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Review Article

Multimodal treatment of hepatocellular carcinoma

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ABSTRACT

Hepatocellular carcinoma (HCC) represents the most common liver cancer with an increasing incidence and it accounts for the third most common cause of cancer-related death worldwide. Even though the clinical diagnosis and management of HCC improved significantly in the last decades, this malignant disease is still associated with a poor prognosis. It has to be distinguished between patients with HCCs, which developed from liver cirrhosis, and patients without underlying liver cirrhosis as classification systems, prognosis estimation and therapy recommendations differ in-between. In case of HCC in patients with liver cirrhosis in Europe, treatment allocation and prognosis estimation are mainly based on the Barcelona-Clinic Liver Cancer (BCLC) staging system. Based on this staging system different surgical, interventional radiological/sonographical and non-interventional procedures have been established for the multimodal treatment of HCC. The BCLC classification system represents a decision guidance; however because of its limitations in selected patients treatment allocation should be determined on an individualized rather than a guideline-based medicine by a multidisciplinary board in order to offer the best treatment option for each patient. This review summarizes the current management of HCC and illustrates controversial areas of therapeutic strategies.

1. Introduction

Worldwide, the incidence of HCC presents the fifth common malignant tumor with rising numbers in Europe, the USA and Japan [1]. Its prognosis is poor and accounts for the third leading cause of cancer-related death [1,2]. In fact, in 2008 the incidence of HCC was about 65.000 cases in Europe and mortality was about 60.000 [3]. The most frequent risk factors for developing HCC are chronic viral hepatitis (hepatitis B and C virus infection), nonalcoholic steatohepatitis (NASH), alcohol consumption and aflatoxin exposure [3]. In 80–90% of patients HCC develops from liver cirrhosis irrespective of the etiology of the liver disease [3], however high risk constellation are HBV-, HCV-, hemochromatosis and alcohol-induced cirrhosis. In patients with liver cirrhosis the incidence of HCC development is about 3–5%/year [4]. Treatment of HCC needs multimodal therapy schedules, which are reviewed below.

Abbreviations: AE, adverse event; BCLC, Barcelona-Clinic Liver Cancer; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIFU, high-intensity focused ultrasound ablation; LITT, laser-induced thermotherapy; LTX, liver transplantation; MWA, microwave ablation; NASH, non-alcoholic steatohepatitis; OS, overall survival; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; SBRT, stereotactic body radiation; SIRT, selective internal radiation therapy; TACE, transarterial chemoembolization.

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2. Barcelona-Clinic Liver Cancer (BCLC)-classification as staging system, prognosis allocation and treatment schedule

In Western countries the Barcelona-Clinic Liver Cancer (BCLC) classification is the most commonly used staging system for HCC in cirrhotic patients and is recommended for management of HCC by the EASL and AASLD [3,5,6]. Validation of BCLC staging systems was confirmed in different clinical settings [3]. Several other staging systems have been established for clinical classification of HCC and prognosis assessment e.g., the 7th TNM edition in accordance with the American Joint Committee on Cancer, the Okuda stage, the French score, the Cancer of the Liver Italian Program (CLIP) classification, the Chinese University Prognostic Index (CUPI score) and the Japan Integrated Staging (JIS) (for review see [7]).The EASL and AASLD guidelines approve the BCLC classification system as a favorable staging system for prognosis allocation and treatment schedule, because it includes prognostic values (tumor stage, liver function, performance status) and treatment-dependent values, which are obtained from cohort studies and clinical randomized trials [3]. However, the BCLC classification also provides limitations, which are summarized in Table 1. In clinical practice, guidelines represent decision recommendations, however often enough guideline conformity does not reflect the best therapeutic approach for each patient. In selected patients treatment allocation should be determined on an individualized rather than a guideline-based medicine by a multidisciplinary board [8].

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Table 1
Limitations of BCLC classification system.

BCLC classification system …
1) does not consider nodule location, which is essential for defining resectability.
2) does not respect etiology of cirrhosis.
3) is based on variables measured at diagnosis, which might change over time.
4) does not consider the possibility of liver transplantation for patients with Child C cirrhosis with HCCs within the Milan criteria.
5) does not reflect contraindications of TACE (see the Transarterial chemoembolization (TACE) section).
6) recommends liver resection to single nodules only in absence of portal hypertension in very early (BCLC 0) and early stage (BCLC A), however probably portal hypertension might not affect survival in resected patients.
7) recommends liver resection in very early (BCLC 0) and early stage (BCLC A), however in selected patients hepatic resection is associated with good survival even in more advanced BCLC stages.
8) does not consider treatment sequences or combination therapies.
9) includes a very heterogeneous population in the intermediate stage (BCLC B) in respect to tumor burden and liver function.
10) does not consider other therapies than sorafenib in selected patients with advanced stage C with performance status 1.
11) is not favorable as classification system in non-cirrhotic patients.

The BCLC classification distinguishes between 5 stages, which are named 0, A, B, C and D (see Fig. 1), thereby dividing HCC patients in different prognostic groups and recommending stage-specific treatment schedules.

2.1. BCLC stage 0

Stage 0 is classified as patients with single HCC < 2 cm in diameter without metastases or vascular invasion with Child A cirrhosis and good performance status. Surgical resection and radiofrequency ablation (RFA) are feasible for patients with BCLC stage 0 HCC. Surgical resection in a curative intention shows 5 year-survival rates between 40 and 70% [3,9], however after surgical resection of HCC in a cirrhotic liver the incidence of a metachronous HCC 3 years after resection is about 50% and more than 70% after 5 years [9]. An alternative treatment regime is radiofrequency ablation (RFA), which shows a feasibility rate of 90%, local control rates of nearly 99% and 5-year survival rates of 68.5% in HCC patients with a single nodule <2 cm [10]. Although LTX has the possibility to eliminate the dysplastic potential of the cirrhotic liver and probably to cure the underlying liver disease, it should not be considered the first option in BCLC 0 patients, because liver transplant waiting lists suffer from high rates of dropouts and patients in early BCLC stages show no clear survival benefit [11].

2.2. BCLC stage A

The definition of stage A (early stage) is a single nodule with a diameter of 2–5 cm or up to 3 nodules < 3 cm in diameter in patients with Child A/B cirrhosis and ECOG performance status 0. Patients in BCLC stage A show a 5-year survival rate of 50–70% after liver transplantation, surgical resection or RFA [3,12]. However, BCLC A patients with Child A cirrhosis have only a very low survival benefit in response to LTX compared to liver resection or RFA and may not constitute the optimal use of scarce liver donor organs [11]. HCC patients, who are not suitable for liver transplantation, showed better prognostic outcome when liver function is preserved, as reflected in the absence of relevant portal hypertension and absence of hyperbilirubinemia [13].

2.3. BCLC stage B

Stage B is classified as patients with multinodular HCC manifestation outside of 3 nodules < 3 cm in diameter, but without distant metastases and vascular invasion in ECOG performance status 0. Nearly 20% of HCC patients are diagnosed as stage B with a 2-year survival rate of about 50% and median survival of 16 months in untreated patients [14,15]. For these patients transarterial chemoembolization as selective technique or with drug-eluting beads is recommended. Nowadays, radioembolization as an investigational procedure becomes more and more established as a treatment option in stage B patients [16].

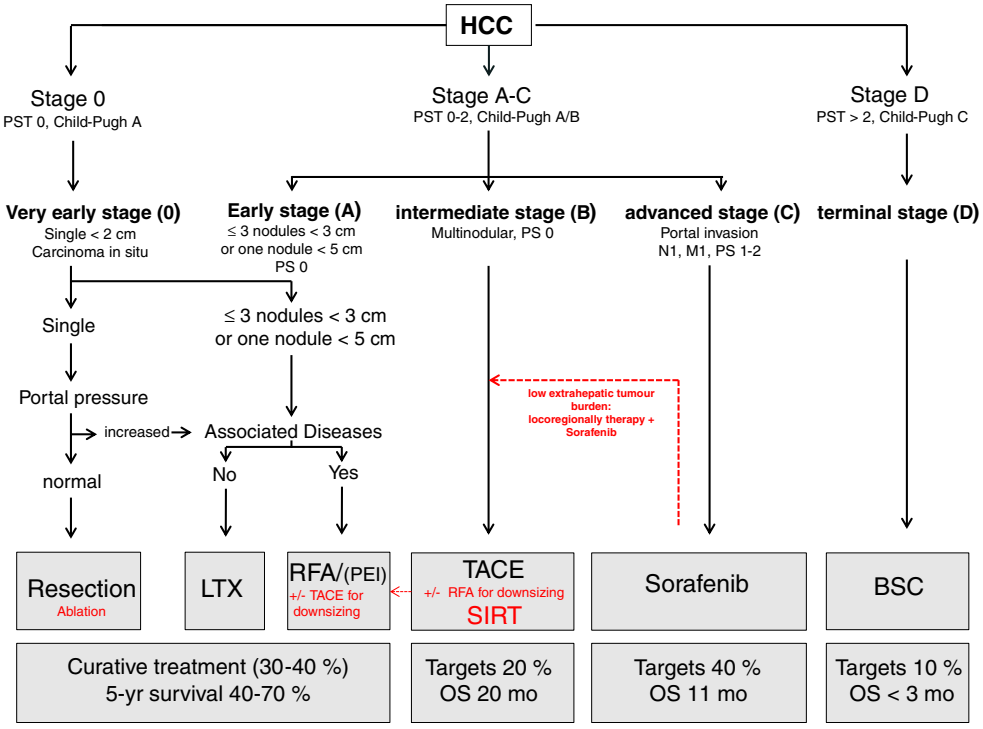

Fig. 1. BCLC staging and treatment allocation adapted from [3,5,6]. Adaptions are marked with color and are discussed in text. ECOG-PST: Eastern Cooperative Oncology Group Performance Status; HCC: hepatocellular carcinoma; LTX: liver transplantation; PEI: percutaneous ethanol injection; RFA: radiofrequency ablation; SIRT: selective internal radiotherapy; TACE: transarterial chemoembolization.