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Liver Resection for Hepatocellular Carcinoma Beyond BCLC A Stage

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The barcelona clinic liver cancer (BCLC) staging systemis regarded as the optimal staging system to predict prognosis and guide treatmentfor hepatocellular carcinoma (HCC) .According to the BCLC classification, only patients with BCLC A stage should undergo liver resection. In contrast, patients with intermediate-advanced HCC should be scheduled for palliative therapies,such as transcatheter arterial chemoembolization (TACE) and target therapy, even if the lesion is resectable. More and more studies report good short-term and long-term outcomes in patients with intermediate-advanced HCC treated by radical resection and many patients benefited from curative resection. The aim of this review was to evaluate the role of surgery beyond the BCLC recommendations. A revision of the BCLC algorithm should be proposed.

INTRODUCTION

Hepatocellular carcinoma (HCC) is ranked as the sixth most common cancer and the third leading cause of cancer-related deaths worldwide. HCC accounts for more than 600,000 deaths every year.[1] Nearly 54% of HCC patients are in China. It is one of the most common malignant tumors in China. Despite the increased frequency of surveillance programs, the majority of patients have an advanced HCC with the poor median survival (6-20 months) at diagnosiswhatever in Eastern or Western countries[2-4] and the overall 5 year survival rates is 3-5%.[5] Curative treatments, including liver transplantation, surgical resection or percutaneous ablation, are able to achieve a long-term survival of more than 50% at 5 years; Thus, in order to provide the best treatment for HCC, numerous HCC staging systems have been proposed in recent decades based on tumor status (defined by tumor size and number, presence of vascular invasion and extrahepatic spread), liver function (defined either by the Child-Pugh's class or individually by the levels of serum bilirubin and albumin, presence of ascites and portal hypertension) and general health status of the patient (defined by the ECOG classification and the presence of symptoms) including the tumor-node-metastasis (TNM) system, the Okuda system, the Barcelona Clinic Liver Cancer (BCLC) system, the Cancer of the Liver Italian Program (CLIP), the Chinese University Prognostic Index and the Japan Integrated Staging score (JIS) etc.[6] The ideal prognostic algorithm should be able to classify patients in subgroups based on shared characteristics that predict outcomes and also determine candidacy for specific therapies.[7,8] Among them, BCLC staging system is regarded as the optimal staging system to predict prognosis and guide treatment of HCC.[9]

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1. BCLC staging

The BCLC system was proposed by Llovet et al.[6] in 1999, and validated extensively in 2002, 2005, and 2010.[7,8] Based on the BCLC grading system, the corresponding recommended treatment for each stage is stratied (Fig. 1). Curative treatment is advocated for early HCC (BCLC A) (defined as a single tumor, or up to three tumors less than 3 cm in diameter), such as surgery, radiofrequency ablation, and liver transplantation. For intermediate HCC (BCLC B)(two to three tumors of which at least one is more than 3 cm in diameter; or more than 3 tumors of any diameter), TACE is recommended as the standardized treatment.[9-11] The advanced stage (BCLC C) relates to patients with extrahepatic spread, vascular invasion and/or mild cancer-related symptoms (ECOG grade 1-2); the tyrosine kinase inhibitor sorafenib is the only treatment with proven survival benefit in this setting.

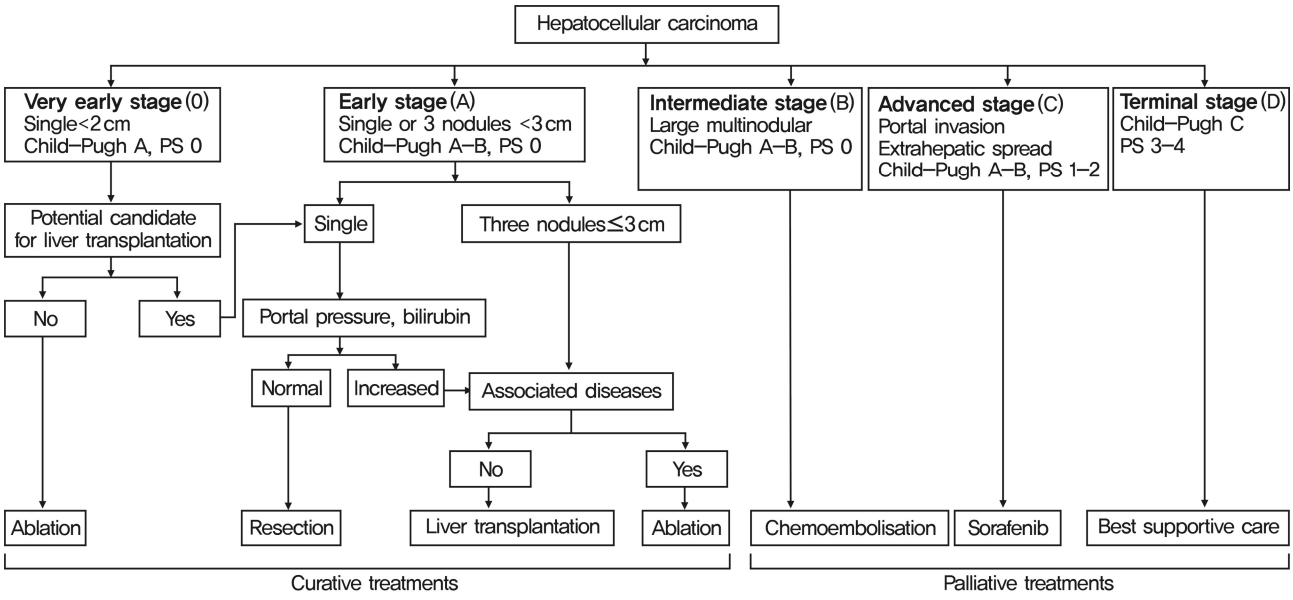

Fig. 1. BCLC staging and treatment strategy.

The BCLC staging system has been externally validated in different clinical settings.[10-12] Since the original publication of the BCLC algorithm in 1999,[13] its parameters have been used in most prospective trials assessing the efficacy of new treatments[14-16] and the usefulness of this tool has been acknowledged by several scientific associations, such as European Association for Study of the Liver (EASL) and American Association for the Study of Liver Disease (AASLD).[17-21]

2. Intermediate HCC (BCLC B)

In patients with BCLC B staging, TACE is the standard of care (SOC) which is based on a meta-analysis of seven studies[19] showing that repeated treatment with TACE was associated with improved survival of an average of 20 months in patients with intermediate HCC.

There is disagreement about the evidence showing increased survival following TACE in the above mentioned meta-analysis because the benefits in survival were based on two randomized studies that enrolled patients with fairly advanced HCC. In fact, in those two studies the 3-year predicted spontaneous survival of 8 and 20 months was definitively lower than the 50% predicted survival of untreated patients with an intermediate HCC originally described by Llovet et al.[14] Another weakness of the meta-analysis was the lack of standardization of studies with TACE in relation to embolization procedures.

In Asia, espcially in China, nearly half of patients with primary HCC are diagnosedin an advanced stage. If you followed the BCLC strategy, a lot of patients will lost the chances of radical treatment. Numerous studies, mostly fromAsian countries, indicate that hepaticresection can be safe and effective in patients with IntermediateHCC[22-29](Table 1). Recently, several large scale studies suggested that hepatic resection might be beneficial to the HCC cases in the BCLC stage B. Torzilli[28] investigate in a retrospective setting the patients' profile and results of those undergoing surgery for hepatocellular carcinoma (HCC) in high-volume surgical centers throughout the world. 2046 consecutive patients resected for HCC in 10 centers were collected. According to the BCLC classification, 737 (36%) BCLC B, and 297 (14%) BCLC C received resection. The 5-year overall survival rates were 57% for BCLC B and 5-year disease-free survival rates were 27% for BCLC B. The author draw the conclusion: hepatic resection provides acceptable short- and long-term results for the cases beyond the BCLC staging and the EASL/AASLD therapeutic guidelines needed to be updated in this sense. In BRIDGE study, Roayaie et al,[30] analyzed the survival of 8,656 cases with HCC between 2005 and 2011, hepatic resection achieved a significantly better survival than TACE for patients in BCLC B. In Vitale et al and Farinati et al's study,[31,32] hepatic resection also achieved better overall survival than TACE for the patiens in BCLC B staging who were enrolled by the Italian Liver Cancer group. Yin 's study,[29] the first one RCT study on resection vs TACE on cases in BCLC B, 173 patients were randomly assigned to the resection group or the TACE group. The 1-, 2-, and 3-year overall survival (OS) rates were 76.1%, 63.5%, and 51.5%, respectively, for the resectiongroup com-

Table 1. Results of liver resection in a recently published surgical series in which surgery was performed in HCC in intermediate hepatocellular carcinoma

Ref.	Year	Patients (n)	Mortality/morbidity %	Median OS month	5-yr survival %
Wang et al[22]	2008	243	NR/NR	60.4	50.5
Ho et al[23]	2009	122	NR/NR	41.8	36.6
Lin et al[24]	2010	93		27.6	30.9 (3-yr)
Hsu et al[25]	2012	268	2.7%/NR	NR	63
Zhonget al[26]	2013	257	3.1/28	42.9	37
Zhonget al[27]	2014	660	NR/NR	NR	44
Torzilliet al[28]	2013	54	NR/NR	NR	12
Yin et al[29]	2014	88	NR/NR	41	51.5 (3-yr)

pared with 51.8%, 34.8%, and 18.1%, respectively, for the TACE group (p<0.001). Multivariate Cox proportional hazards regression analysis revealed the type of treatment (hazard ratio, 0.434; 95% CI, 0.293 to 0.644, p<0.001) was significant independent risk factors associated with OS. In Qin's study,[33] a systemic review and meta-analysis were carried out.Fifty of 2029 retrieved papers were included. One, 15, and 34 studies were of high-, moderate-, and low-quality, respectively. The overall meta-analysis demonstrated a statis tically significantly higher overall survival in hepatic resection group than in TACE group for HCC cases beyond the BCLC stage A. In HCC patients with BCLC stage B alone, the subgroup meta-analysis demonstrated a statistically significantly higher overall survival in hepatic resection group than in TACE group (HR=0.48, 95% CI=0.25- 0.90, p=0.02). In HCC patients with BCLC stage C, the subgroup metaanalysis demonstrated a statistically significantly higher overall survival in hepatic resection group than in TACE group (HR=0.78, 95% CI=0.68-0.91, p=0.0009) .But the author also addressed that the limitations of study is the quality, onlyone high quality study involved, more well-designed randomized controlled trials should be warranted to confirm these findings.

At the meantime, some author[34] stillsurpport the BCLC staging. They pointedout thatthe misclassification in some articles leads so many patients into the wrong BCLC stage (B instead of A) may account for the favorable outcome of surgery. From the original formulation of the BCLC classification up to the last EASL/AASLD guidelines, all single HCCs of any size—with no satellites and/or vascular invasion—should be classified as early BCLC-A stage. while recent developments with TACE including new, more effective embolizing agents such as doxorubicin-loaded (DC) beads and microspheres loaded with Yttrium-90[26] allow a more standardized approach, whichmay enhance the effect of conventional TACE, cohort studies[35,36] with adequate selection of candidates have reported reasonable median survival beyond 40 months after DEB-TACE.

3. Advanced HCC (BCLC C)

HCC at an advanced stage is with extrahepaticmetastases (M1) and/or lymph node metastases (N1) and/orportal invasion established by imaging techniques and/orhepatic impairment (performance status 1-2), which makeup about 40-70 % of the total population of HCC patients, The median survival of untreated HCC with PVTT (portal vein tumor thrombosis) and HVI (hepatic vein invasion) are 2.7 and 5 months, respectively.[36,37] According to the guidelines of the BCLC, should be treatedwith systemic chemotherapy. Until 2005, no chemotherapywas effective in the treatment of advanced-stage HCC with TACE contraindication. From the SHARP trial (phase III)[15] in manycountries in 2008, 602 patients with advanced HCC and C-P classification A cirrhosis were randomly assigned to the sorafenib or placebo group. Improvement of medianoverall survival was seen in the sorafenib group (10.7 mo vs 7.9 mo, HR=0.69, p<0.001). In 2009, another phase III trial in the Asia-Pacific region (ORIENTAL study)[16] reported 226 patients ofadvanced HCC with C-P classification A cirrhosis whoreceived sorafenib 400 mg twice daily or placebo. Patients with sorafenib therapy had better median OS (6.5 mo vs 4.2 mo). Thus, sorafenib was approved by the Food and Drug Administration in November 2007 inthe United States and has now become the standard-care for first line systemic treatment in advanced hepatocellular carcinoma. From then on Sorafenib is considered to be a standard therapy for the advanced HCC (BCLC C).

Even this thereported survival of these patients after Sorafenib treatmentis only 6-10 mo.[15,16] Macrovascular invasion (MVI) is one of the strongestpredictors of survival in patients with HCC because itis related to an increased risk of intrahe-

Table 2. Results of liver resection in a recently published surgical series in which surgery was performed in HCC in advanced hepatocellular carcinoma

Ref.	Year	Patients (n)	Mortality/morbidity %	Median OS month	5-yr survival %
Pawlik et al[40]	2005	102	5.9/NR	11	10
Le Treut et al[41]	2006	26	11.5%/38.5%	12	13
Ruzzenente et al[42]	2009	17	NR/NR	27	20
Inoue et al[43]	2009	49	0%/NR	NR	39-41
Ban et al[44]	2009	45	0.0%/21.1-23.1%	NR	22.4
Chok et al[45]	2013	88	3.4%/37.1%	8.5-10.9	11.2-14.3
Wang et al[46]	2013	25	0.0%/40.0%	19	13.5

patic or extrahepaticmetastases.[38,39] With the development of surgical skills and perioperative management, hepaticresection can be safe and effective in patients with HCC involving PVTT.

Most of these studies[40-46] are from Asian countries (Table 2). A large retrospective study from Japan compared OS of 2093 HCC patients with PVTT who underwent hepatic resectionand 4,381 patients who received other treatments.[47] Median OSwas significantly longer in the resection group (2.87 yr) than in thegroup that received other treatments (1.10 yr), corresponding to asurvival benefit of 1.77 years for hepatic resection. A large multicentricstudy recruiting patients from Asia and Western countries showedlong-term survival approaching 31% at 5 years when surgery wasoffered to these patients.[48] Therefore, the survival benefit of sorafenib is not obvious, also accompanied with high costs. In the literature, better survival rates are reported forselected patients with PVTT, with a 5-year survival rateranging from 11% to 42%.[49-52]

A system review[53] identified 24 studies with 4,389 patients that investigated HR to treat HCC with MVI. 5-yr OS was 14-18%.

Besides the resection, based on the opinions of Asian experts, there are numerous alternative options aside from sorafenib for the treatment of BCLC stage C HCC, including (HAI) hepatic arterial infusion chemotherapy (TACE) transarterialchemoembolization, and external radiotherapy. Moreover, there are several studies[54-65] on the multimodality managementof BCLC stage C HCC, mainly in the form of retrospective studies and a few phase I andII trials. Multimodality management with combinations of various locoregional therapies orlocoregional therapies with systemic targeted therapy using sorafenib needs to be activelyinvestigated. The strength of evidence according to study design or end-points on multimodality management for BCLC stage C (advanced stage) HCC is weak. As a result, a consensus for managing BCLC stage C HCC cannot be easily established. Thus, randomized controlled clinical trials or meta-analyses of randomized studies on multimodality management suitable for BCLC stage C HCC should be actively pursued.

CONCLUSIONS

Currently, the BCLCalgorithm excludes manypatients from curative treatment, although they maybenefit from liver resection. Various and worldwide spread reports suggestthat surgery could be a proper treatment also for many patients withintermediate or advanced HCC. It is not the time to debate whether or not surgery should been given for these patients, It is the time to focus on selection criteria tofurther enhance the prognostic benefits of resection.

Therefore, we know intermediate and advanced stage HCCs encompass a heterogeneous group of patients, subclassification of this heterogeneous patient population and indication of treatment strategy according to its substage is an extremely important issue to address.

Bolondi et al.[66] proposed a subclassification of intermediate-stage HCCs in 2012 (Table 2). Kudo et al.[67] proposed a more simplified subclassification of BCLC B Kinki criteria In 2015. Sinn et al proposed Sub-classification of BCLC stage Caccording to the extent of PVI and type of extrahepatic spread (ES).[68] All these Sub-classification of BCLC stage C will help better predict survival and select optimal treatment strategies. But these criteria should be further validated both retrospectively and prospectively.

The progressive unveiling of genomic changesunderlying hepatocarcinogenesis would allow better stratificationof risk of developing HCC and more preciseselection of patients for best therapy according toindividual molecular signatures. Currently, a widely accepted molecular classificationsystem for HCC is still not available. Future perspectives should include the identification of molecular panel able to classify different patients according to their expected survival. This

molecular classification could suggest the tailored type of treatment including new target therapies. Thus, a revision of the BCLC algorithm should be proposed.

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