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REVIEW

Intermediate hepatocellular carcinoma: How to choose the best treatment modality?

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Abstract

Intermediate stage, or stage B according to Barcelona Clinic Liver Cancer classification, of hepatocellular carcinoma (HCC) comprises a heterogeneous population with different tumor burden and liver function. This heterogeneity is confirmed by the large variability of treatment choice and disease-relate survival. The aim of this review was to highlight the existing evidences regarding this specific topic. In a multidisciplinary evaluation, patients with large (> 5 cm) solitary HCC should be firstly considered for liver resection (LR). When LR is unfeasible, locoregional treatments are evaluable therapeutic options, being transarterial chemoembolization (TACE), the most used procedure. Percutaneous ablation can be an evaluable treatment for large HCC. However, the efficacy of all ablative procedures decrease as tumor size increases over 3 cm. In clinical practice, a combination treatment strategy [TACE or transarterial radioembolization (TARE)-plus percutaneous ablation] is "a priori" preferred in a relevant percentage of these patients. On the other hands, sorafenib is the treatment of choice in patients who are unsuitable to surgery and/or with a contraindication to locoregional treatments. In multifocal HCC, TACE is the first-line treatment. The role of TARE is still undefined. Surgery may have also a role in the treatment of multifocal HCC in selected cases (patients with up to three nodules, multifocal HCC involving 2-3 adjacent liver segments). In some patients with bilobar disease the combination of LR and ablative treatment may be a valuable option. The choice of the best treatment in the patient with intermediate stage HCC should be "patient-tailored" and made by a multidisciplinary team.

Key words: Hepatocellular carcinoma; Percutaneous ablation; Hepatectomy; Chemoembolization; Liver transplantation; Combination therapy

Core tip: Intermediate stage, or stage B according to Barcelona Clinic Liver Cancer classification, of hepatocellular carcinoma (HCC) comprises a heterogeneous population with different tumor burden and liver function. This heterogeneity is confirmed by the large variability in treatment and survival, the choice of the best treatment in the patient with intermediate stage HCC is a difficult task. A multisciplinary evaluation of each intermediate stage HCC patient is recommended

for planning the best therapeutic strategy and this review was aimed to discuss about the existing evidences regarding this topic. Due to the heterogeneity of intermediate HCC, the use of different therapies (combination treatment) is likely the best choice in most of the cases offering the opportunity of a treatment tailored to the single patient.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common malignancy worldwide and the leading cause of death among cirrhotic patients[1,2]. The management of this cancer represents a challenge for physicians being complicated by the coexistence in the same patient of two severe diseases, HCC and cirrhosis. Therefore, in the last two decades several staging and prognostic systems have been proposed to better define the prognosis and the treatment strategy[3-9]. The Barcelona Clinic Liver Cancer (BCLC) classification was first published in 1999 by Llovet *et al*[6] and is actually the most widely used staging system. The BCLC classification takes into account cancer characteristics (number and size of nodules, macrovascular invasion, and extrahepatic metastasis), cirrhosis related variables (liver function and portal hypertension), and general health status of the patients (performance status). Using these parameters, five distinct HCC stages each associated with different prognosis and specific treatment recommendations are identified. In Western countries, between 20% and 30% of the HCC population at their first observation falls into the stage B and many patients progress to this stage during follow-up. Intermediate stage or stage B, according to BCLC, of HCC includes all Child-Pugh A or B patients, with a performance status 0, and with a single nodule > 5 cm, or multiple nodules > 3 in number or at least one of these > 3 cm, without macrovascular invasion and extrahepatic metastases. According to these criteria, the intermediate stage comprises a heterogeneous population with different tumor burden and liver function. This heterogeneity is confirmed by the large variability in survival among control patients of randomized controlled trials on transarterial chemoembolization (TACE), with a 1-year survival rate ranging from 3% and 75% (median 49.6%-test for heterogeneity, $P < 0.0001$)[10]. The unique treatment recommended by BCLC group for stage B patients is TACE with a wide range of expected survival, from 14 to 45 mo[11]. Therefore TACE is effective only in a proportion of intermediate patients, the others might likely benefit from other treatments. Due to this heterogeneity, diverse therapies, single or combined, are offered to intermediate patients in field practice. Unfortunately, guidelines to define the best therapeutic approach in the single patient are lacking. The main problem is to distinguish between stage B patients with expected better survival who could have the largest benefit from an aggressive therapeutic approach, and those with poor prognosis in whom treatment should be modulated to offer the best quality and duration of life to the patient. In the attempt to solve this issue, a panel of European experts in 2012 discussed about unresolved questions in the management of stage B patients and proposed a sub-classification into four stages to facilitate treatment decisions[12]. This sub-classification was based on Child-Pugh score, up-to-seven criteria, ECOG (Eastern Cooperative Oncology Group PS performance status), and portal vein thrombosis. The need for a sub-classification of intermediate patients has been claimed also by Asian experts[13] who recently proposed a modification of the European sub-classification using alpha-feto protein to re-classify patients into three modified stages[14]. Further studies are needed before these sub-classifications can be implemented in field practice.

Actually, a multisciplinary evaluation of each intermediate stage HCC patient is recommended for planning the best therapeutic strategy[15,16] and the aim of this review is to discuss about the existing evidences regarding this topic.

THERAPEUTIC PROCEDURES

Liver resection

According to the BCLC classification, patients with intermediate HCC are unsuitable for liver resection (LR). However, in the last decades advances in surgical technique, preoperative preparation, and postoperative care have expanded LR indications. Nowadays, peri-operative mortality after LR has decreased from 15% to less than 5% in referral centers. To prevent the occurrence of postoperative liver failure, two selection protocols have been proposed based on extimated resection volume and: (1) bilirubin serum level and indocyanine green retention rate at 15 min[17]; and (2) MELD score and serum sodium level[18]. Laparoscopic video-assisted LR is increasingly used as an alternative to the classical open procedure for reducing the risk of postoperative liver deterioration[19]. However, this technique is performed only in few centers and in a restricted proportion of patients due to the stringent selection criteria. In patients with huge cancer masses and poor remnant liver volume after LR, pre-operative percutaneous transhepatic portal vein embolization has been used to increase the size of non-tumorous liver[20,21]. In cirrhotic patients, this procedure may cause severe complications in up to 20% of cases and its use should be carefully evaluated[22].

Table 1 Main transarterial chemoembolization contraindications in Barcelona Clinic Liver Cancer stage B hepatocellular carcinoma

Liver failure
Refractory ascites
Encephalopathy
Bilirubin level > 3 mg/dL
Renal failure
Creatinine > 2 mg/dL or creatinine clearance < 30 mL/min
Coagulopathy
Platelet count < 50×10^9/L
Prothrombin time < 50% or prolonged > 4 s
Portal hypertension
Variceal bleeding within past 3 mo
Varices at high risk of bleeding
Circulatory impairment
Main portal venous thrombosis
Severely reduced portal flow or hepatofugal blood flow
Untreatable arteriovenous fistula
Hepatic artery thrombosis
Severe atheromatosis

Transarterial treatments

According to European and American guidelines, TACE is the first line treatment for BCLC B stage patients, but a large variability exists in the protocols, schedule, and indications among centers[23,24]. TACE can be performed with chemotherapeutic agents emulsified with lipiodol followed by embolic agents (conventional transarterial chemoembolization or c-TACE) or with embolic microspheres preloaded with chemotherapeutic agents [Drug Eluting-Beds-TACE (DEB-TACE)]. Main contraindications to TACE are shown in the Table 1. TACE can be scheduled at fixed intervals or "on demands". Prospective comparative studies between the two schedules are lacking, but this last option is likely more effective reducing the exposure of patients to the toxic effects of the treatment and increasing the compliance. When c-TACE is used, radiological assessment of tumor response must be done with magnetic resonance imaging because computed tomography evaluation is hindered by artifacts caused by lipiodol retention. It is not established how many times TACE can be repeated, but the treatment should be shifted from TACE to sorafenib (stage migration strategy)[11] in patients who have not experienced at least a partial response (according to mRECIST criteria)[25] after two TACE cycles. Furthermore, TACE should be discontinued when a deterioration of the performance status or of the liver function occurr.

Transarterial radioembolization (TARE) is a novel treatment using hepatic intra-arterial infusion of radioactive substances such as β-emitting yttrium-90 integral to the glass matrix of microspheres or Iodine-131-labeled lipiodol. Published series showed comparable median survival and toxic effects among patients treated with TACE and TARE, and therefore no defined selection criteria to choose between these techniques have been established so far[11,26-30]. Further studies are needed to evaluate the utility of TARE and its role in the treatment strategy of BCLC B stage patients. However, a widespread use of TARE is limited by its high costs.

Percutaneous treatments

Thermal ablation using radiofrequency (RFA), microwave (MWA), or laser (LA), is the most widely employed locoregional treatment for HCC. It achieves a complete ablation rate > 90% in nodules ⩽ 3 cm[31-33]. Due to the improvement in devices and techniques, percutaneous ablation has been demonstrated effective also for the treatment of large HCC[34-37]. In these cases, overlapping ablative technique with multiple electrode insertions or simultaneous use of multiple applicators are required to ablate the tumor[38]. This last technique may be more effective because the simultaneous activation of multiple electrodes has a synergistic effect increasing the ablation volume and reducing the procedural time.

Combination of locoregional treatments

The combination treatment strategy, using both transarterial and percutaneous procedures, offers the opportunity of a treatment tailored to the single patient. The occlusion of the hepatic arterial flow supplying the tumor with TACE would theoretically increase the ablation volume after RFA/MWA/LA by reducing the heat loss due to blood flow[39]. Furthermore, the alternate use of intravascular and percutaneous approach allows to increase the time interval between TACE procedures reducing the risk of liver failure caused by cumulating toxic effects. Several studies have evaluated the efficacy of combined locoregional treatments[40-49]. Metanalysis of observational and randomized controlled studies comparing single and combined locoregional treatments showed significant better survival in patients who underwent to combined treatment[50-55].

The combination of TACE and sorafenib has been evaluated in some studies[56-61]. The rationale of sorafenib use is to block vascular endothelial growth factor (VEGF) receptors for counterbalancing the increase in VEGF induced by post-TACE ischemia which facilitates tumor growth and metastasis[62]. It is still unclear if sorafenib potentiate the therapeutic effects of TACE[63]. However, a recent metanalysis including both randomized and retrospective trials showed that TACE-sorafenib combination increased the risk of adverse reactions, but was associated with better overall survival and longer time-to-progression[64].

TUMOR BURDEN AND TREATMENT STRATEGY

Monofocal HCC

In the setting of a multidisciplinary evaluation, patients with large (> 5 cm) solitary HCC should be firstly considered for LR[65-68]. Radical LR can be considered a valuable option in patients with: (1) peripherically located HCC, < 30% of tissue destroyed as evaluated

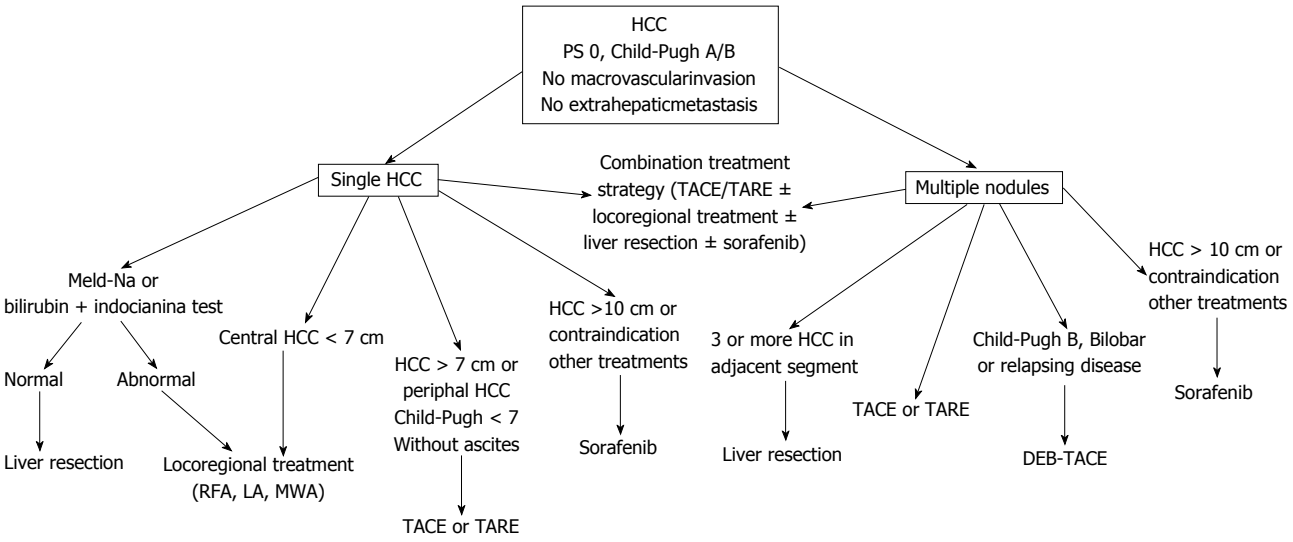

Figure 1 Treatment strategy for monofocal and multifocal hepatocellular carcinoma. HCC: Hepatocellular carcinoma; RFA: Radiofrequency; MWA: Micro-wave; LA: Laser; DEB-TACE: Drug Eluting-Beds-TACE; TACE: Transarterial chemoembolization; TARE: Transarterial radioembolization.

at imaging, or > 50% compensatory hepatic hypertrophy[65]; (2) no or mild portal hypertension; and (3) no history of liver decompensation.

When LR is unfeasible, locoregional treatments are evaluable therapeutic options and the most used is TACE. Best candidates to TACE are patients with well preserved liver function (Child-Pugh score $\leqslant$ 7) and without ascites. Complete HCC necrosis after TACE is seldom observed and local recurrence rates within one year are as high as 60%[69]. Up to now, there are no studies designed to define the maximum tumor size that can be treated. In the two RCTs showing survival benefit of TACE compared to best supportive care, the mean size of HCC was 5-7 cm (range 4-14 cm)[70,71]. In patients with large solitary tumor, TARE may be preferred because there are some evidences of a higher rate of response after TARE as compared to TACE[28].

Percutaneous ablation can be an evaluable treatment for large HCC. However, the efficacy of all ablative procedures decrease as size increases over 3 cm and the probability of obtaining the complete ablation of nodules larger than 7 cm is very low[35,72]. Candidates for percutaneous local ablation are patients with centrally located HCC having a diameter no more than 7 cm, in whom a complete response rate > 80% has been reported[72,73]. In patients with residual peripherical cancer tissue after ablation, the use of TACE increases the rate of complete tumor response[74]. In practice field, a combination treatment strategy (combination of TACE or TARE with percutaneous ablation) is "a priori" preferred in a relevant percentage of these patients.

In patients who are unsuitable to surgery and with contraindication to locoregional treatments or with huge HCC masses (> 10 cm) sorafenib is the treatment of choice. A subanalysis of the SHARP trial has shown that in BCLC B patients sorafenib as compared to placebo increased the median overall survival (14.5 mo *vs* 11.4 mo, HR = 0.72) and the time-to-progression (6.9 mo *vs* 4.4 mo, HR = 0.47)[75] (Figure 1).

Multifocal HCC

Most of BCLC B stage patients are affected by multifocal HCC. In these cases, TACE is the first-line treatment. Best candidates are patients with few nodules having a small size: no more than 5 nodules with a size up to 5 cm is likely a good proposal[12]. According to a multicenter European trial, DEB-TACE is more effective than c-TACE in patients classified as Child-Pugh B, and with bi-lobar or relapsing disease, but differences in survival between patients treated with these techniques have not been demonstrated up to now[76-79]. The role of TARE in the management of BCLC B stage patients with multifocal disease is still undefined. However, in some case TARE might be teoretically more safe than TACE as in patients with portal thrombosis because of only minimal embolic effect of microspheres[80]. In field practice, the combined use of transarterial and percutaneous treatment for multifocal HCC is used by many centers and in the position paper of the AISF (Associazione Italiana per lo Studio del Fegato) this approach is recommended as "particularly evaluable"[66]. The use in the same patient of combined locoregional treatments and sorafenib might be theoretically useful, but due to high costs it should be evaluated by a multidisciplinary team.

Surgery may have also a role in the treatment of multifocal HCC in well selected cases[81]. In fact, LR may be a valuable treatment in patients with up to three nodules and multifocal HCC involving 2-3 adjacent liver segments. In some patients with bilobar disease the combination of LR and ablative treatment may be a valuable option. TACE before surgical resection should

not be recommended because this strategy offers no benefit[82] (Figure 1).

LIVER TRANSPLANTATION AND DOWN-STAGING STRATEGY

In selected BCLC B stage patients treatment can be performed with the aim of reducing the tumor burden within Milan criteria. This is the downstaging strategy and patients who have been successfully treated can undergo to liver transplantation with good results[83-85]. The most used treatment for downstaging is TACE[86]. After downstaging treatment, a waiting period of at least 3-6 mo before performing liver transplantation is recommended[87]. During this time, patients should be carefully monitored for tumor response with imaging. The rationale of this strategy is to evaluate tumor biology and risk of recurrence after transplant. In fact, about a third of these patients can be affected by HCC with aggressive biology that can progress during the waiting period and they are not good candidates for transplantation due to the high risk of recurrence[88,89]. Other factors that can indicate a high risk of post-transplant recurrence are AFP serum level above a threshold of 400-1000 ng/mL[80,81,90,91] and poor HCC differentiation at histology[92]. The use in combination with locoregional treatments of systemic targeted therapy with sorafenib may theoretically further increase the rate of tumor control and reduce the recurrences, but appropriately designed studies are needed to confirm it[93].

CONCLUSION

The choice of the best treatment in the patient with intermediate stage HCC is a difficult task. It should be made by a multidisciplinary team. Due to the heterogeneity of intermediate HCCs, the use of different therapies (combination treatment) is likely the best choice in most of the cases offering the opportunity of a treatment tailored to the single patient.

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