Tailoring Hepatocellular Carcinoma Therapy

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Disclosures

Speaker Bureau:	AbbVie, Eisai, Exelixis, Gilead, Intercept, Mallinckrodt, Salix
Consultant:	Eisai, Exelixis, Gilead, Mallinckrodt

Learning Objectives

- Review necessary clinical, imaging, and laboratory studies in the evaluation of hepatocellular carcinoma
- Provide a tailored approach to the management of hepatocellular carcinoma

Development of Hepatocellular Carcinoma

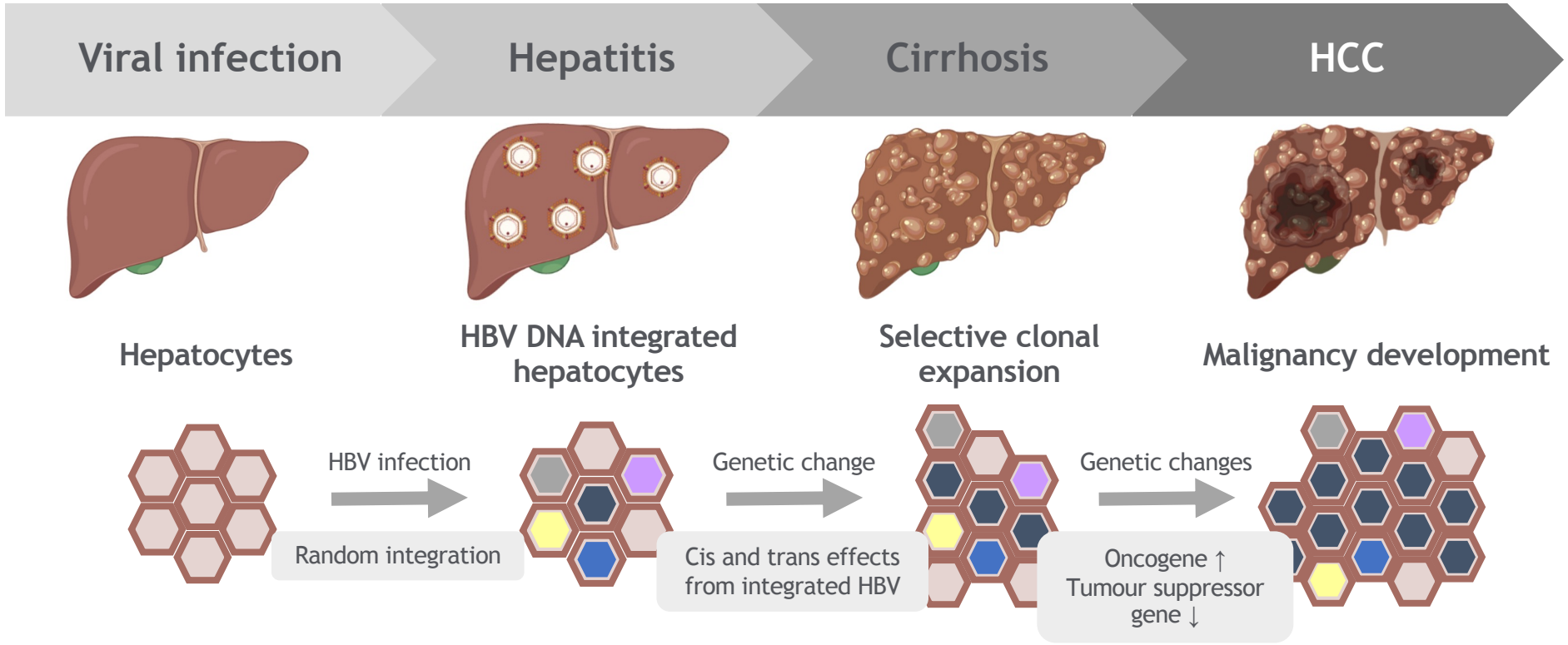
2 Major Mechanisms

- **Without cirrhosis ~ DNA integration into host genetic material (chromosomes)**
- **After development of cirrhosis**

Development of Hepatocellular Carcinoma I

Without cirrhosis ~ DNA integration into host genetic material (chromosomes)

HBV DNA integration can lead to selective clonal expansion and Hepatocellular Carcinoma development

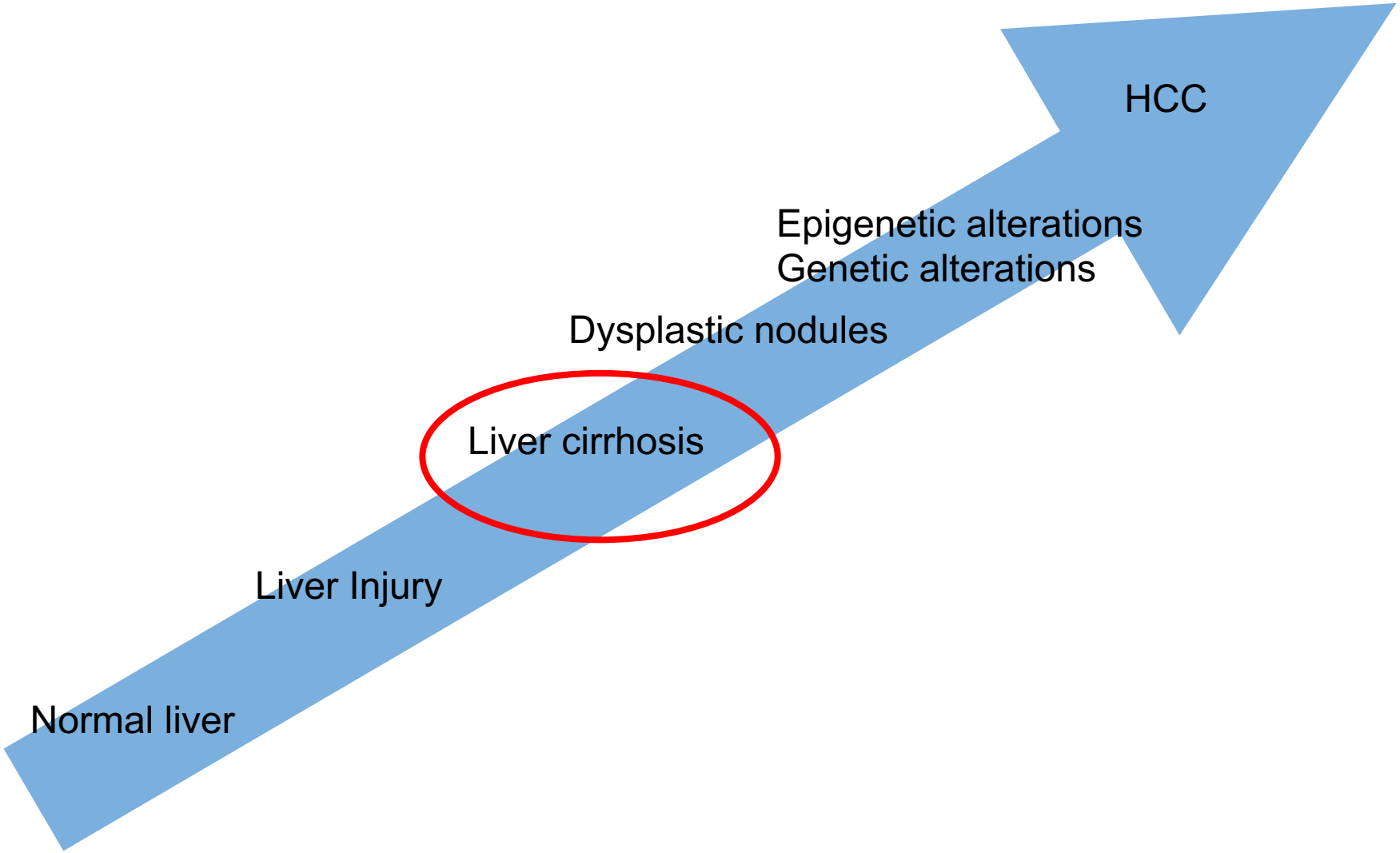


Adapted from Wang SH, et al. *Cancers* 2020

HCC: hepatocellular carcinoma

Development of Hepatocellular Carcinoma II

After development of cirrhosis



Recommendations for Hepatocellular Cancer (HCC) Screening

Screening consists of ultrasound examination with or without AFP every 6 months

Advanced fibrosis

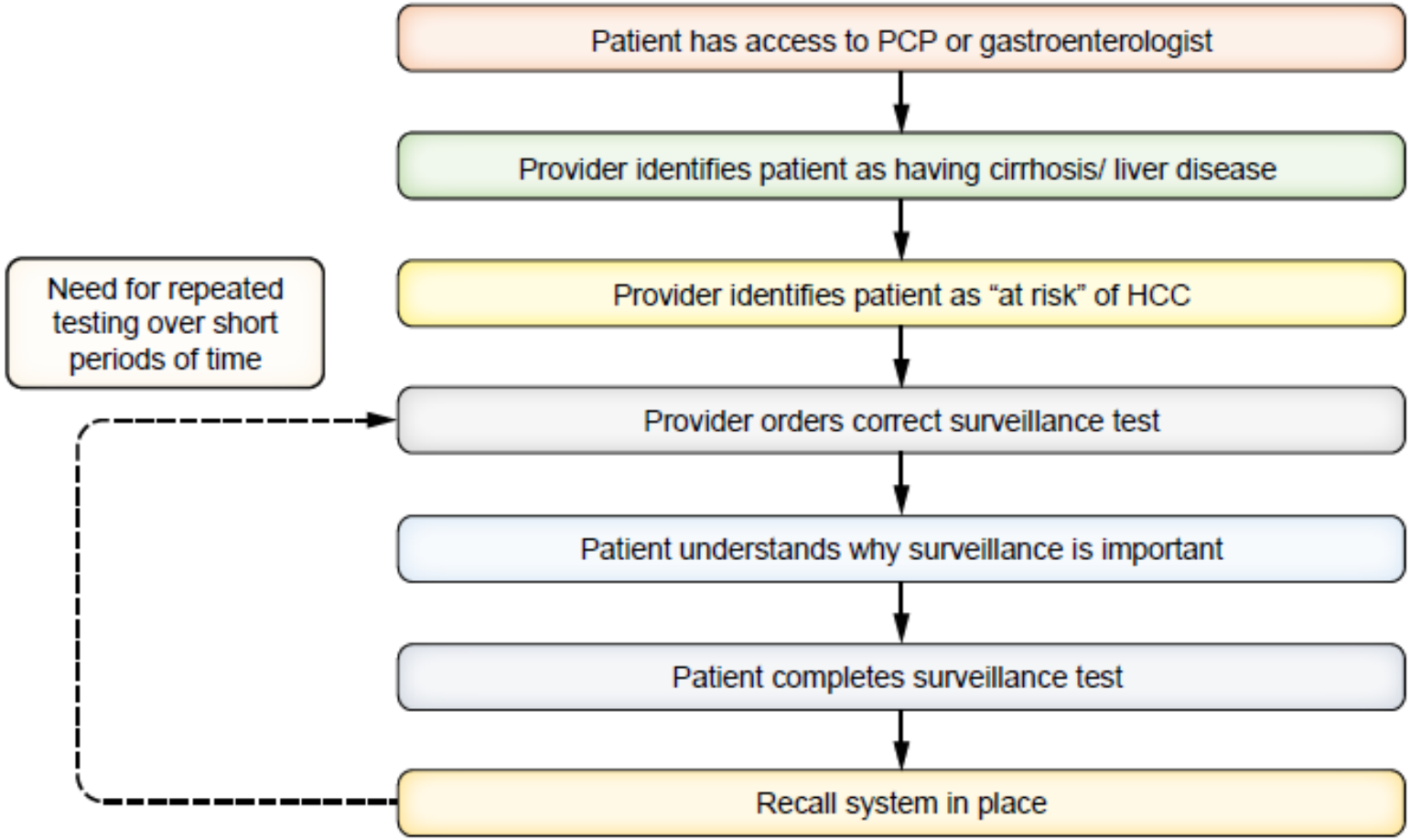
- Patients with bridging fibrosis and/or cirrhosis

Hepatitis B without cirrhosis

- Active hepatitis (elevated serum alanine aminotransferase [ALT] and/or high viral load)
- Family history of HCC
- Africans and African Americans
- Asian males over 40 years of age
- Asian females over 50 years of age

Terrault NA, et al. *Hepatology.* 2018; EASL *J Hepatol* 2018; Kanwal F, Singal AG. *Gastroenterol* 2019.

Vulnerable points in HCC surveillance cascade that can contribute to surveillance underuse

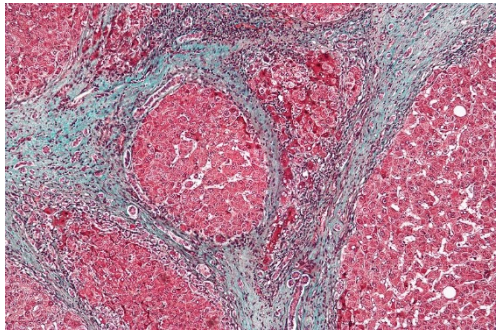


Singal AG, et al. *J Hepatol*. 2023

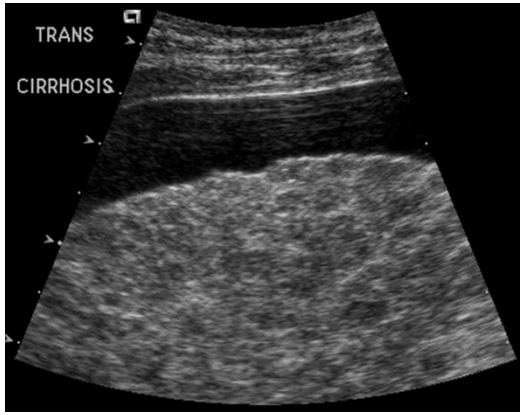
What is Cirrhosis?

- Cirrhosis is a condition in which the liver slowly deteriorates and malfunctions due to chronic injury
- Fibrosis can lead to increased portal pressures and manifestations of portal hypertension

- Cirrhosis can result from:
  - Alcohol-related liver disease
  - Chronic hepatitis C
  - Chronic hepatitis B
  - Chronic hepatitis B and D
  - Metabolic fatty liver disease
  - Autoimmune hepatitis
  - Drugs, toxins, and infections



Histology
Trichrome stain

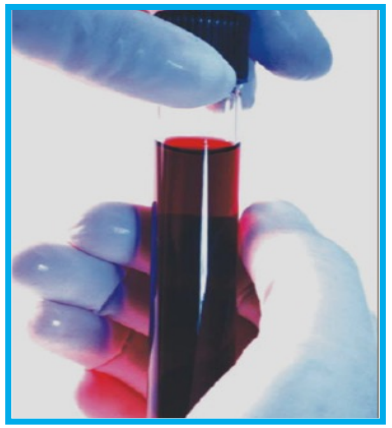


Abdominal ultrasound

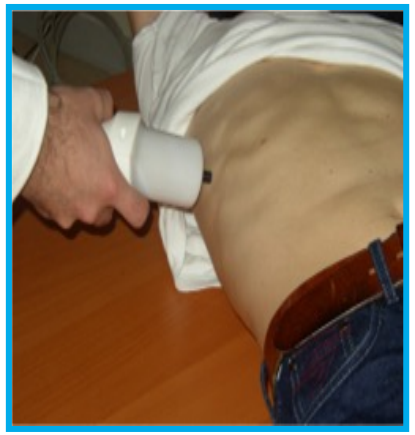
Trichrome stain micrograph from http://en.wikipedia.org/wiki/Cirrhosis. Accessed January 2014; WileyOnlineLiberary. Accessed May 2023

Diagnosing Cirrhosis

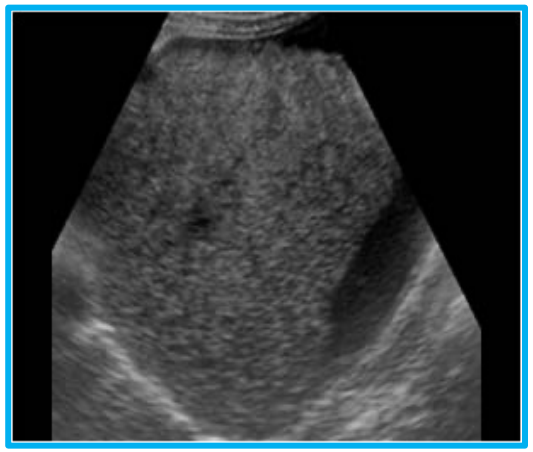
Liver Biopsy



Blood work



Elastography



Routine Imaging

Physical Examination

Classification of Cirrhosis Severity Determinants for Child-Turcotte-Pugh (CTP)

	Points		
	1	2	3
Encephalopathy	None	Grade 1 - 2 (or precipitant-induced)	Grade 3 - 4 (or chronic)
Ascites	None	Mild/Moderate (diuretic-responsive)	Severe (diuretic-refractory)
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8 - 3.5	<2.8
Prothrombin Time (seconds prolonged)	<4	4-6	>6

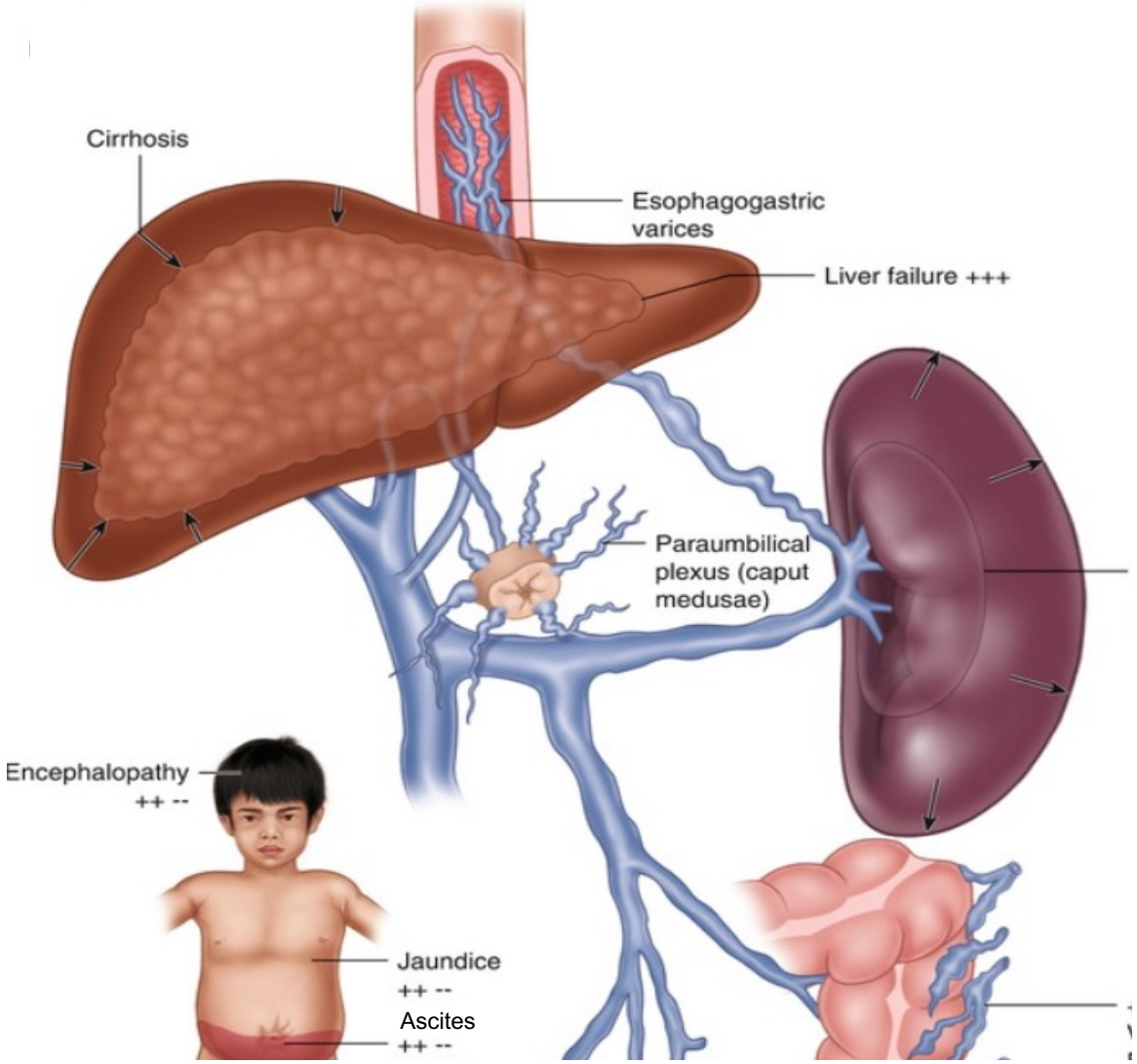
Total Numerical Score	Child-Pugh Class
5 - 6	A
7 - 9	B
10 - 15	C

Patients in Class A are considered “compensated”

Patients in Classes B and C are considered “decompensated”

Adapted from Garcia-Tsao G, et al. *Am J Gastroenterol.* 2009

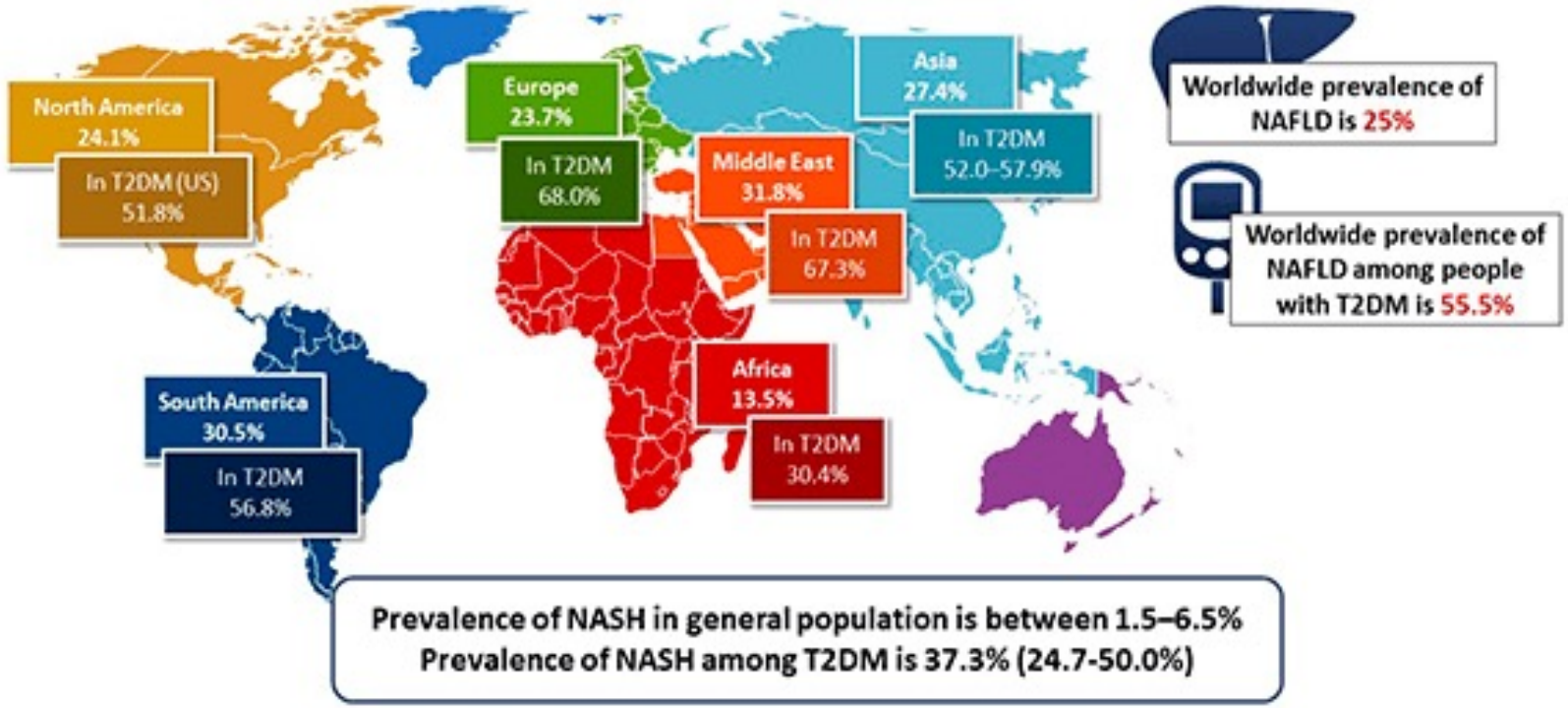
Clinical Manifestations of Portal Hypertension



Impact of Cirrhosis on the Management of Hepatocellular Carcinoma (HCC)

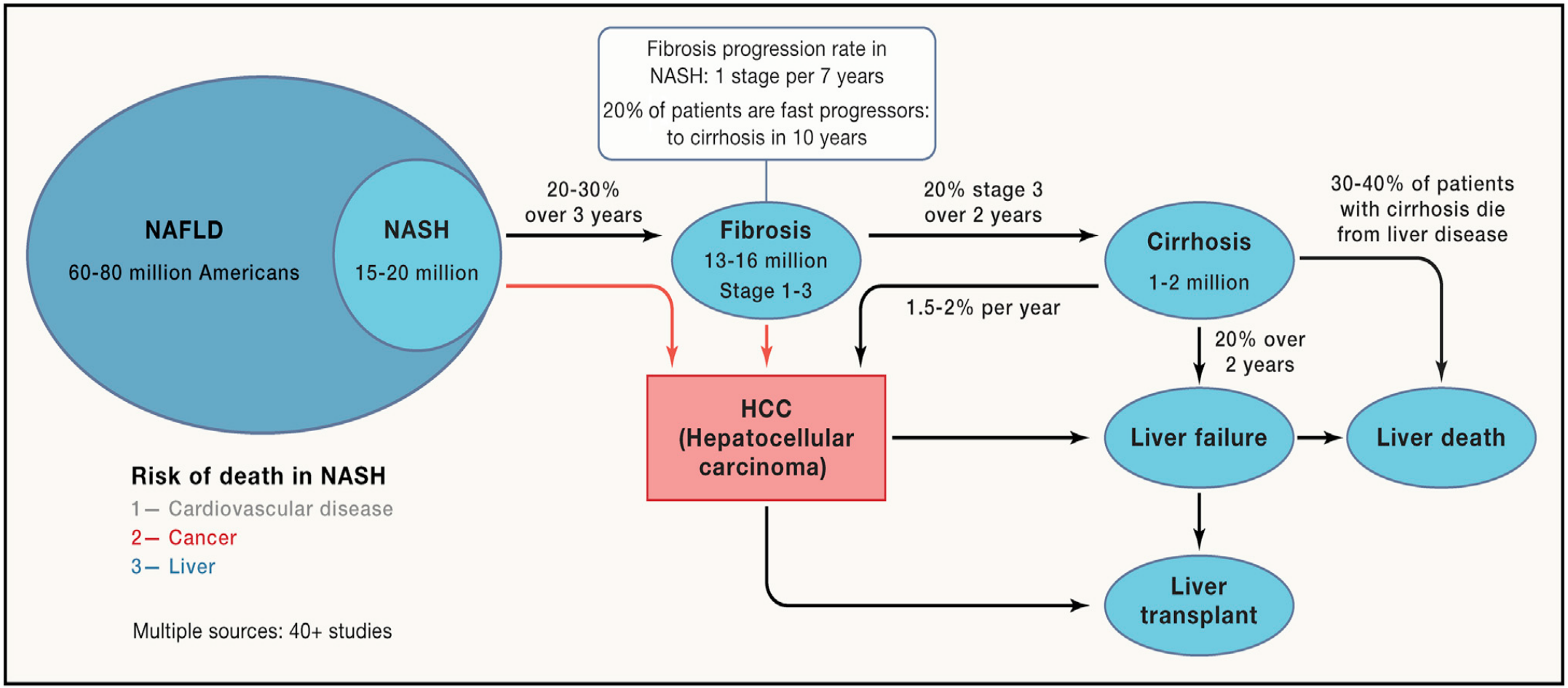
- Cirrhosis independently associated with survival
  - Dealing with two disorder: cirrhosis and HCC
- Certain causes of cirrhosis can reactivate during treatment of HCC
- Patients with cirrhosis can have unique complications not seen in patients with other cancers
  - Manifestations of portal hypertension
  - Drug toxicity
- Patients with cirrhosis require additional preparatory work prior to treatment of HCC
  - Variceal endoscopy

Worldwide Prevalence of Nonalcoholic Fatty Liver Disease



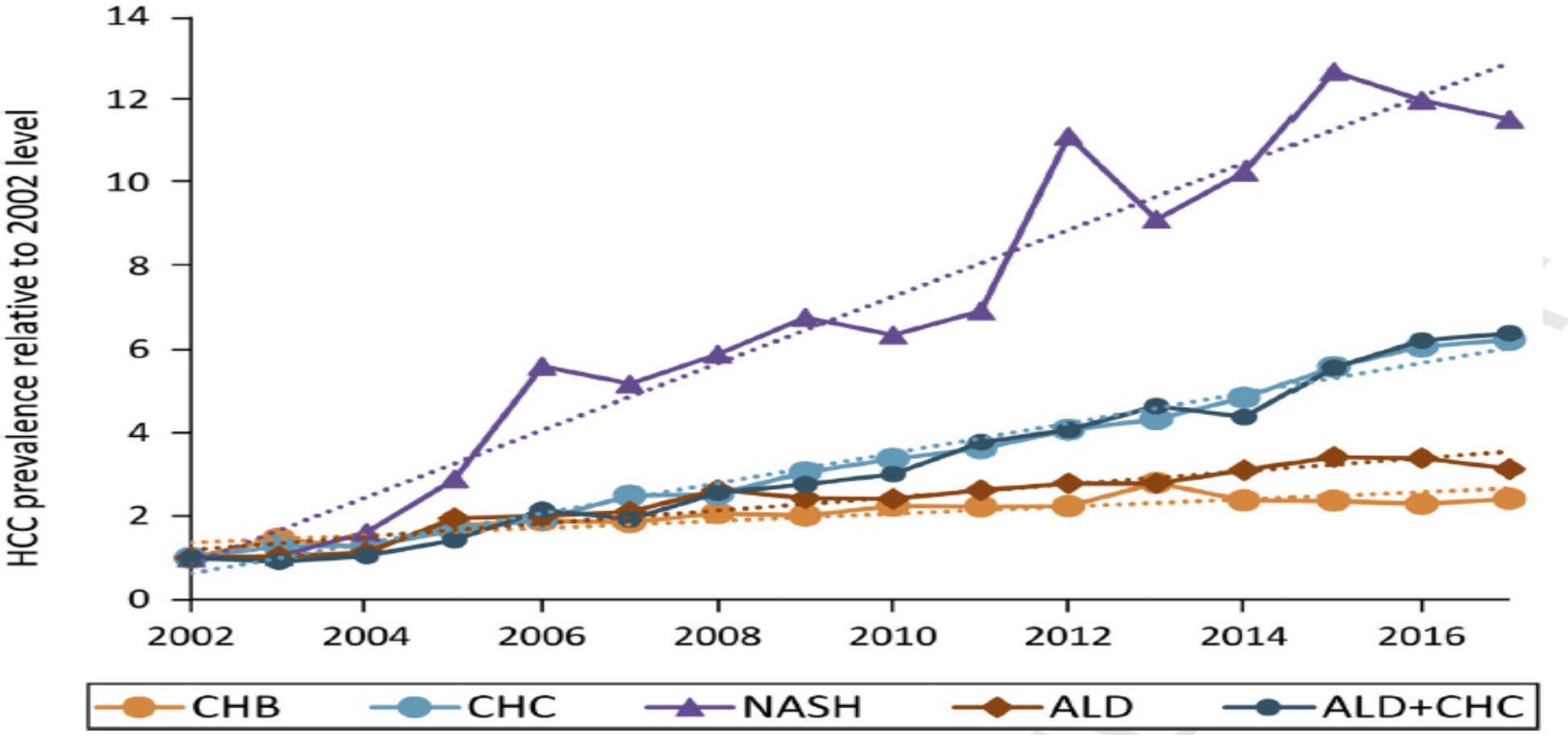
Younossi et al, *Nat Rev Gastroenterol Hepatol*, 2018

Natural history of Nonalcoholic Fatty Liver Disease



Loomba R, et al. *Cell*. 2021

Prevalence of Hepatocellular Carcinoma in Waitlisted Candidates by Etiology



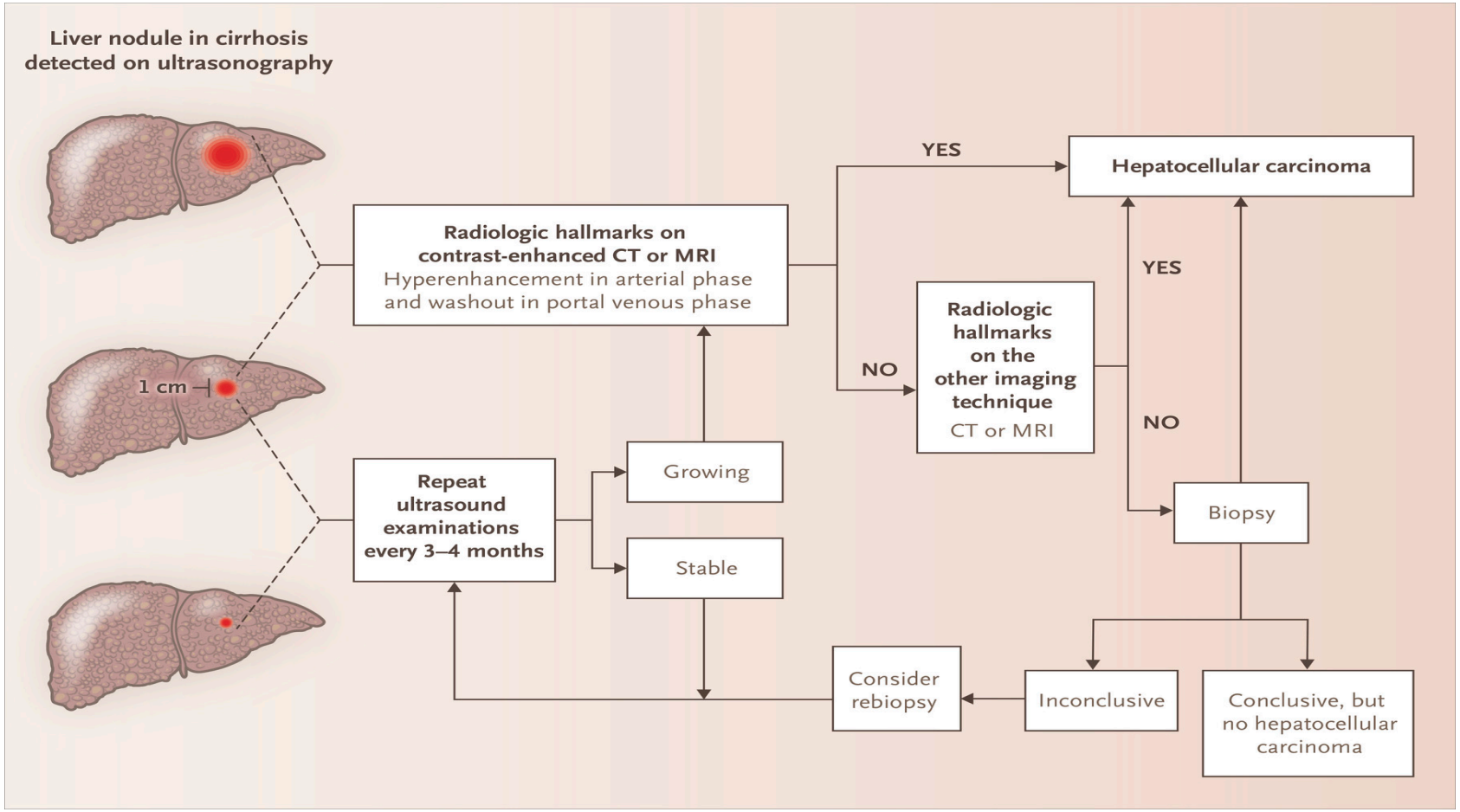
Younossi Z, et al. *Clin Gastroenterol Hepatol.* 2018

Diagnostic Algorithm for a Liver Nodule in a Patient with Cirrhosis

Screening for liver cancer:

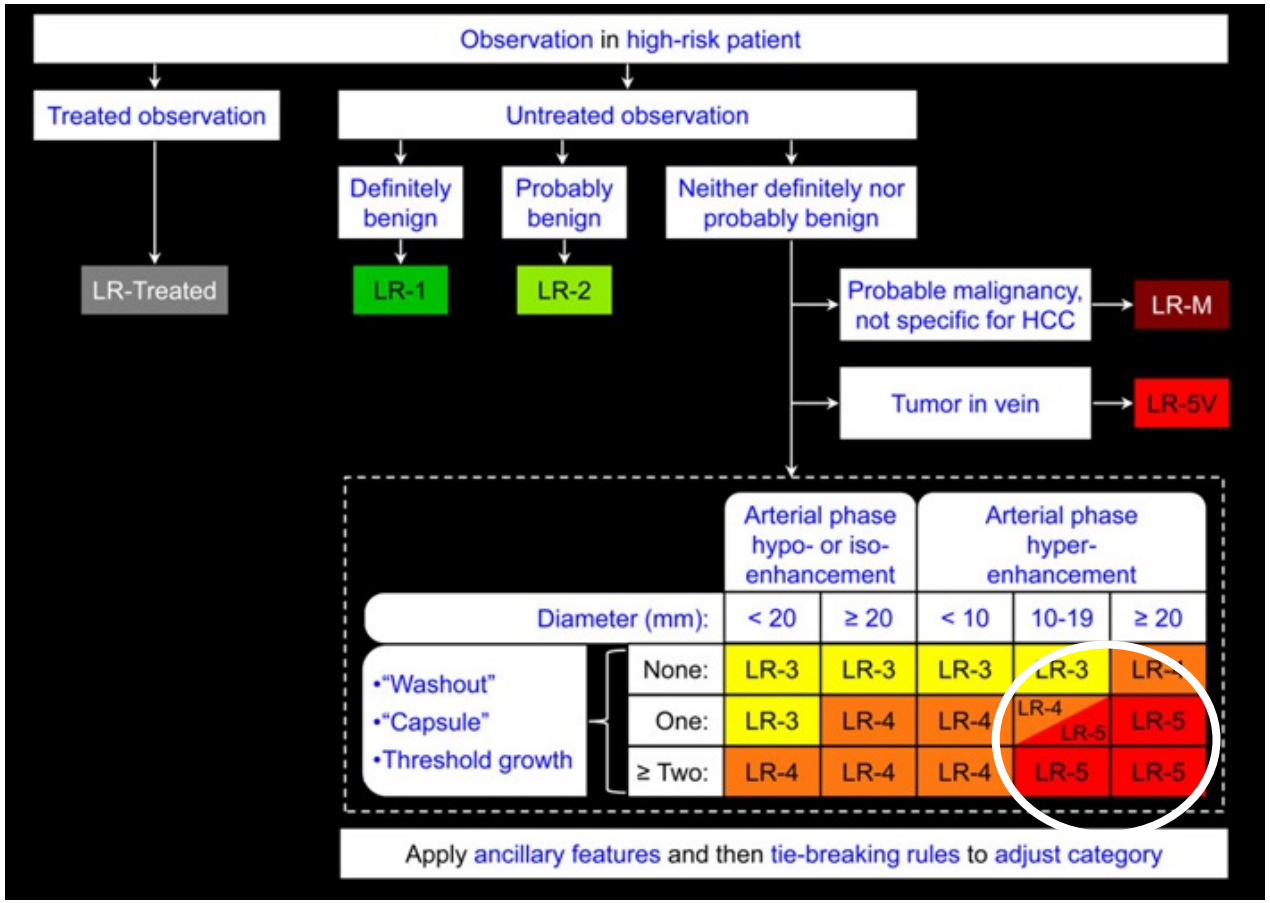
Every 6 months

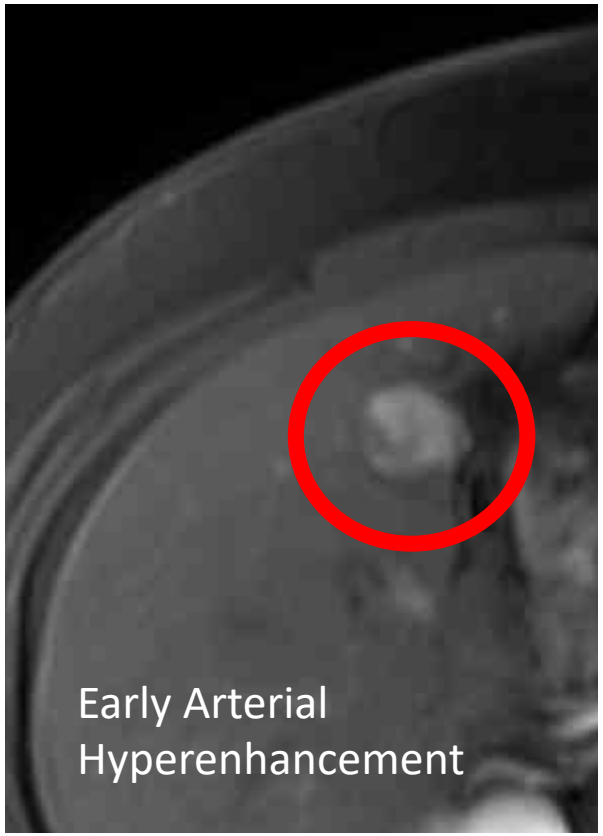
- Abdominal ultrasound
- Alpha-fetoprotein (AFP)



Villanueva A, *N Engl J Med* 2019.

Diagnosis of Hepatocellular Carcinoma Generally Made from CT and/or MRI imaging





Mitchell DG, et al. *Hepatol* 2015

Clinical Algorithm for the Management of Hepatocellular Carcinoma (HCC)

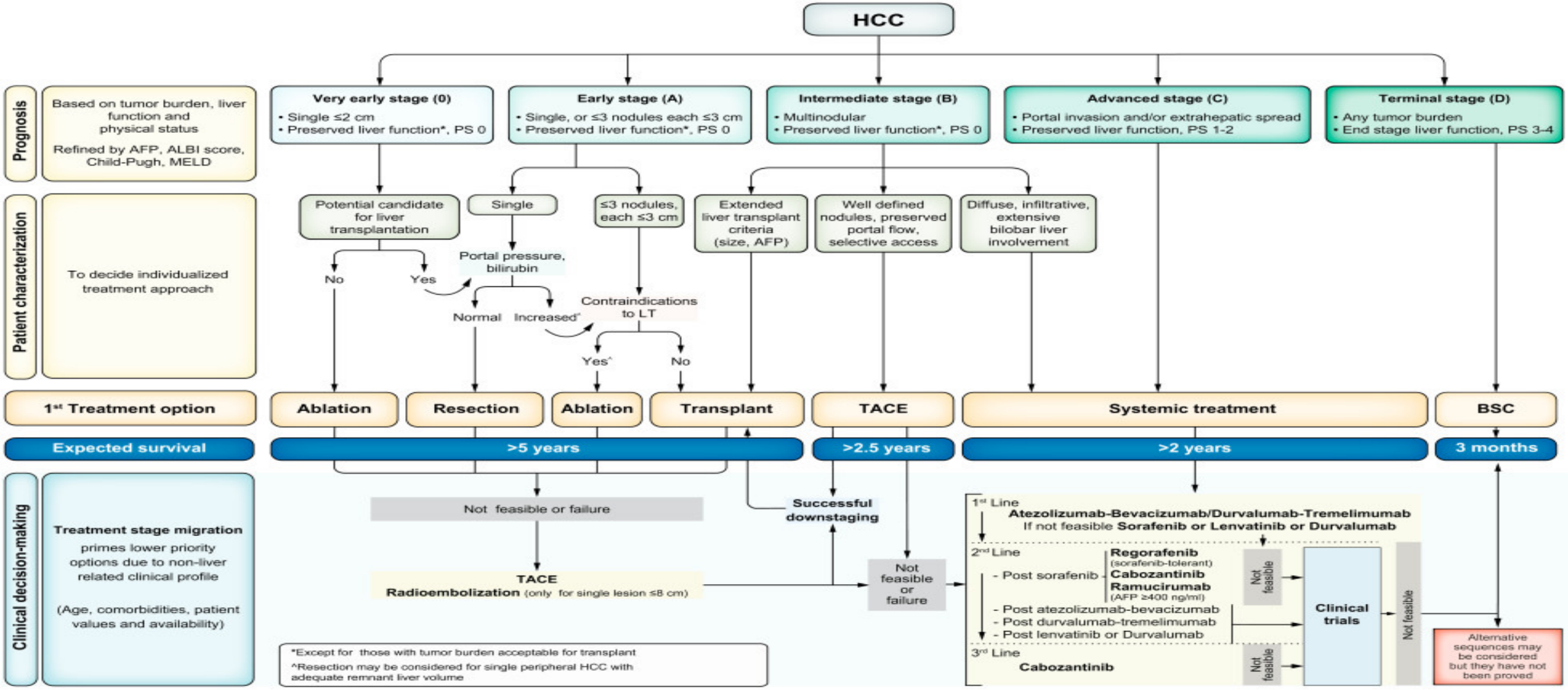
Approach to Management of HCC depends on:

1) Liver disease severity

2) Patient functional status

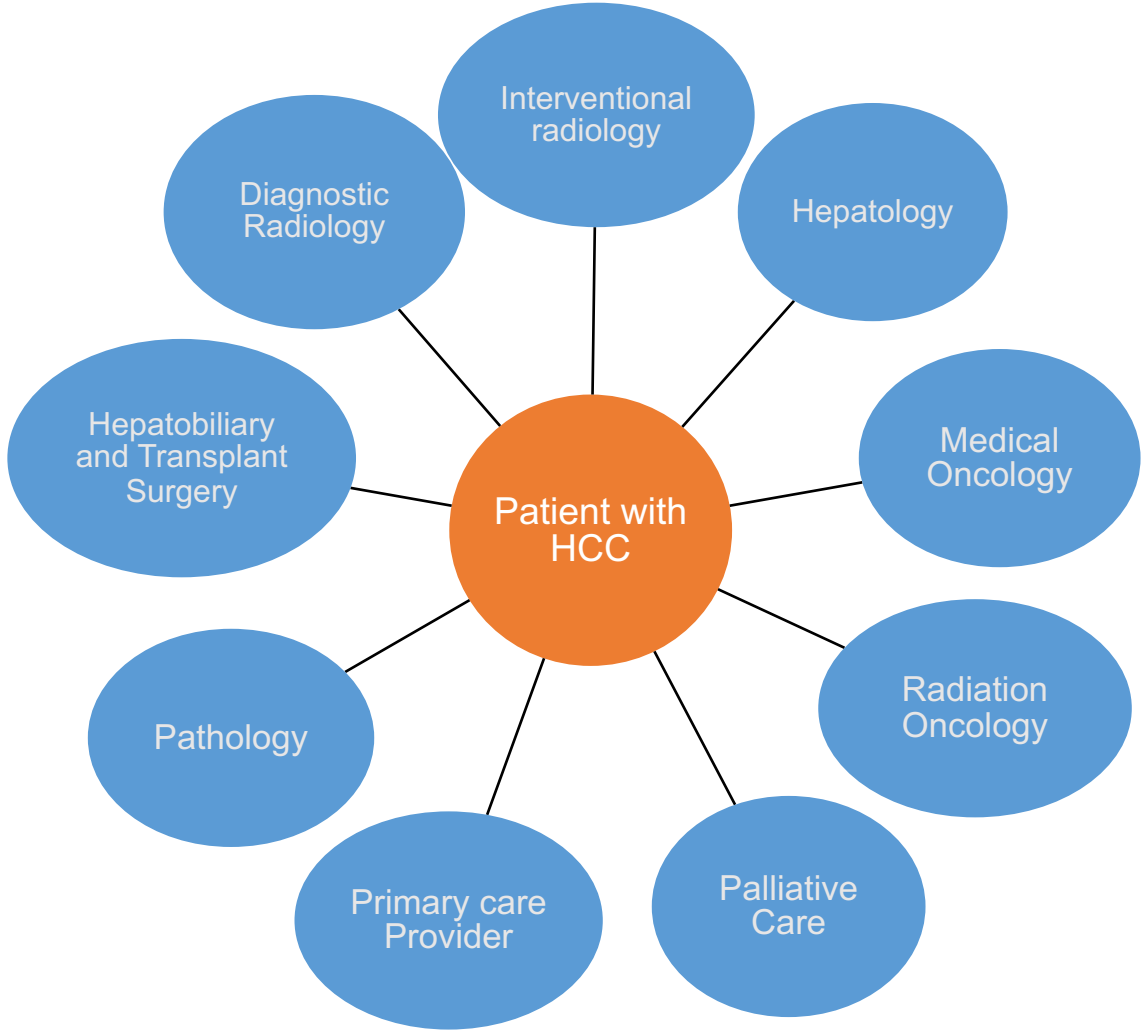
3) Tumor burden, including metastasis

Barcelona clinic liver cancer (BCLC) staging and treatment strategy in 2022



Reig M, et al. *J of Hepatol* 2022

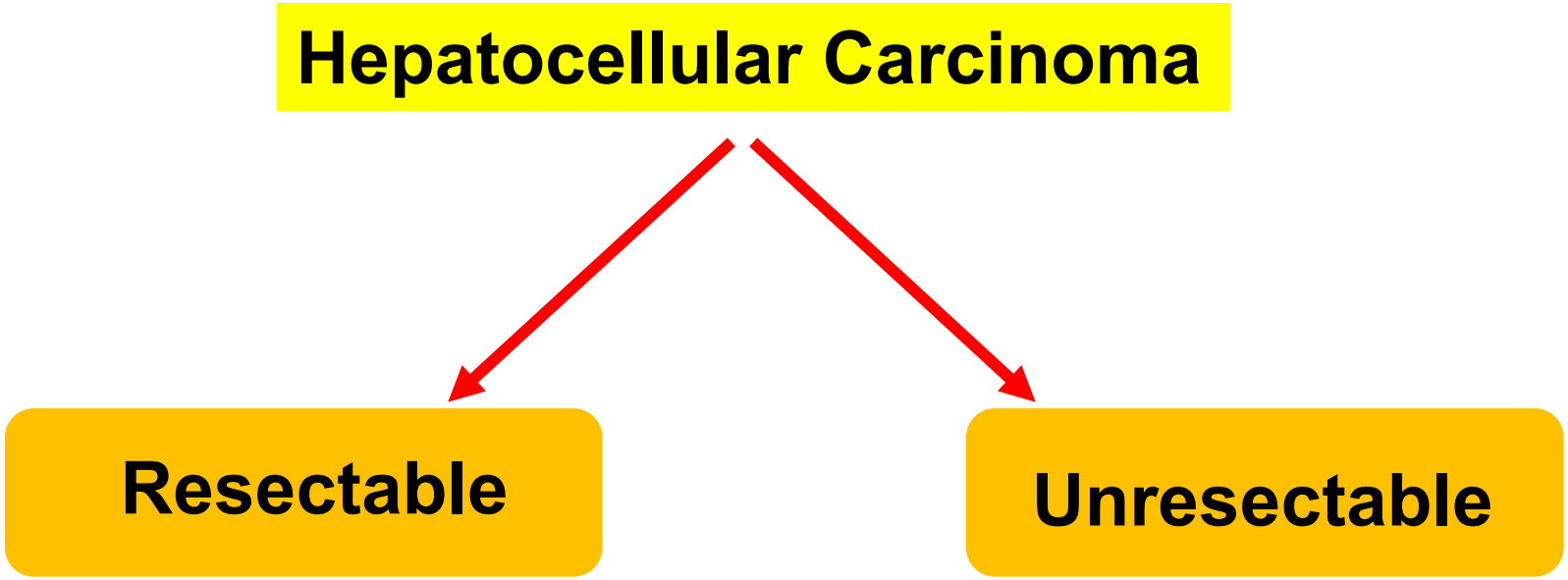
Multidisciplinary Team Is Important to Determine Course of Therapy for Patients with Hepatocellular Carcinoma



HCC ~ Hepatocellular carcinoma

- **Considerations when choosing appropriate therapy**
  - Is curative approach possible
  - Degree of synthetic dysfunction
  - Number and size of lesions
  - Location of lesions (e.g. number of segments involved)
  - Portal vein thrombosis
  - Is this person a liver transplant candidate
  - ECOG Performance Status
  - Social situation

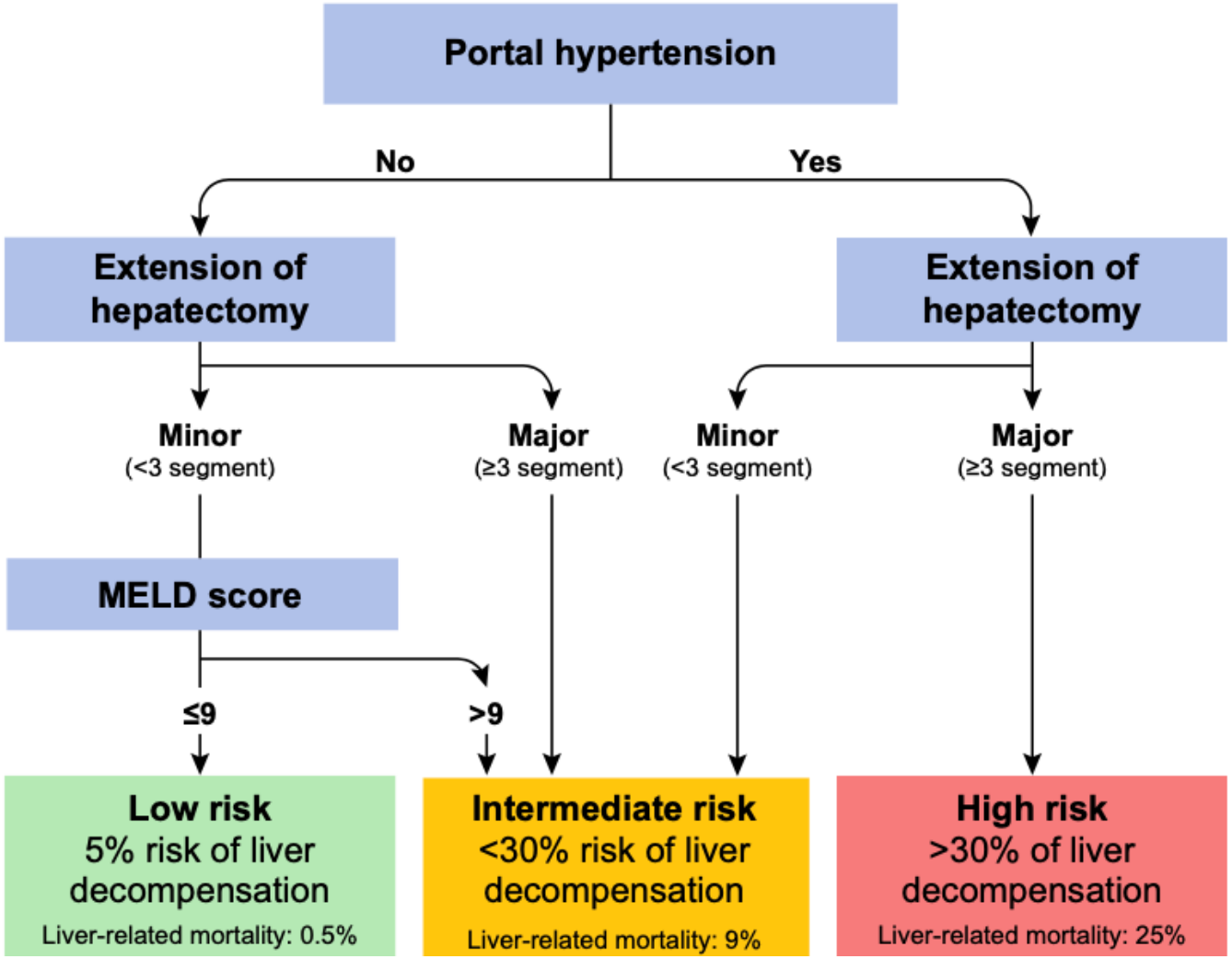
Generalized Treatment Approach to Hepatocellular Carcinoma



- Surgery

- Liver Transplantation
- Liver-directed therapies
- Systemic therapies
- Supportive care

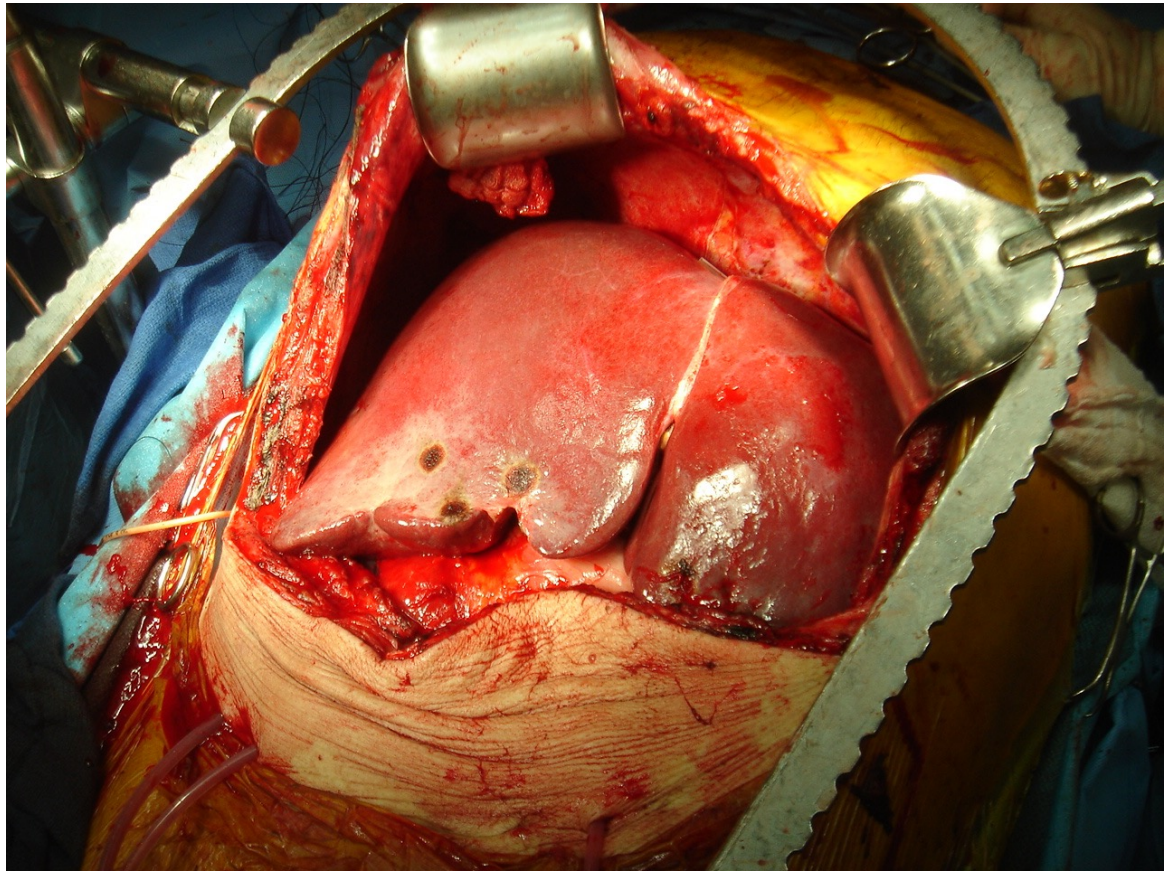
Role of Surgery in Patients with Hepatocellular Carcinoma



Role of Liver Transplantation

Transplant Criteria

- Fulfill Milan Criteria (HCC <5 cm)
- No extra-hepatic malignancy
- No vascular invasion
- No infiltrative tumor



Liver-Directed Therapies

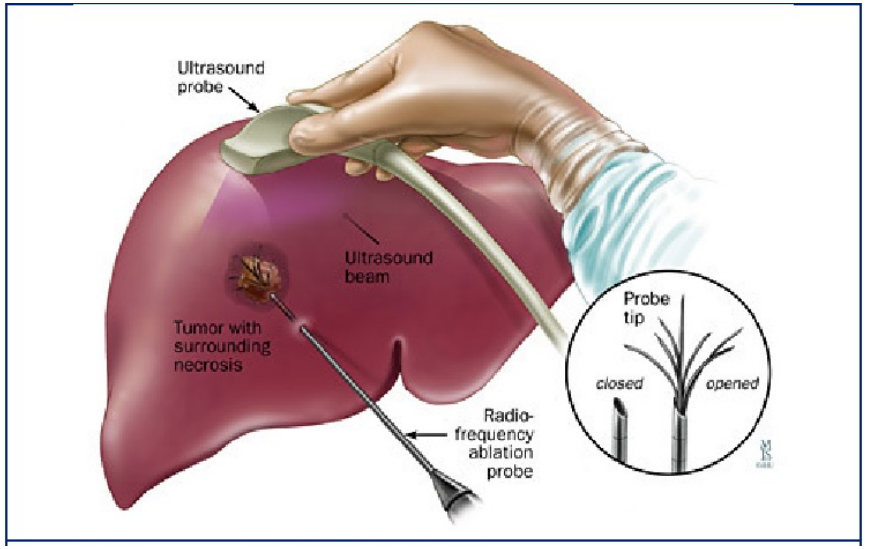
Procedure	Examples	Comments
Local Thermal Ablation	Radiofrequency ablation, Microwave ablation	• For small HCC • No nearby organs or vessels • Child-Pugh A
Transarterial Embolization	Transarterial chemoembolization (TACE), Transarterial radioembolization (Y90)	• TACE not suitable if PVT • Large HCC ok

Ablative Therapies

- Radiofrequency thermal energy applied to the tumor (percutaneous or laparoscopically)
  - Limited by adjacent structures

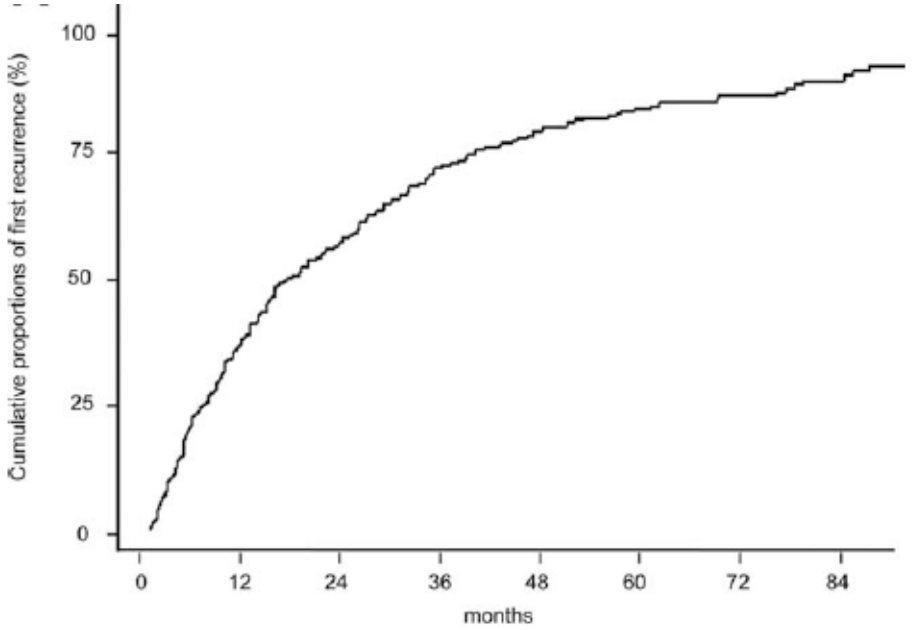
- For patients who do not meet resection criteria and are Child-Pugh A or Child-Pugh B
  - Best for tumors less than 4cm

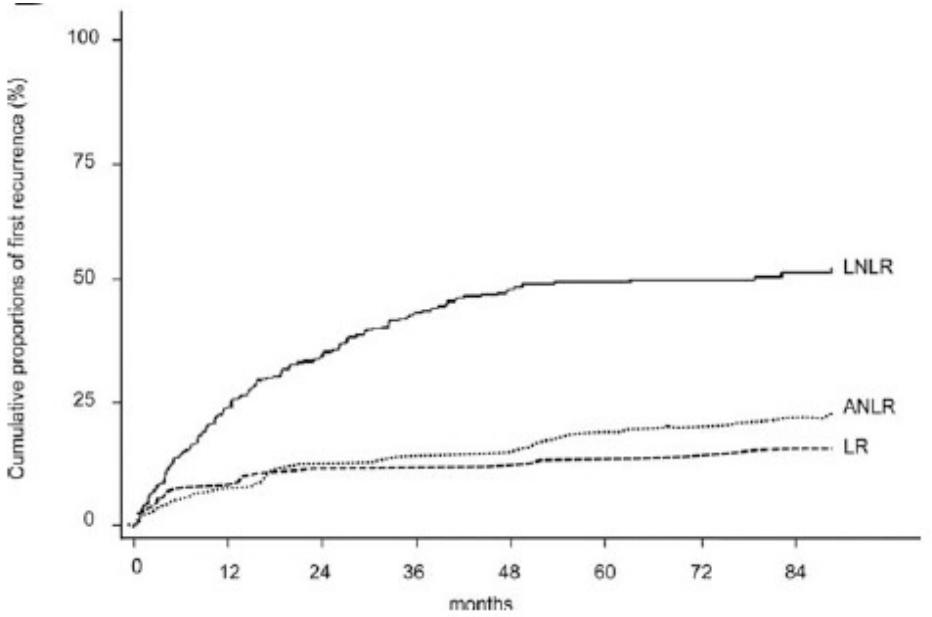
Diameter (cm)	Complete local control
<2.5	90%
2.5-3.5	70-90%
3.5-5.0	50-70%
>5.0	<50%



Livraghi T, et al. *Radiology.* 1999; Lencioni RA, et al. *Radiology.* 2003; Lin SM, et al. *Gastroenterology.* 2004; Hamilton JP. *Hopkins Proceedings* 2013

Recurrence of HCC after RFA

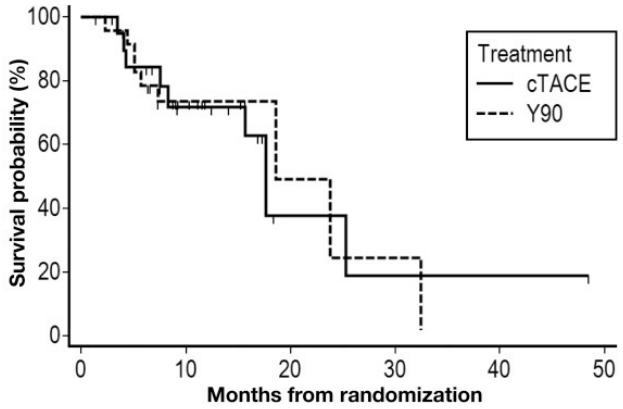




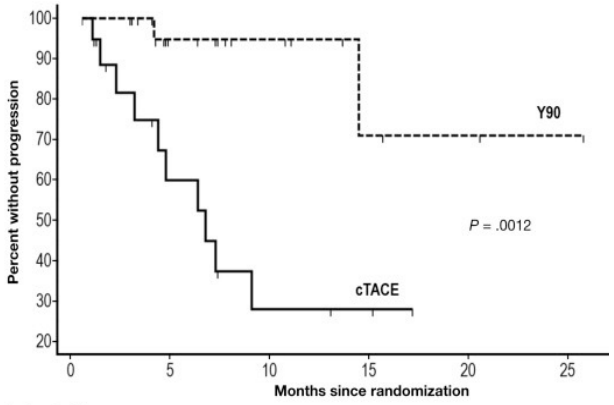
- Overall recurrence rate 70% at 3 years, 81% at 5 years
- Local recurrence (LR) 13% at 5 years
- Nonlocal recurrence (NLR) 50% at 5 years
- Advanced nonlocal recurrence (ANLR) 19.2%

Rossi et al, *Hepatol* 2011

PREMIERE Phase II Trial: TACE vs. TARE



Median survival: 17.7 vs. 18.6 mo
(p=0.99)



TTP: >26 vs.6.8 months
(HR 0.12, 95%CI 0.03-0.56)

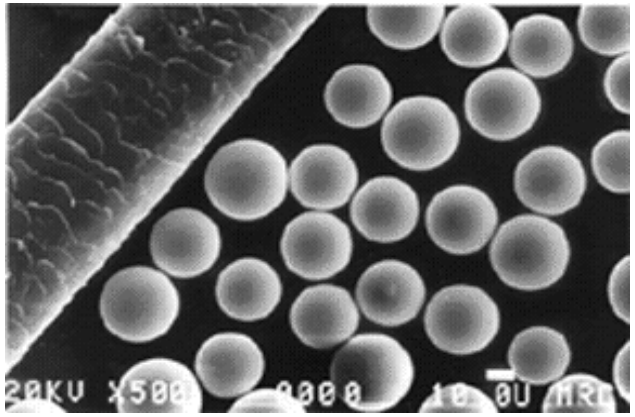
TACE, transarterial chemoembolization; TARE, transarterial radioembolization (Y90); TTP, Time to Progression

Salem et al *Gastroenterol* 2016; Siemens Accessed May 2023

^{90}Yttrium Microspheres

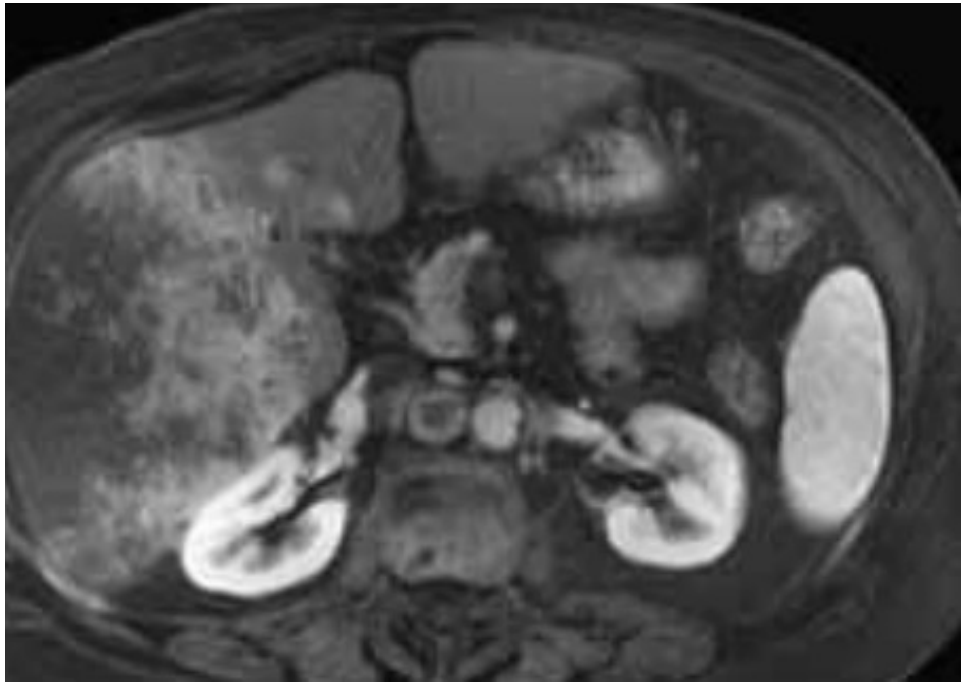
- Glass or resin available
- 10-60 microns in size
- 100% pure beta emitter
- Physical half-life of 64.2 h: gone in 2 weeks
- Average tissue penetration range of 2.5 mm
- With delivery preferentially deposits in tumor tissue due to increased blood flow

- Exposure to radiation causes irreversible cell damage to epithelial, stromal, and endothelial cells
- This leads to compromised tumor growth
- Median time to response
  - 1.2 months for necrosis
  - 6 months for shrinkage
- New lesions elsewhere or within the primary lesion were not treated due to lack of arterialization

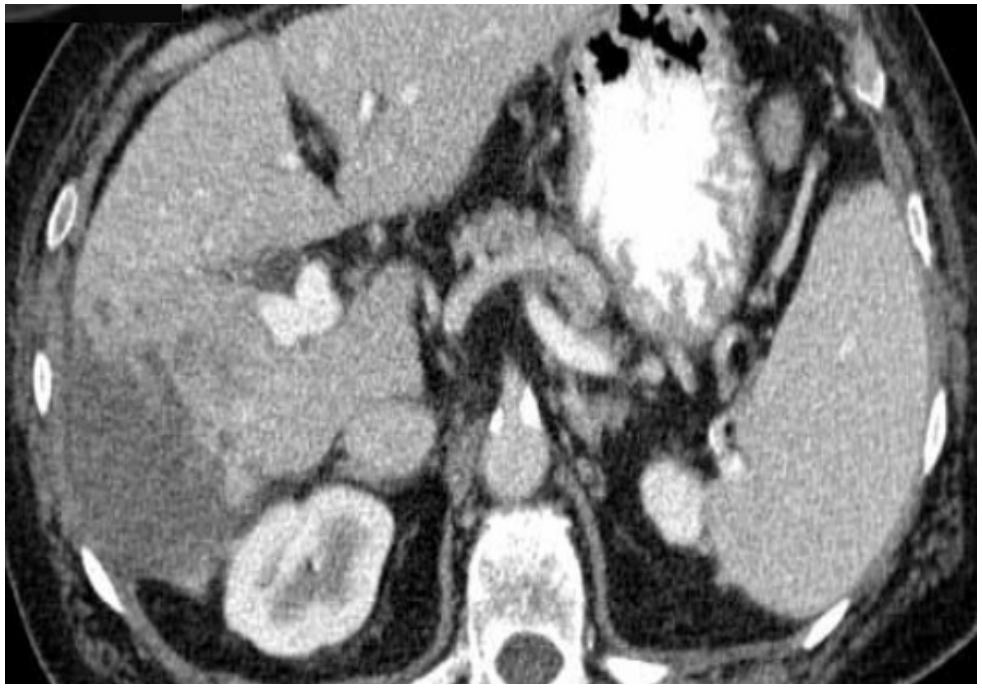


Case Study. Treatment of Hepatocellular Carcinoma with Y90

- 65 yo male with Hep C cirrhosis and huge infiltrative HCC
- Not a surgical candidate.
- Treated with lobar Y90



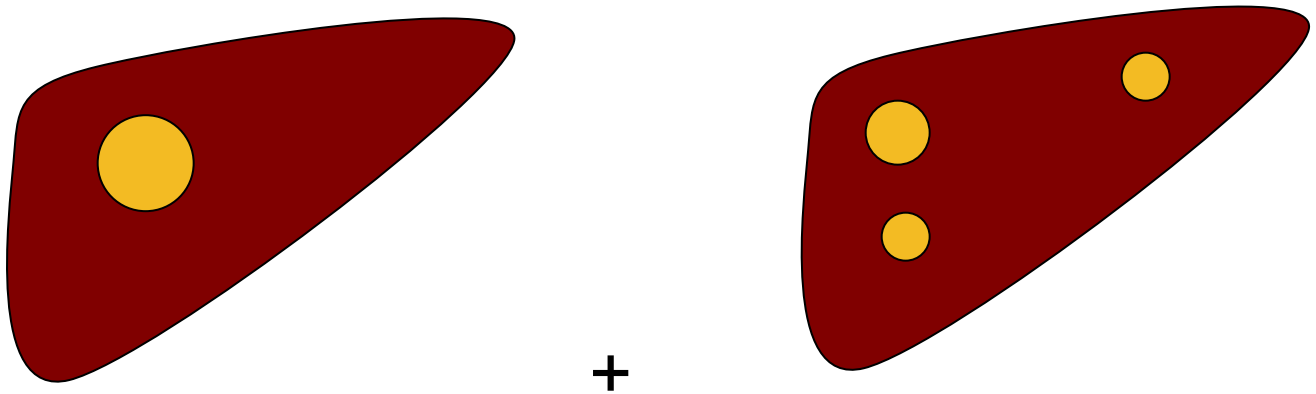
- 18 months s/p lobar Y90 – no residual viable tumor
- Left lobe growth allowing right lobe resection



MILAN Criteria for Hepatocellular Carcinoma

1 lesion ≤ 5 cm

2 to 3 lesions,
none >3 cm



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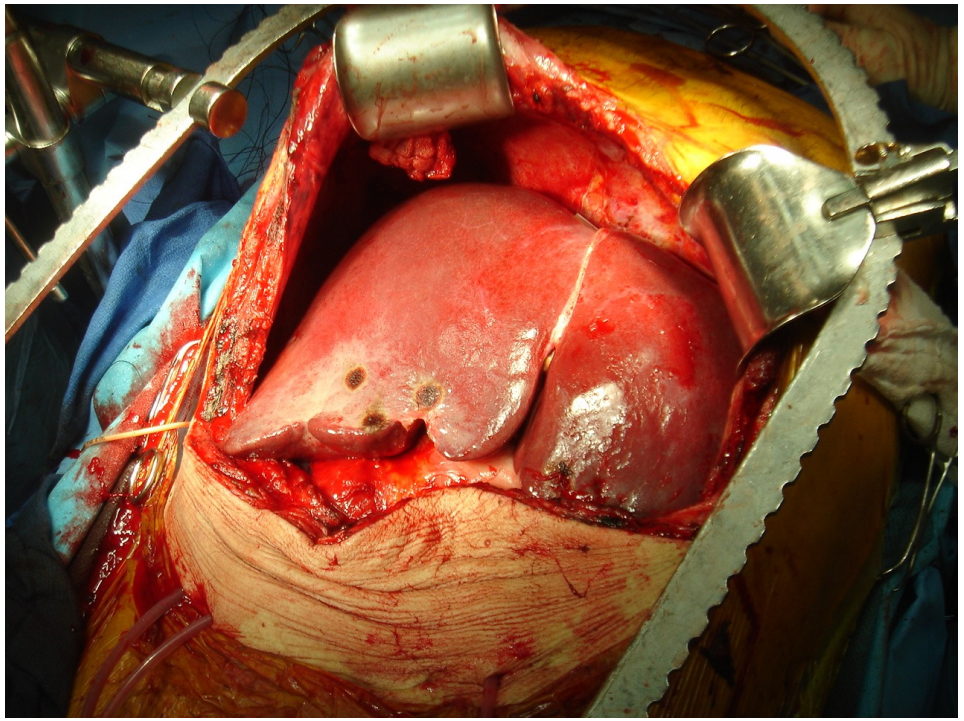
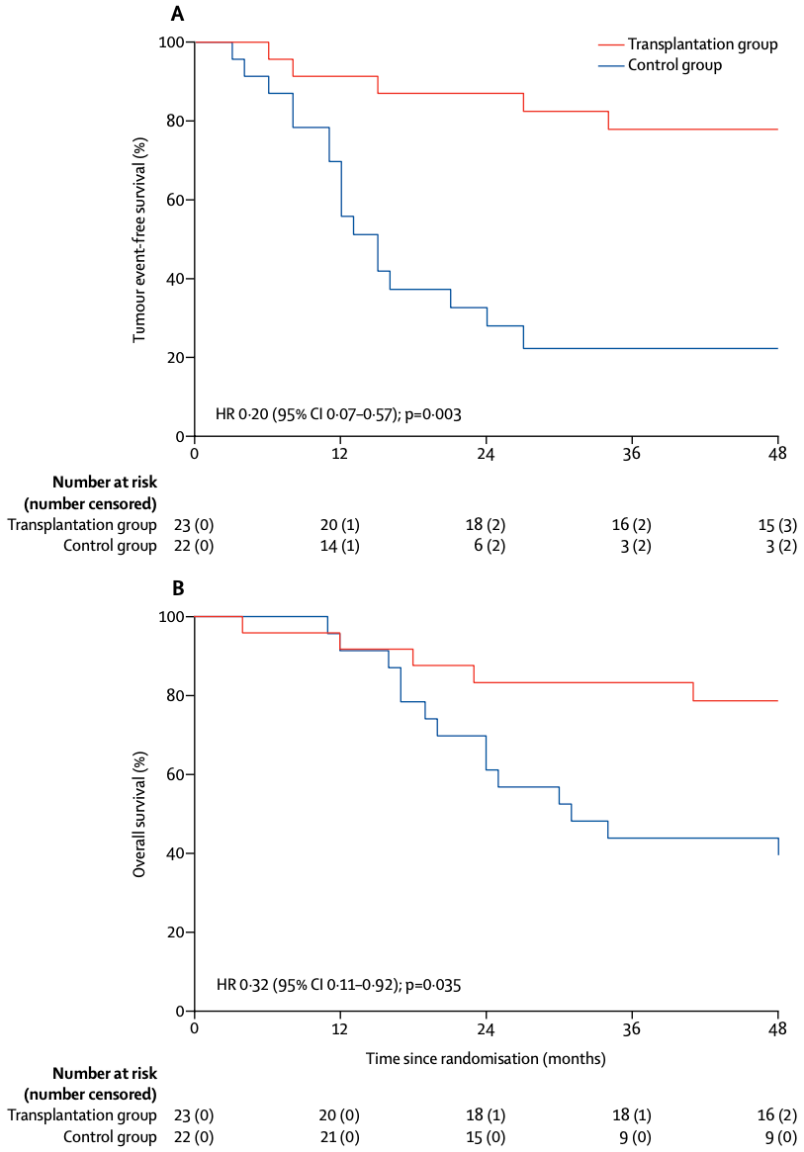
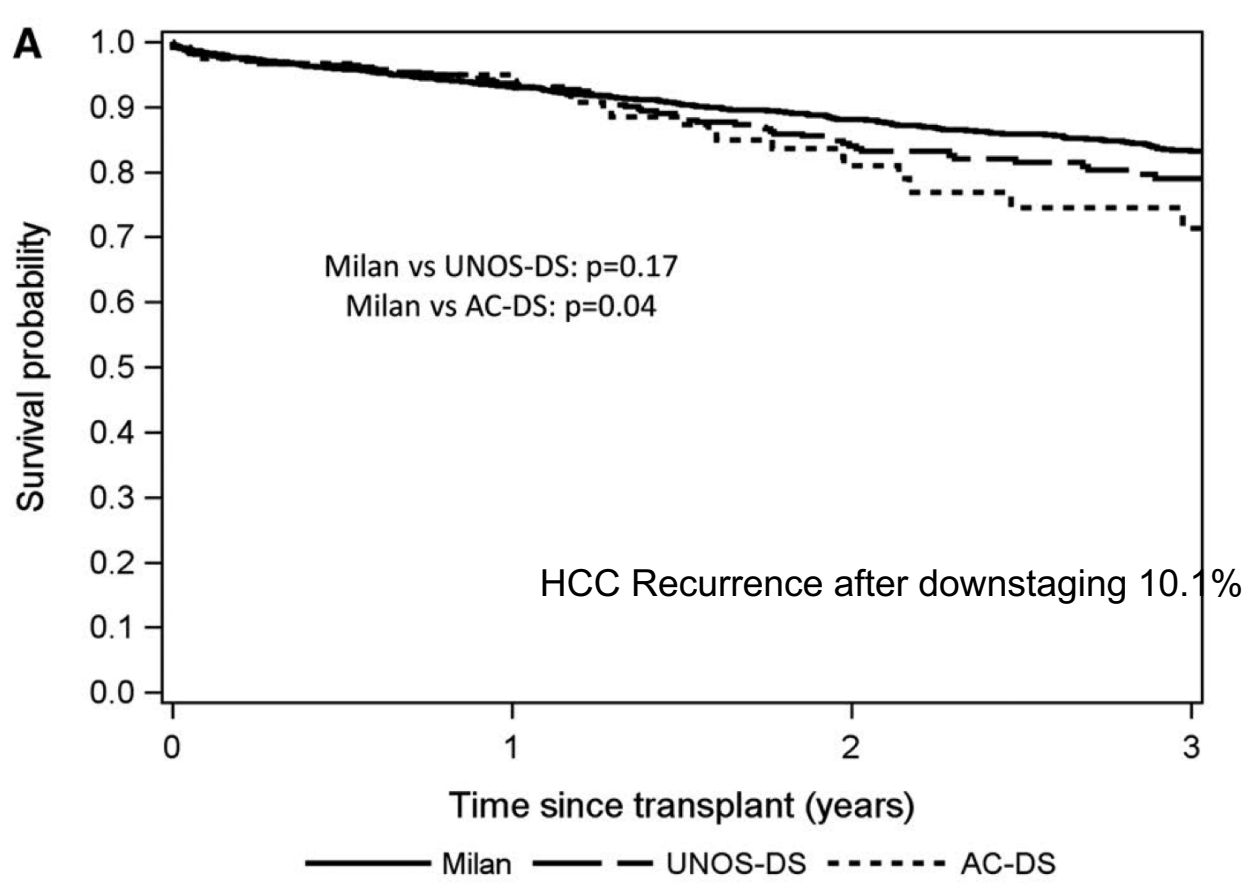
Absence of Macroscopic Vascular Invasion
Absence of Extra-hepatic Spread



Mazzaferri, et al. *N Engl J Med* 1996

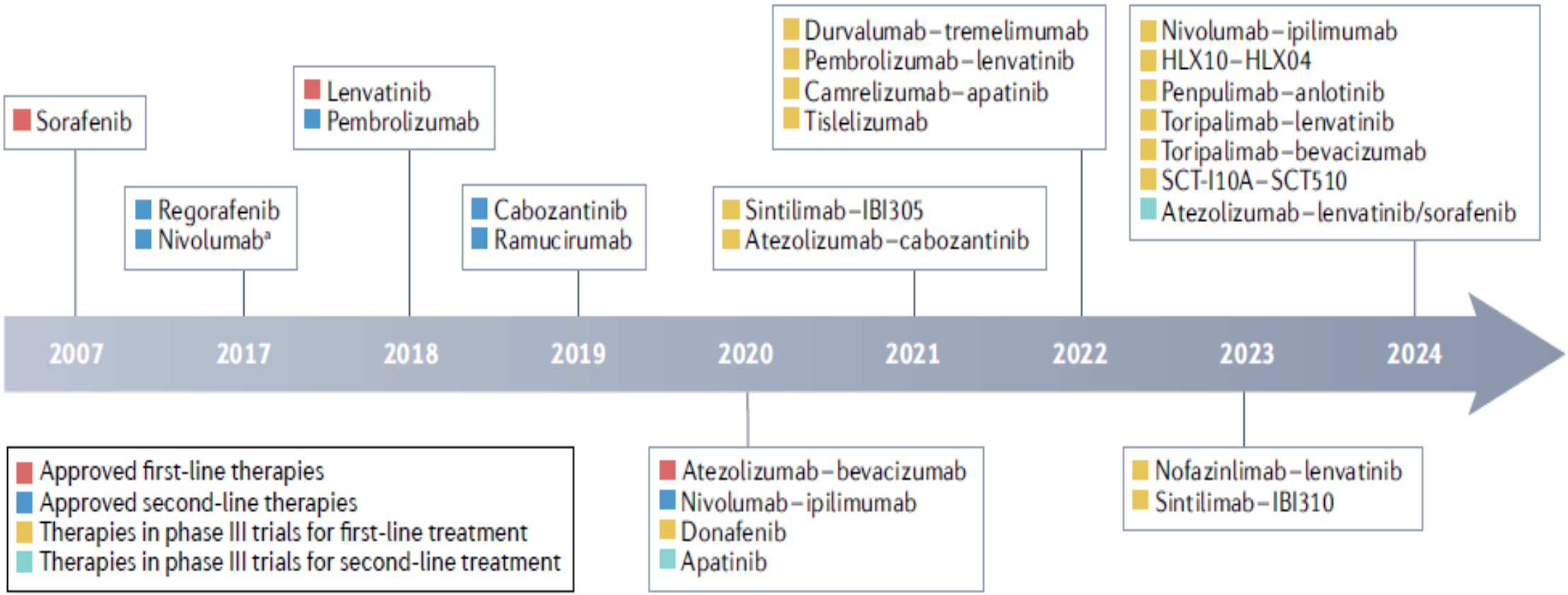
Role of Downstaging to Transplant





Mehta et al Hepatology 2019
Mazaffero Lancet Oncology 2020

Evolving Systemic Therapeutics for Advanced (Unresectable) HCC



Yang C. Et Al. Nature Reviews Gastroenterology & Hepatology. 2023

Available Systemic Therapies*

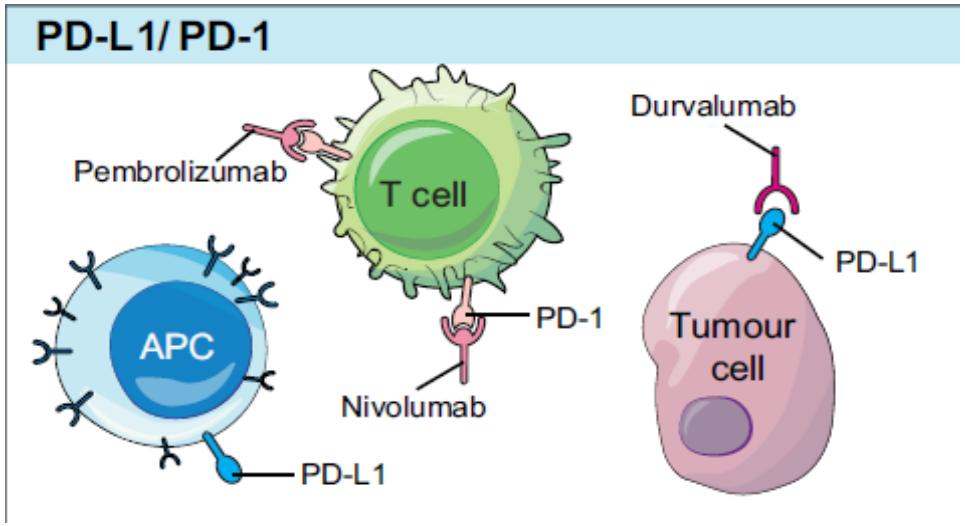
Sequence	Agent	Administration	Class
First Line	Sorafenib	Oral	Tyrosine Kinase Inhibitor
	Lenvatinib	Oral	VGEF Inhibitor
	Bevacizumab†	Injection	VGEF Inhibitor
	Atezolizumab†	Injection	PDL-1 Inhibitor
Second Line	Regorafenib	Oral	Tyrosine Kinase Inhibitor
	Cabozantinib	Oral	Tyrosine Kinase Inhibitor
	Nivolumab	Injection	PD-1 Inhibitor
	Pembrolizumab	Injection	PD-1 Inhibitor

*Choice of drug depend on severity of liver disease and co-morbidities

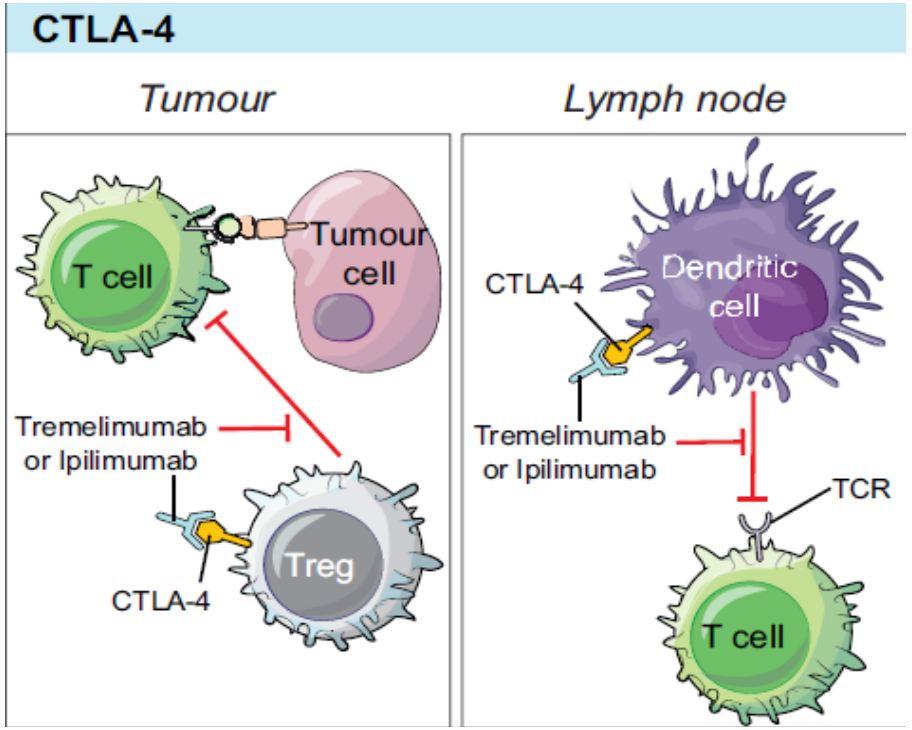
† Bevacizumab/Atezolizumab are used in combination

Immune Checkpoint Inhibitors
Mechanism of Action

PD-1 key for effector phase of immune response, expressed by CD8+ and CD4+ T cells and antigen presenting cells. Cancer cells expressing PD-L1 escape from immunosurveillance.

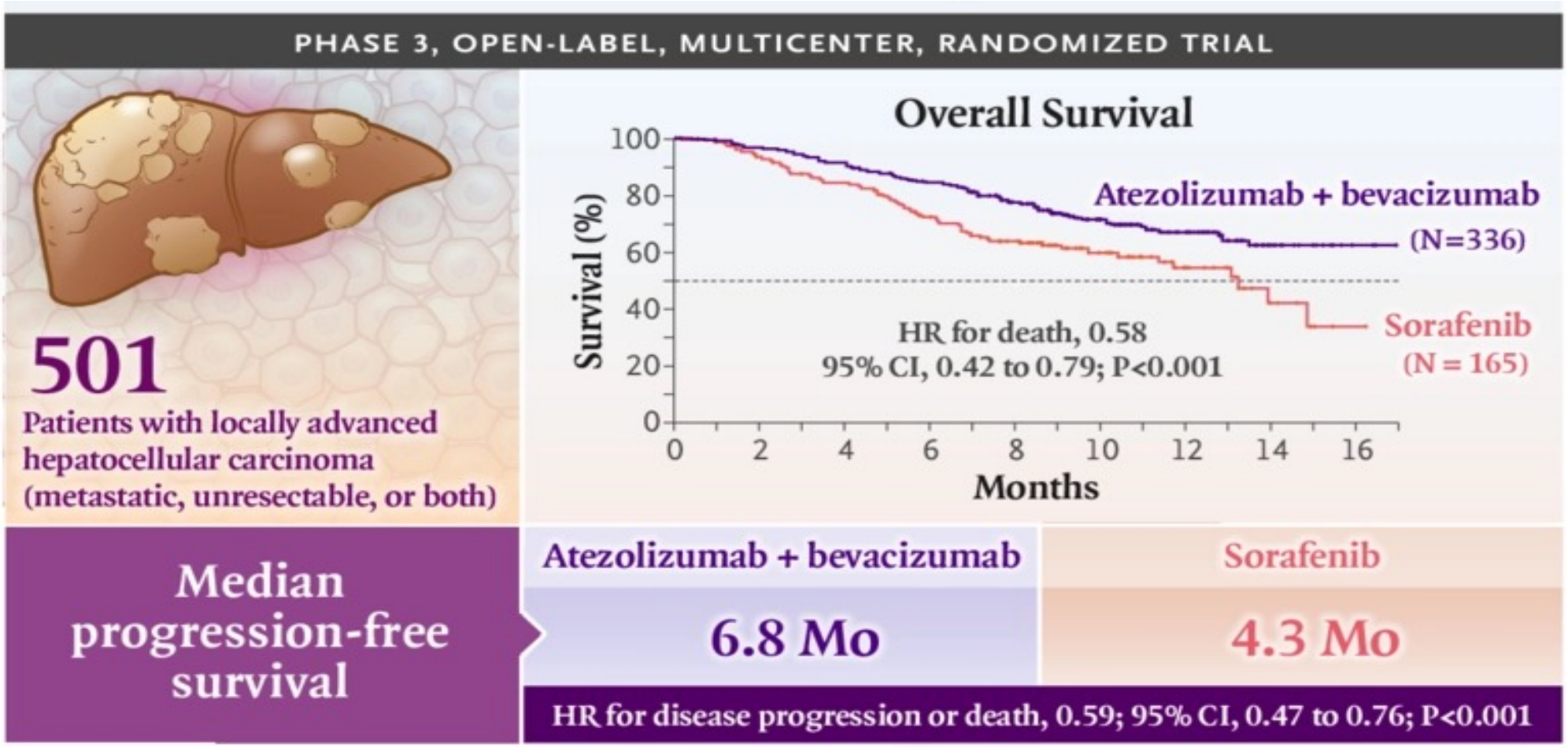


CTLA-4 necessary for activation of CD4+ T cells and Priming Phase of immune response. Also induces Treg activation and differentiation.



Greten and Sangro, *J Hepatol* 2017

Atezolizumab + Bevacizumab as First-Line Therapy for Hepatocellular Carcinoma



Finn R, et al. *N Engl J Med.* 2020

Conclusions

- Hepatocellular carcinoma (HCC) does not usually occur in a vacuum. Generally occurs in the setting of cirrhosis.
- Treatment of HCC has evolved tremendously over the past 20 years
- Coordinated care with gastroenterology/hepatology is essential for preparing and managing patients with cirrhosis in the treatment of HCC