

Subclassification of BCLC B Stage Hepatocellular Carcinoma and Treatment Strategies: Proposal of Modified Bolondi's Subclassification (Kinki Criteria)

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Key Words

BCLC staging · Intermediate stage · Hepatocellular carcinoma · Transarterial chemoembolization

Abstract

Intermediate stage hepatocellular carcinoma (HCC) is a very heterogeneous tumor in terms of tumor size (>3 cm ~ over 10 cm), tumor number (4 ~ over 20) and liver function (Child-Pugh score 5–9). However, transarterial chemoembolization is the only recommended treatment option according to the Barcelona Clinic Liver Cancer (BCLC) staging. Bolondi's subclassification of BCLC B stage is feasible; however, there are several weak points. Therefore, by modifying Bolondi's subclassification, we have proposed a more simplified subclassification, Kinki criteria. The Kinki criteria consist of 2 factors: liver function (Child-Pugh score 5–7 or 8, 9) and tumor status (Beyond Milan and within up-to-7 criteria; IN and OUT). The Kinki criteria classifies BCLC B stage from B1 (Child-Pugh score 5–7 and within up-to-7), B2 (Child-Pugh score 5–7 and beyond up-to-7) and B3 (Child-Pugh score 8, 9 and any tumor status). These criteria are simple and easy to apply to clinical practice. Therefore, these criteria will stratify the heterogeneous population of BCLC B group patient well and give the treatment indication according to each substage. These criteria should be further validated both retrospectively and prospectively.

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Introduction

The Barcelona Clinic Liver Cancer (BCLC) group defines intermediate-stage hepatocellular carcinoma (HCC) as BCLC stage B. The BCLC staging system is applied in the guidelines published by the American Association for the Study of Liver Diseases (AASLD) [1] and the guidelines published collaboratively by the European Association for the Study of the Liver and the European Organization for Research and Treatment of Cancer [2]. However, the concept of intermediate-stage HCC is absent from the Japanese Evidence-based Clinical Practice Guidelines for Hepatocellular Carcinoma [3], the Consensus-based Clinical Practice Guideline for the Management of Hepatocellular Carcinoma [4, 5] and the guidelines published by the Asian Pacific Association for the Study of the Liver (APASL) [6]. If we consider the concept of intermediate-stage HCC for Japanese patients, patients with Child-Pugh grade A or B liver function and tumor size >3 cm or number of tumor >3 nodules and no vascular invasion or extrahepatic spread are included. In the BCLC staging system, only transarterial chemoembolization (TACE) is indicated for intermediate-stage HCC [7, 8] (fig. 1). However, the clinical manifestations of intermediate-stage HCC range extensively from those observed in patients with near early-stage HCC (who are candidates for curative treatment) to those observed in patients with near end-stage HCC

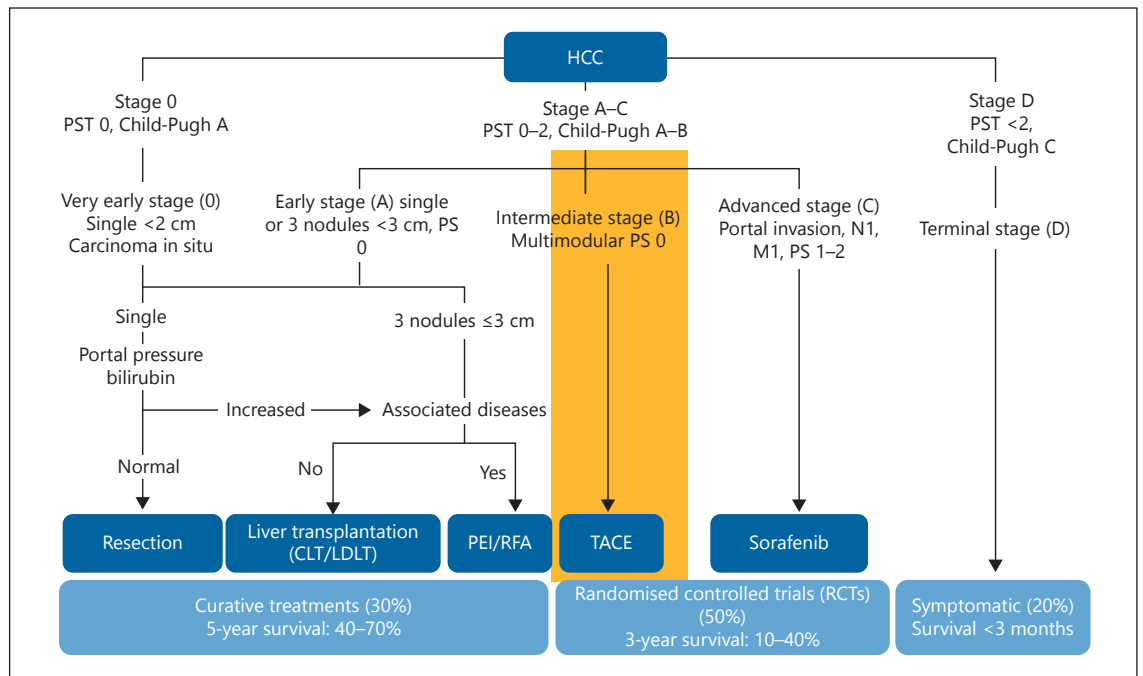


Fig. 1. Proposed AASLD-JNCI modification of BCLC staging: unresectable HCC.

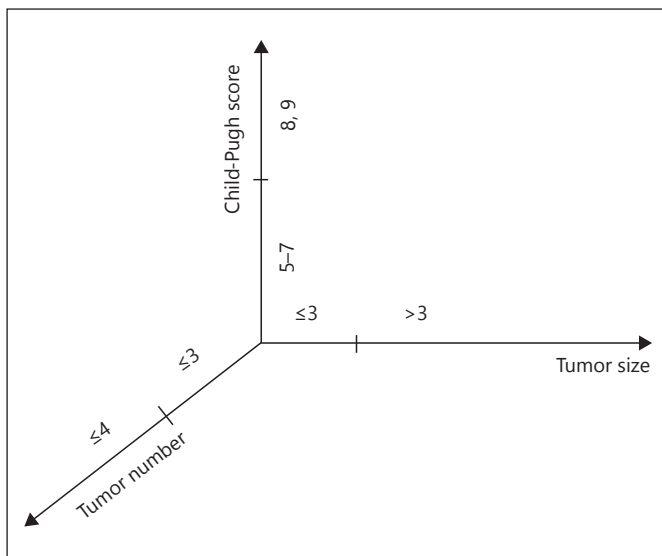


Fig. 2. Three dimensional factors (size, number and CP score) complicate subclassification of BCLC-B stage.

Table 1. Heterogeneity of intermediate-stage HCC

Liver function	Child-Pugh score 5–9
Tumor size	>5 cm ~ over 10 cm
Tumor number	≥ 4 ~ over 20 nodules

(Child-Pugh score of 9 who are candidates for best supportive care (BSC)).

In other words, BCLC staging indicates that intermediate-stage HCC should be treated only by TACE. However, in the real clinical setting, it is not always the case because of its heterogeneity in terms of liver function and/or tumor status. Therefore, subclassification of this heterogeneous patient population and indication of treatment strategy according to its substage is an extremely important issue to address.

Heterogeneity of Intermediate-Stage HCCs

BCLC stage B ranges from Child-Pugh scores 5–9 and thus includes an extremely large patient population even from the hepatic functional reserve alone. BCLC intermediate stage also includes patients with multiple nodules from 4 nodules to over 10–20 bilobar tumors (table 1). Moreover, although tumor size is not clearly defined in the BCLC staging system, tumors beyond Milan criteria (single tumor >5 cm or multiple nodules ≥ 4) are assumed to be classified as intermediate stage. This is a very complicated situation since treatment strategy should be decided based on 3-dimensional factors such as tumor size, number and Child-Pugh score (fig. 2). An extreme ex-

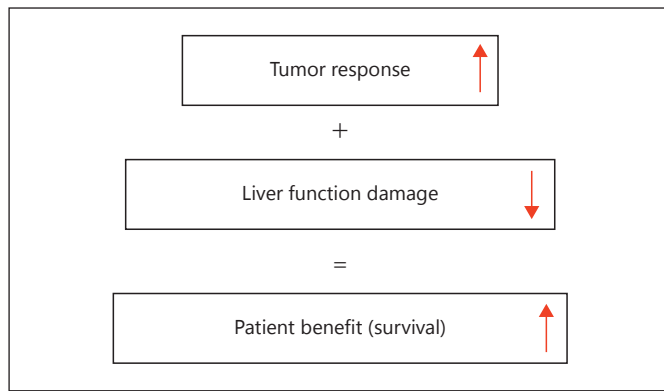


Fig. 3. Patient benefit (survival) from TACE.

ample may be that surgical resection is indicated for patients with less than 3 tumors that are slightly >3 cm in size or single tumor >5 cm, as long as they have well preserved hepatic functional reserve. A combination of preceding TACE and radiofrequency ablation (RFA) [9] can be performed in patients with ≥ 3 HCC nodules or a single 3–5 cm HCC. Furthermore, these large tumors may be good indications for RFA if bipolar RFA equipment is used. In addition, the aim of conventional subsegmental Lipiodol TACE (cTACE) is curative treatment, and complete response may be achieved in patients with 4–6 small tumors by superselective catheterization to a site near individual tumors, where Lipiodol and a gelatin sponge are injected, thereby inducing partial liver infarction. In other words, superselective cTACE is a highly advanced treatment technique that can be frequently used as curative treatment. However, indications for curative superselective cTACE are limited by the size and number of tumors. Therefore, it is not surprising that superselective cTACE is rarely performed in other countries, outside Japan.

Recently, the use of TACE with drug-eluting beads (DEB-TACE) that contains anti-cancer agents is becoming widespread. Specifically, DEB-TACE has been used as palliative treatment tool for mass reduction in patients who are not indicated for curative cTACE because of relatively large-sized HCCs. Because a decline in hepatic functional reserve and post-embolization syndrome are both mild after DEB-TACE as compared with cTACE, DEB-TACE is thought to be more suitable than cTACE when treating patients with a huge HCC that is >5 cm in size.

Patient benefits from TACE depend on the maximization of the tumor response as well as minimization of the liver function damage caused by TACE (fig. 3). In addition, cTACE is not only ineffective in patients with mul-

iple lesions that have spread to both lobes, but also worsens the hepatic functional reserve of patients. These patients are supposed to benefit more from hepatic arterial infusion chemotherapy (HAIC) or sorafenib. Moreover, taking into account the limited efficacy of DEB-TACE in bilobar multinodular HCCs, it may be necessary to select HAIC as the first treatment choice for bilobar multinodular HCCs. Because preservation of liver function determines the prognosis of patients with multiple bilobar HCC nodules, treatment methods that could minimize the damage of liver function should be selected when the patient has poor hepatic liver function. Superselective cTACE is recommended even in such cases, since superselective cTACE is supposed to minimize the damage of hepatic function and maximize the tumor response.

When patients have large or many tumors and liver function reserve near 7 on the Child-Pugh scoring system, DEB-TACE or HAIC rather than cTACE is recommended to minimize the decline of hepatic function as well as to enhance treatment efficacy. In patients with a Child-Pugh score of 8–9, that is, in those with deteriorated hepatic functional reserve, we have no choice but to implement a treatment strategy that is similar to that for Child-Pugh C patients. In other words, superselective cTACE and RFA may be recommended when the number and size of tumors are limited, but in principle, BSC and possibly liver transplantation, in accordance with the extended criteria, will be indicated. For patients with favorable hepatic functional reserve and bilobar multinodular tumors, sorafenib [10, 11] is also feasible as the treatment of choice.

Subclassification of Intermediate-Stage HCC and Treatment Strategy

Because intermediate-stage HCCs encompass a heterogeneous group of patients, Bolondi et al. [12] proposed a subclassification of intermediate-stage HCCs in 2012 (table 2). This substaging system incorporates the ‘beyond Milan and within up-to-7’ criteria [13], a novel concept that combines the size and number of tumors, that appears to be an extremely innovative classification system. However, the substages B1, B2 and B3 are equivalent to Child-Pugh scores of 5–7, 5–6 and 7, respectively, making substaging complicated. In addition, this system basically recommends TACE as the first treatment option for B1 and B2 patients. As far as the treatment strategy (TACE) is concerned, no significant difference is observed between this substaging system and the original classification system by the BCLC staging although no

Table 2. Subgrouping and treatment indication for patients with intermediate HCC

BCLC substage	B1	B2	B3	B4
CPT score	5–6–7	5–6	7	8–9
Beyond Milan and within up-to-7	IN	OUT	OUT	ANY
ECOG (tumor-related) PS	0	0	0	0–1
PVT	NO	NO	NO	NO
1st option	TACE	TACE or TARE		BSC
Alternative	LT TACE + ablation	SOR	Research trials TACE SOR	LT

TARE = Transarterial radioembolization; SOR = sorafenib. Bolondi et al. [12].

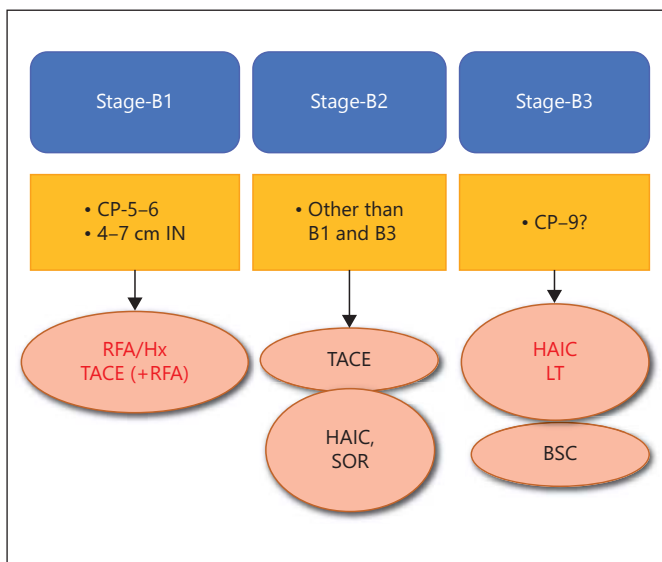


Fig. 4. Treatment guideline for BCLC-B HCC patients proposed by Japan-TAE group.

treatment option is recommended for substage B3 class and BSC is recommended for substage B4. In terms of disease prognosis, this substaging system is reportedly useful in the stratification of intermediate-stage HCC patients because prognosis worsens as substage progresses [14]. However, another report states that this subclassification is not useful [15].

Another important issue related to this substaging system is that portal vein thrombosis (PVT) is indicated as ‘NO’ for all B1–B4 substages. Because PVT has never been a defining factor for intermediate-stage HCC, this PVT factor should be deleted from the substaging system. Moreover, liver transplantation is recommended as an alternative treatment option for patients with Child-Pugh

scores 5–7 in substage B1, but this treatment option is unrealistic because liver transplantation is not a standard of care for patients with Child-Pugh scores 5–7 in Japan. Furthermore, TACE and radioembolization are listed as the first treatment options for patients with substage B2, but radioembolization has not yet been approved in Japan. Instead, HAIC has been performed proactively in patients with bilobar multinodular HCC in Japan [16].

Apart from this subclassification, Yamakado et al. [17, 18] recommended novel subclassification criteria and treatment strategies for Japanese patients with intermediate-stage HCC in 2014 (fig. 4).

Subclassification of Intermediate-Stage HCC and Treatment Approaches: Modified Bolondi’s Subclassification (Kinki Criteria)

Figure 5 shows a conceptual diagram of heterogeneity among intermediate-stage HCCs. The up-to-7 criteria are well-thought out criteria and include from single 6-cm HCC, six 1-cm nodules and nodules of in-between sizes. Therefore, this criteria uses 6 cm and 6 nodules as cutoff values, the up-to-7 criteria may also be called the 6–6 criteria.

As color-coded in green and pink represent good response subgroup to superselective cTACE and poor response subgroup to superselective cTACE, respectively (fig. 5). As color-coded in green, pink and yellow, the main treatment strategy for HCCs corresponding to Beyond Milan and within up-to-7 HCCs are curative therapy such as resection, ablation or superselective cTACE, whereas DEB-TACE is indicated for relatively large tumors. In addition, highly multiple HCCs are thought to be a good indication for HAIC or sorafenib (fig. 6).

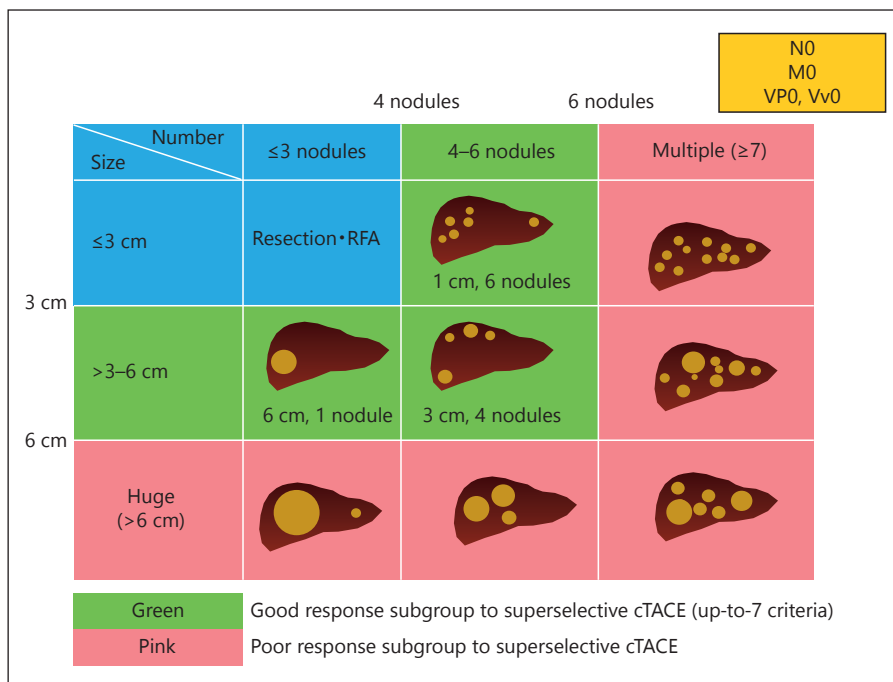


Fig. 5. Heterogeneity of intermediate stage HCC.

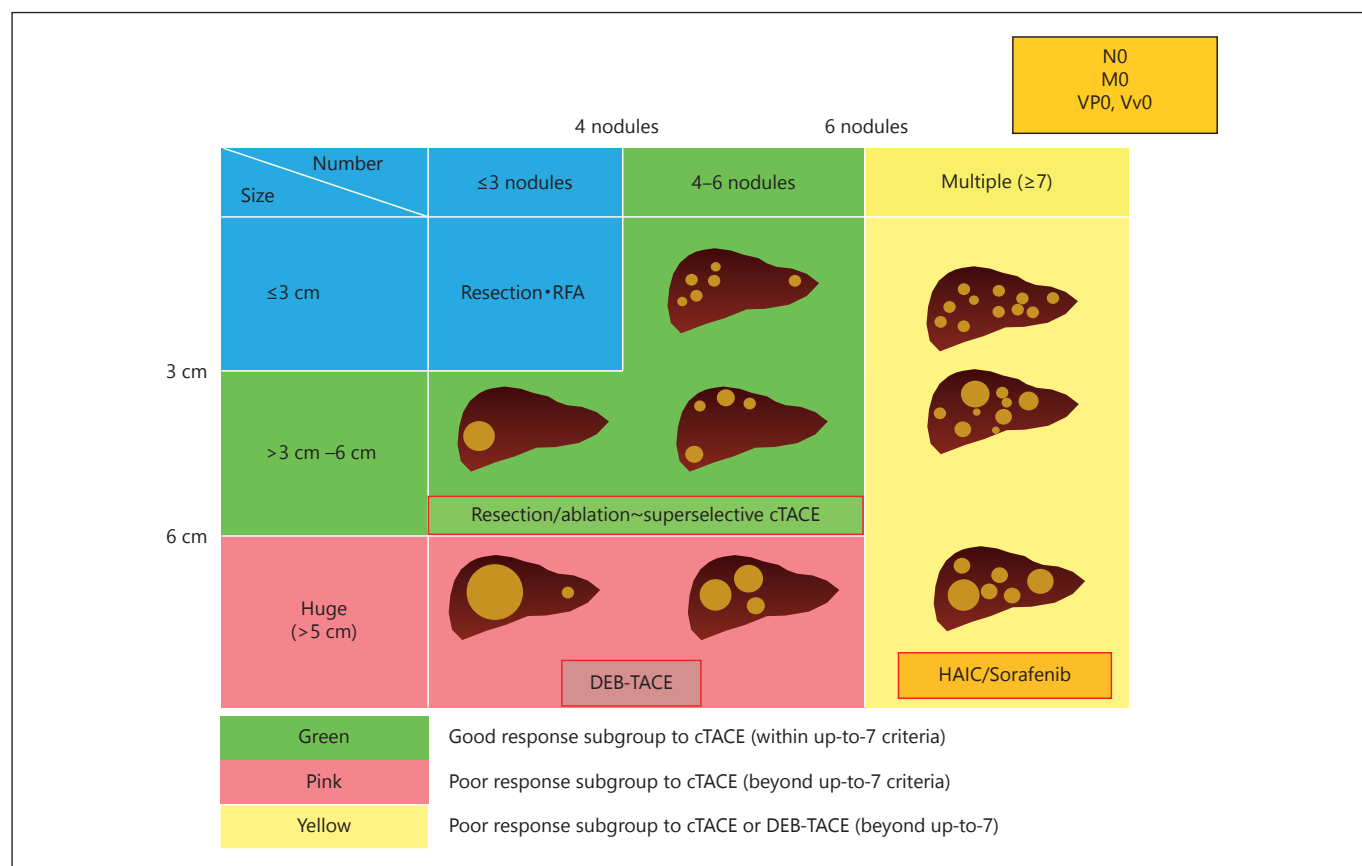


Fig. 6. Heterogeneity and treatment strategy of intermediate stage HCC (sub-stage B1, B2).

Table 3. Subclassification and treatment strategy of intermediate-stage HCC (modified Bolondi)

BCLC substage	B1	B2	B3	
Child-Pugh score	5–7	5–7	8, 9	
Beyond Milan and within up-to-7	IN	OUT	ANY	
			IN	OUT
Sub-substage			B3-a	B3-b
Concept of treatment strategy	Curative intent	Non-curative, palliative	Curative intent if within up-to-7	Palliative, no treatment
Treatment option	Resection Ablation Superselective c-TACE	DEB-TACE ¹ HAIC ² Sorafenib ³	Transplantation Ablation Superselective cTACE	HAIC Selective DEB-TACE
Alternative	DEB-TACE (large, C-P 7) B-TACE ⁴	cTACE	DEB-TACE B-TACE, HAIC	BSC

¹ DEB-TACE is recommended for huge tumors that are >6 cm. ² HAIC is recommended for multiple tumors >6. ³ Sorafenib is recommended for patients with liver function of Child-Pugh score 5 and 6. ⁴ B-TACE is recommended for fewer tumors.

We have been actively utilizing a novel classification system that we developed by modifying the Bolondi's criteria [12] (table 3). In this modified Bolondi's substaging system (Kinki criteria), patients with intermediate-stage HCC are classified into 3 groups based on their Child-Pugh scores (5–7 or 8–9) and the Beyond Milan and within up-to-7 criteria (IN or OUT). Although similar to the Bolondi's substaging system to a certain extent, the Kinki criteria is simpler and easier to apply, and resection and even ablation are included as treatment options for patients with substage B1. Resection is a good treatment option for patients with well-preserved liver function corresponding to Child-Pugh score 5 and single but large tumor, while ablation may be selected for those with 4–6 small tumors. Even if tumor size is near 5 cm, ablation can be applied if preceded by TACE to make the area for ablation larger. In patients with several regional tumors, we can apply superselective cTACE to carefully treat tumors one by one with curative intent. When superselective catheterization is not applicable, DEB-TACE or Balloon-occluded TACE (B-TACE) [19] may be a choice of option (table 3; fig. 5 and 6).

In patients with substage B2 HCC that is beyond the Milan criteria and is also huge, we actively repeat DEB-TACE, which is a good treatment option for huge HCCs (fig. 6). For patients with beyond up-to-7 multiple HCCs, we select HAIC rather than DEB-TACE (fig. 6) because HAIC is effective in this group of patients. If HAIC is not effective, sorafenib may be recommended. We occasion-

ally perform cTACE for some specific reasons but do not recommend the procedure because unselective bilobar cTACE will worsen the liver function. In addition, sorafenib may be an option for patients with numerous bilobar HCCs, who are expected to quickly become refractory to TACE. Sorafenib may be considered as the first treatment option for patients who have beyond up-to-7 bilobar multiple HCCs and are expected to easily become refractory to cTACE with worsening the liver function.

Patients with substage B3 HCCs are basically treated with a concept of palliative or no treatment similar to Child-Pugh C patients, but in those meeting the up-to-7 criteria, it is important to aim for potential cure and survival benefit, as in Child-Pugh C patients, using superselective cTACE or ablation to treat individual HCCs carefully [20]. In patients with up-to-7 HCCs, liver transplantation may be considered as extended criteria or after downstaging. Similar to substage B2 HCCs, 'within up-to-7' substage B3 HCCs may be treated with HAIC or selective DEB-TACE, which minimally decreases liver function. For substage B3 patients with beyond up-to-7 HCCs, HAIC, selective DEB-TACE or BSC are recommended (fig. 7).

We analyzed patients treated with cTACE (either superselective or unselective procedure) at our institution according to the Kinki criteria. Overall survival rates in patients with substage B1, B2 and B3 HCCs are well stratified. Because the survival curve of patients with substage B1 HCC is nearly identical to that of patients with BCLC

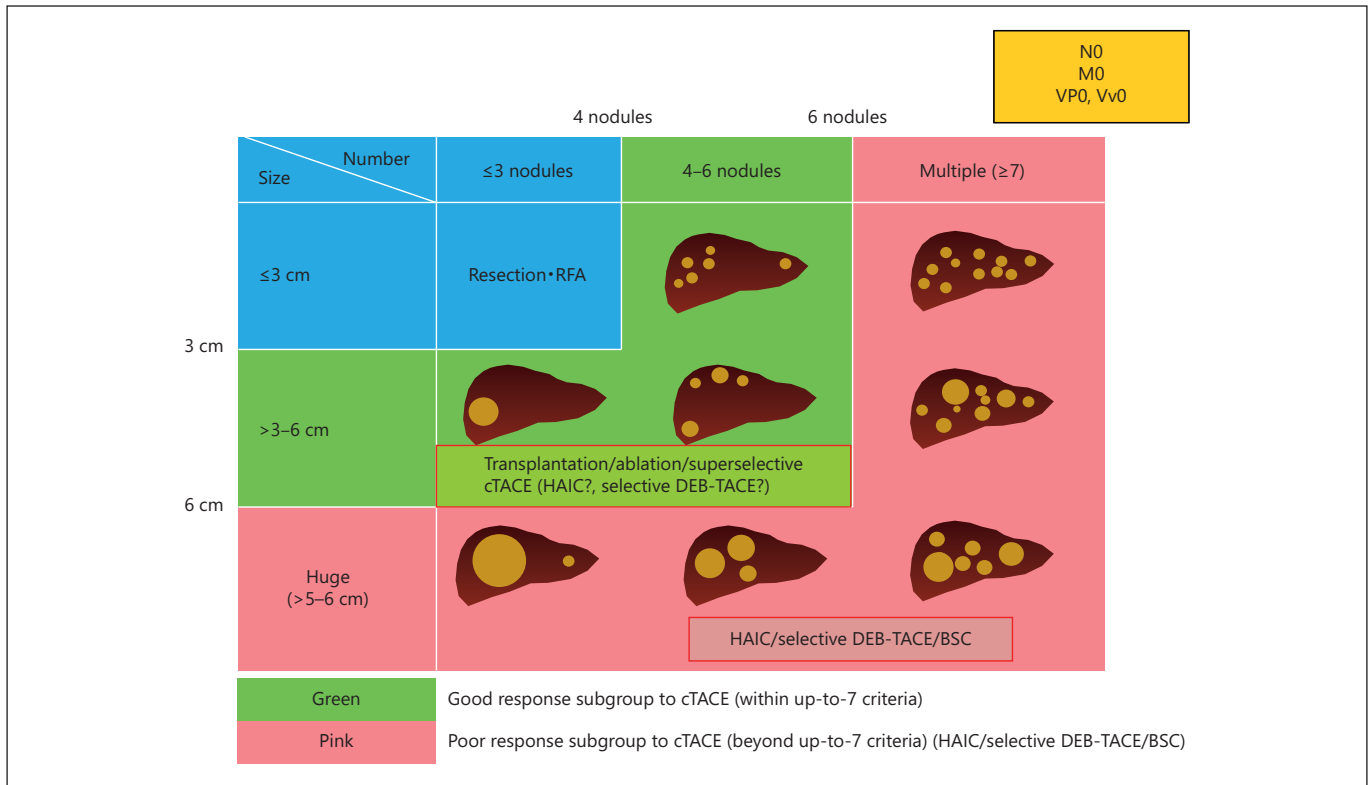


Fig. 7. Heterogeneity and treatment strategy of intermediate stage HCC (sub-stage B3). BSC = Best supportive care.

A HCC, this HCC patient subgroup should be treated with curative treatment including superselective cTACE and/or resection/ablation. As for substage B3 HCC, its survival curve overlaps with that of BCLC C, suggesting that the outcome of repeated cTACE in the patients would not be any better than that in patients with BCLC stage C HCC.

However, for substage B3 patients with tumors within up-to-7 criteria (sub-substage B3-a), superselective cTACE and ablation are recommended since these treatments have a survival benefit by minimizing the liver function damage and maximizing the treatment efficacy. Superselective/selective DEB-TACE, B-TACE, and HAIC are also indicated as alternative therapy in case of patients with sub-substage B3-a HCC.

In contrast, for patients with ‘beyond up-to-7’ BCLC B3 substage HCC (sub-substage B3-b), treatment options that are less toxic to liver function such as HAIC or selective DEB-TACE are indicated in accordance with the treatment results in Child-Pugh C patients [20].

However, as numbers of patients of sub-substage B3-a and B3-b are very small, it will be better to combine them as substage B3 when we analyze the survival data.

Our findings suggest that it is important to subclassify BCLC stage B HCC and establish treatment strategies based on liver function (Child-Pugh score) and tumor factors (within or beyond up-to-7).

Conclusion

In this review, heterogeneity of intermediate-stage HCCs and treatment options were discussed. Although several substaging systems have been proposed previously, we introduced here novel subclassification criteria and treatment approaches that we are currently using (Kinki criteria) by modifying Bolondi’s subclassification. Further study is needed to retrospectively investigate how well our system stratifies intermediate-stage HCCs and to prospectively determine the validity of this modified Bolondi’s subclassification, Kinki criteria.

Disclosure Statement

Authors declare there is no conflict of interest.

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