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Special Report

Response Evaluation Criteria in Cancer of the Liver (RECICL) proposed by the Liver Cancer Study Group of Japan (2009 Revised Version)

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The World Health Organization (WHO) criteria and Response Evaluation Criteria in Solid Tumors (RECIST) are inappropriate to assess the direct effects of treatment on the hepatocellular carcinoma (HCC) by locoreginal therapies such as radiofrequency ablation (RFA) and transcatheter arterial chemoembolization (TACE). Therefore, establishment of response evaluation criteria solely devoted for HCC is needed urgently in the clinical practice as well as in the clinical trials of HCC treatment, such as molecular targeted therapies, which cause necrosis of the tumor. Response Evaluation Criteria in Cancer of the Liver (RECICL) was revised in 2009 by Liver Cancer Study Group of Japan based on the 2004 version of RECICL, which was commonly used in Japan. Major revised points of the RECICL 2009 is to provide TE4a (Complete response with enough ablative margin) and TE4b (complete response without enough ablative margin) for local ablation therapy. Second revised point is that setting the timing at which the overall treatment effects are assessed. Third point is that emergence of new lesion in the liver is regarded as progressive disease, different from 2004 version. Finally, 3 tumor markers including alpha-fetoprotein (AFP) and AFP-L3 and des-gamma-carboxy protein (DCP) were also added for the overall treatment response. We hope this new treatment response criteria, RECICL, proposed by Liver Cancer Study Group of Japan will benefit the HCC treatment response evaluation in the setting of the daily clinical practice and clinical trials as well not only in Japan, but also internationally.

Key words: Response Evaluation Criteria, hepatocellular carcinoma, WHO criteria, RECIST, Liver Cancer, Liver Cancer Study Group of Japan

INTRODUCTION

THE WORLD HEALTH Organization (WHO) criteria[1] and Response Evaluation Criteria in Solid Tumors (RECIST),[2] which are response evaluation criteria for solid tumors after chemotherapy, are commonly used for the evaluation of liver cancer treatment in Western countries. However, it is well known and obvious that both the WHO criteria and RECIST are inappropriate to assess the direct effects of treatment on the liver cancer lesions by ablative treatment and transcatheter arterial chemoembolization (TACE). Although effective treatments may exhibit a necrotizing effect on hepatocellular carcinoma (HCC) with deprivation of its blood flow, the WHO criteria and RECIST do not consider such necrotizing effects to be "effective"; instead, both criteria use only tumor size reduction as measures of effect. It has been shown that the tumor size reduction rate according to the WHO criteria and RECIST following TACE with lipiodol (Lip-TACE) is not correlated with the pathological necrosis rate.[3] When lipiodol is accumulated densely within the tumor, the early arterial staining is masked, and tumor size is not increased, the tumor is completely necrotized as confirmed by histology.[3] Even though the tumor is completely necrotized, it takes a long time to result in reduction of size. The nodule with complete necrosis after Lip-TACE can be seen for several years as a lipiodol more densely

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accumulated nodules than 2 weeks after the intervention. In case of radiofrequency ablation (RFA), the phenomenon is the same with Lip-TACE, though lipiodol accumulation is not seen.

Moreover, the WHO criteria are originally based on bi-dimensional measurement, which was changed to a uni-dimensional measurement in RECIST. Even if tumor necrosis is considered in the response evaluation criteria, uni-dimensional measurement is inappropriate for assessment of the direct treatment effect. Therefore, establishment of response evaluation criteria solely devoted for HCC is needed urgently in the clinical practice as well as in the clinical trials of HCC. The current report describes the newly established response evaluation criteria for HCC by revising the previously existing criteria established by the Liver Cancer Study Group of Japan.

CONCEPT OF THE RESPONSE EVALUATION CRITERIA IN CANCER OF THE LIVER (RECICL)

THE FIRST EDITION of Criteria for the Evaluation of Direct Treatment Effects in Hepatocellular Carcinoma was published in 1994.[4] The revised edition was published in 2004,[5] and is commonly used in Japan, but several problems remained in the revised criteria. Thus, a third revision was carried out before publishing the English edition of the General Rules for the Clinical and Pathological Study of Primary Liver Cancer edited by the Liver Cancer Study Group of Japan (third edition).

Current response evaluation criteria focuses on the following points: (i) development of simple criteria that are sufficiently applicable in routine clinical practice centering on local treatment (ethanol injection therapy, microwave coagulation therapy, RFA) and transcatheter arterial therapy, radiotherapy and systemic chemotherapy can also be included; (ii) assessment of direct treatment effects on intrahepatic target lesions and overall effects are described separately; and (iii) the criteria follow the fifth edition of the General Rules for the Clinical and Pathological Study of Primary Liver Cancer edited by the Liver Cancer Study Group of Japan.[6]

Considering the biological characteristics of HCC, high frequencies of "intrahepatic metastatic recurrence" and "multicentric carcinogenesis", it may not necessarily be appropriate for liver cancer to be indiscriminately diagnosed as "progressive disease" based on the appearance of "a new lesion" alone because such "a new lesion" has not been treated by ablation or TACE when the recurrent nodule exists outside of the treated area. Thus, evaluation of the direct effects of treatment on target lesions should focus on the direct therapeutic effect on the target lesions, and the overall evaluation should be investigated with close association with the prognosis.

Although the chemotherapeutic agent permeates through the liver in chemotherapy, the therapeutic effect of TACE and ablative treatments is limited only to the target lesion or the area fed by embolized artery with the tumor. Treatment is not done for the new lesions appearing outside the area where the ablation or TACE are performed. After the same treatment is carried out on the targeted new lesion, a similar treatment effect may be expected on the formerly treated lesion. Accordingly, when "a new lesion" appears in a region outside the treatment area, the new lesion (intrahepatic metastasis or multicentric carcinogenesis) may not directly indicate the prognosis. The basic concept of the 2004 version of the Japanese response evaluation criteria[5] was to exclude the new lesions from the evaluation of treatment effect on the formerly treated lesions. In other words, the emergence of a new lesion is regarded as out of the evaluation of the treatment effect for the former lesions, which is the most marked difference from the WHO criteria or RECIST.

Therefore, these criteria established by the Liver Cancer Study Group of Japan are exclusively specified for the Evaluation of Therapeutic Effects on Liver Cancer, and differ from other evaluation criteria for solid tumor regarding the various points described above.

The 2004 version of the Criteria for the Evaluation of Direct Treatment Effects in Hepatocellular Carcinoma are superior to the WHO criteria or RECIST because it considers the biological characteristics of HCC as follows: (i) tumor necrosis is regarded as a direct effect of treatment on the target lesion as well as tumor size reduction even though it is minimal; (ii) tumors are measured in two dimensions; (iii) the dense accumulation of lipiodol is regarded as necrosis;[3] and (iv) the emergence of a new lesion is not regarded as a "progressive disease" in evaluation of the treated nodule.

However, several problems remained in the 2004 version: (i) assessment of direct treatment effects was performed at 3 months, while the overall evaluation was performed at 6 months; and (ii) even though the direct effects on target nodules varies among treatment methods, the timing of assessment was not described. To overcome these limitations, some minor changes were made in this 2009 revised version. These criteria may be suitable mainly for local treatment and transcatheter arterial therapy, but are also applicable for radiotherapy and chemotherapy in combination with

the WHO criteria and RECIST. Whether or not some criteria are superior to others will be investigated in future studies. We expect that the 2009 revised edition of Response Evaluation Criteria in Cancer of the Liver (RECICL), will be widely used in clinical practice as well as in the clinical trial settings, not only in our country but also worldwide, as the criteria are clearer and may be more suitable in response evaluation for liver cancer than WHO criteria or RECIST.

MAJOR REVISED POINTS OF THE RESPONSE EVALUATION CRITERIA IN THE 2009 VERSION

FIRST, WE HAVE clarified the direct effect of local treatments on target nodules. When the non-stained low-density area in local ablation therapy such as ethanol injection therapy, microwave coagulation therapy and RFA covers all parts of the low-density area in the late phase of dynamic computed tomography (CT) scan before treatment, the lesion is regarded as 100% necrotized and described as treatment effect 4 (TE4), even though the size of the nodule does not decrease in the follow-up CT scan or multiple resonance imaging (MRI). However, when the non-stained low-density area does not cover the low-density area before the treatment, the risk of local recurrence is high.[7–9] Therefore, for ethanol injection therapy, microwave coagulation therapy and RFA, when the non-stained low-density area is slightly wider across the entire circumference than the low-density area in the late phase of dynamic CT scan before treatment, the lesion is regarded as 100% necrotized (TE4a). When only hypervascularity has disappeared without a slightly wider non-stained region than the low-density area on dynamic CT scan, the condition is judged as TE4b (Table 1).

Second, we have settled the timing at which the overall treatment effects are assessed: (i) the maximum response within 3 months is regarded as the overall treatment effect; (ii) for transcatheter arterial therapy with lipiodol, it is desirable to assess the effect after at least 1 month; (iii) local ablative treatment can be assessed immediately after the treatment; and (iv) for radiotherapy, the maximum response within 6 months may be regarded as the overall effect.

Third, regarding the criteria for "progressive disease" in the overall evaluation, the emergence of a new lesion is regarded as "progressive disease", similar to that advocated in the WHO criteria or RECIST, as shown in the Appendix. However, new lesions are separately described in consideration of the biological characteristics of HCC and the description may contribute to a future review of the criteria, particularly for: (i) intrahepatic solitary lesions (whether it is in the treated area or outside of the treated area by ablation or TACE); (ii) intrahepatic multiple lesions; and (iii) vascular invasion/extrahepatic spread.

Fourth, the RECIST and WHO criteria may be appropriate for radiotherapy and systemic chemotherapy including molecular targeted agents because these are currently used internationally,[10–13] however, we recommend evaluation using the RECICL criteria in combination with the WHO criteria or RECIST in order to clarify which criteria among the three are the most appropriate in future studies. This point is described in the detailed regulation section.

Fifth, in the detailed regulation section, the lowest levels of three tumor markers (α-fetoprotein [AFP], AFP-L3 and Protein induced by vitamine K absence or antagonist [PIVKA-II] or des-gamma-carboxy prothrombin [DCP]) should be measured and described within 3 months and considered with reference to the overall evaluation. It may be useful to prospectively investigate whether there is a difference in the prognosis between complete response (CR) based on imaging alone and CR on imaging in combination with response of tumor markers.

Finally, we include a comparison between the WHO criteria, RECIST[14,15] and RECICL established by the Liver Cancer Study Group of Japan.

Table 1 Treatment effect (TE) on the target nodule

TE4:	The tumor-necrotizing effect is 100% or the tumor size reduction rate is 100%.*
TE4a:	Necrotized area with larger ablated area than original nodule.*
TE4b:	Necrotized area of same size with original nodule.
TE3:	The tumor-necrotizing effect or tumor size reduction rate is between 50% and <100%.*
TE2:	Effects other than TE3 and TE1.
TE1:	The tumor enlarged by >25% regardless of the necrotizing effect.

*For ethanol injection therapy, microwave coagulation therapy, and radiofrequency ablation, when the non-stained low-density area is slightly wider across the entire circumference than the low-density area in the late phase of dynamic computed tomography (CT) scan before treatment, the lesion is regarded as 100% necrotized (TE4a). When only hypervascularity has disappeared without a slightly wider non-stained region than the low-density area on dynamic CT scan, the condition is judged as TE4b. In transcatheter arterial chemoembolization (TACE), the tendency of reduction of tumor size, without tumor staining by CT scan with contrast enhancement, and denser uniform accumulation of lipiodol than just after lipiodol TACE when lipiodol is used, are classified to be TE4.

DESCRIPTION OF RECICL PROPOSED BY LIVER CANCER STUDY GROUP OF JAPAN

Subjects

THE SUBJECTS ARE patients who are treated initially and for recurrence. Because responses to treatment are evaluated, as a rule, by dynamic CT, intrahepatic lesions with hypervascular tumors are the principle targets of the RECICL criteria. It is essential that tumors can be clearly visualized using an imaging technique.

Detailed description

Description of past medical history

1 Methods and date when definitive diagnosis of liver cancer was made.
2 Previous treatment modality (as described in "c. Description of treatment modalities").
3 Dates of initiation and completion of previous treatment.
4 Methods and date when recurrence was diagnosed.

Descriptions of liver cancer at the time of the initiation of treatment

These issues are based on the second English Edition of the General Rules for the Clinical and Pathological Study of Primary Liver Cancer (edited by the Liver Cancer Study Group of Japan).[16] The following items should be noted:

1 Tumor location.
2 Tumor size, number, and vascular invasion. The tumor size is presented as the major axis and maximum diameter crossing the major axis at a right angle.
3 Macroscopic types.[16,17]
4 Macroscopic staging. Even for tumors that are only assessable by imaging, staging should be described following the rules for surgical findings and the resected specimen.[16,17]
5 Histological grading when biopsy is performed.[16,17]

Description of treatment modalities

1 Name of treatment: transcatheter hepatic arterial therapy (transcatheter arterial infusion chemotherapy, transcatheter arterial embolization, TACE), local treatment (ethanol injection therapy, microwave coagulation therapy, RFA), radiotherapy such as Liniac, γ-knife, or proton beam line, systemic chemotherapy.
2 Details of treatment: for treatments using drugs, the name of drugs* (anticancer drugs, Lipiodol, etc.), route of administration, treatment interval and single dose, and the total number of administrations and total dose should be described. For other treatment methods, the details should be described appropriately. When the treatment is discontinued, the reason for discontinuation and the presence or absence of adverse effects should be described. (*In addition to the chemotherapeutic drugs, any drugs directly injected into the tumor to necrotize it, such as ethanol, and/or embolizing materials, should be described.)
3 Dates of initiation and completion or termination of treatment.

Assessment of direct treatment effect on target nodule

1 On assessment of the direct effect of treatment on the target nodule, the tumor-necrotizing effect and tumor size reduction rate are calculated based on the size reduction or disappearance of hypervascularity of the nodule on dynamic CT. Findings of dynamic MRI, and/or contrast-enhanced ultrasonography can substitute dynamic CT.
2 The necrotizing effect is assessed by imaging. The percent ratio of the necrotized area to the cross-sectional area of the tumor should be calculated.* (*When various cross-sections are obtained for a single tumor, the total sum of the necrotic area should be used; however, when the maximum cross-section represents the entire findings of the tumor, assessment may be made based on the maximum cross-sectional area.)
3 The size reduction rate is calculated using the equation below, after calculating the product of the major axis of the maximum cross-section by the maximum diameter crossing the major axis at a right angle: size reduction rate = ([product before treatment] - [product after treatment]) / (product before treatment) × 100.
4 Direct treatment effect (TE) on target nodule: effects on individual lesions are categorized into four degrees based on the tumor-necrotizing effect observed within a fixed term* after the initiation of treatment or the maximum tumor size reduction rate, as shown in Table 1. (*For local treatments [such as ethanol injection therapy, microwave coagulation therapy, RFA], the effects are assessed immediately after treatment. For transcatheter arterial chemotherapy using lipiodol, transcatheter arterial embolization and transcatheter arterial chemoembolization, it is desirable to assess the effect after at least 1 month. For radiotherapy, the effect assessed based on the maximum response within 6 months.)
5 When multiple lesions are present in the liver, TE is determined in individual lesions.

Table 2 Overall response evaluation (effect of treatment on all intrahepatic lesions at 3 months; radiotherapy can be evaluated at 6 months)

Overall evaluation of treatment effect	Effect of treatment on the tumor
CR (complete response)	100% tumor-necrotizing effect or 100% tumor size reduction rate
PR (partial response)	The tumor-necrotizing effect or tumor size reduction rate is between 50% and <100%
SD (stable disease)	Effects other than PR and PD
PD (progressive disease)	The tumor growth >25% regardless of the necrotizing effect, or emergence of a new lesion*

*With regard to the emergence of new lesions, the lesion should be classified as either: (i) intrahepatic solitary lesion (within or outside the treatment area); (ii) intrahepatic multiple lesions (within or outside the treatment area); or (iii) vascular invasion (the portal vein, hepatic vein, bile duct)/extrahepatic spread.

OVERALL EVALUATION OF THE TREATMENT RESPONSE

1 The overall evaluation is determined, based on the effect in the entire liver and its persistence, and categorized as CR, partial response (PR), stable disease (SD) and progressive disease (PD), as defined in Table 2.
2 To use this method to predict the prognosis, TE is determined and recorded at 3 months when retreatment is not performed after the initiation of treatment, as an overall response evaluation, except for radiotherapy, in which the overall evaluation is performed at 6 months.
3 When multiple lesions are present, but the assessment of all of the lesions is difficult, evaluation of the five largest lesions may be considered to represent the overall evaluation of the entire liver, but it is not regarded as CR. In addition, CR should not be given when the findings of the maximum cross-section is regarded to represent the entire tumor. Tumors may only be described as CR when all of the intrahepatic lesions are assessable as well as the effect shown in Table 2 (100% tumor-necrotizing effect or 100% tumor size reduction rate) is obtained.

DETAILED REGULATIONS

THE NECROTIZING EFFECT is assessed based on the response evaluation criteria of treatment on target nodules.

1 The presence, on dynamic CT with an i.v. bolus injection, of a non-stained low-density area after treatment is regarded as a necrotizing effect. A non-stained low-density area represents an apparently lower level than that in the surrounding liver parenchyma in the early and late phases* of dynamic CT with an i.v. bolus injection. Usually, the CT attenuation value of a non-stained low-density area does not increase on dynamic imaging. (*The early phase represents the arterial dominant phase of dynamic CT. The late phase represents the equilibrium phase of dynamic CT.)
2 When lipiodol is used, the presence of a region retaining lipiodol homogeneously and densely in the tumor shown on CT 1 month after therapy is regarded as a necrotizing effect. Dynamic MRI, Doppler ultrasonography and contrast-enhanced ultrasonography can be also used.
3 The effects of radiotherapy, systemic chemotherapy (including treatment with molecular targeted agents) and hepatic arterial chemotherapy should be described by both RECIST and present criteria, RECICL.
4 The lowest levels of three tumor markers (AFP, AFP-L3 fraction, PIVKA-II or DCP) should be recorded as reference values for the overall response evaluation.

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APPENDIX I

TOVERALL EVALUATION OF treatment effects on liver cancer: a comparison between the World Health Organization (WHO) criteria, Response Evaluation Criteria in Solid Tumors (RECIST) and Response Evaluation Criteria in Cancer of the Liver (RECICL)

	WHO criteria (after 4 weeks)	RECIST (after 4 weeks)	RECICL (after 3 months)
Lesion evaluated	All evaluable lesions	All measurable lesions, target lesions (five lesions, a maximum of 10 lesions when lesions are present over 2 or more organs)	Target lesions (a maximum of five lesions when more than 5 lesions are present)
Evaluation method	Bi-dimensional measurement (changes in the product of the major axis and the diameter crossing the major axis at a right angle). Sum of the all lesions.	Uni-dimensional measurement (changes in the sum of the major axis)	Bi-dimensional measurement (changes in the product of the major axis and the diameter crossing the major axis at a right angle, non-stained regions on dynamic CT and/or lipiodol-deposited regions are measured as necrosis). Sum of the all target lesions.
Overall evaluation			
CR (complete response)	Disappearance of all lesions	Disappearance of all target lesions	100% tumor-necrotizing effect or 100% tumor size reduction rate
PR (partial response)	50% or greater disappearance of all lesions	30% or greater reduction of target lesions	A tumor-necrotizing effect or tumor size reduction rate between 50% and <100%
SD (stable disease)	Effects other than PR and PD	Effects other than PR and PD	Effects other than PR and PD
PD (progressive disease)	≥25% enlargement of a lesion or appearance of a new lesion	≥20% increase or appearance of a new lesion	≥25% enlargement of the tumor regardless of the necrotizing effect or appearance of a new lesion (categorized into three groups: intrahepatic solitary lesion, intrahepatic multiple lesions, and vascular invasion/extrahepatic spread).

APPENDIX II

Example RECICL Evaluation Sheet

Patient Age Male/female ID

1. **Description of Liver Cancer**
   (1) Past medical history
      (i) Method and date of definite diagnosis of liver cancer
      (ii) Past treatment history (only patients treat for recurrence)
   (2) Condition of liver cancer
      Tumor location, number and size of lesions, vascular invasion, macroscopic classification, macroscopic staging, histological type or degree of differentiation

2. **Description of Treatment Method**
   (1) Initial treatment or treatment for recurrence
   (2) Name of treatment (describe all treatments when multiple treatments were performed)
   (3) Details of treatment, including the reason for the discontinuation and the presence or absence of an adverse event when treatment is discontinued
   (4) Dates of initiation and completion of treatment

3. **Treatment Effect on Target Nodule (TE1, 2, 3, 4)**[*1] _____

   (Describe TE4a or 4b for local ablation) Assessment results: Lesion 1 / Lesion 2 / Lesion 3 / Lesion 4 / Lesion 5

4. **Overall Evaluation (CR, PR, SD, PD)**[*2] _____

   Assessment results: _____

When a new lesion appears in PD (new lesion: a, b, c)

Additional notes: tumor markers

Name of tumor marker	Before treatment	Lowest level within 3 months Time point ( )	6 months (only for radiotherapy)
AFP			
AFP-L3 fraction			
PIVKA-II (DCP)			

*1: Refer to Table 1. *2: Refer to Table 2.

The Oncologist®

The Challenge of Prognosis and Staging for Hepatocellular Carcinoma

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ABSTRACT

Hepatocellular carcinoma (HCC) is a heterogeneous condition, with multiple confounding factors making patient assessment extremely complex. Tumor burden, the presence of symptoms, liver function, and comorbidities must all be considered to ensure accurate patient assessment, thereby providing physicians with a common language on which to base treatment decisions and guide research. Although many staging classifications have been developed, there is no consensus on the best classification to use. The Barcelona Clinic Liver Cancer system is a promising candidate for a standard western classification, because it has been externally validated and is endorsed by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. Similarly, the biomarker-combined Japanese Integrated Staging (JIS) score is the most promising candidate for a standard Asia-Pacific classification, because it has been externally validated and shown to be superior to conventional JIS. Because risk factors vary significantly by region, so too does the predictive power of current staging classifications; any standard global staging classification would need to be validated in both western and Asia-Pacific patients. To date, no such globally validated classification exists. Findings from scientific research have improved our understanding of HCC and enabled us to refine current classifications. The role of tumor markers to predict survival was recently reported, and α-fetoprotein, *lens culinaris* agglutinin-reactive α-fetoprotein, and des-γ-carboxyprothrombin have now been incorporated into some classifications. Molecular markers have also been linked with poor outcomes and will likely play a role in future classifications. Although more work is required, it is hoped that these and other ongoing research efforts will eventually enable the development of a global staging classification. *The Oncologist* 2010;15(suppl 4):23–33

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Introduction

Hepatocellular carcinoma (HCC) is a heterogeneous condition with multiple variables that vary from region to region, complicating diagnosis, prognosis, and treatment recommendations. The presence of comorbidities is a common confounding factor that can compromise liver function and affect outcomes. For example, 80% of patients present with liver cirrhosis [1] and 85.5% of patients are carriers of either hepatitis B virus (HBV), which is particularly prevalent in Africa and Asia, or hepatitis C virus (HCV), prevalent in western countries and Japan [2, 3]. The characteristics of HCC also vary with geographic location. In rural South Africa, HCC is commonly diagnosed at a more advanced stage than in North America [4]. Because HBV is often acquired at an early age in Africa and Asia, HCC may also develop in younger patients and in the absence of liver cirrhosis [5]. Conversely, in North America, many patients have long-term liver cirrhosis and subsequently develop HCC. Clinical presentation in these patients is therefore dominated by complications of cirrhosis. These confounding factors mean that multiple variables must be considered when assessing patients with HCC.

The aims of HCC staging classifications are to: stratify patients to determine their overall survival (OS) probability prior to treatment, facilitate treatment, and enable objective comparison among the outcomes of research studies. What separates HCC from other solid tumors is that the presence of chronic liver disease and cirrhosis affects OS and the ability to treat this tumor. Therefore, liver disease is a very important variable, together with the overall health of the patient [6, 7]. In considering all these variables, it is hoped that accurate and consistent assessment of all patients can be achieved, thereby providing a common language for physicians as well as the broader multidisciplinary team. This, in turn, should facilitate appropriate treatment selection and ensure optimum patient management. However, with >15 HCC staging classifications available, each measuring a range of different factors and developed in different patient populations, physicians are faced with the complicated task of choosing which classification to use.

In this article, we review the major HCC staging classifications used globally and examine the factors assessed, as well as how each of the staging classifications was developed and validated. We also provide an overview of comparisons among various staging classifications reported in the literature. The paper does not aim to assess the relative values of individual classifications, nor to provide any endorsement of one system over another. However, we suggest possible areas for improvements that are necessary if we are to achieve a globally applicable HCC staging classification.

Staging Classifications in HCC

The factors influencing the development of HCC and its disease course vary considerably from region to region. As a result, various staging classifications have been developed that take into account a range of factors (Table 1), and although some classifications appear to be effective across broad regions, such as western or Asia-Pacific patient populations, others have been evaluated only in a single country. However, there is no globally applicable staging classification, and thus no common language on which to base treatment decisions and guide research.

Tumor–Node–Metastasis Staging System

The first staging classification for solid tumors was developed >50 years ago by the French surgeon Pierre Denoix [8]. In 1968, his recommendations for various tumors were compiled and published by the International Union Against Cancer and the American Joint Committee on Cancer in the first edition of the tumor–node–metastasis (TNM) staging system. Since then, this staging classification has undergone several amendments, and the most recent, sixth edition, was published in 2003 [9, 10].

The TNM staging classification provides an assessment of solid tumors based only on size and extent of invasion. This is measured according to the size of the primary tumor (T), presence of tumor in the regional lymph nodes (N), and presence of metastatic spread beyond the lymph nodes (M). Assessment of TNM staging can be prior to treatment (clinical staging) or after surgery (pathologic staging) [8]. Clinical staging is performed using imaging procedures, but in patients with HCC, the presence of cirrhosis and/or swelling of the lymph nodes as a result of chronic liver disease may prevent accurate assessment. Pathologic staging is therefore needed, but this may not be possible in the majority of patients because very few undergo surgical therapies that allow appropriate sampling.

The prognostic value of the sixth edition of the TNM staging system was compared with three other staging classifications (the Okuda, Cancer of the Liver Italian Program [CLIP], and Chinese University Prognostic Index [CUPI] classifications) in 234 patients with HCC who underwent curative resection at the Southwestern Hospital in China. Both the Okuda and the TNM systems were better at stratifying patients according to survival than the CLIP or CUPI system. However, the TNM classification was also better for predicting prognosis than the three other classifications, and was significantly better than the CLIP score ($p < .05$) [11]. The sixth edition of the TNM staging system also proved to be more effective than six other classifications (the Okuda, Barcelona Clinic Liver Cancer [BCLC], Japanese Integrated Staging [JIS], CLIP, and Groupe d'Etude et

Table 1. Key characteristics of various staging classifications available to assess the prognosis of patients with hepatocellular carcinoma

	Variables measured					
Staging classification	**Tumor staging**	**Liver function**	**Performance status**	**Serum tumor markers**	**Year published**	**Study**
CLIP	Tumor morphology (uninodular and extension ≤50%, multinodular and extension ≤50%, massive or extension >50%), portal vein thrombosis	Child-Pugh	No	AFP	1998	CLIP Investigators [16]
BCLC	Tumor size, number of nodules, portal vein thrombosis	Child-Pugh, bilirubin, portal hypertension	PST	No	1999	Llovet et al. [24]
GRETCH	Portal vein thrombosis	Bilirubin, alkaline phosphatase	Karnofsky	AFP	1999	Chevret et al. [34]
U.S. nomogram	Resection margin status, tumor size >5 cm, satellite lesions, vascular invasion	No	Age, operative blood loss	AFP	2008	Cho et al. [45]
Okuda	Tumor size (</>50% of liver)	Ascites, albumin, bilirubin	No	No	1985	Okuda et al. [13]
CUPI	TNM fifth edition	Ascites, bilirubin, alkaline phosphatase	Presence of symptoms	AFP	2002	Leung et al. [37]
JIS	Japanese TNM fourth edition	Child-Pugh	No	No	2003	Kudo et al. [23]
bm-JIS	Japanese TNM fourth edition	Child-Pugh	No	AFP, AFP-L3, DCP	2008	Kitai et al. [39]
SLiDe	Stage and liver damage categories from the Japanese TNM fourth edition	No	No	DCP	2004	Omagari et al. [41]
Tokyo	Size and number of tumors	Albumin, bilirubin	No	No	2005	Tateishi et al. [42]
BALAD	No	Albumin, bilirubin	No	AFP, AFP-L3, DCP	2006	Toyoda et al. [44]
ALCPS	Tumor size, portal vein thrombosis, lung metastases	Ascites, Child-Pugh, alkaline phosphatase, bilirubin, urea	Abdominal pain, weight loss	AFP	2008	Yau et al. [46]

Abbreviations: AFP, α-fetoprotein; AFP-L3, *lens culinaris* agglutinin-reactive AFP; ALCPS, Advanced Liver Cancer Prognostic System; BALAD, bilirubin, albumin, AFP-L3, AFP, DCP; BCLC, Barcelona Clinic Liver Cancer; bm-JIS, biomarker-combined JIS; CLIP, Cancer of the Liver Italian Program; CUPI, Chinese University Prognostic Index; DCP, des-γ-carboxyprothrombin; GRETCH, Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire; JIS, Japanese Integrated Staging; PST, performance status test; SLiDe, Stage, Liver damage, DCP; TNM, tumor–node–metastasis.
From Meier V, Ramadori G. Clinical staging of hepatocellular carcinoma. Dig Dis 2009;27:131–141. Reproduced with permission from S. Karger AG, Basel, Switzerland.

de Traitement du Carcinome Hépatocellulaire [GRETCH] classifications) at assessing prognosis in 163 patients with HCC following resection in a retrospective study at a single institution in Korea [12]. Those studies were limited to the postsurgery setting, and evaluation in a larger sample size and broader patient population is still required.

Okuda Classification

The Okuda classification was published in 1985 and was the first staging system to include parameters related to tumor size (>50% versus <50% of the liver involved) and liver function (albumin, ascites, bilirubin) [13]. Its ability to predict prognosis according to treatment was evaluated as part of a retrospective analysis among 850 patients treated in three different institutes in Japan, with patients stratified into three stages (I, not advanced; II, moderately advanced; III, very advanced). These findings showed that surgically treated patients had a longer survival time than medically treated patients, and that medical treatment prolonged survival in stage II and stage III patients but not in stage I patients. However, because stage at diagnosis as well as the available medical interventions have moved on since the time this staging classification was developed, stratifying patients to receive radical or palliative therapies using this system alone would not be appropriate. Moreover, although its simplicity makes it clinically attractive, its ability to predict prognosis is relatively modest [5]. Indeed, in a retrospective study in Canada, the Okuda classification failed to identify two thirds of the 37 patients with a poor prognosis who were identified by the CLIP criteria [14]. Furthermore, in an evaluation of staging systems for HCC patients undergoing surgery, the Okuda system was not superior to TNM staging [15].

CLIP Scoring

The CLIP scoring system was derived from a retrospective analysis of 435 patients with HCC from 16 Italian institutions and was published in 1998 [16]. Here, four independent predictive factors of survival were identified (Child-Pugh score, tumor morphology, α-fetoprotein [AFP], and

portal vein thrombosis), and a simple linear scoring system (0, 1, or 2) was assigned to the covariates in order to give patients a total score of 0–6. This scoring system was subsequently validated by the same group in a prospective trial of 196 patients with HCC and cirrhosis [17] and was also shown to be effective in predicting survival among a group of 145 patients in the Middle East [18] and in 662 Japanese patients [19]. However, whereas the median survival time associated with each CLIP score (0–6) appears to be similar between patients included in the prospective validation conducted by the founding group and those included in the study conducted in the Middle East [18, 20], the median survival times reported for Japanese patients were higher for all CLIP scores [19], and it has been suggested that these findings could compromise the external validation of the CLIP scoring system [21].

In a comparison of the CLIP, BCLC, and Okuda staging systems using a pooled database from two randomized trials of French patients with mainly alcoholic HCC, the performances of all three systems were disappointing; different systems performed differently according to patient populations and for individual prognostic factors. None clearly emerged as an unquestionable reference [22]. However, for all statistics, the CLIP system had better prognostic ability. The authors concluded that the CLIP staging seems to be most adapted to the palliative setting and that it could be improved by associating World Health Organization performance status.

A number of limitations of the CLIP scoring system have been reported [23]. First, the tumor morphology categories used may be too general to be globally applicable, particularly in countries such as Japan, where more patients are diagnosed with very small solitary tumors, largely because of the established screening programs in place. Secondly, although patient populations with different CLIP scores appear to be well discriminated from each other, there is no clear difference among patient populations with CLIP scores of 4–6 [17]. Indeed, in the prospective validation of this scoring system performed by the founding group [20], they grouped patients with a CLIP score of 4–6 into one group. Finally, all studies evaluating the CLIP score reported to date show that a high proportion of patients are categorized as CLIP score 0–2, suggesting poor stratification ability with this system.

Taken together, these findings suggest that, although the CLIP scoring system is associated with a good prognostic ability, this staging system may not be sensitive enough to be applicable to all patient populations and cannot easily be applied to a patient's management.

BCLC Staging

The BCLC staging classification was proposed by Llovet and colleagues in 1999 [24]. One of the most important observations for the development of the BCLC staging system came from the follow-up of patients with nonresectable and nontransplantable HCC who were randomized to placebo in two different clinical trials [25]. In that study, the multivariate analysis identified performance status, constitutional syndrome, vascular invasion, and extrahepatic spread as independent predictors for mortality. The authors showed that the 1-, 2-, and 3-year survival rates for the 48 patients without predictors of mortality (i.e., intermediate stage) were 80%, 65%, and 50%, respectively, and these were 29%, 16%, and 8% in the 54 patients with at least one adverse factor (i.e., advanced stage). This has been externally validated [26]. This allowed patients to be divided into different categories based on tumor stage (tumor size, number of nodules, and presence of portal vein thrombosis), liver function (Child-Pugh score, portal hypertension, bilirubin level), physical status (performance status test), and cancer-related symptoms. Furthermore, four categories were created (A, early; B, intermediate; C, advanced; D, end-stage disease). It is also unique in that it is the only system that provides treatment recommendations for each of the assigned stages based on the best treatment options currently available. The BCLC staging classification has been externally validated in the U.S. [6], Europe [27, 28], and Taiwan [29] and has demonstrated superior survival stratification and prognosis prediction over a range of other classifications, including the Okuda, TNM, CLIP, GRETCH, CUPI, and JIS classifications [28, 30]. Moreover, BCLC staging is endorsed by both the European Association for the Study of the Liver (EASL) [5] and the American Association for the Study of Liver Diseases (AASLD) [31], and it is emerging as a standard staging classification in western populations [32]. The most important aspect of this staging classification is that it is linked to an evidence-based treatment algorithm and can easily be used in a clinical setting. However, it should be noted that, in a study investigating which of the available staging systems was the most informative for the medical oncologist [33], the BCLC system was found to be less informative than the GRETCH and CLIP classifications when ranked using a concordance index, a likelihood ratio, and the Akaike information criterion. However, that study mostly evaluated patients with advanced tumors and may not be generally applicable.

GRETCH Scoring

The GRETCH scoring system was based on findings from a prospective study among 761 patients from 24 western medical centers and was published in 1999 [34]. The aim of

the study was to compile a classification system for predicting survival among these patients using a multivariate Cox model. Five prognostic factors were selected (Karnofsky index <80%, bilirubin >50 μmol/l, alkaline phosphatase ≥2× the upper limit of normal, AFP >25 μg/l, and ultrasonographic portal vein obstruction) in order to divide patients in the study training sample (n = 506) into three prognostic classification groups (A, B, C). The 1-year survival rates associated with these three groups were derived (72%, 34%, and 7% for groups A, B, and C, respectively) and independently validated in the study test sample (79%, 31%, and 4% for groups A, B, and C, respectively; n = 255). This system has not been validated in nonwestern patient populations. Furthermore, because this system originated from a multivariate analysis, it may not be reproducible or easily used in clinical practice.

Liver Cancer Study Group of Japan TNM Staging

In 1965, the Liver Cancer Study Group of Japan (LCSGJ) started a nationwide registration of clinicopathologic and prognostic data from patients with primary liver cancer, and using data collected in this database they introduced the Japanese version of the TNM staging system in 1983. This has subsequently undergone a number of revisions, and in 2007 the LCSGJ evaluated data from their database of 63,736 patients with primary liver cancer, 13,772 of whom underwent curative resection, in order to present evidence to develop and validate this staging classification [35]. Based on univariate and multivariate survival analyses, they selected three factors (vascular or bile duct invasion, tumor diameter ≤2 cm versus >2 cm, and number of tumors—single versus multiple), and classified patients as T1–T4 based on the number of adverse factors present (patients with none were considered T1, those with one were T2, those with two were T3, and those with three were T4). Significant survival differences were demonstrated among patients in each of the four assigned stages, with 5-year survival rates of 70% (T1), 58% (T2), 41% (T3), and 24% (T4) (p < .0001). A potential weakness of the LCSGJ staging system is that it assumes equal weight for growth pattern, size, and vascular or bile duct invasion. No external validation has been reported to date.

The Vauthey Simplified Staging System

In 2002, Vauthey and colleagues evaluated the efficacy of using the TNM's T categories to stratify patients according to survival and assessed a range of independent prognostic factors among 557 patients undergoing resection [36]. Independent predictors of death in that study were major vascular invasion, microvascular invasion, severe fibrosis/cirrhosis of the liver, multiple tumors, and tumors >5 cm. Based on these findings, Vauthey and colleagues proposed a simplified model of patient stratification using vascular invasion, tumor number and size, and the effect of fibrosis on survival. Patients were divided into three stages (I, II, III) and these were associated with a significant survival difference, with 5-year survival rates of 55% (I), 37% (II), and 16% (III) (p < .001) [36]. This is limited to postsurgery patients and has not been externally validated.

CUPI Score

The CUPI score was developed at the Chinese University in Hong Kong and was published in 2002 [37]. In that study, 19 potential prognostic factors were evaluated in a multivariate analysis using a Cox regression model among 926 Chinese patients, mostly with HBV-associated HCC. From this, five additional prognostic factors (asymptomatic disease at presentation, AFP, total bilirubin, alkaline phosphatase, and ascites) were added to the fifth edition of the TNM staging classification. Patients were divided into three risk groups (high, medium, and low risk for dying within 3 months), and highly significant differences in survival were observed among these groups (p < .00001). Findings from that study also showed that the CUPI system was better at classifying patients into different risk groups than the TNM staging system alone, or the Okuda or CLIP scoring systems, although the authors advise that validation across broader patient populations is needed. In a more recent study, the CUPI staging system was compared with the Okuda, CLIP, and sixth edition of the TNM staging systems among 234 Chinese patients who underwent resection [11]. The authors concluded that the TNM sixth edition was superior in discriminating survival among patients stratified into different stages, and suggested that a possible limitation of the CUPI score is that it is based on the fifth edition of the TNM. The CUPI system has not been externally validated.

JIS Score

In 2003, an integrated prognostic classification system was published by Kudo and colleagues [23]. This scoring system combines the Japanese TNM staging (stages I, II, III, and IV are converted to scores 0, 1, 2, and 3, respectively) and the conventional Child-Pugh (stages A, B, and C are converted to scores 0, 1, and 2, respectively) to produce a JIS score of 0–5. This scoring system was evaluated in 722 Japanese patients with HCC, and statistically significant differences were observed in the survival curves among JIS scores of 0–3, but not among scores of 4–6 [23]. It has been noted that the JIS system may be limited in its ability to stratify patients with advanced scores because it uniformly

assigns tumor stage and liver function [35]. However, this system has been externally validated [38] and it appears to be one of the most promising candidates for a standard classification system across the Asia-Pacific region. However, it has not been validated in a western patient population.

The JIS staging classification was further modified by Kitai and colleagues to include evaluation of three tumor markers for HCC, namely AFP, *lens culinaris* agglutinin-reactive AFP (AFP-L3), and des-γ-carboxyprothrombin (DCP). This biomarker-combined JIS (bm-JIS) scoring system was evaluated in 1,924 patients with HCC, and findings published in 2008 showed that the bm-JIS scoring system had superior stratification ability and was a better predictor of prognosis than the conventional JIS scoring system [39]. This system has now been externally validated but still requires validation in a western patient population [40].

Stage, Liver Damage, DCP Staging System

The stage, liver damage, DCP (SLiDe) staging system was established in 2004 when Omagari and colleagues evaluated a range of prognostic markers in univariate and multivariate analyses using the medical records of 177 patients with HCC from the Nagasaki University School of Medicine in Japan [41]. In that analysis, only the "stage" and "liver damage" categories from the fourth edition of the Japanese TNM staging classification, as well as serum DCP, remained significant prognostic factors of survival. Thus, in the SLiDe staging system, patients were assigned a score based on these covariates (0, 1, 2, or 3), and findings from this retrospective analysis showed that there was clear discrimination among the survival curves plotted for patients with different SLiDe scores [41]. Although the authors concluded that this is a useful system to assess the prognosis of patients, they also advised that, because the Japanese TNM staging classification must be used, which includes some parameters that are not routinely assessed in other parts of the world, external validation in a large patient population would be needed before this system could be adopted.

Tokyo Classification

In a study published in 2005, 403 patients with HCC treated with percutaneous ablation at the University of Tokyo were used as a training sample to identify prognostic factors and to develop the Tokyo score based on four factors (albumin, bilirubin, and size and number of tumors) [42]. Prognostic factors were then analyzed in a testing sample of 203 patients with HCC who had undergone resection. Clear survival differences were demonstrated among Tokyo scores, with 5-year survival rates of 78.7% (0), 62.1% (1), 40.0% (2), 27.7% (3), and 14.3% (4–6). This system was validated by the same group, whereby it showed similar predictive ability to the CLIP scoring system and superior predictive ability to the BCLC staging classification. However, in a comparison of the JIS, BCLC, and Tokyo classifications in a Japanese cohort of HCC patients mainly with early-stage disease treated with radical therapy, the JIS score provided the best prognostic stratification [43]. Further external validation of the Tokyo classification in different patient populations is needed.

Bilirubin, Albumin, AFP-L3, AFP, DCP Score

The bilirubin, albumin, AFP-L3, AFP, DCP (BALAD) score, published by Toyoda and colleagues in 2006 [44], is a staging classification devised using only serum markers (bilirubin, albumin, AFP-L3, AFP, DCP). This scoring system, calculated as the sum of the remnant liver function score (i.e., albumin and bilirubin scoring, as devised by Tateishi and colleagues [42]) plus the tumor progression score (measured as the number of elevated tumor markers), was evaluated among 2,600 patients with HCC from five institutions. Patients were divided into six groups on the basis of the five laboratory values, with clear survival differences observed among the groups. Toyoda and colleagues also compared the BALAD scoring system with two staging classifications that consider both tumor progression and liver function factors (the JIS and CLIP classifications). They demonstrated that all three systems showed comparable prediction and discrimination of patient survival [44]. However, in a study comparing the BALAD scoring system with the JIS and bm-JIS systems conducted by Kitai and colleagues [40], there were significant differences between the BALAD and bm-JIS scores and the BALAD and JIS scores, even though all three systems effectively predicted patient survival. The authors concluded that the bm-JIS classification was superior to both the JIS and BALAD scoring systems, especially among patients with a good prognosis [40].

A U.S.-Based Prognostic Nomogram

In a recent study published in 2008, 184 patients with HCC undergoing resection at a single institution in the U.S. were classified according to eight staging classifications [45]. The ability of these classifications to predict postoperative survival was evaluated in randomly selected pairs using Harrell's concordance index. A novel nomogram was then developed using age, AFP level, operative blood loss, surgical resection margin status, tumor size, satellite lesions, and vascular invasion. Using this nomogram, survival could be predicted with a higher concordance level between randomly tested pairs than with any of the eight conven-

tional classification systems tested (concordance index of 0.74 for the nomogram versus 0.54–0.59 for the eight staging classifications tested) [45]. That analysis relied on a single institutional data set of HCC patients, which may introduce selection bias. These findings have not yet been externally validated and this nomogram is not currently used clinically.

Advanced Liver Cancer Prognostic System Score

Because patients with advanced HCC who are not amenable to locoregional therapy are candidates for inclusion in clinical trials providing they have a good 3-month survival probability, the advanced liver cancer prognostic system (ALCPS) scoring system was devised to objectively predict the 3-month survival probability among these patients [46]. In a study by Yau and colleagues published in 2008, the prognostic significance of a range of factors was evaluated by univariate and multivariate Cox regression analyses in a training set of 1,109 patients. From this, 11 significant prognostic factors were identified (ascites, abdominal pain, weight loss, Child-Pugh score, alkaline phosphatase, total bilirubin, AFP, urea level, tumor size, portal thrombosis, and lung metastases) and assessed to provide patients with a score of 0–39 (with a higher score being associated with a lower survival probability). These scores were then divided into three groups in order to categorize patients as having a good (ALCPS score, 0–8), intermediate (ALCPS score, 9–15), or poor (ALCPS score, 16–39) probability of surviving at least 3 months. Patients assessed in the training set were stratified according to their ALCPS score, and Kaplan–Meier estimates for each group showed clear survival differences, with median OS times of 7.9 months, 3.2 months, and 1.4 months for the good, intermediate, and poor groups, respectively. In the same study, ALCPS scores were subsequently assessed in a validation sample of 320 patients, and outcomes very similar to the testing sample were reported (median OS time, 7.5 months, 3.2 months, and 1.2 months for the good, intermediate, and poor groups, respectively) [46]. Moreover, patients in the validation set were also assessed by the Okuda and CLIP scoring systems, and the discriminatory ability of each prognostic scoring system, assessed by constructing receiver-operating characteristic curves, showed that the ALCPS scoring system had significantly better predictive power than either the Okuda (area under the curve [AUC], 0.77 versus 0.66 for the ALCPS and Okuda classifications, respectively; $p < .001$) or CLIP (AUC, 0.77 versus 0.71 for ALCPS and CLIP classifications, respectively; $p = .002$) scoring systems. It must be noted that the data set used to construct ALCPS system was from a single institute, consisting predominantly of an HBV-prevalent Chinese population. It is not known whether ALCPS system can be applied to other populations.

Summary of Staging Classifications: What Is the Best System Available?

The number of staging classifications for HCC has increased in recent years, and more recent classifications have demonstrated better prognostic ability than earlier systems (Table 2). However, improvements are still ongoing and there is no agreement on a standard classification that could be used globally.

Earlier classifications, such as the TNM staging system, only considered tumor staging factors, and as such their prognostic ability was regarded as limited. Given the impact that HCC and common comorbidities such as cirrhosis, HBV, and HCV have on liver function, most classifications now consider both tumor staging factors and liver function to predict patient outcomes. In recent years, there has been increasing interest in the role of biomarkers to predict survival. However, although adding further parameters to staging classifications may help improve the accuracy of these systems, it is important to ensure we do not create systems that are overly complex, because this may limit their clinical utility.

One of the goals of staging systems today is to provide an evidence-based treatment guide [6, 7, 21]. Although all staging classifications have been designed to predict prognosis, the BCLC staging classification is currently the only system that also provides a recommended treatment algorithm linked to each stage of disease [24]. However, the main strength of the BCLC staging system is that the four categories of patients have distinct natural histories and it is easy to apply clinically. Whether the treatment that is linked to each BCLC stage is used will depend on factors such as institutional strength and patient selection.

Because most patients with HCC present with advanced disease, many of the staging classifications, including the CUPI, CLIP, GRETCH, and ALCPS classifications, were constructed among this patient group [16, 34, 37, 46]. This could represent a limitation of these systems in terms of the accuracy of predicting prognosis in patients with earlier-stage HCC. Thus, systems such as the Japanese TNM staging system, which was constructed based on a large database of clinicopathologic data from patients at all stages of disease, including 13,772 who were eligible for curative resection, may be more appropriate for assessing patients with earlier-stage disease [35].

Because there are significant regional differences in HCC in terms of tumor morphology and the presence of comorbidities, which affect the disease course and ultimately patient prognosis, a staging classification needs to be validated in both western and Asia-Pacific patient populations

Table 2. Comparison of externally validated staging classifications available for hepatocellular carcinoma

Staging classification	Region developed	*n* of patients	Validation studies	Comparator staging classifications used	*n* of patients	Main outcomes
CLIP [16]	Italy	435	Italy [17, 20]	CLIP, Okuda	196	CLIP demonstrated greater survival predictive power than Okuda
			Middle East [18]	CLIP, Okuda	145	CLIP was more reliable than Okuda in predicting survival
			Japan [19]	CLIP, TNM, Okuda	662	CLIP had the highest stratification ability. Median survival times greater in this study than two previous studies
BCLC [24]	Spain	239	USA [6]	Okuda, TNM, BCLC, CLIP, GRETCH, CUPI, JIS	239	BCLC demonstrated the best independent predictive power for survival
			Italy [28]	Okuda, CLIP, Child-Pugh, BCLC, CUPI	187	BCLC was the best prognostic system among patients suitable for resection or ablation
			Italy [30]	Okuda, TNM, BCLC, CLIP, GRETCH, CUPI, JIS	112	BCLC showed superior discriminatory power among a group of patients who underwent radiofrequency ablation therapy
JIS [23]	Japan	722	Japan [38]	JIS, CLIP	4,525	The prognostic predictive power of JIS was superior to that of CLIP JIS score was simple to obtain and remember
bm-JIS [39]	Japan	1,924	Japan [40]	JIS, bm-JIS, BALAD	1,173	bm-JIS score showed good stratification ability and was superior in predicting prognosis, especially among patients with a good prognosis

Abbreviations: BALAD, bilirubin, albumin, *lens culinaris* agglutinin-reactive α-fetoprotein, α-fetoprotein, des-γ-carboxyprothrombin; BCLC, Barcelona Clinic Liver Cancer; bm-JIS, biomarker-combined JIS; CLIP, Cancer of the Liver Italian Program; CUPI, Chinese University Prognostic Index; GRETCH, Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire; JIS, Japanese Integrated Staging; TNM, tumor–node–metastasis.

before it can be considered globally applicable. Unfortunately, none of the staging classifications currently available has been validated in all these patient populations, and as such none can be recommended for worldwide use. However, the BCLC system has been validated in the U.S., Europe, and Taiwan, and it is the only system that has so far been validated in three continents.

A number of studies have been conducted to compare various staging classifications in the same patient population (Table 3), and findings suggest that the staging classification to show superior predictive power depends on the region. In western patient populations, the BCLC staging system appears to be superior based on findings in separate studies (two conducted in Italy, one in Taiwan, and one in North America) [6, 28, 29, 30]. In Japan, Kudo and colleagues demonstrated that the JIS scoring system was superior to the CLIP classification among 4,525 patients with HCC [38]. However, it has not been validated outside Japan.

Taken together, these findings show that, as our knowledge of this complex disease improves, staging classifications continue to be refined. As more is known about the pathogenesis of HCC and molecular markers, better staging systems will be developed.

Conclusions

HCC is a heterogeneous condition, with multiple confounding factors making assessment of these patients extremely complex. Many elements, including tumor burden, the presence of symptoms, liver function, comorbidities, and the likely effect of treatment, need to be considered in order to ensure accurate and consistent assessment of all patients, thereby providing physicians with a common language on which to base treatment decisions and guide research. This review examines each classification but does not assess their relative value. Although many different staging classifications have been developed and there is currently no consensus on the best classification to use, the BCLC staging classification is emerging as a promising candidate for a standard classification in western regions, because it has been externally validated [6, 28, 30] and it is also endorsed

Table 3. Comparison of studies evaluating different staging classifications in the same hepatocellular carcinoma patient population

Study	*n* of patients	Region	Staging classifications compared	Superior classification identified
Choi et al. [12]	163	Korea	TNM (fifth and sixth editions), Okuda, BCLC, CLIP, GRETCH, JIS	TNM sixth edition
Lu et al. [11]	234	China	Okuda, CLIP, TNM, CUPI	TNM sixth edition
Cillo et al. [28]	187	Italy	Okuda, BCLC, CLIP, GRETCH, CUPI	BCLC
Guglielmi et al. [30]	112	Italy	Okuda, TNM, BCLC, CLIP, GRETCH, CUPI, JIS	BCLC
Marrero et al. [6]	239	USA	Okuda, TNM, BCLC, CLIP, GRETCH, CUPI, JIS	BCLC
Kitai et al. [40]	1,173	Japan	JIS, bm-JIS, BALAD	bm-JIS
Kudo et al. [38]	4,525	Japan	CLIP, JIS	JIS

Abbreviations: BALAD, bilirubin, albumin, *lens culinaris* agglutinin-reactive α-fetoprotein, α-fetoprotein, des-γ-carboxyprothrombin; BCLC, Barcelona Clinic Liver Cancer; bm-JIS, biomarker-combined JIS; CLIP, Cancer of the Liver Italian Program; CUPI, Chinese University Prognostic Index; GRETCH, Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire; JIS, Japanese Integrated Staging; TNM, tumor–node–metastasis.

by both the EASL [5] and the AASLD [31]. However, because risk factors vary significantly from region to region, any standard global staging classification needs to be validated in both western and Asia-Pacific patient populations; to date, no such staging classification exists.

Continued research efforts have improved our understanding of this complex disease, which has allowed us to refine staging classifications and improve our therapeutic approach. In recent years, a significant amount of research has reported on the role of tumor markers to predict survival in HCC, and the markers AFP, AFP-L3, and DCP have now been incorporated into some staging classifications. In addition, molecular markers such as hepatocyte growth factor, vascular endothelial growth factor, and transforming growth factor β 1 have been linked with poor outcomes in HCC patients [47], and so may play a role in helping us to further improve staging classifications. In addition to the added information that tumor and molecular markers bring, data from ongoing studies may contribute. The Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib (GIDEON) study is a large global, noninterventional study of patients with unresectable HCC receiving sorafenib (Nexavar®; Onyx Pharmaceuticals, Inc., Emeryville, CA; Bayer HealthCare Pharmaceuticals, Inc., Wayne, NJ; Bayer Schering Pharma AG, Berlin, Germany) therapy. That study will collect details of local, regional, and global methods of patient evaluation, diagnosis, and follow-up, and assess comorbidities and their influence on treatment and outcome. Information collected in this database may be of value in further refining current staging classifications. However, further research efforts are needed for us to gain a full understanding of the factors that affect the prognosis of patients with HCC.

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