Classification of HCC: Looking beyond the TNM staging

Dr. Pooja Nandwani Patel
Sr. Consultant & Head
Dept. of Radiation Oncology
Sterling Cancer Hospital, Ahmedabad
HCC Staging Background

• Accurately staging patients is essential to oncology practice. Cancer staging contributes to prognostication, guides management decisions, and informs clinical, epidemiologic, and health services research.

• In hepatocellular carcinoma (HCC), staging poses unique challenges due to the geographic and biological heterogeneity of the disease and lack of consensus on how to best classify patients.

• The challenge of measuring the contributions of the cancer and hepatic dysfunction to the overall prognosis was recognized with the first modern era liver cancer staging system, which was proposed at the Hepatocellular Carcinoma International Symposium in Kampala, Uganda in 1971.
HCC Staging Evolving...

- The features included in various HCC classifications systems have evolved over the last 50 years, but in general, need to account for both tumor characteristics as well as the burden of underlying liver disease - 15+ staging systems - **there is still no single system that could be called the “standard” for classifying HCC**

- Subsequent attempts at HCC staging have continued to employ both tumor and liver specific variables in the setting where there is often very limited diagnostic tissue, which means that there may be no information from a pathological examination

- This reflects the fact that biopsy may not be a pre-requisite to diagnosis of HCC. Serum alpha-fetoprotein (AFP) is a commonly used screening biomarker in patients at risk for HCC but is not sufficient for surveillance or diagnosis due to lack of sensitivity and specificity. Although retrospective data have established high AFP at presentation as a negative prognostic factor, serum AFP level is included in only a subset of HCC staging systems
TNM CLASSIFICATION

Primary Tumor (T)
TX Tumor is present but cannot be assessed.
T0 No evidence of tumor
T1 Small solitary tumor (<3.0 cm) confined to one lobe
T2 Large tumor (>3.0 cm) confined to one lobe
T2a Single tumor nodule
T2b Multiple tumor nodules (any size)
T3 Tumor involving both major lobes
T3a Single tumor nodule (with direct extension)
T4b Multiple tumor nodules
T4 Tumor invading adjacent organs

Nodal Involvement (N)
NX Nodes cannot be assessed.
N0 No histological evidence of metastasis to regional or distant lymph nodes
N1 Histologically confirmed spread to regional lymph nodes in porta hepatitis
N2 Histologically confirmed spread to lymph nodes beyond porta hepatitis

Distant Metastasis (M)
MX Not assessed
M0 No known metastasis
M1 Distant metastasis present
Specify site

Stage Grouping
Stage IIA T1, N0, M0, without cirrhosis
Stage IIB T1, N0, M0, with cirrhosis
Stage IIA T2, N0, M0, without cirrhosis
Stage IIIB T2, N0, M0, with cirrhosis
Stage IIA T3, N0, M0, without cirrhosis
Stage IIIB T3, N0, M0, with cirrhosis
Stage IVA T4, N0-N2, M1; without cirrhosis
Stage IVB T4, N0-N2, M1, with cirrhosis

Postsurgical Resection Residual Tumor (R)
R0 No residual tumor
R1 Microscopic residual tumor
R2 Macroscopic residual tumor

Other Site-Specific Information
Symptom [ ] Pain
[ ] Weight loss
Sign [ ] Jaundice
[ ] Ascites
Paraneoplastic syndrome: specify
Congenital or metabolic liver disease; specify

Laboratory Tests
Bilirubin ______ mg/dl
Alkaline phosphatase _____ U/ml (specify type of unit)
Albumin ______ mg/dl
ALT ______ U/ml
AFP ______ ng/ml
HBsAg Positive [ ] Negative [ ]
Other markers of HB infection; specify
Portal vein obstruction by angiography present [ ]

PERFORMANCE STATUS OF HOST (H)
Performance status of the host should be recorded because this information at times is pertinent to the treatment of the patient.

HISTOPATHOLOGY
A. Epithelial Tumors
A. Benign
1. Liver cell adenoma (hepatocellular adenoma)
2. Intrahepatic bile duct adenoma
3. Intrahepatic bile duct cystadenoma

B. Malignant
4. Hepatocellular carcinoma (liver cell carcinoma)
5. Hepatocellular carcinoma (fibrolamellar type)
6. Cholangiocarcinoma (intrahepatic bile duct carcinoma)
7. Mixed hepatocellular cholangiocarcinoma
8. Bile duct cystadenocarcinoma
9. Hepatoblastoma
a. Predominantly fetal type
b. Predominantly embryonal type
c. Small cell undifferentiated type
10. Undifferentiated carcinoma

B. Nonpithelial tumors
11. Hemangiomata
12. Infantile hemangioendothelioma
13. Embryonal sarcoma
14. Other
Specify

C. Miscellaneous tumors
15. Teratoma
16. Carcinosarcoma
17. Other
Specify

D. Unclassified tumors
E. Hemopoietic and lymphoid neoplasms

BIBLIOGRAPHY
AJCC TNM Staging

The American Joint Committee on Cancer (AJCC) TNM Staging for Hepatocellular Cancer (6th ed., 2017)

**Table 1. Definitions for T, N, M**

<table>
<thead>
<tr>
<th>T</th>
<th>Primary Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>T1</td>
<td>Solitary tumor ≤2 cm, or &gt;2 cm without vascular invasion</td>
</tr>
<tr>
<td>T1a</td>
<td>Solitary tumor ≤2 cm</td>
</tr>
<tr>
<td>T1b</td>
<td>Solitary tumor &gt;2 cm without vascular invasion</td>
</tr>
<tr>
<td>T2</td>
<td>Solitary tumor &gt;2 cm with vascular invasion, or multiple tumors, none &gt;5 cm</td>
</tr>
<tr>
<td>T3</td>
<td>Multiple tumors, at least one of which is &gt;5 cm</td>
</tr>
<tr>
<td>T4</td>
<td>Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein, or tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum</td>
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<table>
<thead>
<tr>
<th>N</th>
<th>Regional Lymph Nodes</th>
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<tbody>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis</td>
</tr>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
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<table>
<thead>
<tr>
<th>M</th>
<th>Distant Metastasis</th>
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<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
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**Table 2. AJCC Prognostic Groups**

<table>
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<th>Stage</th>
<th>T</th>
<th>N</th>
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<tr>
<td>IA</td>
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<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIB</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
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<tr>
<td>IVA</td>
<td>Any T</td>
<td>N1</td>
<td>M0</td>
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<tr>
<td>IVC</td>
<td>Any T</td>
<td>Any N</td>
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**Histologic Grade (G)**

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<th>Grade</th>
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<tr>
<td>G1</td>
<td>Well differentiated</td>
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<tr>
<td>G2</td>
<td>Moderately differentiated</td>
</tr>
<tr>
<td>G3</td>
<td>Poorly differentiated</td>
</tr>
<tr>
<td>G4</td>
<td>Undifferentiated</td>
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**Fibrosis Score (F)**

The fibrosis score as defined by Ishak is recommended because of its prognostic value in overall survival. This scoring system uses a 0-6 scale.

- F0: Fibrosis score 0-4 (none to moderate fibrosis)
- F1: Fibrosis score 5-6 (severe fibrosis or cirrhosis)

***AJCC staging provides information on resected specimen only***
The Okuda staging system - 1985

- was the first staging system developed three decades ago in Tokyo to analyze the relationship between survival and treatment in 850 patients with HCC

- The authors noted that irrespective of the geographic location and the time of diagnosis, the primary clinical features and the prognosis of patients affected with HCC were similar and reported that a staging system should be as simple and practical as possible based on their analysis

- They indirectly determined the functional hepatic reserve by taking into account the serum bilirubin and serum albumin levels (as 3 mg/dL and 3 g/dL, respectively) as well as the presence or absence of ascites apart from determining the tumor burden by measuring the tumor size (the separating level being 50%)
The Okuda staging system

Stage I - none (tumor involvement < 50% of the liver, without ascites, > 3 g/dL albumin, and < 3 mg/dL bilirubin)

Stage II - when one or two of the following features were positive: tumor size more than 50%, ascites, < 3 g/dL albumin, and > 3 mg/dL bilirubin

Stage III - three or four of these features
Limitations of Okuda Staging System

• The Okuda staging classified patients appropriately when the diagnosis of HCC happened in the advanced/symptomatic phase and was a useful tool to identify the end-stage patients (stage III), who should not be included in clinical trials as they had a poor prognosis.

• However, in the later decades, when a diagnosis of HCC happened early due to the improved diagnostics, the Okuda staging was insufficient to stratify patients before radical or palliative therapy.
CTP score

- The CTP score is the simplest and most widely used grading system for liver function
- Child-Turcotte Pugh publication in 1964, where patients being considered for surgery for portal venous shunting were risk-stratified into three categories
- However, the drawbacks are many, including interlaboratory variations, day-to-day fluctuations in the key parameters and the subjective nature of the clinical grading of encephalopathy and ascites
- Though the CTP score by itself does not include any HCC-specific parameters, it has been incorporated into multiple contemporary scoring systems including Cancer of the Liver Italian Program (CLIP) and Barcelona Clinic Liver Cancer (BCLC)
The CLIP scoring system - 1998

• The CLIP scoring system for prognosticating HCC patients was proposed by Italian investigators in the year 1998 to verify the value of the known prognostic factors in producing a prognostic index more sensitive than Okuda that accounts for both the liver function and tumor characteristics.

• The CLIP score incorporated variable factors (CTP score: A, B, or C; tumor morphology: uninodular or multinodular with extension ≤ 50% or > 50%; alpha fetoprotein [AFP]: levels < 400 or ≥ 400 ng/dL; and presence or absence of portal vein thrombosis [PVT]) into a Cox model and analyzed the overall survival in 435 patients treated with locoregional and systemic therapies.
maximum was 6 (CTP stage C, massive tumor involving > 50% of the liver with PVT, and AFP ≥ 400 ng/dL). The CLIP score was externally validated by randomized clinical trial in the year 2000 by the same collaborative group.
The CLIP scoring system

- The CLIP investigators state that this scoring system is simple, has increased predictive efficiency, and better defines the prognostic heterogeneity of Okuda stage 2 as it incorporates a higher number of variables with higher discriminant ability.

- It can identify a subgroup of patients with favorable prognosis who may be candidates for more radical therapy, such as resection.

- The score can also identify a subset of patients with a worse prognosis but having a median survival long enough to be considered for clinical trials of palliative anti-neoplastic therapy.
Barcelona Liver Cancer Classification BCLC - 1999

- Inception in 1999 - clarifies the decision-making process regarding the management of patients having cirrhosis and HCC according to the tumor burden, liver function, and physical condition

- Tumor extent is estimated based on the size and number of the tumors and portal vein invasion or extrahepatic spread

- The performance scale (PS) measures the daily living ability of an affected patient, and the scale proposed by the Eastern Cooperative Oncology Group (ECOG) is commonly used by clinicians to assess the functional status of patients affected by HCC

- The liver functional reserve is determined by the Child-Turcotte-Pugh (CTP) score. Hepatic venous pressure gradient (HVPG) greater than 10 mm Hg is the best predictor of the development of portal venous hypertension
Fig. 2  The Barcelona Clinic Liver Cancer classification. HCC hepatocellular carcinoma, PS performance status, TACE transarterial chemoembolization
Limitations of BCLC

• Include the use of subjective components, particularly performance status and heterogeneity of patient prognosis within a given category

• CLIP investigators argue that the BCLC classification groups the patients based on treatment options and that it represents only a treatment decision algorithm but not a prognostic evaluation

• It has also been stated by other research groups that the BCLC algorithm does not recognize the potential roles of RFA for very early-stage HCC and TARE (a safe and effective therapy for unresectable tumors)

• The BCLC staging system provides limited information about the expanding role of liver transplantation in the management of HCC, such as, the improved overall survival in tumors of size less than 2 cm

• Also, the expanding role of TARE (in the form of segmentectomy) and combination therapies (ablation plus embolization) for single large tumors and the role of TACE and TARE in patients with PS of 1 or with limited portal venous invasion are not adequately addressed

• To address the specific limitations of the BCLC staging system, some authors proposed sub-classifications - need further external validation to be adopted as a standard staging model
Groupe d’Etude et de Traitement du Carcinome Hépatocellulaire (GRETCH) - 1999

• The French scoring system, proposed by GRETCH in 1999 - objective measures and an estimate of performance status to predict survival

• A cohort of 761 consecutive patients across 24 institutions in Europe and Canada were randomly assigned

• Predictors of survival were identified using univariate analysis with Kaplan-Meier estimates and then included in a Cox proportional hazards model. Using a forward stepwise selection, five factors were found to affect 1-year survival from the time of diagnosis. These are performance status by Karnofsky score, serum bilirubin, serum alkaline phosphatase, AFP, and presence or absence of portal obstruction by ultrasonography
An advantage of the French classification is that its variables are generally available at the time of initial diagnosis and do not require invasive procedures or sophisticated imaging.

The increasing use of cross-sectional imaging as a diagnostic modality could impact the prognostic value of this scoring system by altering the sensitivity for diagnosis of portal obstruction.

To date, however, this classification system has not improved prognostic discrimination in comparison to other systems when tested on various cohorts.

<table>
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<th>Table 10 French classification</th>
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<tbody>
<tr>
<td>Weight</td>
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<tr>
<td>0</td>
</tr>
<tr>
<td>Karnofsky index (%)</td>
</tr>
<tr>
<td>≥80</td>
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<tr>
<td>Serum bilirubin (μmol/L)</td>
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<tr>
<td>&lt;50</td>
</tr>
<tr>
<td>Serum alkaline phosphatase (ULN)</td>
</tr>
<tr>
<td>&lt;2</td>
</tr>
<tr>
<td>Serum alpha-fetoprotein (μg/L)</td>
</tr>
<tr>
<td>&lt;35</td>
</tr>
<tr>
<td>Portal obstruction (ultrasonography)</td>
</tr>
<tr>
<td>no</td>
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<tr>
<td>ULN, upper limit of normal.</td>
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</tbody>
</table>

Groupe d’Etude et de Traitement du Carcinome Hépatocellulaire (GRETCH)
Chinese University Prognostic Index (CUPI) - 2002

• The original investigators were able to prospectively validate CUPI in a group of 595 largely hepatitis-B positive Asians

• The CUPI is well-designed and easy to use. The weighted scoring system in CUPI is more refined than the rather blunt assignment of points in CLIP and JIS. A Cox regression model was constructed containing TNM staging followed by forward stepwise addition of 18 other relevant clinical variables

• CUPI is derived from a cohort which is predominantly hepatitis B and performs well in similar Asian populations

• However, it has not performed well in comparative studies in Western populations, which are characterized by a greater proportion of patients with hepatitis C.

<table>
<thead>
<tr>
<th>Table 9 Weight of six prognostic factors in Chinese University Prognostic Index (CUPI)</th>
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</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>TNM Stage</td>
</tr>
<tr>
<td>I and II</td>
</tr>
<tr>
<td>IIIa and IIIb</td>
</tr>
<tr>
<td>IVa and IVb (reference)</td>
</tr>
<tr>
<td>Asymptomatic disease on presentation</td>
</tr>
<tr>
<td>Ascites</td>
</tr>
<tr>
<td>AFP ≥500 ng/mL</td>
</tr>
<tr>
<td>Total bilirubin (μmol/L)</td>
</tr>
<tr>
<td>&lt;34 (reference)</td>
</tr>
<tr>
<td>34-51 (reference)</td>
</tr>
<tr>
<td>≥52</td>
</tr>
<tr>
<td>Alkaline phosphatase ≥200 IU/L</td>
</tr>
<tr>
<td>CUPI Stages: score ≤1 (Low risk); 2-7 (Intermediate risk); ≥8 (High risk)</td>
</tr>
</tbody>
</table>
JIS (Japan Integrated Staging) Scoring System

• In 2003, the The Liver Cancer Study Group of Japan (LCSGJ) proposed the JIS score. Arguing that the CLIP score, previously validated in a Japanese population, did not provide sufficiently accurate prognostication for the early stage patients commonly diagnosed in Japanese centers due to screening programs and increased awareness of HCC, these investigators directed their efforts towards emphasizing the very favorable group from other early stage patients.

• The JIS score was developed from a cohort 722 consecutive Japanese patients and appears superior at prognosticating survival compared to CLIP, particularly in patients with early stage disease. The JIS system incorporates the LCSGJ’s modification of the TNM system and the Child-Pugh score.
JIS (Japan Integrated Staging) Scoring System

- While it has been validated in Japan and in other Asian populations, the JIS has not been prospectively validated in a Western population.
- There have been attempts to modify the JIS, as well as to incorporate biomarkers like AFP into the system; these versions have also not been validated and have not gained traction outside of Japan.
These BCLC sub-classification models need further external validation to be adopted as a standard staging model.
The Alberta HCC algorithm - 2010

- The algorithm recognizes the importance of tumor properties (size, number, extrahepatic spread, and AFP levels), patient characteristics (performance status and candidacy for transplantation), and liver function (CTP class along with elevated portal vein pressure or thrombosis of the portal vein) and links patients to the most appropriate therapy.

- Compared to BCLC - this recognizes potential role of RFA in very early-stage HCC and the role of 90Y radioembolization especially for patients who are not candidates for TACE because of PVT.

- In contrast to the BCLC treatment recommendations, sorafenib therapy is offered only to CTP class A cirrhotic patients with advanced HCC.
Fig. 3 The Alberta HCC algorithm. Tumor characteristics (blue boxes), patient characteristics (red boxes), and liver function (yellow boxes). The dotted line represents the potential role of RFA in very early-stage HCC. Dashed line recognizes the potential role of 90 Yttrium (Y) TARE, especially for patients who are not candidates for TACE because of bland PVT. HCC hepatocellular carcinoma, LT liver transplantation, PS performance status, RFA radiofrequency ablation, PEI percutaneous ethanol injection, PVI portal venous invasion, PVT portal venous thrombosis, Milan Milan criteria, N lymph node, TTV total tumor volume, TACE transarterial chemoembolization, TACE transarterial chemoembolization.
The MESIAH score - 2012

• developed by the members of the Mayo group in 2012 to predict survival of HCC patients based on objective parameters, including the model of end-stage liver disease (MELD) score, as a gauge of liver dysfunction to provide a refined prognostication and supplementation to the BCLC classification

• The MESIAH score can further classify patients with substantially different prognosis, particularly in BCLC B to D patients. The computation of this score may be implemented easily using a spreadsheet program, a web-based worksheet, or a handheld device

• The survival model incorporated the age of the patient, the number of tumor nodules, and the size of the largest nodule, vascular invasion, metastasis, serum albumin, AFP levels, and the MELD score. The MESIAH score is calculated by the following equation
The MESIAH score

\[
\text{The MESIAH score} = 0.232 \times \text{(age in decades)} \\
\quad + 0.099 \times \text{(MELD)} - 0.391 \times \text{(serum albumin level)} \\
\quad + 0.290 \times \text{(tumor size)} + 0.153 \times \text{(tumor number)} \\
\quad + 1.122 \times \text{(vascular invasion)} \\
\quad + 1.130 \times \text{(extrahepatic metastasis)} \\
\quad + 0.082 \times \text{(serum AFP level)} + 1
\]

(↑MELD scores = < 13 set to 13;

↑↑Number of nodules: 1 = 1, 2 = 2, 3 = 3, 4 = 4, 5 = 5, or greater;

↑↑↑Size of the largest nodule: 1 = < 1, 2 = 1 – 2, 3 = 2 – 3, 4 = 3 – 5, 5 = 5 – 10, 6 = 10 – 15, 7 = 15 – 20, 8 = > 20 cm;

↑↑↑↑ln(AFP) with AFP capped at 10,000 units).
The authors claim that the MESIAH score complements the BCLC and other staging models and that it is a valuable tool to estimate the prognosis of HCC patients in epidemiological research.

Since the system was developed from a small dataset of patients, whether MESIAH may inform treatment decisions, such as the BCLC staging system, remains to be determined.
The HKLC classification - 2014

• developed by the HongKong group of investigators in 2014, aims to create an improved staging system relative to the BCLC, to identify patients in need of more aggressive treatment

• Like BCLC - incorporated CTP score, ECOG and extent of tumor spread

• The higher prognostic accuracy and treatment efficacy proposed for the HKLC over the BCLC staging system needs further external validation studies in different cohorts
The HKLC classification

**Early tumor** is ≤ 5 cm, ≤ 3 tumor nodules, and no intrahepatic venous invasion

**Intermediate tumor** is (a) ≤ 5 cm, either > 3 tumor nodules, or with intrahepatic venous invasion or (b) > 5 cm, ≤ 3 tumor nodules, and no intrahepatic invasion

**Locally advanced tumor** is (a) ≤ 5 cm, > 3 tumor nodules, and with intrahepatic venous invasion or (b) > 5 cm, > 3 tumor nodules, or/and with intrahepatic venous invasion, or (c) diffuse tumor
The Italian Liver Cancer tumor staging and integrated prognostic staging system - 2016

• The ITA.LI.CA, another novel staging system of HCC, is derived from a prospectively collected multicenter database of over 5000 HCC patients from Italy and Taiwan

• following four main stages:
• 0 (very early)
• A (early)
• B (intermediate) - size and number of tumor nodules, vascular invasion, and metastasis.
• C (advanced).

• In contrast to the BCLC, the ITA.LI.CA tumor staging does not include the CTP score or the ECOG PS.

<table>
<thead>
<tr>
<th>ITA.LI.CA tumor stage</th>
<th>Points</th>
<th>CTP score</th>
<th>Points</th>
<th>ECOG PS</th>
<th>Points</th>
<th>AFP level</th>
<th>Points</th>
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<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>≤1000 μ/L</td>
<td>0</td>
</tr>
<tr>
<td>A</td>
<td>1</td>
<td>6–7</td>
<td>1</td>
<td>1–2</td>
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<tr>
<td>C</td>
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AFP alpha-fetoprotein, CTP Child-Pugh score, ECOG PS the Eastern Cooperative Oncology Group performance status.
The Italian Liver Cancer tumor staging and integrated prognostic staging system

- Selecting overall survival as the outcome of interest and using a multivariable survival parametric model estimate based on the ITA.LI.CA tumor stage, functional status, CTP score, and AFP concentration (≤ 1000 or > 1000 ng/mL), a prognostic score (ITA.LI.CA functional score) is derived.
- The least score (ITA.LI.CA score = 0) corresponds to best prognosis, and the highest score (ITA.LI.CA score = 13) corresponds to worst prognosis.
- Another unique feature of the ITA.LI.CA prognostic system is that it can be synthesized in a single simplified, user-friendly formula, $TS_{FA}$ (where TS is the tumor stage, F is the point value of the ITA.LI.CA functional score, and A is the AFP value), which not only provides an accurate clinical description of each HCC patient but also has a potential to be used for deciding patient treatment or designing clinical trials.
• When compared with the most commonly used staging systems, BCLC, CLIP, MESIAH, HKLC, and JIS, the ITA.LI.CA showed the best discriminatory ability and monotonicity of gradients and demonstrated broad applicability in both European and Asian populations.

• The ITA.LI.CA prognostic staging system, however, needs to be further validated through prospective trials in populations having poor performance status and hepatic decompensation since the study was retrospective, including almost all patients with good performance status with only 2% in the derivation cohort undergoing liver transplantation.
<table>
<thead>
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<th>Staging system</th>
<th>Tumor characteristics</th>
<th>Patient characteristics</th>
<th>Liver function status</th>
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<tbody>
<tr>
<td></td>
<td>Size</td>
<td>Number</td>
<td>PVI</td>
</tr>
<tr>
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</tbody>
</table>

PVI portal venous invasion, AFP alphafetoprotein, PS performance status, CTP Child-Pugh score, Cr creatinine, ALP alkaline phosphatase, PT/INR prothrombin time/international normalized ratio, CLIP Cancer of the Liver Italian Program score, BCLC Barcelona Clinic Liver Cancer, GRETCHE Groupe d’Etude et de Traitement du Carcinome Hepatocellulaire, CUPIC Chinese University Prognostic Index, MESIAH Model to Estimate Survival in Ambulatory HCC patients, HKLC Hong Kong Liver classification, ITALIICA Italian Liver Cancer
<table>
<thead>
<tr>
<th>Author(s) and year of publication</th>
<th>Type of study, number of patients included</th>
<th>Country</th>
<th>Compared staging systems</th>
<th>Conclusion</th>
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<tr>
<td>Cillo et al. [60], 2004</td>
<td>Retrospective analysis, 187 patients</td>
<td>Italy</td>
<td>Five systems</td>
<td>BCLC system was the best in prognosticating patients treated with potentially radical therapies.</td>
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<td>Sirivatanauksorn et al. [61], 2011</td>
<td>Retrospective cohort study, 181 patients</td>
<td>Thailand</td>
<td>Six systems</td>
<td>TNM and CTP determined the survival best in post-surgical resection patients.</td>
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<td>Memon et al. [62], 2014</td>
<td>Prospective cohort study, 728 patients</td>
<td>USA</td>
<td>Seven systems</td>
<td>CLIP was most accurate in predicting HCC survival in patients following Y-90 TARE.</td>
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<tr>
<td>Liu et al. [63], 2016</td>
<td>Prospective cohort study, 3128 patients</td>
<td>Taiwan</td>
<td>11 systems</td>
<td>CLIP score is the most accurate prognostic model.</td>
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<tr>
<td>Su et al. [64], 2016</td>
<td>Retrospective prognostic analysis, 307 patients</td>
<td>China</td>
<td>Four systems</td>
<td>China staging system best predicts the overall survival in patients with HCC in the Shandong province of China.</td>
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<td>Chen et al. [65], 2017</td>
<td>Retrospective prognostic analysis, 220 patients</td>
<td>China</td>
<td>Seven systems</td>
<td>CLIP score best predicts the 3- and 6-month overall survival rates.</td>
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<tr>
<td>Li et al. [66], 2017</td>
<td>Retrospective study, 1270 patients</td>
<td>Singapore</td>
<td>Two systems</td>
<td>BCLC performs better than HKLC in allocating patients to curative treatment as well as predicting survival.</td>
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<tr>
<td>Zhou et al. [67], 2017</td>
<td>Retrospective cohort study, 249 patients</td>
<td>China</td>
<td>Seven systems</td>
<td>Okuda, CUPL, and Chinese Guangzhou 2001 staging systems are the best for prognosticating HCC patients undergoing radiotherapy.</td>
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<tr>
<td>Wallace et al. [68], 2017</td>
<td>Prospective cohort study, 292 patients</td>
<td>Australia</td>
<td>Two systems</td>
<td>HKLC triages more HCC patients to curative therapies and is associated with better survival.</td>
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<tr>
<td>Sohn et al. [69], 2017</td>
<td>Retrospective cohort study, 1009 patients</td>
<td>USA</td>
<td>Two systems</td>
<td>HKLC system determined prognosis in patients following intraarterial therapy.</td>
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<tr>
<td>Selby et al. [70], 2017</td>
<td>Retrospective prognostic analysis, 766 patients</td>
<td>Singapore</td>
<td>Two systems</td>
<td>HKLC has better performance in guiding treatment.</td>
</tr>
<tr>
<td>Parikh et al. [71], 2018</td>
<td>Retrospective cohort study at 4 US health systems</td>
<td>USA</td>
<td>Four systems</td>
<td>Prognostic performance of HKLC and MESIAH is better than that of BCLC.</td>
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</table>

BCLC Barcelona Clinic Liver Cancer staging, CUPI Chinese University Prognostic Index, CLIP Cancer of the Liver Italian Programme score, MESIAH Model to Estimate Survival in Ambulatory HCC patients, HKLC Hong Kong Liver classification, ITALI CA Italian Liver Cancer staging, TNM tumor node metastasis staging, Y-90 TARE Yttrium-90 transarterial radioembolization
AJCC TNM Staging

No cancer would be complete without a TNM staging algorithm

**** AJCC staging provides information on resected specimen only
Conclusion

• Despite its enormous global impact, there is much disagreement about how best to stage and characterize this cancer. The differences in approach to HCC are due in part to its inherent clinical and biologic heterogeneity, but are also a function of the prism through which clinicians and clinical researchers observe the cancer.

• Despite numerous validation and comparative studies, and “consensus” panel recommendations generated by hepatologists, oncologists, surgeons and radiologists, with varying degrees of multidisciplinary collaboration, there is still no single system that could be called the “standard” for classifying HCC.

• Like with any cancer, the goals of a tumor staging system in HCC are to estimate a patient’s prognosis, which allows for appropriate therapy to be selected.
Conclusion

• The perfect unifying HCC staging system does not exist

• Striving to better characterize and classify this disease remains a worthy endeavor, particularly if we are able to identify subsets of patients who garner substantial benefit from interventions (possible resectable/transplantable or unresectable, inoperable because of comorbid conditions, liver confined or metastatic disease)

• Because of its widespread presence in contemporary HCC research, BCLC - de facto reference staging system and Okuda, TNM, CLIP also used by many practitioners to guide clinical decision-making

• With emerging and better understanding of HCC genomics, it is now apparent that common molecular subclasses exist & are associated with prognosis (5-gene score, IGF-modified CTP staging, genomic signatures)

• Depending upon the direction in which the field moves, we may be discussing entirely different systems a few years from now