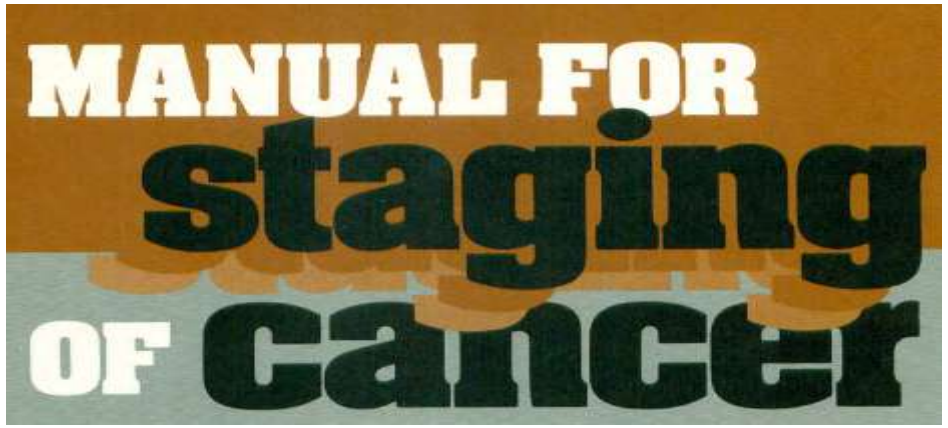
Classification of HCC: Looking beyond the TNM staging



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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

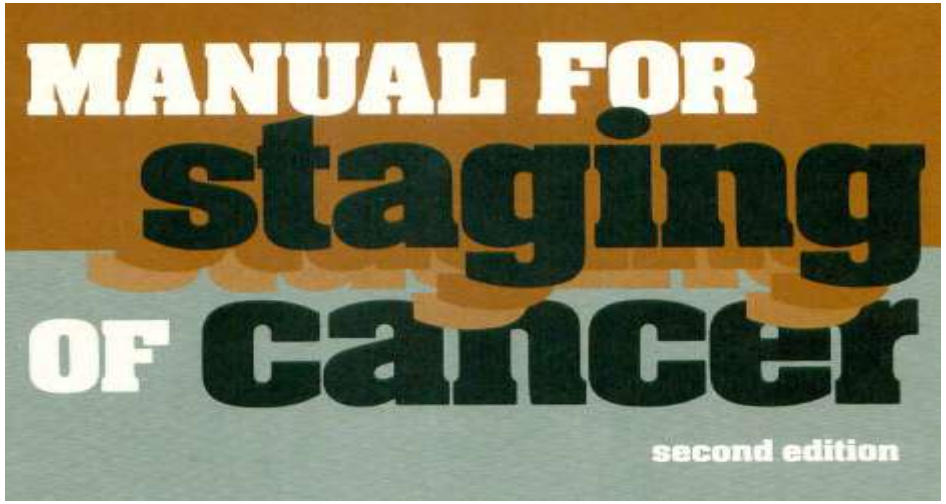
- The challenge of measuring the contributions of the cancer and hepatic dysfunction to the overall prognosis was recognized with the first modern era liver cancer staging system, which was proposed at the Hepatocellular Carcinoma International Symposium in Kampala, Uganda in 1971

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



1978

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 hepatis
- N2 Histologically confirmed spread to lymph nodes beyond porta hepatis

Distant Metastasis (M)

- MX Not assessed
- M0 No known metastasis
- M1 Distant metastasis present
  Specify site _____

Stage Grouping

Stage IA	T1, N0, M0, without cirrhosis
Stage IB	T1, N0, M0, with cirrhosis
Stage IIA	T2, N0, M0, without cirrhosis
Stage IIB	T2, N0, M0, with cirrhosis
Stage IIIA	T3, N0, N1; M0, without cirrhosis
Stage IIIB	T3, N0, N1; M0, with cirrhosis
Stage IVA	T4, N0–N2; M0, M1; without cirrhosis
Stage IVB	T4, N0–N2; M0, 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
[ ] Mass
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.

AJCC	PERFORMANCE	ECOG SCALE	KARNOFSKY SCALE (%)
H0	Normal activity	0	90-100
H1	Symptomatic but ambulatory; cares for self	1	70-80
H2	Ambulatory more than 50% of time; occasionally needs assistance	2	50-60
H3	Ambulatory 50% or less of time; nursing care needed	3	30-40
H4	Bedridden; may need hospitalization	4	10-20

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. Nonepithelial tumors
    11. Hemangioma
    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

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2. Malt R et al: Manifestations and prognosis of hepatocellular carcinoma. Surg Gynecol Obstet 135:361-364, 1972

AJCC TNM Staging

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Hepatobiliary Cancers

NCCN Guidelines Index
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Discussion

American Joint Committee on Cancer (AJCC)
TNM Staging for Hepatocellular Cancer (8th ed., 2017)

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

T	Primary Tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Solitary tumor ≤2 cm, or >2 cm without vascular invasion
T1a	Solitary tumor ≤2 cm
T1b	Solitary tumor >2 cm without vascular invasion
T2	Solitary tumor >2 cm with vascular invasion, or multiple tumors, none >5 cm
T3	Multiple tumors, at least one of which is >5 cm
T4	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

N	Regional Lymph Nodes
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

M	Distant Metastasis
M0	No distant metastasis
M1	Distant metastasis

Table 2. **AJCC Prognostic Groups**

	T	N	M
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T4	N0	M0
Stage IVA	Any T	N1	M0
Stage IVB	Any T	Any N	M1

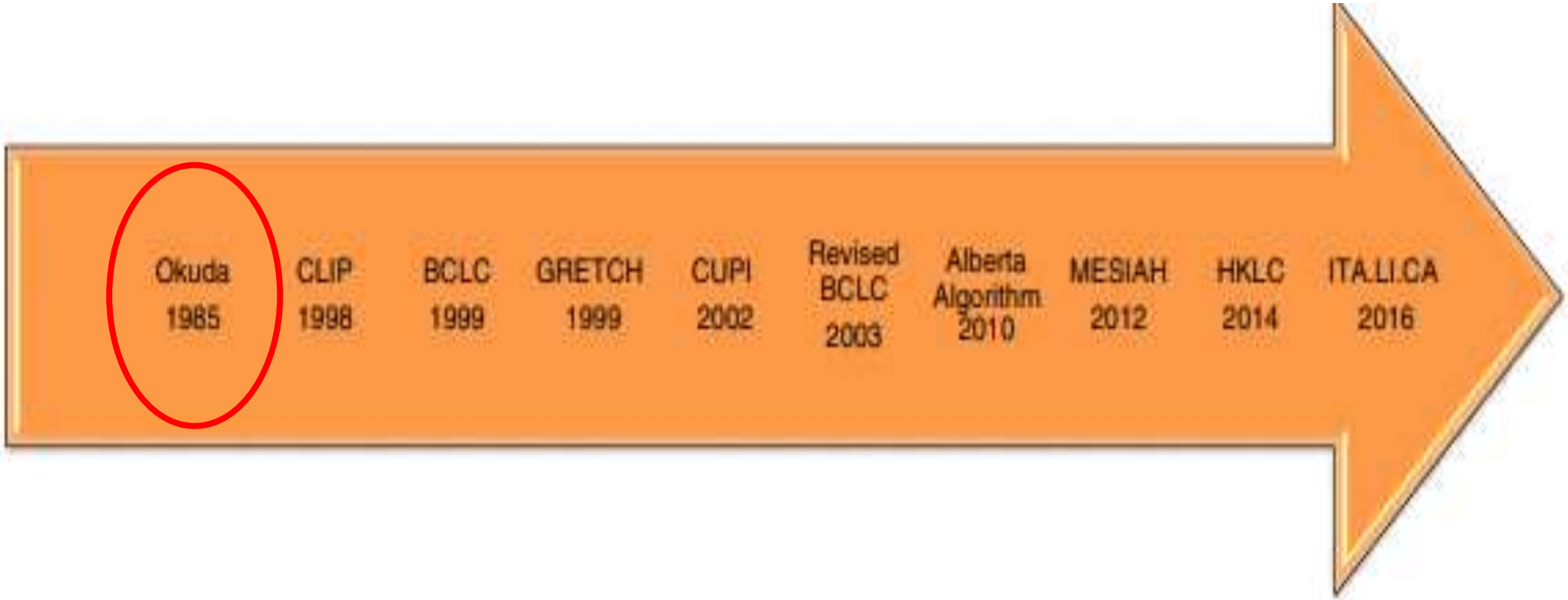
Histologic Grade (G)

GX	Grade cannot be accessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

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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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 thar 50%, ascites, < 3 g/dL albumin,
and > 3 mg/dL bilirubin

Stage III - three or four of these features

Table 4 Okuda staging

Factors representing advanced disease - Tumor size >50% of liver - Ascites - Albumin <3 g/dL - Bilirubin >3 mg/dL	
Stage I	No factors present
Stage II	1-2 factors
Stage III	3-4 factors

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

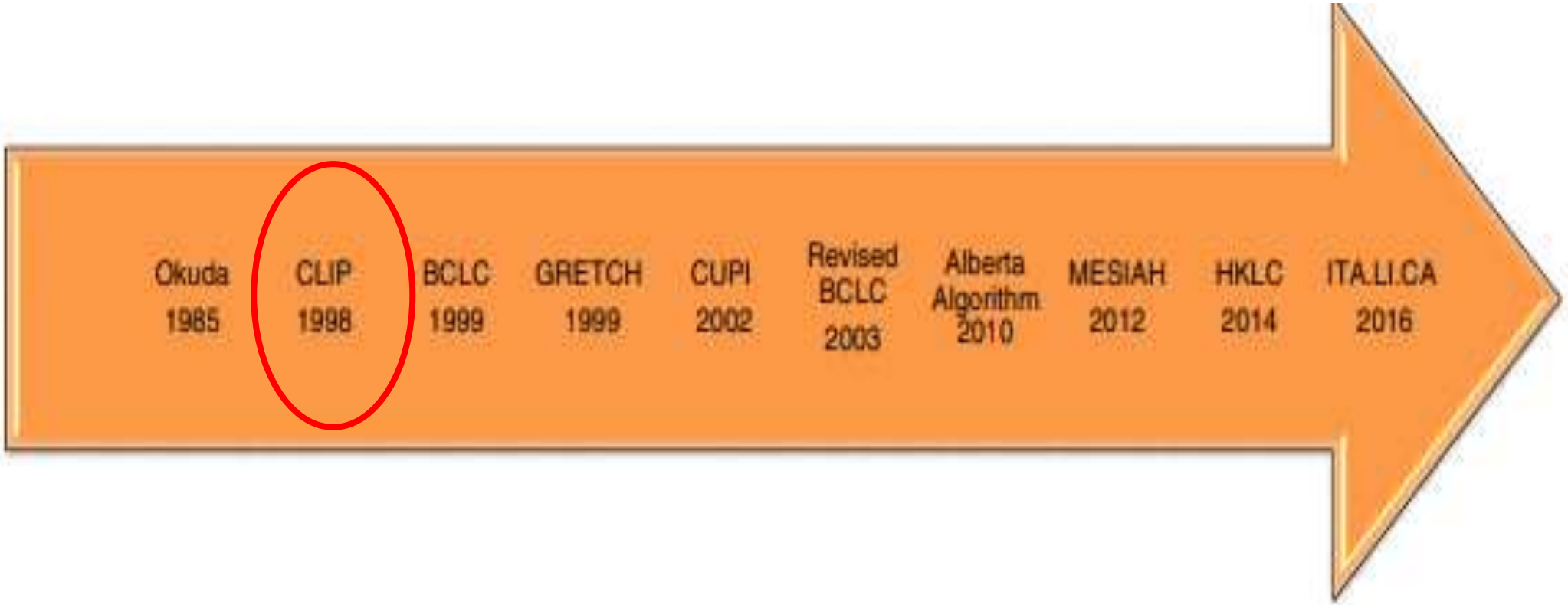
CTP score

- 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)

Table 2 Child-Turcotte-Pugh score

Measurements	Score		
	1	2	3
Encephalopathy	None	Mild	Moderate
Ascites	None	Slight	Moderate
Bilirubin (md/dL)	1-2	2-3	>3
Albumin (mg/dL)	>3.5	2.8-3.5	<2.8
PT (seconds prolonged)	<4	4-6	>6

Stage A, 5-6 points; Stage B, 7-9 points; Stage C, 10-15 points.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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

Table 3 The Cancer of the Liver Italian Program score and its elements

Variables	Scores		
	0	1	2
CTP score	A	B	C
Tumor morphology	Uninodular and extension ≤ 50%	Multinodular and extension ≤ 50%	Massive or extension > 50%
AFP (ng/dL)	< 400	≥ 400	
Portal vein thrombosis	No	Yes	

AFP alpha-fetoprotein, *CTP* Child-Pugh score

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


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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

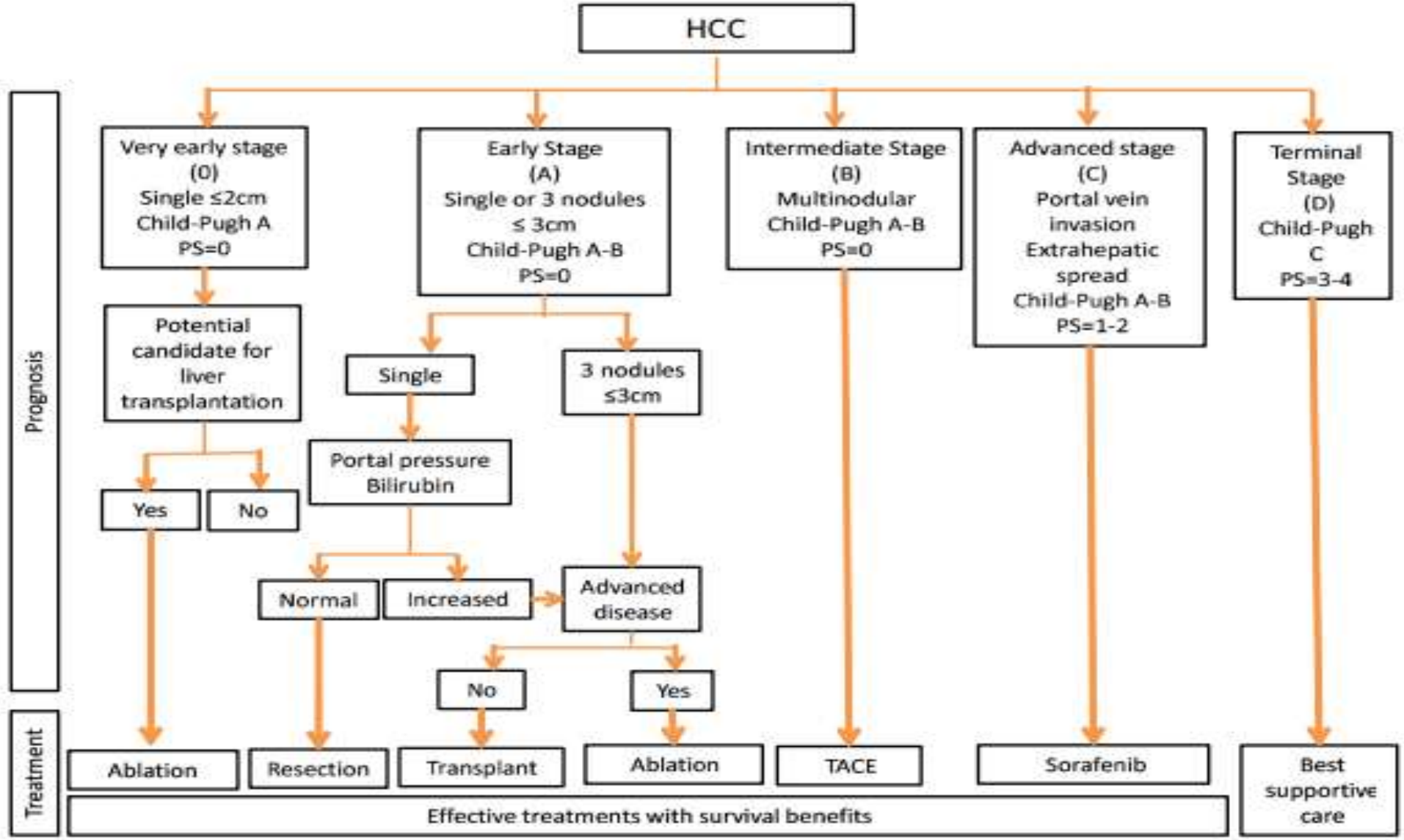

Fig. 2 The Barcelona Clinic Liver Cancer classification. *HCC* hepatocellular carcinoma, *PS* performance status, *TACE* transarterial chemoembolization

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


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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

Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire (GRETCH)

- 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 crosssectional 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 10 French classification

Weight	0	1	2	3
Karnofsky index (%)	≥80			<80
Serum bilirubin (μmol/L)	<50			≥50
Serum alkaline phosphatase (ULN)	<2		≥2	
Serum alpha-fetoprotein (μg/L)	<35		≥35	
Portal obstruction (ultrasonography)	no	yes		

ULN, upper limit of normal.


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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 9 Weight of six prognostic factors in Chinese University Prognostic Index (CUPI)

Variable	Weight
TNM Stage	
I and II	−3
IIIa and IIIb	−1
IVa and IVb (reference)	0
Asymptomatic disease on presentation	−4
Ascites	3
AFP ≥500 ng/mL	2
Total bilirubin (μmol/L)	
<34 (reference)	0
34-51	3
≥52	4
Alkaline phosphatase ≥200 IU/L	3
CUPI Stages: score ≤1 (Low risk); 2-7 (Intermediate risk); ≥8 (High risk)	

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

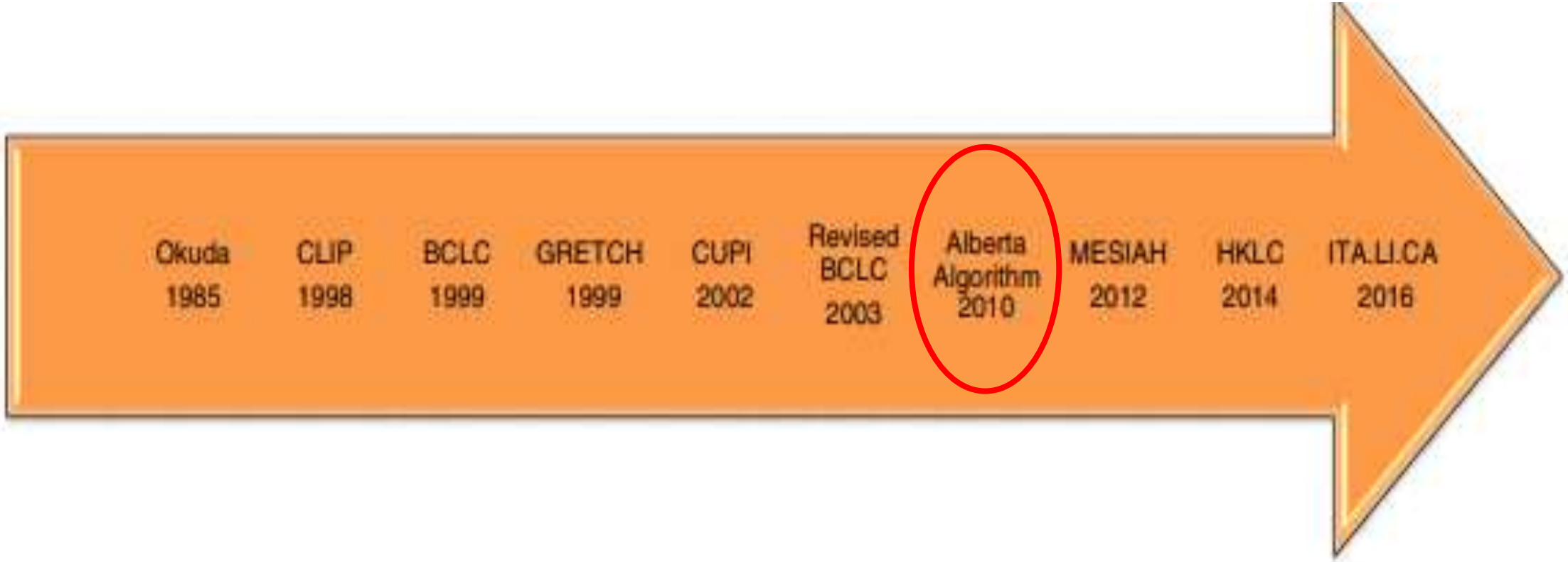
JIS (Japan Integrated Staging) Scoring System

- 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.

Table 8 Japan integrated staging (JIS) scoring system

Variables	Scores			
	0	1	2	3
Child-Pugh stage	A	B	C	
TNM stage by LCSGJ	I	II	III	IV

LCSGJ, Liver Cancer Study Group 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

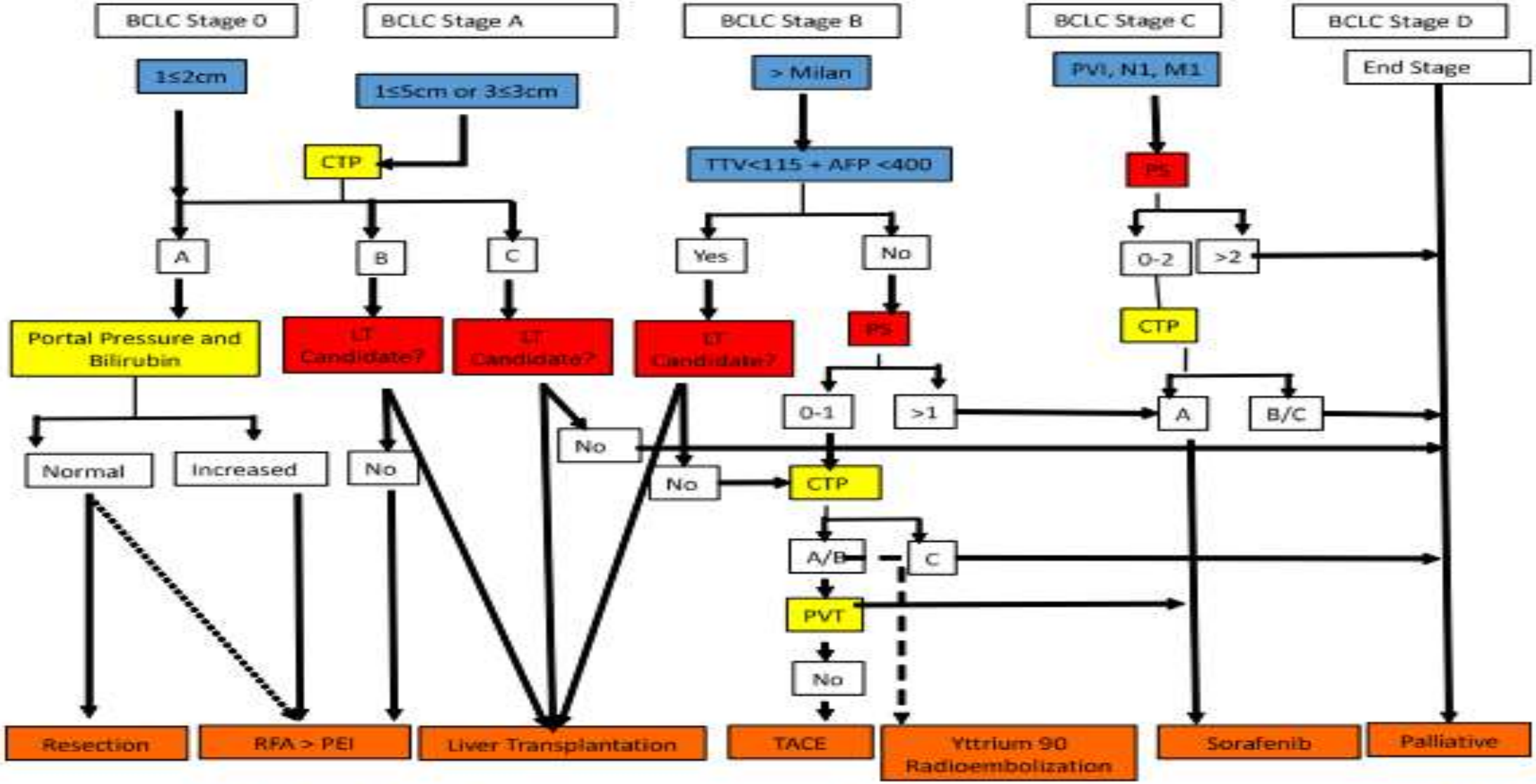
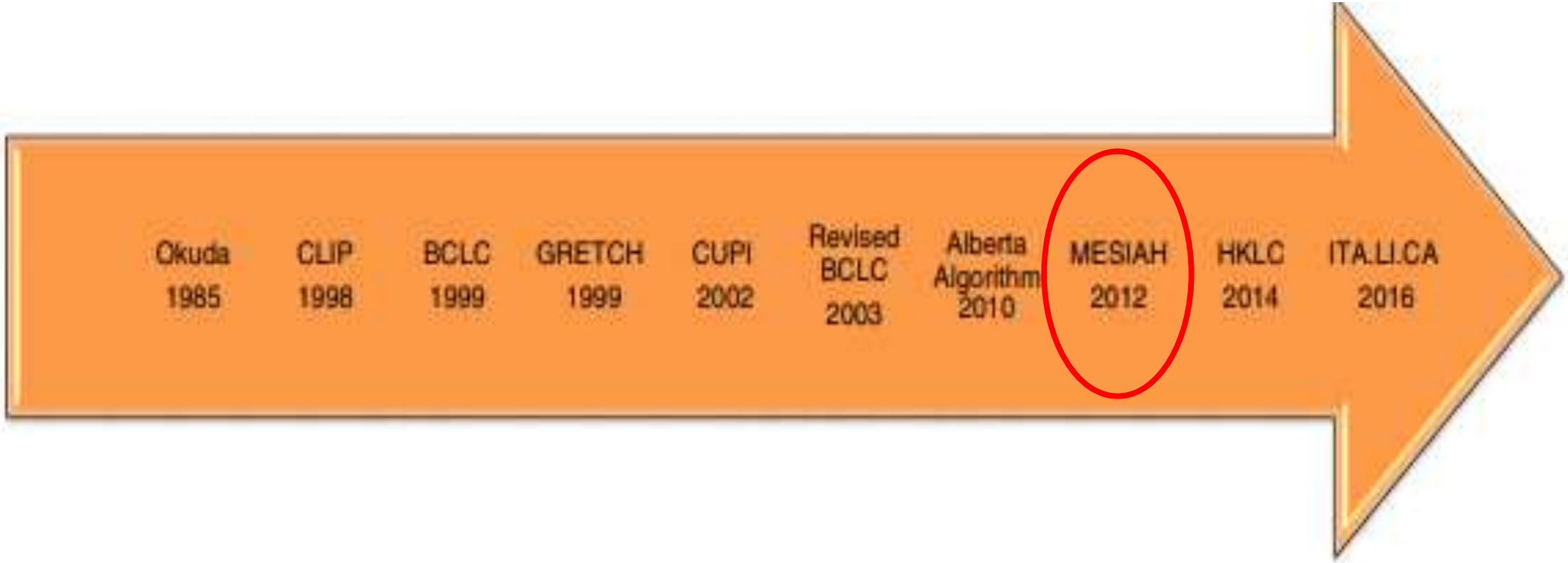


Fig. 3 The Alberta HCC algorithm. Tumor characteristics (blue boxes), patient characteristics (red boxes), and liver function (yellow boxes). The dotted line represents the potential role of RFA in very early-stage HCC. Dashed line recognizes the potential role of 90 Yttrium (Y) TARE, especially for 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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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

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

(†MELD scores=< 13 set to 13;

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

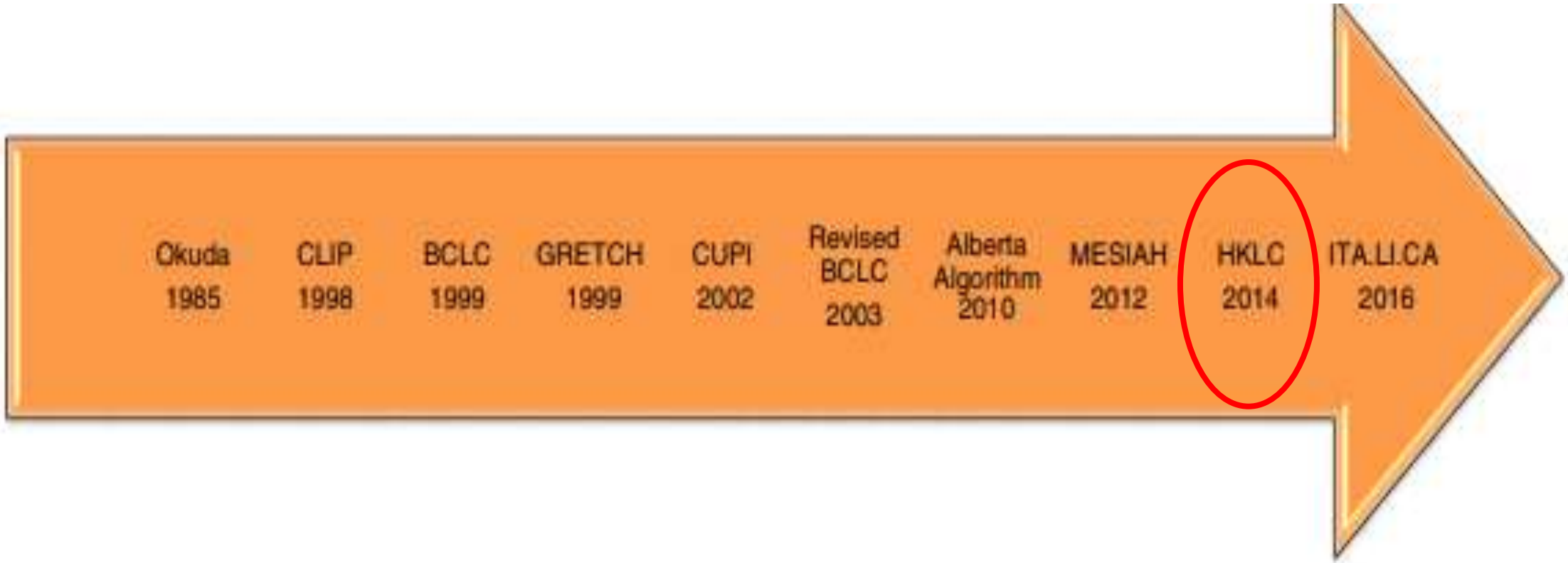
†††Size of the largest nodule : 1=<=1, 2 = 1−2, 3 = 2−3, 4 = 3−5, 5 = 5−10, 6 = 10−15, 7 = 15−20, 8=>20 cm;

††††ln(AFP) with AFP capped at 10, 000 units].

The MESIAH score

- 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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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

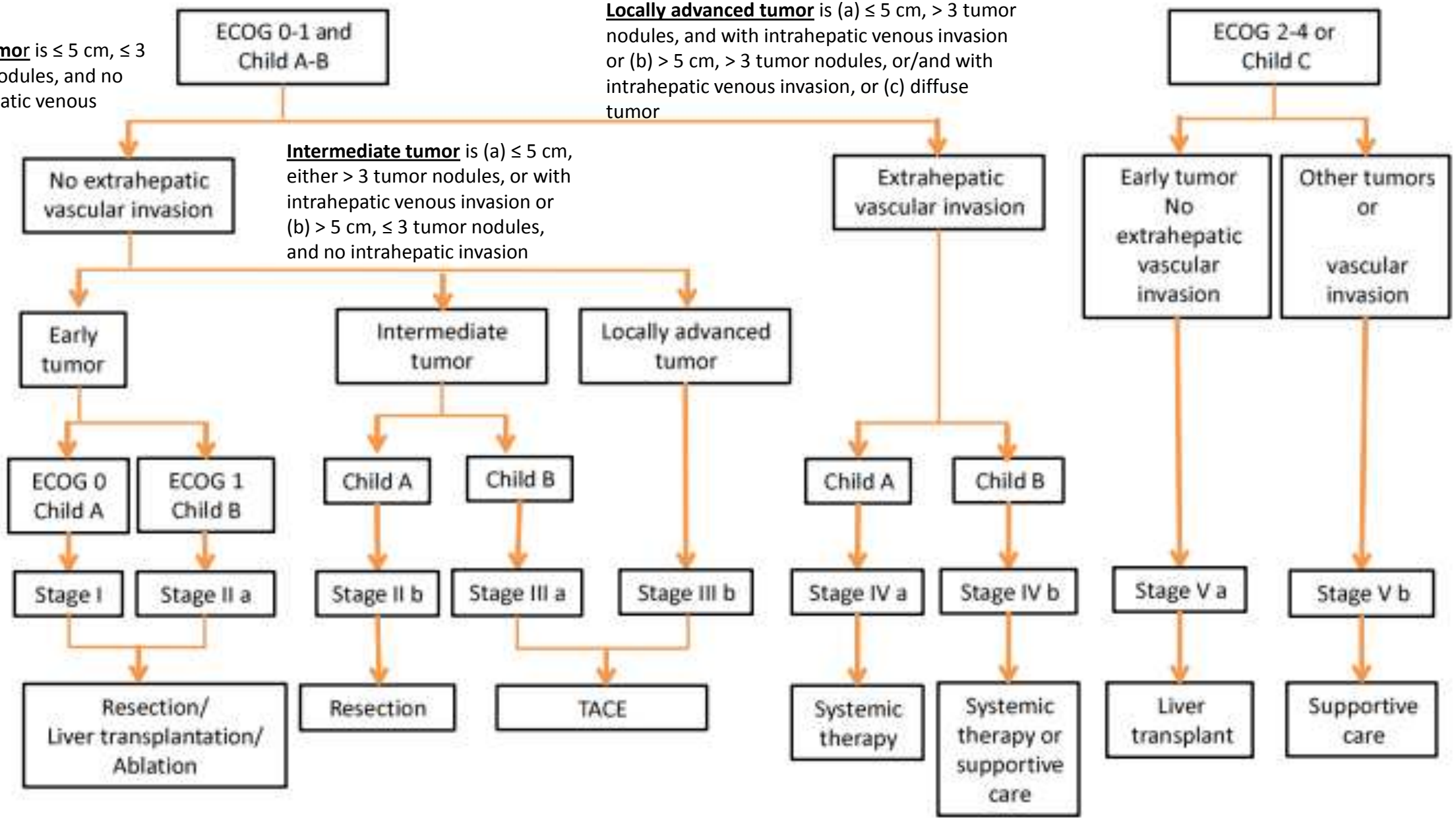
The HKLC classification

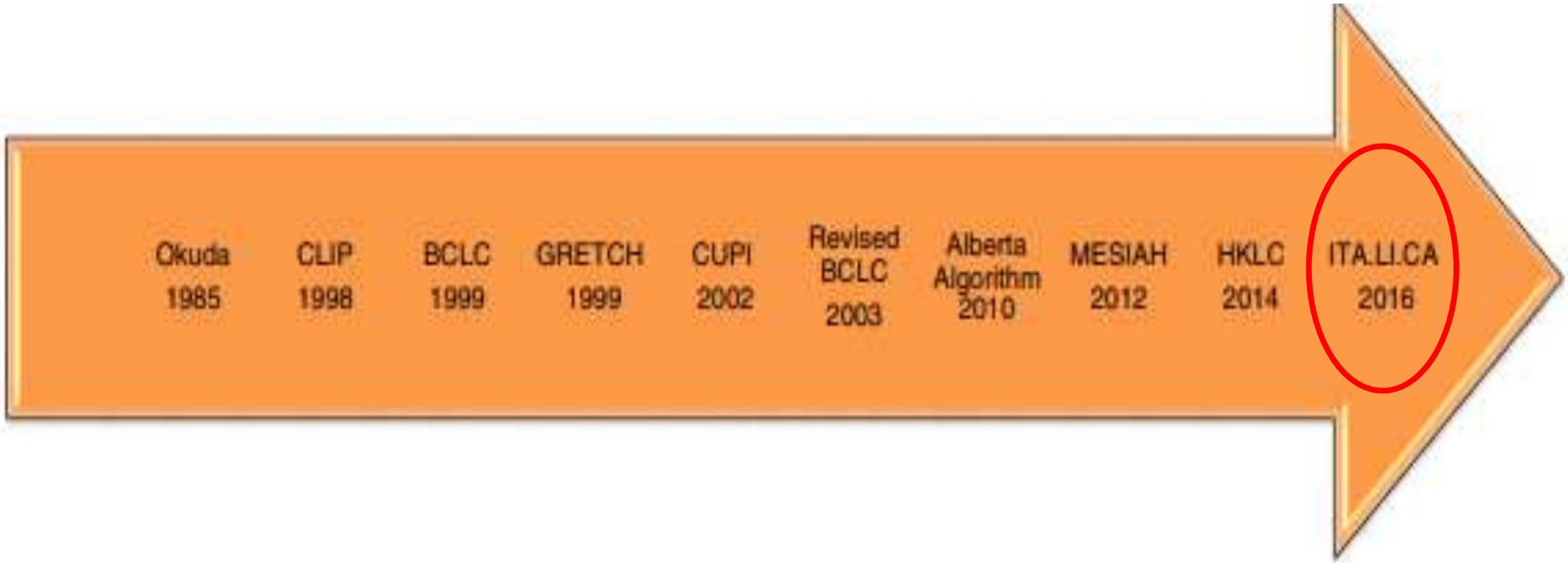
Indian J Gastroenterol

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

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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.

The ITA.LI.CA tumor staging system

Number and diameter of largest nodule (cm)	Stage
A single nodule of ≤ 2 cm	0
2–3 nodules of ≤ 3 cm or a single nodule of 2–5 cm	A
2–3 nodules of 3–5 cm or single nodule of > 5 cm	B1
2–3 nodules of > 5 cm or > 3 nodules of ≤ 5 cm	B2
> 3 nodules of > 5 cm without an intrahepatic spread or any number of nodules with any size with intrahepatic spread	B3
Any number of nodules with any size with extrahepatic spread	C

The ITA.LI.CA integrated prognostic score

ITA.LI.CA tumor stage	Points	CTP score	Points	ECOG PS	Points	AFP level	Points
0	0	5	0	0	0	≤ 1000 μ/L	0
A	1	6–7	1	1–2	1	> 1000 μ/L	2
B1	2	8–9	2	3–4	3		
B2	3	10–15	3				
B3	4						
C	5						

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 1 Comparison of different hepatocellular carcinoma staging systems: tumor and patient characteristics and liver function

Staging system	Tumor characteristics						Patient characteristics		Liver function status						
	Size	Number	PVI	Metastasis	Nodes	AFP	PS	Age	CTP	Albumin	Serum bilirubin	Serum Cr	PT/INR	Ascites	ALP
Okuda	✓									✓	✓			✓	
CLIP	✓		✓			✓			✓	✓	✓		✓	✓	
BCLC	✓	✓	✓	✓			✓ (ECOG)		✓	✓	✓		✓	✓	
HKLC	✓	✓	✓	✓			✓ (ECOG)		✓	✓	✓		✓	✓	
Alberta algorithm	✓	✓	✓	✓			✓ (ECOG)		✓	✓	✓		✓	✓	
MESIAH score	✓	✓	✓	✓		✓		✓		✓	✓	✓	✓		
GRETCH score			✓			✓	✓(Karnofsky index)				✓				✓
CUPI	✓			✓	✓	✓					✓			✓	✓
ITA.LI.CA	✓	✓	✓	✓		✓	✓(ECOG)		✓	✓	✓		✓	✓	

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, *GRETCH* Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire, *CUPI* Chinese University Prognostic Index, *MESIAH* Model to Estimate Survival in Ambulatory HCC patients, *HKLC* Hong Kong Liver classification, *ITA.LI.CA* Italian Liver Cancer

Table 5 Studies comparing various staging models for overall survival discrimination

Author(s) and year of publication	Type of study, number of patients included	Country	Compared staging systems	Conclusion
Cillo et al. [60], 2004	Retrospective analysis, 187 patients	Italy	Five systems	BCLC system was the best in prognosticating patients treated with potentially radical therapies.
Sirivatanauksorn et al. [61], 2011	Retrospective cohort study, 181 patients	Thailand	Six systems	TNM and CTP determined the survival best in post-surgical resection patients.
Memon et al. [62], 2014	Prospective cohort study, 728 patients	USA	Seven systems	CLIP was most accurate in predicting HCC survival in patients following Y-90 TARE.
Liu et al. [63], 2016	Prospective cohort study, 3128 patients	Taiwan	11 systems	CLIP score is the most accurate prognostic model.
Su et al. [64], 2016	Retrospective prognostic analysis, 307 patients	China	Four systems	China staging system best predicts the overall survival in patients with HCC in the Shandong province of China.
Chen et al. [65], 2017	Retrospective prognostic analysis, 220 patients	China	Seven systems	CLIP score best predicts the 3- and 6-month overall survival rates.
Li et al. [66], 2017	Retrospective study, 1270 patients	Singapore	Two systems	BCLC performs better than HKLC in allocating patients to curative treatment as well as predicting survival.
Zhou et al. [67], 2017	Retrospective cohort study, 249 patients	China	Seven systems	Okuda, CUPI, and Chinese Guangzhou 2001 staging systems are the best for prognosticating HCC patients undergoing radiotherapy.
Wallace et al. [68], 2017	Prospective cohort study, 292 patients	Australia	Two systems	HKLC triages more HCC patients to curative therapies and is associated with better survival.
Sohn et al. [69], 2017	Retrospective cohort study, 1009 patients	USA	Two systems	HKLC system determined prognosis in patients following intraarterial therapy.
Selby et al. [70], 2017	Retrospective prognostic analysis, 766 patients	Singapore	Two systems	HKLC has better performance in guiding treatment.
Parikh et al. [71], 2018	Retrospective cohort study at 4 US health systems	USA	Four systems	Prognostic performance of HKLC and MESIAH is better than that of BCLC.

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, *ITA.LI.CA* Italian Liver Cancer staging, *TNM* tumor node metastasis staging, *Y-90 TARE* Yttrium-90 transarterial radioembolization

AJCC TNM Staging

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Hepatobiliary Cancers

NCCN Guidelines Index
Table of Contents
Discussion

American Joint Committee on Cancer (AJCC)
TNM Staging for Hepatocellular Cancer (8th ed., 2017)

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

T	Primary Tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Solitary tumor ≤2 cm, or >2 cm without vascular invasion
T1a	Solitary tumor ≤2 cm
T1b	Solitary tumor >2 cm without vascular invasion
T2	Solitary tumor >2 cm with vascular invasion, or multiple tumors, none >5 cm
T3	Multiple tumors, at least one of which is >5 cm
T4	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

N	Regional Lymph Nodes
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

M	Distant Metastasis
M0	No distant metastasis
M1	Distant metastasis

Table 2. **AJCC Prognostic Groups**

	T	N	M
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T4	N0	M0
Stage IVA	Any T	N1	M0
Stage IVB	Any T	Any N	M1

Histologic Grade (G)

GX	Grade cannot be accessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

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)

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 disesase)
- 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