

# Lenvatinib for Hepatocellular Carcinoma

Subjects: **Gastroenterology & Hepatology**

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Lenvatinib, which is an oral multikinase inhibitor, showed non-inferiority to the sorafenib in terms of overall survival (OS) and a higher objective response rate (ORR) and better progression-free survival (PFS) in patients with hepatocellular carcinoma (HCC). A good liver function and Barcelona Clinic Liver Cancer (BCLC) intermediate stage were key factors in achieving therapeutic efficacy. The management of adverse events plays an important role in continuing lenvatinib treatment. While sequential therapies contributed to prolonging overall survival, effective molecular targeted agents for administration after lenvatinib have not been established. Repeated transcatheter arterial chemoembolization (TACE) was associated with a decline in the liver function and poor therapeutic response in BCLC intermediate patients. Recently, the Asia-Pacific Primary Liver Cancer Expert (APPLE) Consensus Statement proposed the criteria for TACE unsuitability. Upfront systemic therapy may be better for BCLC intermediate stage HCC patients with a high tumor burden, while selective TACE will be recommended to obtain a curative response in patients with a low tumor burden. This entry introduce the therapeutic response, management of adverse events, post-progression treatment after lenvatinib and treatment strategy for BCLC intermediate stage HCC.

lenvatinib

hepatocellular carcinoma

progression-free survival

overall survival

adverse events

post-progression treatment

BCLC intermediate stage

transcatheter arterial chemoembolization

nutrition assessment

sarcopenia

## 2. Therapeutic Response of Lenvatinib

### 1.1. The Objective Response Rate of Lenvatinib

Many real-world studies have reported the short-term therapeutic response of lenvatinib, resulting in an ORR of 29.9–53.5%, as assessed by mRECIST [1][2][3][4][5][6][7][8], and 14–25%, as assessed by RECIST ver.1.1 [3][6][9][10]. These findings seemed to be in agreement with the results of phase 2 and 3 studies (Table 1). To date, many researchers have also investigated the ORR as a predictive factor in the clinical setting. Ueshima et al. [1] reported that the high ORR was found in patients with albumin-bilirubin (ALBI) grade 1 at baseline. We reported that BCLC intermediate stage was a significant predictive factor that was associated with the ORR in a multivariate analysis [2], which agreed with the results regarding the ORRs in the analysis of a Japanese subpopulation in the REFLECT trial [11]. A high ORR was found in patients with a good PS [5], Child-Pugh class A [5], and Child-Pugh score 5 (CP-5A) [7]. Some of the researchers also reported that the high relative dose intensity (RDI) at four weeks (30 days) [7][12][13] or eight weeks (60 days) [3][5][14][15] was relevant to therapeutic response of lenvatinib, including the PFS and

OS (Table 2). The cut-off values of the RDI were similar, ranging from 66% to 75%. A high RDI was associated with a good liver function at baseline [3][12][13][14][15], low tumor stage [3][14], and an initial full dose of lenvatinib [3][14], which indicated that the liver function and early tumor stage would play an important role in obtaining a high RDI. Interestingly, low body weight [12] or BMI [3] were relevant to low RDI. While the reason for this is unclear, it might be related to the high incidence of adverse events (AEs) in patients with low BMI values [8]. In contrast, a retrospective study showed that the delivered dose intensity/body surface area ratio (DBR) was better a predictive factor than the RDI [15]. Because only one retrospective study has compared the RDI and DBR, further research was conducted in order to assess the usefulness of DBR. Some researchers reported the utility of contrast-enhanced ultrasonography at day 7 [16], AFP change at two weeks [17], and radiological imaging at two weeks [18] in order to predict the ORR of lenvatinib early, although the numbers of subjects were limited in these studies. These findings suggest that it is preferable to start lenvatinib at a full dose for patients with ALBI grade 1 and BCLC intermediate stage. When possible, an early tumor assessment was also preferable.

**Table 1.** The therapeutic response to lenvatinib treatment.

Author/Ref. No.	Years	Country	No. of pts	ORR (%) mRECIST	Median RECIST ver.1.1 (Months)	Median PFS (Months)	Median OS (Months)	Predictive Factors of ORR	Commentary
Kudo M./[19]	2018	Global	478	40.6	18.8	7.3	13.6	NA	REFLECT trial
Ueshima K./[1]	2019	Japan	82	39.0	NA	7.6	could not be reached	ALBI grade 1	ALBI grade 1; ORR of 57.1%, median PFS of 18.9 months
Hatanaka T./[2]	2020	Japan	94	30.4	NA	5.4	NA	BCLC intermediate stage	BCLC intermediate stage; ORR of 47.6%, median PFS 8.0 months
Sasaki R./[3]	2019	Japan	81	34.6	17.3	NA	11.6	NA	The patients with the good ORR and those with high RDI had significantly good OS.
Sho T./[4]	2020	Japan	105	53.5	NA	9.8	NA	NA	

Author/Ref. No.	Years	Country	No. of pts	ORR (%) mRECIST	Median RECIST ver.1.1 (Months)	Median PFS (Months)	Median OS (Months)	Predictive Factors of ORR	Commentary
Ogushi K./ <a href="#">[5]</a>	2020	Japan	181	30.4	NA	NA	369 (days)	CP-A, PS 0, RDI > 0.70	CP-A; ORR of 36.5%. RDI > 0.70: ORR of 47.7%. CP-A and BCLC intermediate stage were the predictive factors affecting the OS.
Maruta S./ <a href="#">[6]</a>	2020	Japan	152	40.8	15.8	5.1	13.3	NA	RDI > 70%; ORR of 45.2%, RDI ≤ 70%; ORR of 11.4%. The significant factors associated with the PFS were CP-5A, tumor size ≥ 40 mm among pretreatment factors.
Ohki T./ <a href="#">[7]</a>	2020	Japan	77	29.9	NA	5.6	NA	CP-A, RDI > 70% at 30 days, AFP reduction	mALBI 2b or 3 was unfavorable predictive factor relevant to the OS.
Hiraoka A./ <a href="#">[8]</a>	2019	Japan	152	38.7	NA	NA	could not be reached	NA	CP-A, BCLC intermediate
Author/Ref. No.	Years	No. of pts	Assessment Time	Cut-off Value	Associated Factors	Therapeutic Response	Commentary		
Sasaki R./ <a href="#">[3]</a>	2019	81	RDI	8 weeks	67%	BMI, PS, BCLC stage, platelet count, PT,	OS	Median OS could not be reached during the observation.	

Author/Ref. No.	Years	No. of pts	Assessment	Time	Cut-off Value	Associated Factors	Therapeutic Response	Commentary
Ogushi K./ <a href="#">[5]</a>	2020	181	RDI	8 weeks	70%	albumin, initial dose	ORR	Mean RDI gradually decreased from the start of lenvatinib to 2 months.
Ohki T./ <a href="#">[7]</a>	2020	77	RDI	30 days	70%	NA	ORR, PFS	RDI > 70%; median PFS of 9.3 months
Kirino S./ <a href="#">[12]</a>	2020	60	RDI	4 weeks	70%	Body weight, ALBI score, albumin, grade 3 or 4 adverse events	OS, time to discontinuation of treatment	Median OS could not be reached and median duration of lenvatinib was 9.5 months in patients with RDI > 70%.
Ono A./ <a href="#">[13]</a>	2020	41	RDI	4 weeks	70%	Platelet count, albumin, AST, AFP-L3, DCP, ALBI score, TKI experience	PFS	RDI > 70%; median PFS of 6.7 months. RDI in 3–4 weeks significantly reduced compared to 1–2 weeks.
Takahashi A./ <a href="#">[14]</a>	2019	50	RDI	8 weeks	75%	Child-Pugh class A, ALBI, EHS, initial dose	ORR, PFS	RDI > 75%; ORR of 68%, median PFS of 7.4 months
Eso Y./ <a href="#">[15]</a>	2019	49	DBR, RDI	60 days	DBR of 238.9, RDI of 66%	BSA, mALBI grade 1 + 2a, BTR	ORR, PFS	DBR was calculated as the delivered DI divided by BSA. (studies) to

disease progression or death. The median PFS in lenvatinib-treated patients was reported to be 7.3 months (95% confidence interval (CI) 5.6–7.5) in a phase 3 study [\[19\]](#), while some of the retrospective studies reported the median PFS of 4.3–9.8 months [\[1\]](#)[\[2\]](#)[\[4\]](#)[\[6\]](#)[\[7\]](#)[\[9\]](#)[\[10\]](#). Our retrospective study reported that the BCLC intermediate stage was significantly associated with PFS in a multivariate analysis (median PFS; 8.0 months in intermediate stage, 4.0 AFP-L3; Lens culinaris agglutinin-reactive fraction of alpha-fetoprotein, ALBI score; albumin-bilirubin score, AST; months in advanced stage) [\[2\]](#). There were no differences in PFS between the treatment-naïve patients and aspartate transaminase, BCLC stage; Barcelona Clinic Liver Cancer stage, BMI; body mass index, BSA; body patients who had received previous treatment. The PFS in patients with extrahepatic spread was shorter in surface area, BTR; branched-chain amino acids tyrosine ratio, CONUT, Controlling Nutrition Status, DBR; the comparison to the patients without extrahepatic spread [\[2\]](#). Another retrospective study showed that CP-5A, tumor

size and dose intensity/burdyn are factors, and that dose intensity of thyroid dyslipidemia is not dose and time dependent. These were appropriate findings, while PFS is available. Not all of these present studies indicated that PFS, good response rate, small tumor, size and cancer status are prognostic factors during treatment, distributed to the subjects PFS, ST [2]; Cytostatic response rate and an RDI of >70% at four weeks was correlated with PFS [13]. Takahashi et al. revealed that patients with an RDI of ≥75% at eight weeks showed better PFS in comparison to those with RDI < 75% [14]. These studies indicated that a maintained RDI was associated with longer PFS [13][14]. Because the liver function and early tumor stage would play an important role in obtaining a high RDI, as we mentioned above, the administration of full-dose lenvatinib to patients with BCLC intermediate stage (or low tumor burden) would be expected to result in good PFS. The management of AEs was crucial in obtaining good PFS ([Table 1](#)).

The median OS was 13.6 months (95% CI 12.1–14.9) in a phase 3 study [19]. The median OS was shown to be 7.1–13.3 months, according to some retrospective studies [3][5][6][10], and modified ALBI (mALBI) grade 2b or 3 [8], Child-Pugh class B [5], BCLC advanced stage [5][20], and elevated C-reactive protein [21] were found to be significant unfavorable factors. While the starting dose of sorafenib did not influence OS according to one retrospective study [22], the patients with the higher RDI of lenvatinib (>67%) at eight weeks had significantly better OS in comparison to those with lower RDI (≤67%) [3]. However, care is required in the interpretation of the results of OS, because the observation period in many previous reports was insufficient. Accordingly, further research with an adequate follow-up period is warranted for investigating predictors of OS ([Table 1](#)).

The results of these real-world studies were mainly reported from Japan. According to the Japanese subpopulation analysis of the REFLECT trial [23], the Japanese patients were older, had a lower body weight, better PS, lower serum level of AFP, and, more frequently, had BCLC intermediate stage and underlying liver diseases of HCV in comparison to the overall population of the REFLECT trial. The OS of Japanese patients was better than that in the overall population of the REFLECT trial (17.6 months vs. 13.6 months), which may be explained by a low HCC stage, low serum level of AFP, and high percentage of patients receiving anticancer therapy after lenvatinib [23]. Hence, these tendencies might be found in these real-world studies and it might be necessary to pay attention to the interpretation of the results of the real-world studies.

## 2. Adverse events

While physicians were accustomed to sorafenib toxic profile based on ten-year experience, the experience in the management of lenvatinib toxicity was limited [24]. Therefore, we described not only the common adverse events (AEs), but also those requiring special attention in this paragraph.

### 2.1. The fatigue, appetite loss and treatment discontinuation

Adverse events that were frequently reported in many previous studies included fatigue, appetite loss, hand-foot skin reaction (HFSR), diarrhea, hypertension, hypothyroidism, and proteinuria [19][2][5][6][7][8][25]. The rate of discontinuation due to AEs was 8.6–43.5% [2][6][25]. Thus, the management of AEs plays a central role in lenvatinib treatment. The median onset of fatigue, appetite loss, HFSR and diarrhea was approximately 1 months after the

start of lenvatinib while the median onset of hypertension was on day 4 [25]. Among these frequent AEs, the occurrence of appetite loss was strongly correlated with the therapeutic effect [2][7][8]. In addition, fatigue and appetite loss were risk factors for treatment discontinuation [40]. Some studies showed that these AEs [2] and the incidence of discontinuation due to AEs [1][25] were less frequently found in patients with ALBI grade 1 in comparison to those with ALBI grade  $\geq 2$ , indicating that AEs of lenvatinib were manageable in the patients with a good baseline liver function. In contrast, other studies reported that the frequency of appetite loss and fatigue was not significantly associated with the mALBI score [6][8]. One of the reasons was presumed to be the small number of the patients with a relatively poor liver function. Another reason was considered to be the shorter period of lenvatinib administration in patients with a poorer liver function in comparison to those with a better liver function. Hence, the liver function will play a central role in the management of AEs.

Dose reduction or dose interruption are performed as countermeasures against fatigue and appetite loss. However, this decreases the efficacy of lenvatinib and possibly causes tumor regrowth. The weekend-off protocol, which was defined as a scheduled protocol with administration for a period of 5 days on and 2 days off, was the one of the methods for improving tolerability and sustaining efficacy [26]. Although no medical agents relieving these symptoms have been established, one study showed that lenvatinib-related fatigue was associated with carnitine insufficiency [27]. Thus, carnitine supplementation may be effective for improving fatigue in patients receiving lenvatinib. The efficacy of other medical agents, including dexamethasone and Chinese herbal medicines, remains unknown.

While older patients seem to experience more AEs, a retrospective study showed that there were no significant differences in the incidence or severity of AEs between elderly ( $\geq 75$  years old) and non-elderly patients [28]. Lenvatinib may be safe for elderly patients; however, the study population was relatively small. Incidentally, few reports have investigated whether sex differences or the presence of comorbidity have an impact on AEs.

## 2.2. The hemorrhage events

Vascular endothelial growth factor (VEGF) inhibitor treatment was found to be associated with an increased incidence of hemorrhage events according to a meta-analysis [29][30]; the major frequent hemorrhage events were reported to be upper gastrointestinal hemorrhage and intracranial hemorrhage [31]. Indeed, intracranial hemorrhage was found in 3 patients treated with lenvatinib in the REFLECT trial [19]. Moreover, intraperitoneal or intratumoral hemorrhage is a rare but life-threatening complication. As the original nature, HCC tends to cause intraperitoneal or intratumoral hemorrhage spontaneously. Although there is geographic variation in the incidence of spontaneous HCC rupture, it is reported to be 2.6% in Western countries and 10-26% in Asian countries [32]. Spontaneous tumor rupture was found in approximately 2.6% patients according to the latest nationwide survey of Japan [33]. Accordingly, lenvatinib treatment was deemed to increase the risk of tumor hemorrhage. While the incidence of tumor hemorrhage during lenvatinib treatment remains unknown, Uchida-Kobayashi et al. [34] reported that the lenvatinib-induced tumor hemorrhage was found in 5 patients with a median onset of 3 days after the initiation of lenvatinib. The median maximum tumor diameter was 10 cm in these 5 patients, in agreement with the risk factors for spontaneous HCC bleeding [35]. Hence, careful monitoring is required when administering lenvatinib to patients.

with huge HCC and further research is warranted to clarify the clinical features of tumor hemorrhage during lenvatinib treatment.

## 2.3. Hepatic encephalopathy and ascites

Hepatic encephalopathy rarely occurred during lenvatinib treatment. The risk factors for hepatic encephalopathy were shown to be an elevated blood concentration of ammonia at baseline and the presence of portosystemic shunt [6]. The mechanism has remained unclear. One hypothesis is that VEGF inhibitors, including lenvatinib, increase intrahepatic vascular resistance and reduce intrahepatic blood flow via a reduction in nitric oxide production [36]. In fact, the portal venous flow velocity assessed by Doppler ultrasonography during lenvatinib treatment was significantly reduced in comparison to baseline [37][38]. Accordingly, the administration of lenvatinib aggravated the portal hypertension and increased the blood flow in portosystemic shunt, resulting in the occurrence of hepatic encephalopathy. In this connection, a retrospective study revealed that hepatic ascites was found in approximately 29% patients during lenvatinib treatment and that Child-Pugh score 6 and a low platelet count ( $<12 \times 10^4/\mu\text{L}$ ) were significant risk factors [20]. Because the patients with a low platelet count tend to have portal hypertension, lenvatinib was presumed to have an impact on the further increase in portal hypertension, resulting in the appearance of hepatic ascites.

## 2.4. Thyroid dysfunction

Thyroid dysfunction is a frequent complication in patients treated with tyrosine kinase inhibitors (TKIs). According to the phase 3 trial in renal cell carcinoma, sunitinib and pazopanib, which are oral multi-TKIs, caused treatment-related hypothyroidism in approximately 24% and 12% patients, respectively [39]. In the REFLECT trial, hypothyroidism was found in 78 (16%) and 8 (2%) patients who received lenvatinib and sorafenib, respectively [19]. While the clear mechanism underlying the development of thyroid dysfunction due to TKIs remains uncertain, several possible mechanisms have been proposed. One plausible mechanism is that the TKIs cause the destructive thyroiditis [40]. Another mechanism is that TKIs inhibited the binding of VEGF to normal thyroid cells and/or reduce the thyroid flow, resulting in thyroiditis [40].

According to a retrospective study that included 50 lenvatinib-treated patients, subclinical hypothyroidism, overt hypothyroidism, and thyrotoxicosis occurred in 7 (14.0%), 26 (52.0%), and 5 (10.0%) patients, respectively [41]. PFS in patients with hypothyroidism was longer than that in those without hypothyroidism. However, one retrospective study showed that grade 1 and 2 thyroid dysfunction occurred in 6 (7.8%) and 14 (18.2%) patients, respectively, and grade 2 thyroid dysfunction was found to be a significantly unfavorable factor for PFS in a multivariate analysis [7]. On the other hand, another study showed that lenvatinib-induced hypothyroidism of grade 1, 2 and 3 was found in 6 (13%), 12 (26%) and 1 (2%) patients, respectively, and grade 2/3 hypothyroidism was found to be a favorable factor that affected OS in a multivariate analysis [42]. Thus, based on the obtained results of these studies, the relevance of thyroid dysfunction to the clinical outcomes remains controversial.

### 3. Lenvatinib for patients with Barcelona Clinic Liver Cancer intermediate stage

#### 3.1 Transcatheter arterial chemoembolization and heterogeneity

Transcatheter arterial chemoembolization significantly improved OS in patients with unresectable HCC in comparison to a placebo group [43][44]. It has become the standard treatment for patients with BCLC intermediate stage and is widely used in the clinical setting [45]. However, various molecular targeted agents (MTAs) have been available for advanced HCC and the treatment strategy for BCLC intermediate stage will be reconsidered.

According to a systemic review of 10,108 patients treated with lipiodol-based TACE, the survival rate at 1-, 2-, 3- and 5-year was reported to be 70.3%, 51.8%, 40.4%, and 32.4%, respectively, with median OS of 19.4 months [46]. However, not all patients can obtain benefits from TACE [47]. The heterogeneity in BCLC intermediate stage has led to the development of several prognostic scores based on liver function and tumor burden that attempt to determine who might benefit most [48]. To date, Bolondi's subclassification [49], hepatoma arterial embolization prognostic (HAP) score [50], the Kinki criteria [51] were proposed. Based on these subclassification, TACE was recommended in either patients with low tumor burden or those with good liver function or both.

A retrospective study analyzed the clinical outcomes in treatment-naïve patients who initially received TACE treatment, and indicated that patients who achieved an objective response with initial TACE showed the longest survival, followed by patients who subsequently obtained an objective response after at least 2 sessions and those who did not achieve an objective response during the course of treatment [52]. This study also showed that large (>5 cm) and multiple (>4) tumors were independently associated with failure to achieve a complete response [52]. The response rate of additional TACE reduced in comparison to that of initial TACE [53]. Moreover, additional TACE increased the risk of deterioration of the liver function. Therefore, repeated TACE was not recommended based on its association with the deterioration of the liver function and a poor therapeutic response.

#### 3.2 Transcatheter arterial chemoembolization refractoriness

During the sorafenib era, TACE failure/refractoriness was proposed as a criterion for switching from TACE to systemic therapy [54]. The TACE failure/refractoriness was defined as the following characteristics: (1) two or more consecutive insufficient responses of the treated tumor (viable lesion >50%); (2) two or more consecutive progressions in the liver (tumor number increases as compared to tumor number before the previous TACE procedure) [54]. Two retrospective studies [55][56] demonstrated that switching to sorafenib treatment was associated with better survival in comparison to repeated TACE. A prospective international observational trial (OPTIMIS trial) showed that, in TACE-refractory patients, survival time was better in those who received sorafenib in comparison to those who continued TACE [57]. In addition, a recent study showed that the median PFS in TACE-refractory patients treated with lenvatinib, sorafenib and TACE was 5.8, 3.2 and 2.4 months, respectively [58]. Our retrospective studies reported that lenvatinib treatment was associated with a high ORR and good PFS in patients with

intermediate stage HCC [2]. Therefore, lenvatinib treatment could result in a good outcome in TACE-refractory intermediate stage HCC patients.

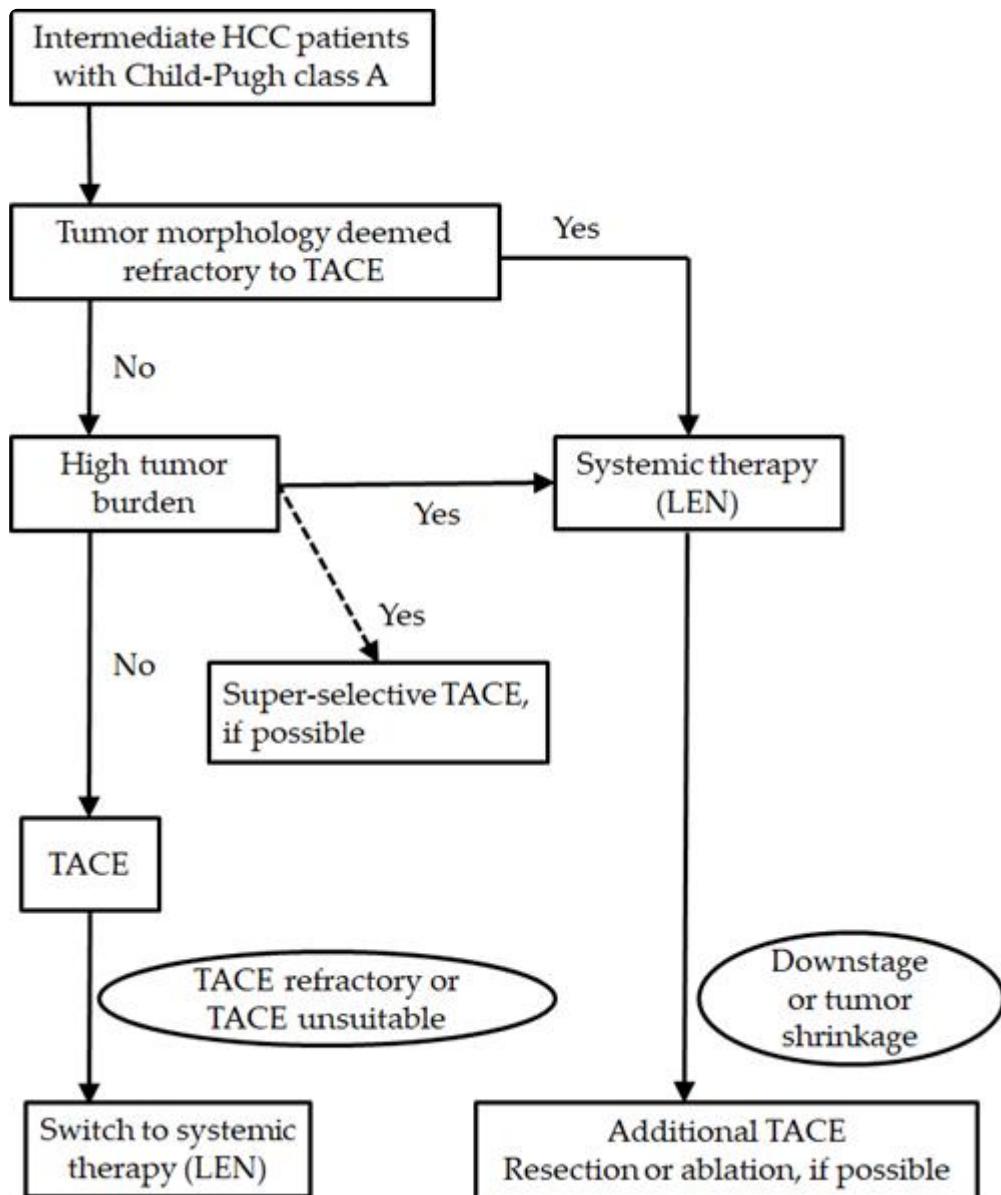
### 3.3 Exceeding the up-to seven criteria, transcatheter arterial chemoembolization unsuitability and upfront systemic therapies

The up-to seven criteria were defined as the sum of the maximum tumor diameter in the liver (cm) and the number of tumors and were originally developed for liver transplantation [59]. In patients exceeding the up-to seven criteria TACE treatment was reported to be likely to worsen the liver function, which may result in missing the chance to receive MTA treatment [60][61]. The proof of concept study demonstrated that among intermediate stage HCC patients who exceeded the up-to seven criteria, the lenvatinib group had a higher ORR, longer PFS and OS than the TACE group [62]. When the ALBI scores at baseline and at the end of treatment were compared, the ALBI score was sustained in the lenvatinib group while it worsened in the TACE group [62]. The results of this study demonstrated that lenvatinib is superior to TACE in intermediate stage HCC patients exceeding the up-to seven criteria. The Asia-Pacific Primary Liver Cancer Expert (APPLE) Consensus Statement proposed the TACE unsuitability should be defined by the following characteristics: (1) unlikely to respond to TACE (confluent multinodular type, massive or infiltrative type, simple nodular type with extranodular growth, poorly differentiated type, intrahepatic multiple disseminated nodules, or sarcomatous changes after TACE); (2) likely to develop TACE failure/refractoriness (Exceeding the up-to seven criteria); and (3) likely to become Child-Pugh B or C after TACE (Exceeding the up-to seven criteria and mALBI grade 2b) [63]. The AASLD Consensus Conference showed that locoregional TACE may still be best approach when patients have a low tumor burden and nodules accessible super-selectively [64]. In contrast, upfront systemic therapy may be better for the patients exceeding the up-to seven criteria [64].

Considering these previous reports, when patients have a low tumor burden, selective TACE will be recommended to obtain a curative response. Non-selective TACE was not recommended due to the low rate of curative response and the risk of deterioration of the liver function. When patients meet the definitions of TACE refractoriness or TACE unsuitable, switching to systemic therapy, including lenvatinib, may be better in order to avoid impairment of the liver function. Upfront lenvatinib may be better in patients with a high tumor burden or who are deemed to be refractory to TACE. When a tumor responds well, additional TACE (or surgical resection or ablation) will be considered. Because lenvatinib rapidly reduced the tumor enhancement on radiological imaging and achieved the high ORR in BCLC intermediate stage, upfront lenvatinib strategy is promising treatment. However, the efficacy and safety of this strategy has not been validated. In addition, the optimal timing of additional TACE treatment has not been established. Further research to investigate the efficacy and safety of this strategy will be necessary in the future (Figure 1).

Recently, an RCT comparing the efficacy and safety of TACE plus sorafenib to TACE alone (TACTICS trial), indicated that PFS in a TACE plus sorafenib group was significantly longer than that in a TACE alone group; however, a benefit in OS was not proved [65]. Systemic therapy improves the clinical outcomes of TACE,

presumably by promoting vascular normalization and contributing to the denser deposition of lipiodol [63]. Hence, lenvatinib-TACE sequential therapy might be a promising treatment for patients with intermediate HCC.



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