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Sub-classification of intermediate-stage (Barcelona Clinic Liver Cancer stage-B) hepatocellular carcinomas

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Abstract

Hepatocellular carcinoma (HCC), the fifth most common cancer in the world, shows increasing incidence worldwide. Curative treatments such as hepatectomy, liver transplantation, and radiofrequency ablation are applied in only 30%-60% of cases. Most remaining

patients receive transarterial chemoembolization (TACE). Patients with intermediate-stage HCCs are regarded as good candidates for TACE. However, the intermediate stage includes non-homogeneous patients. Some movements are underway to stratify patients using prognostic factors to identify patient groups exhibiting greater benefit from TACE than other patient groups. This review describes two substaging systems that subclassify intermediate-stage HCCs and discusses the importance of dividing intermediate-stage patients.

Key words: Hepatocellular carcinoma; Intermediate-stage; Chemoembolization; Child-Pugh score; Prognosis

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Core tip: There are movements to divide the intermediate stage of hepatocellular carcinoma (HCC) because of the diversity of intermediate-stage patients. This review describes two substaging systems (Bolondi substaging system and substaging system proposed by Japanese Society of Transcatheter Hepatic Arterial Embolization) that subclassify intermediate-stage HCCs and discusses the importance of dividing intermediate-stage patients.

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INTRODUCTION

Hepatocellular carcinoma (HCC), the fifth most common cancer in the world, shows increasing incidence worldwide^[1]. Curative treatments such as hepatectomy, liver

Table 1 Substaging of intermediate-stage; Bolondi substaging system

Intermediate substage	B1	B2	B3	B4
Child-Pugh score	5-7	5-6	7	8-9
Up-to-7 criterion	In	Out	Out	Any
1 st option	TACE	TACE or TARE		BSC
Alternative	LT TACE + Ablation	Sorafenib	Research trial TACE Sorafenib	LT
Median survival time (mo)	41.0	22.1	14.1	17.2

Modification from Reference^[9,11]. TACE: Transarterial chemoembolization; TARE: Transarterial radioembolization; LT: Liver transplantation; BSC: Best supportive care.

transplantation, and radiofrequency ablation (RFA) are applicable in only 30%-60% of patients having HCCs^[1]. Most remaining patients undergo transarterial chemoembolization (TACE) as a palliative treatment. Several studies have demonstrated that TACE provides better survival than the best supportive care^[2-5].

The Barcelona Clinic Liver Cancer (BCLC) staging system, which has come to be accepted world-wide for clinical practice, divides HCC patients according to five stages (0, A, B, C, and D) depending on tumor-status-related parameters (size, number, vascular invasion, N1, M1), liver function (Child-Pugh grade), and health status (ECOG)^[6]. In fact, TACE is recommended as the standard treatment, which is positioned as a palliative treatment, of BCLC stage-B HCC patients^[2]. Actually, BCLC stage-B, which is defined as intermediate stage, includes diverse patients having Child-Pugh grade-A and grade-B liver function with four or more tumors irrespective of size, or 2-3 tumors larger than 3 cm in maximal diameter, in the absence of cancer-related symptoms, macrovascular invasion, or extrahepatic spread^[2]. Untreated patients at an intermediate stage - BCLC stage-B reportedly present median survival of 16 mo^[3,7], or 49% at two years^[8]. TACE can extend the survival of these patients to a median of up to 19-20 mo according to RCT and meta-analysis of pooled data^[3].

Although inhomogeneous patients make up the intermediate stage, it remains unclear whether there might be any subgroup stratification for which TACE can provide better prognosis than others. To explore this question, there are movements underway to divide the intermediate stage into several substages to stratify patients based on the prognosis following TACE.

This review presents subclassification of the intermediate stage and describes new strategies to treat intermediate-stage HCCs.

BOLONDI SUBGROUP SYSTEM

Bolondi *et al*^[9] advocated the division of the intermediate

stage to tailor therapeutic interventions based on the evidence and expert opinion available to date. To distinguish major from minor tumor burdens, which would influence the allocation of patients to TACE/TAE or to alternative treatments such as radioembolization, transplantation or sorafenib, they selected the up-to-seven (up-to-7) criterion, which enables identification of a subgroup of patients with long survival after transplantation^[10]. Regarding liver function, subgroups are defined by the Child-Pugh score and grade. They divided the intermediate stage into four sub-stages and suggest recommended treatments based on each sub-stage (Table 1).

Recently, one study validated this substaging system^[11]. The system respectively classified 101 (21.7%), 232 (49.8%), 35 (7.5%), and 98 (21.0%) patients as B1, B2, B3, and B4. Median survival times were 41.0 mo, 22.1 mo, 14.1 mo, and 17.2 mo, respectively, in B1, B2, B3, and B4 patients. A significant difference was found in median survival time between B1 and B2 ($P < 0.001$), and B2 and B3 ($P = 0.004$), but not between B3 and B4 ($P = 0.48$).

In the Bolondi substaging system, TACE is recommended as the first therapeutic option for patients with well-preserved liver function (Child-Pugh scores 5-7) (B1 and B2) (Table 1). However, TACE is not recommended as the first therapeutic option in patients with Child-Pugh scores of 8 and 9 (B4). Furthermore, research trials are recommended for patients with Child-Pugh score 7 liver function and HCCs beyond up-to-7 criterion.

PROPOSAL FROM THE JAPANESE SOCIETY OF TRANSCATHETER HEPATIC ARTERIAL EMBOLIZATION

The Japanese Society of Transcatheter Hepatic Arterial Embolization (JSTHAE) proposed an intermediate-stage subclassification using 4-of-7 cm (4-of-7 cm) criterion and the Child-Pugh score^[12,13]. Yamakado *et al*^[12] demonstrated that four tumors measuring 7 cm or smaller (4-of-7 cm criterion) and Child-Pugh grade-A were favorable prognostic factors for intermediate-stage HCC patients. First, they divided the intermediate stage into four subgroups by combination of 4-of-7 cm (in and out) and Child-Pugh grade (A and B). A patient subgroup including patients having a Child-Pugh grade-A liver profile and HCC lesions within the 4-of-7 cm criterion exhibited significantly better overall survival than the other three patient subgroups^[12]. However, it was impossible to find a patient subgroup that does not reap a benefit from TACE. They sought poor prognostic factors by assessing the relation between the Child-Pugh score and prognosis after TACE^[13]. Two-year survival rates were 77.5% in Child-Pugh-5 patients ($P = 0.047$, vs Child-Pugh-6), 65.1% in Child-Pugh-6 patients (P

Table 2 Substaging of intermediate-stage; proposal from Japanese society of transcatheter hepatic arterial embolization

Intermediate-substage	B1	B2	B3
Child-Pugh score	5-6	5-8	9
4-of-7 cm criterion	In	In (CP 7-8) or Out (CP 5-8)	Any
2-yr survival rate	77.2%	59.5%	16.7%
Median survival time (mo)	40.5	28.1	13.0

CP: Child-Pugh.

= 0.038 vs Child-Pugh-7), 51.3% in Child-Pugh-7 patients ($P = 0.30$ vs Child-Pugh-8, $P = 0.034$ vs Child-Pugh-9), 50.3% in Child-Pugh-8 patients ($P = 0.0065$ vs Child-Pugh-9), and 16.7% in Child-Pugh-9 patients. Although patient subgroups having Child-Pugh classes 5-8 reaped a survival benefit from TACE compared to those assessed by patient history (2-year survival rate of 22%-27%), patients having Child-Pugh score-9 did not reap a benefit from TACE^[4,8].

They divided the intermediate-stage into three substages based on the 4-of-7 cm criterion and Child-Pugh score (Table 2). One substage (B1) consisted of Child-Pugh grade-A patients with HCC lesions within the 4-of-7 cm criterion. The second substage (B2) included patients other than B1 and B3. The third substage (B3) included patients with Child-Pugh score 9. The 2-year survival rates and the median survival time were 77.2% and 40.5 mo in B1, 59.5% and 28.1 mo in B2 and 16.7% and 13.0 mo in B3. Significant differences were found in survival between patient groups: B1 vs B2 ($P < 0.0001$) and B2 vs B3 ($P = 0.0014$).

DISCUSSION

The problem of the BCLC staging system lies in its simplicity of recommending only TACE, although the intermediate-stage includes an extremely diverse set of patients. This review introduced two substaging systems to divide intermediate stage patients. The review shows that patient subgroups that benefit more from TACE than other subgroups can be identified. Subgroups including patients having a better liver profile (Child-Pugh grade-A) and less tumor burden (up-to-7 or 4-of-7 cm criterion) benefit more. Furthermore, both substaging systems reveal patient subgroups that do not reap a benefit from TACE. Bolondi *et al*^[9] do not recommend TACE in Child-Pugh score of 7 patients beyond up-to-7 criterion (B3) and Child-Pugh score of 8-9 patients, irrespective of the HCC condition (B4). However, Yamakado *et al*^[13] pointed out that TACE is not as beneficial as patient history for patients with Child-Pugh score 9. Little controversy has arisen for alternatives to TACE for patients with poor liver function.

Two prognostic scoring systems have been recently developed in patients with HCC who undergo HCCs^[14,15].

Kadalayil *et al*^[14] have proposed the Hepatoma arterial-embolisation prognostic (HAP) score to predict clinical outcomes after TACE. They use the serum albumin level, bilirubin level, alpha-fetoprotein level, and tumor size of 7 cm as prognostic factors. Huckle *et al*^[15] have developed the Selection for TrAnsarterial chemoembolisation TrEatment (STATE) score in order to guide the decision for the first treatment with TACE in patients with HCCs. They used the serum albumin level, up-to-seven criteria, and C-reactive protein^[15].

There have been no consensus which subclassification or scoring system is superior to others.

Recent studies have demonstrated the utility of hepatectomy and RFA even in intermediate-stage HCC patients^[16-18]. Results of many studies have demonstrated that tumor diameter is not a limitation of hepatectomy with 5-year survival rates of 20%-30% in patients with large HCCs greater than 10 cm that are much better than those derived from patient history^[19,20]. Although therapeutic results following hepatectomy worsen as the tumor number increases, these results are better than those following other palliative treatments and supportive care^[21,22]. No evidence exists for a tumor number that provides a survival benefit to patients undergoing surgical intervention, although a tumor number of up to three has been widely accepted as a good indication for locoregional treatments such as RFA. Therefore, hepatectomy is recommended when the tumor number is 3 or fewer, irrespective of tumor size.

Bolondi *et al*^[9] recommended a combination of RFA with TACE as the alternative to TACE in B1 subgroup patients (Table 1). Yamakado *et al*^[13] reported the application of curative treatments such as hepatectomy and RFA in the intermediate stage. However, it is not clear for two criteria derived from the tumor number and size: Results show that the up-to-seven criterion and the 4-of-7 cm criterion can be useful milestones for locoregional treatment in patients with intermediate-stage HCCs.

Bolondi *et al*^[9] suggested the use of sorafenib in B2 and B3 substage patients (Table 1). After TACE fails to control HCC lesions, sorafenib is recommended to treat HCCs^[23]. The median survival times after sorafenib administration were 10.7 mo in SHARP trial and 6.5 mo in the Asia-Pacific trial, although not all patients had TACE-refractory HCC in these studies^[23,24]. According to Japanese guidelines, sorafenib is usually used after both TACE and hepatic arterial infusion chemotherapy fail to control disease, although few data exist to show that hepatic arterial infusion chemotherapy is useful for prolonging survival of TACE-refractory patients^[25,26]. One prospective study featuring hepatic arterial infusion chemotherapy using a suspension of iodized-oil and cisplatin has shown the encouraging one-year survival rate of 57% with median survival time of 13 mo in patients with TACE-refractory HCCs^[27]. However, another study featuring fine-powder formulation of cisplatin has shown limited clinical utility, with a one-

year survival rate of 27% and median survival time of 7.1 mo in patients with TACE failure HCCs^[28].

In conclusion, movements to divide the intermediate stage of HCCs are underway because of the diversity of intermediate-stage patients. Validation of the substaging system must be done to allocate therapy appropriately in the new substaging systems, not only with TACE but also locoregional treatments such as hepatectomy and RFA, liver transplantation, hepatic arterial infusion chemotherapy, sorafenib, and best supportive care depending on the tumor number and size, and liver function reserve.

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