

## **Classification and Staging** of Hepatocellular Carcinoma

### An Aid to Clinical Decision-Making

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#### **KEYWORDS**

Hepatocellular carcinoma
Tumor staging
Classification
Treatment selection

#### **KEY POINTS**

- Hepatocellular carcinoma is a heterogeneous malignancy and classification and staging methods help in stratifying patients for determining prognosis and planning treatments.
- Tumor characteristics, degree of liver dysfunction, and patient's performance status have been found to be key factors that determine prognosis and what treatment modalities are appropriate.
- There is no one classification method that is globally applicable in all populations.
- A multidisciplinary team approach is needed for planning individualized treatment for the best outcome.

#### INTRODUCTION

Hepatocellular carcinoma (HCC) is a clinically and pathologically heterogeneous neoplasm. The outcomes of patients with HCC depend on the stage of disease at the time of diagnosis and the underlying biologic behavior of the tumor. HCCs fall along a broad spectrum of biologic behavior ranging from initiation as a single welldemarcated mass that progresses to a single large lesion to tumors that initiate as multifocal, infiltrative tumors with a high propensity to local, regional, or distant metastases. There seems to be a wide range of tumor phenotypes between these two extremes. A large subgroup of HCCs begin as single nodules that acquire more invasive characteristics as they grow, becoming multifocal with either local satellite lesions or more distant intrahepatic or extrahepatic metastases. Small unifocal HCCs are the

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most easily treated, either by liver transplantation, surgical resection, or thermal ablation, with excellent long-term outcomes. As HCCs become larger and more invasive and metastatic in their phenotypes, it becomes progressively more difficult to achieve a radical cure. The effectiveness of local or locoregional therapies, surgical resection, or liver transplantation for HCC depends on tumor size; unifocality or multifocality; the presence, type, and extent of extrahepatic metastases; and the exact locations of tumor sites. Optimal treatment selection heavily depends on the tumor phenotype at the time of diagnosis. There are also important patient characteristics that determine the likely outcome in response to therapy. These characteristics are particularly important in the case of patients with HCC because most of these cases worldwide occur in individuals with cirrhotic stage chronic liver disease. The presence of cirrhosis further complicates the decision-making in patients with HCC because it substantially limits the ability of patients to tolerate surgical resection or extensive ablative or embolic therapy for HCC tumors, thus requiring careful evaluation of liver functional state in relation to tumor burden. Classification and staging of HCC in a way that allows optimal treatment selection is therefore challenging. There have been several advances in understanding the natural history and pathogenesis of HCC, and these advances have spurred changes in treatment that have improved the long-term outcomes of patients with HCC. However, mortality from HCC is still rising worldwide, indicating the need for further improvements in surveillance and early detection, access to care, and individualized selection of treatment options based on each patient's unique clinical and molecular phenotype.

Over the past three decades, several classification and staging systems have been used to stratify this heterogeneous malignancy and to aid providers in determining prognosis and treatment. These systems use different variables to objectively score tumor and patient characteristics. These factors have typically included tumor number, extent and location, severity of liver dysfunction, and performance status of the patient (Fig. 1). Some classification schemes use a combination of these variables for improved performance. The classification systems vary and do not necessarily overlap. Some are used more frequently than others and there is notable geographic variability in their use. This article summarizes some of these classification and staging schemes and discusses the conceptual framework that guides optimal treatment selection for each patient. The aim of this article is not to exhaustively discuss each staging system proposed in the last three decades, but to review the most commonly used staging systems, evaluate the rationale behind some of the newer staging systems, and compare them focusing on their use in clinical decision-making, notably choice of therapy.

#### COMMON CLASSIFICATION AND STAGING METHODS Tumor-Node-Metastasis Classification

The TNM classification for solid tumors is a staging system that has been and is still a method that is widely used for all solid tumors. It was first described in 1968 by the French surgeon Pierre Denoix.<sup>1</sup> It is the accepted staging system by the International Union Against Cancer and the American Joint Committee on Cancer for staging of solid tumors in general, with amendments and modifications for different kinds of tumors.<sup>2</sup> The TNM system is based on tumor size, extent of regional lymph node involvement, and whether or not there is spread to distant structures. The staging may be based on clinical or imaging findings (ie, clinical) or after open surgical resection or exploration (ie, pathologic) (Table 1). The TNM classification method had been shown to have superior prognostic power in HCC when compared with three other commonly used

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