



# Is Transarterial Chemoembolization Only Treatment Option in Patients with Intermediate Stage of Hepatocellular Carcinoma?: in Perspectives of Surgery

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In the Barcelona Clinic Liver Cancer staging system, intermediate stage hepatocellular carcinoma (HCC) is defined as large multinodular tumors without vascular invasion or extrahepatic spread in an asymptomatic patient with good performance status. Intermediate stage HCC includes various subgroups and it is characterized by extensive heterogeneity. Current guidelines recommend transarterial chemoembolization (TACE) as the standard treatment modality for patients with intermediate stage HCC. Although TACE provides improved survival benefits compared with supportive care for patients with intermediate stage HCC, all of them are not good candidates for TACE. TACE refractoriness is another obstacle to effective treatment of patients with intermediate stage HCC. Given that many studies recently reported improved survival in patients treated with hepatic resection over TACE, we reviewed the survival outcomes of TACE and hepatic resection as a treatment strategy of intermediate stage HCC. (**J Liver Cancer 2020;20:113-119**)

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## INTRODUCTION

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related deaths globally.<sup>1</sup> Despite advances in treatment, the overall prognosis of HCC remains poor compared to other cancers.<sup>1</sup> The management of HCC is complicated in that not only the tumor burden itself, but also the liver function should be considered. The Barcelona Clinic Liver Cancer (BCLC) staging system is widely used for the treatment and

prognosis of HCC.<sup>2</sup> The BCLC system takes account of liver function, tumor burden, as well as the performance status of the patient classified as HCC into 5 stages (0, A-D).<sup>3</sup> In the BCLC staging system, intermediate stage is referred to multinodular lesions, well-preserved liver function (Child-Pugh class A or B), and good performance status.<sup>3</sup> As per the BCLC staging system, the recommended treatment for patients with intermediate stage HCC, i.e., BCLC B, is transarterial chemoembolization (TACE). However, TACE may not be suitable for all patients with intermediate stage HCC. In these cases, other forms of treatment should be considered, such as surgery. Recent studies have demonstrated that hepatic resection provides a survival benefit over TACE in intermediate stage HCC.<sup>4,5</sup> This review evaluates the role of TACE and hepatic resection in the treatment of intermediate stage HCC.

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## TRANSARTERIAL CHEMOEMBOLIZATION

According to the current guidelines, TACE is the standard care for patients with intermediate stage HCC.<sup>3</sup> The survival benefit of TACE has been noted in several randomized controlled studies. As the first randomized controlled study showing the efficacy of TACE, Llovet et al.<sup>6</sup> reported that patients with unresectable HCC who were not suitable for curative treatment showed a longer mean survival time (28.7 months) in the TACE group compared to the group receiving conservative management (17.9 months). Additionally, a randomized controlled study in Hong Kong demonstrated significantly better 1- and 3-year survival rates in the TACE group (57% and 26%, respectively) than those in control group (32% and 3%, respectively).<sup>7</sup> A meta-analysis has suggested that patients with unresectable HCC demonstrate prolonged survival when treated with TACE in comparison to conservative management.<sup>8</sup> It analyzed 7 trials (total of 545 patients) to compare the survival benefits of TACE and conservative treatment in unresectable HCC. TACE group showed significantly better 2-year survival than the control group (odds ratio 0.53,  $P=0.017$ ).

Recently, drug-eluting bead TACE (DEB-TACE) has been introduced as a novel regimen to conventional TACE (cTACE). It involves polymeric microspheres that are loaded with anti-neoplastic drugs, and after delivery to the tumor vasculature, drugs are released slowly over time allowing lower systemic toxicity and the higher drug concentrations in the target tumor.<sup>9</sup> However, the superior clinical efficacy of DEB-TACE over cTACE is still debatable due to the lack of

evidence. In randomized controlled trials conducted with the Western population, DEB-TACE did not show superiority as compared to cTACE in terms of 2-year survival, 56.8% vs. 55.4%, respectively ( $P=0.95$ ).<sup>10</sup> Similarly, a retrospective study reported comparable overall survival after cTACE and DEB-TACE, 13.6 months vs. 12.3 months, respectively.<sup>11</sup> In a recent randomized controlled trial comparing DEB-TACE and cTACE, both were found to be equally effective and safe, with the only advantage of DEB-TACE being less post-procedural abdominal pain.<sup>10</sup>

## HETEROGENEITY OF INTERMEDIATE STAGE HCC

In most of the previous studies reporting the efficacy of TACE, it was indicated for patients with asymptomatic, multinodular HCC without vascular or extrahepatic invasion, and preserved liver function; however, it is unclear whether all patients with intermediate stage HCC should be treated with TACE because of extensive heterogeneity in tumor burden and liver function.<sup>12,13</sup> The necessity of subclassification of intermediate stage was recognized because of different prognosis even in the same 'intermediate stage'. Tumor burden and residual liver function were classified in more detail according to prognosis of these patients.

Bolondi et al.<sup>13</sup> suggested to divide the intermediate stage into four subgroups (B1-B4) based on tumor burden and liver function, and proposed first and alternative treatment options for each subgroup (Table 1). In a retrospective study to validate the Bolondi subclassification, the median overall survival in each

**Table 1.** Bolondi's subclassification for intermediate stage of HCC

Subclassification	B1	B2	B3	B4
Child-Pugh score	5-7	5-6	7	8-9
Beyond Milan within up-to-7 criteria	In	Out	Out	Any
ECOG-PS	0	0	0	0-1
Portal vein thrombosis	No	No	No	No
First treatment	TACE	TACE or TARE	(-)	Best supportive care
Alternative option	Liver transplantation or TACE+ablation	Sorafenib	Research trials TACE+sorafenib	Liver transplantation

ECOG-PS, Eastern Cooperative Oncology Group tumor-related performance status; TACE, transarterial chemoembolization; TARE, transarterial radioembolization.

group was different according to B1-B4 subgroups: 31.9, 26.9, 13.5, and 10.9 months, respectively.<sup>14</sup> Ciria et al.<sup>15</sup> also reported different survival outcomes in subgroups (5-year survival rate, 62.9%, 28.1% and 15.4%, respectively, for B1, B2, and B3-4 subgroups,  $P=0.004$ ). In addition, Kinki criteria was also developed as a modification of the Bolondi criteria, which classified the intermediate stage HCC into three subgroups based on the Child-Pugh score, beyond Milan, and up-to-7 criteria (Table 2).<sup>16</sup> Arizumi et al.<sup>17</sup> demonstrated validation of Kinki criteria for patients with intermediate stage HCC in the Asian population. In this study, each subgroup showed significantly different median overall survival: 4.3 years, 2.9 years, and 1.1 years for B1, B2, and B3, respectively ( $P<0.001$ ). Another study to validate Kinki criteria with a retrospective design showed similar results of different median survival rates as 3.9 years, 2.5 years, and 1.1 years for B1, B2, and B3, respectively ( $P<0.001$ ).<sup>17</sup>

## TACE REFRACTORINESS

Repeated cycles of TACE can increase the efficacy of treatment, but may also increase the incidence of complications. In some patients, HCC may not respond well to TACE. Thus, when TACE is repeated in a particular patient, it is necessary to consider whether to continue or stop TACE, and switch to alternative treatment; TACE refractoriness.<sup>18</sup> In general, the discontinuation of TACE is recommended if the

tumor is non-responsive to two consecutive TACE treatment or if complications occur.<sup>19,20</sup> Recently, in Asia-Pacific Primary Liver Cancer Expert Consensus Statements,<sup>21</sup> it was emphasized that TACE should be discontinued in patients who showed TACE failure/refractoriness in order to preserve residual liver function. Targeted therapy such as sorafenib is the recommended first-line treatment for TACE-unsuitable patients. In a retrospective study reporting this issue, among 249 patients with intermediate stage of HCC who underwent first TACE, 122 showed TACE-refractoriness. The median overall survival was significantly longer in the sorafenib conversion group compared to the TACE-repeated group (25.4 months vs. 11.5 months, respectively,  $P=0.003$ ).<sup>22</sup> A retrospective cohort study reported similar results. When 56 patients with intermediate stage HCC who were diagnosed to be refractory to TACE were divided into TACE-repeated group (24 patients) and switching to sorafenib group (32 patients), the median overall survival was significantly different: 13.6 months for TACE-repeated group, and 24.7 months for sorafenib switching group ( $P=0.002$ ).<sup>23</sup>

## SURGICAL RESECTION, AN ALTERNATIVE TO TACE IN THE INTERMEDIATE STAGE?

Surgical treatment of HCC should be determined based on sufficient consideration of tumor burden, liver functional re-

**Table 2.** Kinki criteria (modified Bolondi's subclassification)

Subclassification	B1	B2	B3	
Child-Pugh score	5-7	5-7	8-9	
Beyond Milan within up-to-7 criteria	In	Out	In (B3a)	Out (B3b)
Concept of treatment	Curative	Palliative Non-curative	Curative intent if within up-to-7	Palliative No treatment
Treatment option	Resection, ablation, c-TACE	DEB-TACE <sup>†</sup> , HAIC <sup>‡</sup> , sorafenib <sup>§</sup>	Liver transplantation, ablation, c-TACE	HAIC <sup>‡</sup> , DEB-TACE <sup>†</sup>
Alternative	DEB-TACE <sup>†</sup> (if large HCC, Child-Pugh score 7) B-TACE <sup>§</sup>	c-TACE	DEB-TACE <sup>†</sup> , B-TACE <sup>§</sup> , HAIC <sup>‡</sup>	Best supportive care

c-TACE, conventional transarterial chemoembolization; DEB-TACE, drug-eluting beads transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; B-TACE, balloon-occluded TACE.

<sup>†</sup>DEB-TACE is recommended for tumor >6 cm; <sup>‡</sup>HAIC is recommended for multiple tumors >6; <sup>§</sup>Sorafenib is recommended for Child-Pugh score 5-6; <sup>§</sup>B-TACE is recommended for fewer tumors.

serve, and shortage of liver graft.<sup>24</sup> Patients with chronic liver disease who have poor liver function have less range of resection than those with normal liver function.<sup>25</sup> According to the BCLC staging system, surgical resection of HCC is limited to those in the early stage of HCC.<sup>26,27</sup> It recommends surgical resection only when patients had a single nodule of HCC or multiple tumors  $\leq 3$  in number with  $< 3$  cm of tumor diameter with good liver function.<sup>26,27</sup> However, BCLC staging classification is based on a study that is more than 20 years old and leads to a conclusion from the analysis of a cohort of 77 early HCC patients and 102 intermediate or advanced HCC patients.<sup>28</sup>

Recent studies suggested that the indication of surgery for HCC treatment could be expanding to more advanced stages due to the development of surgical techniques and perioperative management.<sup>29</sup> Many studies have reported survival benefits of surgery for patients with HCC, particularly intermediate stage (summarized in Table 3).<sup>4,15,30-35</sup> In a randomized controlled study for the Asian population, 173 HCC patients beyond Milan criteria were randomly assigned to

surgery or TACE groups. It was reported that surgical resection demonstrated superiority over TACE in terms of overall survival (1-year and 3-year overall survival, 76.1% and 51.5% in the surgical group, 51.8% and 18.1% in the TACE group, respectively,  $P < 0.001$ ).<sup>4</sup> The global study using a longitudinal cohort, categorized patients into four groups depending on whether or not they were an “ideal candidate” for resection, and whether or not they underwent resection. Of the 8,656 enrolled patients, 1,624 who had undergone hepatic resection were non-ideal candidates as per the current guidelines. There was a survival benefit when non-ideal patients underwent surgery rather than TACE (hazard ratio for survival 1.26,  $P < 0.001$ ).<sup>5</sup> Although it may be prudent to suggest hepatic resection to patients who do not meet international criteria, it is noteworthy that resection of non-ideal candidate yielded better survival benefit compared to other treatments.<sup>36</sup>

Several recent studies have shown that surgery in patients with intermediate stage HCC is as good as an early stage in terms of survival benefit.<sup>37,38</sup> In a retrospective study con-

**Table 3.** Comparison of hepatic resection versus TACE in HCC patients with intermediate stage

Year	Study design	Treatment group	Patients number	Tumor burden	Child-Pugh A/B (n)	Median OS (months)	3-year OS (%)	5-year OS (%)	P-value*
2014	Randomized controlled trial	Surgery	88	Resectable outside Milan criteria (no vascular invasion and extrahepatic metastasis)	87/1	41	51.5	NR	$< 0.001$
		TACE	85		80/5	14	18.1	NR	
2011	Prospective	Surgery	85	Intermediate stage and solitary tumor $\geq 5$ cm	81/4	22.5	35.3	23.9	0.26
		TACE	83		82/1	19.5	26.0	18.9	
2017	Retrospective	Surgery	132	Intermediate stage	132/0	64	63.4	53.1	0.01
		TACE	132		132/0	41	53.0	34.1	
2016	Retrospective	Surgery	52	Intermediate stage	51/1	61	65.0	51.8	0.02
		TACE	225		187/38	30	39.2	27.9	
2016	Retrospective	Surgery	274	Intermediate stage	274/0	31.9	46	37	$< 0.001$
		TACE	169		169/0	14.3	15	12	
2015	Retrospective	Surgery	36	Intermediate stage	32/4	NR	52.8	44.4	0.23
		TACE	44		29/15	NR	47.7	38.6	
2014	Retrospective	Surgery	433	Intermediate stage	328/105	24.8	71.1	61.2	$< 0.001$
		TACE	490		381/109	26.9	62.2	45.1	

TACE, transarterial chemoembolization; HCC, hepatocellular carcinoma; OS, overall survival; NR, not reported.

\*Multivariate Cox regression models were used for P-value.

ducted in Asia, HCC patients with intermediate stage showed comparable 5-year survival rates and median survival (50.5% of 5-year survival, 60.4 months of median survival time in patients with intermediate stage HCC).<sup>38</sup> A multi-institutional database enrolled 875 patients who underwent surgery, of which 380 had tumor burden of single >5 cm or multinodular. The results showed that the overall survival rate was superior as compared to survival rates in patients treated with TACE in previous studies (1-year, 3-year, and 5-year overall survival, 74%, 50%, and 39%, respectively,  $P<0.001$ ).<sup>39</sup> Furthermore, a prospective study comparing TACE and hepatic resection as initial treatment enrolled 168 patients with resectable, multiple nodules, and diameter of main tumor 5 cm or larger. Overall survival rates were 23.9% for the hepatic resection group and 18.9% for the TACE group although there was no significant difference of survival between the two groups because of small study numbers ( $P=0.26$ ).<sup>32</sup>

## CONCLUSIONS

According to the current treatment guideline, TACE is the standard care for intermediate stage HCC. However, there are three major aspects that should be considered while indicating TACE in patients with intermediate stage HCC: 1) heterogeneity of intermediate stage, a wide range of tumor burden and liver function, 2) TACE refractoriness, and 3) good survival outcomes of surgical treatment in some HCC patients with intermediate stage. Expanding the indications for hepatic resection in patients with intermediate stage HCC still remains controversial, and most of the previous studies comparing survival benefit of resection and TACE were retrospective. However, surgical resection may provide survival benefits in patients with intermediate stage HCC who had good liver function and resectable HCCs, and particularly who were predicted to have a poor prognosis after TACE treatment such as TACE refractoriness. More evidence through a well-designed, randomized control study is required for expanding surgical criteria for intermediate stage HCC and identifying patients who have survival benefits when treated with resection over TACE.

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## Conflicts of Interest

The authors declare no conflicts of interest relevant to this article.

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