

Evolution and current status of the subclassification of intermediate hepatocellular carcinoma

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Abstract

The staging and treatment of intermediate hepatocellular carcinoma (HCC) remains controversial. According to the recommendations of Barcelona Clinic Liver Cancer staging system, patients with intermediate HCC are candidates for transcatheter arterial chemoembolization. However, not all patients with intermediate HCC benefit from transcatheter arterial chemoembolization. Therefore, it is meaningful to propose a novel staging system of intermediate HCC in order to allocate different treatments for different subgroups. Bolondi *et al* proposed the first subclassification system of intermediate HCC. Subsequently, investigators performed studies to validate the feasibility of Bolondi's criteria and proposed several novel staging systems. The present study reviewed the literatures and provided a general overview of the evolution and current status of the subclassification of intermediate HCC. We propose to expand the indication of liver resection and add radical treatments as the first option of the treatment for patients with intermediate HCC.

Key words: Subclassification; Intermediate hepatocellular carcinoma; Treatment; Staging; Transcatheter arterial chemoembolization; Liver resection

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Core tip: The present study reviewed the literatures and provided a general overview of the evolution and current status of the subclassification of intermediate hepatocellular carcinoma. We propose to expand the indication of liver resection and add radical treatments as the first option of the treatment for patients with intermediate hepatocellular carcinoma.

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INTRODUCTION

Hepatocellular carcinoma (HCC) ranks the fifth cause of cancer-associated mortality worldwide, and > 50% of patients with HCC are diagnosed in China^[1,2]. Considering the etiology of HCC, hepatitis C virus infection and alcohol abuse are the main causes of HCC in Western countries. However, patients in China are mainly derived from the trilogy chronic hepatitis B virus infection-liver cirrhosis-HCC onset^[3]. Novel staging and treatment recommendations are critical for improving the prognosis of HCC. The Barcelona Clinic Liver Cancer (BCLC) staging system is widely accepted by investigators and endorsed by the American Association for the Study of Liver Diseases and European Association for the Study of the Liver^[4]. According to the recommendations of BCLC staging system, patients with very early and initial stage HCC within the Milan criteria and without associated diseases are suitable for radical treatments, including liver transplantation, liver resection and radiofrequency ablation. Patients with intermediate HCC (BCLC B stage) are recommended to receive transcatheter arterial chemoembolization (TACE), which is a palliative treatment^[5]. However, 50% of patients with HCC are diagnosed at intermediate stage when the first presentation of symptoms occur^[6], and the prognosis of these patients remains unsatisfactory.

Intermediate HCC comprises heterogenous patients with varying tumor burden, liver function and performance status, and TACE cannot provide survival benefit for all these patients. The survival benefit of radical treatments for intermediate HCC has been explored in recent years. Mazzaferro *et al*^[7] analyzed the survival of patients beyond the Milan criteria based on largest tumor size, tumor nodule and microvascular invasion (MVI). Patients beyond the Milan criteria but within the sum of largest tumor size and tumor number < 7 had comparable 5-year survival rates to those within the Milan criteria. Thus, they proposed novel criteria for selecting patients with HCC for liver transplantation, called the “ up to-7 criteria”^[7]. To improve the prognosis of intermediate HCC, it is of great importance to divide these patients into subgroups and allocate feasible treatments to different subgroups. Bolondi *et al*^[8] proposed a subclassification of intermediate HCC in 2012. The Bolondi criteria sub-divides intermediate HCC into 4 groups and provides first-line and alternative treatment options for different subgroups^[8]. Numerous subsequent studies were conducted to validate or clarify this subclassification system. Certain studies demonstrated the ability of the Bolondi criteria in predicting prognosis of intermediate HCC and supported the application of this system in clinical practice^[9-11]. By contrast, other studies advocated to modify this system and proposed novel subclassification systems^[12-14]. To date, the staging and management of intermediate HCC remains controversial. The present review aims to provide a clear summary of the evolution and general view of current status of the subclassification of intermediate HCC.

PROPOSAL AND VALIDATION OF THE BOLONDI CRITERIA

Patients with intermediate HCC are defined as those with a single tumor > 5 cm, or with 2-3 > 3 cm in maximum diameter, or with > 3 tumors regardless of tumor size, without portal vein thrombosis and extra-hepatic metastasis^[8]. Due to the varying tumor burden, liver function and physical status, patients differ significantly in terms of survival outcomes and treatment response. Bolondi *et al*^[8] proposed to subdivide intermediate HCC into 4 subgroups: Stage B1, which comprises patients with compensated cirrhosis and preserved liver function, who have a Child-Pugh score of 5-7, are within the up to-7 criteria, and have a ECOG PS completely preserved (PS0). The treatment recommendation is controversial in this subgroup, with TACE being recommended to be the first option and liver transplantation or TACE plus ablation being considered alternative options. Stage B2 comprises patients with Child-Pugh A, who are beyond the up to-7 criteria and have good well PS (PS0). TACE or transarterial radioembolization are suggested for these patients, and sorafenib is

recommended as an alternative option. Stage B3 comprises patients with Child-Pugh score of 7, who are beyond the up to seven criteria and have a good PS (PS0). No particular treatment recommendation for this subgroup has been provided thus far, although these patients may be suitable for inclusion in a research randomized clinical trial, with TACE or sorafenib being potential treatment options. Stage B4 comprises patients with decompensated Child-Pugh class B (score of 8 or 9) with severe ascites or jaundice. The treatment allocation for this subgroup is also controversial, the first recommendation is basic supportive care and the alternative option is liver transplantation (Table 1).

Ciria *et al*^[9] performed a retrospective analysis of 80 patients with intermediate HCC, and subdivided these patients according to the Bolondi criteria. Taken together, the study revealed that the 5-year survival rate did not differ between the liver resection group and the TACE group, in the subgroups of intermediate HCC, the 5-year survival rate was higher in stage B1 when compared with stages B2 and B3-4 who had been subjected to liver resection or TACE. However, the overall survival was not significantly different among continuous substages. By multivariate analysis, total bilirubin and subclassification stages B2 and B3-4 *vs* B1 to be independent risk factors of survival. Ciria *et al*^[9] proposed to perform liver resection for stage B1 and partial of patients at B2 and B3-4 stage when the pathological and anatomical criteria were matched. Other retrospective studies obtained similar results to those reported by Ciria *et al*^[9]. Two previous studies did not find significant difference in survival outcomes among continuous subgroups according to the Bolondi criteria^[13,14], while a previous study even reported poor survival outcomes in patients at stage B3 compared with stage B4^[14]. However, several studies also obtained different results compared with above studies. Various studies observed significantly different survival outcomes among continuous subgroups of patients with intermediate HCC. Therefore, they recommended that the Bolondi criteria could feasibly predicting the prognosis of intermediate HCC and advocated the allocation of such criteria in clinical practice^[9-11]. In addition, several studies demonstrated that the subclassification of intermediate HCC was an independent prognostic factor of survival outcomes^[9,11,12]. In summary, Bolondi criteria can predict the prognosis of intermediate HCC to certain extent. However, additional prospective studies are required to clarify its feasibility (Table 2).

PROPOSAL OF A NOVEL SUBCLASSIFICATION OF INTERMEDIATE HCC

Although the feasibility of the Bolondi criteria have been validated by numerous studies, there are certain limitations of this subclassification system. First, the Bolondi criteria stratify intermediate HCC based on 4 factors, but, ECOG PS is a relatively subjective factor; thus, it is difficult to definitely evaluate it and does not discriminate between cancer or cirrhosis-associated symptoms. Second, none of the radical treatments are recommended as first option for intermediate HCC. However, recent studies have demonstrated the survival benefit of radical treatments for intermediate HCC, and liver resection and liver transplantation have been demonstrated to prolong survival in superselective patients with intermediate HCC^[15,16]. Third, no first treatment option for stage B3 is recommended by the Bolondi criteria, which limits the application of this subclassification system in clinical practice.

In order to develop a more reasonable subclassification system for intermediate HCC, previous studies have attempted to modify the Bolondi criteria in recent years. Yamakado *et al*^[17] subdivided BCLC B stage based on the tumor number, size and Child-Pugh grade of patients receiving TACE. They observed that presence of 4 tumors of 7 cm in diameter and Child-Pugh score were significant prognostic factors of intermediate HCC. Therefore, the authors subdivided intermediate HCC into 4 substages based on these two prognostic factors. According to this subclassification, stage B1 had better survival than stage B2, B3 and B4. However, no significant difference was observed in survival among continuous stages (Table 3). The authors concluded that the best candidates for TACE were patients with Child-Pugh grade A and HCC lesions with the tumor criteria of exhibiting 4 tumors and 7 cm in diameter. Subsequently, Kudo *et al*^[18] proposed the Kinki Criteria criteria based on a modified version of the Bolondi criteria. Intermediate HCC in this case was subclassified into 3 stages based on Child-Pugh score, the Milan criteria and the up to-seven criteria. The Kinki Criteria is similar to the Bolondi criteria to certain extent, although the Kinki Criteria is simplified version and the treatment recommendations are more rational, since even radical treatments are recommended as first option for selected patients. Thus, the Kinki Criteria appears to provide more strategies than the Bolondi criteria

Table 1 Bolondi criteria

BCLC sub-stage	B1	B2	B3	B4
CPT score	5-7	5-6	7	8-9 ¹
Beyond Milan and within Ut-7	In	Out	Out	Any
ECOG (tumor related) 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 ²

¹With severe/refractory ascites and/or jaundice.

²Only if Up-to-7 IN and PS0. CPT: Child Pugh score; BSC: Best supportive care; LT: Liver transplantation; SOR: Sorafenib; TACE: Transcatheter arterial chemoembolization; TARE: Transarterial radioembolization; PVT: Portal vein thrombosis; Ut-7: Up to-7 criteria.

for intermediate HCC. However, further studies are required to clarify the predicting value of prognosis of the Kinki Criteria (Table 4). Arizumi *et al.*^[19,20] compared survival outcomes among subgroups according to the Kinki Criteria, they noticed significant differences in survival among continuous subgroups. However, no significant difference in survival between BCLC A and B1 stage or BCLC C and B3 stage was observed^[19,20]. Wang *et al.*^[12] validated the feasibility of the Bolondi criteria in predicting prognosis of intermediate HCC, and they demonstrated that alpha-fetoprotein (AFP) levels > 200 ng/mL and AST levels > 40 IU/L were prognostic factors. Thus, they proposed stratifying stages B1 and B2 according to AFP levels. Stages B1 and B2 were consequently subdivided into B1a (AFP < 200 ng/mL) and B1b (AFP > 200 ng/mL) and B2a (AFP < 200 ng/mL) and B2b (AFP > 200 ng/mL), respectively. The newly proposed substaging system comprises modified B1, B2 and B3 (Table 5). Survival difference is observed among continuous substages of this modified criteria.

Recently, Lee *et al.*^[21] proposed a subclassification system similar to that of Yamakado, which was based on Child-Pugh score (A or B) and tumor size (< 5 or > 5 cm). This newly proposed subclassification system comprises 3 substages, and survival differences were observed among continuous substages (Table 6). Kim *et al.*^[14] compared survival outcomes in different subgroups according to the Bolondi criteria, but no significantly differences in survival among substages were observed. Thus, they proposed a novel subclassification system based on Child-Pugh score, within up to-11 and ECOG PS. Instead of the up-to-7 criteria, up-to-11 was used as a measure of tumor burden. When patients were stratified using this substaging system, significantly differences in survival were observed among continuous substages of intermediate HCC following TACE treatment (Table 7). A recent study proposed a subclassification system based on the up to-7 criteria and the levels of two serum biomarkers, namely AFP and des-r-carboxy prothrombin^[22]. This subclassification system subdivides BCLC B stage into B1, B2 and B3 (Table 8). Notably, B2 stage in this staging system is not clearly defined and treatment recommendation is not provided, which limits its utilization in clinical practice.

DISCUSSION

The clinicopathological characteristics of patients with intermediate HCC vary in tumor burden, liver function and physical status. The treatment and subclassification of intermediate HCC remains controversial. Therefore, it is necessary to develop a novel substaging system for intermediate HCC. Bolondi *et al.*^[8] proposed the first substaging system and provided treatment options for each substage. Subsequently, several studies investigated its feasibility, and a number of them proposed modifying this system. The Bolondi criteria subdivide intermediate HCC based on liver function, tumor burden and ECOG PS. However, ECOG PS is difficult to be objectively evaluated, and treatment recommendation does not include radical treatments, which limits the utilization of this system.

Subsequent studies proposed various novel subclassification systems. Several of them stratified intermediate HCC based on prognostic factors of survival, and reported the predicting value for survival of these systems. Notably, radical treatments were recommended as treatment options for patients with intermediate HCC^[18], which may prolong short and long-term survival of intermediate HCC. However, there are various limitations of these newly proposed systems. First, all these studies were retrospective analyses of cohort of consecutive patients, thus,

Table 2 Studies validation and modification of Bolondi criteria

Patients (n)	Treatment	Median follow-up	Ref.	B1	B2	B3	B4	Independent risk factor of survival
80	LR, TACE	28.19 mo	Ciria <i>et al</i> ^[9]	OS rate: 43.75%; 5-yr survival rate (62.9%)	OS rate: 40%; 5-yr survival rate (28.1%)	OS rate: 11.25%; 5-yr survival rate (28.1%)	OS rate: 5%; 5-yr survival rate (15.1%)	Total bilirubin, subclassification stages B2 and B3-4 vs B1
90	TAE	NR	Scaffaro <i>et al</i> ^[10]	Mean OS: 33.6 mo	Mean OS: 28.6 mo	Mean OS: 19.0 mo	Mean OS: 13.0 mo	NR
580	TAE	NR	Wang <i>et al</i> ^[12]	Median OS: 28.8 mo; 1, 3, 5-yr survival rate: 80%, 39.5%, 21.4%	Median OS: 15.6 mo; 1, 3, 5-yr survival rate: 59.2%, 23%, 13.9%	Median OS: 6 mo; 1, 3, 5-yr survival rate: 39.5%, 11.2%, 7.4%	Median OS: 9.6 mo; 1, 3, 5-yr survival rate: 46.2%, 23.1%, 7.7%	AFP level, AST, and substage B2, B3, and B4 vs B1
254	TACE, LR, OLT	15.4 mo	Weinmann <i>et al</i> ^[13]	Median OS: 31.9 mo; 1, 2-yr survival rate: 82.93%, 60.98%	Median OS: 26.9 mo; 1, 2-yr survival rate: 72.9%, 52.44%	Median OS: 13.5 mo; 1, 2-yr survival rate: 65%, 40%	Median OS: 10.9 mo; 1, 2-yr survival rate: 48.98%, 38.35%	Total bilirubin, MELD score, presence of ascites, and the therapies resection and OLT.
269	NR	NR	Giannini <i>et al</i> ^[11]	Median OS: 25 mo	Median OS: 16 mo	Median OS: 9 mo	Median OS: 5 mo	Subclassification of BCLC B, MELD score, and platelet count.
821	TACE	NR	Kim <i>et al</i> ^[14]	1, 3, 5-yr survival rate: 95.1%, 66.4%, 41.2%	1, 3, 5-yr survival rate: 78.4%, 33%, 20.3%	1, 3, 5-yr survival rate: 59.3%, 10.5%, 0	1, 3, 5-yr survival rate: 57.4%, 43.7%, 17%	NR

LR: Liver resection; OS: Overall survival; TACE: Transcatheter arterial chemoembolization; OLT: Orthotopic liver transplantation; MELD: Model of end-stage liver disease; NR: Not reported.

further prospective studies are required to clarify the feasibility of these systems. Second, only a few newly proposed systems provide treatment recommendations for a specific substage, resulting in difficult decision making in clinical practice.

CONCLUSION

Substaging and treatment of intermediate HCC remains confounded for clinicians. Since the survival benefit of radical treatments has been previously demonstrated^[23,24], the present study proposes expanding the indication of radical treatments and adding radical treatments into first option for patients with intermediate HCC.

Table 3 Yamakado criteria

Substage	B1	B2	B3	B4
Child-Pugh grade	A	A	B	B
4 tumors and 7 cm of maximal diameter	Within	Beyond	Within	Beyond

Table 4 Kinki Criteria

BCLC substage	B1	B2	B3	
Child-Pugh score	5-7	5-7	8-9	
Beyond Milan and within up-to-7	In	Out	Any	
Sub-substage			In	Out
Concept of treatment strategy	Curative intent	Non-curative, palliative	B3-a	B3-b
Treatment option	Resection Ablation Superselective c-TACE	DEB-TACE ¹ HAIC ² Sorafenib ³	Transplantation Ablation Superselective c-TACE	HAIC Selective DEB-TACE
Alternative	DEB-TACE (large, C-P 7) B-TACE ⁴	c-TACE	DEB-TACE B-TACE, HAIC	BSC

¹DEB-TACE is recommended for huge tumors that are > 6 cm;

²HAIC is recommended for multiple tumors > 6;

³Sorafenib is recommended for patients with liver function of Child-Pugh score 5 and 6;

⁴B-TACE is recommended for fewer tumors. TACE: Transcatheter arterial chemoembolization; c-TACE: Conventional subsegmental lipiodol TACE; DEB-TACE: TACE with drug-eluting beads; B-TACE: Balloon occluded TACE; HAIC: Hepatic arterial infusion chemotherapy; BSC: Best supportive care; C-P: Child-Pugh score; BCLC: Barcelona Clinic Liver Cancer.

Table 5 Wang criteria

Bolondi substage	Modified B1	Modified B2	Modified B3
B1a (AFP < 200 ng/mL)	B1a		
B1b (AFP > 200 ng/mL)		B1b + B2a	
B2a (AFP < 200 ng/mL)			
B2b (AFP > 200 ng/mL)			B2b + B3
B3			

AFP: Alpha-fetoprotein.

Table 6 Lee criteria

Substage	B1	B2	B3
Tumor size < 5 cm	In	Out	Out
Child-Pugh	Not concerned	A	B

Table 7 Kim criteria

BCLC substage	B1	B2	B3	
Child-Pugh	A	A	B	B
Within up to-11	In	Out	In	Out
ECOG performance status (tumor related)	0	0	0	0
Portal vein thrombosis	No	No	No	No

Table 8 Kimura criteria

Substage	B1	B2	B3
Within up to-7 criteria	In	Other than those include in B1 and B3	Out
DCP < 150 mAU/mL	In		Not concerned
AFP > 100 ng/mL	Not concerned		In

AFP: Alpha-fetoprotein; DCP: Des-r-carboxy prothrombin.

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