



## Opinions

## The leading and key role of hepatologists in the multidisciplinary management of patients with hepatocellular carcinoma

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## ARTICLE INFO

## Article history:

Received 14 March 2023

Accepted 24 April 2023

Available online 29 April 2023

## Keywords:

Leadership

Health policy makers

Hepatocellular carcinoma (HCC) is a public health problem with increasing incidence and mortality rates [1]. Cirrhosis and chronic hepatitis are the target risk populations for HCC surveillance. Its diagnosis is crucial for considering patients eligible for screening, aiming at early HCC diagnosis and mortality rate reduction [2,3]. Liver decompensation in these patients competes with the risk of mortality and may preclude the feasibility and safety of different locoregional and systemic treatments for HCC. In this scenario, it is crucial for the hepatologist's role in the early diagnosis, application of correct surveillance policies, and management of these patients.

The Barcelona Clinic Liver Center staging of HCC (BCLC), first described in 1999, is the most accepted staging system in clinical practice guidelines. It has been developed and proposed by hepatologists [2]. Its strength relies on different factors. First, not only includes prognostic variables associated with the tumor burden but also those

associated with liver disease. Ignoring these features may lead to serious mistakes in their therapeutic management.

The BCLC classifies patients into 5 stages, very early stage or BCLC 0, BCLC A or early stage, intermediate or BCLC-B stage, advanced or BCLC-C, and terminal stage or BCLC-D. Early stages (0 and A), which include an option for curative therapies such as surgical resection, liver transplantation (LT), or ablation through radiofrequency or microwave. During these stages, hepatologists should lead the care and indication for radical treatments in parallel with liver surgeons. The presence of portal hypertension, its correct diagnosis, risk stratification, and treatment, is the *Achilles heel* of surgical indication. Child-Pugh or MELD or ALBI scores may help this decision-making process, but in the end, hepatologists' role is essential for correct staging and management of liver disease and clinically significant portal hypertension. An incorrect surgical indication, extension, or the presence of subclinical portal hypertension may result in liver decompensation and an increased risk of postoperative mortality [4].

Liver transplant indications have relied on hepatobiliary surgeons over decades. However, transplant hepatologists have developed new selection models that optimize the selection process even

Abbreviations: AFP, Alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; HCC, Hepatocellular carcinoma; ICIs, immune checkpoint inhibitors; LT, Liver Transplantation; PD-1, programmed cell death protein-1; TACE, trans-arterial chemoembolization; UCSF, University of California San Francisco; VEGF, vascular endothelial growth factor

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beyond Milan criteria. Composite models, incorporating pre-LT alpha-feto protein serum levels (AFP), have outperformed the Milan criteria and have been proposed in the most recent guidelines [5,6]. The AFP score (0 to 9 points) is calculated depending on largest tumor diameter ( $\leq 3$  cm = 0 points, 3–6 cm = 1 point,  $> 6$  cm = 4 points), number of HCC nodules (1–3 nodules = 0 points,  $\geq 4$  nodules = 2 points), and AFP levels ng/ml ( $\leq 100$  = 0 points, 101–1000 = 2 points, and  $> 1000$  = 3 points) [5]. The Metroticket 2.0 includes the sum of the largest nodule diameter with the total number of HCC nodules, and the  $\log^{10}$  AFP values [6]. Our region, was the first to externally validate the AFP score around the world [7–9]. Downstaging strategies, such as the University of California San Francisco (UCSF) downstaging protocol, were proposed by other transplant hepatologists [10]. The UCSF-DS protocol includes at least one of the following tumor size criteria: a) single lesion  $\leq 8$  cm, b) 2 or 3 lesions each  $\leq 5$  cm and the sum of total tumor diameter  $\leq 8$  cm and c) 4–5 lesions each  $\leq 3$  cm and the sum of total tumor diameter  $\leq 8$  cm, additionally, in absence of macro-vascular invasion or extrahepatic spread, or AFP values above 1,000 ng/ml. Consequently, transplant selection, locoregional therapy indication, and clinical management of HCC patients on the transplant waiting list are other essential role of hepatologists.

Intermediate BCLC-B stage is a multifocal HCC in which the recommended treatment is trans-arterial chemoembolization (TACE). Some BCLC-B patients may become candidates for LT following locoregional treatments (downstaging) or being selected by composite models [5–10], while other group of patients presenting with diffuse infiltrative or extensive bilobar HCC will be suitable for systemic therapies. Selection of these strategies again demands the hepatologist's participation. Moreover, the ischemic injury following TACE on the remnant liver may lead to liver decompensation precluding sequential locoregional or systemic treatment. Despite TACE is usually performed by surgeons or interventional radiologists, clinical patient selection, management of complications, and stopping rules of sequential TACE avoiding untreatable progression, should be led by hepatologists [11].

The advanced HCC stage (BCLC-C) includes patients amenable to systemic therapies [2]. Since 2008, and a decade of repeated alternative failures, Sorafenib was the only approved systemic therapy [12]. After 2016, different first- and second-line treatments, Lenvatinib, Regorafenib, Cabozantinib, and Ramucirumab, also demonstrated efficacy in clinical trials. These agents were mostly indicated and managed by hepatologists as their common adverse events were easily handled in daily practice. However, intravenous medications such as Ramucirumab or Bevacizumab, and immune checkpoint inhibitors (ICIs), have revolutionized the management of HCC. ICIs indication and adverse event management are led by oncologists in other cancers. However, concomitant cirrhosis challenges this usual care. The combination of Atezolizumab, an antibody against programmed cell death protein-1 (PD-1), with bevacizumab, an anti-angiogenic monoclonal antibody binding to vascular endothelial growth factor (VEGF), was the first ICI-based regimen showing superiority over Sorafenib [13]. The issue of associated complexity with the intravenous requirement or the need for deep immunological knowledge does not preclude hepatologists to treat these patients. Indeed, deep immunological knowledge considering hepatitis C or B chronic infections, treatment with pegylated interferon alpha, and local experiences around the world participating in ICIs clinical trials of HCC, support the management and care of these patients. This also goes for other first-line ICIs combinations such as tremelimumab (anti-CTLA4 antibody) and durvalumab (anti-PDL-1) [14]. On the other hand, extrapolation of management of immune-mediated adverse events from other cancers to cirrhotic patients can lead to liver decompensation or bacterial infections [15]. Excessive steroids use following incorrect or misinterpretation of abnormal

liver tests, assuming immune-mediated hepatitis, demands a key role of hepatologist in this setting.

These novel systemic therapies have led to a controversy in health systems and scientific associations: *who should lead the management of patients with hepatocellular carcinoma?* The answer for this question is that HCC requires a multidisciplinary team management including hepatobiliary surgeons, radiologists, interventionists, oncologists, and palliatives. However, hepatologists have a key role in early diagnosis, and management of HCC at all BCLC stages. Undoubtedly, hepatologists dedicated to liver cancer play a very important role in leading multidisciplinary medical boards. This will for sure translate into the greatest cost-effectiveness use of resources, and should be underlined in scientific societies. Consequently, it further demands development of educational networking for updating the management of HCC patients. In other words, the comprehensive approach to HCC should include health policy efforts in epidemiological characterization, improve adherence to surveillance programs, access to curative, locoregional, and systemic treatments. Latin American health systems and policy makers should recognize the urgency of developing multidisciplinary groups in the care of these patients, but on the other hand, underline the central role of hepatologists. This for sure will lead to better patient reported outcomes and health resources optimization.

#### Declaration of Competing Interest

None.

#### Acknowledgments

We would like to thank the Latin American Association for the Study of Liver Diseases (ALEH). All the authors approved the final version of the manuscript.

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