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Hot Topic Commentary

R0 Liver Resection should be a First-line Treatment for Selected Patients with Intermediate Hepatocellular Cancer

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Introduction

Hepatocellular cancer (HCC) is the sixth most common malignancy worldwide and the second most common cause of mortality among all malignancies. Most HCCs occur in cirrhotic livers, but an increasing proportion of cases occur in livers without cirrhosis, particularly in Hepatitis B virus infection or in nonalcoholic fatty liver disease patients.[1] Liver resection (LR) is the treatment of choice in most noncirrhotic patients, therefore most discussion is related to patients with cirrhosis. Overall survival (OS) depends on the stage at the time of diagnosis. Barcelona Clinic Liver Cancer (BCLC) staging is the currently preferred staging system for HCC in Europe and North America[2] Only a small proportion of patients with HCC are diagnosed at a very early or early stage (BCLC 0-A) when curative treatment, including LR, is generally recommended.

Treatment options for intermediate stage HCC

BCLC defines intermediate stage HCC as multifocal disease beyond the Milan criteria, with preserved liver function, no cancer-related symptoms (performance status 0), and no vascular invasion or extrahepatic spread.[2] LR in intermediate stage HCC (BCLC B) is a topic of discussion based on the variable definition of this stage. A recent BCLC consortium update,[2] in contrast to current European Society for Medical Oncology (commonly referred to as ESMO) guidelines,[3] does not recommend LR in this stage, with liver transplantation as the only curative option is in a select group of patients beyond Milan criteria. In most patients at this stage, transcatheter arterial chemoembolization (TACE) is the first-line treatment. That treatment is not curative, and the mean OS is approximately 2.5 years. Systemic therapy is recommended in intermediate stage HCC in patients who are not candidates for liver transplantation or TACE. The ESMO guidelines consider LR in most Child-Pugh A patients without significant portal hypertension, provided that R0 resection can be achieved with a sufficient volume of functional liver parenchyma remaining and if there is no macrovascular invasion (level of recommendation III, B), and can also be considered in Child-Pugh B patients.[3] Recent European Association for the Study of the Liver (commonly referred to as EASL) guidelines take a conciliatory approach, with a firm recommendation for LR in ideal patients (solitary tumors and very well-preserved liver function, hepatic vein to portal system gradient <10 mmHg or a platelet count ≥100,000/mL), but open a way to extension of these criteria.[1] Recent data is lacking but it is estimated that only 10–37% of HCC patients are suitable for LR,[4] which is performed in approximately half of the patients with intermediate stage disease, mainly in tertiary centers in Asia.

Outcomes of LR for intermediate stage HCC

Advances in surgical technique and postoperative management make it possible to perform hemihepatectomy for HCC in patients with intermediate HCC stages, even in patients with compensated liver cirrhosis. According to the 2017 revised Asia-Pacific clinical practice guidelines of management of hepatocellular carcinoma, LR is a first-line curative treatment for HCC in Child-Pugh class A patients when resectability is confirmed in terms of tumor burden and liver functional reserve by multidisciplinary evaluation.[5] The optimal type of LR for large HCC is R0 resection, which is defined as no tumor cells found microscopically at the surgical margin. The median OS for correctly indicated R0 LR is approximately 4 years. The 5-year OS rate is approximately 45%, and the 5-year disease-free survival (DFS) is approximately 30%.[6]

Decision for LR: risk versus benefit analysis

When deciding whether to perform LR in intermediate stage HCC, the multidisciplinary board must consider the benefit of the surgery (expected increase in OS) and risks associated with the surgery (mainly perioperative mortality and liver failure). This decision is unique for each patient, and the number of relevant variables preclude the possibility of a simple decision-making flowchart (Fig. 1). Major variables that influence

Abbreviations: ALPPS, associating liver partition and portal vein ligation for staged hepatectomy; BCLC, Barcelona clinic liver cancer; DFS, disease free survival; EASL, European Association for the Study of the Liver; ESMO, European Society for Medical Oncology; HCC, hepatocellular cancer; LR, liver resection; MVI, microscopic vascular invasion; NAFLD, nonalcoholic fatty liver disease; OS, overall survival; RLV, remnant liver volume; TACE, transcatheter arterial chemoembolization; TLV, total liver volume.

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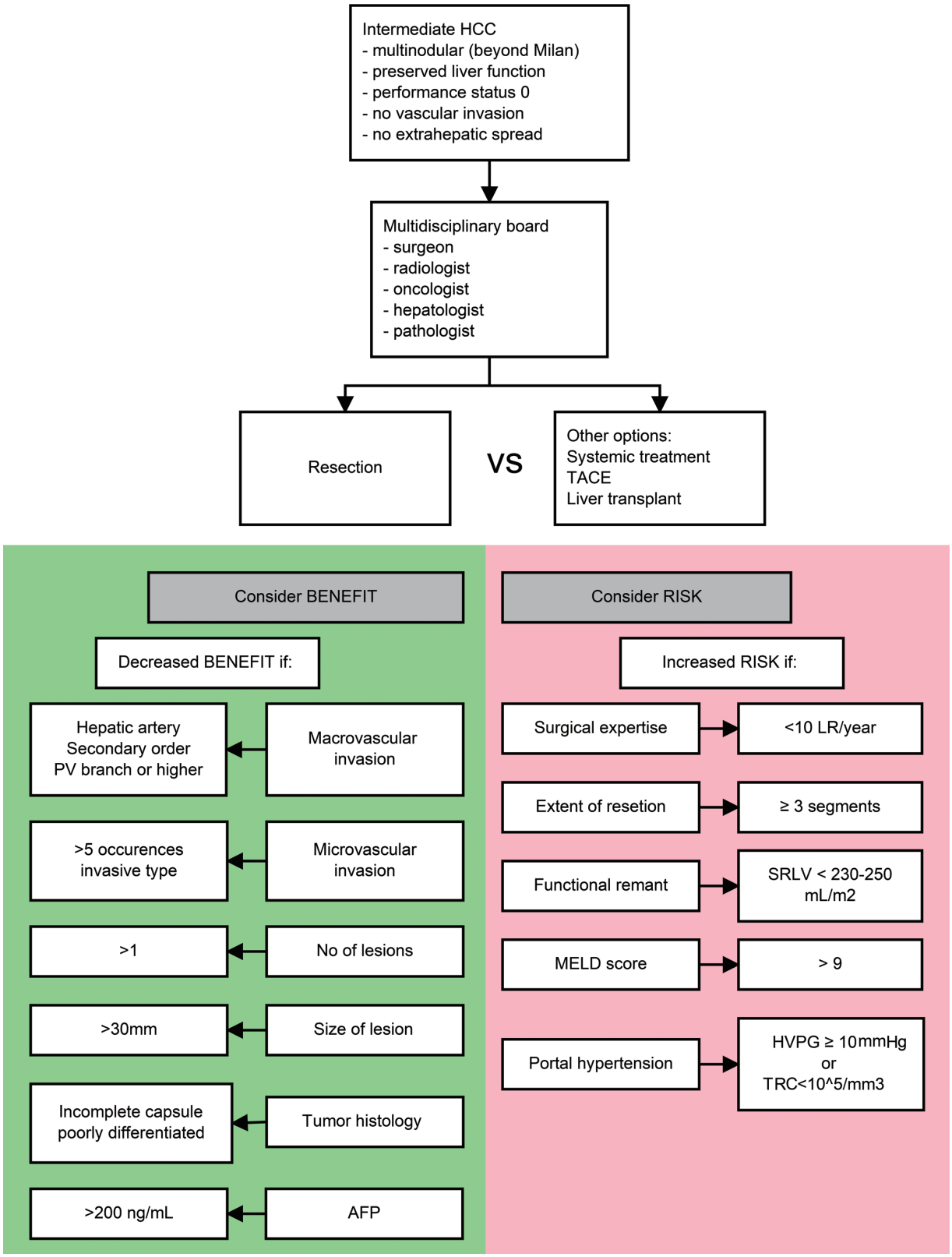

Fig. 1. Decision-making algorithm for the management of large intermediate hepatocellular carcinoma. AFP, alphafetoprotein; HCC, hepatocellular carcinomacer; HVPG, hepatic vein pressure gradient; LR, liver resection; SRLV, standard remnant liver volume; TACE, transcatether arterial chemoembolisation; TRC, platelets; PV, portal vein.

the risk/benefit ratio are the size, location, histological character, micro- and macrovascular invasion of the tumor, liver functional reserve, portal hypertension, surgical feasibility, experience of the surgeon, extent of hepatectomy, and the performance status of the patient, including comorbidities.

The immediate risk of complications after successful resection was nicely outlined in a study by Citterio *et al*.[7] who identified that major factors influencing the risk of postsurgical liver failure and liver-related death are extent of hepatectomy, model for end-stage liver disease score and portal hypertension. In patients with minor hepatectomy (<3 segments) even with portal hypertension the risk of liver decompensation was <30% and liver related death was 9%. The risks were comparable to patients with major hepatectomy (≥3 segments) without portal hypertension. Computed tomography (commonly known as CT) with computer calculation of non-tumor liver volume should be performed at the LR planning stage. A computed tomography scan with non-tumor liver volume calculation can be combined with the 15 m retention rate of indocyanine green (ICG-R15) to assess liver functional reserve at the same time. Zuo *et al*.[6] proposed the calculation of non-TLV/ICG index where AUROCs for prediction of OS and DFS at 1, 3, and 5 years were 0.717, 0.723, 0.788 in the training and 0.606, 0.662, 0.741 in the validation cohort, respectively. Before considering LR, it is recommended to calculate the remnant liver volume to total liver volume ratio (RLV/TLV) and remnant liver volume to body weight ratio. With RLV/TLV values <25% or RLV to body weight ratio <0.5, performing LR is risky. For HCC in the right lobe of the liver, a significant portion of the non-TLV is the volume of the left liver lobe. When blood flow in the right portal vein is stopped, compensatory hypertrophy of the left liver lobe occurs. That can be exploited preoperatively either by right portal vein embolization via invasive radiology approach or by associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), a two-stage surgical procedure.[8] Liver regeneration is faster and the degree of hypertrophy of the future remnant is higher compared with the portal vein embolization procedure. On the other hand, patients with ALPPS have a significantly higher rate of major complications, including perioperative mortality, which may limit the use of this surgical method, especially in centers where ALPPS is not routinely performed.

Hepatic venous pressure gradient measurement is available at tertiary centers, but it is mostly unavailable outside those centers. A large meta-analysis found that clinically significant portal hypertension (≥10 mmHg) increased risk of post-surgical decompensation (odds ratio [OR]: 3.04; 95% confidence interval [CI]: 2.02–4.59; $p<0.00001$) and 3-year mortality (OR: 2.09; 95% CI: 1.52–2.88; $p<0.00001$).[9] In the Asia-Pacific clinical practice guidelines of management of hepatocellular carcinoma, the ICG-R15 is recommended, but it is rarely used in Western countries.

The morphological and histological characteristics of the tumor also predict patient survival of the patient after LR. Vascular invasion of the tumor worsens the prognosis. Macroscopic vascular invasion can be detected by routine radiological examination, whereas microscopic vascular invasion (MVI) can be detected by histological examination. Feng *et al*.[10] proposed a classification of MVI: M1–low risk, no risk factor, noninvasive type MVI with the number of MVI ≤5; M2–moderate risk, one risk factor, invasion type MVI with the number of MVI ≤5 or noninvasive type MVI with the number of MVI >5; and M3–high risk, two risk factors: invasive type MVI with a number of MVI >5. Patients with M1 type MVI after R0 resection for HCC had a 5-year OS of approximately 80%. Patients with M3 type MVI had a 5-year OS of <40%. Patients with an incomplete capsule and multiple tumors had a poorer prognosis. Patients with poorly differentiated HCC had shorter tumor volume doubling times, more frequent smaller non-TLV, and often poor liver condition. Therefore, poorly differentiated HCC is associated with a poor prognosis. Higher alpha fetoprotein levels in HCC patients also predict poorer survival.[5,6]

Macrovascular invasion, particularly to the portal vein also affects the efficacy of LR. Prospective or randomized data are lacking, however retrospective data indicate that in selected cases (portal vein thrombosis limited to first order branch of portal vein) LR can be superior in regard to survival compared with nonsurgical treatment.[1] Single nodules of ≤2 cm RFA offer competitive results to LR, however in single HCC ≥3 cm LR is more effective. Also, LR has a better OS than TACE for patients with large solitary HCC.[11] That is also reflected in the EASL guidelines that note that LR can be offered to any solitary HCC nodule if it is surgically feasible and there is a sufficient functional liver remnant. There is no clear recommendation for single HCC between 2 and 3 cm. LR is also a viable option in multinodular HCC within Milan criteria if the overall risk is acceptable. There is a lack of data for tumors beyond Milan criteria to provide a clear recommendation. Although various reports from Western populations show survival benefit of LR compared with locoregional treatment across all stages of tumor presentation, the retrospective observations suffered from selection bias, where patients selected for surgery had better clinical characteristics.

Subclinical inflammation plays a crucial role in the pathogenesis of the development and recurrence of HCC after LR. Increased values of inflammation indexes such as neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and systemic immune-inflammation index predict HCC recurrence after LR. Tumor burden score can also be used to prediction of HCC recurrence after LR.[12] Structuralized analysis of all the predictor variables (clinical, pathological, laboratory and imaging results, including previously developed indexes) refines the prediction of prognosis for DFS and OS in large HCC after LR. Zuo *et al*.[6] constructed a nomogram based on the non-TLV/ICG index, and it predicted DFS and OS more accurately than the non-TLV/ICG index alone. The study was limited to single nodule HCC, almost 80% of patients were HBsAg positive, it was retrospective with significant dropouts because of data unavailability, and it lacked external validation. Thus, it is difficult to extrapolate the results to other HCC patients.

Conclusion

LR may be a viable treatment option for patients with intermediate stage HCC. However careful evaluation and selection of patients in important. It should be performed by multidisciplinary tumor boards in experienced centers. In this case, median survival may be almost 4 years, significantly higher than after TACE. Multidisciplinary boards that include a hepatologist, surgeon, radiologist, and oncologist must consider the benefit of the surgery (expected increase in OS) and risks associated with the surgery (mainly perioperative mortality and liver failure). The decision is highly unique for each patient, and the number of relevant variables preclude the possibility of a simple decision-making flowchart. There is currently an unmet clinical need for a predictive model that integrates all relevant variables that influence the risk/benefit ratio and support the physicians in decision making.

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Conflict of interest

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Author contributions

Manuscript conceptualization, writing and revision (MJ, SD, PJ). All authors made a significant contribution to this study and approved the final manuscript.

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