clinical practice, but in Japan, two clinical practice guidelines have been used for HCC: the Evidence-Based Clinical Practice Guidelines and the Consensus-Based Clinical Practice Guidelines. Although, in Japan, chemoembolization is the first-line treatment of intermediate-stage (stage B) HCC patients in the BCLC staging system, along with chemoembolization, locoregional treatments, such as resection and radiofrequency ablation, and hepatic arterial infusion chemotherapy are incorporated into the treatment algorithm based on the tumor number and size as well as on the liver profile.

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world, and it shows increasing incidence worldwide [1, 2]. The Barcelona Clinic Liver

Cancer (BCLC) staging system is accepted worldwide for clinical practice. The BCLC classification divides HCC patients into stages according to prognostic variables and allocates therapies according to treatment-related status [3]. For example, BCLC stage B is defined as intermediate stage. It includes extremely inhomogeneous patients. Chemoembolization is recommended as the standard treatment of intermediate-stage (BCLC stage B) HCC patients [3].

In contrast, two clinical practice guidelines for HCC have become common in Japan. One is the Evidence-Based Clinical Practice Guidelines created based on highly evidenced data [4]. The other is the Consensus-Based Clinical Practice Guidelines created by consensus among expert opinions [5]. In both guidelines, treatment algorithms have been fabricated based on liver function, extrahepatic lesions, vascular invasion, as well as tumor number and size. Although no definition of intermediate stage exists in these Japanese guidelines, not only chemoembolization [6], but also locoregional treatments, such as hepatic resection [7, 8], and radiofrequency ablation (RFA) [9], hepatic arterial infusion chemotherapy, and sorafenib [10] are incorporated into the treatment tactics in patients corresponding to intermediated-stage disease.

This study presents an explanation of the differences in the treatment strategies of intermediate-stage HCC patients by examining the Japanese guidelines and clarifying the BCLC staging system.

BCLC Staging System

The BCLC classification divides HCC patients according to 5 stages (0, A, B, C, and D) depending on tumor status-related variables (size, number, vascular invasion, N1, and M1), liver function (Child-Pugh class), and health status (ECOG) (fig. 1). Treatment allocation depends on variables that have been shown to influence therapeutic outcomes, e.g. bilirubin, portal hypertension, and the presence of symptoms. Actually, BCLC stage B, which is defined as intermediate stage, consists of patients having Child-Pugh class A and class B liver function with ≥ 4 tumors irrespective of size, or 2–3 tumors of >3 cm in maximal diameter, in the absence of cancer-related symptoms, macrovascular invasion, or extrahepatic spread.

Untreated patients at an intermediate stage (BCLC stage B) reportedly present a median survival of 16 months [11, 12] or 49% at 2 years [13]. Chemoembolization is recommended as the standard treatment, which is positioned as a palliative treatment, extending the survival of these patients to a median of up to 19–20 months according to randomized controlled trials and meta-analyses of pooled data [11].

Evidence-Based Clinical Practice Guidelines in Japan

These guideline were first issued in 2005. They have been twice revised since, in 2009 and 2013. The treatment algorithm is based on liver function damage (or Child-Pugh class), tumor number and size, vascular invasion, and extrahepatic lesions [4]. Although no definition of intermediate stage exists, treatment strategies for patients corresponding to intermediate-stage disease consist of locoregional treatments, such as hepatectomy and RFA, hepatic arterial infusion chemotherapy, and sorafenib in addition to chemoembolization (fig. 2).

Many studies have demonstrated that tumor diameter is not a limitation of hepatectomy. The 5-year survival rates have been reported to be 20–30%, which are much better than natural history [13–16]. Although therapeutic results following hepatectomy worsen as the tumor number increases, these results are still better than those after other palliative treatments and supportive care [17, 18]. No evidence exists for tumor number that provides a survival benefit to patients undergoing surgical intervention, although a tumor number of ≥ 3 has been widely accepted as a good indication for locoregional treatments such as RFA. Therefore, hepatectomy is recommended when the tumor number is ≤ 3 , irrespective of the tumor size. Recent studies also have demonstrated

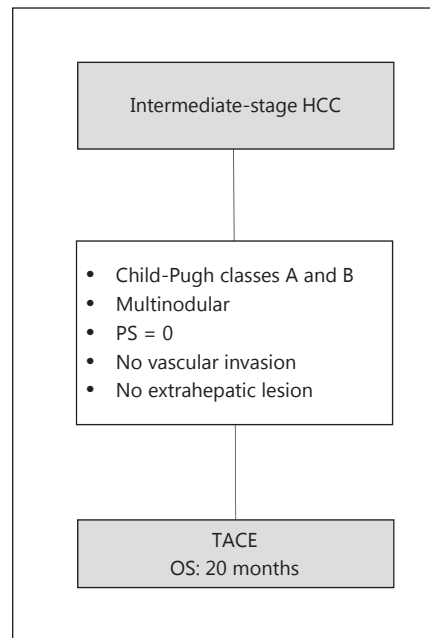


Fig. 1. Treatment strategy of intermediate-stage HCC patients (stage B) in the BCLC staging system. PS = Performance status; TACE = transarterial chemoembolization; OS = overall survival.

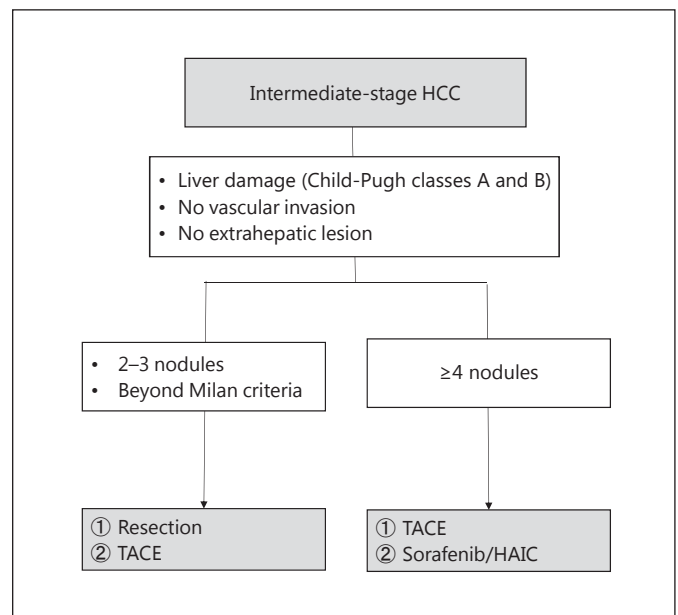


Fig. 2. Treatment strategy of intermediate-stage HCC patients in the Evidence-Based Clinical Practice Guidelines in Japan. TACE = Transarterial chemoembolization; HAIC = hepatic arterial infusion chemotherapy.

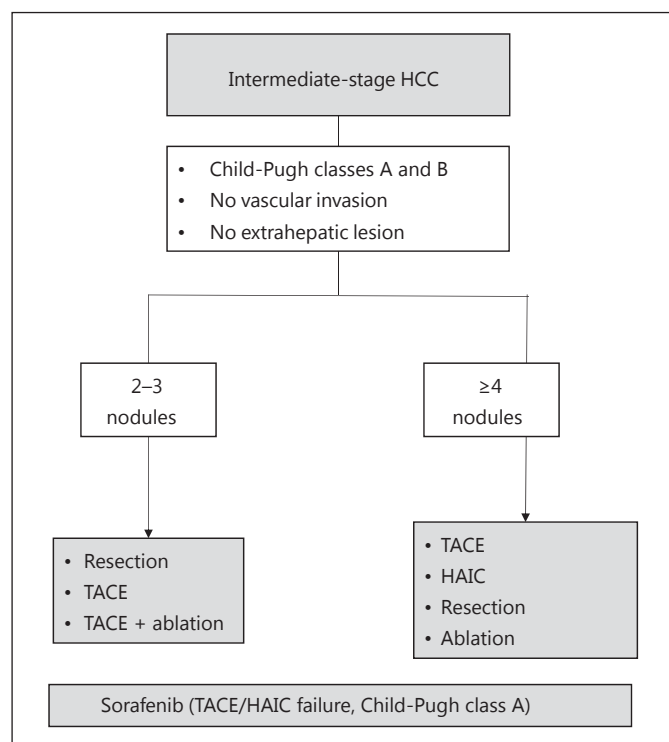


Fig. 3. Treatment strategy of intermediate-stage HCC patients in the Consensus-Based Clinical Practice Guidelines in Japan. TACE = Transarterial chemoembolization; HAIC = hepatic arterial infusion chemotherapy.

the utility of hepatectomy, even in intermediate-stage HCC patients [19].

When the tumor number is ≥ 4 , chemoembolization is recommended as the first-line treatment. Sorafenib can be used after chemoembolization fails to control tumors in patients with Child-Pugh class A.

The literature provides little evidence that hepatic arterial infusion chemotherapy improves patient survival in HCC. However, many studies have proved a benefit to survival using this treatment instead of historical control [20]. Therefore, hepatic arterial infusion chemotherapy is listed in these guidelines.

Consensus-Based Clinical Practice Guidelines

This treatment algorithm, created based on experts' experiences, reflects clinical practices of managing HCC patients in Japan (fig. 3). When the tumor number is 2 or 3, in addition to chemoembolization, resection or combination of chemoembolization and RFA are considered for

the therapeutic option. Combination therapy of chemoembolization and RFA is usually applied for the treatment of HCC lesions ≥ 3 cm [21].

When the tumor number is ≥ 4 , chemoembolization is the first-line treatment. Hepatic arterial infusion chemotherapy is used when chemoembolization fails to control tumors. Even for patients having ≥ 4 tumors, resection and ablation are applicable if possible. Sorafenib is usually used when both chemoembolization and hepatic arterial infusion chemotherapy fail to control tumors and the patients' liver function is Child-Pugh class A.

Discussion

A great difference exists in the treatment strategy of HCC patients between the BCLC staging system and the Japanese treatment algorithms, as shown in this study.

In Japan, the BCLC staging system problem lies in its simplicity of recommending only chemoembolization, although the intermediate stage includes extremely inhomogeneous patients. Neither surgical intervention nor ablation therapy has been considered for intermediate-stage patients in the BCLC staging system, although both treatments are applied, particularly in Japanese patients with ≤ 3 HCC nodules.

Recently, some movements have been underway to stratify patients using some prognostic factors to identify patient groups showing a greater benefit from chemoembolization than other patient groups [22, 23]. Bolondi et al. [22] advocated the division of intermediate stage into 4 substages based on the up-to-7 criteria (in vs. out) and Child-Pugh scores (5–7 vs. 8–9). Recently, one study validated this substaging system and reported the difficulty in stratifying the patient group that benefits least from chemoembolization [23].

Aside from the up-to-7 criteria, the 4 tumors of the 7-cm criteria (4-of-7 cm) and Child-Pugh class A were identified as favorable prognostic factors in patients with intermediate-stage HCCs undergoing chemoembolization [24].

Sorafenib is usually used in Western countries after chemoembolization fails to control HCC lesions. The median survival times after sorafenib administration were 10.7 months in the SHARP trial and 6.5 months in the Asia-Pacific trial, although not all patients had chemoembolization-refractory HCC in these studies [25, 26]. In Japan, sorafenib is usually used after both chemoembolization and hepatic arterial infusion chemotherapy fail to control the disease, although there has been few data that hepatic arterial infusion chemotherapy is useful

in chemoembolization-refractory patients. One prospective report has described that hepatic arterial infusion chemotherapy using a fine-powder formulation of cisplatin appears to have only modest activity [27].

In conclusion, not only chemoembolization but also locoregional treatments, hepatic arterial infusion chemotherapy, and sorafenib are incorporated for the treatment algorithm of patients with intermediate-stage HCC depending on the tumor number and size. Liver function reserve in Japan, unlike chemoembolization, is the only

standard treatment in BCLC staging. Since these differences in the treatment tactics are mostly attributable to the inhomogeneity of BCLC stage B patients, subclassification of BCLC stage B and its validation are necessary to allocate therapy appropriately in the new substaging system.

Disclosure Statement

The authors declare that no financial or other conflicts of interest exist in relation to the content of this article.

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