Review

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Liver cancer: Approaching a personalized care

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Summary

The knowledge and understanding of all aspects of liver cancer [this including hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA)] have experienced a major improvement in the last decades. New laboratory technologies have identified several molecular abnormalities that, at the very end, should provide an accurate stratification and optimal treatment of patients diagnosed with liver cancer. The seminal discovery of the *TP53* hotspot mutation [1,2] was an initial landmark step for the future classification and treatment decision using conventional clinical criteria blended with molecular data. At the same time, the development of ultrasound, computed tomography (CT) and magnetic resonance (MR) has been instrumental for earlier diagnosis, accurate staging and treatment advances. Several treatment options with proven survival benefit if properly applied are now available. Major highlights include: i) acceptance of liver transplantation for HCC if within the Milan criteria [3], ii) recognition of ablation as a potentially curative option [4,5], iii) proof of benefit of chemoembolization (TACE), [6] and iv) incorporation of sorafenib as an effective systemic therapy [7]. These options are part of the widely endorsed BCLC staging and treatment model (Fig. 1) [8,9]. This is clinically useful and it will certainly keep evolving to accommodate new scientific evidence.

This review summarises the data which are the basis for the current recommendations for clinical practice, while simultaneously exposes the areas where more research is needed to fulfil the still unmet needs (Table 1).

Epidemiology

Liver cancer (including HCC and iCCA) is the 2nd cause of cancer related death [10] and one of the cancers with a still increasing incidence rate [11]. Since risk factors are well known, prevention is an achievable aim. Control of hepatitis B (HBV) and C (HCV) infection, as well as reduction in alcohol consumption would have a huge impact if applied on a large scale. While health plans are implemented to achieve this goal, the epidemic of overweight and metabolic syndrome has emerged as a relevant risk factor [12]. Prospective follow-up data about incidence and specific high-risk individuals in this subset as compared to HBV, HCV or alcohol are still scarce. However, the future reduction in viral related cases because of HBV and HCV control is counterbalanced by the increase in such an etiologic group.

Cancer related death will decrease due to a reduction in exposure to risk factors and because of a higher rate of early diagnosis leading to effective treatment with long term disease free survival. This is the basis to recommend screening for HCC in the population at risk [4,5]. Some restrictions should be in place to make screening cost-effective [13]. Risk should be high enough and modelling studies have placed such cut-offs at an annual rate of 1.5% [14]. Such a figure is exceeded in liver cirrhosis of most etiologies [15,16]. In addition, patients entering screening should be suitable for treatment if they would be diagnosed with HCC. If comorbidities or end-stage liver disease not leading to transplant exist, screening and diagnosis of HCC and its potential treatment will be of no benefit. Finally, diagnosis, accurate and effective options should be available. Unfortunately, an unknown proportion of patients with cirrhosis may not be yet diagnosed, and even so, implementation of screening is usually suboptimal. In the future, the evaluation of the specific risk in an individual patient and prognostic prediction will be refined by molecular profiling of the oncogenic cirrhotic liver and the tumor.

Molecular pathogenesis and signalling pathways

Molecular classification should aid in understanding the biological subclasses and drivers of cancer and optimize benefits from molecular therapies and enrich trial populations [5]. From the biological standpoint, different HCC classes have been characterized including a Wnt subclass (25% of cases; enriched with *CTNNB1* mutations and HCV etiology), a proliferation class (with two subclasses: S1-TGF-beta and S2-EpCAM positive) and an inflammation/interferon class [17–20]. The proliferation subclass accounts for 50% of cases and is enriched with tumors derived from progenitor cells (e.g., "EpCAM"2) and tends to have worse

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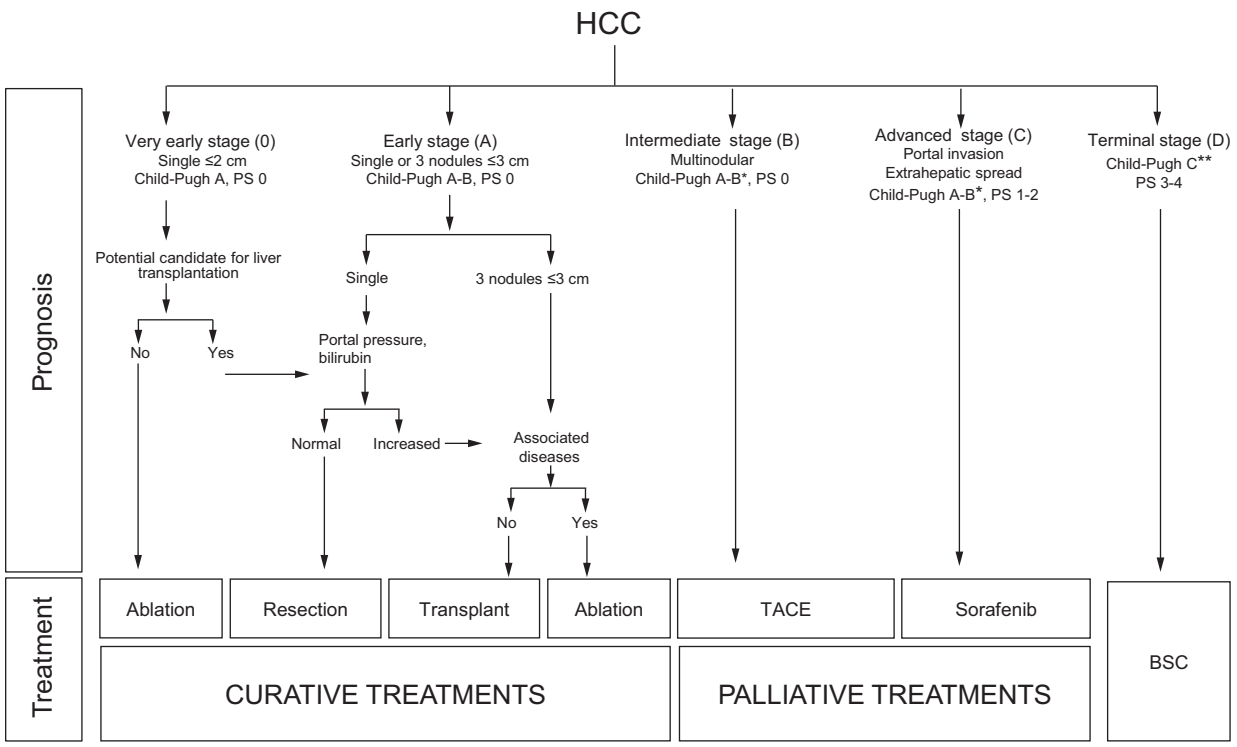

Fig. 1. BCLC staging and treatment strategy [as per Semin Liver Dis. 2014 Nov;34(4):444–55]. The figure represents the first approach to the evaluation of the patients with expected prognosis and initial treatment option to be considered. As shown, the upper part of the scheme defines prognosis according to the relevant clinical and tumor related parameters. Bottom part depicts the decision process to select a treatment option for first consideration. As in all recommendations, final treatment indication should take into account a detailed evaluation of additional characteristics (age, comorbidities) of the patients that imply a personalized decision making. *Note that Child-Pugh classification is not sensitive to accurately identify those patients with advanced liver failure that would deserve liver transplant consideration. Some patients fitting into Child-Pugh B, and even A, may present a poor prognosis because of clinical events not captured by such system, i.e. spontaneous bacterial peritonitis, recurrent variceal bleeding, refractory ascites with or without hepatorenal syndrome, recurrent encephalopathy, severe malnutrition. **Patients with end-stage cirrhosis due to heavily impaired liver function (Child-Pugh C or earlier stages with predictors of poor prognosis, high MELD score) should be considered for liver transplantation. In them, HCC may become a contraindication if exceeding the enlistment criteria.

prognosis. Nonetheless, no molecular subclass has been reported to respond to specific targeted therapy [5].

Several prognostic mRNA-based molecular signatures from tumor or non-tumoral adjacent tissue have been reported [21,22]. Signatures identifying progenitor cell-like and/or a cholangiocyte profile (EPCAM signature3, CK19 signature [22]) display worse prognosis. Similarly, a 5-gene score signature (*TAF9*, *RAN*, *RAMP3*, *KRT19*, and *HN1* genes) predicted overall survival in four independent cohorts of Caucasian and Asian patients [23]. In parallel, gene expression profiling of adjacent non-tumoral liver tissue has highlighted the importance of tumor microenvironment in HCC prognosis. The poor prognosis with 186-gene signature was associated with both survival after resection and survival, HCC occurrence and decompensation in cirrhotic HCV patients without tumors [24,25]. Molecular profiling together with assessment or major clinical predictors of risk of HCC and death (degree of portal hypertension, concomitant treatments during follow-up, sustained alcohol intake or coffee consumption) and comorbidities will permit a more personalised approach.

Oncogenic drivers and tumor suppressors

High-resolution analysis of molecular alterations in human malignancies has allowed for the identification of new drivers, which are ideal targets for treatments in some solid malignancies (lung, breast or melanoma). Recent studies have provided a broad picture of the mutational profile in HCC and identified an average of 30–40 mutations per tumor, among which 6–8 are considered drivers [26,27]. Main mutations are in the promoter region of *TERT*, *TP53*, *CTNNB1*, *ARIDA1A*, and Axin 1 (Table 2). Deep-sequencing studies confirmed *TP53* and *CTNNB1* are frequently mutated. Mutations in these genes are mutually exclusive – an indication that they could act as drivers of tumor progression. In addition, these studies discovered novel mutations in genes involved in the chromatin remodelling pathway (*ARID1A* and *ARID2*), in ubiquitination (*KEAP1*), RAS/MAPK signalling (*RPS6KA3*) and oxidative stress (*NFE2L2*) and JAK1 in 9% of HBV-related HCC. Genes commonly mutated in other solid tumors such as *EGFR*, *PIK3CA* or *KRAS* are rarely mutated in HCC (<5% of cases, Table 2 [26,27]). Several chromosomal alterations have been recurrently identified.