Update on Hepatocellular carcinoma: pearls for primary care management

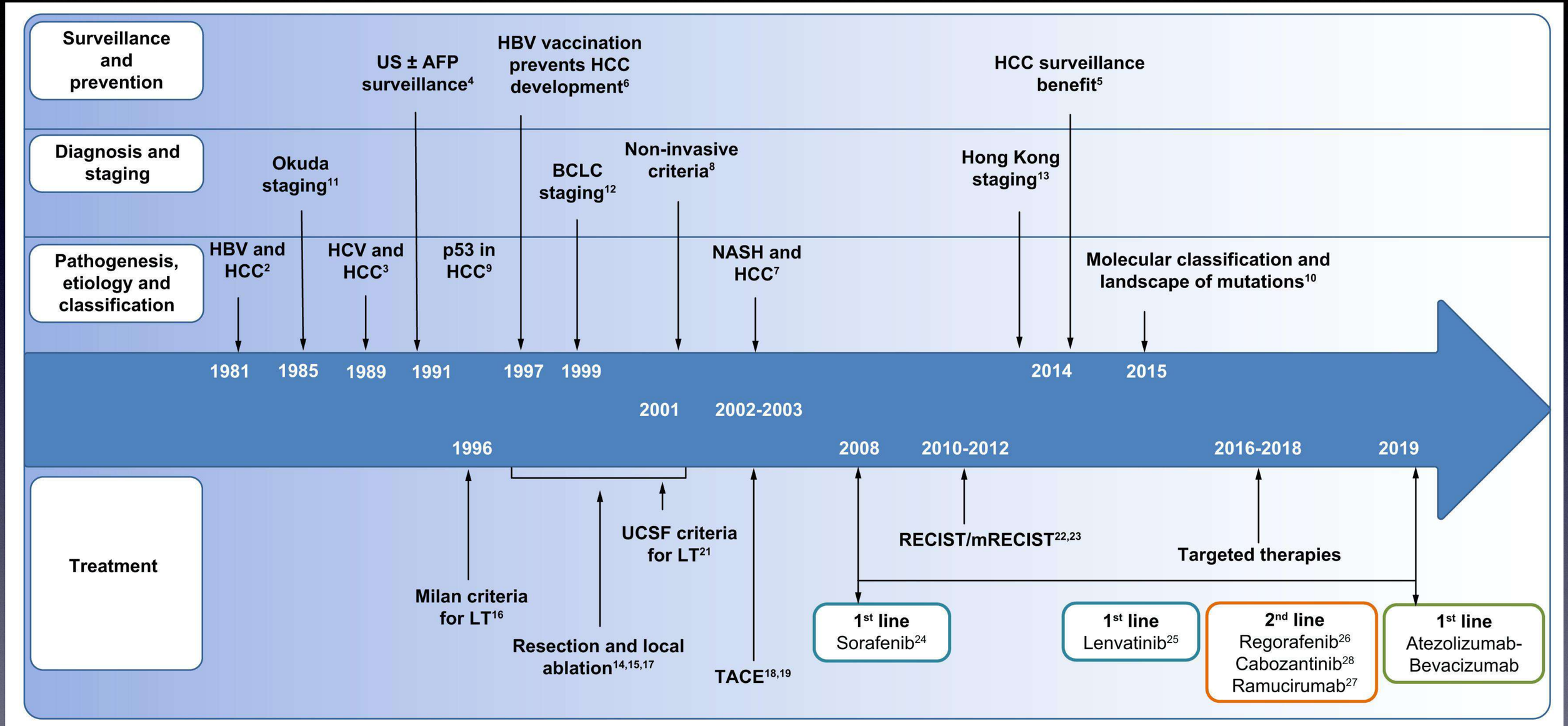
Jose E Rivera-Acosta MD, MSc.
Assistant Professor, UPR, School of Medicine
Transplant Hepatologist, Hospital Auxilio Mutuo

Objectives

- Pathogenesis of HCC
- New trends in epidemiology and surveillance
- Radiological assessment
- Resection and transplantation

Objectives

- Locoregional treatment
- Immunotherapy and systemic therapies
- HCC in the COVID-19 pandemic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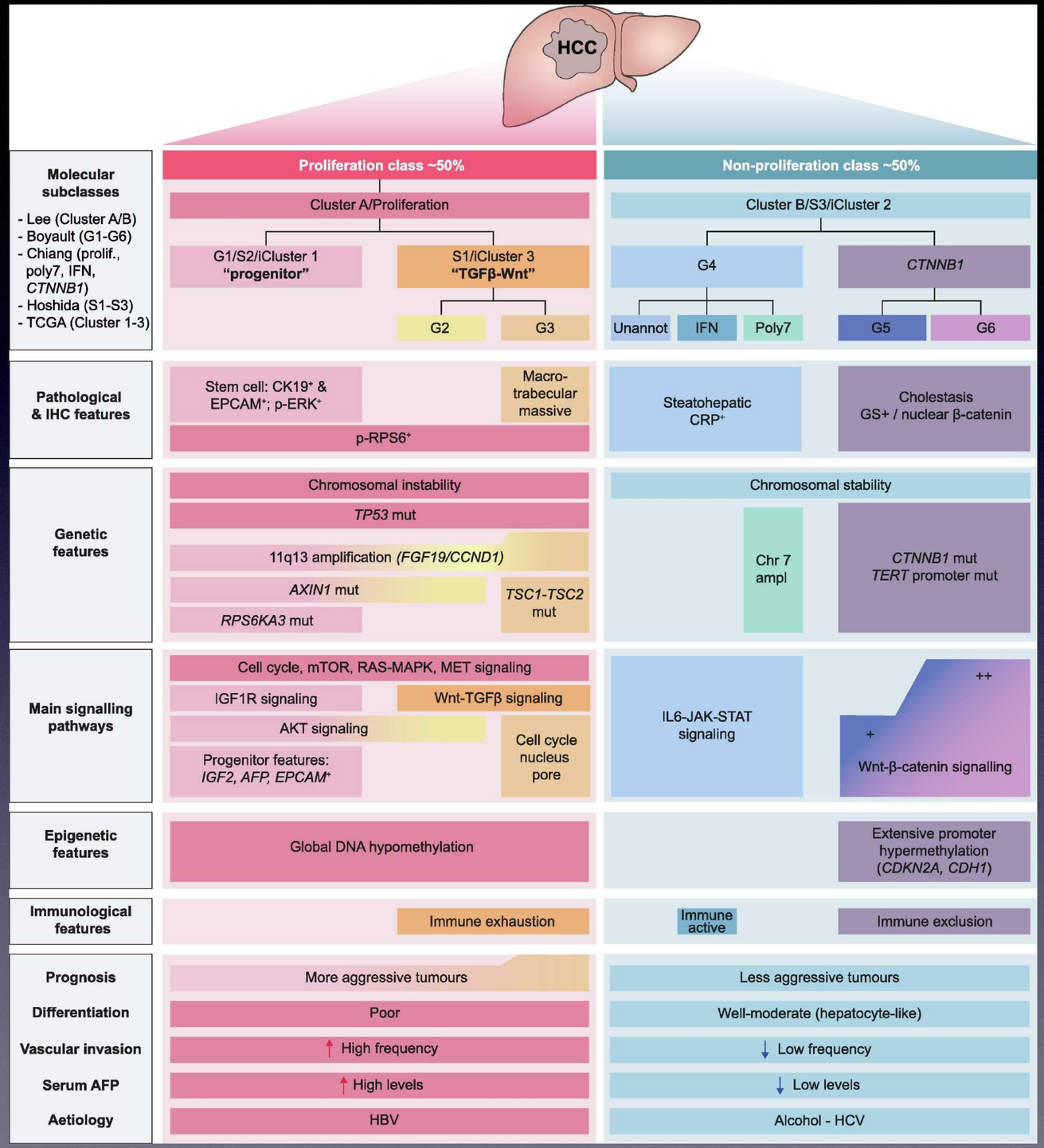
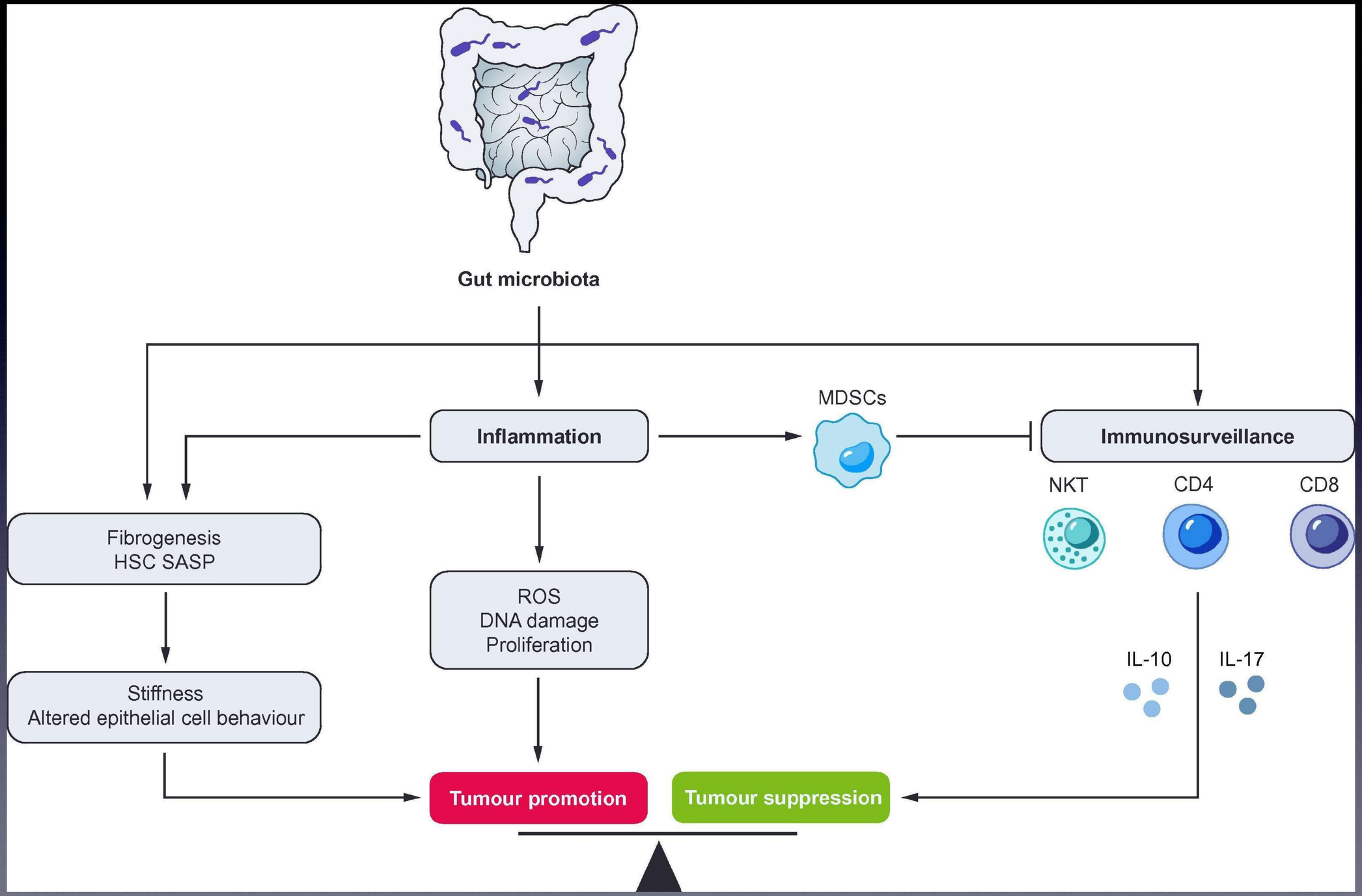
Pathogenesis of HCC

- Next generation sequencing and identification signaling pathways
- Clinical and pathological features defining HCC sub-groups
- Role of microbiota on HCC development.


HCC
Molecular subclasses
- Lee (Cluster A/B)
- Boyault (G1-G6)
- Chiang (prolif., poly7, IFN, CTNNB1)
- Hoshida (S1-S3)
- TCGA (Cluster 1-3)
Proliferation class ~50%
Non-proliferation class ~50%
Cluster A/Proliferation
Cluster B/S3/iCluster 2
G1/S2/iCluster 1 "progenitor"
S1/iCluster 3 "TGFβ-Wnt"
G4
CTNNB1
G2
G3
Unannot
IFN
Poly7
G5
G6
Pathological & IHC features
Stem cell: CK19+ & EPCAM+; p-ERK+
Macro-trabecular massive
p-RPS6+
Steatohepatic CRP+
Cholestasis GS+ / nuclear β-catenin
Genetic features
Chromosomal instability
TP53 mut
11q13 amplification (FGF19/CCND1)
AXIN1 mut
TSC1-TSC2 mut
RPS6KA3 mut
Chromosomal stability
Chr 7 ampl
CTNNB1 mut
TERT promoter mut
Main signalling pathways
Cell cycle, mTOR, RAS-MAPK, MET signaling
IGF1R signaling
Wnt-TGFβ signaling
AKT signaling
Cell cycle nucleus pore
Progenitor features: IGF2, AFP, EPCAM+
IL6-JAK-STAT signaling
++
+
Wnt-β-catenin signalling
Epigenetic features
Global DNA hypomethylation
Extensive promoter hypermethylation (CDKN2A, CDH1)
Immunological features
Immune exhaustion
Immune active
Immune exclusion
Prognosis
More aggressive tumours
Less aggressive tumours
Differentiation
Poor
Well-moderate (hepatocyte-like)
Vascular invasion
↑ High frequency
↓ Low frequency
Serum AFP
↑ High levels
↓ Low levels
Aetiology
HBV
Alcohol - HCV


Gut microbiota
Inflammation
MDSCs
Immunosurveillance
NKT
CD4
CD8
Fibrogenesis
HSC SASP
ROS
DNA damage
Proliferation
Stiffness
Altered epithelial cell behaviour
IL-10
IL-17
Tumour promotion
Tumour suppression

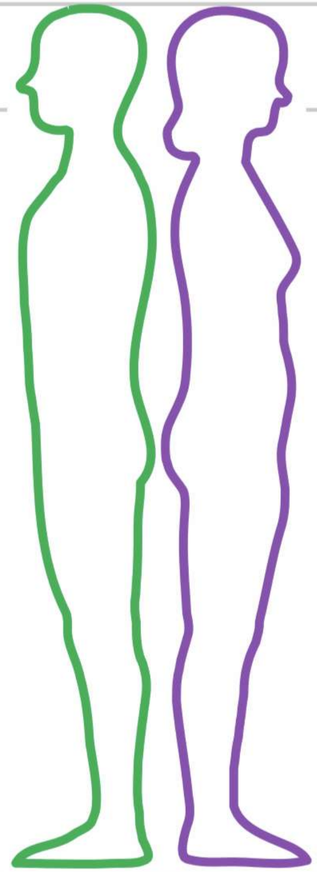
Epidemiology and surveillance

- Sixth most common diagnosed cancer worldwide
- Fourth leading cause of death in the world
- Most cases occur in chronic liver disease, cirrhosis main risk factor
- Incidence expected to increase
  - Population growth
  - Aging

FIGURA 8: PRIMEROS DIEZ TIPOS DE CÁNCER: MORTALIDAD: PUERTO RICO, 2010-2014

FIGURE 8: TOP TEN CANCER SITES: MORTALITY: PUERTO RICO, 2010-2014

Hombres / Males (N = 14,848)	%	Mujeres / Females (N =11,694)	%
Próstata/Prostate	16.9	Mama/Breast	18.4
Pulmón y bronquios/Lung and bronchus	13.5	Colon y recto/Colon and rectum	13.4
Colon y recto/Colon and rectum	13.0	Pulmón y bronquios/Lung and bronchus	9.6
Hígado y ducto biliar/Liver and bile duct	6.7	Páncreas/Pancreas	6.0
Páncreas/Pancreas	5.0	Hígado y ducto biliar/Liver and bile duct	4.6
Estómago/Stomach	4.3	Cuerpo del útero, NOS/Corpus and uterus, NOS	4.4
Leucemia/Leukemia	3.3	Ovario/Ovary	4.4
Cavidad oral y faringe/Oral cavity and pharynx	3.2	Estómago/Stomach	3.8
Linfoma no-Hodgkin/Non-Hodgkin Lymphoma	3.1	Leucemia/Leukemia	3.3
Esófago/Esophagus	3.1	Linfoma no-Hodgkin/Non-Hodgkin Lymphoma	2.8
Otros sitios primarios/Other sites	27.9	Otros sitios primarios/Other sites	29.5



Fuente de Datos: Archivo de Mortalidad provisto por el Registro Demográfico de Puerto Rico, octubre de 2016.
(Data Source: Mortality Case File provided by the Demographic Registry of Puerto Rico, October, 2016.)

Groups that will benefit from screening and surveillance

TABLE 1. PATIENTS AT THE HIGHEST RISK FOR HCC

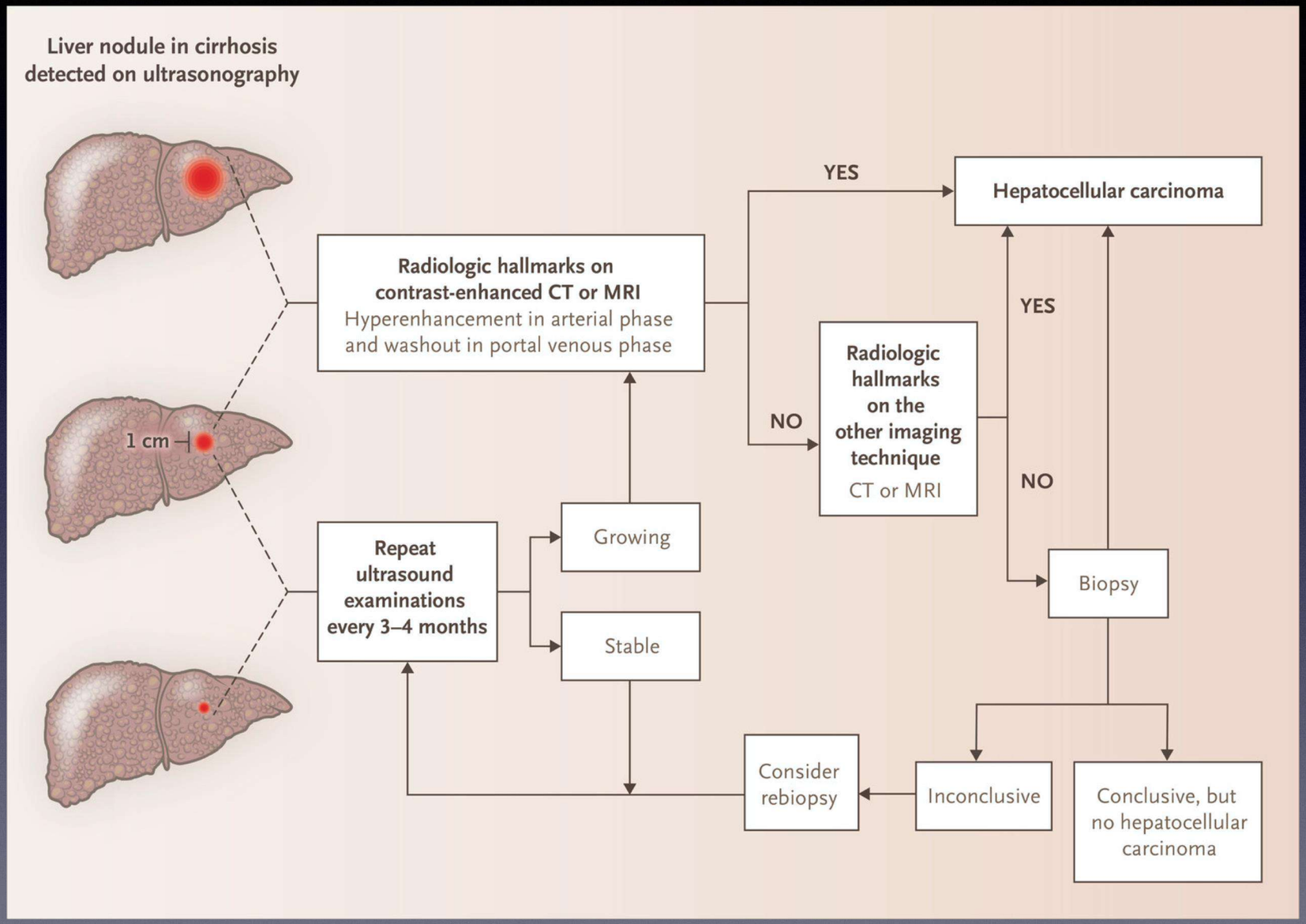
Population Group	Threshold Incidence for Efficacy of Surveillance (>0.25 LYG; % per year)	Incidence of HCC
Surveillance benefit		
Asian male hepatitis B carriers over age 40	0.2	0.4%-0.6% per year
Asian female hepatitis B carriers over age 50	0.2	0.3%-0.6% per year
Hepatitis B carrier with family history of HCC	0.2	Incidence higher than without family history
African and/or North American blacks with hepatitis B	0.2	HCC occurs at a younger age
Hepatitis B carriers with cirrhosis	0.2-1.5	3%-8% per year
Hepatitis C cirrhosis	1.5	3%-5% per year
Stage 4 PBC	1.5	3%-5% per year
Genetic hemochromatosis and cirrhosis	1.5	Unknown, but probably >1.5% per year
Alpha-1 antitrypsin deficiency and cirrhosis	1.5	Unknown, but probably >1.5% per year
Other cirrhosis	1.5	Unknown
Surveillance benefit uncertain		
Hepatitis B carriers younger than 40 (males) or 50 (females)	0.2	<0.2% per year
Hepatitis C and stage 3 fibrosis	1.5	<1.5% per year
NAFLD without cirrhosis	1.5	<1.5% per year

Abbreviation: LYG, life-years gained.

HCC screening and surveillance

- Abdominal US with or without AFP very 6 months
  - Low sensitivity on early stages
  - Surveillance effectiveness on cohorts (NASH, post SVR HCC)

Diagnostic algorithm for a liver nodule



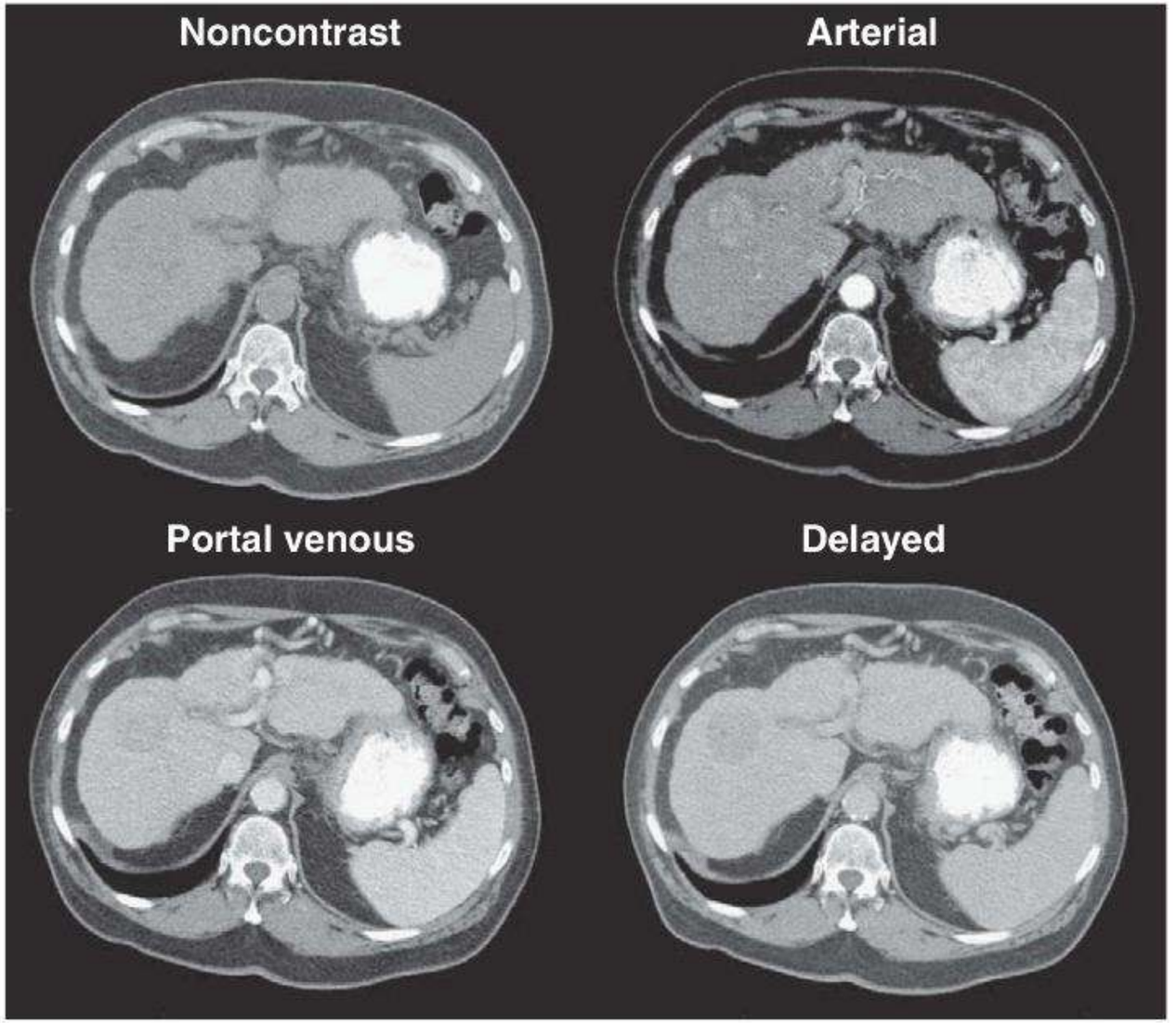
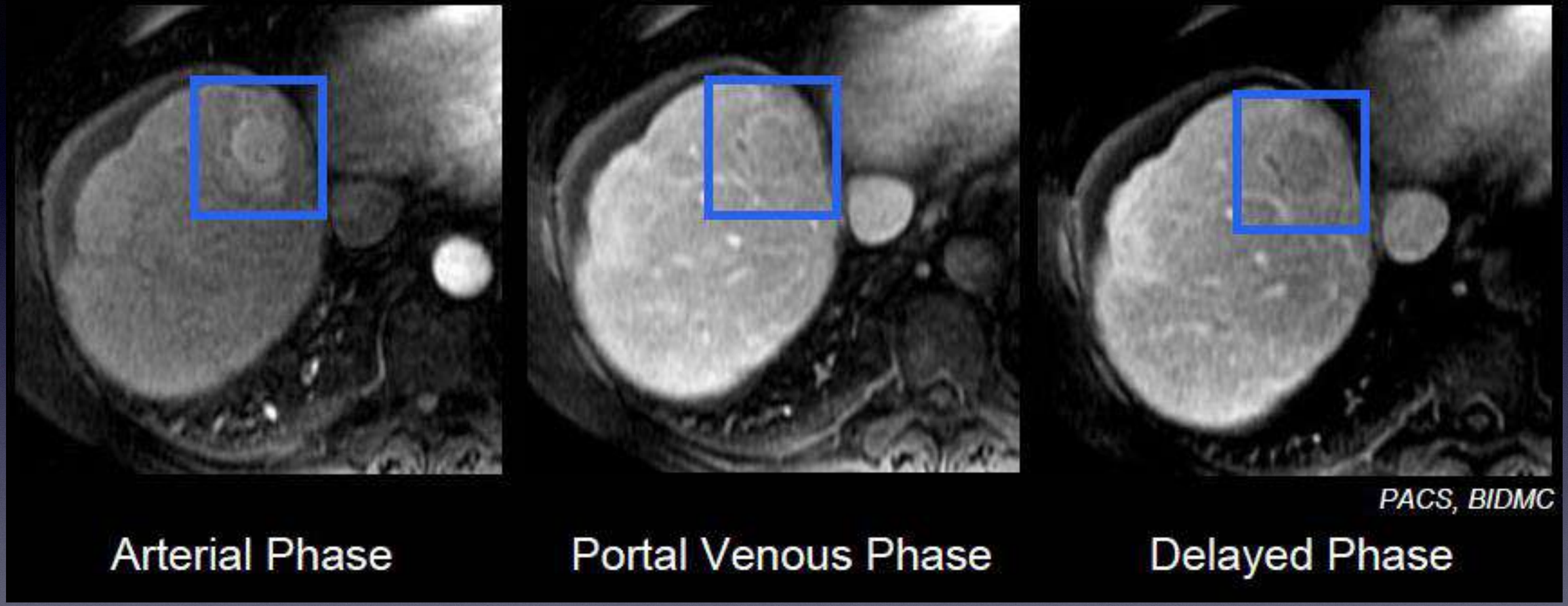


Figure 94-2. Dynamic computed tomography scan of a patient with hepatocellular carcinoma showing no lesion in the noncontrast phase, an enhancing lesion in the arterial phase of contrast administration, and a faint lesion in the portal venous phase seen better in the delayed phase.


PACS, BIDMC
Arterial Phase
Portal Venous Phase
Delayed Phase

CT/MRI LI-RADS® v2018 CORE

Untreated observation without pathologic proof in patient at high risk for HCC

- If cannot be categorized due to image degradation or omission → LR-NC
- If definite tumor in vein (TIV) → LR-TIV
- If definitely benign → LR-1
- If probably benign → LR-2
- If probably or definitely malignant but not HCC specific (e.g., if targetoid) → LR-M

Otherwise, use CT/MRI diagnostic table below

- If intermediate probability of malignancy → LR-3
- If probably HCC → LR-4
- If definitely HCC → LR-5

Treatment for HCC

- Resection
- Liver Transplant
- Locoregional therapies
- Systemic or targeted directed therapies

Liver transplant is the best treatment for HCC that is confined to the liver

Resection

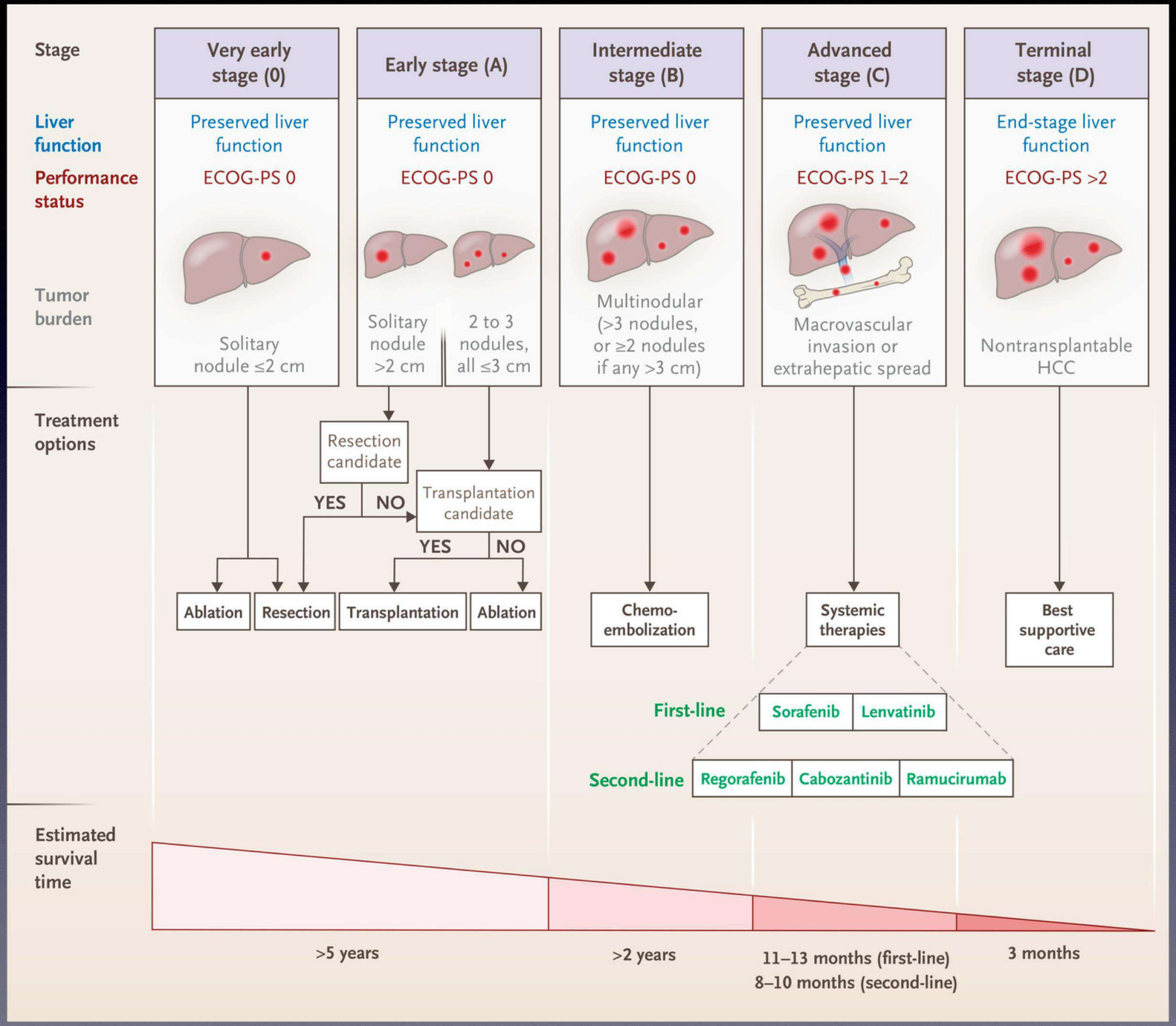
- 10 year recurrence free survival 22-25%
- In selected patients benefits over systemic therapy and locoregional therapy alone
- Perioperative mortality 5%
- Liver decompensation beyond 3 months 10-12%

Liver Transplant

- 10 year recurrence free survival 50-70%
- BCLC system
- Milan criteria for selection
  - Solitary <5 cm or up to 3 nodules each 3 cm
  - No macrovascular invasion or distant disease

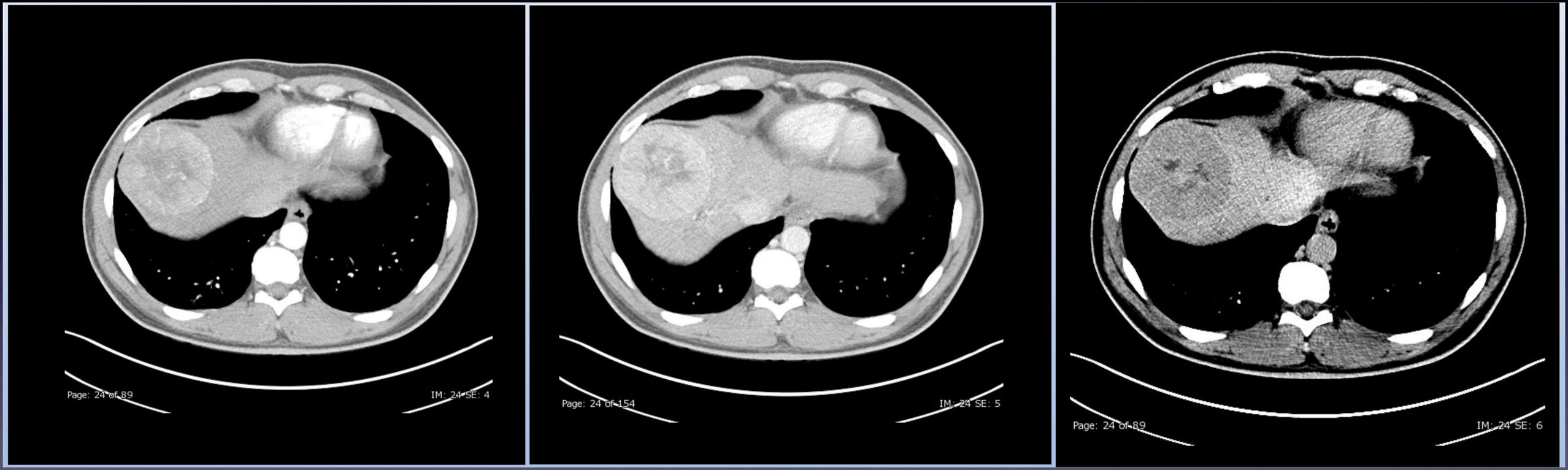
Liver Transplant

- “Exception points”
- Mandatory 6 month waiting period
- Regional mean MELD at transplant
- Down-staging of lesion beyond Milan criteria has acceptable outcomes

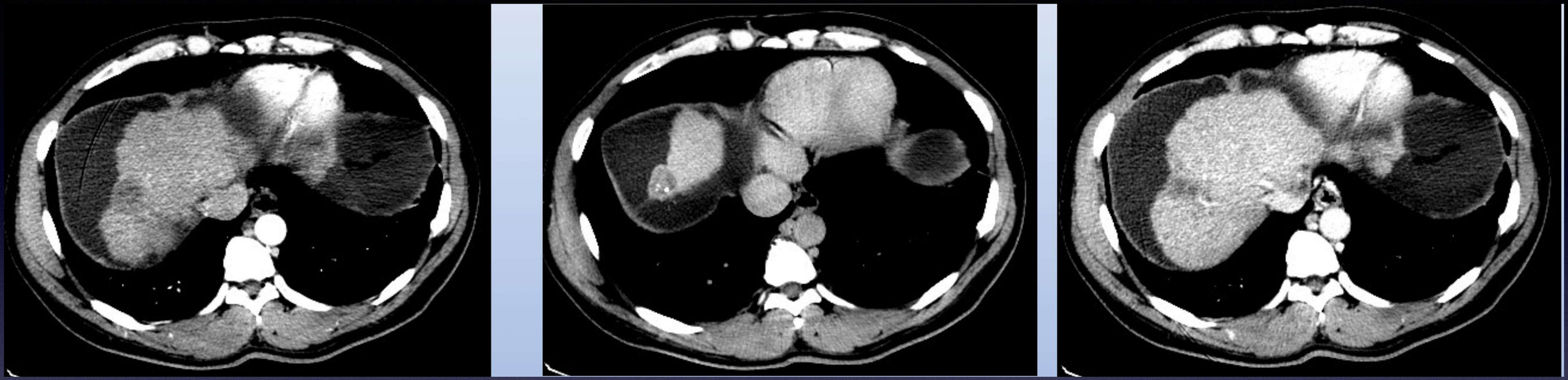

Stage
Very early stage (0)
Early stage (A)
Intermediate stage (B)
Advanced stage (C)
Terminal stage (D)
Liver function
Preserved liver function
Preserved liver function
Preserved liver function
Preserved liver function
End-stage liver function
Performance status
ECOG-PS 0
ECOG-PS 0
ECOG-PS 0
ECOG-PS 1–2
ECOG-PS >2
Tumor burden
Solitary nodule ≤2 cm
Solitary nodule >2 cm
2 to 3 nodules, all ≤3 cm
Multinodular (>3 nodules, or ≥2 nodules if any >3 cm)
Macrovascular invasion or extrahepatic spread
Nontransplantable HCC
Treatment options
Resection candidate
YES
NO
Transplantation candidate
YES
NO
Ablation
Resection
Transplantation
Ablation
Chemo-embolization
Systemic therapies
Best supportive care
First-line
Sorafenib
Lenvatinib
Second-line
Regorafenib
Cabozantinib
Ramucirumab
Estimated survival time
>5 years
>2 years
11–13 months (first-line)
8–10 months (second-line)
3 months

Locoregional therapies

- Transarterial chemoembolization (TACE)
  - Most widely use intervention for intermediate stage
  - Median survival exceeds 40 months in selected cases
  - Considered palliative treatment
- Transarterial radioembolization (TARE)
  - Safe in patients with microvascular invasion
  - Cost!!



7.9x 7.6 cm lesion with arterial enhancement and washout at right hepatic lobe



e after TACE where a 3x2.3cm lesion is observed on segment VII consistent with pa

Immunotherapies and systemic therapies

Trial Name	Line of therapy	Active agent	Control	Primary end-point	Results
SHARP	First-line	Sorafenib	Placebo	OS	10.7vs7.9 HR 0.69 (95% CI 0.55-0.87)
REFLECT	First-line	Levatinib	Sorafenib	OS	13.6 vs 12.3 HR 0.92 (95% CI 0.79-1.06)
RESORCE	Second-line	Regorafenib	Placebo	OS	10.6 vs 7.8 HR 0.63 (95% CI 0.50-0.79)
CELESTIAL	Second- and third-line	Cabozantinib	Placebo	OS	10.2 vs 8.0 HR0.76 (95% CI 0.63-0.92)
REACH-2	Second-line and AFP>400 ng/mL	Ramucirumab	Placebo	OS	8.5 vs 7.3 HR 0.71 (95%CI 0.531-0.949)
Checkmate-440	Second-line	Nivolumab	None	ORR, OS, safety	17%, 15.0
KEYNOTE-224	Second-line	Pembrolizumab	None	ORR, OS, safety	17%, 12.9
KEYNOTE-240	Second-line	Pembrolizumab	Placebo	PFS, OS	PFS 3.0 vs 2.8 HR 0.718 (95%CI 0.570-0.904) OS 13.9 vs 10.6 HR 0.781 (95%CI 0.611-0.998)
Checkmate-459	First-line	Nivolumab	Sorafenib	OS	16.4 vs 14.7 HR 0.85 (95%CI 0.72-1.02)
IMbrave150	First-line	Atezolizumab + bevacizumab	Sorafenib	OS% 12 mo., PFS	PFS 6.8 vs 4.8 HR 0.59 (95%CI 0.47-0.76) OS 67.2% vs 54.6% (95%CI 45.2-64.0)

HCC and SARS-CoV-2

- Not available data that HCC as risk factor increase mortality of SARS-CoV-2
- Worse outcomes of COVID-19 on patient with non-hepatic types of cancer
- Fewer patients presented to Tumor Boards
- More than 21% patient experience delays in treatment of more than 1 month
- COVID-19 infection more common cause of delay of treatment on 2019

Questions?