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Prognosis prediction and staging



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Alejandro Forner, M.D., PhD., Specialist in the Liver Unit ^{a, b, *},
Álvaro Díaz-González, M.D., Research Fellows ^a,
Alexandre Liccioni, M.D., PhD., Research Fellows ^a,
Ramón Vilana, M.D., PhD., Senior Consultant in the Radiology
Department ^{b, c}

^a Liver Unit, Barcelona Clinic Liver Cancer (BCLC) Group, Hospital Clinic Barcelona, IDIBAPS, University of Barcelona, Spain

^b Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Spain

^c Radiology Department, Barcelona Clinic Liver Cancer (BCLC) Group, Hospital Clinic Barcelona, University of Barcelona, Spain

A B S T R A C T

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Staging and prognosis assessment are critical steps in the management of patients with hepatocellular carcinoma. This cancer is a complex disease usually associated with chronic liver disease, and any attempt to assess the prognosis should consider tumour burden, degree of liver function impairment and evaluation of cancer-related symptoms. In addition, for any staging system to be meaningful it has to link staging with treatment indication and this should be based on robust scientific data. Currently, the only proposal that serves both aims is the Barcelona Clinic Liver Cancer (BCLC) staging system. It divides patients into very early/early, intermediate, advanced and end-stage. Very early/early stage HCC patients should be considered for potentially curative options such as resection, transplantation and ablation. Patients at intermediate stage benefit from chemo-embolization, while patients at an advanced stage or who cannot benefit of options of higher priority have sorafenib as standard of care. Finally, patients at end-stage should receive best supportive care.

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* Corresponding author. Liver Unit, BCLC Group, Hospital Clinic, c/ Villarroel, 170, Escala 7, Planta 3, 08036 Barcelona, Spain. Tel.: +34 932279803; fax: +34 932279317.

E-mail address: aforner@clinic.ub.es (A. Forner).

In the last twenty years, major advancements have been achieved in the prognosis assessment and management of hepatocellular carcinoma (HCC) [1]. In previous decades, HCC was considered infrequent in Western countries and was usually diagnosed at an advanced stage, closely associated with the development of cirrhosis decompensation and constitutional symptoms, when potential curative treatments were unfeasible and prognosis was dismal. Nowadays, this scenario has completely changed. HCC is recognized as one of the most frequent neoplasia worldwide, the third most common cause of cancer-related death [2], and is currently the leading cause of death among patients with cirrhosis [3]. The application of surveillance programmes for early detection of HCC, and the improved diagnostic capacity of current imaging techniques have permitted the diagnosis of the disease at earlier stages, when effective treatments are feasible [1].

Prognosis estimation and treatment allocation are main issues that physicians have to face when a patient is diagnosed with HCC. HCC appears frequently associated with a chronic liver disease and, therefore, any attempt to assess the prognosis should consider not only the tumour burden, but also the degree of liver function impairment [4]. Moreover, the assessment of cancer-related symptoms should be incorporated in the prognosis evaluation, since symptoms have shown an unquestionable predictive value [5]. Several prognostic systems have been proposed. All of them may successfully divide the cohorts according to outcome but, unfortunately, their application in clinical practice and research is not optimal. In this Review, we will summarize the main prognostic systems with special emphasis on the Barcelona Clinic Liver Cancer (BCLC) staging system. The BCLC was first reported in 1999 [6], and constitutes an evolving approach, as it has regularly incorporated changes that have emerged since its original publication [1,7].

Prognostic prediction

Decades ago, prognosis prediction was easy, since the majority of the patients were diagnosed at an advanced symptomatic stage that usually was associated with liver decompensation [8–13] and dismal outcome with no chance for effective therapy. Data retrieved from those years showed that heavily impaired liver function and presence of intense cancer-related symptoms easily predicted poor short-term survival and thus, HCC patients with impaired performance status or with severely impaired liver function should be classified as end-stage. Evidently, patients with heavily impaired liver function should be considered for liver transplantation (LT) [14,15] and, in this setting, the presence of HCC could just only constitute a contraindication for LT if tumour burden exceeds the criteria for being enlisted in LT program [1]. In this case, the evaluation of the patient should be done because of end-stage liver disease and not because of HCC. This distinction is critical when staging is linked to treatment and should be taken into account when an HCC patient is classified as end-stage because of the impossibility of offering LT due to decompensated cirrhosis.

If end-stage patients are easily identified, it is controversial how to establish a stage for those HCC patients that are diagnosed before such a dismal scenario. Several proposals have been suggested to stratify patients according to the expected outcome. Table 1 summarizes the proposals that have gained more visibility [6,16–25]. Most of them result from an analysis of the association of any clinical or pathological parameter with survival, ultimately resulting in a division according to an equation derived from the multivariate Cox regression analysis or to a score obtained by the sum of the values allocated to the significant parameters. The value of each variable would vary according to the statistical predictive power and, in that way, balance their relevance. In almost all instances, these systems are the result of assessing liver function and tumour burden. Regrettably, in most of these staging systems, the presence of cancer-related symptoms is not registered despite its unquestionable prognostic value [16,17,19,22–24]. Assessment of cancer-related symptoms by Karnofsky index [26] or ECOG performance status [27] is a well-established procedure in an oncology practice, and patients with a performance status >2 have a grim prognosis with unlikely survival impact of any therapy. Furthermore, any system aimed to be clinically successful should optimally attempt to link prognostic prediction and treatment indication. Regrettably, this is not the case with most of the scoring or category allocation systems, which, to some extent, may include in the same category patients who would be candidates for potential curative therapies and patients who would merely receive palliation [17].

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