Hepatocellular Carcinoma

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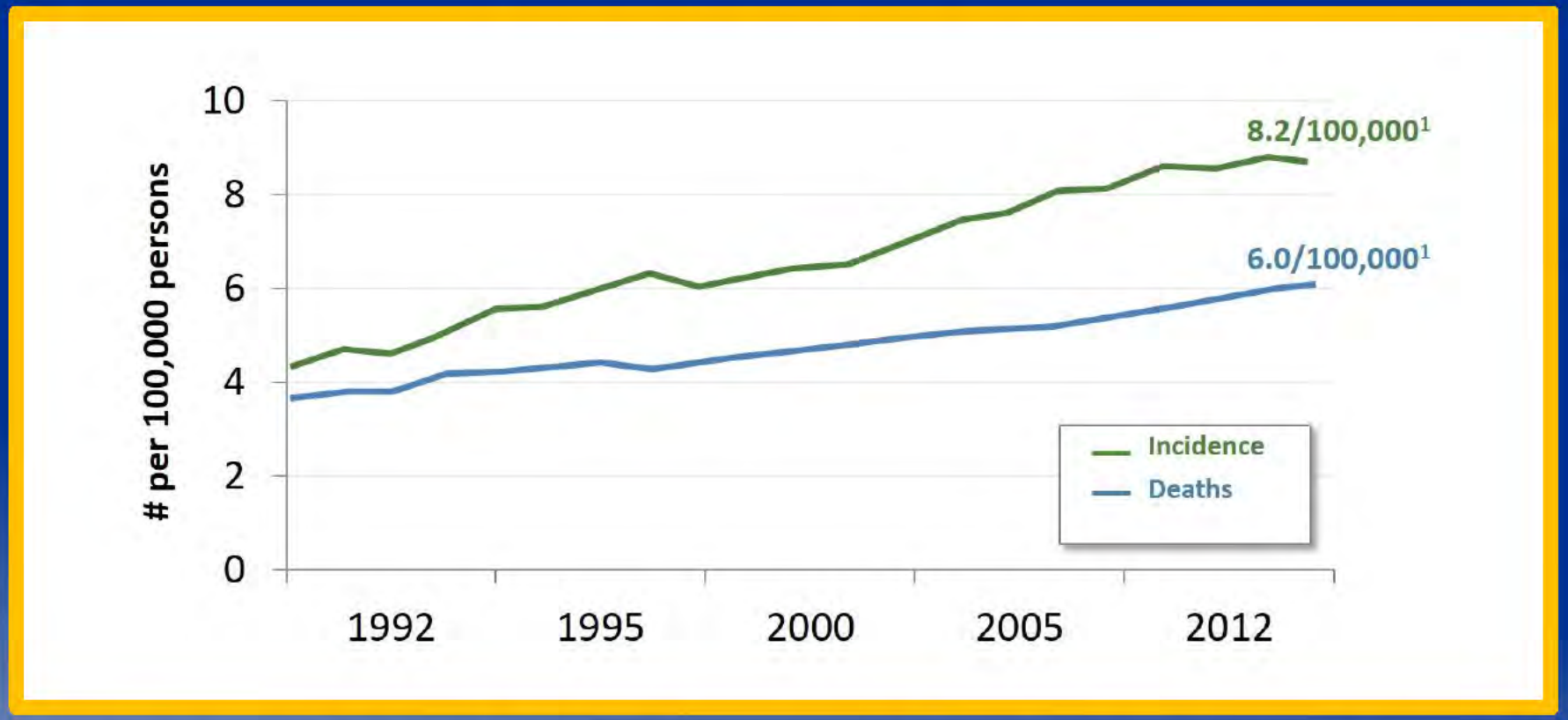
Hepatocellular Carcinoma

- Epidemiology
- Screening
- Diagnosis
- Staging
- Treatment

Epidemiology

Liver Cancer Incidence and Death Rates in the US



90% are HCC

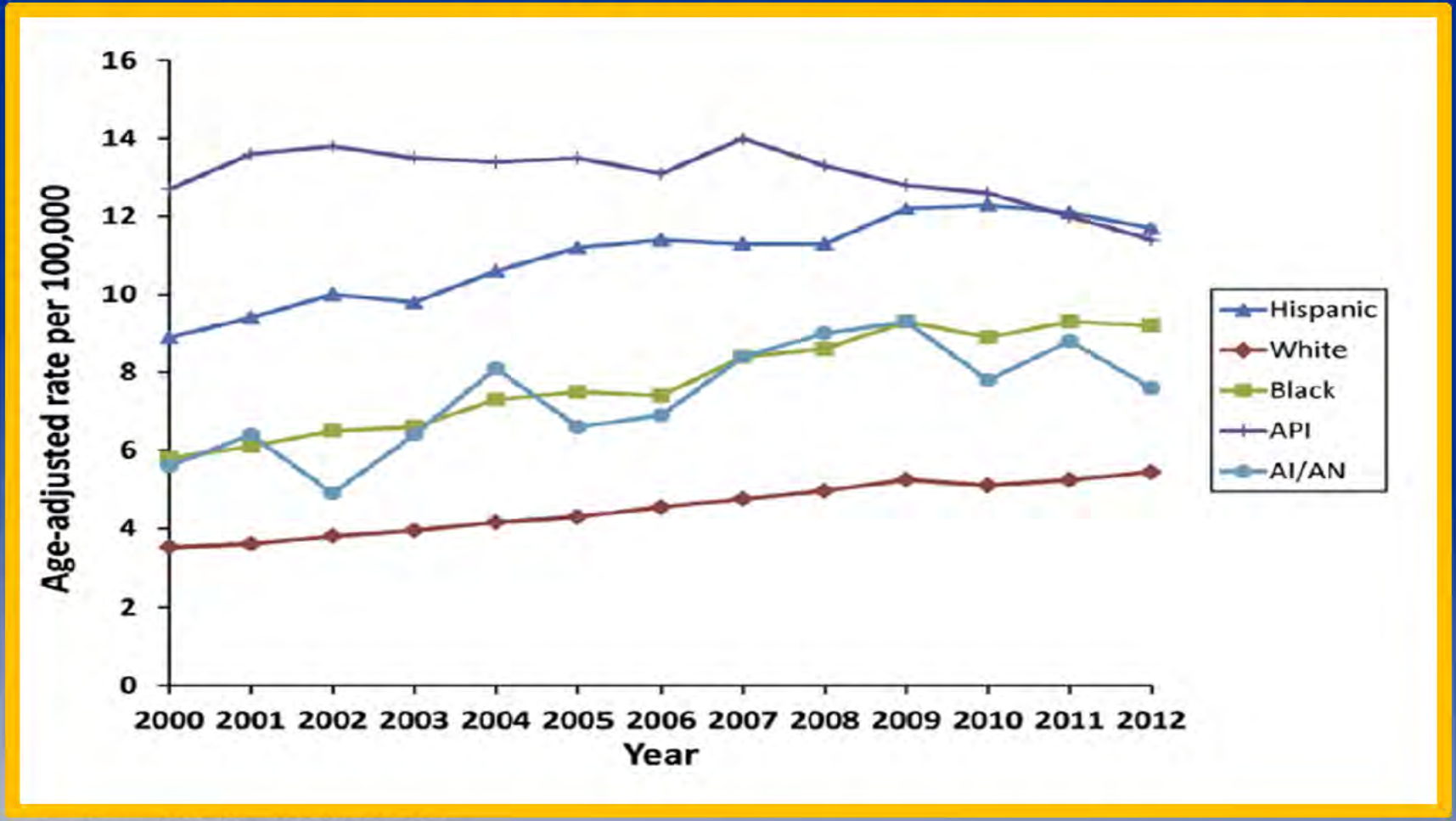
- Since 1980, the incidence of liver and intrahepatic bile duct cancer has more than tripled[2].

1. National Cancer Institute. Available at: http://seer.cancer.gov/statfacts/html/livibd.html. Accessed February 7, 2016;
2. American Cancer Society. Available at: http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-047079.pdf. Accessed February 7, 2016.

HCC Epidemiology in USA

Fifth most common Cancer and second cause of Cancer-Related Death in the World

236,960 cases of HCC diagnosed in the US between 2000 and 2012

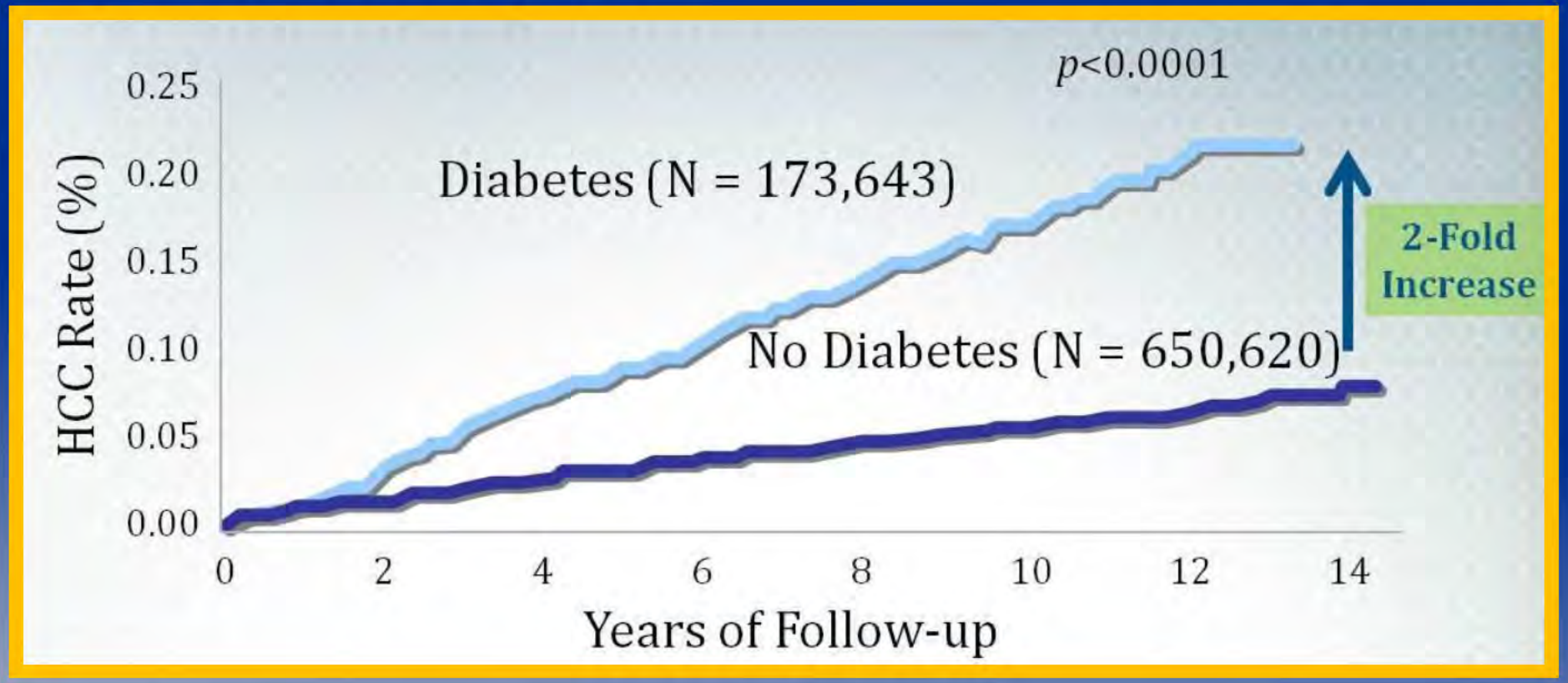


White DL et. al. Gastroenterology. 2017 Mar;152(4):812-820

Diabetes and HCC Risk

Diabetes significantly increases HCC Risk; OR, 2.5 [95% CI, 1.9-3.2]

- Independent of alcohol use [1]
- Independent of viral hepatitis [1]

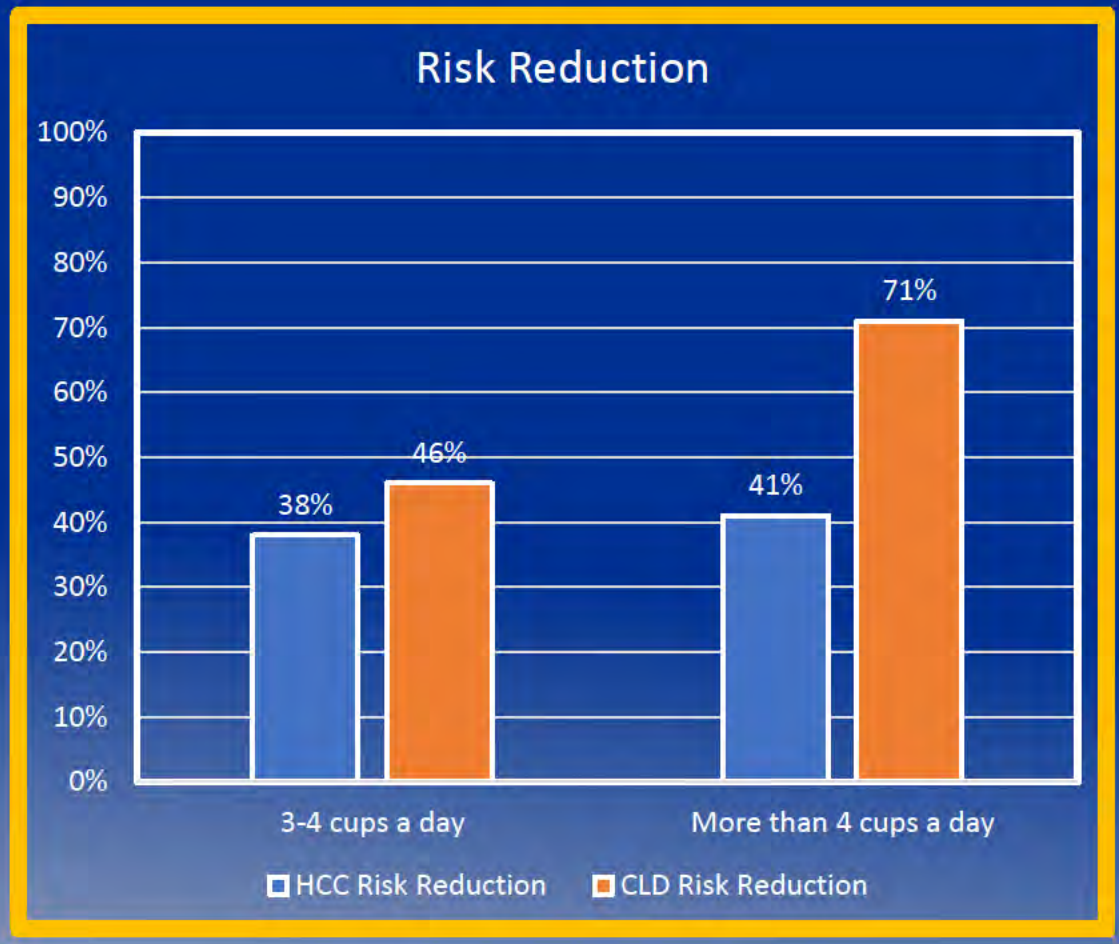


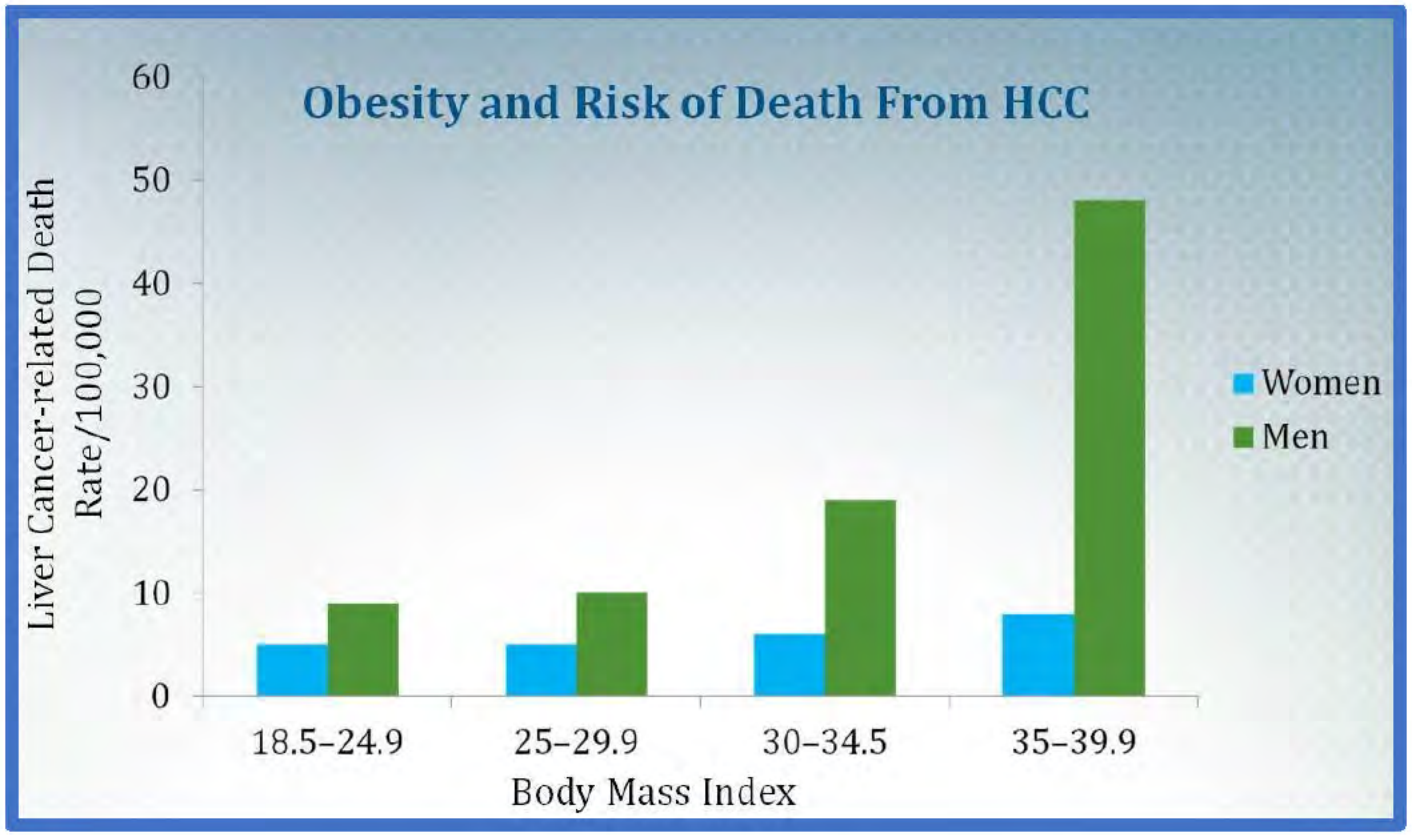
1. El-Serag HB, et al. Clin Gastroenterol Hepatol. 2006;4:369-380
2. El-Serag HB, et al. Gastroenterology. 2004;126:460-468

Association of coffee intake with reduced incidence of liver cancer and death from chronic liver disease in the US multiethnic cohort

Setiawan VW et al. Gastroenterology. 2015 Jan;148(1):118-25

- Large Prospective study: Multi-ethnic Cohort (MEC): >215,000 participants
  - Designed to assess diet, lifestyle and genetic risks for cancer and chronic disease.
  - CA and Hawaii: established 1993-1996
- Looked at CLD, HCC and coffee consumption
- Equal for **decaf and caffeinated**
- Equal among all ethnic groups and gender
- Results were also independent of BMI, smoking status, alcohol intake and Diabetes status.





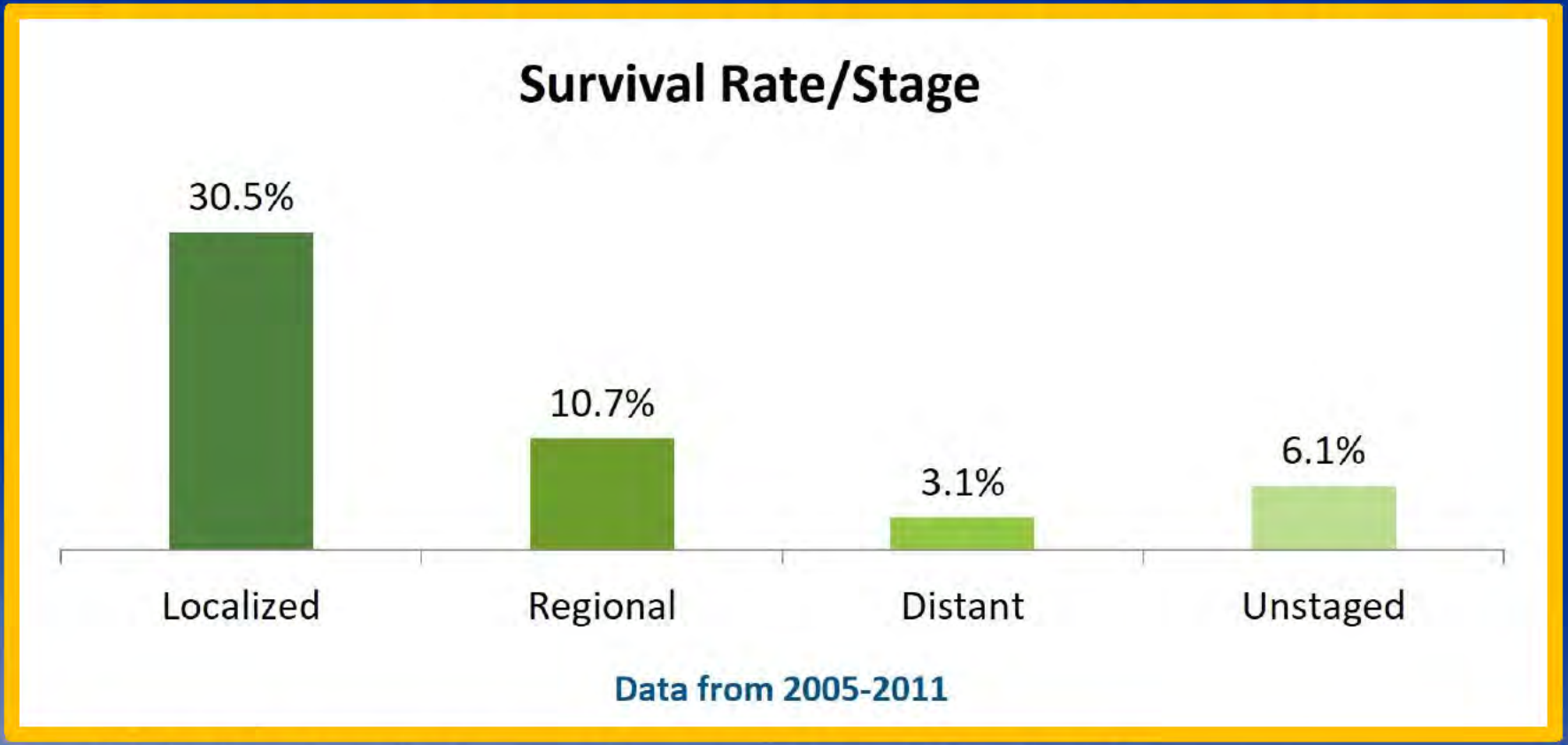
Obesity and Risk of Death from HCC

Calle EE, et al. N Engl J Med. 2003;348:1625-1638

Screening for HCC

HCC: Prognosis

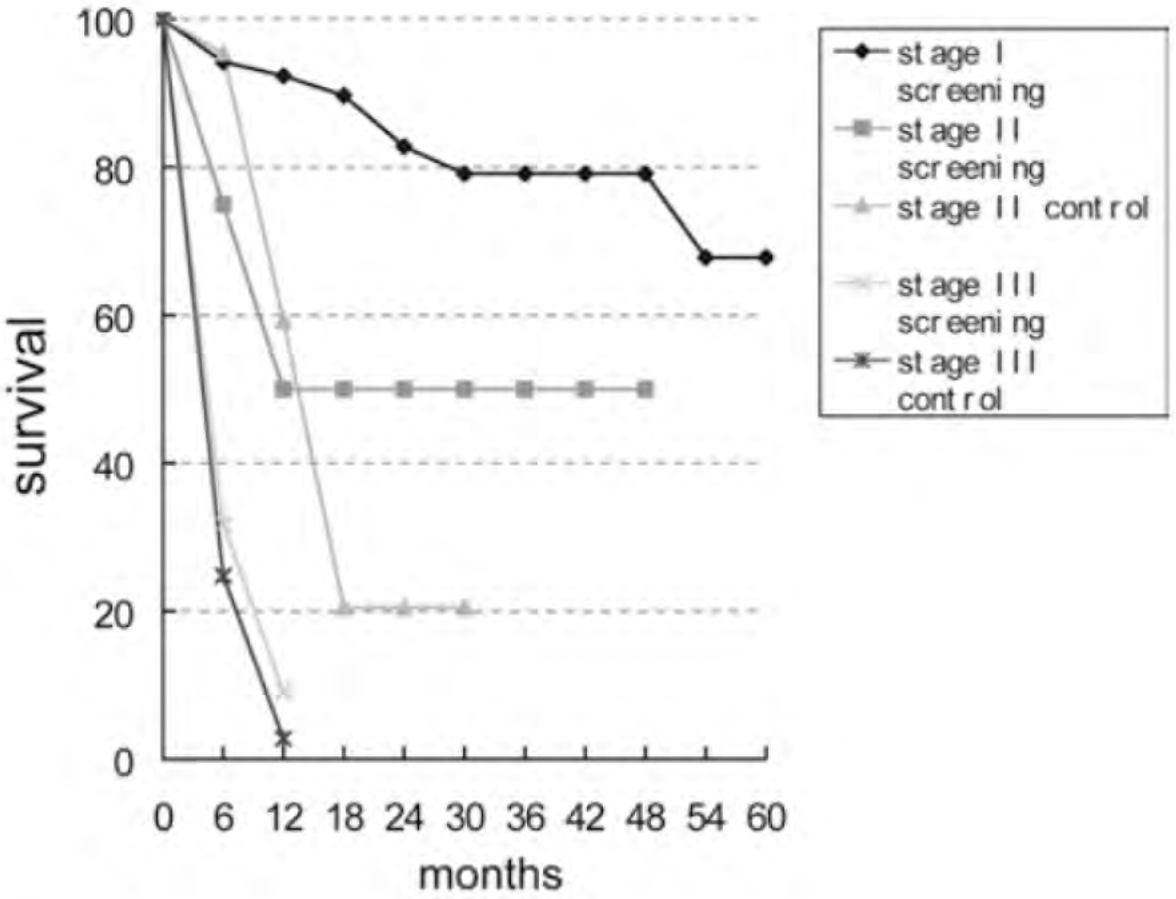
- 5-year survival is substantially worse when liver cancer is diagnosed at a late stage[2]:



- **Majority of patients are diagnosed at a late stage[1,2]**

1. Llovet J.M. et al. Lancet 2003;362:1907-1917
2. National Cancer Institute. Available at: http://seer.cancer.gov/statfacts/html/livibd.html. Accessed February 7, 2016.

Surveillance reduces HCC-related mortality in chronic hepatitis B

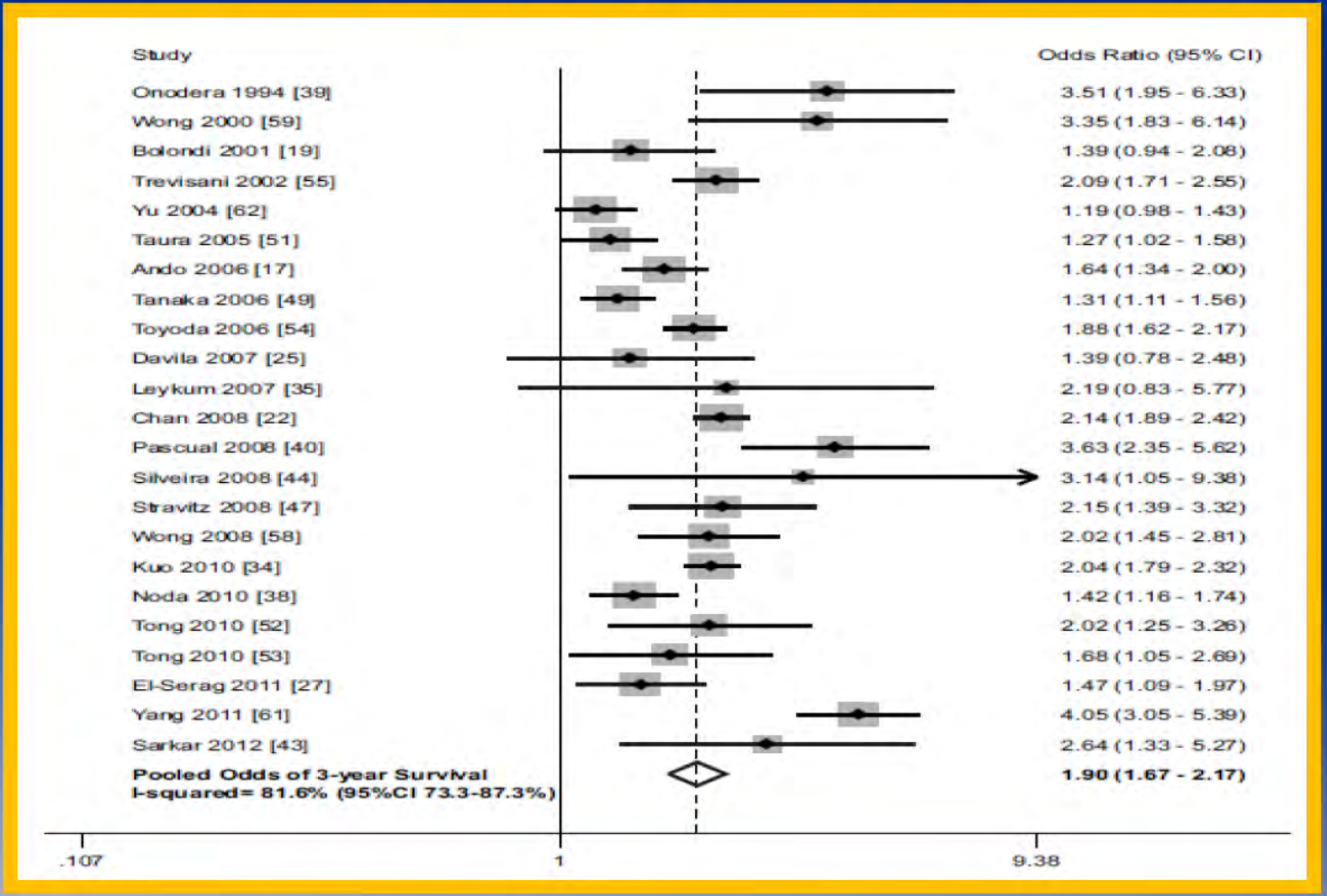


Variable	Screen Group (n=9373)	Control Group (n=9443)
HCC cases	86	67
% Stage I	60.5%	0%
% Curative treatment	46.5%	7.5%
# HCC death	32	54
Mortality (per 100,000)	83.2	131.5
Rate Ratio	0.63 (0.4-0.9)	

Zhang et al, J Cancer Res Oncol 2004

Screening and Surveillance of HCC

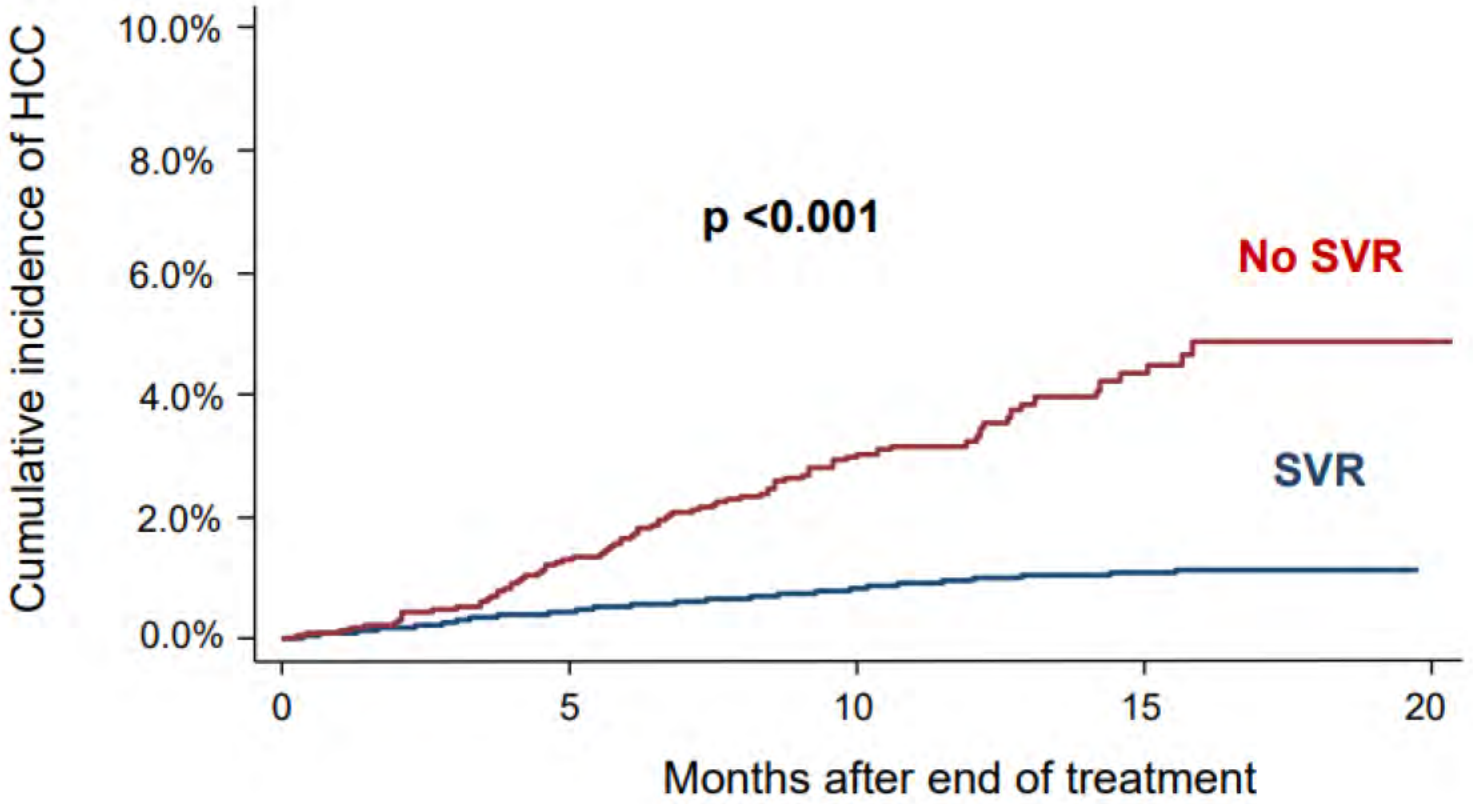
HCC Surveillance is Associated With Improved Survival in Patients With Cirrhosis



1.90-fold improved odds of 3-year survival

Singal AG et al. *PLoS Med.* 2014;11:e1001624.

Patients with SVR have decreased albeit continued risk of HCC



Kanwal et al. Gastroenterology 2017

Groups with Surveillance Benefit for HCC

Population group	Threshold for Surveillance Efficacy	HCC Incidence
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
PBC Stage 4 (cirrhosis)	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

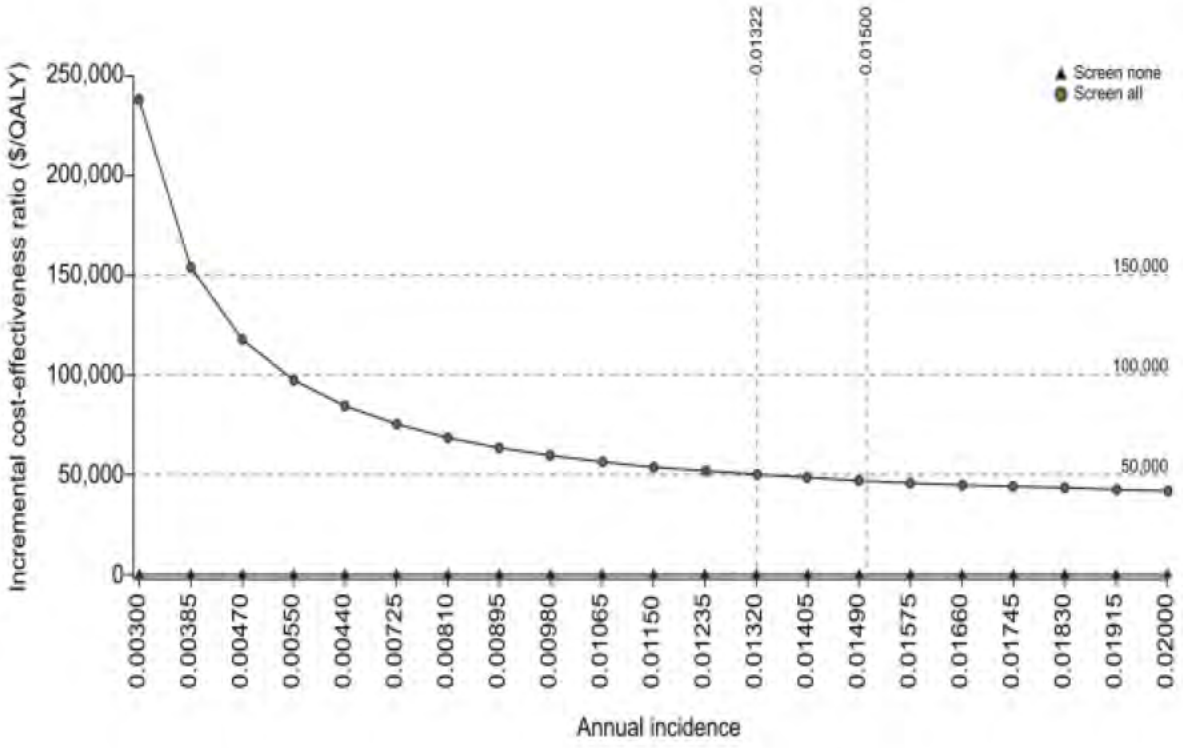
Bruix J et al. HEPATOLOGY, Vol. 53, No. 3;1020-1022, March 2011, and Bruix J et al. HEPATOLOGY, July: 1-35, 2010

Groups with Uncertain Surveillance Benefit for HCC

Population group	Threshold for Surveillance Efficacy	HCC Incidence
Hepatitis B carriers younger than 40 (males) or 50 (females), without family history of HCC	0.2	< 0.2% per year
Hepatitis C with stage 3 fibrosis	1.5	< 1.5% per year
NAFLD without cirrhosis	1.5	< 1.5% per year

Bruix J et al. HEPATOLOGY, Vol. 53, No. 3;1020-1022, March 2011 and Bruix J et al. HEPATOLOGY, July: 1-35, 2010

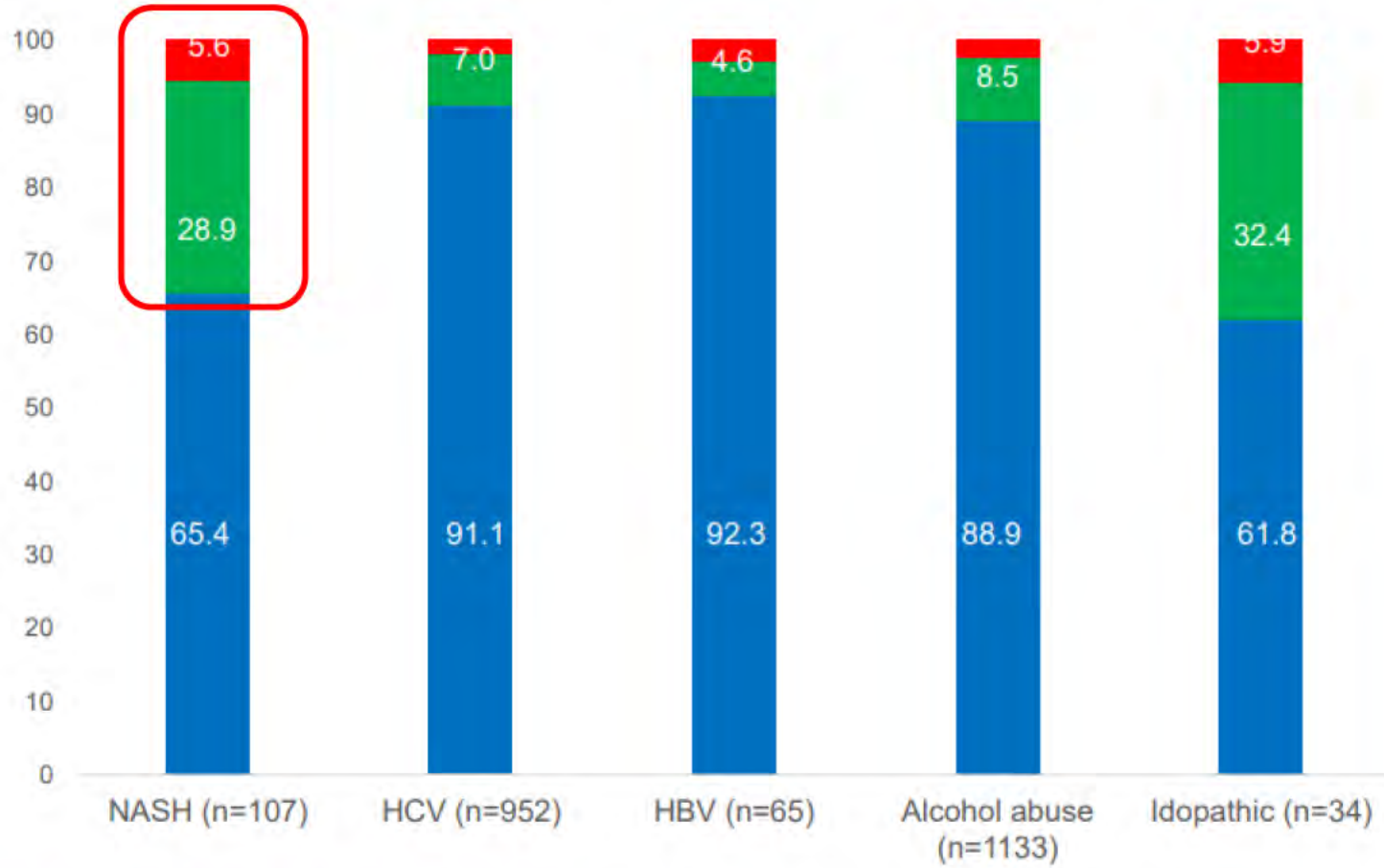
Surveillance does not appear to be cost effective in those with advanced fibrosis but without cirrhosis



Population	HCC incidence	Surveillance	ICER vs no surveillance, $/QALY
Base case F3/F4 with IFN-induced SVR	0.5%/y	None	-
		US every 6 mo	106,792
		US every 12 mo	72,105
	0.5%/y age-stratified	None	-
		US every 6 mo	48,432
		US every 12 mo	37,201
Cirrhosis with IFN-induced SVR	1.39%/y	None	-
		US every 6 mo	48,729
		US every 12 mo	72,105
Cirrhosis with DAA-induced SVR	1.82%/y	None	-
		US every 6 mo	43,229
		US every 12 mo	34,307
F3 with IFN-induced SVR	0.23%/y	None	-
		US every 6 mo	484,160
		US every 12 mo	204,708
F3 with DAA-induced SVR	0.34%/y	None	-
		US every 6 mo	188,157
		US every 12 mo	111,667

Zangneh et al. Clin Gastro Hep 2019

Many NASH HCC patients do not have cirrhosis



Very high probability non-cirrhotic: Histology and no features on imaging
High probability non-cirrhotic : APRI <1; no features on imaging; NL albumin, plt, INR

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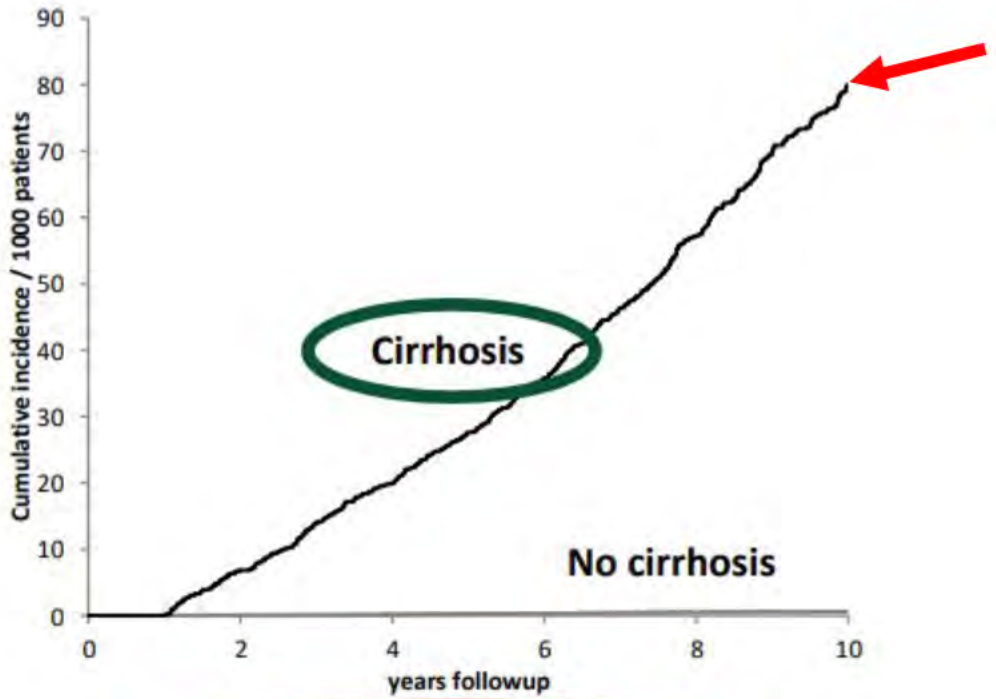
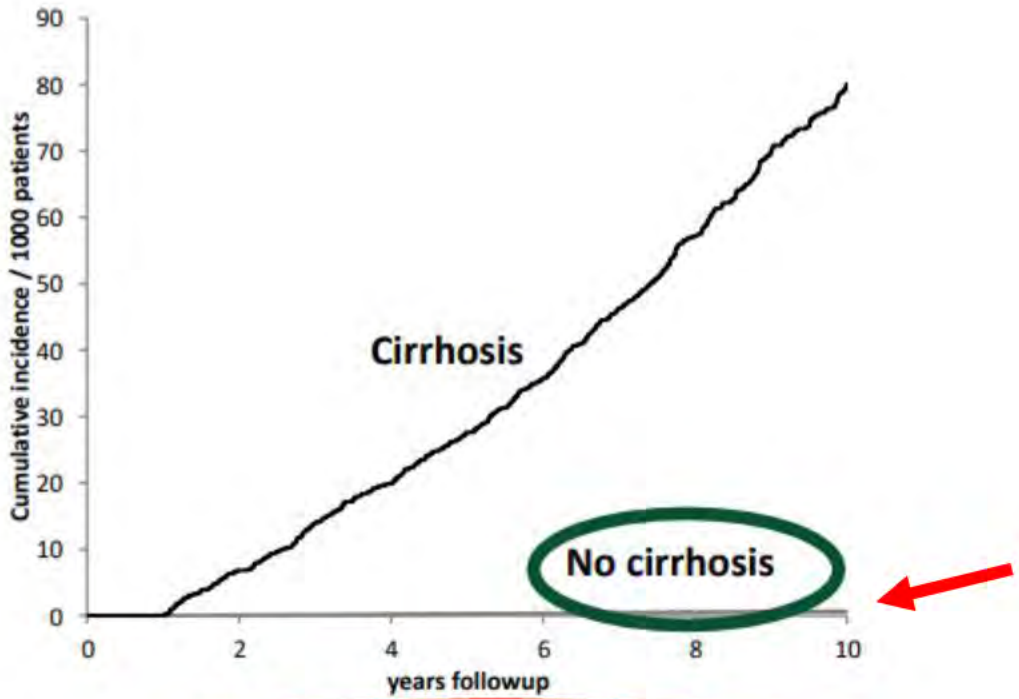
Mittal et al. Clin Gastro Hep 2015

HCC risk in patients with NASH restricted to those with cirrhosis

N= 4235 cirrhosis; 292,366 no cirrhosis



1.06 per 100 patient-years



0.008 per 100 patient-years

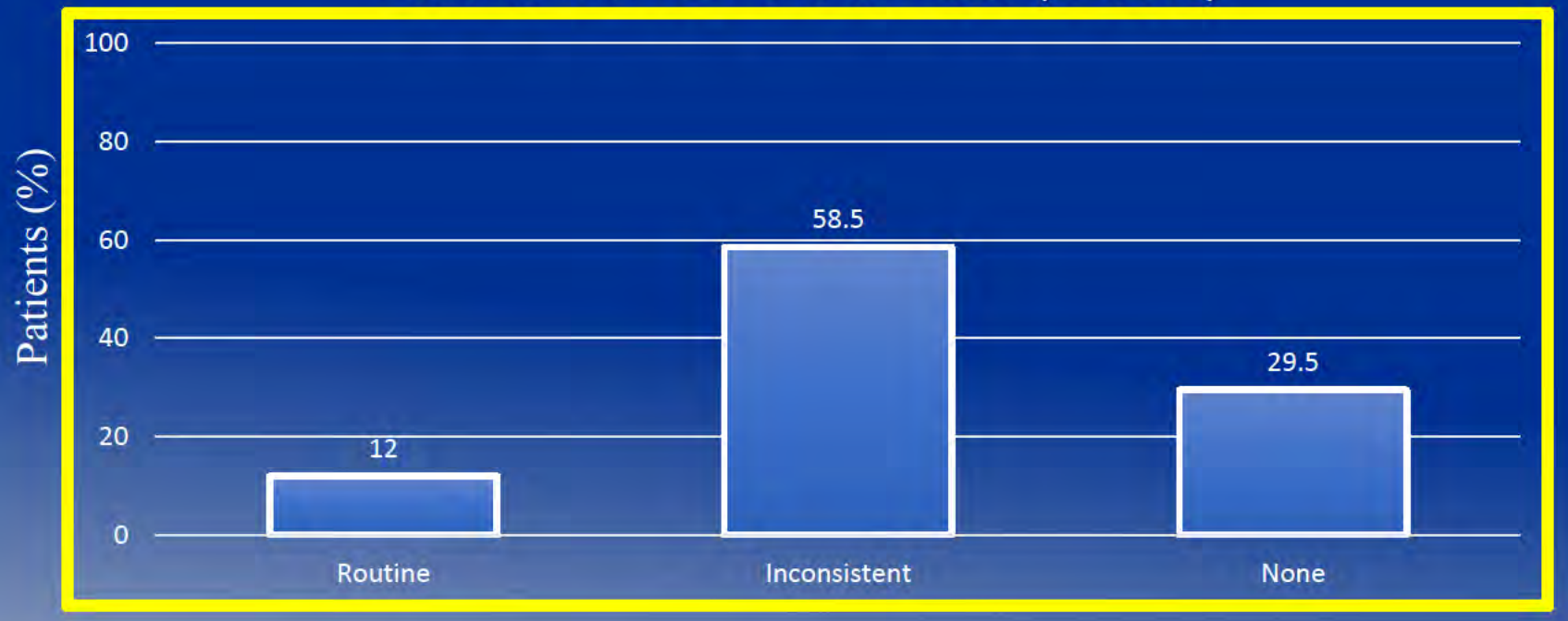
Despite the large number of Non-cirrhotic NASH-HCC Surveillance is not indicated in Non-Cirrhotic NASH

Kanwal et al. Gastroenterology 2018

HCC Surveillance Practices

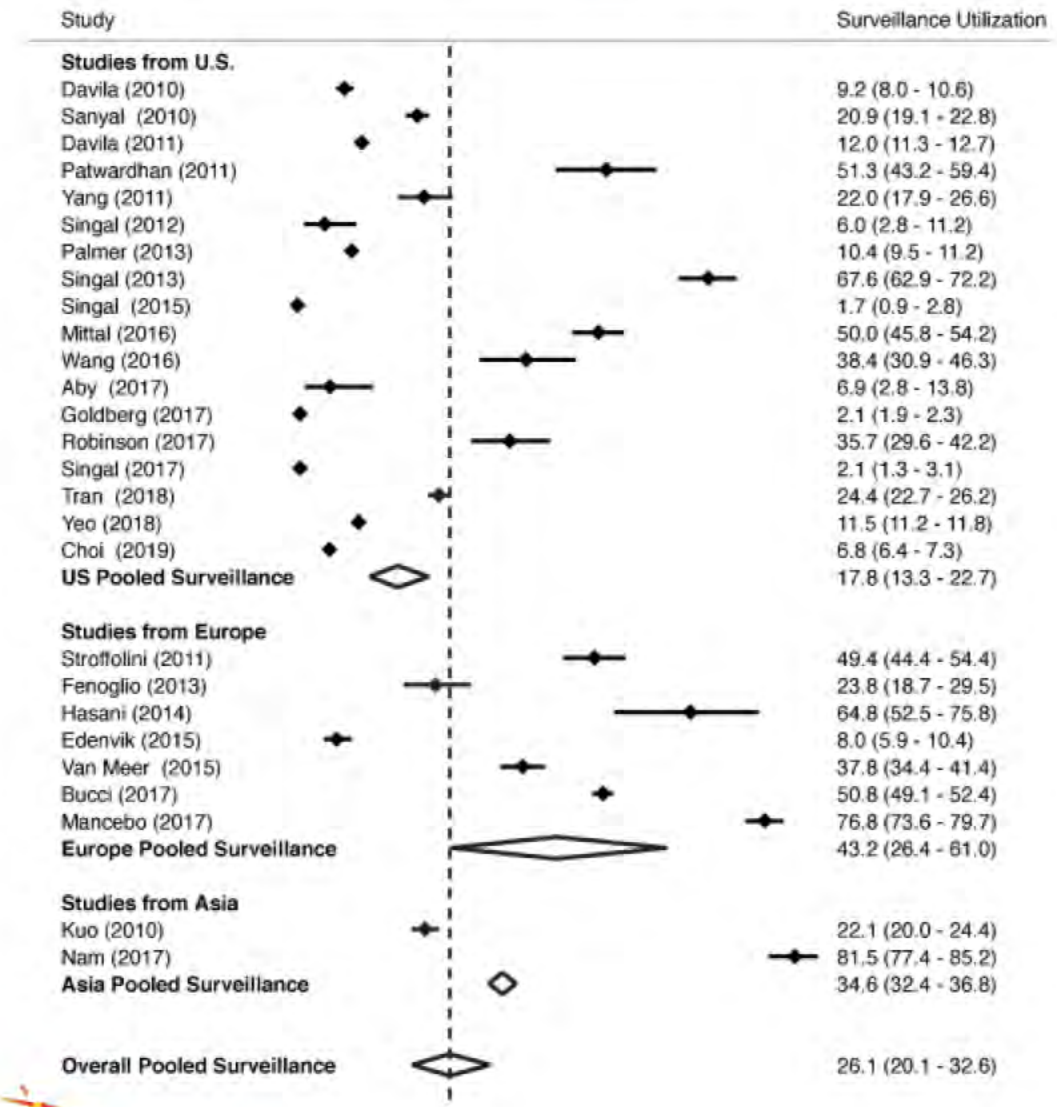
Even Very High-Risk Patients Rarely Receive Routine Surveillance

Annual HCC Surveillance With Either US or AFP in Patients With HCV and Cirrhosis (N=9369)



Routine testing = tests done during at least 2 consecutive years in the 4 years after diagnosis of cirrhosis; inconsistent testing = ≥1 test during the same timeframe but not routine. AFP=alpha-fetoprotein; US=ultrasound;
Davila JA et al. *Ann Intern Med.* 2011;154:85-93.

HCC screening is underused in clinical practice



Identified 29 studies between Jan 2010 – Aug 2018

Pooled surveillance estimate was only 26.1%

- Lower surveillance in US studies vs. Europe and Asia (17.8% vs. 43.2% and 34.6%)
- Higher surveillance in GI/Hepatology clinics vs. academic primary care clinics and population-based cohorts (73.7% vs. 29.5% and 8.8%)

Consistent correlates included higher surveillance with GI/Hepatology subspecialty care and increased number of clinic visits and lower surveillance in patients with NASH or alcohol-related cirrhosis.

Wolf et al Hepatology 2020

Surveillance Testing Method

Modified from: Marrero JA et al. Hepatology, VOL. 68, NO. 2, 723-750, 2018

Ultrasound + Alpha-Fetoprotein, every 6 months.

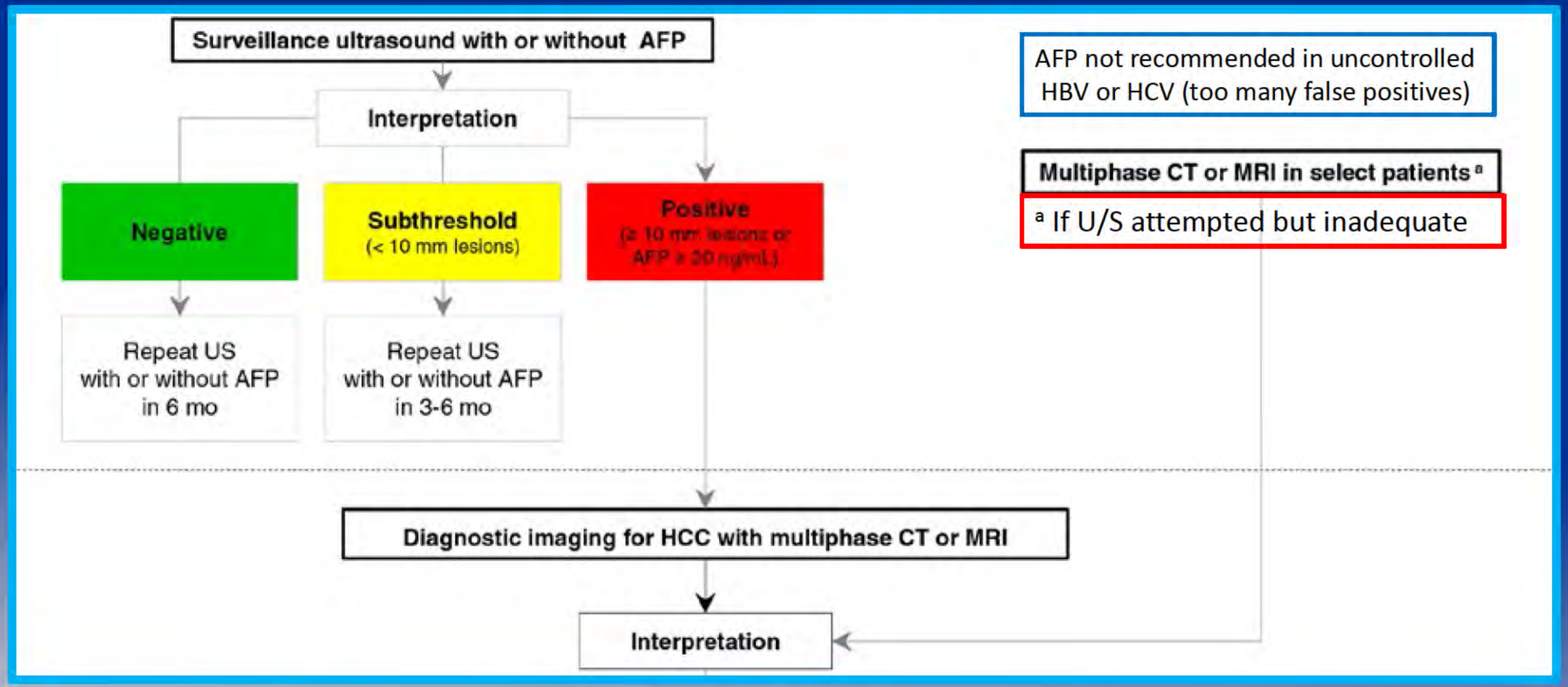
- Not recommended in cirrhosis with Child's class C unless on the transplant waiting list (low anticipated survival).
- AFP not recommended in uncontrolled HBV or HCV (too many false (+))
- Multiphase CT and MRI are not recommended as the primary modality for surveillance. **May be utilized in**:
  - Select patients with a high likelihood of having an inadequate Ultrasound
  - If Ultrasound is attempted but inadequate.

RECALL: US lesions 1 cm or larger, or AFP higher than 20 ng/mL (or raise > 5 ng/mL/month) should be followed with Multi-phase CT Scan or Four-phase MRI, "liver mass" protocol.

- Lesions < 1 cm should be followed with U/S +/- AFP in 3-6 months.

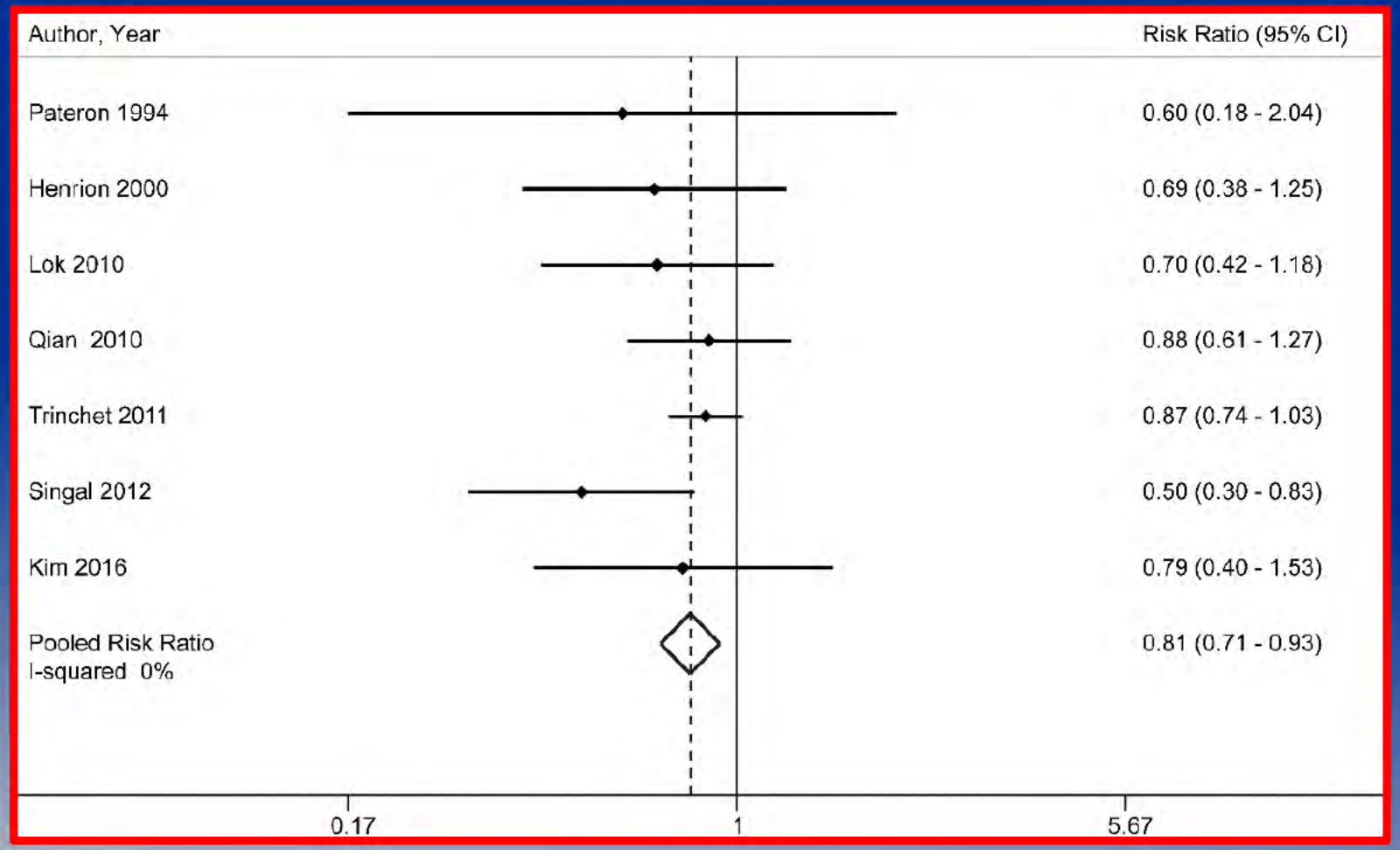
HCC Surveillance

AASLD Practice Guidance 2018



Marrero JA et al. Hepatology, VOL. 68, NO. 2, 723-750, 2018

Accuracy of Ultrasound +/- AFP for Early HCC



Sensitivity

Ultrasound: 45% (30-62%)

US + AFP: 63% (48-75%)

Specificity

Ultrasound: 92% (85-96%)

US + AFP: 84% (77-89%)

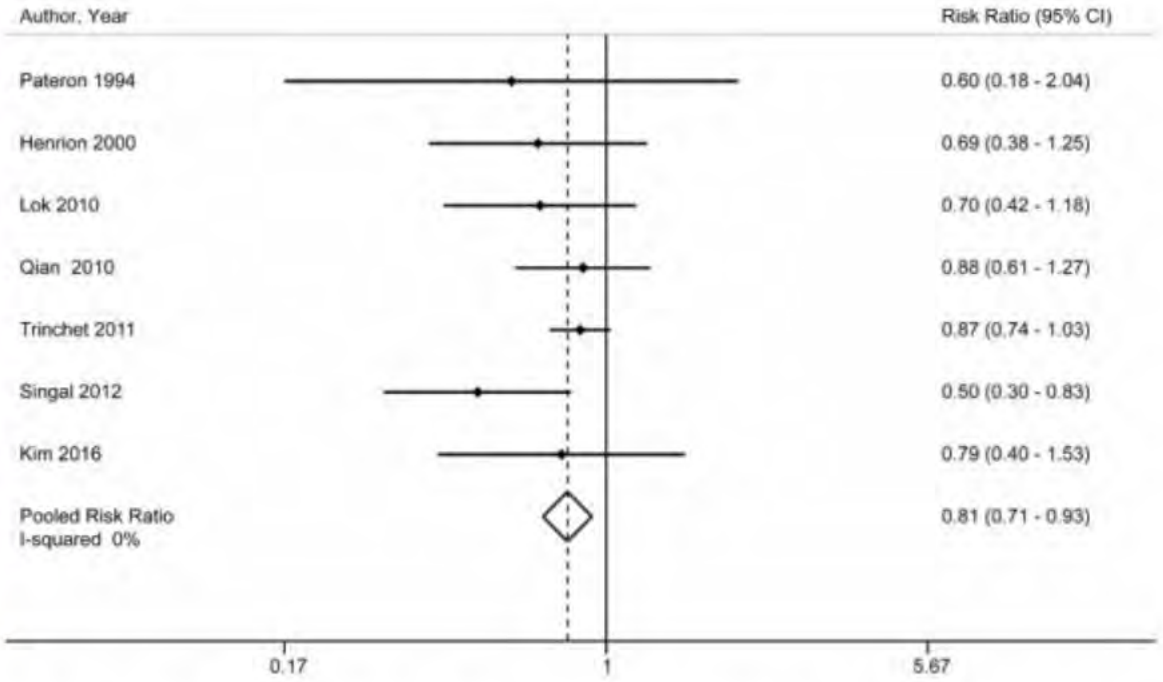
Diagnostic odds ratio

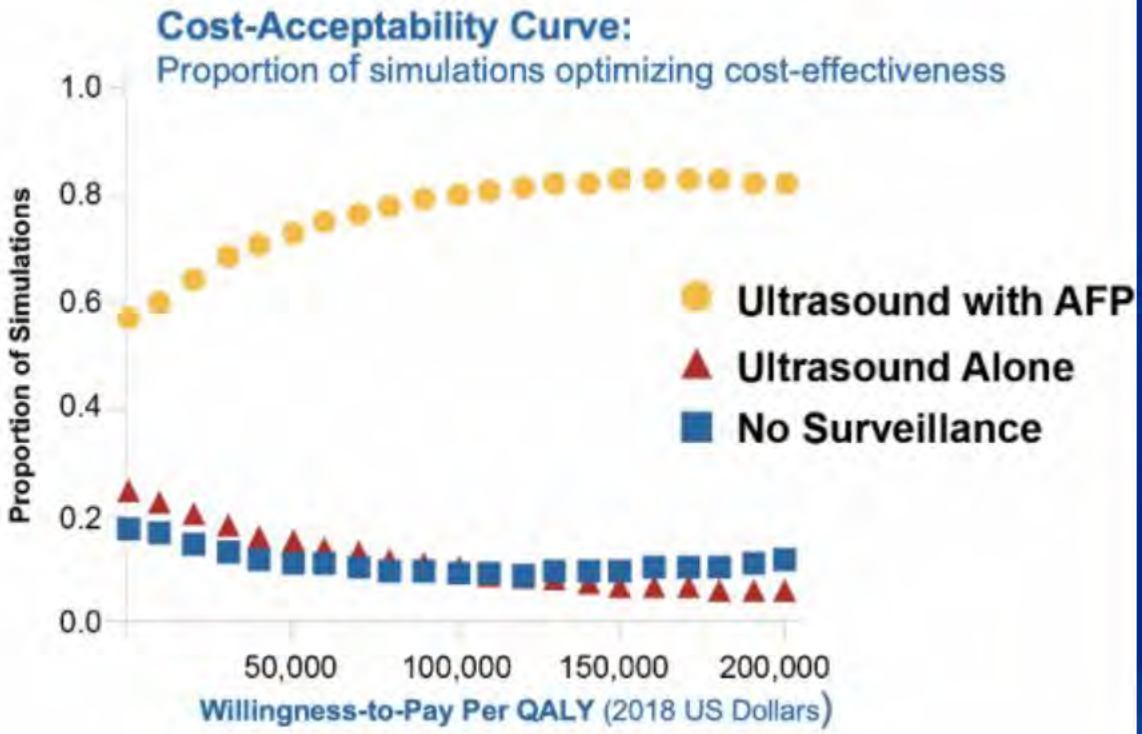
Ultrasound: 7 (3-15)

US + AFP: 8 (3-23)

Singal et al, ILCA 2018

AFP appears to be of benefit for early HCC detection





Sensitivity of US with vs without AFP for early-stage HCC:
63% vs. 45% (*p*=.002)

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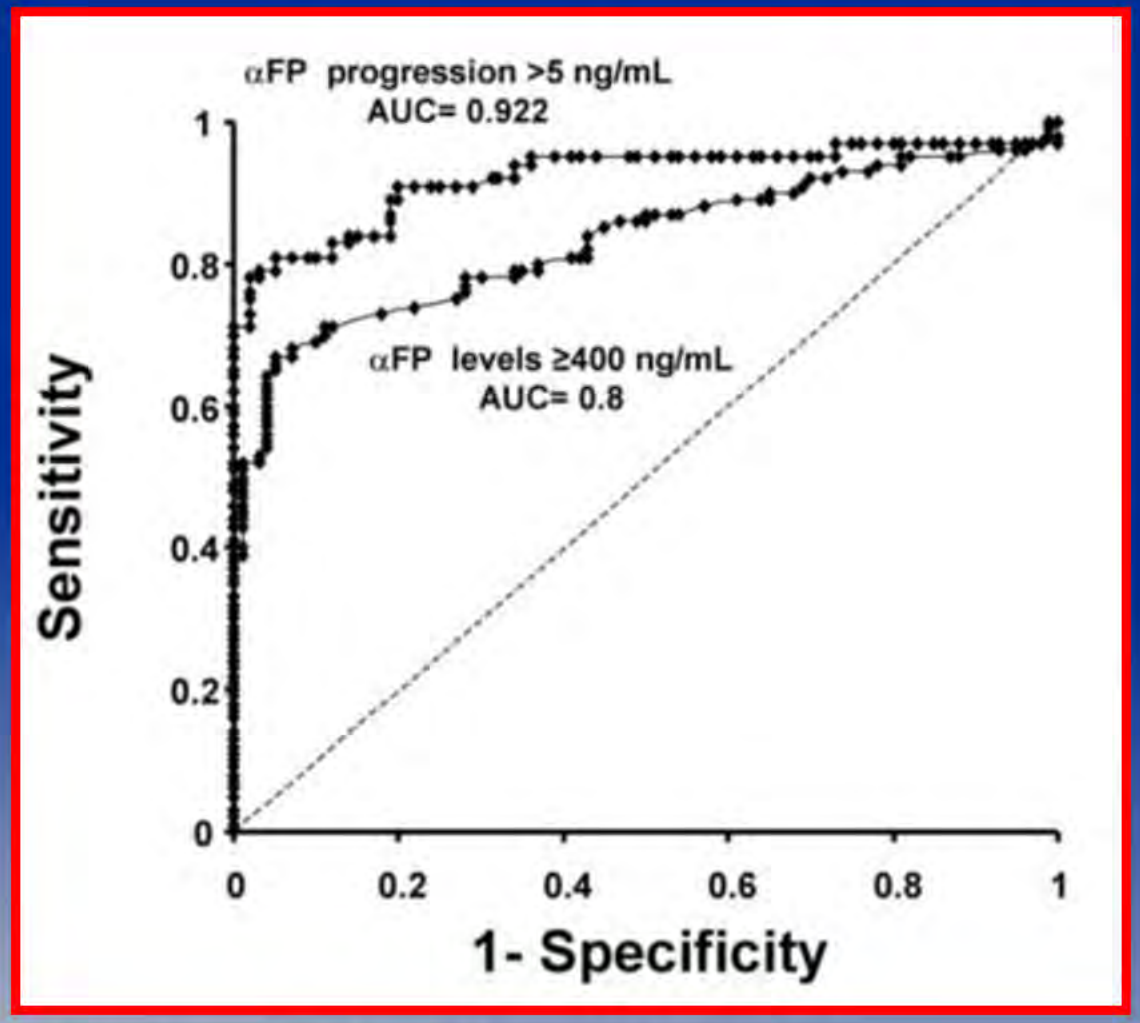
Tzartzeva et al. Gastroenterology 2018
Parikh and Singal et al. Am J Gastro 2020

Progressive Rise of AFP over Time



αFP	HCC Prevalence (%)	PPV (%)	NPV (%)
≥200 ng/ml	10	97.58	93.4
	5	95.03	96.7
≥400 ng/ml	10	95.7	91.86
	5	91.4	95.97
Elevation ≥7 ng/ml/month	10	98.7	96.92
	5	97.4	98.52

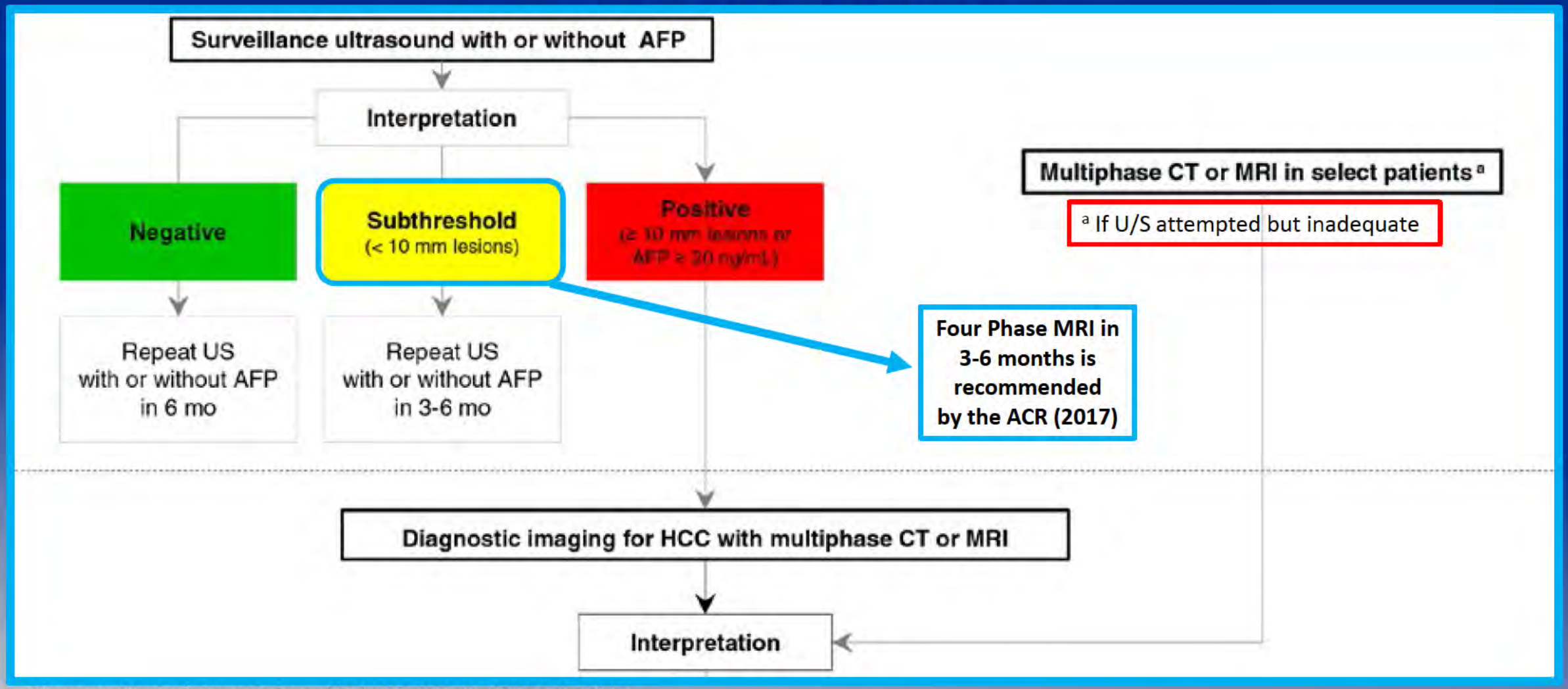
AFP is NOT very useful in Uncontrolled HCV and/or HBV

Arrieta et al, BMC Cancer 2007, Lee et al, Clin Gastro Hep 2013

Diagnosis of HCC

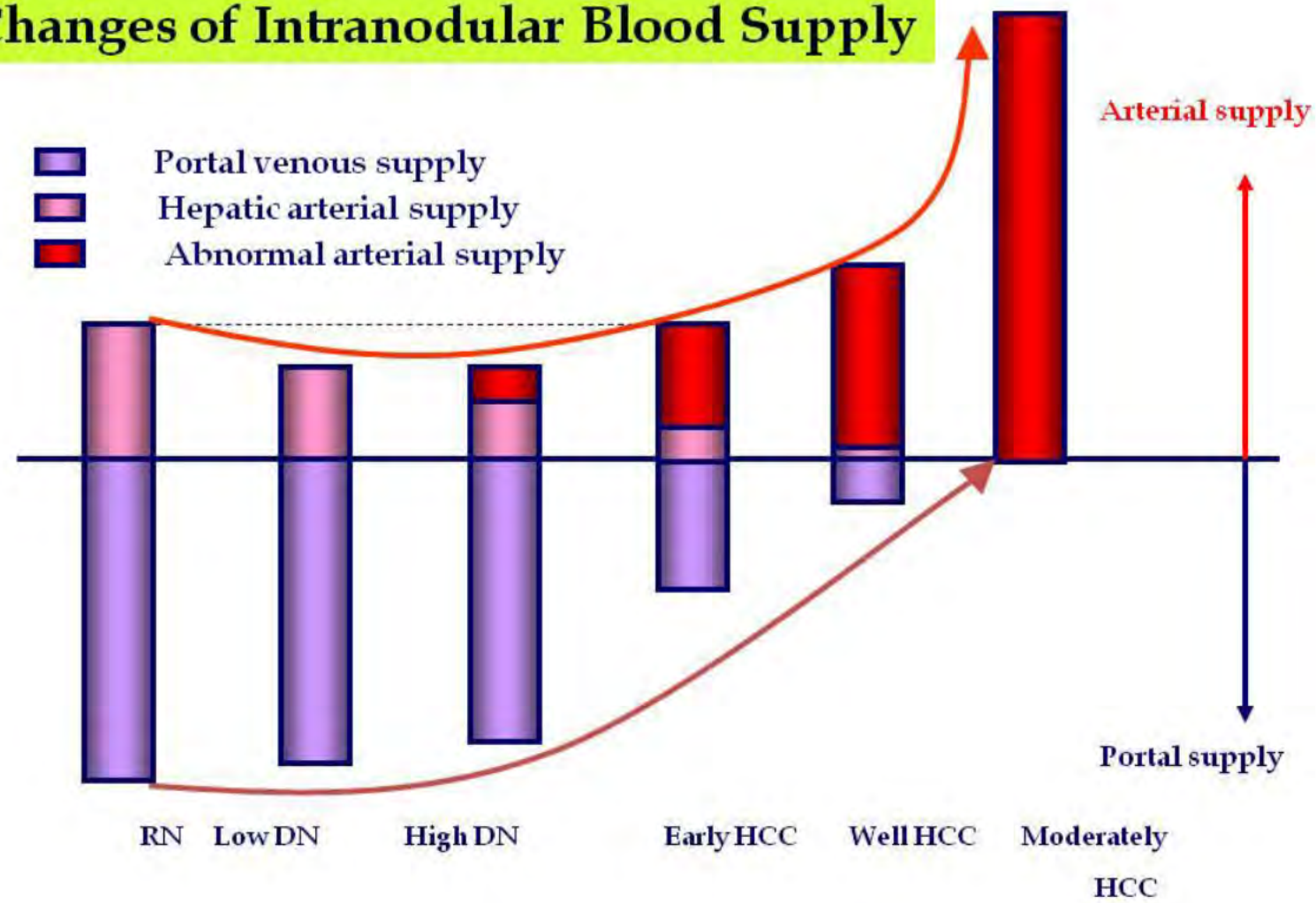
HCC Surveillance every 6 months

AASLD Practice Guidance 2018

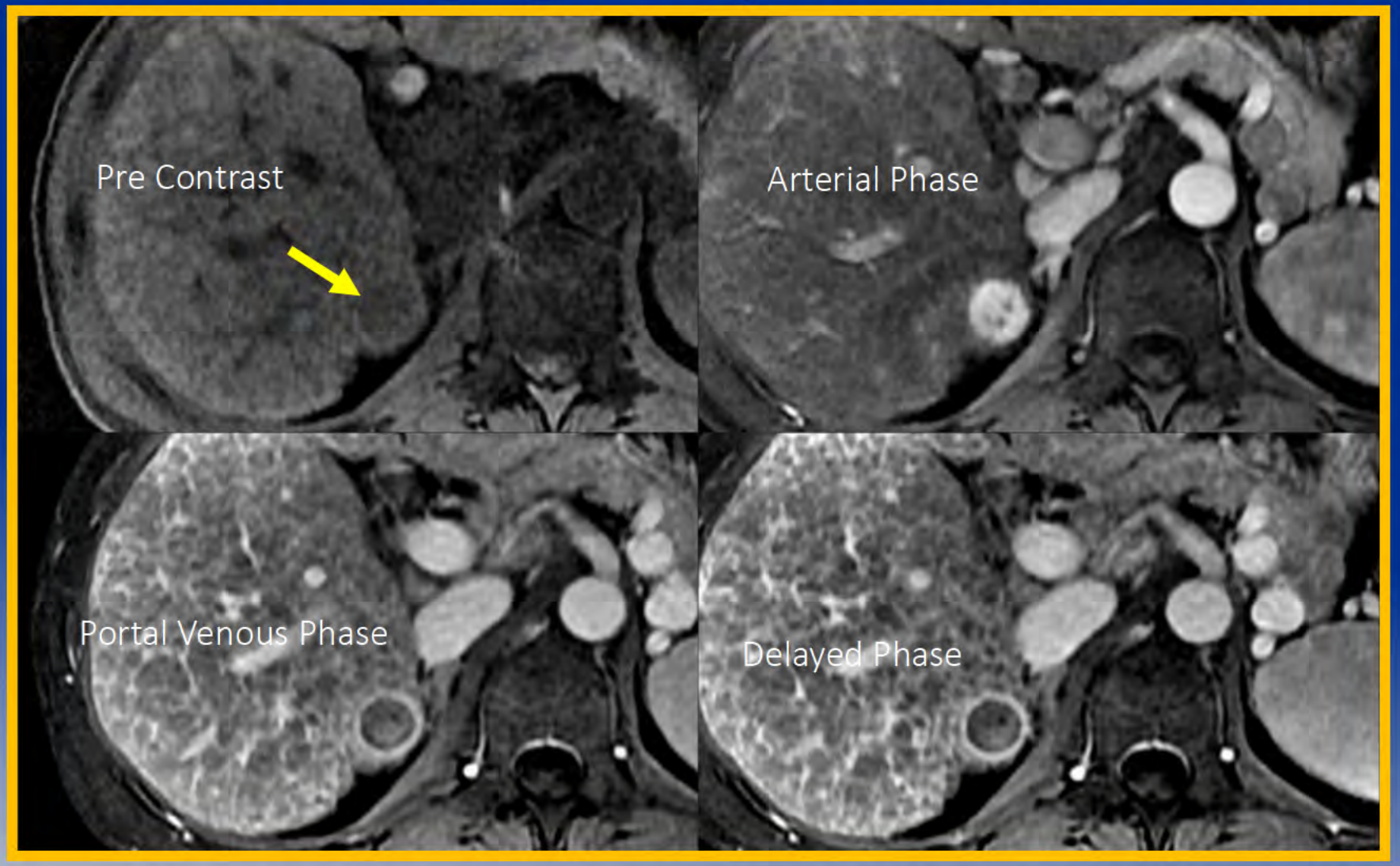


Marrero JA et al. Hepatology, VOL. 68, NO. 2, 723-750, 2018

Stepwise Hepatocarcinogenesis and Changes of Intranodular Blood Supply



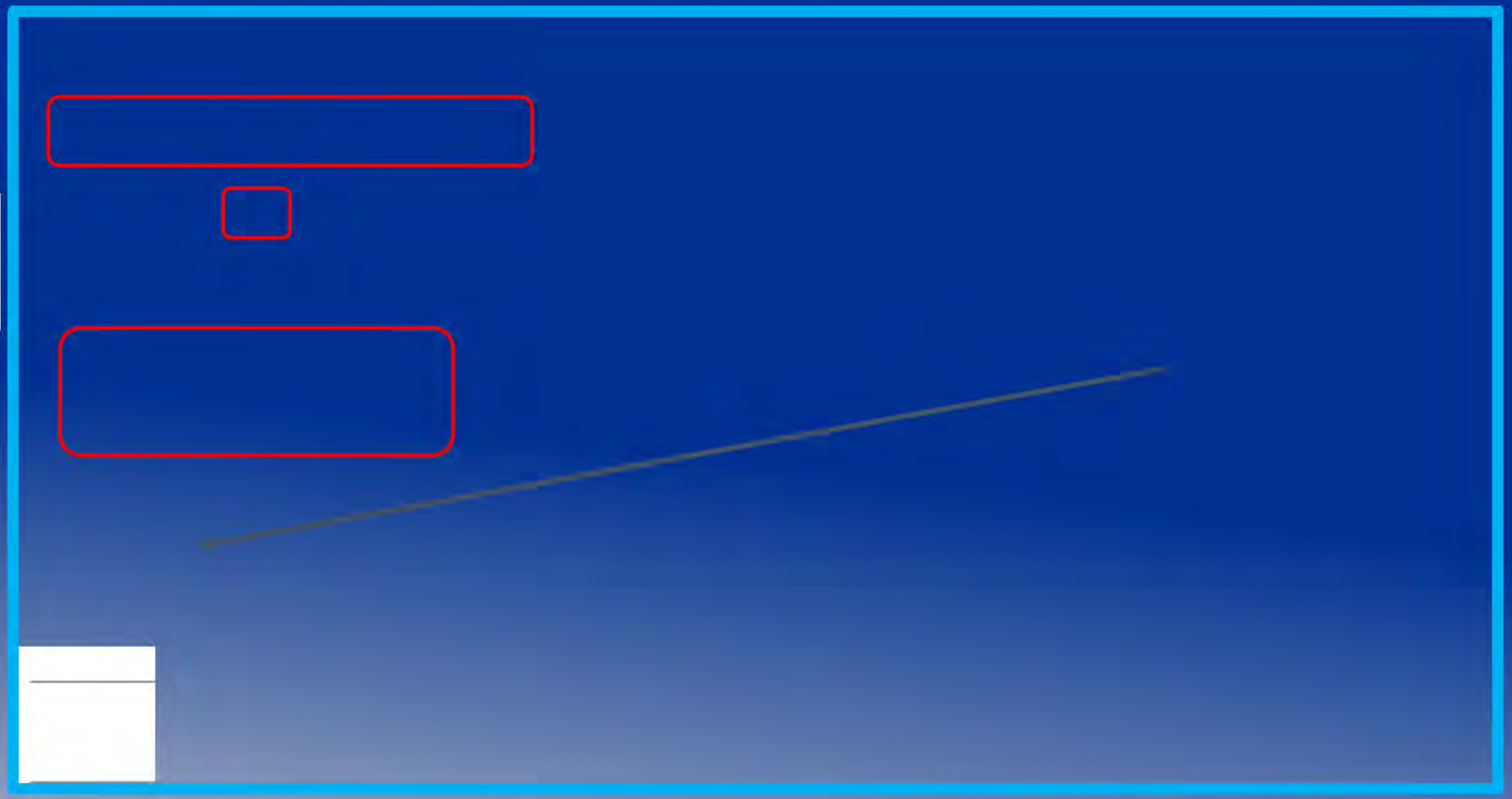
Four Phase Imaging of Hepatocellular Carcinoma



Li-RADS Criteria for HCC Diagnosis 2018

https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/LI-RADS/CT-MRI-LI-RADS-v2018 (accessed 9/7/2019)

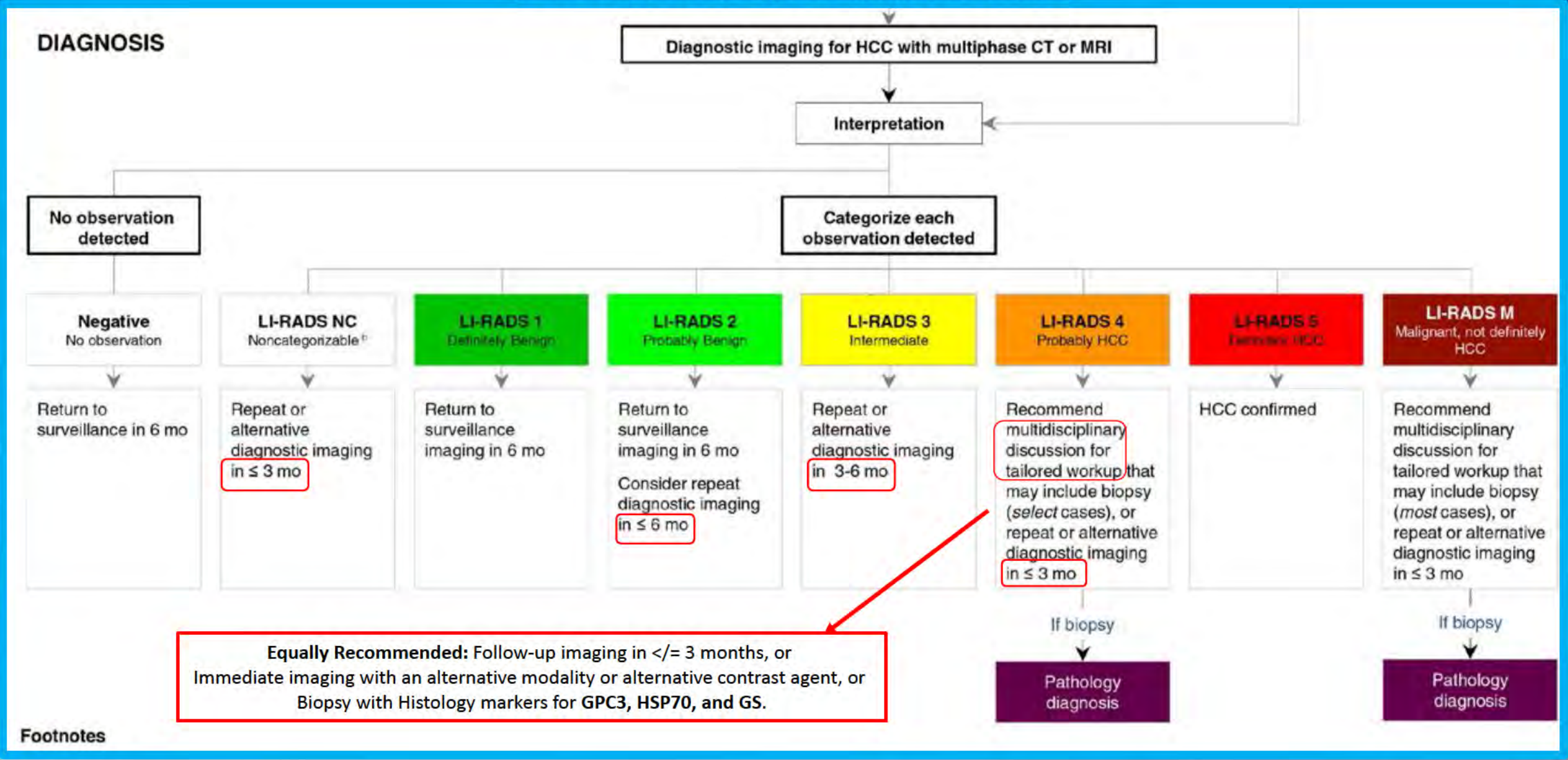
LR-3= Intermediate
LR-4= Probably HCC
LR-5= Definitely HCC



Threshold of growth = size increase of a mass by ≥ 50% in ≤ 6 months

Evaluation of Cirrhosis with Liver Nodule >/= 1 cm or AFP > 20 ng/mL
AASLD Practice Guidance 2018

Marrero JA et al. Hepatology, VOL. 68, NO. 2, 723-750, 2018



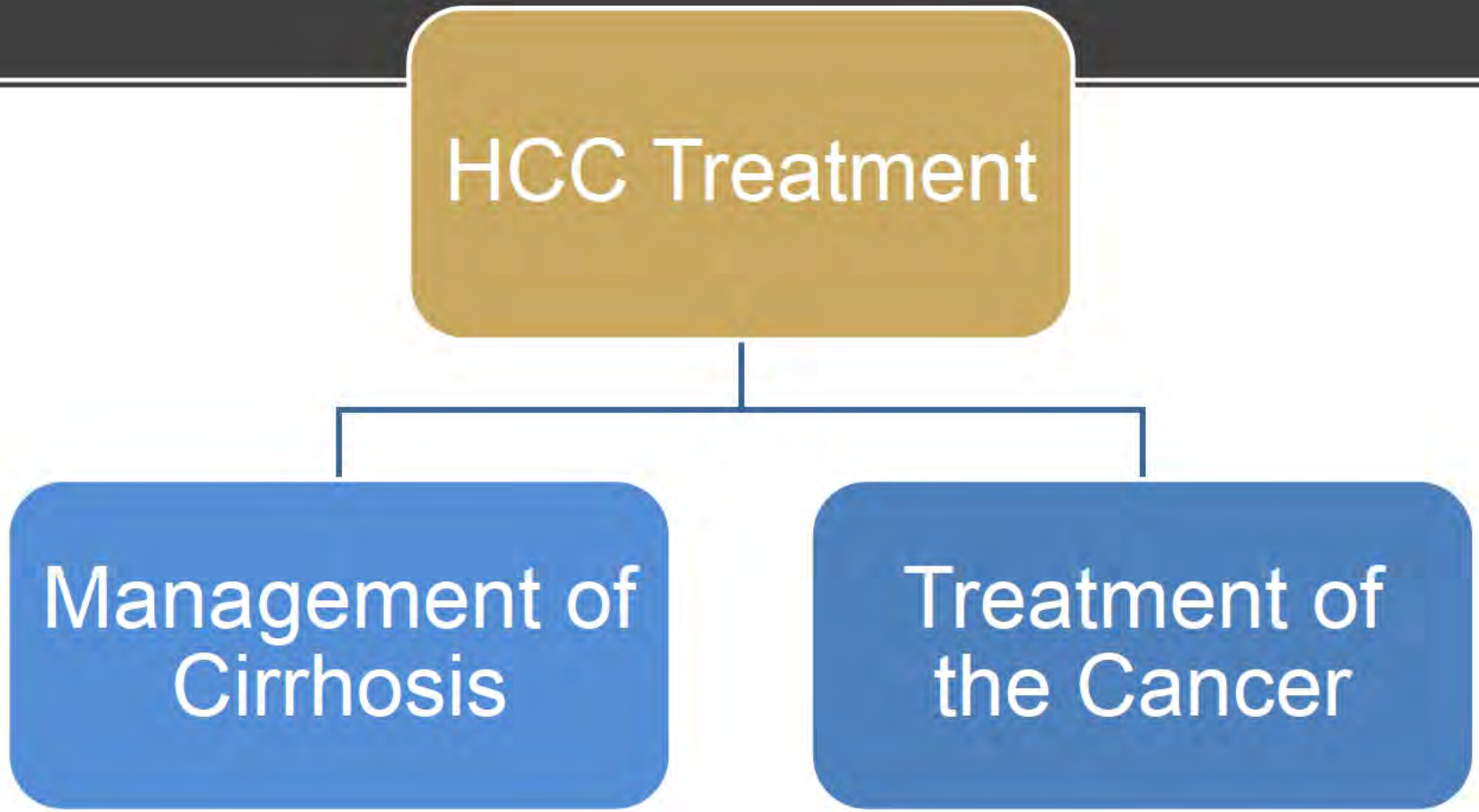
Probability of Malignancy and HCC by LiRADS

van der Pol CB et al. Gastroenterology 156; 976-986, 2019

Probability	LiRADS 1	LiRADS 2	LiRADS 3	LiRADS 4	LiRADS 5	LiRADS M
Malignancy (%)	0	14	40	80	97	93
HCC (%)	0	13	38	74	94	36

Staging and Treatment of HCC

HCC Treatment



Treatment Options for HCC

Surgical Therapy

- Tumor Resection
- Liver Transplantation

Loco-Regional Therapy

- RFA, MWA, PEI
- Embolization: TACE, TAE, Radio-embolization (Ytrium-90 beads)

Radiotherapy

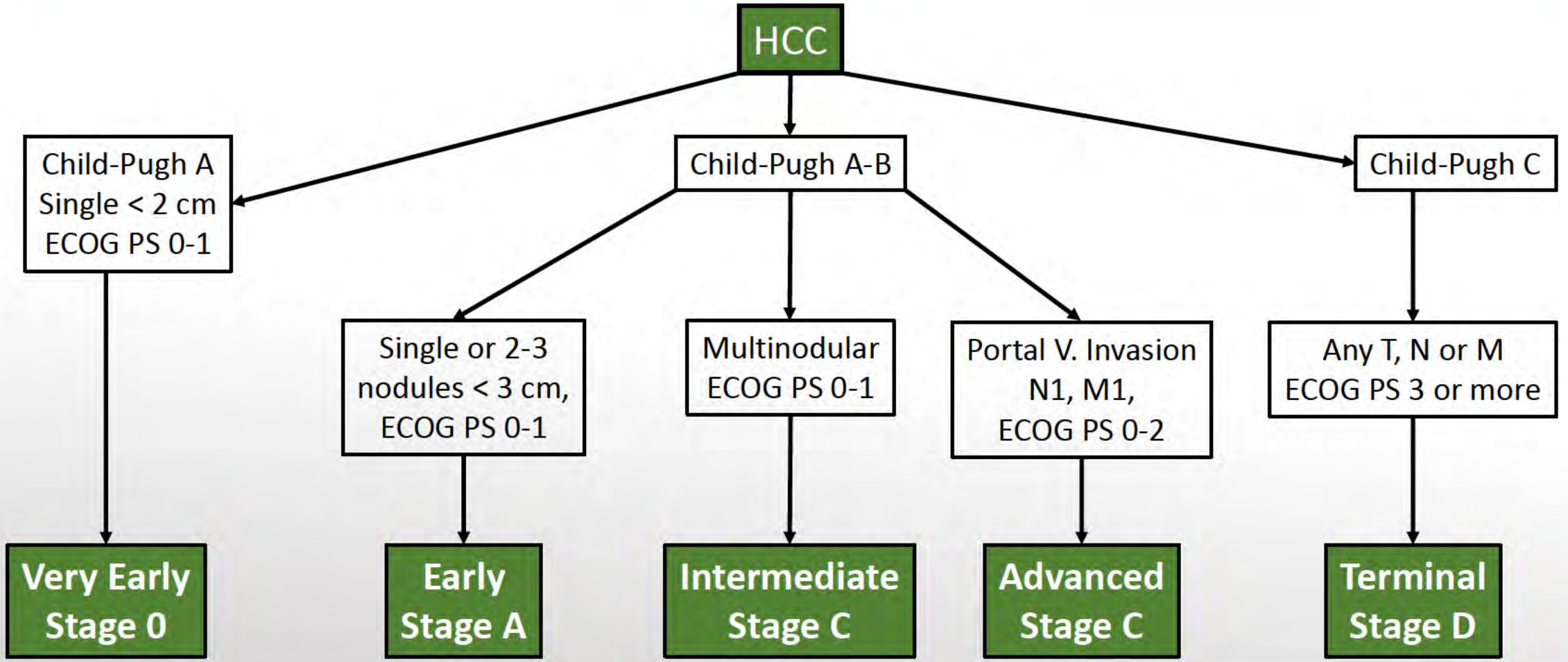
- Stereotactic body radiation Therapy (SBRT)

Systemic Medical Therapy

Immunotherapy

BCLC Staging of HCC

Modified from: Marrero JA et al. Hepatology, VOL. 68, NO. 2, 723-750, 2018



ECOG PS = Performance Status

T = Tumor size, N = Nodal metastasis; M = Extrahepatic metastasis

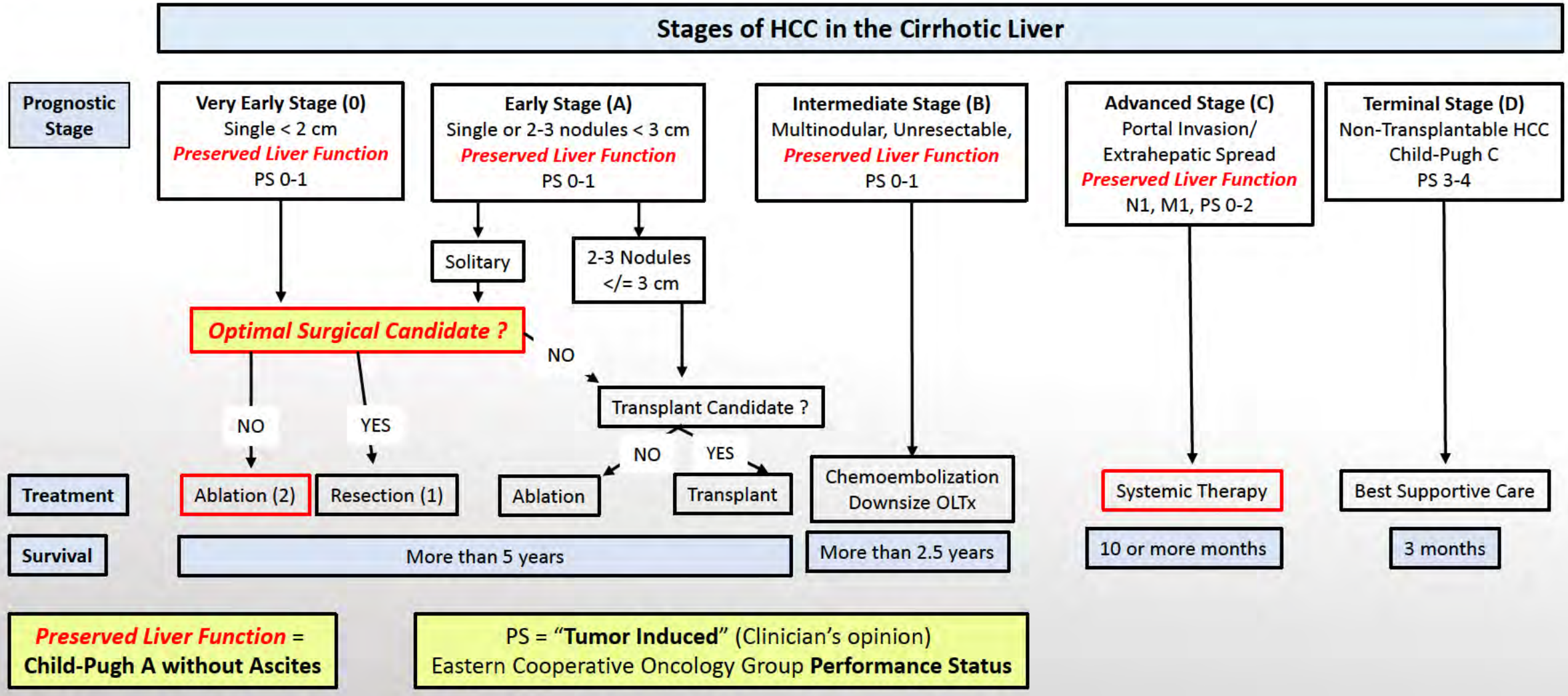
Eastern Cooperative Oncology Group (ECOG)
Performance Status & HCC Treatment Options

GRADE	ECOG PERFORMANCE STATUS	BCLC OPTIONS
PS 0	**Fully active**, able to carry on all pre-disease performance without restriction	Resection, or Ablation, TACE, or TARE, Systemic Therapy. Transplant, Downsize + Transplant
PS 1	**Restricted** in physically **strenuous activity** but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work	Resection, or Ablation TACE, or TARE Systemic Therapy, Transplant, Downsize + Transplant
PS 2	Ambulatory and **capable of all selfcare** but unable to carry out any work activities; **up and about more than 50% of waking hours**	TACE, or TARE, Systemic Therapy, Transplant, Downsize + Transplant
PS 3	Capable of **only limited selfcare**; confined to **bed or chair more than 50% of waking hours**	Best Supportive Care, Transplant (?)
PS 4	Completely disabled; cannot carry on any selfcare; **totally confined to bed or chair**	Best Supportive Care
PS 5	Dead	

* TUMOR INDUCED (Physician Opinion)

Management and Prognosis of HCC

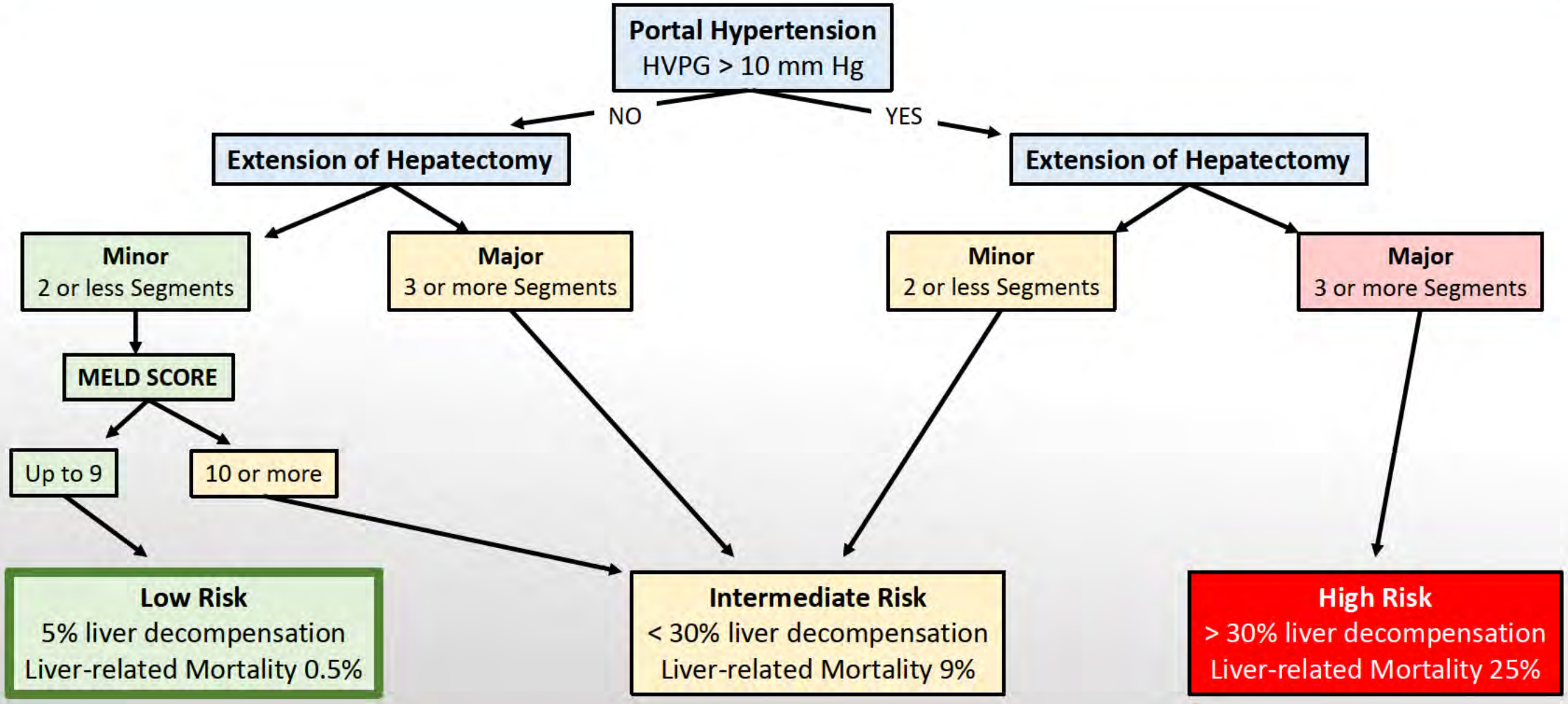
Modified from: Journal of Hepatology 2018 vol.69; 182-236



Optimal Surgical Candidate

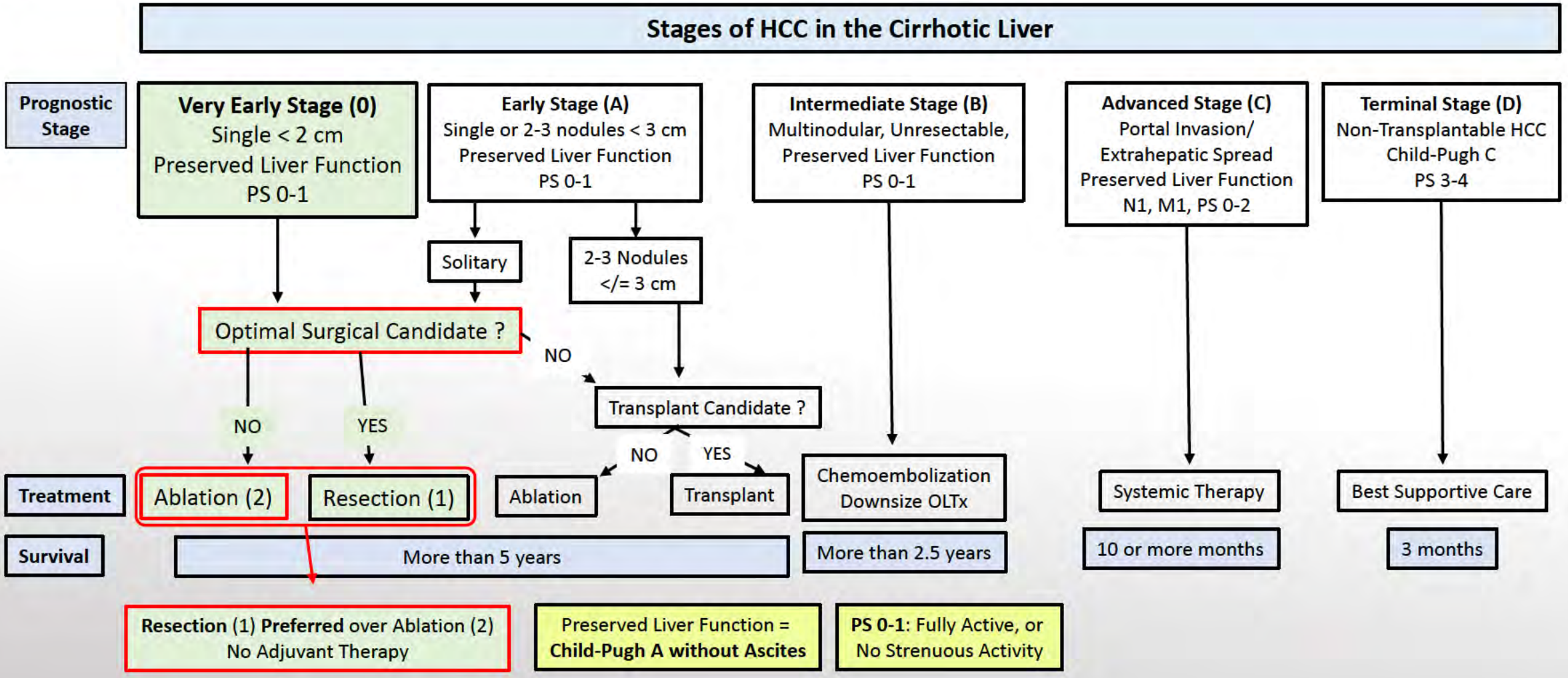
Barcelona Clinic Liver Cancer

Modified from: Journal of Hepatology 2018, Vol. 69: 182-236



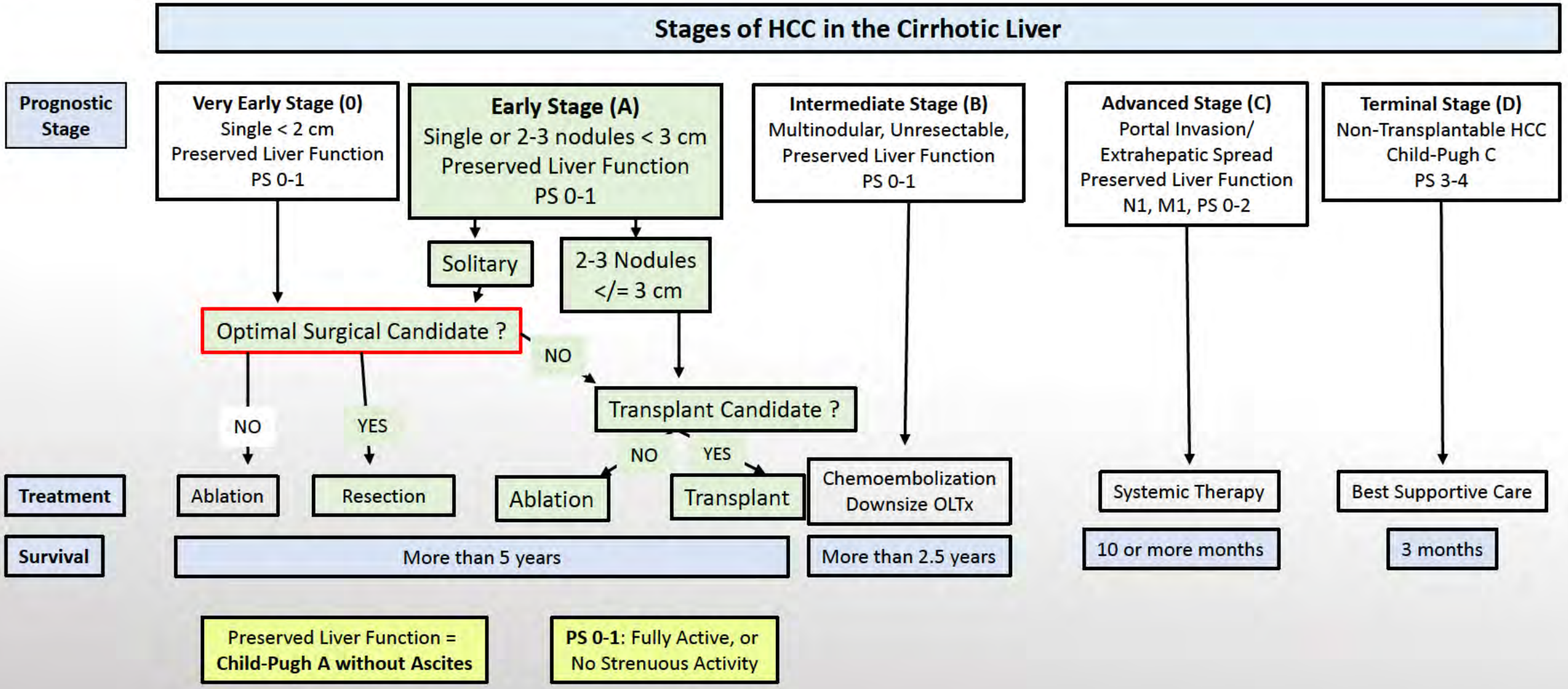
Management and Prognosis of HCC
Very Early Stage

Modified from: Journal of Hepatology 2018 vol.69; 182-236



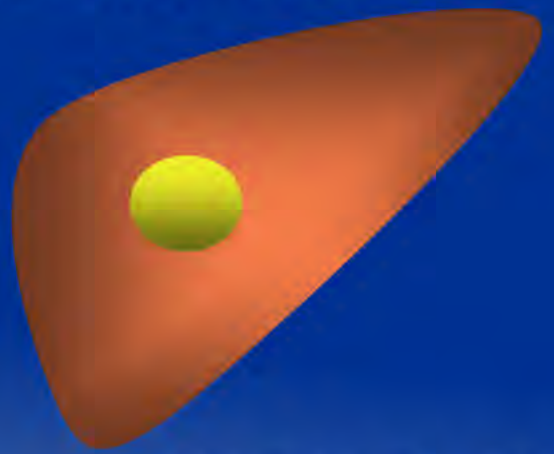
Management and Prognosis of HCC
Early Stage

Modified from: Journal of Hepatology 2018 vol.69; 182-236

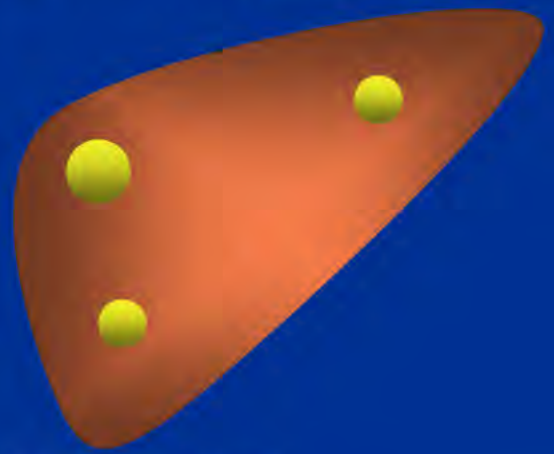


UNOS: Liver Transplantation for HCC: Milan Criteria

Single tumor, at least 2 cm and not > 5 cm



Up to 3 tumors, none > 3 cm



Plus:
Absence of macroscopic vascular invasion, absence of extrahepatic spread

- **5-year survival with transplantation: ~70%**
- **5-year recurrence rates: <15%**

Mazzaferro V. *N Engl J Med*. 1996;334:693-699; Llovet JM. *J Gastroenterol Hepatol*. 2002;17(suppl 3):S428.

UNOS Criteria for Liver Transplantation for HCC

Liver CT or MRI of abdomen showing tumor(s) that meet Li-RADS Class 5 criteria and either:

- One lesion greater than or equal to 2 cm and less than or equal to 5 cm in size.
- Two or three lesions each greater than or equal to 1 cm and less than or equal to 3 cm in size.

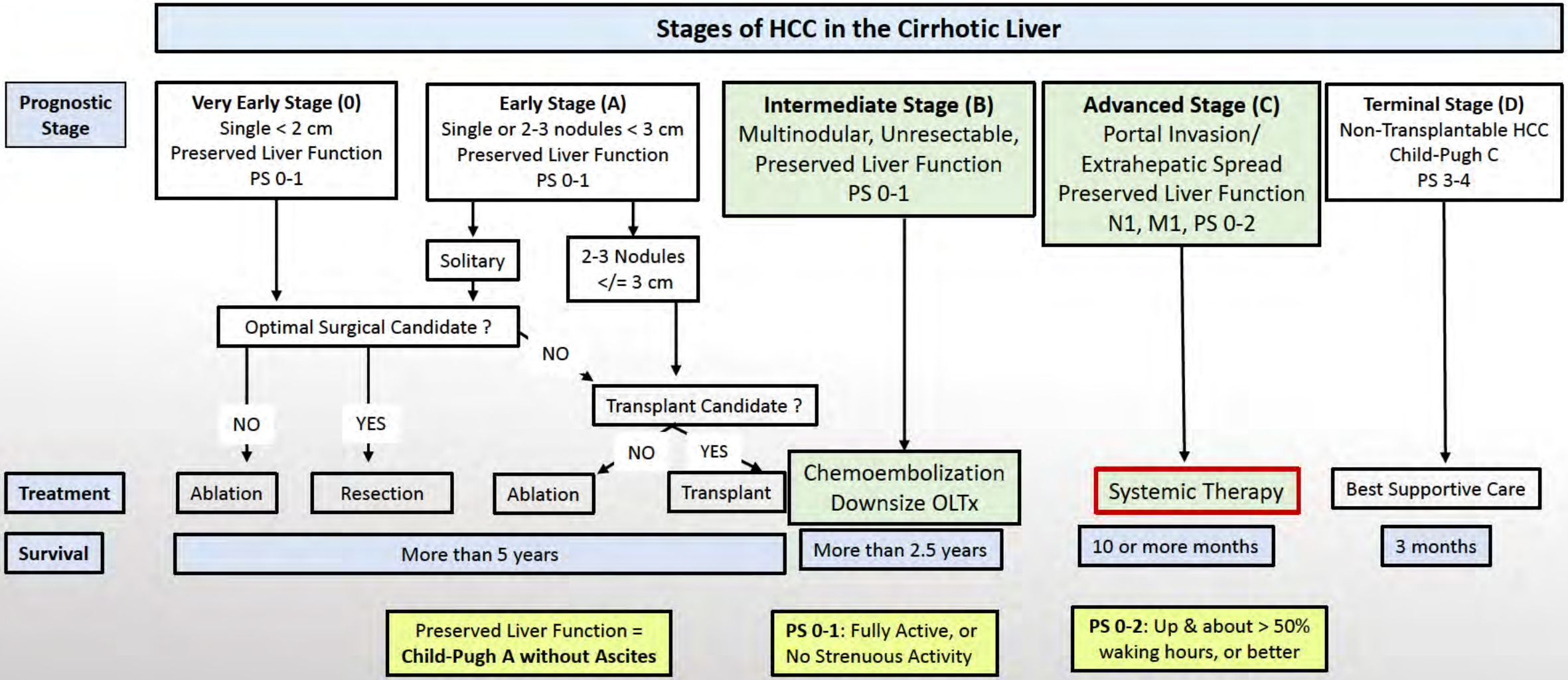
CT of chest that rules out metastatic disease

AFP < 1000

- If patient has history of AFP > 1000, then the AFP needs to fall below 500 after LRT to be eligible for transplantation

Management and Prognosis of HCC Intermediate and Advanced Stage

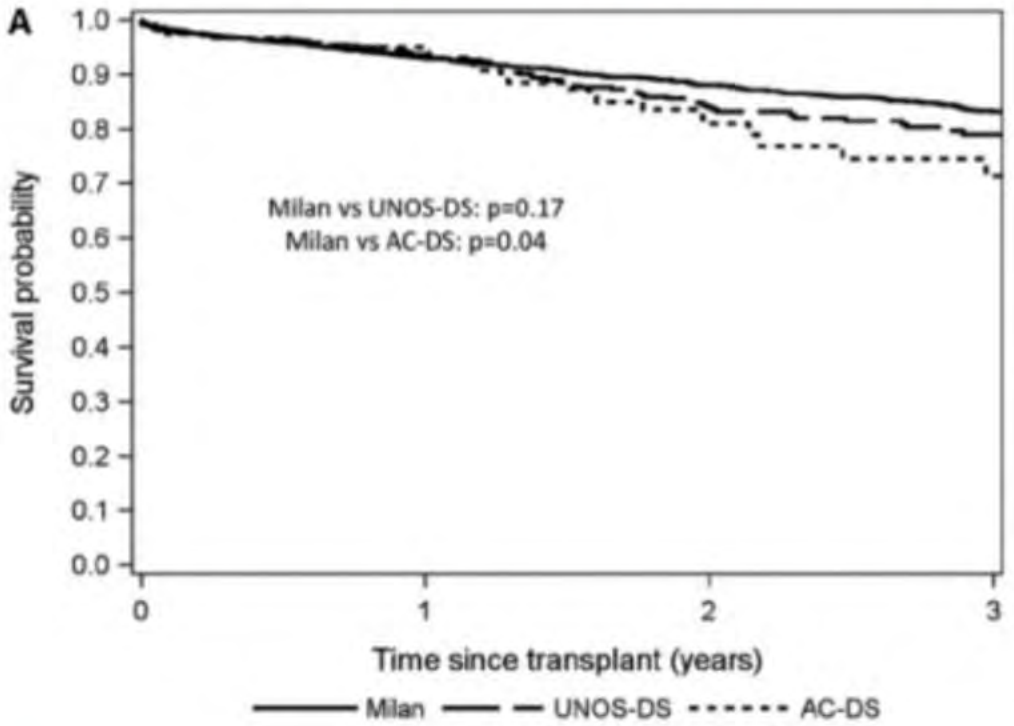
Modified from: Journal of Hepatology 2018 vol.69; 182-236

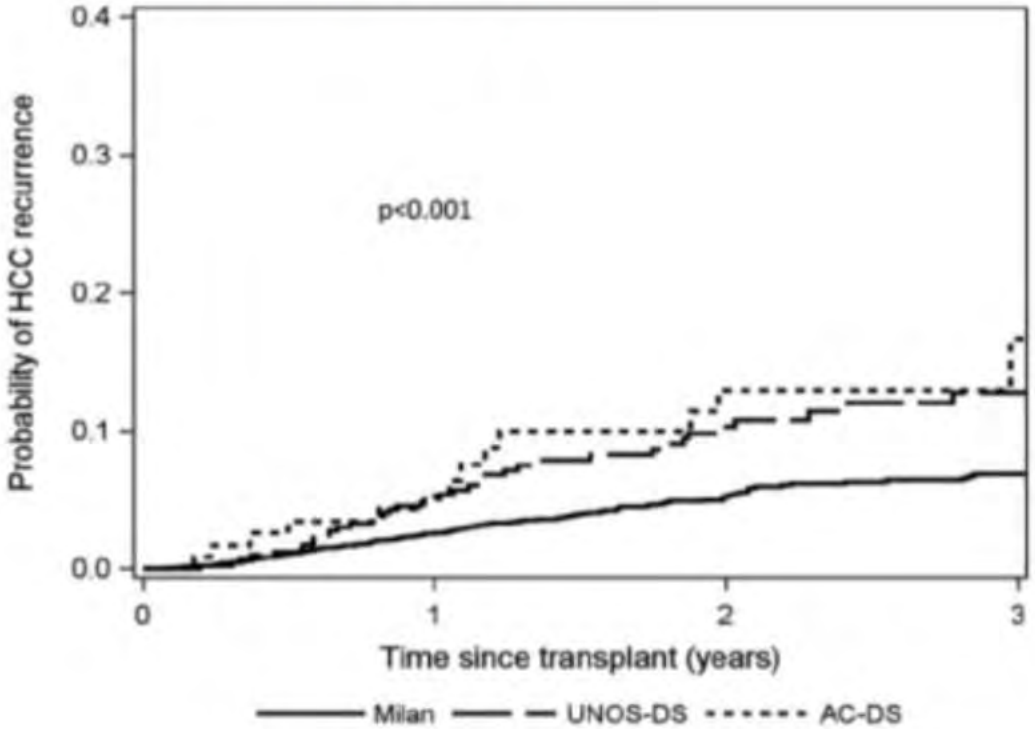


Patients within UNOS-DS criteria can achieve good survival

Multicenter study of patients undergoing LT from 2012-2015
comparing downstaged patients (n=422) vs. within Milan (n=3276) vs. beyond Milan (n=121)

UNOS-DS: One HCC >5 and ≤8 cm, two to three HCC >3 cm and ≤5 cm and diameter ≤8 cm, or four to five lesions each ≤3 cm and diameter ≤8 cm

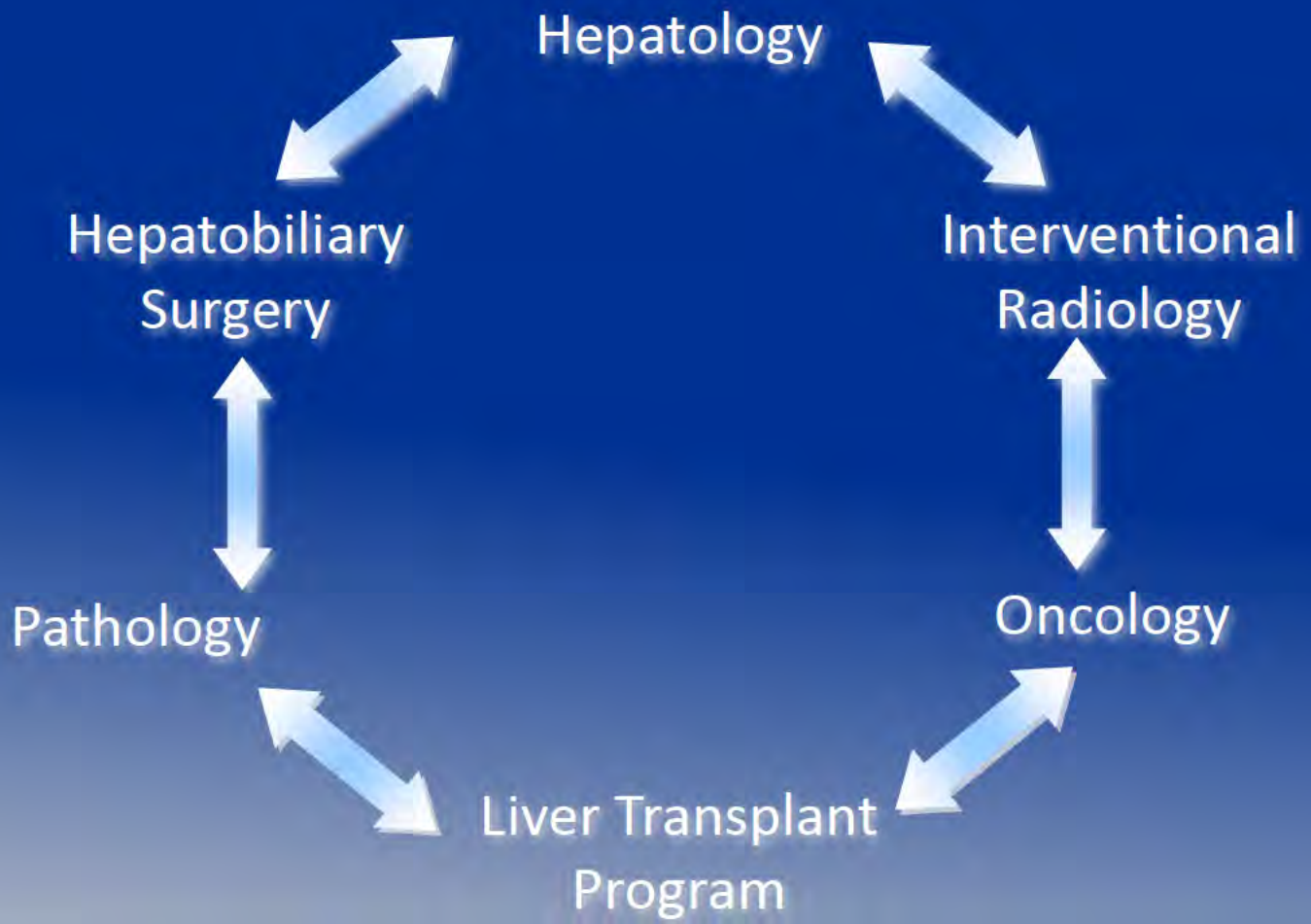




ACG 2021
October 22-27
Las Vegas, NV

Mehta et al. Hepatology 2020

Management of Hepatocellular Carcinoma Requires a Multidisciplinary Approach



Multidisciplinary Care Is Associated with Improved Outcomes

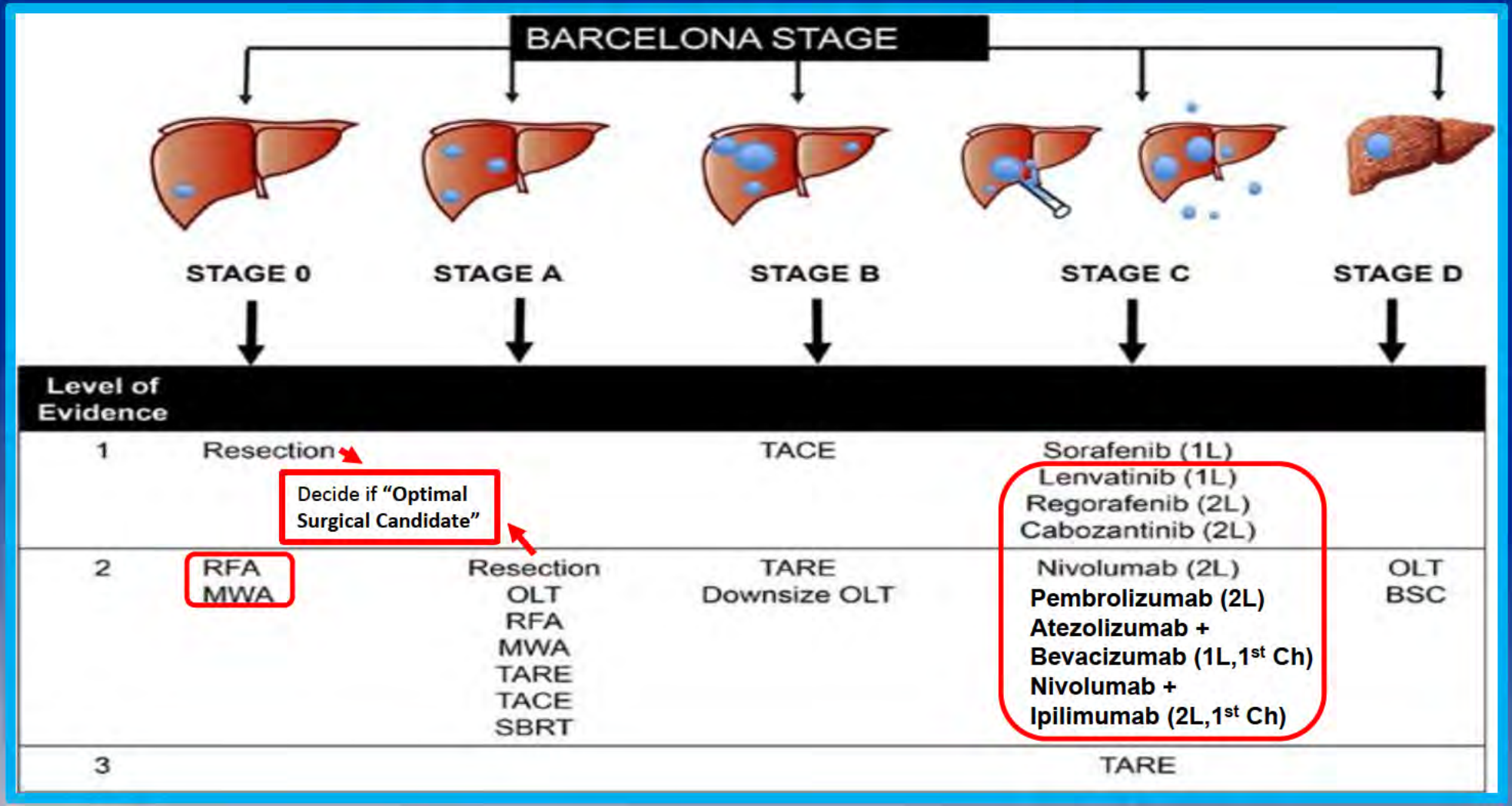
- Chang, et al. *HPB.* 2008; Zhang, et al. *Curr Oncol.* 2013; Yopp, et al. *Ann Surg Oncol*. 2014; Stark, et al. *ILCA.* 2012; Charriere, et al. *J Surg Oncol.* 2017; Gaba, et al. *Ann Hepatol*. 2013; Dyson, et al. *J Hepatol.* 2014

Study	# Patients	Description	Outcomes
Yopp 2014	355	Single day MDT clinic and conference	Improved early detection, curative treatment, time to treatment, and survival
Zhang 2013	343	Single day MDT clinic	Changed imaging/pathology interpretation and therapy plan
Chang 2008	183	Fluid referrals and joint conference	Improved early detection, curative treatment, and survival
Stark 2012	122	Single day MDT clinic and conference	Improved rates of any treatment
Charriere 2017	387	MDT conference	Improved survival
Gaba 2013	167	MDT conference	Increased access to curative therapies and transplantation, improved survival
Dyson 2014	632	Centralized team	Improved referral to specialty care, improved early detection

Treatment Recommendation for HCC

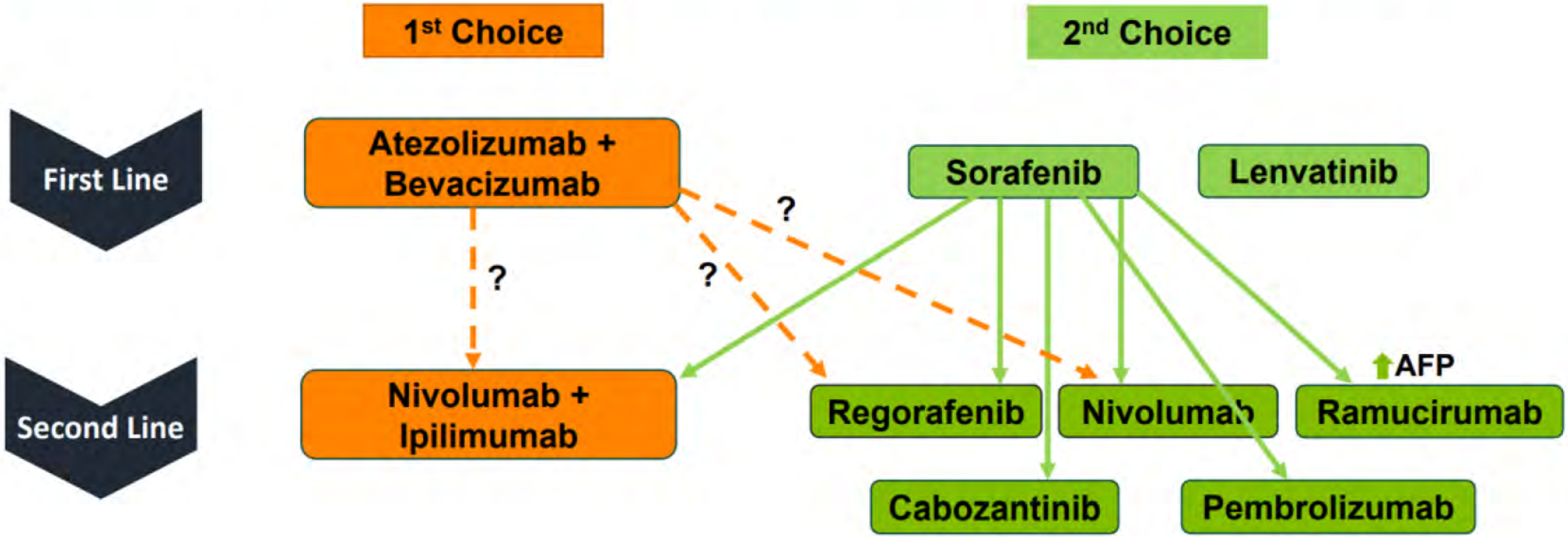
AASLD Practice Guidance 2018

Marrero JA et al. Hepatology, VOL. 68, NO. 2, 723-750, 2018



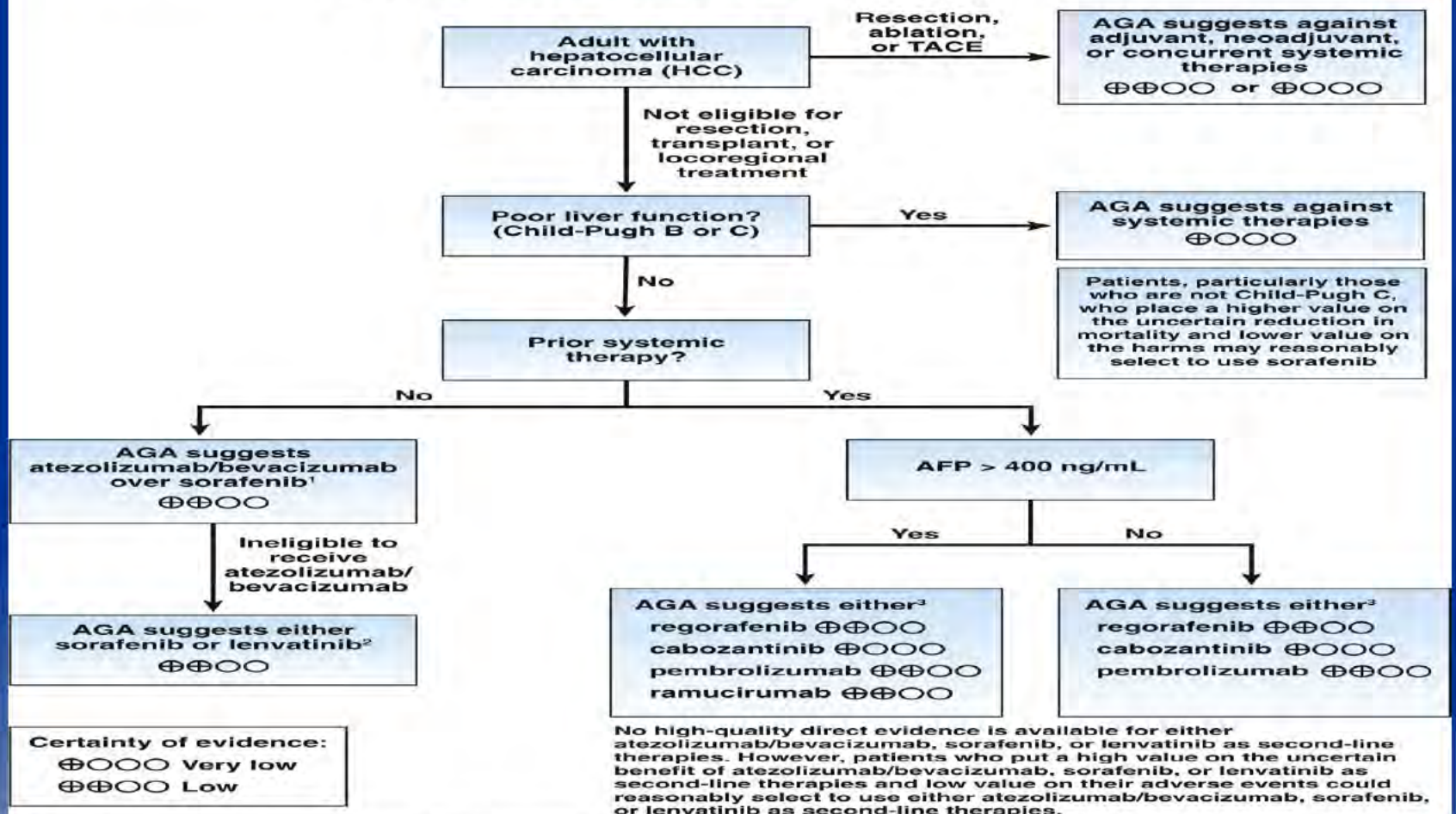
Systemic Medical Therapy for HCC

Current Therapeutic Options in Advanced HCC



Systemic Therapy for Hepatocellular Carcinoma

Clinical Decision Support Tool



[1]Esophageal varices screening and treatment prior to starting treatment is recommended. Although no prior studies compared atezolizumab/bevacizumab versus lenvatinib, the results of the REFLECT trial suggest that sorafenib and lenvatinib are comparable.

[2a]Patients who place a higher value on delayed radiologic disease progression and lower value on the increase in adverse events (both serious and leading to discontinuation of the drug) may reasonably choose lenvatinib.

[2b]Patients who place a higher value on blood pressure control and a lower value on the adverse skin reactions would reasonably select sorafenib.

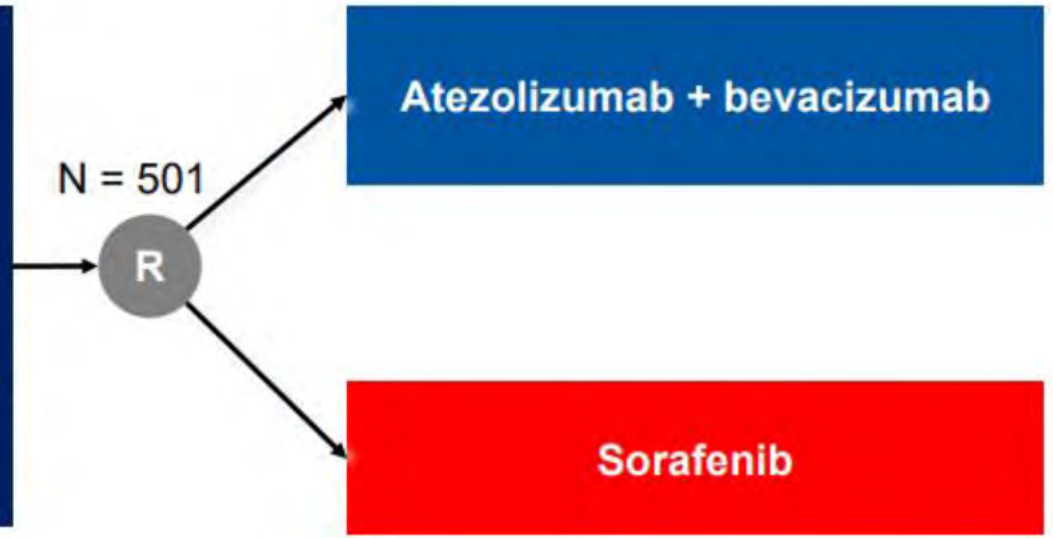
[3]Patients who place a higher value on adverse effects associated with any of the second-line therapies (regorafenib, cabozantinib, pembrolizumab, or ramucirumab) and lower value on the reduction in mortality (1.2 to 2.8 months) may reasonably decline second-line therapies.

Gastroenterology 2022 162DOI: (10.1053/S0016-5085(22)00065-8)

IMBrave150: Atezolizumab/Bevacizumab vs. Sorafenib

Key eligibility criteria

- Locally advanced or metastatic and/or unresectable HCC
- No prior systemic therapy for HCC
- ≥1 measurable untreated lesion
- ECOG PS 0 or 1
- Adequate hematologic and end-organ function
- Child–Pugh class A



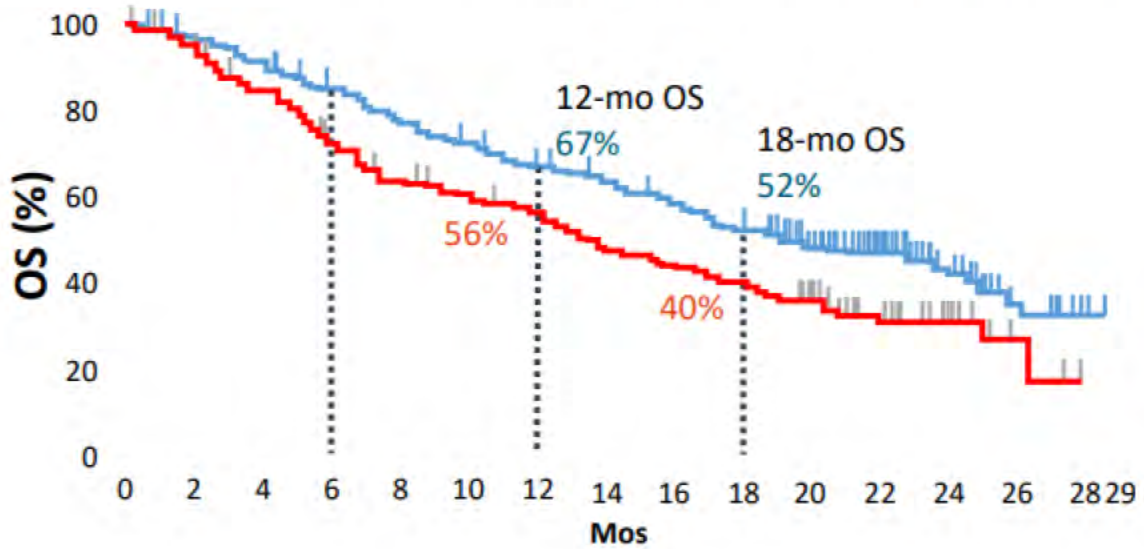
- **Primary endpoints:** PFS and OS

All patients were required to have recent EGD to risk stratify risk of bleeding

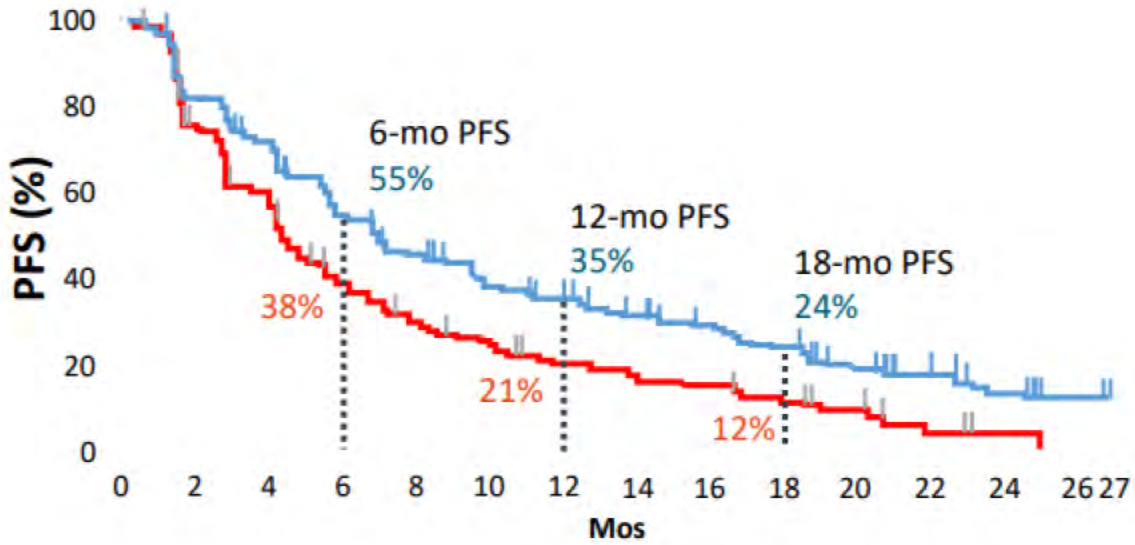
Finn et al New Eng J Med 2020

Atezolizumab and bevacizumab is new standard of care for patients with advanced-stage HCC

	Atezo + Bev (n = 336)	Sorafenib (n = 165)
Median OS, mos	**19.2**	**13.4**
Stratified HR (95% CI)	0.66 (0.52-0.85)	



	Atezo + Bev (n = 336)	Sorafenib (n = 165)
Median PFS, mos	**6.9**	**4.3**
Stratified HR (95% CI)	0.65 (0.53-0.81)	



ACG 2021
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Finn et al New Eng J Med 2020
Finn et al. ASCO GI 2021

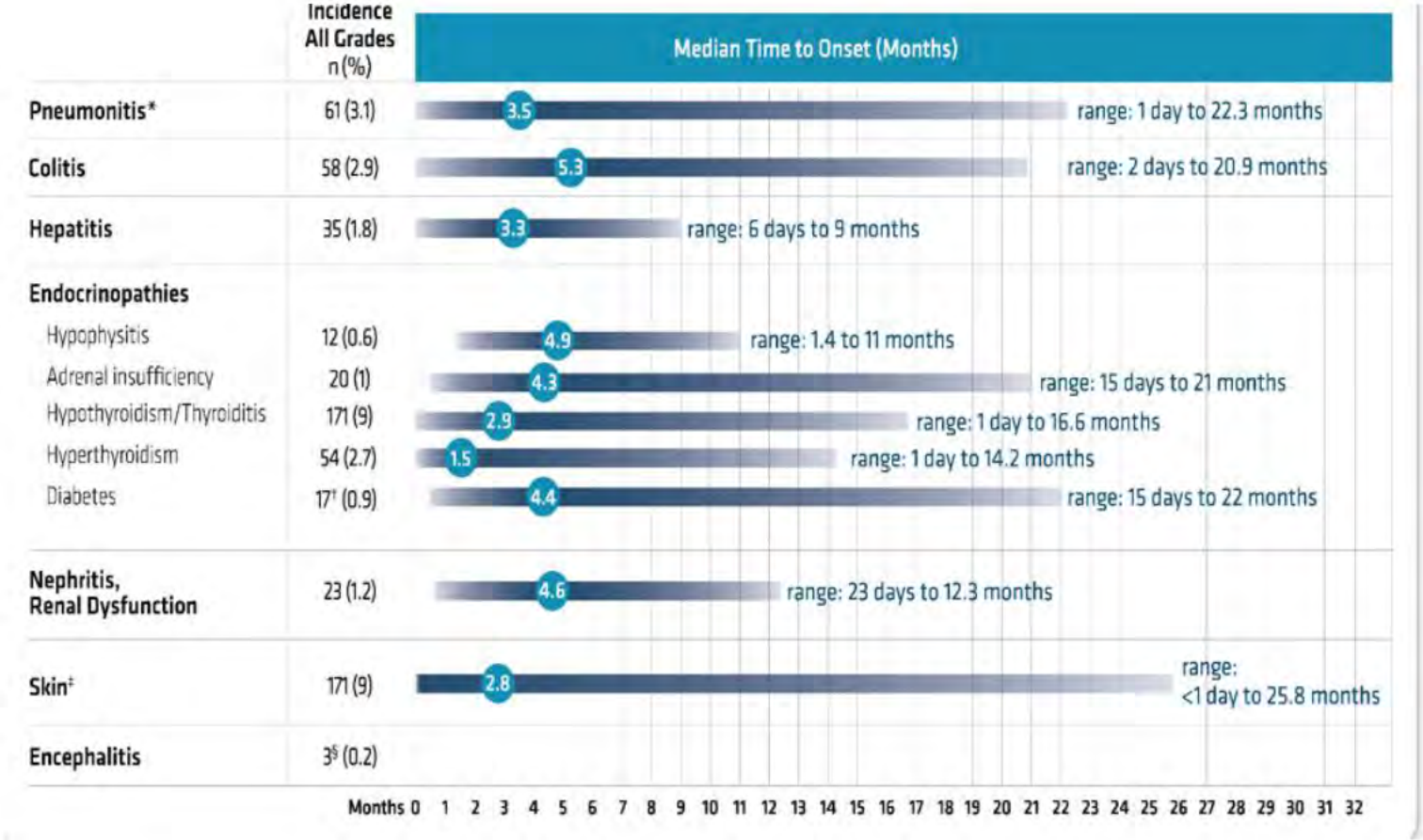
Immunotherapy Related Adverse Effects (irAEs) Menzies et al. Ann Oncol 2016

PD-1 blockade associated with less irAEs than CTLA-4 antibodies

In melanoma trials of nivolumab, 24% required immunosuppressive therapy for management of irAEs

- Need for immunosuppression did not affect response to drug

Immune Related Adverse Events (irAEs)



Infusion-related reactions in 6.4%

Immunotherapy Adverse Effects

Patients should be monitored closely during treatment for immune-mediated Endocrinopathies, Pneumonitis, **Colitis, Hepatitis**, nephritis, etc.

Hormone replacement may be necessary

Corticosteroids are the mainstay of therapy for immune related side effects

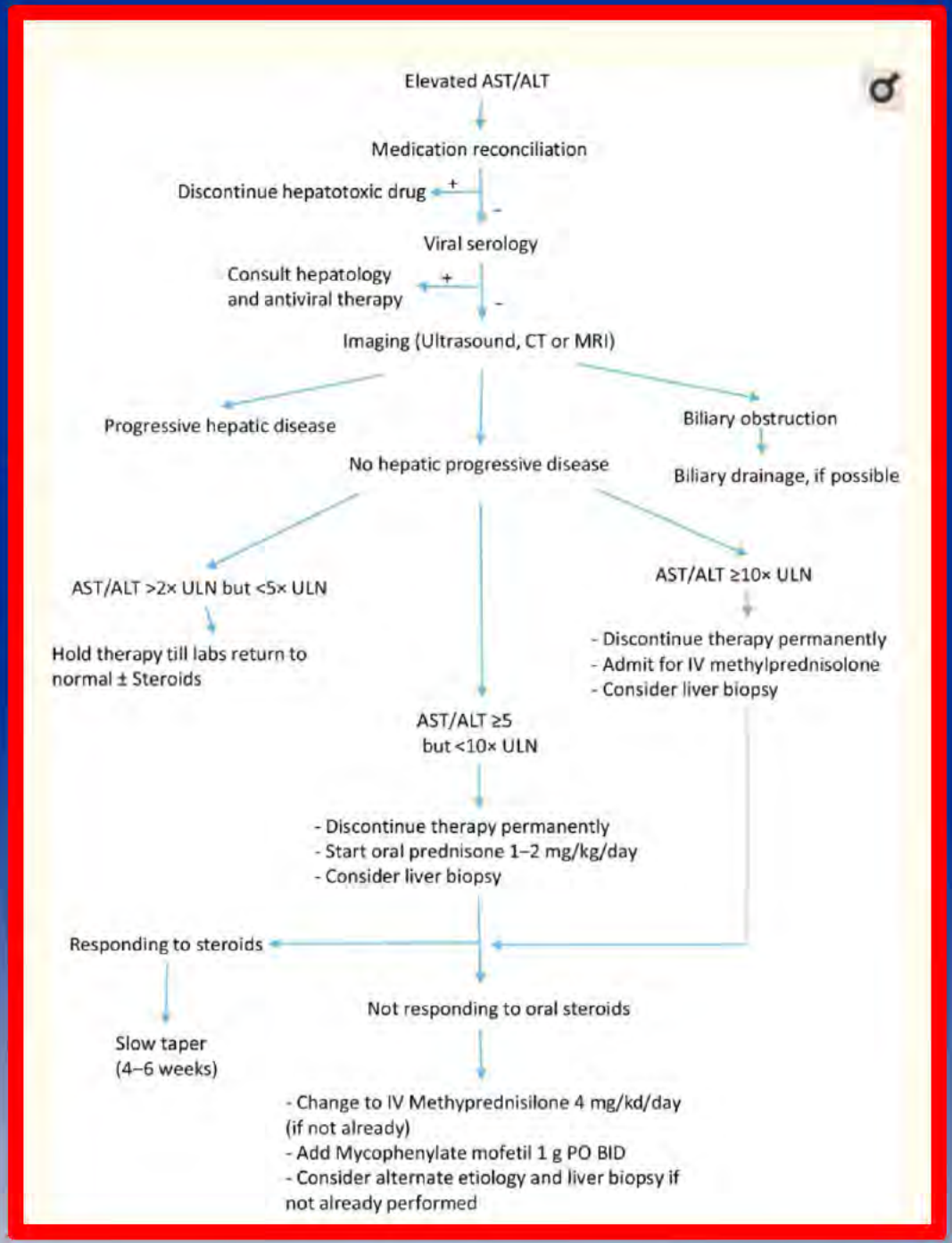
Dose delay may be required in up to 1/3 of patients

11% discontinue therapy due to AEs

Some fatal reactions have been reported

Check-point Inhibitor-Related Hepatitis

J Gastrointest Oncol. 2018 Feb; 9(1): 220–224



AIH vs Checkpoint Inhibitor (ICI) Hepatitis

	Autoimmune Hepatitis	ICI Hepatotoxicity
Gender	Female predominant	Equal sex incidence
Symptoms	Malaise, jaundice	Fever, rash
Antibody—ANA, ASMA	Positive	Negative or low titer
Gamma globulin level	Increased	Normal range
Histology	Interface hepatitis, fibrosis	Hepatitis (lobular, pan-lobular, centrilobular, granulomatous). Portal fibrosis.
Cell infiltration	Plasma cell: CD4+ CD8+	Histiocyte: CD4+ CD8+
Recurrence after ICI withdrawal	Yes	No

ANA—antinuclear antibody, ASMA—anti-smooth-muscle antibody.

Histology

Anti-PD-1/PD-L1: acute hepatitis with lobular inflammation, acidophilic bodies and centrilobular necrosis.
CTLA-4 inhibitors: central vein endotheliosis and granulomatous hepatitis.
Immune Mediated Cholangitis: bile duct injury (100%), portal inflammation (87.5%), ductular reaction (54.2%), bile duct loss (16.7%), cholestasis (29.2%) and lobular injury (45.8%)

ICI Immune-Mediated Cholangitis

Pi, Borui et al. European Journal of Gastroenterology & Hepatology: September 1, 2021

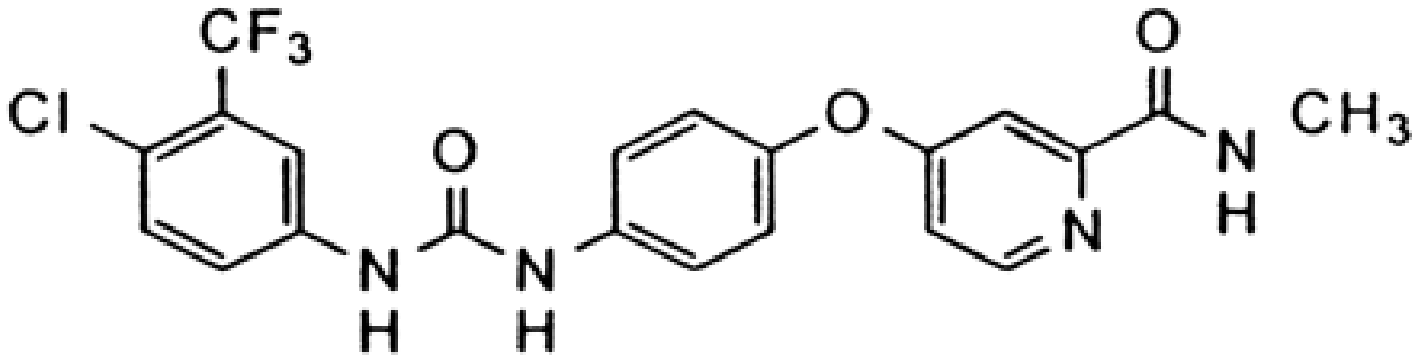
- **Patients:** 53 patients; gender 35M/18W; age 43-89.
- **Injury Type:** 12 with small-ducts type, 29 with large-ducts type and 12 with mixed type cholangitis.
- **Drug Type:** 47 anti-PD-1 therapy, 3 anti-PD-L1 therapy, 1 anti-CLTA-4 and 2 anti-PD-1/PD-L1 + anti-CLTA-4 therapy.
- **Number of ICIs cycles until IMC onset:** five (range, 1–27).
- **Biochemistry:** Median Alkaline Phosphatase 1328 (237-4635) being higher in large duct disease; Median ALT 156 (31-1536).
- **Histology:** bile duct injury (100%), portal inflammation (87.5%), ductular reaction (54.2%), bile duct loss (16.7%), cholestasis (29.2%) and lobular injury (45.8%)

Immunotherapy-Related Hepatitis

	Immunotherapy Recommendations and monitoring	Treatment
AST/ALT <3x ULN Total bilirubin <1.5x ULN	• Continue therapy • Monitor labs 1-2x/week	• None
AST/ALT 3-5x ULN Total bilirubin 1.5-3x ULN	• Hold therapy until recovered • Monitor labs every 3 days	• Prednisone 0.5-1 mg/kg/d if persists more than 3-5 days • Taper over at least 1 month
AST/ALT 5-20x ULN Total bilirubin 3-10x ULN	• Permanently discontinue • Monitor labs every 1-2 days	• Methylprednisolone 1-2 mg/kg • If no improvement after 3 days, consider mycophenolate mofetil or azathioprine (test for TPMT deficiency) • Taper steroids around 4-6 weeks
AST/ALT >20x ULN Total bilirubin >10x ULN Decompensated liver function	• Permanently discontinue • Inpatient monitoring • Consider transfer to tertiary care facility	• Methylprednisolone 2 mg/kg • If no improvement after 3 days, consider mycophenolate mofetil • Taper steroids around 4-6 weeks

In Immune-Mediated Cholangitis the treatment is longer (4-6 months or longer);
Pred 60 mg/d + UDCA; tapper steroids after resolution of inflammation in F/U Liver biopsy)

Brahmer JR, JCO 2018 epub ahead of print



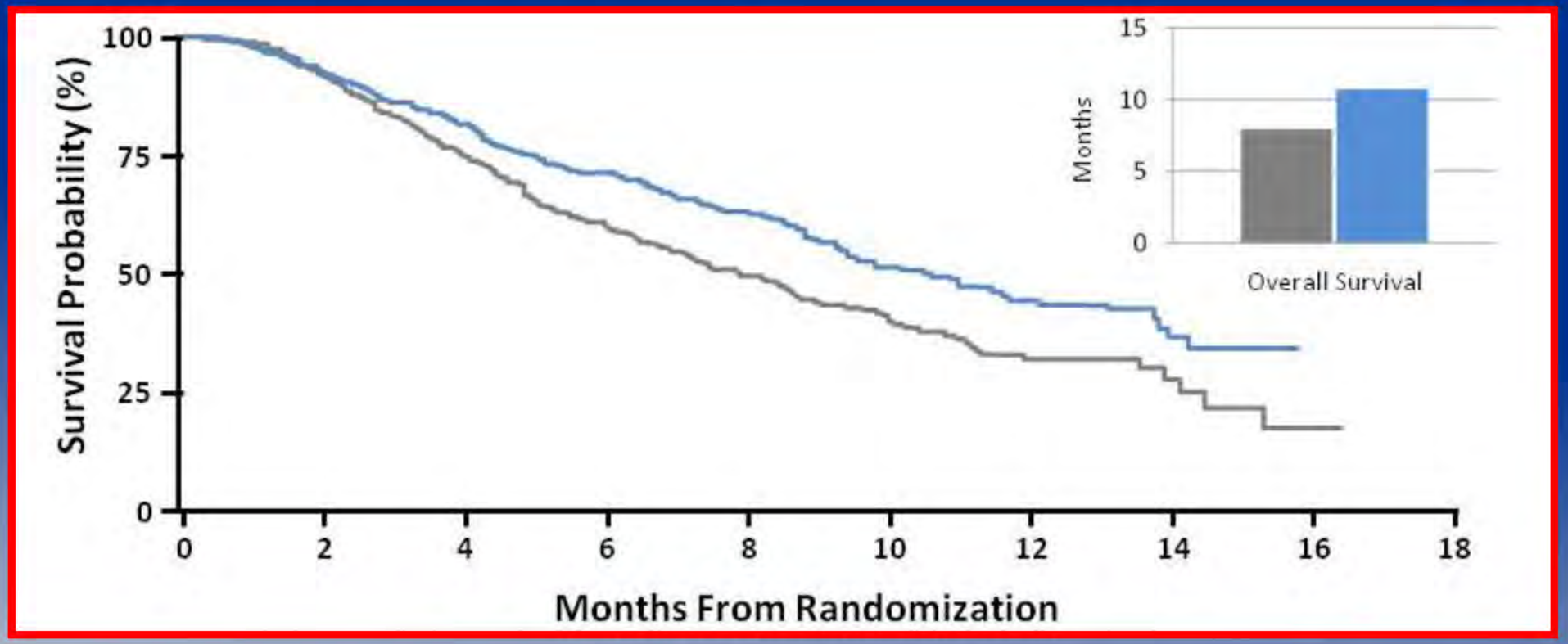
Sorafenib

- SORAFENIB, is a oral multikinase inhibitor
- It is active against:
  - Serine/threonine kinases c-Raf and B-Raf
  - Receptor tyrosine kinases: e.g. VEGFR 2 (Vascular Endothelial Growth Factor Receptor), PDGFR (Platelet Derived Growth Factor Receptor), c-Kit receptor

Phase 3 SHARP Trial

Overall Survival (Intention-to-treat)

Sorafenib	Median Overall Survival (n=299) = **10.7 months (95% CI, 9.4-13.3)**
Placebo	Median Overall Survival (n=303) = **7.9 months (95% CI, 6.8-9.1)**
	HR: 0.69; 95% CI, 0.55-0.87; *P*<0.001



Phase 3 SHARP Trial

Adverse Effects

	Sorafenib		Placebo	
Adverse Reaction	Any Grade	Grade ¾	Any Grade	Grade 3/4
Fatigue	46%	10%	45%	14%
Weight loss	30%	2%	10%	1%
Hand Food Skin Rxn	21%	8%	3%	<1%
Hypertension	9%	4%	4%	1%
Alopecia	14%	0%	2%	0%
Diarrhea	55%	10%	25%	2%
Anorexia	29%	3%	18%	3%

Patients with grade 2 HFSR within one month of initiation had longer Overall Survival (28.9 months vs 16.8 months) Zhao et al. Internation Journal of Cancer 2016;139(4):928-37

Lenvatinib

Oral multiple tyrosine kinase inhibitor

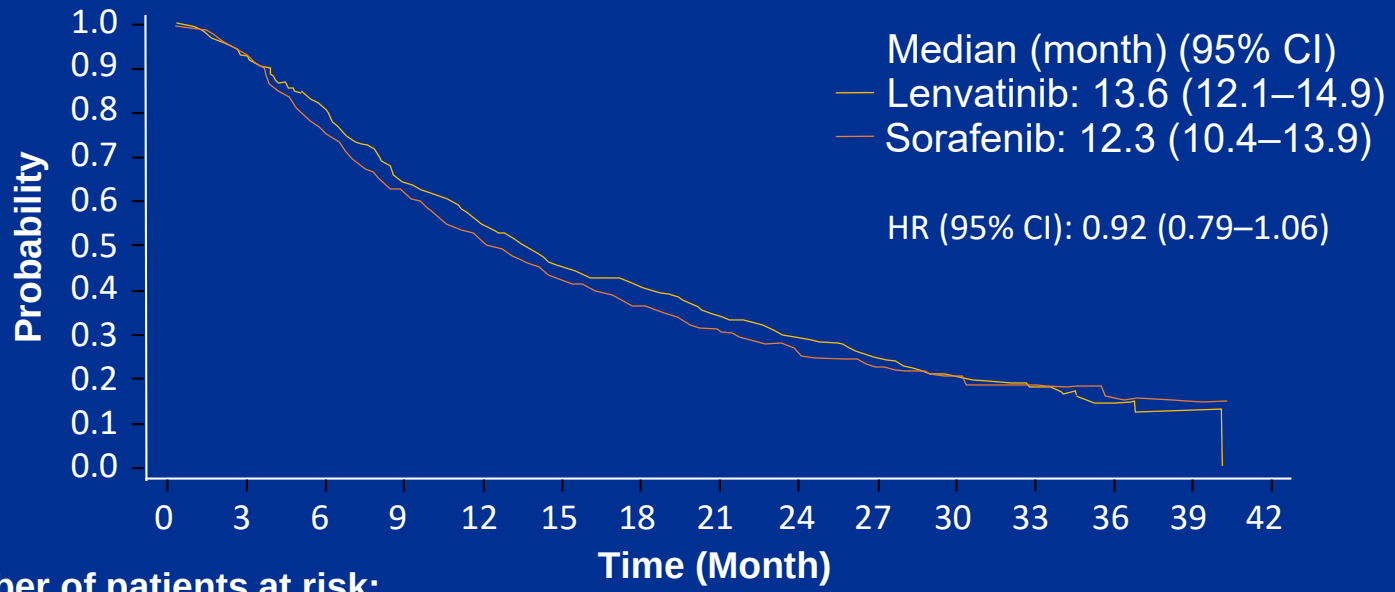
Mainly active against VEGFR1, VEGFR2, and VEGFR3

Also inhibits FGFR1, 2, 3, and 4, PDGFR, KIT, RET

REFLECT: Lenvatinib 8 mg or 12 mg daily (based on body weight) vs Sorafenib

- 954 patients enrolled globally
- BCLC B or C, Child-Pugh A, ECOG PS ≤1
- No prior systemic therapy
- No portal vein invasion allowed
- Primary endpoint OS with target of non-inferiority

REFLECT: Primary Endpoint

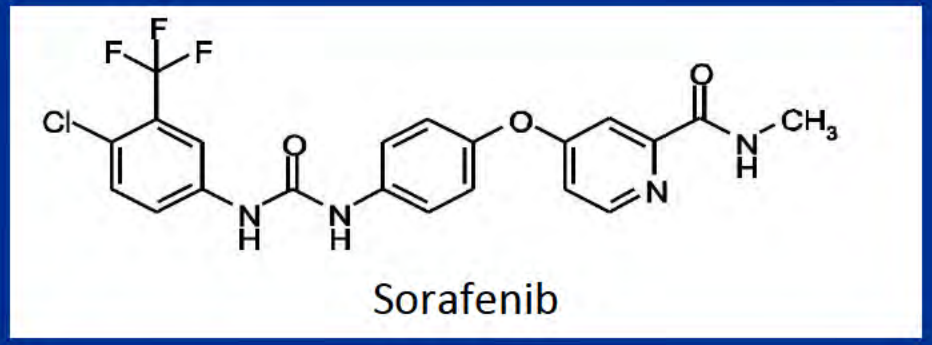


Number of patients at risk:

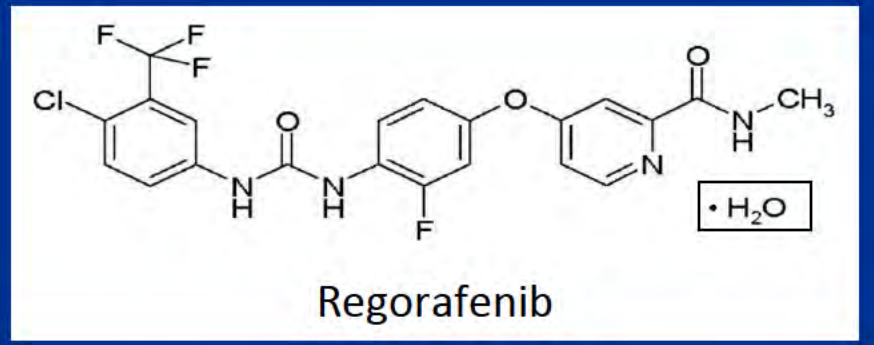
Lenvatinib	478	436	374	297	253	207	178	140	102	67	40	21	8	2	0
Sorafenib	476	440	348	282	230	192	156	116	83	57	33	16	8	4	0

Cheng AL et al. Presentation: ASCO 2017; Chicago IL

Regorafenib



Sorafenib



Regorafenib

- REGORAFENIB, is also an oral multikinase inhibitor
- It is active against:
  - Protein kinases involved in angiogenesis, oncogenesis, metastasis and tumor immunity
  - Very similar to sorafenib in structure and function.
  - More potent than sorafenib

RESORCE Trial Design

Regorafenib for HCC patients who progressed on Sorafenib

- HCC patients with documented radiological progression during sorafenib treatment. Liver function was CP-A
- 152 sites in 21 countries
- Stratified by:
  - Geographic region (Asia vs ROW)
  - Macrovascular invasion
  - Extrahepatic disease
  - ECOG PS (0 vs 1)
  - AFP (<400 ng/mL vs ≥400 ng/mL)

R
2:1

Regorafenib
160 mg po once daily
3 weeks on / 1 week off
(4-week cycle)
(n=379)

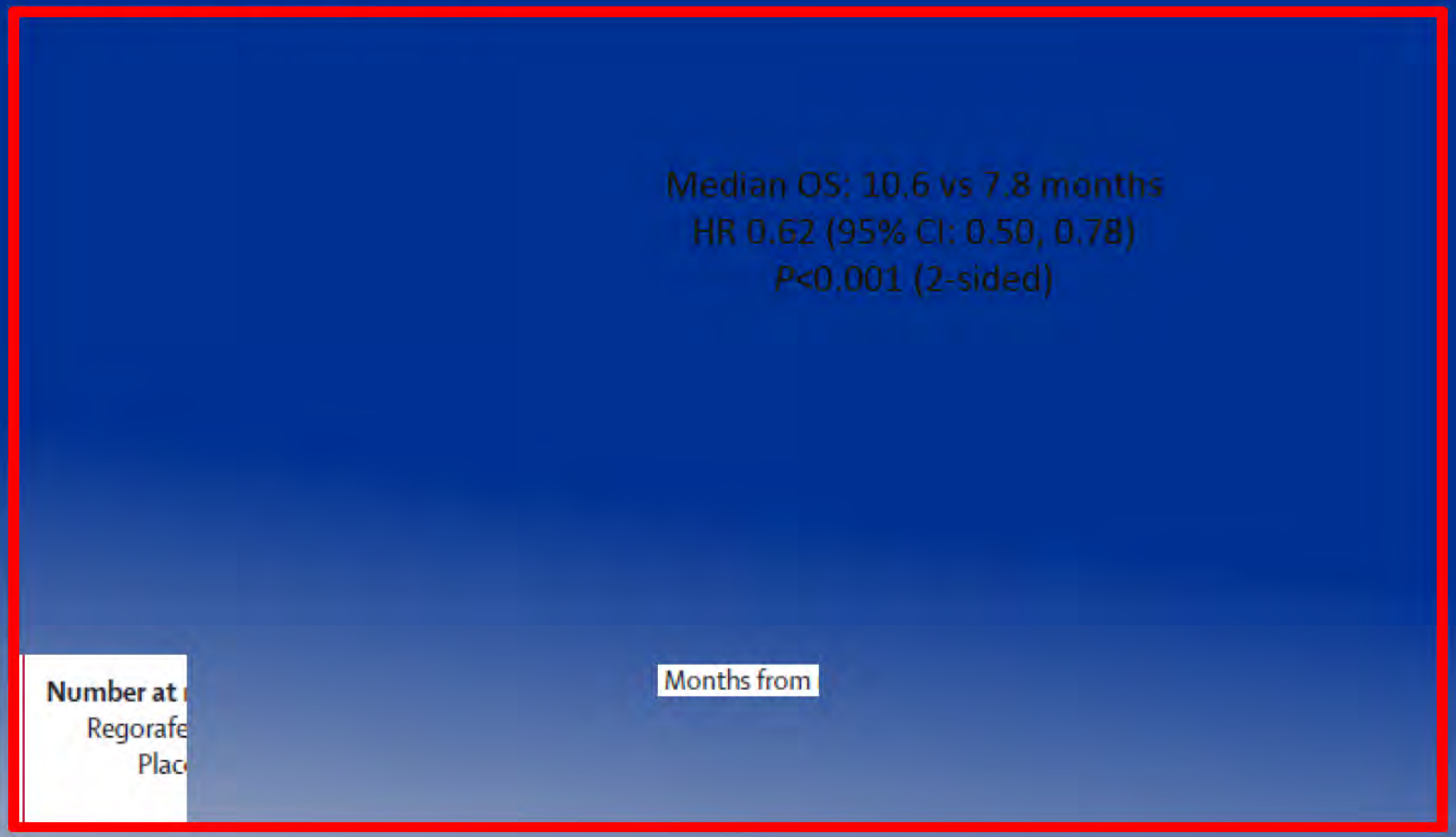
Placebo
(n=194)

Primary Endpoint: Overall Survival

Bruix J, et al. Lancet January 2017;389:56-66

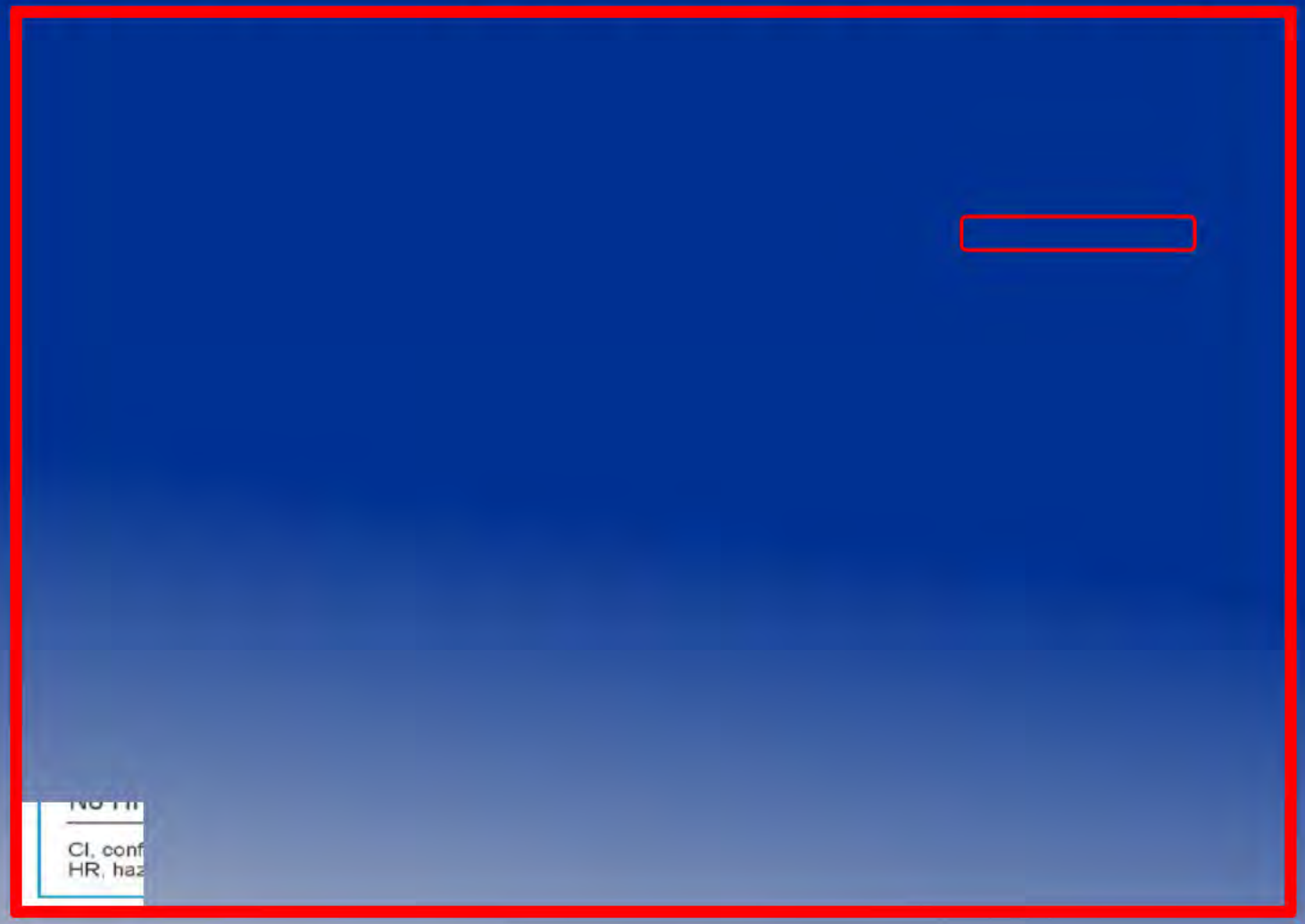
RESORCE Trial - Results

Overall Survival (OS)



Bruix J, et al. Lancet January 2017;389:56-66

HFSR May Mean Improved OS with Regorafenib



Bruix et al, ASCO GI 2018 Abstract 412

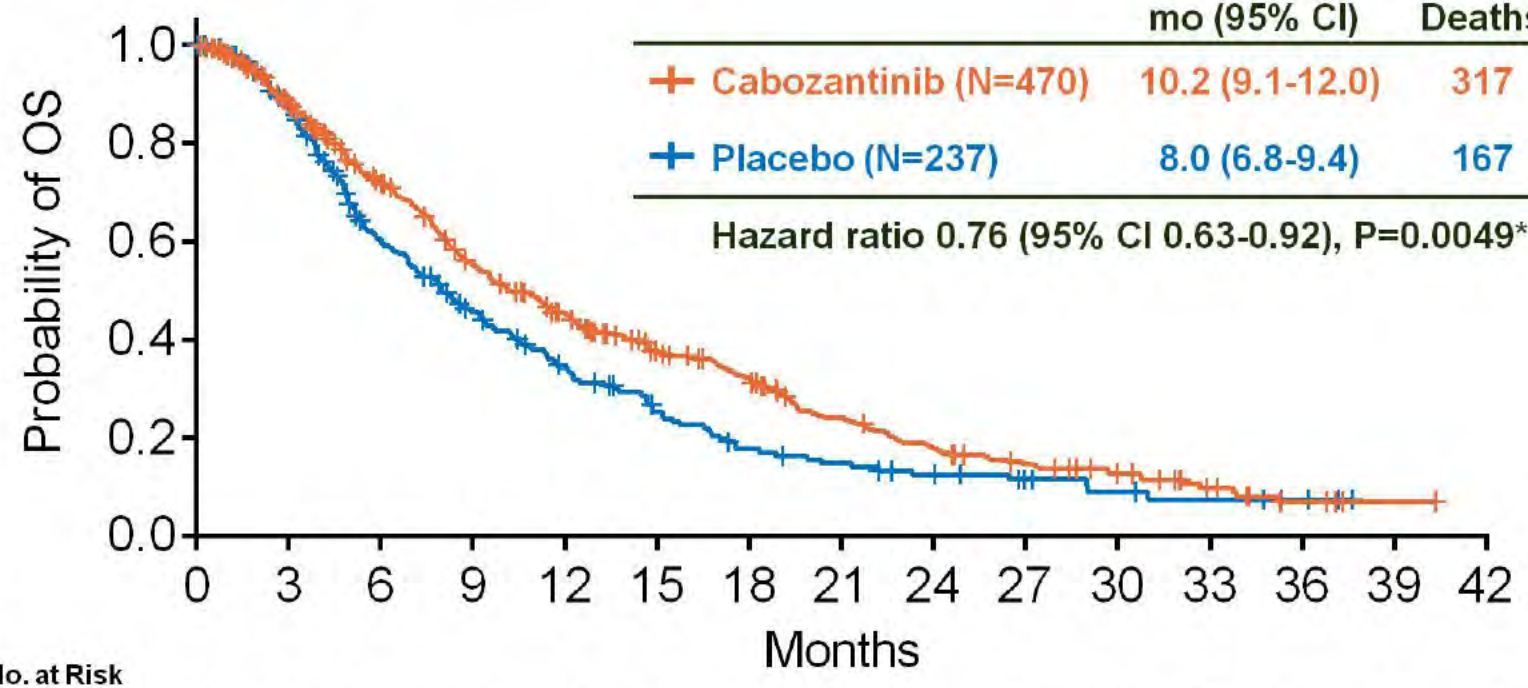
Cabozantinib

- Oral multiple tyrosine kinase inhibitor
- Active against VEGFR1, VEGFR2, and VEGFR3
- Also inhibits MET and AXL – which play a role in invasion and metastases and resistance to anti-angiogenic therapy
- High expression of MET and AXL may be associated with poor prognosis in HCC
- **CELESTIAL:** Cabozantinib 60 mg daily vs Placebo randomized 2:1
  - 773 patients enrolled
  - Patients must have progressed after systemic treatment, up to 2 prior systemic treatments allowed
  - BCLC B or C, CTP A, ECOG PS ≤1
  - HBV 40%, HCV 22%, other 40%
  - 5 months median duration of sorafenib prior to enrollment

Abou-Alfa et al. N Engl J Med. 2018 Jul 5;379(1):54-63

Cabozantinib in Second Line Treatment

Overall Survival



	Median OS mo (95% CI)	No. of Deaths
Cabozantinib (N=470)	10.2 (9.1-12.0)	317
Placebo (N=237)	8.0 (6.8-9.4)	167

Hazard ratio 0.76 (95% CI 0.63-0.92), P=0.0049*

No. at Risk

Cabozantinib	470	382	281	206	159	116	93	63	44	31	22	12	4	1	0
Placebo	237	190	117	82	57	37	25	20	15	10	7	5	3	0	0

*Critical p-value ≤ 0.021 for second interim analysis

Presented By Ghassan Abou-Alfa at 2018 Gastrointestinal Cancers Symposium

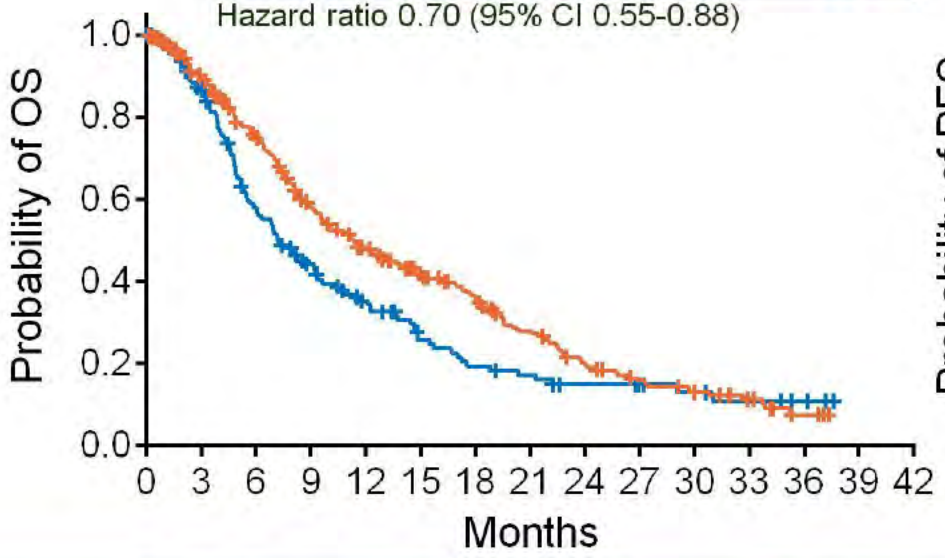
Cabozantinib in Second Line Treatment

Overall Survival and Progression-free Survival

Sorafenib as only prior therapy for HCC

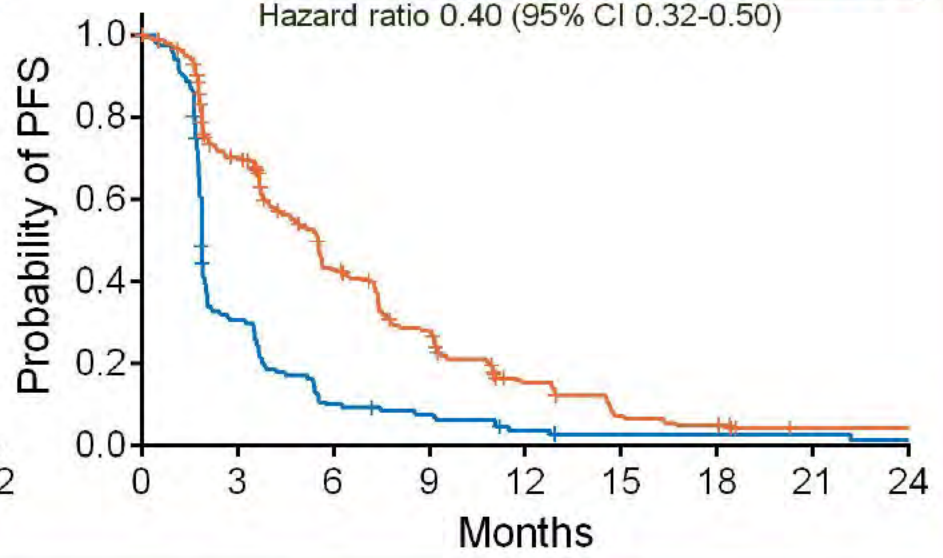
	Median OS mo (95% CI)	No. of Deaths
Cabozantinib (n=331)	11.3 (9.5-13.9)	219
Placebo (n=164)	7.2 (5.8-9.3)	114

Hazard ratio 0.70 (95% CI 0.55-0.88)



	Median PFS mo (95% CI)	No. of Events
Cabozantinib (n=331)	5.5 (4.6-5.7)	246
Placebo (n=164)	1.9 (1.9-1.9)	142

Hazard ratio 0.40 (95% CI 0.32-0.50)



Presented By Ghassan Abou-Alfa at 2018 Gastrointestinal Cancers Symposium

Nivolumab

Nivolumab is FDA approved for patients with HCC who have previously failed sorafenib (accelerated approval)

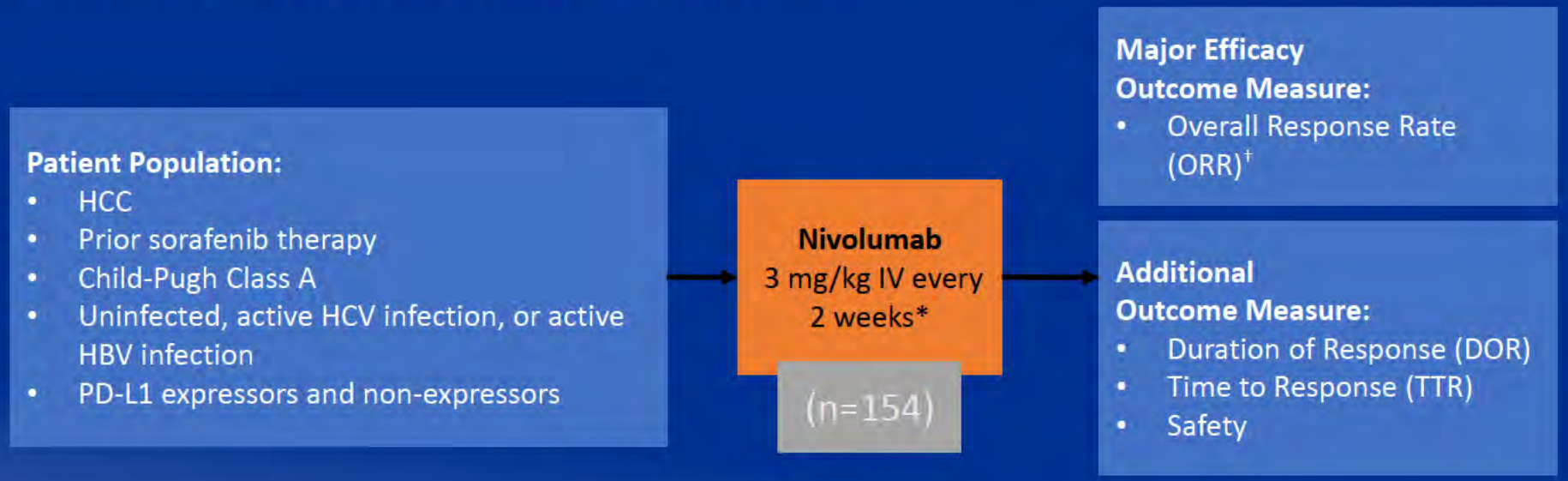
Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial

*Anthony B El-Khoueiry,*Bruno Sangro,* Thomas Yau, Todd S Crocenzi, Masatoshi Kudo, Chiun Hsu, Tae-You Kim, Su-Pin Choo, Jörg Trojan, Theodore H Welling 3rd, Tim Meyer, Yoon-Koo Kang, Winnie Yeo, Akhil Chopra, Jeffrey Anderson, Christine dela Cruz, Lixin Lang, Jaclyn Neely, Hao Tang, Homa B Dastani, Ignacio Melero*

Lancet. 2017 Apr 20. [Epub ahead of print].

Nivolumab in Patients Previously Treated with Sorafenib

CheckMate 040 Study Design and Result

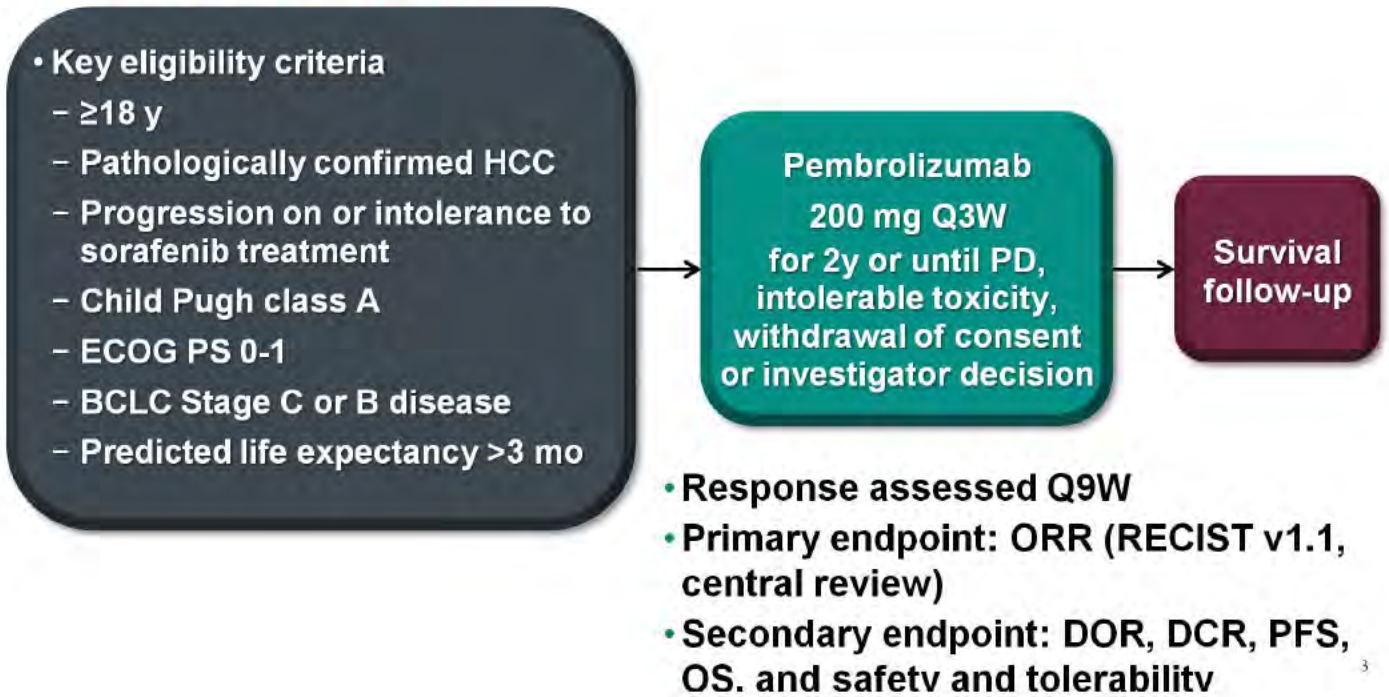


- Included a phase 1/2, multicenter, open-label study conducted in patients with HCC who progressed on or were intolerant to sorafenib
- The trial excluded patients with infection with HIV and active co-infection with HBV/HCV or HBV/HDV
- Patients were required to have an AST and ALT of no more than five times the ULN and total bilirubin of less than 3 mg/dL
- **RESULT: Disease control rate in all patients by BICR (RECIST v1.1) was 55.9%**

Pembrolizumab for Second Line Treatment in HCC
KEYNOTE 224 Study

Zhu et al, ASCO GI 2018

Study Design



Pembrolizumab for Second Line Treatment in HCC KEYNOTE 224 Study

Zhu et al, ASCO GI 2018

Anti-tumor Activity

Response†	Total N=104 n (%)	95% CI‡
ORR (CR+PR)	17 (16.3)	9.8 - 24.9
Disease control (CR+PR+SD)	64 (61.5)	51.5 - 70.9
Best overall response		
CR	1 (1.0)	0.0 - 5.2
PR	16 (15.4)	9.1- 23.8
SD	47 (45.2)	35.4 - 55.3
PD	34 (32.7)	23.8 - 42.6
No Assessment§	6 (5.8)	2.1-12.1

†Confirmed best response by independent central review per RECIST v1.1. ‡Based on binomial exact confidence interval method. §Subjects who had a baseline assessment by investigator review or central radiology but no post-baseline assessment on the data cutoff date including discontinuing or death before the first post-baseline scan. Data cutoff date: Aug 24, 2017.

Thank you for your attention

Major Guidelines Recognize the Importance of Routine Surveillance in High-Risk Populations

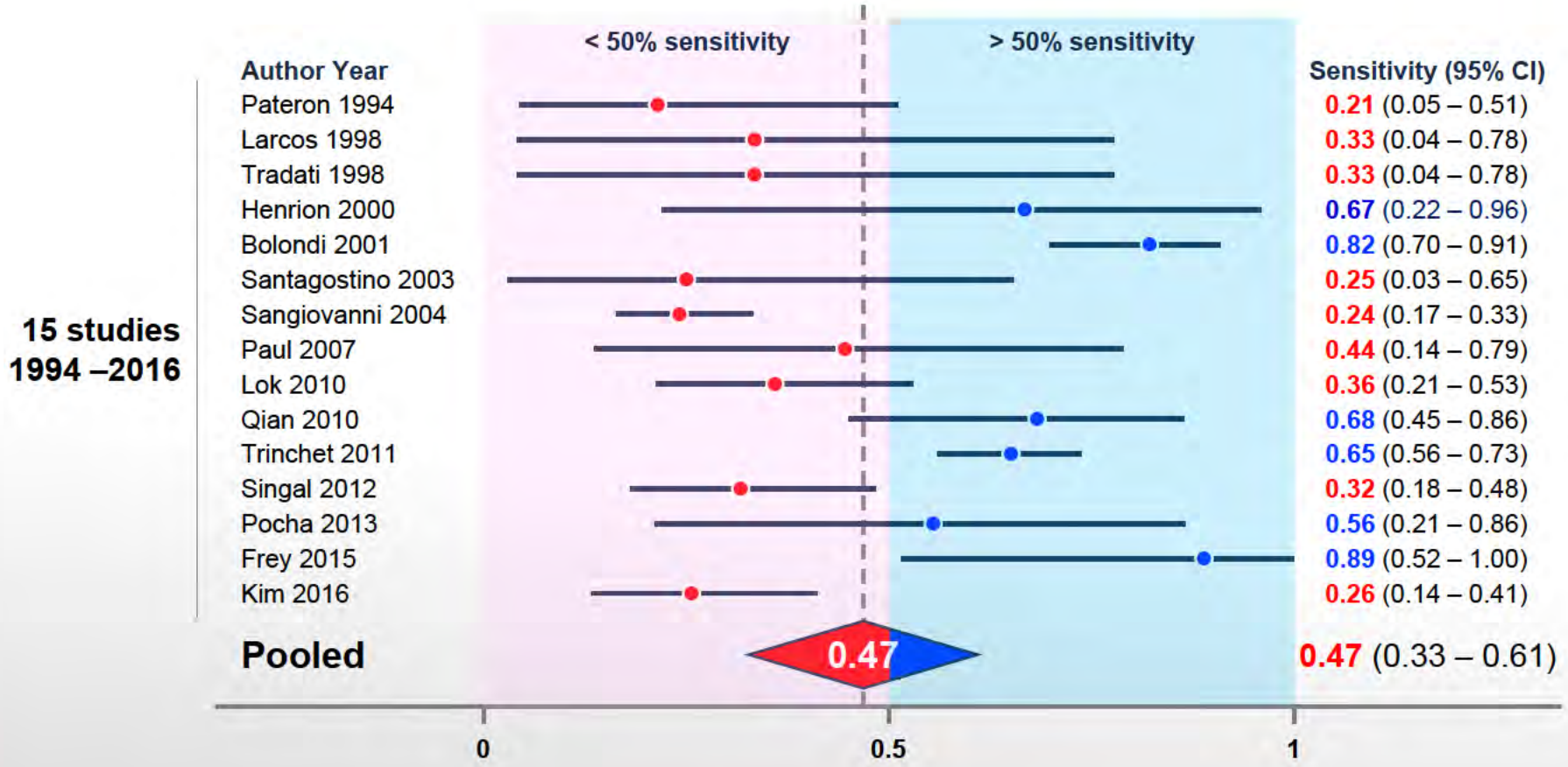
Society/Institution	Guidelines
AASLD[1] American Association for the Study of Liver Diseases	US +/- AFP every 6 months
EASL[2] European Association for the Study of the Liver	US +/- AFP every 6 months
APASL[3] Asian-Pacific Association for the Study of the Liver	AFP + US every 6 months
NCCN[4] National Comprehensive Cancer Network	AFP + US every 6-12 months
VA[5] United States Department of Veterans Affairs	AFP + US every 6-12 months
JSH-HCC[6] Japan Society of Hepatology	High-risk: US every 6 months + AFP/DCP/AFP-L3 every 6 months Very high risk: US every 6 months + AFP/DCP/AFP-L3 every 6 months + CT/MRI (optional) every 6-12 months

AFP not useful in uncontrolled HCV or HBV

AFP=alpha-fetoprotein; AFP-L3=*Lens culinaris* agglutinin-reactive fraction of AFP; CT=computerized tomography; DCP=des-γ-carboxyprothrombin; MRI=magnetic resonance imaging.

1. Bruix J et al. *Hepatology*. 2011;53:1020-1022; Marrero JA et al *Hepatology*. 2018;68(2):723-750 2. EASL, EORTC. *J Hepatol*. 2012;56(4):908-943; 3. Omata M et al. *Hepatol Int*. 2010;4(2):439-474; 4. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hepatobiliary Cancers v1.2016. © National Comprehensive Cancer Network, Inc. 2016. All rights reserved. Accessed February 10, 2016; 5. US Dept of Veterans Affairs. Available at: http://www.hepatitis.va.gov/pdf/2009HCC-guidelines.pdf. Accessed September 23, 2015; 6. Kokudo N et al. *Hepatol Res*. 2015;45.

Sensitivity of Ultrasound Alone for Early HCC



Singal et al, ILCA 2018

Thank you for your attention