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Rethinking the Barcelona clinic liver cancer guidelines: Intermediate stage and Child-Pugh B patients are suitable for surgery?

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Abstract

According to Barcelona Clinic Liver Cancer recommendations, intermediate stage hepatocellular carcinomas (stage B) are excluded from liver resection and are referred to palliative treatment. Moreover, Child-Pugh B patients are not usually candidates for liver resection. However, many hepatobiliary centers in the world manage patients with intermediate stage hepatocellular carcinoma or Child-Pugh B cirrhosis with liver resection, maintaining that hepatic resection is not contraindicated in selected patients with non-early-stage hepatocellular carcinoma and without normal liver function. Several studies demonstrate that resection provides the best survival benefit for selected patients in very early/early and even in intermediate stages of Barcelona Clinic Liver Cancer classification, and this treatment gives good results in the setting of multinodular, large tumors in patients with portal hypertension and/or Child-Pugh B cirrhosis. In this review we explore this controversial topic, and we show through the literature analysis how liver resection may improve the short- and long-term survival rate of carefully selected Barcelona Clinic Liver Cancer B and Child-Pugh B hepatocellular carcinoma patients. However, other large clinical studies are needed to clarify which patients with intermediate stage hepatocellular carcinoma are most likely to benefit from liver resection.

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Core Tip: According to Barcelona Clinic Liver Cancer recommendations, intermediate stage hepatocellular carcinomas are excluded from surgery. Also, Child-Pugh B patients with hepatocellular carcinoma are not usually candidates for liver resection. Nevertheless, several recent studies demonstrated that surgical resection can provide good survival benefit for patients with large and multinodular (diameter > 5 cm, number > 3) hepatocellular carcinoma or Child-Pugh B cirrhosis. In this review we discuss that liver resection may improve the short- and long-term survival of selected patients who have a stage B hepatocellular carcinoma or underlying Child-Pugh B cirrhosis.

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INTRODUCTION

The most common primary liver tumor is hepatocellular carcinoma (HCC), which is the third leading cause of cancer mortality worldwide[1]. The incidence of HCC is increasing in Western countries due to the effects of nonalcoholic fatty liver disease[2-5]. Literature data show how surgery is the therapeutic approach for HCC associated with the most favorable results[6]. The surgical treatments available for patients with HCC are liver resection (LR) or liver transplantation (LT)[2,4,7]. LT is theoretically considered the best treatment of HCC because in addition to treating the neoplasm it also corrects the underlying liver cirrhosis, minimizing the tumor recurrence[2,4,8]. Given the limited number of liver grafts, it is applied only in a small group of patients who meet the Milan criteria[9]. LR can be applied much more widely than LT, but it is usually performed on an unhealthy liver[2,3,7]. LR is a nonprojectable therapeutic option that includes the risk of cancer progression pending a suitable organ[10]. Nevertheless, LR is associated with considerable postoperative morbidity and mortality, and the early and late recurrence rates after this surgical approach remain high[11,12].

The American Association for the Study of Liver Diseases, the European Association for Study of the Liver, and the European Organization for Research and Treatment of Cancer have endorsed the Barcelona Clinic Liver Cancer (BCLC) staging and management system for treating HCC[13-16]. These Western guidelines limit LR to ideal patients, including those in BCLC stage 0 and a subset of patients in BCLC stage A, *i.e.* those with a single tumor without invasion of the main branches of the hepatic or portal vein, preoperative hepatic venous gradient < 10 mmHg, normal bilirubin values, Child-Pugh class A liver function, and good general condition (Figure 1). These stringent surgical indications combine low postoperative mortality rates and optimal long-term results with 5-year survival rates of up to 60%[3,5,17,18].

BCLC stage B include patients with Child-Pugh A and B scores with asymptomatic multicentric tumors (> 3) without vascular invasion or extrahepatic spread. For this group of patients, the BCLC staging system indicates transarterial chemoembolization (TACE) as the main treatment option[13]. TACE seems to provide a better 2-year survival rate than supportive treatment with an average life expectancy of 18-27 mo[19,20]. However, it is unclear whether TACE offers an effective benefit to long-term survival in these patients. BCLC stage B is a heterogeneous category that includes cases that vary widely in size of tumor, number of lesions, and liver function[19,21]. Due to this heterogeneity, TACE may not be the optimal therapy for all patients with stage B HCC[22,23]. Considering the poor prognosis associated with a nonresected HCC, several centers have moved away from these guidelines, reporting acceptable

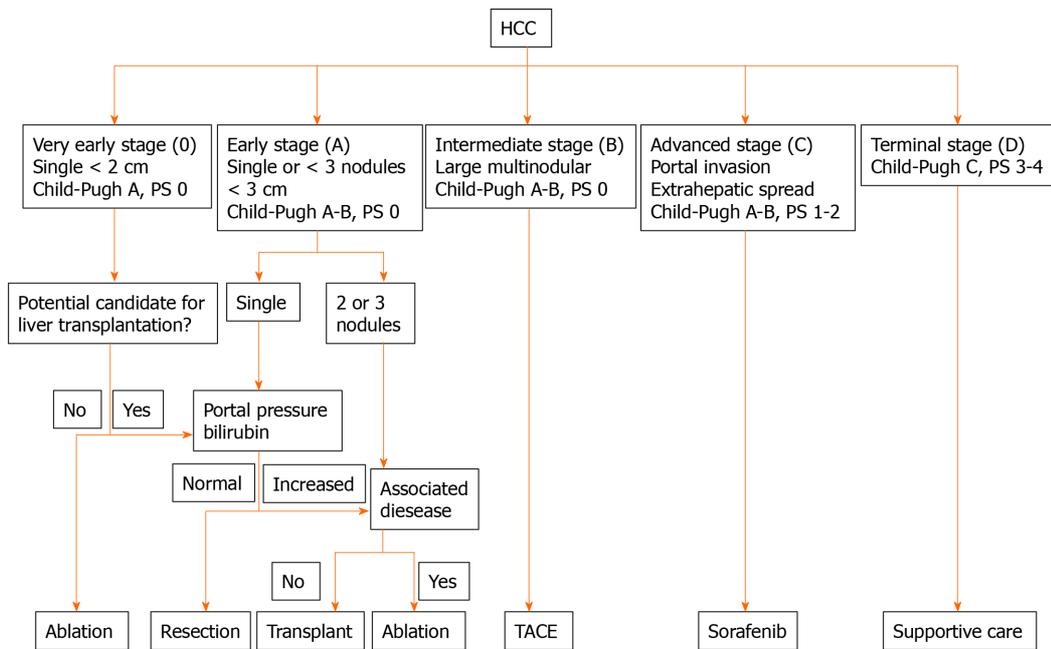


Figure 1 Child-Pugh class A liver function and good general condition. HCC: Hepatocellular carcinoma; TACE: Transarterial chemoembolization.

short-term survival (mortality from 0% to 5%) and long-term survival rates (ranging from 40% to 60% at 5 years) in BCLC stage B patients treated with LR[24-27]. These recent studies have verified that surgical resection can be safely performed on a subset of patients presenting BCLC stage B HCC, resulting in a long-term survival rate longer than patients that underwent TACE[28,29]. In addition, TACE can only be performed in cases of preserved liver function, and consequently it is not indicated in patients with impaired hepatic functional reserve for the high risk of postoperative liver failure[19,20,30].

In the past decades the presence of underlying cirrhosis was noted to be a negative prognostic factor for HCC recurrence in patients treated with surgery[31,32]. The 5-year survival rates after LR for HCC were different between cirrhotic and noncirrhotic patients (55% vs 80%); moreover the survival in Child-Pugh B cirrhosis was poorer than in Child-Pugh A cirrhosis (55% vs 28%)[31]. The primary reason of this marked survival difference is currently considered the multicentric carcinogenesis associated with the chronic liver disease. Consequently, in the clinical setting, surgical resection in Child-Pugh B patients tends to be avoided due to the high incidence of postoperative complications and discouraging long-term results[27,33,34]. Minimally invasive techniques have recently been applied to liver surgery with important benefits for patients. In particular, laparoscopic techniques seem to be associated with a lower rate of liver failure in the postoperative period, allowing LR to be performed with satisfactory results even in patients with Child-Pugh B or C cirrhosis[35].

The purpose of this minireview is to illustrate the possible surgical treatment of HCC in intermediate stage of BCLC classification and in Child-Pugh B patients.

LIVER RESECTION IN BCLC-B STAGE PATIENTS

About 20% of patients with HCC are classified as BCLC-B (intermediate stage). These patients present a survival of 50% at 2-year follow-up[2,5,7]. According to Western international recommendations, patients with intermediate HCC are considered unresectable, and TACE is recommended as a standard treatment[14,15]. The cumulative survival time of patients with BCLC-B HCC has been reported to vary from 24 to 60 mo (with overall 5-year survival rate ranging from 0% to 10%) for the best responders to TACE[36,37]. Advances in surgical technique and perioperative care expanded the indications for LR, and consequently surgery has recently been proposed for stage B patients[26,29]. Several studies have shown that LR for an intermediate stage HCC is associated with a promising 5-year survival rate ranging from 25% to 60% with median survival time varying from 20 to 60 mo[38-41]. Moreover, data from other groups show that LR offers satisfactory results for patients

selected at intermediate and advanced stages of the BCLC classification (stage B and C), in the context of large or multinodular tumors[24,42,43].

In 2013, Torzilli *et al*[44] promoted a multicenter East-West observational study on LR in HCC, questioning the European Association for Study of the Liver-American Association for the Study of Liver Diseases guidelines. This study found that the patients who underwent resection for BCLC-B, defined as “single tumor with a diameter greater than 5 cm; two to three tumors with at least one greater than 3 cm in diameter; more than three tumors with any diameter” were characterized by 1-, 3-, and 5-year survival rates of 88%, 71%, and 57%, respectively. These figures were higher than those expected after TACE. Recently, a systematic review about the role of resective surgery in large (> 5 cm) and multinodular HCC found that LR was associated with a 5-year survival of 42% in Asian studies and 32% in non-Asian studies[45]. Chang *et al*[46] analyzed a large cohort grouped according to the tumor size and found that patients with large (between 5 and 10 cm) and huge (> 10 cm) HCCs were associated with 1-year survival of 82% and 68% respectively, and 5-year survival of 50% and 35%, respectively, after curative LR. Similar survival rates about huge (> 10 cm) HCCs were also recorded by other authors[42,47-49]. To date, patients with a single HCC larger than 5 cm are in a “grey area.” Initially, large (HCCs > 5 cm) were categorized as BCLC stage B. Currently, some Western experts and Eastern guidelines propose to classify these patients as initial stage, beyond the size[6,50,51].

Another systematic review excluded all those patients in the so-called “grey area” of intermediate BCLC stage with a single large lesion (> 5 cm). Median survival of patients resected for multinodular HCCs in BCLC stage B was 37 mo with a 5-year survival rate of 35%[22]. The 5-year survival was higher for patients with a number of carcinomas less than four *vs* four or more (49% *vs* 23%). In fact, a substantial percentage of patients with multiple HCCs in the early stage and exceeding the BCLC criteria for surgery, survived longer than expected after curative resection[52-55].

A large meta-analysis, based on high-quality studies, suggested that LR may increase the overall survival in patients with intermediate and advanced liver cancer in comparison to TACE[56]. In a recent study, Tada *et al*[57] concluded that LR is superior to TACE in BCLC-B patients with HCC with three nodules or less in Child-Pugh A cirrhosis. The superiority of surgery over TACE in class B BCLC patients was confirmed in four meta-analyses[58-61], one clinical trial[28], and one large observational study[62].

Not all BCLC-B HCC patients are good candidates for surgery. LR is even considered a futile procedure for patients with unfavorable short and mid-term outcomes, such as 90-d postoperative death or early tumor recurrence (within 1 year)[63]. Xu *et al*[64] proposed a discriminant criterion (tumor size < 11 cm or number of lesions < 4) for selecting stage B patients with the aim of receiving curative surgery. Moreover, Wada *et al*[65] identified three types of HCC based on the number and the diameter on imaging: type 1, up to 3 lesions < 5 cm; type 2, up to 3 lesions ≥ 5 cm or 4 tumors of any size; and type 3, > 4 tumors. These authors demonstrated that type 1 patients were associated with better survival than type 3. Intuitively the prognosis of type 2 patients was intermediate between type 1 and type 3 patients.

According to these large and high-quality studies, the Japanese Society of Hepatology, the Asian Pacific Association for the Study of the Liver, and the Chinese Liver Cancer Staging System recently proposed treatment algorithms in which patients with intermediated stage HCC are potential candidates for hepatectomy[8,50,66].

LIVER RESECTION IN CHILD-PUGH B CIRRHOSIS PATIENTS

According to BCLC guidelines, the ideal candidate for LR is the early-stage cirrhotic patient with a single small size lesion[13-15]. On the contrary, it is generally accepted that early stage HCC in Child-Pugh C cirrhosis patients without significant associated diseases should be listed for LT, according to the inclusion criteria[9,67]. Moreover, the indications for TACE should be carefully evaluated in patients with impaired hepatic functional reserve for the high risk of liver failure[19,30]. Furthermore, definitive treatment indications for patients, presenting with HCC with underlying Child-Pugh B cirrhosis, are lacking, and consequently therapeutic allocation remains controversial [27,31,34,68]. In the clinical setting, the indication for LR is dictated by the severity of the hepatic dysfunction and the resection volume that should be performed on the basis of the size and number of HCCs.

In the past decades the presence of cirrhosis in HCC patients undergoing LR was associated with a higher rate of perioperative complications and reduced 5-year

survival rate compared to patients treated with LT; this prognostic difference was more evident in Child-Pugh class B patients[31]. Nevertheless, as a result of recent interest in expanding eligibility for LR, many surgeons believe that well-selected Child-Pugh B patients should not be excluded a priori because good short and long-term survival rates could probably be obtained[31,33,69]. In accordance with this approach, consensus-based HCC treatment guidelines of the Japan Society of Hepatology consider LR for a wide range of HCC patients, including those with Child-Pugh B liver function, multiple tumors (regardless of size), or minimal portal invasion[66]. However, it must be highlighted that surgical resection in Child-Pugh B cirrhosis is associated with considerable postoperative morbidity and mortality, and surgical indications should be carefully weighed. In a recent study the 90-d mortality in Child-Pugh B patients was 10% in cases of major hepatectomies and 3% in segmentectomies[70]. However, it should be remembered that the frequency of adverse events in hepatic surgery still remains significant[71]. A systemic review reported a postoperative complication rate ranging from 27% to 32% and mortality rate from 2.7% to 7.3% after LR among Child-Pugh A and B patients[45].

In a cohort of 137 cases of Child-Pugh B cirrhosis with primary HCC, Harimoto *et al*[72] demonstrated that the overall survival rate in patients that underwent LR was not different from the rate in living donor LT. The main difference between these two types of surgical treatment consisted in the higher incidence of HCC recurrence in patients undergoing LR[31,72,73]. In this context, LR for HCC in Child B patients can be performed with acceptable postoperative morbidity and mortality with a 5-year overall survival of 50%-70%[72,73].

Laparoscopic liver surgery has recently been associated with a lower rate of hepatic failure, ascites production, and overall postoperative complications. This is mainly due to the conservation of extrahepatic collaterals and reduced liver mobilization compared to the open approach[74-76]. Therefore, the development of the minimally invasive laparoscopic approach, aiming to minimize surgical stress and improve patient recovery, allows the subsequent application of these techniques in advanced cirrhotic patients[35,77]. Laparoscopic indications for LR was recently expanded to include major hepatectomies[78]. In the English literature the laparoscopic approach to HCC is well described for Child-Pugh A cirrhosis[74,76,79]. Recently, a single institution series reported LRs in Child-Pugh B and C cirrhotic patients with acceptable results. To date, these data are scarce and come mainly from Asian studies[80-83]. Brytska *et al*[81] performed a subgroup analysis in advanced cirrhotic patients undergoing laparoscopic resection for HCC, including 13 Child-Pugh B and 3 Child-Pugh C patients. Laparoscopic LRs included ten tumorectomies, two segmentectomies, three left lateral sectionectomy, and one right anterior sectionectomy. The authors reported an overall complication rate of 19%, with a 12% occurrence of major postoperative complications (pleural effusion and variceal bleeding), without 90-d mortality. They reported an overall survival of about 85% and a disease-free survival of 42% at the 5-year follow-up.

CONCLUSION

Currently, TACE and sorafenib are indicated for intermediate and advanced HCCs; surgery is not recommended for HCC in BCLC stage B or associated with Child-Pugh B cirrhosis because of unproven survival benefit.

With the advancement of surgical techniques and the consequent reduction of postoperative complications, many experiences have been accumulated to support the advantages of surgery in treating intermediate HCC patients[26,28,29,62]. Recent systematic reviews show how LR is associated to better long-term survival than TACE in patients with stage B HCC. The 5-year survival rate associated with LR can be up to 35%[22,23]. Indeed, in the past decades, several studies have highlighted that LRs performed on multinodular HCC offer satisfactory long-term results, associated with acceptable perioperative morbidity and mortality[52,84,85]. Moreover, the Japanese and Chinese guidelines recommend surgery as a treatment modality for a wide spectrum of HCC patients, including those with Child-Pugh B liver function, multiple tumors, or minimal portal invasion[50,66]. Based on encouraging data, many hepatobiliary centers around the world manage patients with intermediate stage liver cancer with LR, claiming that surgical resection is not contraindicated in selected patients with non-early-stage liver cancer[17,29,38,40,41].

Hence, the restriction of surgical resection to a small subset of patients, as suggested by the Barcelona approach, can be rethought for various reasons. First, the safety of

extensive hepatic surgery improved significantly, making LR a feasible option even for patients with suboptimal liver function or poor performance status[35,70]. Second, surgery does not counterpose TACE. The latter can be used as an additional procedure to decrease tumor volume and give chance for surgery in selected BCLC stage B[86-89]. Finally, the accuracy of the current diagnostic exams may be limited in particular cases of macronodular cirrhosis, leading to possible erroneous classifications with serious consequences on the therapeutic objectives (curative *vs* palliative). Preoperative case selection is essential to reduce surgery risks, possibly identifying the candidate who could profit rather than be harmed by LR.

In 2012, Bolondi *et al*[21] proposed a classification of BCLC B stage into four substages to better identify the prognosis of this heterogeneous class of patients and at the same time suggested the therapeutic options for each category. In this context, a multicenter observational study highlighted how surgical resection is associated with better results in B1/B2 stage than B3/B4[29], according to the subclassification proposed by Bolondi *et al*[21]. Moreover we believe that the type of resection must be balanced with the underlying liver function to direct the patient towards the safest effective oncological treatment. Indeed, the removal of the tumor and preservation of the liver parenchyma are equally important, as both contribute to determining patient survival. In this perspective the Kinki criteria simplify the Bolondi substaging system[90]. Based on Child-Pugh score (5-7 or 8-9) and “up-to-7” rule (the sum of the number of nodules plus the diameter of the largest lesion), BCLC stage B HCCs are subdivided into three subgroups (B1, B2, B3). B1 class is characterized by relatively preserved liver function (Child-Pugh A 5-6 or Child-Pugh B7) and tumor burden within “up-to-7” criterion. According to these authors only patients with B1 HCC can benefit from LR[90].

LR in Child-Pugh B cirrhosis has been reported as an alternative treatment to LT, with promising short and long-term outcomes[72,73]. Moreover laparoscopic LR can be safely performed in selected Child-Pugh B patients with acceptable perioperative outcomes, although to date long-term results are not available[80-83]. Further studies are needed to clarify which Child-Pugh B patients with HCC are suitable candidates for laparoscopic LR, hoping to optimize the chances of long-term survival[35]. To date minimally invasive surgery could be proposed in patients with a satisfactory functional reserve of the liver and less aggressive tumors[74]. Nevertheless, it should be noted that data are scanty and come mainly from single institution case series. Moreover, LR in Child-Pugh B patients is characterized by significant 90-d mortality and morbidity rates, and consequently a tailored therapeutic approach could reduce the frequency of adverse events, offering good long-term results[63,54,70].

In our opinion additional radiological and laboratory data (*e.g.*, tumor location and distribution, serological markers), predictive of radical resection, should be incorporated into the staging system to select patients who may benefit from surgery. In this perspective, the Japanese Society of Hepatology indicated contrast-enhanced magnetic resonance imaging the pivotal exam in the preoperative work-up[66].

According to the most recent experiences, LR may improve the survival of Child-Pugh B and BCLC B carcinoma when patients are carefully selected and surgery is performed in specialized centers. Moreover, the mini-invasive approach allows pushing up the limits of LR in this stage of the disease[75,82]. Consequently, indications for resection could be expanded to include patients from therapies associated with satisfactory results. Nevertheless, randomized controlled trials must be planned to clarify which patients presenting with HCC beyond the classical indications are most likely to benefit from LR. In conclusion, these findings support the future expansion of indications for surgical resection in Western therapeutic guidelines.

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