A Common Staging System for Hepatocellular Carcinoma

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Abstract

The Consensus Panel makes the following recommendations based on the above currently available evidence.

1. The primary staging should be clinical staging, which can be applied to all patients. The CLIP system should be the clincial staging system of choice, because it is generally applicable to most patients, it includes easily collected variables. Most importantly, it has been externally and prospectively validated. As a caveat, the CLIP system may not be applicable to patients with chronic hepatitis B.

2. A secondary staging system for patients undergoing resection or liver transplantation is needed. The AJCC version of the modified TNM system should be used because it has been internally validated, although external and prospective validation is still lacking. Furthermore, it conforms to the TNM standard.

3. Since neither of these systems is free of limitations, other factors which might be included in accessing prognosis include treatment-directed variables (according to BCLC), the etiology of the underlying liver disease, and newly discovered factors affecting tumor biology.

4. All studies on HCC where it is appropriate to use staging should use one or both of these staging systems (CLIP and AJCC) to define the patient population. Medical journals considering such manuscripts for publication should insist on cohorts being classified according to these staging systems (excluding, of course, those studies looking at improving staging systems).

5. Further studies on the validation of staging systems and harmonization of the different systems are urgently required.

Comments

Until recently, hepatocellular carcinoma (HCC) was a disease confined largely to Africa and the Far East. However, the incidence of HCC is rising steadily in the West, requiring physicians to stage disease severity, to assign prognosis, and to assess treatment outcomes in this often fatal cancer.[1] To do this, an accurate staging system is required. Several systems have been developed for staging HCC, each claiming to be the most useful. The lack of a uniform system for staging of HCC has made it difficult to compare outcomes in different institutions within this country and around the world. For these reasons, among others, the American-Hepatico-Pancreatico-Biliary Association convened a panel jointly with the American Joint Committee on Cancer to review existing systems and make recommendations for a uniform system for staging of HCC.

Oral presentations from the proponents of several staging systems were made to the panel and to a select audience, which along with the panel interrogated the presenters. The panel evaluated the staging systems based on the presentations and published literature using evidence-based medicine guidelines to determine how well each HCC staging system fulfilled relevance criteria of cancer staging systems. The panel concluded that no single staging system fulfills the needs of all physicians caring for patients with HCC, including accurate categorization of all patients, determination of appropriate treatment options, and establishment of prognosis.[2] Systems that arise from surgical interest groups are focused appropriately on resectable lesions, which comprise only a small proportion of all HCCs. Hepatologists manage a much broader spectrum of HCC. Consequently, staging systems based on this intake will categorize the overall population of HCCs more effectively, without, however, providing the precision of categorization needed for surgical treatment. Recommendations also were based on the fact that the prognosis in HCC is highly dependent on the presence and severity of underlying liver disease, a concept first promoted by Okuda et al.[3]

Based on the preceding, the panel recommended that the primary staging for all patients should be by the Cancer of the Liver Italian Program (CLIP) system, one of the broad clinical systems. A secondary staging system, based on a modification of the TNM system endorsed by the American Joint Committee on Cancer, was recommended for patients undergoing resection or liver transplantation.[2] The CLIP system allocates points for four variables that affect prognosis, including Child-Pugh stage, tumor morphologic features (single, multiple, or massive), serum alpha-fetoprotein level (more than or less than 400 ng/mL), and portal vein thrombosis.[4] Clearly, universal adoption of these recommendations would be a step forward in dealing with HCC. Ideally, all new clinical trials and clinical descriptions of HCC should include categorization by CLIP score. Adopting CLIP would not negate the need to work toward better systems, but having a universal system in the interim will allow comparison of studies among centers and countries.

Several issues in HCC still need to be addressed. These include having a closer link between tumor stage and therapeutic plan. Currently, the Barcelona Clinic system does this, although it does not seem to indicate prognosis as accurately as CLIP score and may not make allowance for new treatments.[5] Another issue that requires attention is better integration of staging into the system used for allocation of cadaveric livers. Currently, livers are allocated in the United States based on the Model for End-Stage Liver Disease. This allows some prioritization for patients with HCC, but seems to represent a mixture between TNM stage and Model for End-Stage Liver Disease score, without apparent validation. Also, certain factors identified in the CLIP score need further validation. For example, portal vein invasion is cited as an important prognostic factor, but it is not clear if microscopic vascular invasion identified in resected or explanted liver specimens carries the same significance. If microvascular invasion was a good predictor of tumor recurrence, it may be used as an indication for the use of adjuvant or neoadjuvant chemotherapy. It also will be very important to validate the CLIP score in other populations, including patients with HCC in the United States.

Finally, it is necessary to educate physicians, hospitals, pathology departments, and cancer registries about these new recommendations and for these organizations to implement their use. The value of the current recommendations should be reassessed periodically to ensure their ongoing usefulness and validity.

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Prognostic Prediction in HCC: Did Anybody Expect It to Be Easy?

Staging and prognostication of patients with hepatocellular carcinoma (HCC) is a very controversial area where a wide consensus is lacking.[1] A well-validated and internationally accepted staging system is critical in order to fulfill several needs.[2] Firstly, it should allow healthcare providers to give accurate information to patients about long-term life expectancy. In addition, it should stratify patients into subgroups with significantly different outcomes. Obviously, the outcome of each strata should be reproduced in different studies applying the same system, as one of the aims of any classification is to facilitate comparison between studies. Finally, a staging system should help healthcare providers to indicate the most adequate treatment and to predict the outcome after therapy.[2] Accordingly, the task is not simple, and as will be discussed below, it is far from being solved. Part of the difficulty is related to the fact that more than 90% of HCC cases appear in a cirrhotic liver.[3] Thus, prognostication should consider both the tumor extent and the degree of liver function impairment.[3] This is different from most solid tumors in which the outcome is predicted by the tumor itself and by the feasibility of applying effective treatment.

The article by Henderson et al.[4] summarizes the effort conducted by a Consensus Panel set up by the AHPBA to review the available systems to stage HCC patients and suggests which of the several prognostic models should currently be used. The proposals that were discussed included the Okuda staging system,[5] the Cancer of the Liver Italian Program (CLIP),[6] the BCLC,[7] the CUPI,[8] the modified TNM,[9,10] and the Japanese proposal recommended by the IHPBA and supported by the UICC (Makuuchi et al., manuscript submitted). Among the clinical methods, the panel endorsed the CLIP score, because it has been partially validated and is the easiest to use. In addition, they recommended the modified TNM as the best pathologic system. The effort made by the panel has to be acknowledged, but unfortunately it seems they have stretched themselves too far by producing a statement in support of one of the systems, as they simultaneously accept that no system fulfils the requirements of acceptance because of several limitations. These limitations are listed in the manuscript and unequivocally argue against the panel's recommendation.

The use of scoring systems that divide patients into strata with different prognoses, without any link to treatment indication or the ability to predict the outcome after therapy, has no major clinical value. Furthermore, despite some positive suggestions, it is unfortunate to note that

even if some systems such as the CLIP[5] or CUPI[7] properly stratify patients according to outcome, the survival of the strata has not been reproduced in studies from different geographic origins,[11] nor do they retain their prognostic power in comparison with other staging systems.[7] This lack of reproducibility suggests that the characteristics and evolutionary stages of the patients recruited in the investigations are heterogeneous and/or that some important predictors that may determine a different outcome have not been taken into account. Thereby, most systems are useful for identification of end-stage patients, but lack the accuracy needed to identify early stage patients and distinguish them from intermediate cases (the survival of the best CLIP strata is 50% at 3 years). At the same time, pathologic systems have proven to be useful for resected HCC, but their usefulness after transplantation is controversial, and can not be applied to non-surgical patients. Furthermore, early stage patients are usually treated by surgery or percutaneous ablation (the reason for no treatment represents an important bias) and thus, prognostication at this stage should always incorporate treatment-dependent variables. With all these comments in mind, it might finally appear more useful to postpone the search for a single staging system to serve all HCC patients. Instead, efforts should be focused on the development of prognostic models for any relevant evolutionary stage of the disease (early, advanced, and terminal), each of them with specific needs.[3,12]

Hence, with the current evidence, the most reliable statement that the Consensus Panel has released is that neither of the available staging systems are free of limitations and in the future other factors such as etiology, treatment variables, and new markers may have to be incorporated. In that sense, it is expected that molecular markers may overcome some of the limitations currently faced when using merely clinical or pathological variables. Accordingly, no answer can be given to the question of which system should be used to stage HCC patients. Thus, instead of supporting the use of the easiest system at the cost of reduced clinical usefulness and reliability, the request should be to further develop prognostic investigations. If designed to answer well-defined questions, they will very likely deal with specific scenarios (transplantation, resection, non-surgical HCC) and again skip the search for a common model for all patients.

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The Strategic Role of Staging in the Treatment of HCC

Comments

Many failures in the treatment of patients with hepatocellular carcinoma (HCC) are the result of incorrect tumor staging. Despite progress in statistical methods and gains in knowledge of the natural history of liver cancer, the ideal staging system for HCC has yet to be determined. This is in part because of the epidemiologic and clinical heterogeneity of the tumor, which depends mainly on the interplay between constitutional and environmental risk factors for the tumor and the presence and severity of the underlying liver disease. Difficulties in developing staging systems for HCC also have originated from the differences in expertise and treatment algorithms adopted in different centers world-

wide, thus raising the issue of whether it is worthwhile to attempt to reach consensus on a single model for staging HCC. Indeed, to our knowledge, all staging systems reported to date tend largely to reflect the demographic features of the patients seen locally, the center's resources, the professional attitudes of the physicians involved, and the unavoidable bias of patient selection. The Consensus Statement on Staging for Hepatocellular Carcinoma, published elsewhere,[1] provides a negligible contribution to the clinical management of patients with HCC because it endorses staging systems that stratify patients with different prognoses but has no link with treatment indications or treatment outcome.

In our experience, the primary purpose of staging a progressive tumor such as HCC is to distinguish those patients with a potentially curable disease from those with more advanced disease and a dismal outlook, for whom curative treatments are not applicable. Therefore, we disagree with the Consensus Statement that the Cancer of the Liver Italian Program (CLIP) staging system [2] is the staging system of choice for patients with HCC because we believe it to have suboptimal sensitivity for tumor invasiveness (patients with a CLIP score of 0 may have from 0–50% of their liver replaced by the tumor) and to be definitively skewed toward more severely affected patients whose disease is not amenable to curative treatment. As a consequence, too many patients with a CLIP score of 0 will not meet the currently accepted criteria for surgical and percutaneous interstitial treatments that have been proven to be efficacious in patients in whom there is 1 cancerous node measuring < 5 cm in size. Conversely, a score of 1 includes patients with up to 3 cancerous nodes measuring < 3 cm in size (who have a potentially good prognosis because they fit the criteria for liver transplantation and percutaneous interstitial therapies) with those patients who have extended liver involvement by the tumor (whose poorer prognosis means they stand little chance of receiving curative treatment). Vascular invasiveness by the tumor and tumor cell differentiation are reported to be the dominant predictors of survival in surgically treated patients,[3] and are reliably assessed by surgical specimens only. The size and number of cancerous nodes that we believe to be the best clinical surrogates of the above cited pathologic predictors[4] are not properly weighted by the CLIP score. We also hesitate to endorse the American Joint Committee on Cancer TMN staging system as an adequate approach for predicting survival after tumor resection or liver transplantation. The TNM classification does not take into proper account the significant prognostic value of liver impairment in patients with HCC.[5,6]

In the near future, genomics and proteomics could help in implementing the staging of HCC patients because different pathways of liver cell carcinogenesis exist that are linked to the expression of different cell genes and are believed to be correlated with different outcomes of the disease.[7]

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