What Is the Best Staging System for Hepatocellular Carcinoma in the Setting of Liver Transplantation?

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The purposes of cancer staging are (1) to accurately predict a patient’s prognosis and (2) to determine the appropriate interventions. Hepatocellular carcinoma (HCC) is somewhat unique: it usually affects patients with underlying liver disease, and both tumor burden and liver function need to be carefully evaluated at the time of the prognostic prediction and the treatment recommendation. The liver disease stage has a significant impact on the chosen treatment, and symptoms such as encephalopathy, coagulopathy, fluid overload, and poor synthetic function affect a patient’s ability to endure the treatment. The extent of the tumor, symptoms such as limiting asthenia, anorexia, and pain, and impaired performance status also have a high prognostic value. Conversely, the type of treatment can have a significant impact on the prognosis. Therefore, when the optimal staging system for HCC is being considered, it is important for the tumor burden, the presence of symptomatic diseases, and the functional status to be considered in the assessment of each system.

In the setting of liver transplantation, however, we have to determine which patients will benefit most from liver transplantation. Hence, the staging systems in this scenario should not be focused on the selection of the best treatment for patients. Instead, the staging systems should be designed to identify the best candidates for liver transplantation, and the results should be compared to those for patients without HCC.

MATERIALS AND METHODS

MEDLINE and PubMed searches were performed with specific and relevant keywords (hepatocellular carcinoma, staging system, and liver transplantation), and
articles were retrieved and reviewed. We critically reviewed all original descriptions of the various HCC staging systems and recent literature on comparisons of the various HCC staging systems. This literature included reviews and articles describing single-center and multicenter analyses and summary reports from recent consensus conferences and societies.

RESULTS

For our review of the current staging systems for HCC, we decided to separate the analysis into several questions. First, what are the current staging systems for HCC, and what evidence supports their validity? Second, what are the best HCC staging systems for making decisions about liver transplantation as a treatment option (ie, which patients will benefit from liver transplantation versus other treatments)? Finally, what staging system is best for determining the prognosis after liver transplantation?

What Are the Current Staging Systems for HCC?

The degree of liver disease affects the prognosis as well as the chosen treatment, and the type of treatment can have a significant impact on the prognosis. Over the years, several groups have developed different systems or scores for stratifying HCC patients (Table 1). Most of these classifications have resulted from analyses of the association of clinical or pathological parameters with survival. Each system is characterized by the patient population on which it is based. Numerous comparisons have been made, but because the patient selection criteria and the preferred treatments in these published studies vary significantly, no final conclusion about the optimal system has been made.

The tumor-node-metastasis (TNM) classification, which was developed by the International Union Against Cancer and the American Joint Committee on Cancer (AJCC), is based on the size and spread of the tumor. It has been criticized for its failure to adequately stratify patients and for its complexity. In 2002, a revision of the AJCC TNM staging system for primary liver malignancies (the sixth edition) was published; it was based on a simplified staging system proposed by Vauthey et al. This new TNM staging system has been validated for good discrimination between stages for patients undergoing hepatic resection.

The Okuda classification, which was the first to include both tumor parameters and liver function tests, is based on the extent of the tumor (≤50% or >50% of the liver) and liver function7; it was widely accepted in the past but is now seen as limited because of the lack of details about the tumor burden. Japanese researchers revised the TNM staging method according to general rules of the Liver Cancer Study Group of Japan (LCSGJ) for the clinical and pathological study of primary liver cancer; this revision includes 3 liver damage grades and thus 12 classifications. This system has not been fully integrated into clinical practice because of its complexity and lack of prognostic correlation. A simplified staging

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**TABLE 1. Comparison of the Prognostic Staging Systems for Predicting Outcomes for HCC Patients**

| Prognostic Staging System | Tumor Stage | Liver Function | Health Status | Stages |
|---------------------------|-------------|----------------|---------------|-------|
| Okuda classification^7 (1985) | Tumor involvement > 50% | Bilirubin, albumin, and ascites | Child-Pugh stage | I-III |
| CLIP system^10 (1998) | Tumor morphology, AFP, and portal vein invasion | Bilirubin and alkaline phosphatase | Karnofsky index | A-C |
| GRETCH system^3 (1999) | Portal vein invasion and AFP | Child-Pugh stage and portal hypertension | Performance status | 0 and A-D |
| BCLC system^6 (1999) | Number of nodules, tumor size, portal vein invasion, and metastases | — | — | — |
| CUPi system^5 (2002) | TNM and AFP | Bilirubin, ascites, and alkaline phosphatase | Symptoms 0-12 (score) with 3 risk groups | — |
| JIS score^4 (2003) | TNM by LCSGJ criteria | Child-Pugh stage | — | 0-5 |
| SLiDe score^6 (2004) | TNM by LCSGJ criteria | Liver damage by LCSGJ criteria and PIVKA | — | 0-3 |
| AJCC TNM system^11 (2002) | Number of nodules, tumor size, portal vein invasion, and metastases | — | — | I-IV |
| Tokyo score^9 (2005) | Number of nodules and tumor size | Albumin and bilirubin | — | 0-8 |
| Taipei Integrated Scoring system^12 (2010) | Total tumor volume and AFP | Child-Pugh stage | — | 0-6 |

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system based on the LCSGJ criteria, the Japan Integrated Staging (JIS) score, was introduced in 2003; it combines the TNM stage and the Child-Pugh stage into a score of 0 to 5. Recently, the JIS score was compared to the Cancer of the Liver Italian Program (CLIP) score and the Barcelona Clinic Liver Cancer (BCLC) system; it was found to be superior with respect to prognostic determination, but it has yet to be validated in populations other than Japanese patients with HCC.

The CLIP score was introduced in 1998 and was later validated in prospective trials in 2000. This is a simple computation involving the Child-Pugh stage, the morphology and extent of the tumor, the presence of portal vein thrombosis, and the alphafetoprotein (AFP) level. This score, which is calculated at the time of diagnosis, has been very successful in discriminating between patients with HCC with respect to their prognosis. The addition of tumor-specific prognostic factors has improved the prognostic accuracy of the CLIP score versus the Okuda and Child-Pugh systems. The BCLC staging system was introduced in 1999 and includes the performance status, the unifocality or multifocality of the tumor, the presence of vascular invasion, the presence of extrahepatic spread, the Child-Pugh stage, and the presence of portal hypertension. Initially developed for patients undergoing liver resection, this system has been broadened so that the algorithm can be used for all HCC patients. The CLIP and BCLC systems are based on patients with earlier stage disease.

Several other systems, including systems from France [the Groupe d’Etude et de Traitement du Carcinome Hepatocellulaire (GRETCH) system], China [the Chinese University Prognostic Index (CUPI) system], and, most recently, Tokyo, have been introduced. The GRETCH and CUPI systems were developed with samples of patients with advanced disease and very short median survival times. The GRETCH system is intended to distinguish between patients whose survival is expected to be prolonged and who can benefit from aggressive treatment and patients who have a high risk of death in the short term and for whom treatment will be futile. The CUPI system is the result of an effort to determine the prognosis of patients in a Southeast Asian population in which hepatitis B–related HCC was predominant. Nineteen variables, including liver function and liver-related symptoms, were studied. The Tokyo score was developed with a cohort of Japanese patients with end-stage disease who were treated with percutaneous ablation, and it was validated with a cohort undergoing resection surgery. The researchers’ aim was to develop a simple system for patients undergoing radical treatment for early-stage HCC. Finally, the Taipei Integrated Scoring system defends the use of the total tumor volume as the best tool for assessing the tumor burden.

In almost all instances, the currently used systems focus on assessments of the liver function and the tumor burden. The tumor burden is assessed by radiological or pathological criteria. Few of these systems include an assessment of the presence of cancer-related symptoms. The assessment of the Eastern Cooperative Oncology Group performance status or the Karnofsky index is a well-established item in oncology practices; patients with a performance status > 2 are usually considered to have a grim prognosis, and the survival impact of any therapy is highly doubtful. Among the recently assessed systems that are used today, only the BCLC and GRETCH systems assess the performance status, and the CUPI system assesses the presence or absence of symptomatic disease.

Because a staging system should optimally attempt to link the prognostic prediction and the treatment indication, any system designed to be clinically successful has to serve both aims. A European Association for the Study of the Liver panel of experts recommended the consideration of 4 related aspects: the tumor stage, the degree of functional impairment, the general condition of the patient, and the treatment efficacy. It is clear that patients with early-stage HCC (whatever definition is used) will be considered for treatment by resection, liver transplantation, or ablation, and their survival is expected to be relatively good; for patients whose disease is terminal and malignant [severe symptoms, liver impairment (Child-Pugh class C with no chance for liver transplantation), or huge tumors], the survival time will be very short. In patients with untreated, non–early-stage, nonterminal HCC, 3 independent predictive factors have been identified for a poor prognosis: constitutional and cancer-related symptoms (according to the Eastern Cooperative Oncology Group performance status), vascular invasion, and extrahepatic spread.

According to this concept, there are 2 well-defined populations (patients with early-stage HCC and patients with end-stage HCC) as well as a middle group with a mix of patients with a very heterogeneous profile with respect to liver function, tumor burden, and the presence or absence of symptoms. These stages defined the BCLC staging system in the initial proposal, which was prospectively validated by a number of later studies. In addition to these prospective validations, several studies have demonstrated the ability of the model. It has been recently endorsed by numerous groups and is included in the guidelines for the management of HCC from the American Association for the Study of Liver Diseases.

Other staging systems such as the CLIP system have also been externally validated. A recent study compared the BCLC, CLIP, Tokyo, JIS, and TNM staging systems in 1713 Taiwanese patients, and the CLIP staging system was found to be the best overall for early to advanced HCC, regardless of the treatment strategy; this system was followed by the Tokyo, JIS, BCLC, and TNM systems. Notably, only 46.8% of the patients in this report received curative treatment, which included resection (n = 448), transplantation (n = 4), and locoregional therapy (n = 862).
Because the number of patients who underwent orthotopic liver transplantation was small, it is hard to use these results in the transplant setting. The CLIP system seems superior for predicting survival in patients with advanced disease treated by oncologists, but it disregards the presence of symptoms, does not link the stage to treatment recommendations, and is insufficient for early-stage disease.

What Are the Best HCC Staging Systems for Making Decisions About Liver Transplantation as a Treatment Option?

The findings that we have outlined in response to the first question cannot necessarily be used for patients listed for and potentially undergoing liver transplantation because patients with advanced disease will not qualify for liver transplantation in most parts of the world. Therefore, the best staging system for making decisions about liver transplantation needs to focus on patients with early-stage HCC. It is important to determine which patients will benefit from liver transplantation versus other curative treatments; furthermore, any staging system in this scenario should not be focused on the selection of the best treatment for the patient. Instead, the best patient for liver transplantation should be selected. Unfortunately, most scoring and allocation systems include in the same category a broad range of patients who may be candidates for curative therapy as well as patients who merely deserve palliation. The BCLC, CLIP, and Tokyo systems seem to be focused more on patients with early-stage and potentially curable HCC.

It is important to clarify that none of the staging systems discussed in the previous section have been analyzed and compared in detail or validated with respect to the prognosis of liver transplantation. Although there has been much discussion about appropriate allocation systems and criteria, the aforementioned staging classifications have not been assessed for their value in determining whether transplantation is the best treatment option. On the other hand, several investigators have tried to determine the predictive value of various systems for posttransplant outcomes.

Although the TNM staging system seems to have inferior prognostic ability for predictions of long-term survival overall (most likely because the severity of liver disease and cirrhosis is not included in this system), there may be a larger role for patients who qualify for surgical treatment. Despite the relatively poor prognostic ability of TNM for all patients with HCC, it has been used almost exclusively for patients undergoing liver resection. Although the Milan criteria, which were proposed for liver allocation, were based on a small number of patients, they have stood the test of time. At their core is the idea that transplantation is appropriate for patients with stage T2 lesions. The acceptance of the Milan criteria for liver allocation is based on numerous studies demonstrating that transplantation for patients whose tumors fall within stage T2 results in excellent posttransplant outcomes. The obvious limitation of using only the tumor size and number for staging before surgical intervention is that the staging is based on radiological findings and not on pathological findings. There are some relatively recent studies suggesting that the TNM system has the highest predictive value after liver transplantation. Unfortunately, the TNM system has other limitations, including a broad tumor range in stage 2, at which transplantation may be considered.

The Tokyo score was developed to determine the prognosis for patients undergoing radical treatments for HCC, including percutaneous ablation and liver resection; therefore, patients with advanced disease are excluded. In Tateshii et al.’s study, the Tokyo score demonstrated a predictive ability comparable to that of the CLIP system and better than that of the BCLC system. Liver transplantation could be considered a radical surgical treatment; however, no transplant patients were included in this analysis, and this system has yet to be validated outside Japan. Another recent article compared the BCLC, CLIP, and GRETCH systems for treated or untreated patients. For 178 treated patients who underwent resection (n = 14), transplantation (n = 11), or locoregional therapy (n = 153), the BCLC system had a higher discriminatory score and was better at predicting 24-month survival. One could postulate that because the BCLC system takes into account the degree of liver disease, it identifies patients who can tolerate resection or locoregional therapy and thus avoid transplantation. The severity of liver disease, however, has little role in liver transplantation, except that a sicker patient may receive a transplant more quickly; therefore, the patient may have a better outcome. Unfortunately, the aforementioned study included very few transplant recipients.

The transplant community has also shown that some patients who fall outside the Milan criteria, such as those who fulfill the University of California San Francisco criteria and those who are selected with the Metroticket approach, can still benefit from transplantation. These patients form the basis for supporting broader criteria for transplantation, and this is discussed in detail elsewhere in this supplement. It is possible that the need for careful pretransplant staging is most important for these patients who fall just outside the Milan criteria because the general outcomes for patients within the Milan criteria who receive liver transplants are very good overall. The TNM system also shows its greatest limitations with these patients. Although T1 and T2 patients in general have excellent outcomes with transplantation, it is important to recognize that T2 and T3 patients have a wide range of disease expression. The seventh edition of the TNM system, which was published in 2009, may partly address this problem by subdividing stage 3 into groups based on the presence or absence of large-vessel invasion. However, the clinical utility of this approach requires validation in prospective studies.
Many of the cited studies have confirmed that patients with earlier stage HCC will be better served by prognostic models different from those used for patients with advanced HCC both at baseline and after the proposal for treatment. Additionally, the prognosis can change with the potential treatment. In that sense, for patients with early-stage HCC who are candidates for surgical resection, liver function and the presence of portal hypertension have important prognostic value; in contrast, for patients treated with liver transplantation, liver function has little impact on the outcome, but waiting time and availability of a donor organ are essential prognostic factors. For the potential transplant recipient, the anatomic and pathological state of the tumor determine the prognosis more than the functional status because liver function and symptoms will return to normal after successful transplantation. Unfortunately, the details of the pathological stage are not available before transplantation.

Among other potential risk factors for recurrence and prognosis that should be considered in the transplant setting, AFP is likely to gain more relevance as it emerges as an important predictor of prognosis after resection and/or transplantation. Numerous publications have cited a strong correlation between recurrent disease and high AFP levels, and some have suggested an AFP level > 400 ng/mL as a cutoff. There is still no agreement about or strong evidence for using a specific AFP level as a cutoff in clinical practice.

**What Staging System Is Best for Determining the Prognosis After Liver Transplantation?**

Currently in the field of transplantation, staging and organ allocation for patients are based on imaging studies. Although the quality of imaging has significantly improved, the results often do not correlate with findings from surgical specimens, and the preoperative staging may change as a result of the pathological assessment of the transplanted liver. For those patients who have undergone transplantation, the postoperative staging should include pathological features, which are obviously not available before transplantation and thus cannot be used for determining a patient’s suitability for transplantation or allocation. In addition, up to 30% of patients who are diagnosed with HCC by preoperative imaging or AFP levels have alternative histological diagnoses and should thus be down-staged and many small HCCs that are detected by pathological examinations are not diagnosed preoperatively (mostly small lesions with little impact on survival). Although the decision to perform transplantation or to consider a patient within the criteria for transplantation may be based on the imaging stage, the new TNM staging system by definition includes the results of a pathological examination.

The tumor size and the number of tumors remain important prognostic features for the pathological assessment of HCC in the explanted liver. Additional staging features that are prognostically important and can be diagnosed by an examination of the explanted liver include microscopic vascular invasion, satellite nodules, and lymph node metastases. Important prognostic information can also be obtained from features that are related to the tumor grade rather than the stage, such as differentiation (including nuclear size/atypia and mitotic activity). A 4-point grading scheme proposed by Edmondson and Steiner in 1954 is still widely cited in studies of prognostic factors for recurrence. In a recent consensus document, a 3-point grading system that combines grades 1 and 2 from the Edmondson-Steiner scheme into 1 well-differentiated grade has been advocated for reporting lesions in explanted livers to large clinical databases. Other tissue-based studies, including studies of emerging molecular markers that may identify an aggressive phenotype, may be incorporated into pretransplant and posttransplant grading systems. These details are covered elsewhere in this supplement, but they should be mentioned in any discussion about cancer staging.

**SUMMARY**

To assess the prognosis of all HCC patients, the best staging system should take into account tumor stage, liver function, and physical status. In addition, the prognosis should be modified according to the treatment. There is no worldwide consensus about the use of any HCC staging system for all HCC patients, and the systems vary significantly by country. The TNM and Okuda staging systems are most commonly used internationally. The BCLC and CLIP staging systems are used most frequently in Europe, whereas the JIS system has been accepted as a standard in Japan. The BCLC staging system is the only system that links the prognosis with treatment recommendations, and it has been used in several major trials of HCC therapy to define the patient population to be recruited and to stratify the patients into separate prognostic categories. It has been validated in several large patient populations around the world and has been endorsed by several societies as a guide for clinical decision making. The sixth edition of the TNM system is most widely used for determining a patient’s prognosis after surgery or transplantation, and it has high predictive value after transplantation and resection. It has been validated in numerous patient populations and forms the basis for many other staging systems and allocation policies. Unfortunately, the pathological TNM stage is not known before transplantation, and it plays an important role in determining posttransplant survival.

**RECOMMENDATIONS**

1. To assess the prognosis of all HCC patients, the BCLC system should be used for determining treatment options (evidence level 2b, grade B).
2. In clinical decision making, the BCLC system is most appropriate for determining the best candidates for liver transplantation patients meeting the Milan criteria, which are equivalent to TNM stage T2; (evidence level 2b, grade B).

3. In addition to staging before liver transplantation, pathological staging of the explant based on the tumor size and number, vascular invasion (macroscopic or microscopic), and lymph node metastases should be performed. The combination of the 2 prognoses can be used for assessing outcomes with liver transplantation (evidence level 2b, grade B).

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