Management of Hepatocellular cancer-A Multidisciplinary Approach

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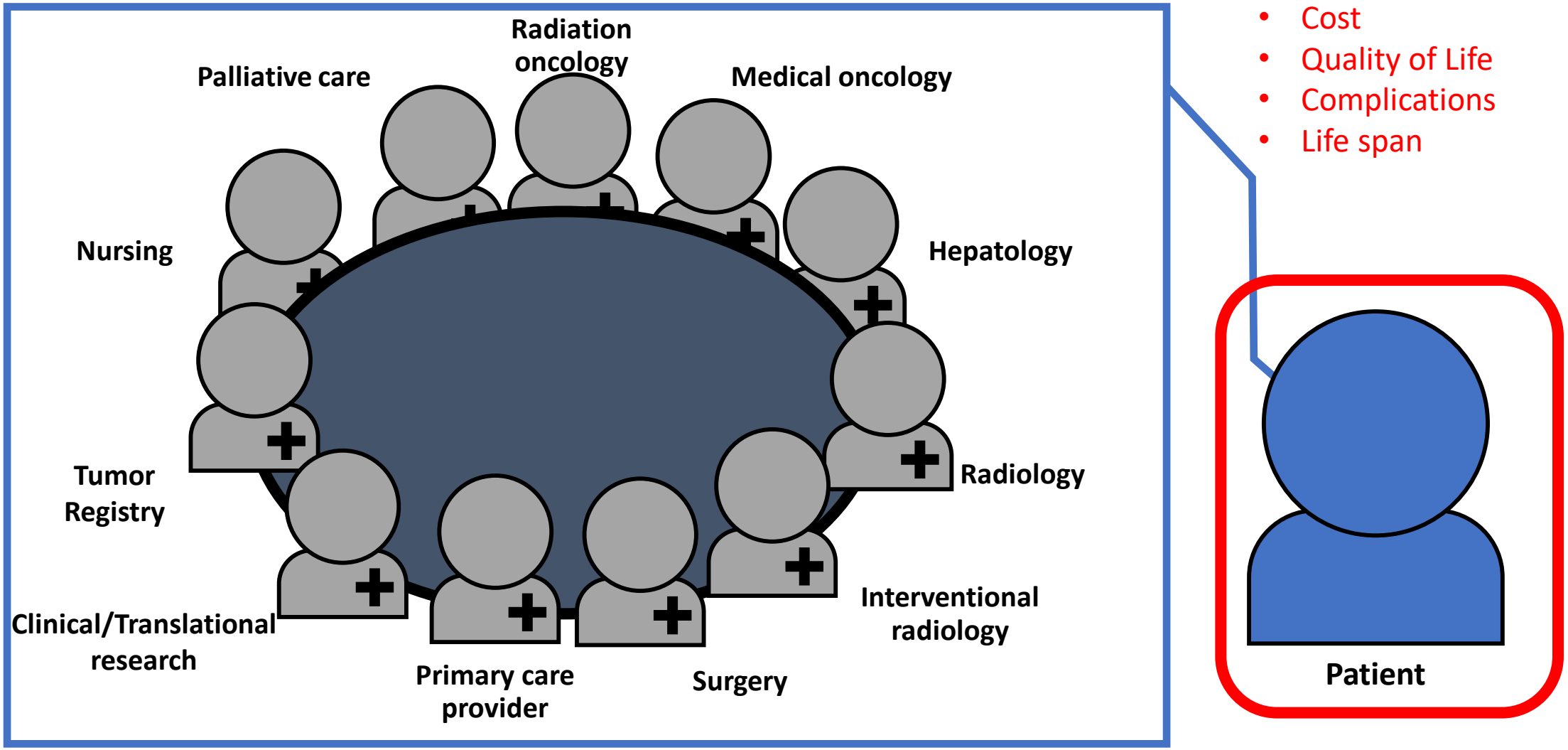
Panelists:

Dr. Armeen Mahvash:	IR	MDACC
Dr Nasir Siddiqi:	IR	BCM
Dr. Ahmed Kaseb:	Med onc	MDACC
Dr. Ben Musher:	Med onc	BCM
Dr. S Khaderi:	Hepatology	BCM
Dr A Rana:	Transplant surgeon	BCM

Multidisciplinary Approach to the Patient With HCC



- Cost
- Quality of Life
- Complications
- Life span

Case 1:

65 yrs/F Hispanic

2015: Metabolic syndrome: Type 2 DM, Hypertension, Hyperlipidemia, BMI 35
Family history: Father and Uncle died of cirrhosis, history of alcohol
She does not drink alcohol

Labs: AST 65, ALT 45, Platelet 200, Albumin 3.7

Fibroscan: CAP score 320 dB/m(S3), Fibrosis score 10 kPa (F3)
US liver: Steatosis, no evidence of cirrhosis/portal hypertension

Should the patient have surveillance for HCC?

Q1. What is true regarding surveillance?

1. Recommended because the patient is above 40 years of age

2. Recommended because the patient is a female

3. Recommended due to increased risk of HCC in NASH

4. Not recommended because surveillance of patients NASH without cirrhosis is not cost-effective

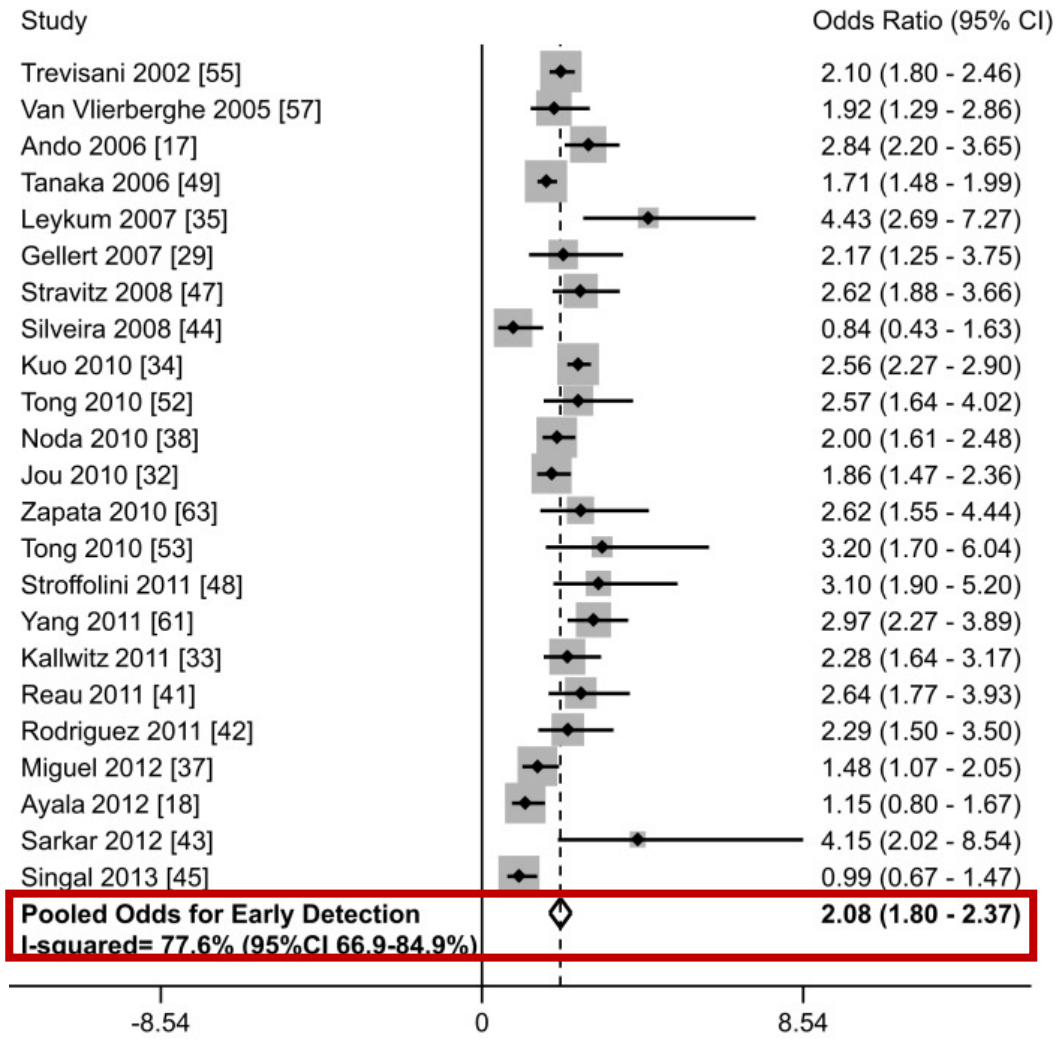
Surveillance for HCC:

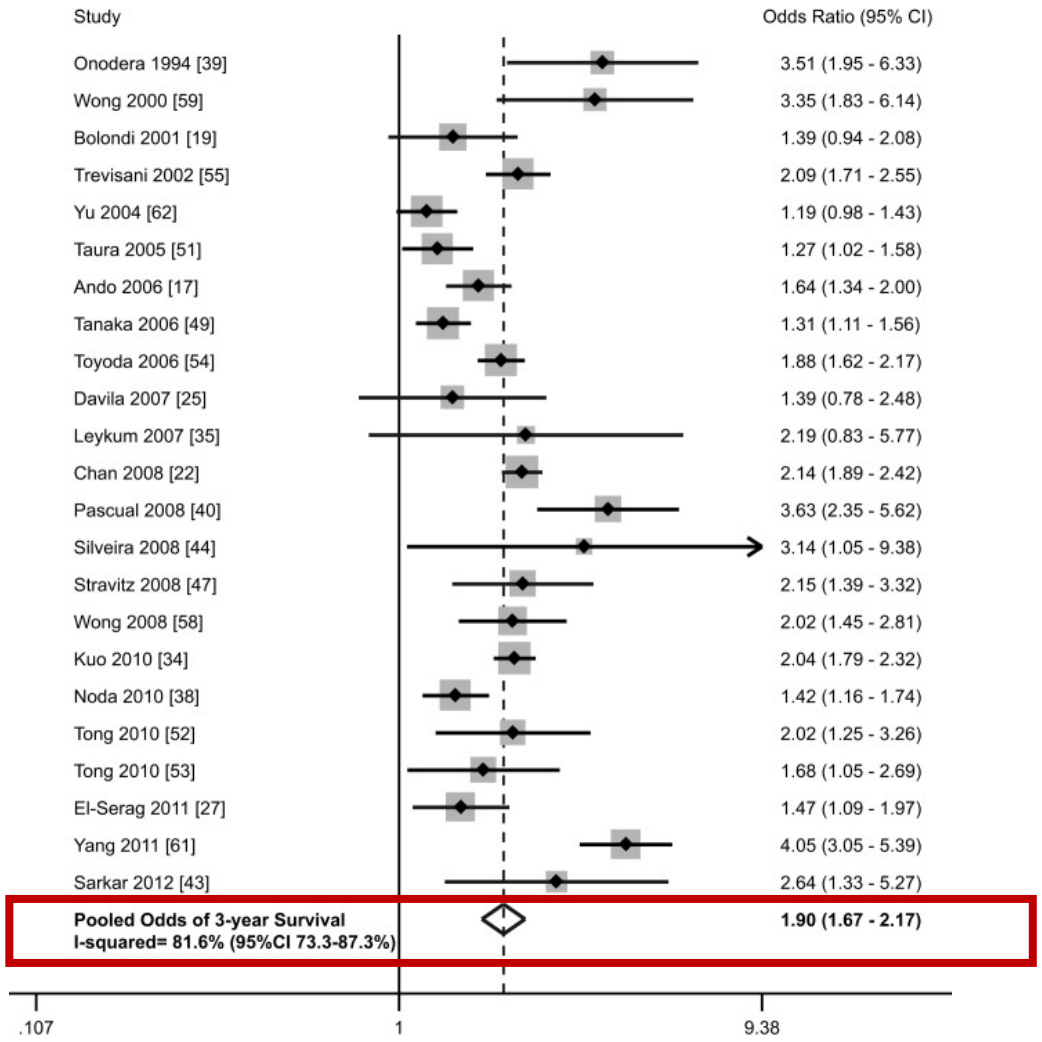
Threshold Incidence for Efficacy of Surveillance (>0.25 LYG; % per year)	Hepatology, Vol. 68, No. 2, 2018
Population Group Surveillance benefit	
Asian male hepatitis B carriers over age 40	0.4%-0.6% per year
Asian female hepatitis B carriers over age 50	0.3%-0.6% per year
Hepatitis B carrier with family history of HCC	Incidence higher than without family history
African and/or North American blacks with hepatitis B	HCC occurs at a younger age
Hepatitis B carriers with cirrhosis	3%-8% per year
Hepatitis C cirrhosis	3%-5% per year
Stage 4 PBC	3%-5% per year
Genetic hemochromatosis and cirrhosis	Unknown, but probably >1.5% per year
Alpha-1 antitrypsin deficiency and cirrhosis	Unknown, but probably >1.5% per year
Other cirrhosis	Unknown
Surveillance benefit uncertain	
Hepatitis B carriers younger than 40 (males) or 50 (females)	<0.2% per year
Hepatitis C and stage 3 fibrosis	<1.5% per year
NAFLD without cirrhosis	<1.5% per year

Surveillance for HCC

- Benefit vs. Harms
- What tests should be used
- What is the optimum surveillance interval

Surveillance for HCC in Cirrhosis: A systematic review of 47 studies (including 15,158 patients with cirrhosis)



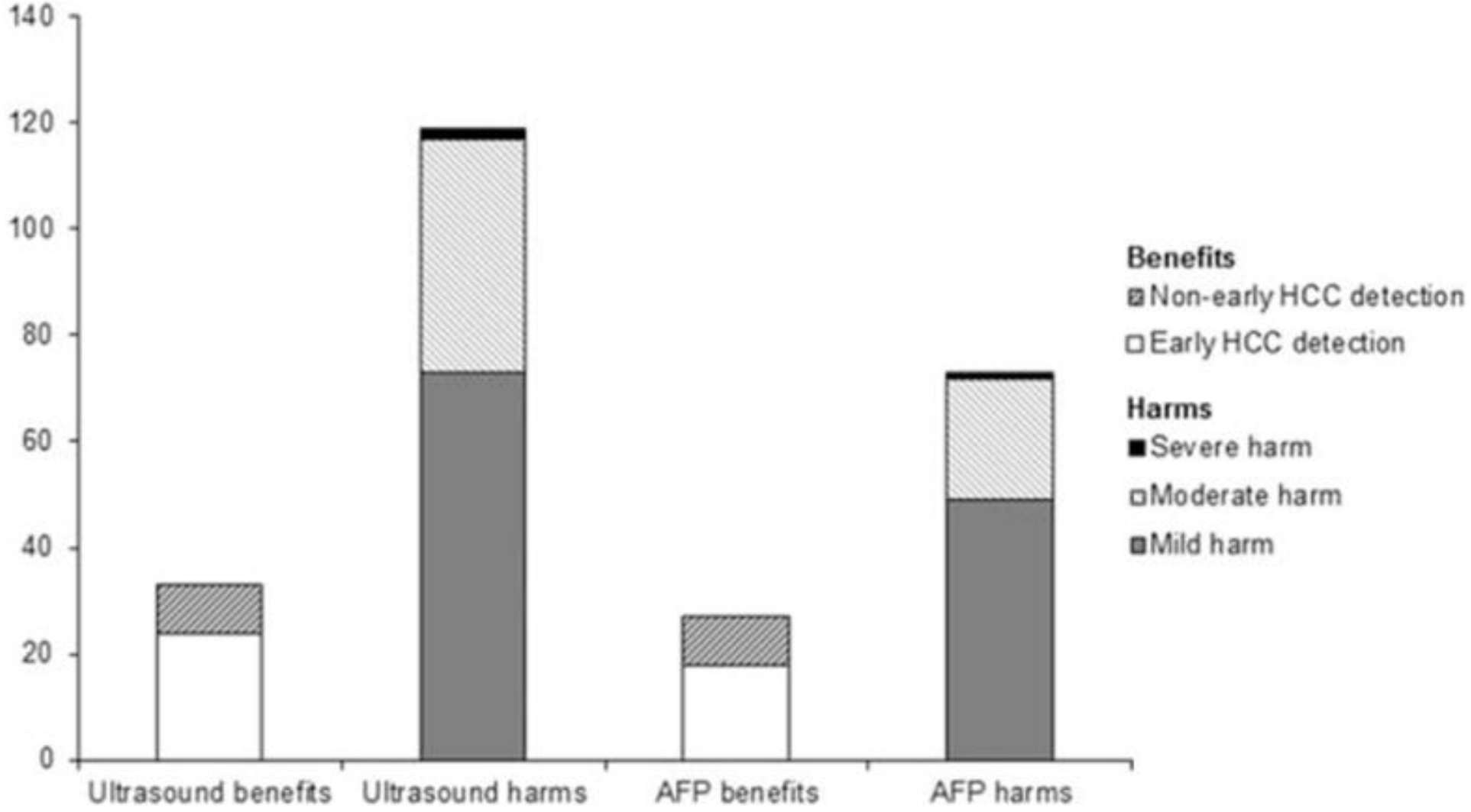


Singal A.G, Pillai A, Tiro J. Early detection, curative treatment, and survival rates for hepatocellular carcinoma surveillance in patients with cirrhosis: a meta-analysis.*PLoS Med.* 2014; **11**: e1001624

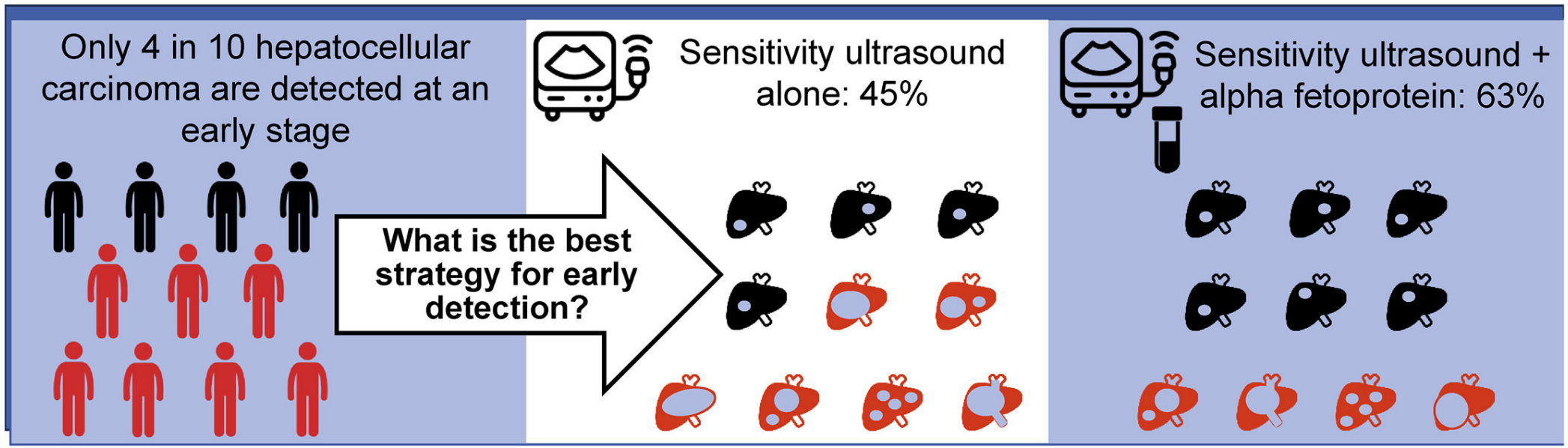
No association between screening for hepatocellular carcinoma and reduced cancer-related mortality in patients with cirrhosis. *Gastroenterology.* 2018; 155: 1128-1139.

Controls (n = 238), n (%)	Cases (n = 238), n (%)	Odds ratio [b] (95% CI)	Adjusted [c] Odds ratio (95% CI)	
0–4 y before index date				
USS	129 (54.2)	126 (52.9)	0.95 (0.66–1.37)	0.95 (0.63–1.43)
AFP	175 (73.5)	178 (74.8)	1.07 (0.70–1.65)	1.08 (0.67–1.75)
USS or AFP	189 (79.4)	193 (81.1)	1.12 (0.70–1.81)	1.11 (0.68–1.82)
0–3 y before index date				
USS	117 (49.2)	112 (47.1)	0.92 (0.63–1.32)	0.91 (0.60–1.37)
AFP	164 (68.9)	168 (70.6)	1.09 (0.73–1.63)	1.13 (0.72–1.77)
USS or AFP	177 (74.4)	182 (76.5)	1.13 (0.73–1.74)	1.14 (0.72–1.79)
0–2 y before index date				
USS	95 (39.9)	91 (38.2)	0.93 (0.63–1.36)	0.93 (0.60–1.43)
AFP	145 (60.9)	151 (63.4)	1.13 (0.76–1.69)	1.18 (0.76–1.83)
USS or AFP	160 (67.2)	165 (69.3)	1.12 (0.74–1.68)	1.12 (0.73–1.73)
0–1 y before index date				
USS	62 (26.1)	70 (29.4)	1.20 (0.79–1.81)	1.20 (0.77–1.86)
AFP	109 (45.8)	121 (50.8)	1.24 (0.85–1.80)	1.22 (0.82–1.82)
USS or AFP	127 (53.4)	143 (60.1)	1.33 (0.92–1.94)	1.40 (0.95–2.08)

An assessment of benefits and harms of hepatocellular carcinoma surveillance in patients with cirrhosis. *Hepatology.* 2017; **65**: 1196-1205



Surveillance Imaging and Alpha Fetoprotein for Early Detection of Hepatocellular Carcinoma in Cirrhosis: A Meta Analysis



Authors: Tzartzeva, Obi, Rich, Parikh, Marrero, Yopp, Waljee, Singal

Gastroenterology

Hepatocellular Carcinoma Detection Rate, False-Positive Rate, and Positive Predictive Value of the 2 Surveillance Methods

Table 3. Hepatocellular Carcinoma Detection Rate, False-Positive Rate, and Positive Predictive Value of the 2 Surveillance Methods[a]

Surveillance Method and Category	No. of Tests	No. of Patients With HCC	Cumulative Total of Tests, No.	Cumulative True-Positive Results, No.	Detection Rate for Any HCC (Sensitivity), %	Detection Rate for Very Early and Early Stage HCC (Sensitivity), %	Detection Rate Very Early Stage HCC (Sensitivity), %	Specificity, %	False-Negative Rate, %	False-Positive Rate, %	PPV, %	No. of Biopsy Procedures Performed
US												
4 (Suspicious)	71	12	71	12	27.9	26.2	27.3	94.4	72.1	5.6	16.9	4
3 (Equivocal)	5	0	76	12	27.9	26.2	27.3	93.9	72.1	6.1	15.8	0
2 (Probably benign)	32	2	108	14	32.6	31.0	33.3	91.1	67.4	8.9	13.0	2
1 (Definitely benign/ negative)	992	29	1100	43	100	100	100	0.0	0.0	100	3.9	14
MRI												
5 (Highly suggestive)	33	26	33	26	60.5	59.5	54.5	99.3	39.5	0.7	78.8	12
4 (Suspicious)	36	11	69	37	86.0	85.7	84.8	97.0	14.0	3.0	53.6	6
3 (Equivocal)	15	1	84	38	88.4	88.1	84.8	95.6	11.6	4.4	45.2	1
2 (Probably benign)	92	0	176	38	88.4	88.1	84.8	86.9	11.6	13.1	21.6	0
1 (Definitely benign/ negative)	924	5	1100	43	100	100	100	0.0	0.0	100	3.9	1

Abbreviations: HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; PPV, positive predictive value; US, ultrasonography.

[a] The results have been calculated on the basis of data on patients with HCC that were detected during the 3 rounds of screening tests and by follow-up dynamic CT scan 6 months after the last screening round. No interval cancer was detected between the screening rounds and before the follow-up CT scan. The positive screening criterion was a category 5 or 4 on US or MRI. The cumulative number of true positive results is the number of patients with HCC found in a specific imaging category or higher; the HCC detection rate is the percentage of patients with HCC with a positive test result in a specific category or higher (the cumulative number of true positive results divided by the total number of patients with HCC); the false positive rate is the percentage of positive test results in patients without a cancer; and the PPV is the percentage of true positive test results in patients with the positive tests in a specific imaging category or higher (the cumulative number of true positive test results divided by the cumulative number of tests).

MRI With Liver-Specific Contrast for Surveillance of Patients With Cirrhosis at High Risk of Hepatocellular Carcinoma

JAMA Oncol. 2017;3(4):456-463. doi:10.1001/jamaoncol.2016.3147

Test characteristics of alpha-fetoprotein for detecting hepatocellular carcinoma in patients with hepatitis C. A systematic review and critical analysis.

Ann Intern Med. 2003; 139: 46-50

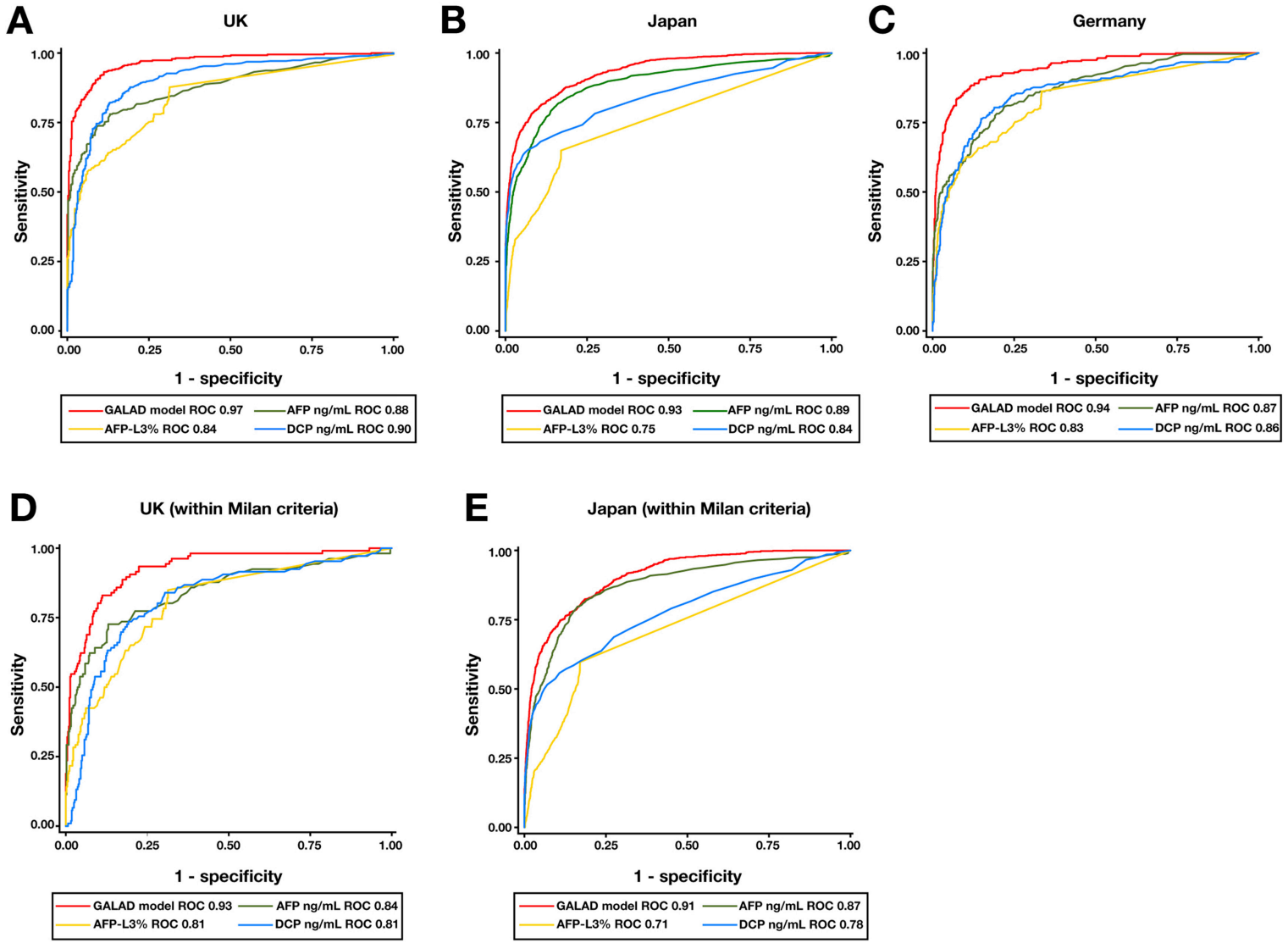
Table 2. Abstracted Test Characteristics of α-Fetoprotein Levels Higher than 20 μg/L for Detecting Hepatocellular Carcinoma*

Study, Year (Reference)	Sensitivity of AFP Level > 20 μg/L (95% CI), %	Specificity of AFP Level > 20 μg/L (95% CI), %	Positive Likelihood Ratio (95% CI)	Negative Likelihood Ratio (95% CI)
Peng et al., 1999 (20)	65 (58–71)	87 (79–93)	4.9 (3.0–8.0)	0.5 (0.3–0.5)
Cedrone et al., 2000 (18)†‡	55	88	4.6	0.5
Tong et al., 2001 (15)‡	41	94	6.8	0.6
Trevisani et al., 2001 (21)‡	60	91	6.7	0.4
Nguyen et al., 2002 (19)	63 (56–70)	80 (73–86)	3.1‡	0.5‡

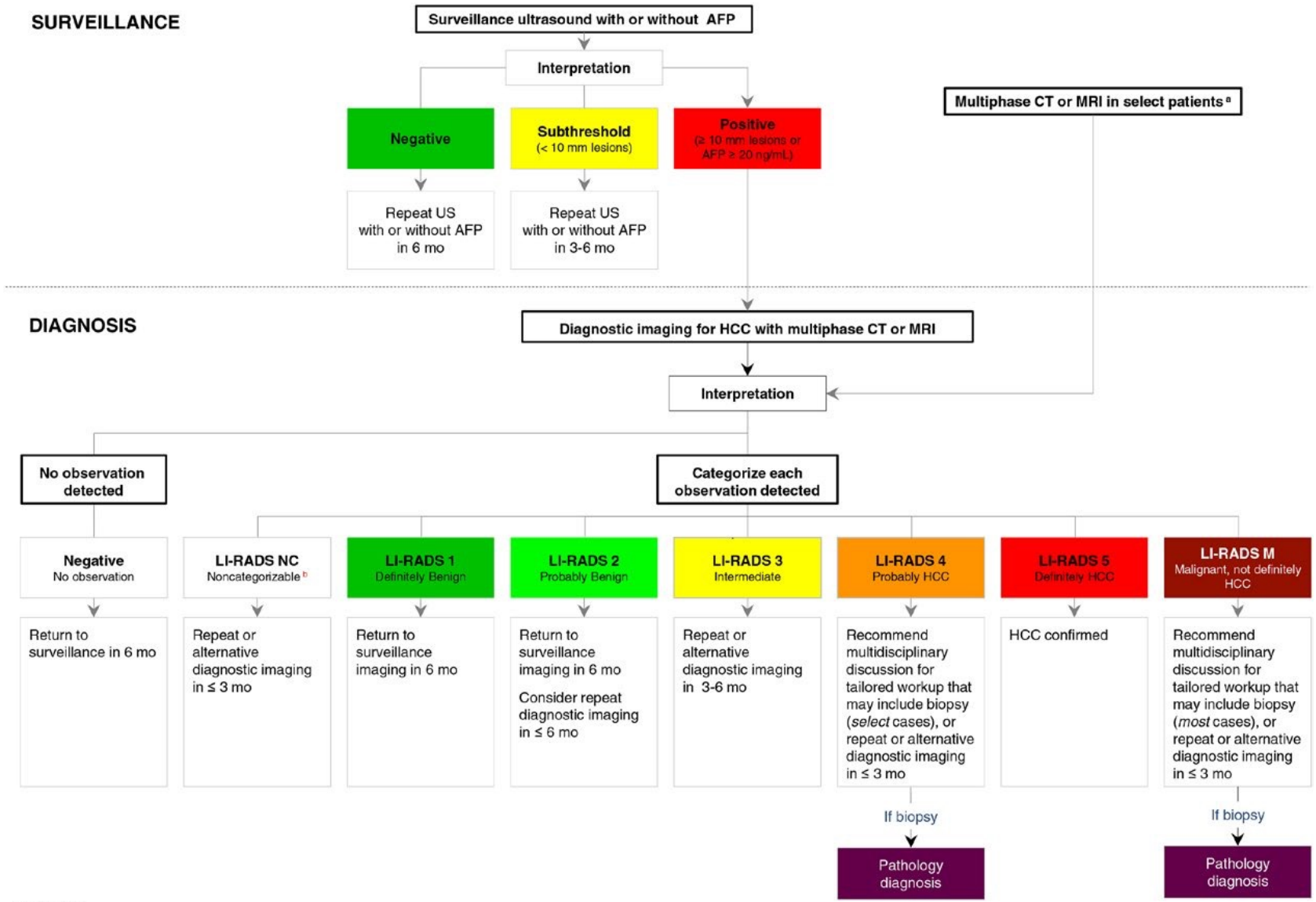
* AFP = α-fetoprotein.
† Data for patients with hepatitis C virus and hepatitis B virus analyzed together.
‡ Data for CIs are not available or calculable.

GALAD model: Z=−10.08+0.09 × **age**+1.67 × **sex**+2.34log10(**AFP**)+0.04 ×**AFP-L3**+1.33 ×log10(**DCP**)

sex = 1 for males and 0 for females



Clinical Gastroenterology and Hepatology 2016 14875-886.e6DOI: (10.1016/j.cgh.2015.12.042)



Footnotes

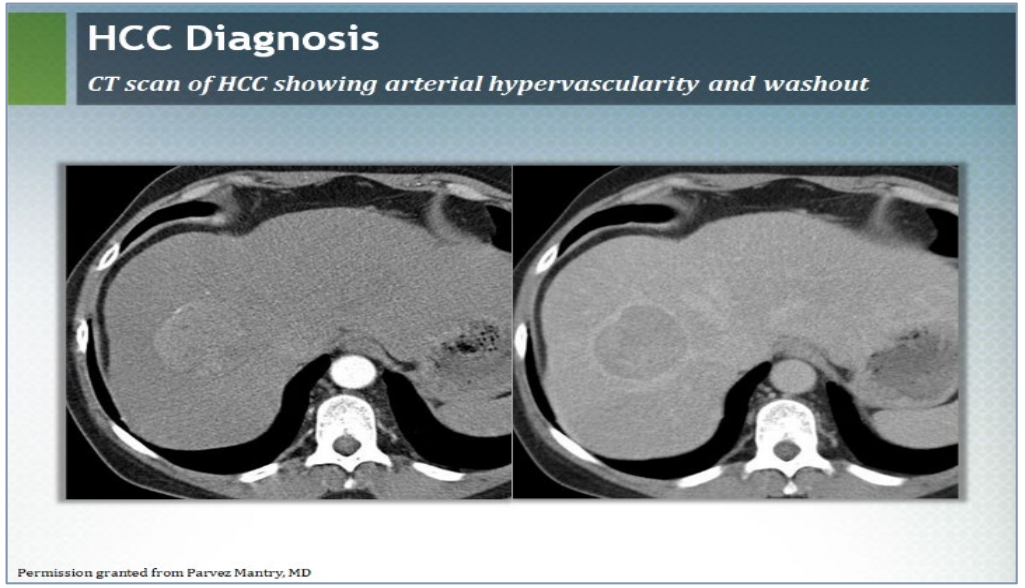
a. Multiphase CT or MRI in select patients	Some high-risk patients may undergo multiphase CT or MRI for HCC surveillance (depending on patient body habitus, visibility of liver at ultrasound, being on the transplant waiting list and other factors).
b. Noncategorizable	These are due to technical problem such as image omission or severe degradation

AASLD Practice Guidance: Hepatology, August 2018

Diagnosis of HCC:

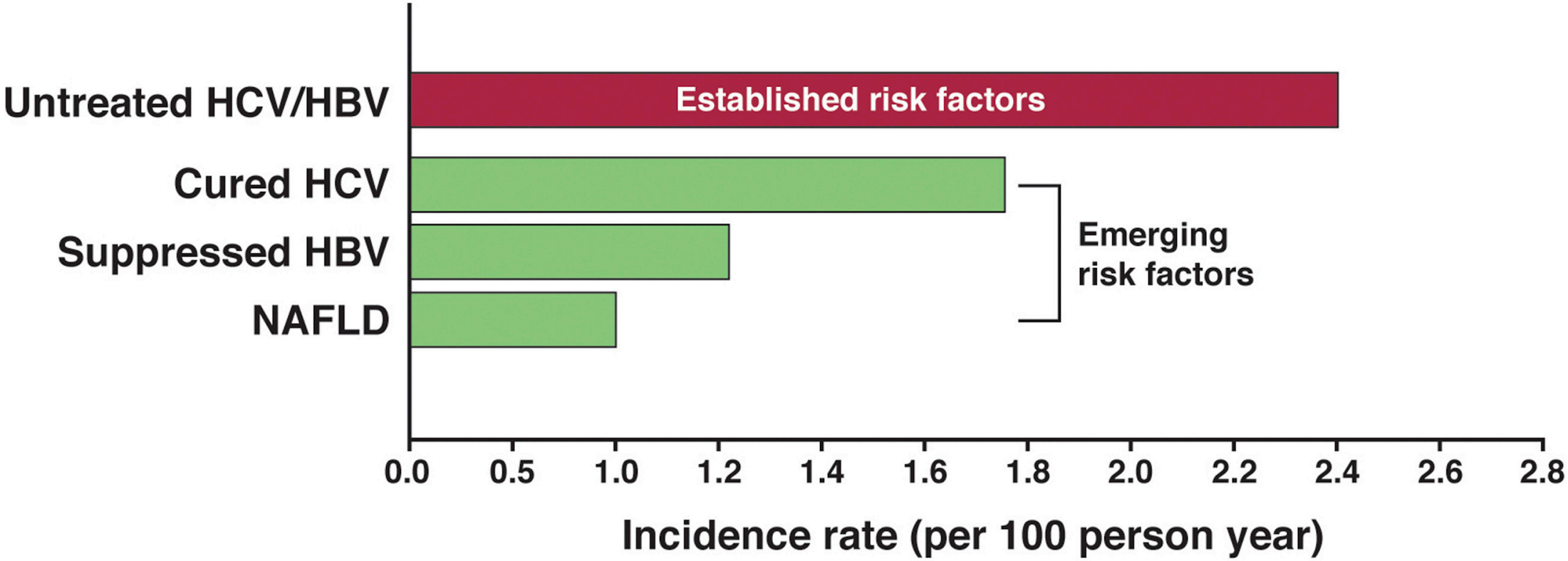
Liver Imaging Reporting and Data System (LI-RADS) system

≥20 mm	APHE (nonrim) **AND** one or more of following: • "Washout" (nonperipheral) • Enhancing "capsule" • Threshold growth
10-19 mm	APHE (nonrim) **AND** the following: • "Washout" (nonperipheral) • Enhancing "capsule" • Threshold growth



Threshold growth = size increase of a mass by ≥ 50% in ≤ 6 months; "Washout" = washout appearance; "Capsule" = capsule appearance.
Abbreviation: APHE, arterial phase hyperenhancement.

Annual risk of HCC in cirrhosis patients with established and emerging cohorts



Surveillance for Hepatocellular Carcinoma: Current Best Practice and Future Direction . Fasiha Kanwal, Amit G. Singal Gastroenterology Volume 157 Issue 1 Pages 54-64 (July 2019) DOI: 10.1053/j.gastro.2019.02.049

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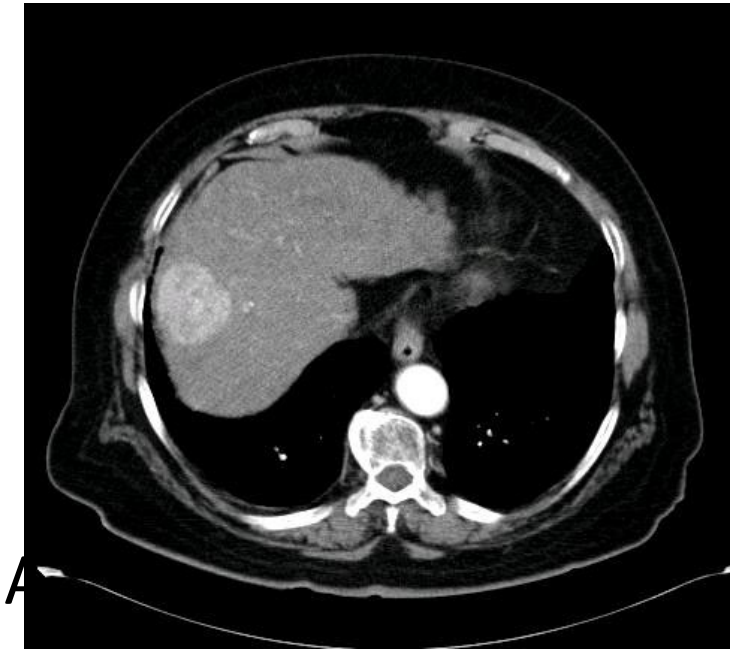


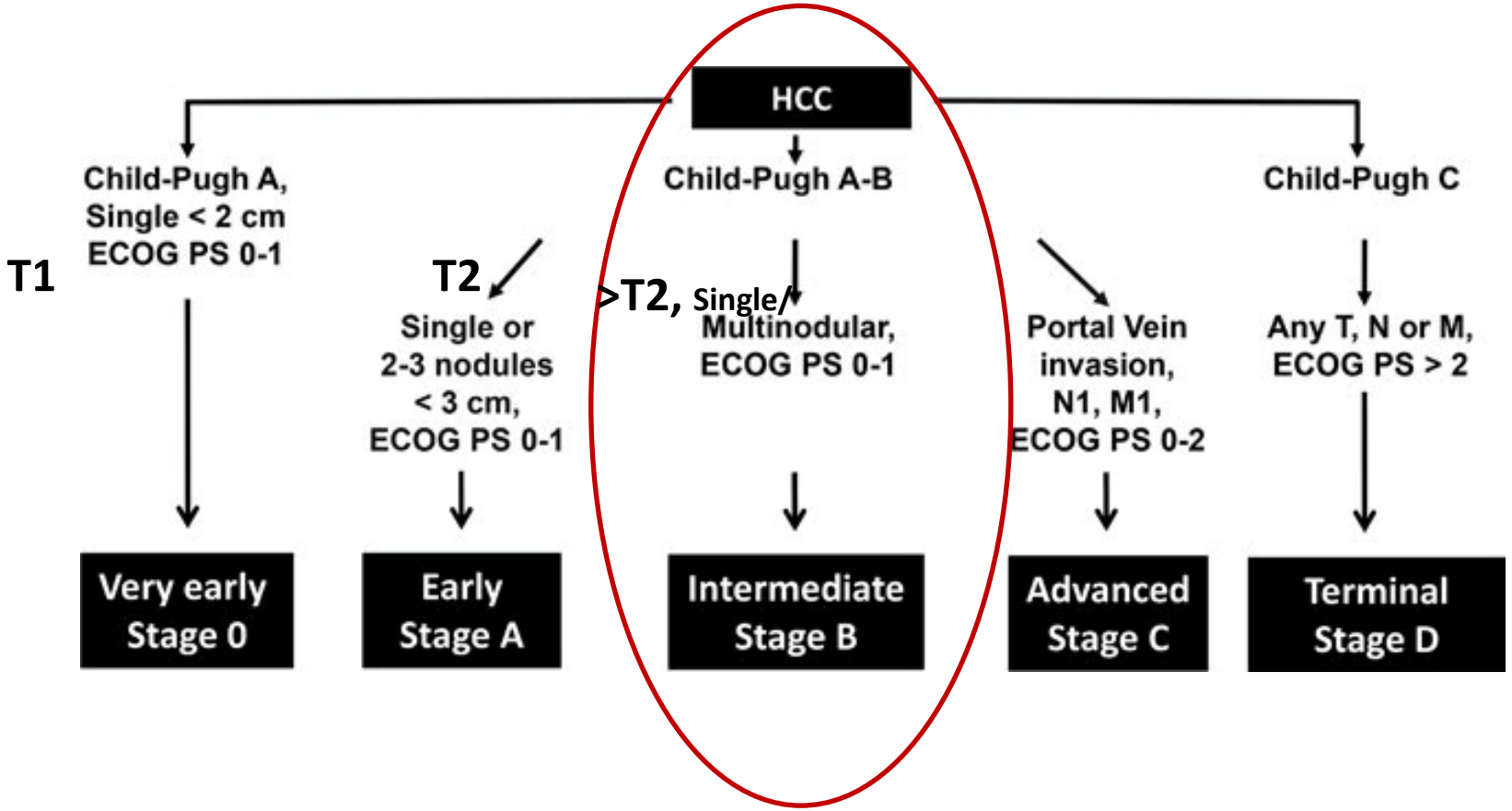
2019: Presented with upper abdominal discomfort
Contrast imaging showed **6.5 cm HCC**
Cirrhosis, Well compensated, Bili 1.2, Platelet 150, A

Q2. What is the next best step?

1. Surgical resection
2. Initiate transplant evaluation
3. Locoregional therapy (TACE or TARE) by IR for downstaging before transplant
4. Surgical resection with neoadjuvant therapy before resection or adjuvant systemic therapy after resection

A solitary 6.5-cm HCC in a compensated cirrhotic liver:
HCC parameters to consider for management

- *Size-individual lesions and total volume*
- *No. of lesions*
- *Liver function-CTP status, Bilirubin*
- *Presence of portal hypertension*
- *Vascular invasion*
- *Extrahepatic spread*
- *Overall functional status*

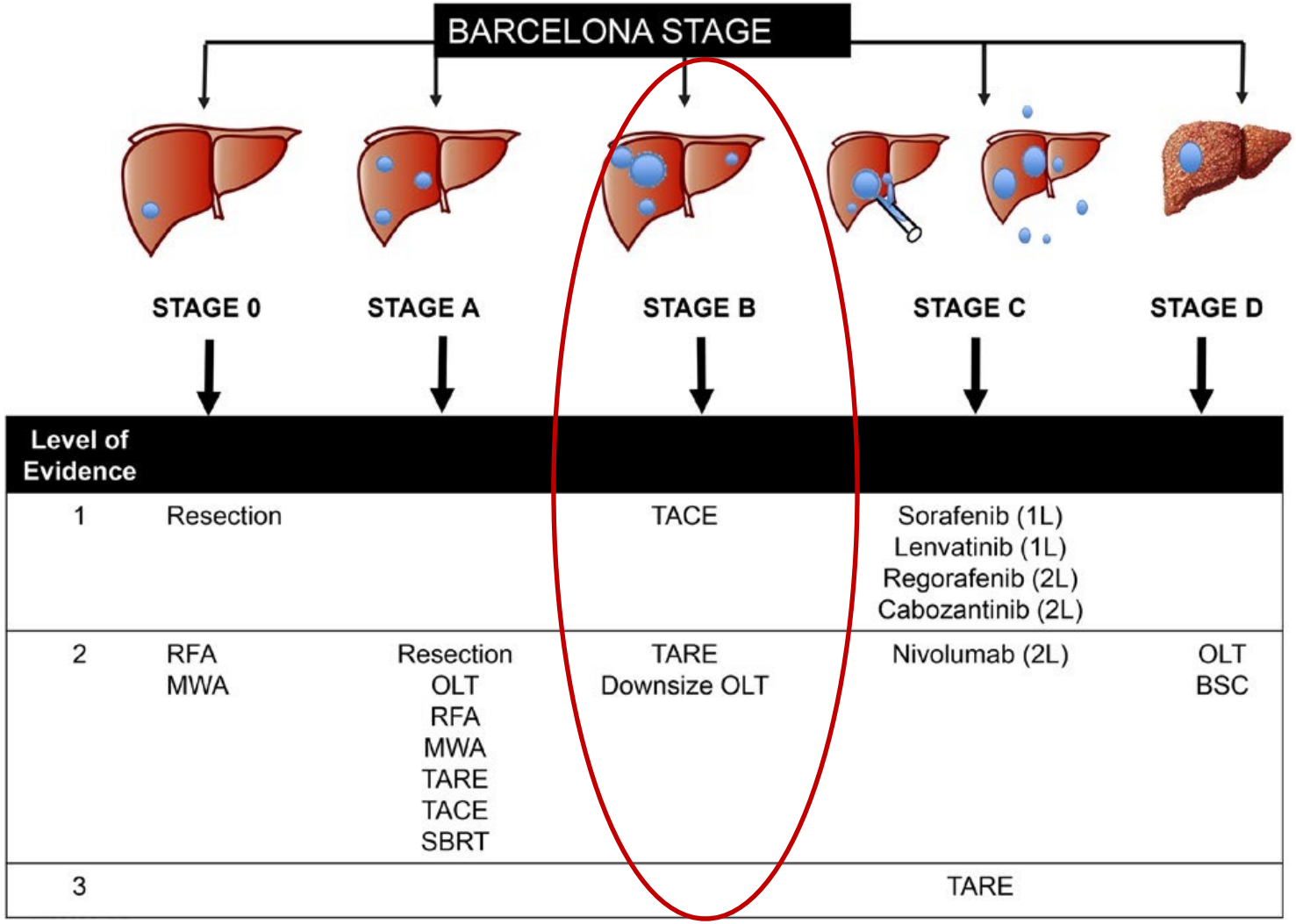


BCLC HCC staging system. Abbreviations: N, nodal metastasis; M, extrahepatic metastasis.

Hepatology, Vol. 68, No. 2, 2018

Treatment recommendations according to BCLC Stage.

Abbreviations: MWA, microwave ablation; BSC, best supportive care; 1L, first-line therapy; 2L, second-line therapy.

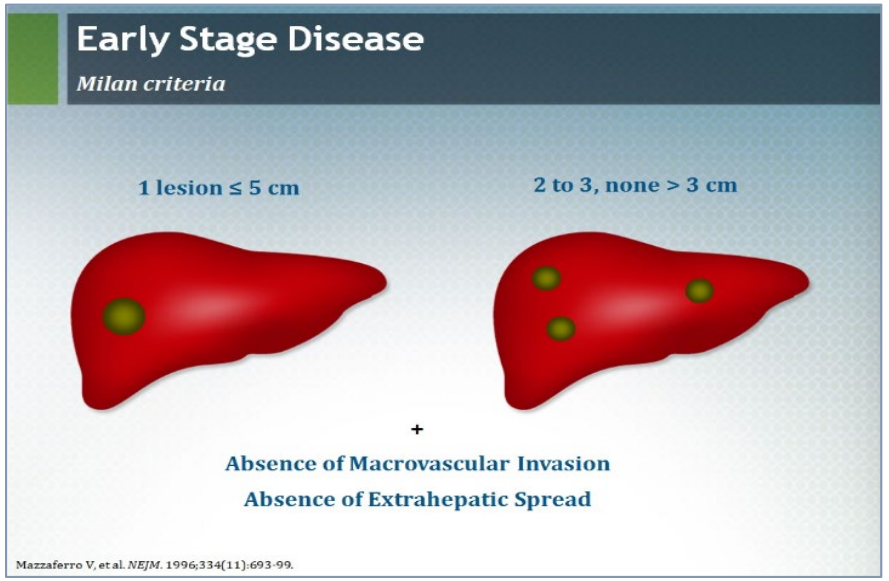


Level of Evidence	STAGE 0	STAGE A	STAGE B	STAGE C	STAGE D
1	Resection		TACE	Sorafenib (1L) Lenvatinib (1L) Regorafenib (2L) Cabozantinib (2L)	
2	RFA MWA	Resection OLT RFA MWA TARE TACE SBRT	TARE Downsize OLT	Nivolumab (2L)	OLT BSC
3				TARE	

Criteria for Transplant for HCC

Milan Criteria (Mazzaferro et al, 1996) **T2** **Universally Accepted**

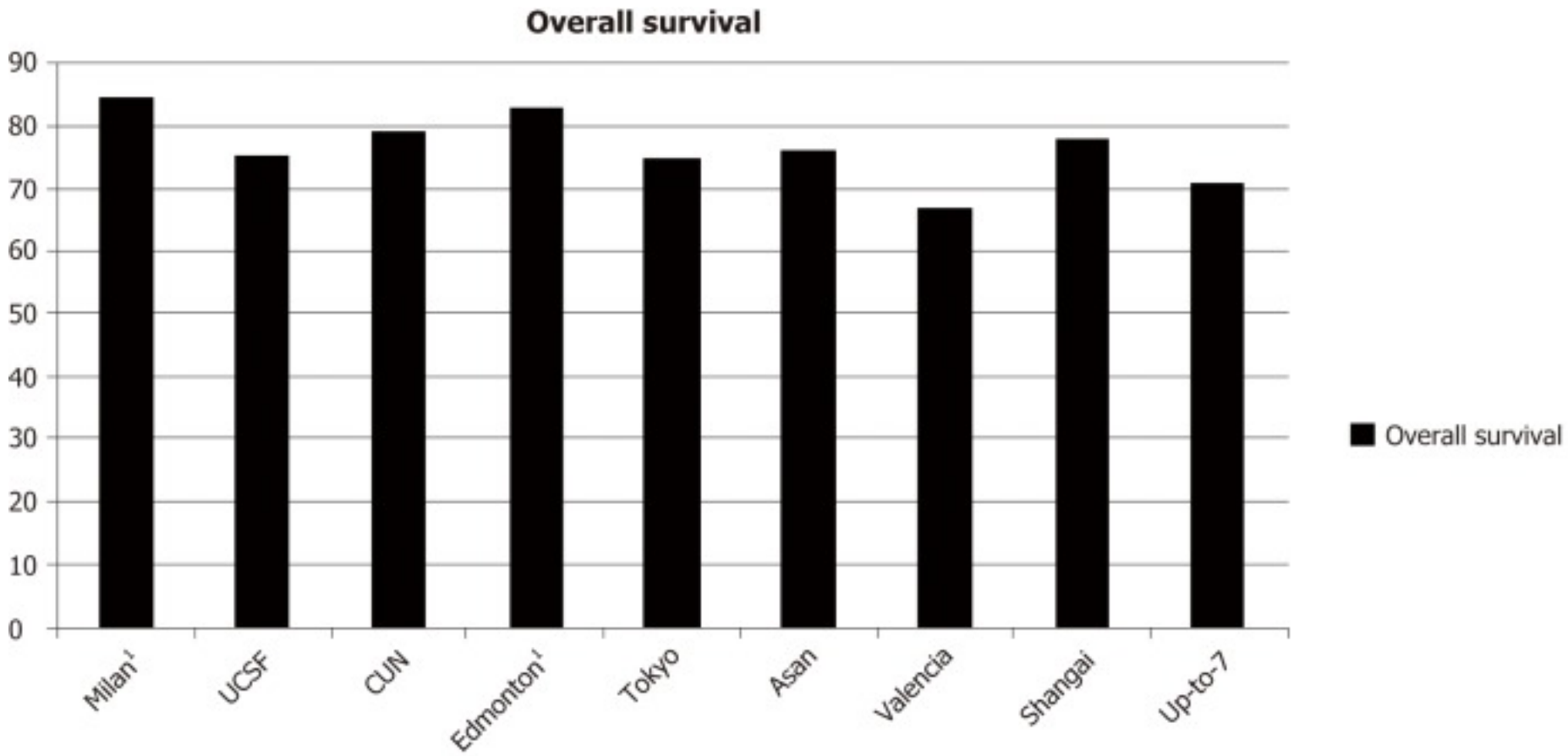
- Single tumor ≤ 5 cm, or
- 2-3 tumors none exceeding 3 cm, and
- No vascular invasion and/or extrahepatic spread



Expanded Criteria:

UCSF Criteria (Yao et al, 2001)

- Single tumor ≤ 6.5 cm, or
- 2-3 lesions, none exceeding 4.5 cm, with total tumor diameter ≤ 8 cm
- No vascular invasion and/or extrahepatic spread



Overall 5-yr survival rates.

Liver Resection (LR)

- The risk of recurrence following resection is up to 70% at 5 years

- *Tumor size is not an independent predictor of recurrence*

*(t*hough increasing tumor size is associated with increased frequency of microvascular invasion and other poor histological features)

- **Resection is the treatment of choice for localized HCC**

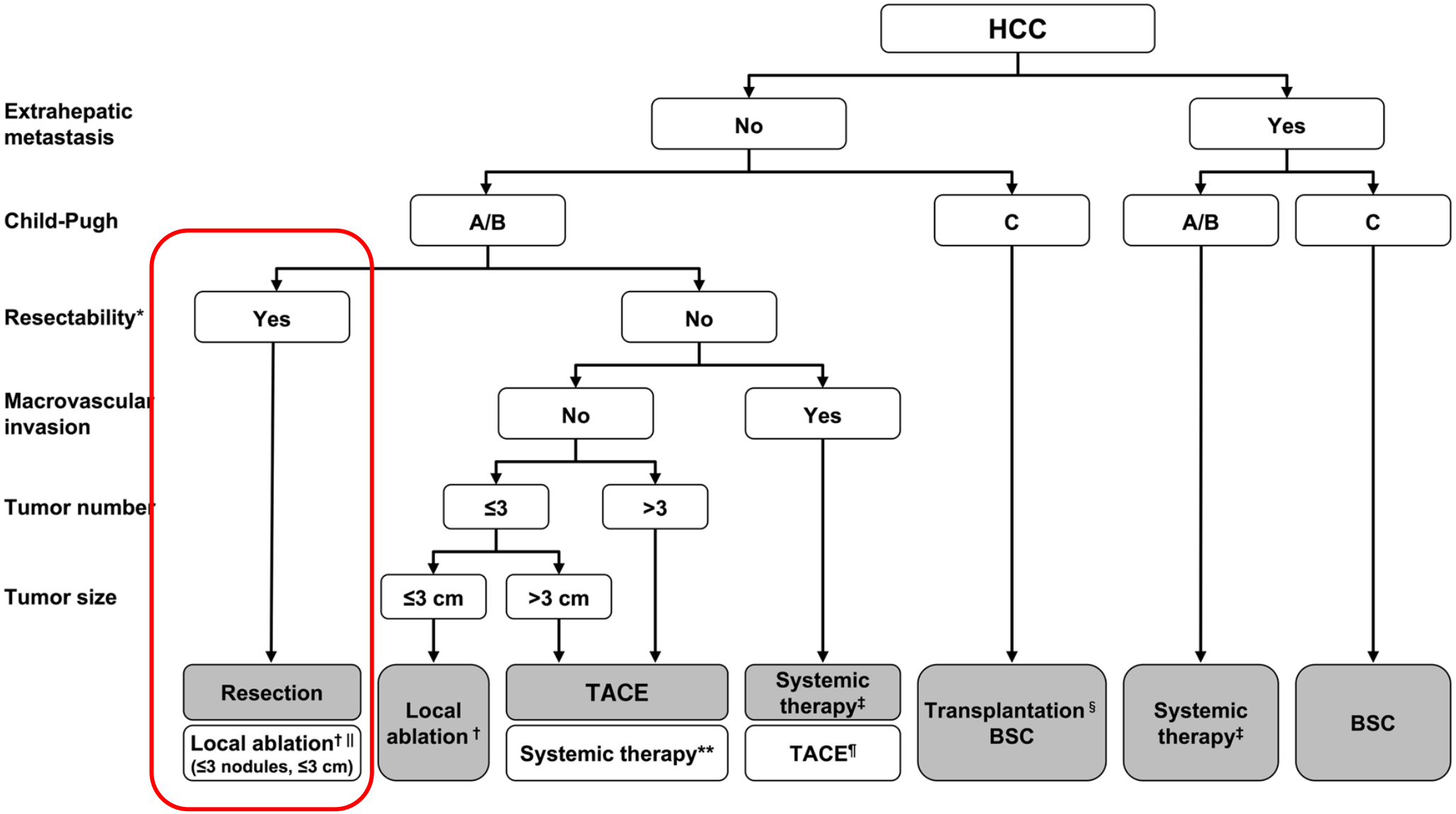
  in the absence of cirrhosis, or

  resectable HCC occurring in the setting of cirrhosis with intact liver function and absence of CSPH

Recent multicenter study showed 50% of patients with intermediate or advanced HCC are treated routinely with surgery in tertiary referral centers worldwide

LR is recommended in guidelines for more progressed HCC in the treatment algorithms of Asian countries

Poon RT, et al. Ann Surg 2002;235:373-382. Tabrizian P, et al.. Ann Surg 2013;257:929–937. Torzilli G, et al. Ann Surg 2015;261:947-955.

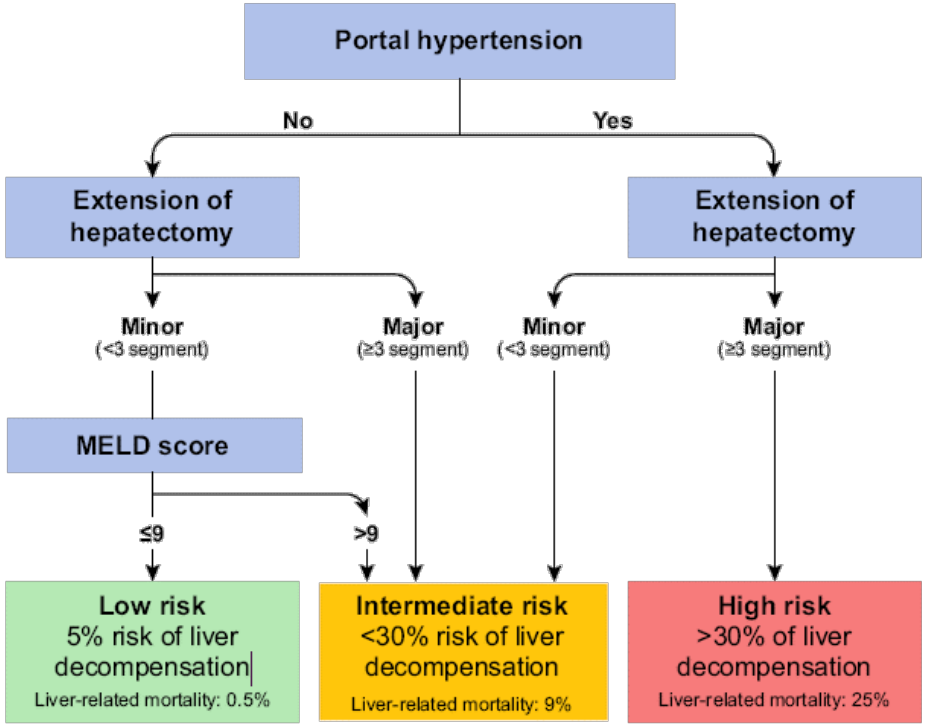


Asia–Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update

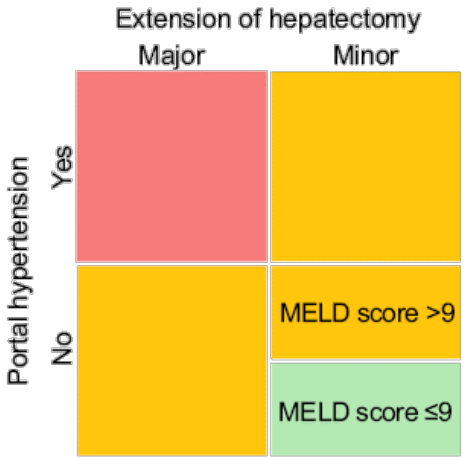
Hepatol Int (2017) 11:317–370

Assessment of post-resection risk of hepatic decompensation

- Multi-parametric assessment
- Risk of decompensation based on three determinants of liver insufficiency
  - Portal hypertension
  - **Extent of resection**
  - Liver function



- **Likelihood of decompensation**
  - High: >30%
  - Intermediate: <30%
  - Low: 5%



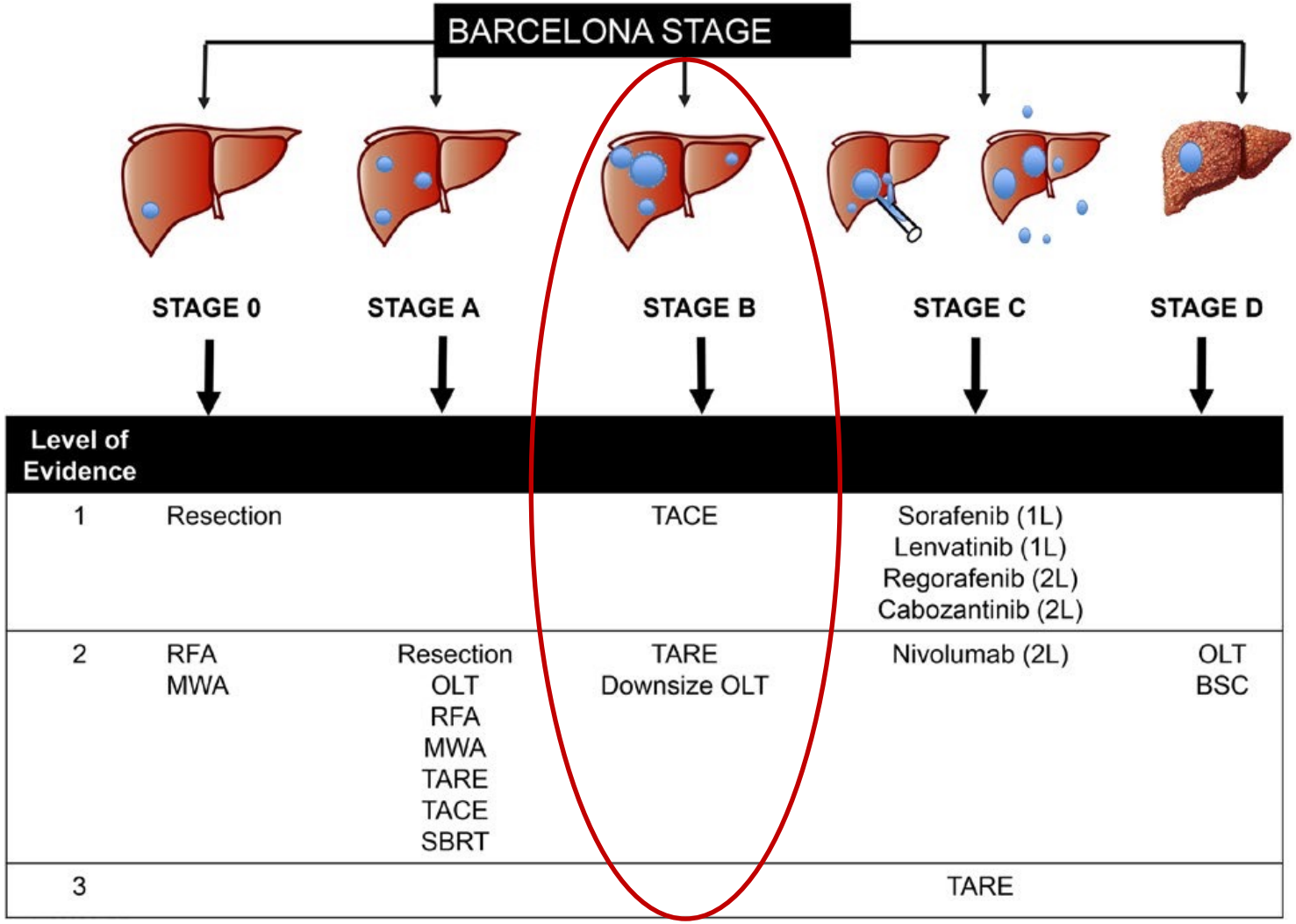
Salvage LT for patients who have developed HCC recurrence (or liver decompensation) following resection may be considered

EASL CPG HCC. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.019

- **Any role of LRT/Downstaging as a bridge to transplant?**
- **What is the best LRT?**
  - **Selection criteria for RFA, TACE, TARE?**

Treatment recommendations according to BCLC Stage.

Abbreviations: MWA, microwave ablation; BSC, best supportive care; 1L, first-line therapy; 2L, second-line therapy.



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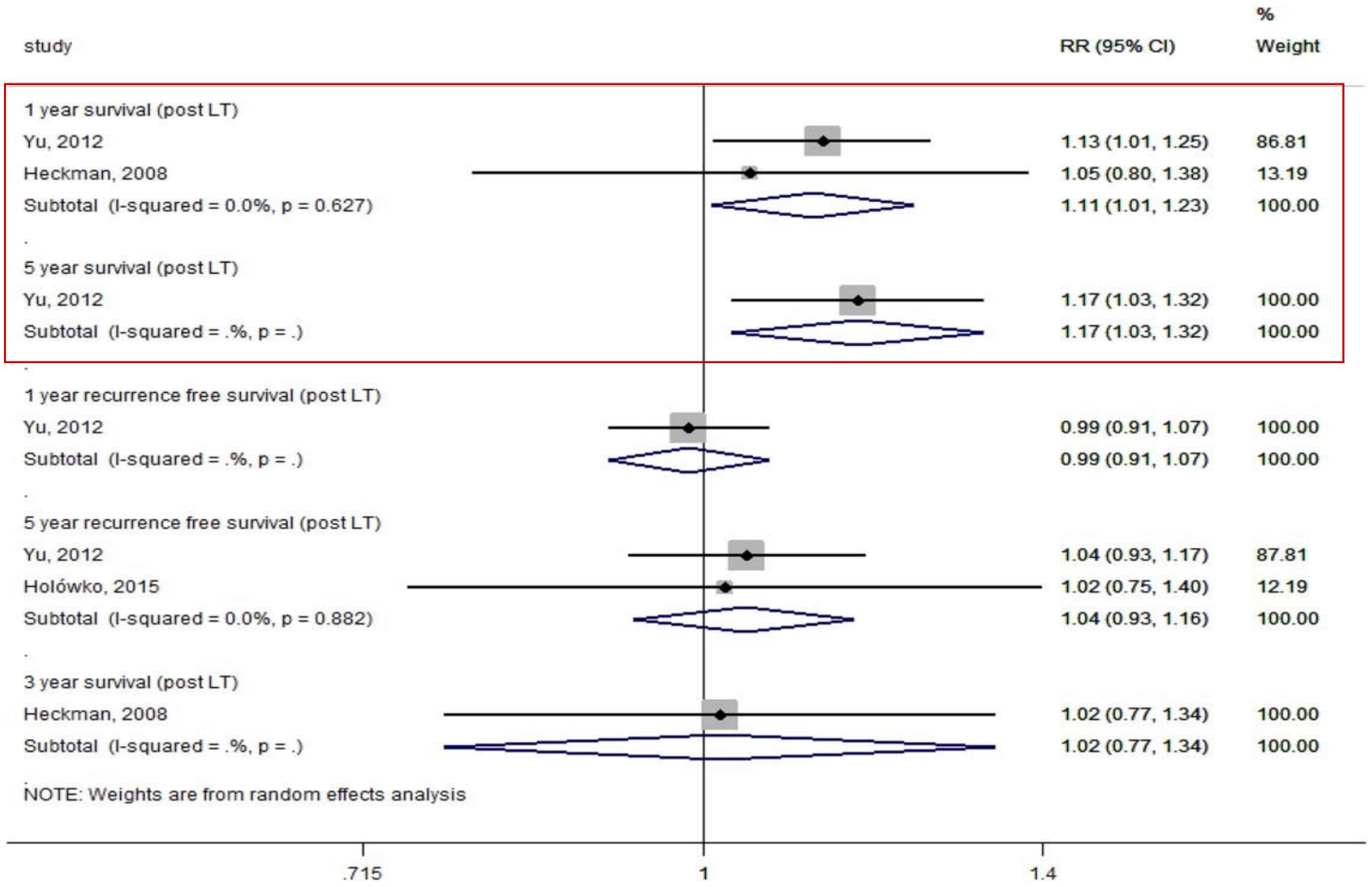
2	RFA MWA	Resection OLT RFA MWA TARE TACE SBRT	TARE Downsize OLT	Nivolumab (2L)	OLT BSC
3				TARE	

Outcomes of transplant with down-staged therapy for adults with cirrhosis awaiting LT and HCC beyond Milan criteria (T3).

Heckman et al.,Holowko et al.,Yu et al.



The AASLD suggests that patients beyond the Milan criteria (T3) should be considered for LT after successful downstaging into the Milan criteria (T2)

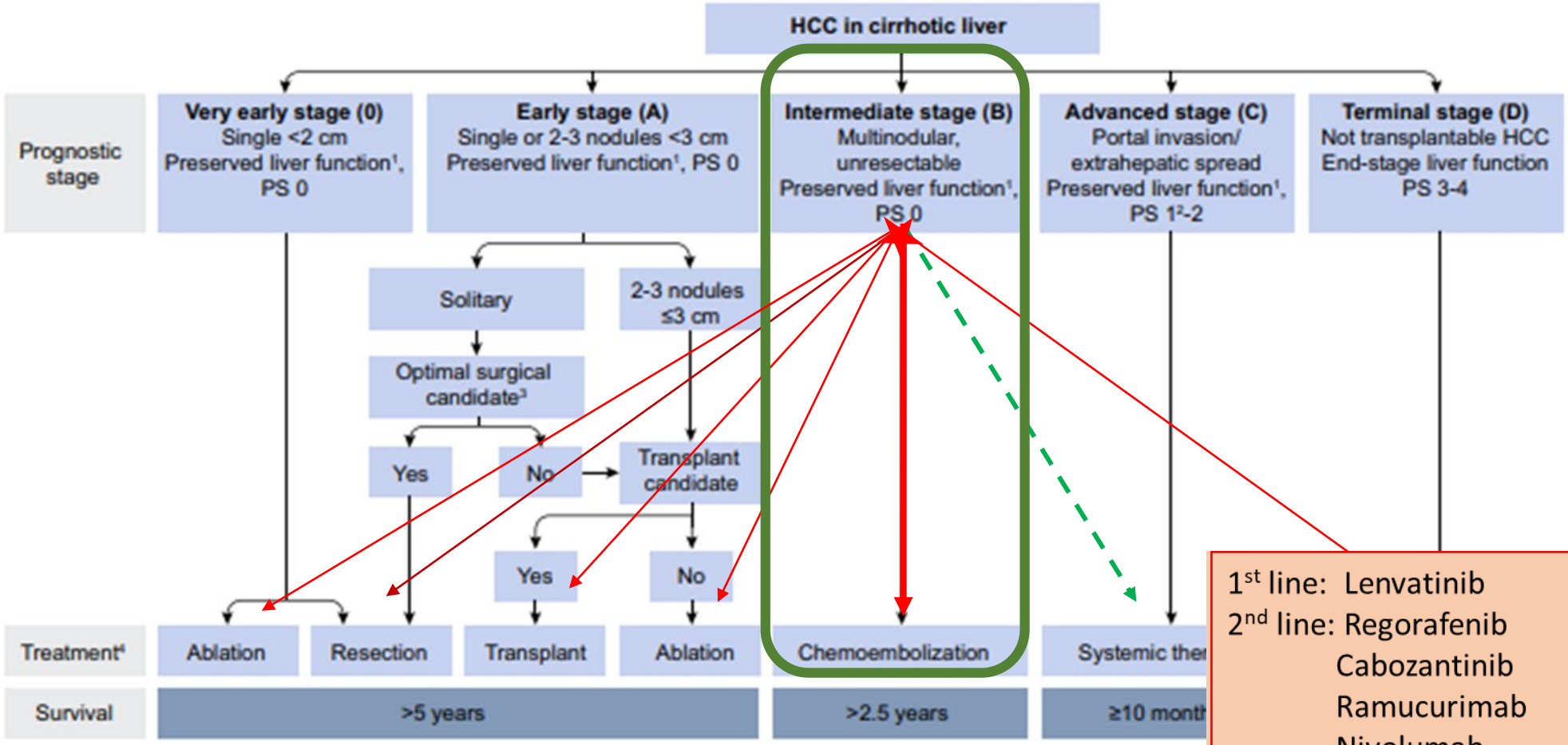
Role of AFP?

- Several studies have shown AFP to be an independent predictor of overall survival.
- AFP (log) level was a pretransplant predictor for HCC recurrence: OR 1.2 per increase in AFP ($P < 0.001$)
- Patients presenting with an AFP >1,000 regardless of tumor size do not receive MELD score exception unless the AFP was reduced to <500 after LRT

Harper AM,et al. Liver Transpl 2016;22:757- 764.

Role of Neoadjuvant/Adjuvant therapy?

Updated Barcelona staging system (BCLC 2018)



Stage Migration (L>R or R>L)

1st line: Lenvatinib
2nd line: Regorafenib
Cabozantinib
Ramucurimab
Nivolumab
Pembrolizumab

EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma, J, Hepatol.2018

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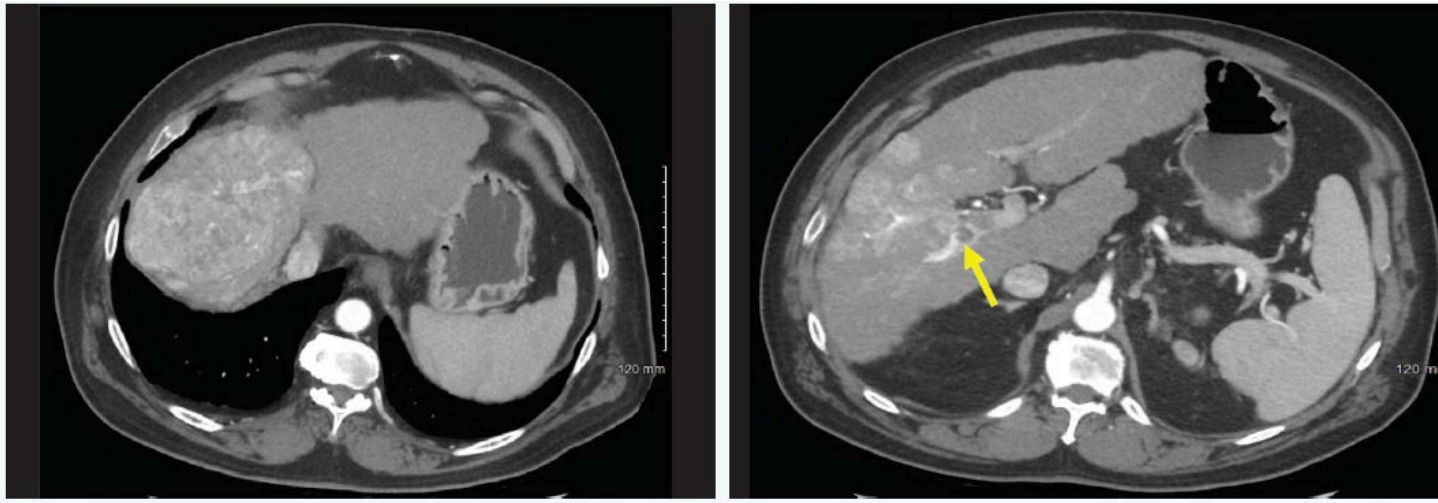


2019: New imaging: PVT extending to right main portal vein

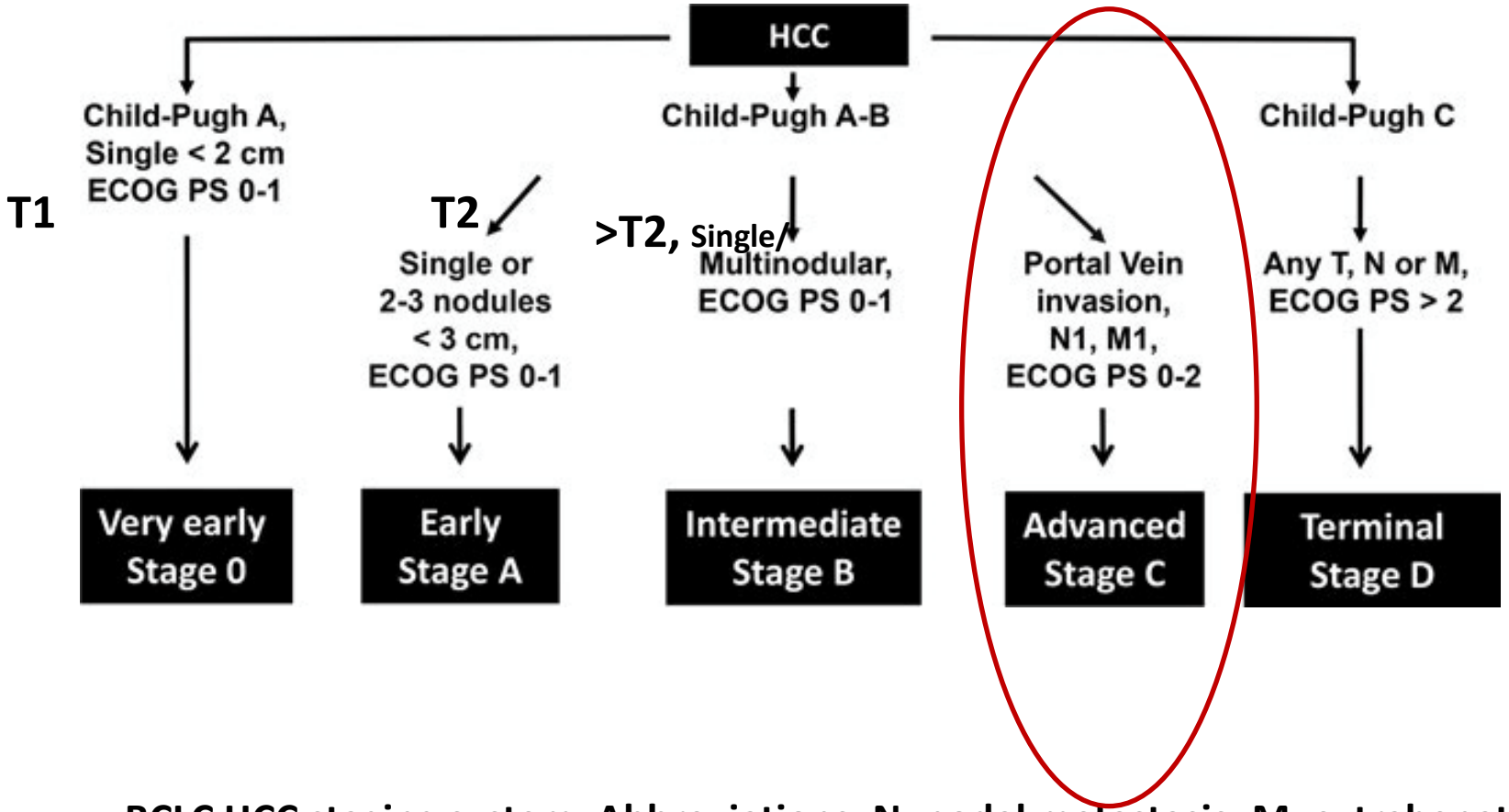
Elevated AFP > 13000

Discussed at Liver MDC and Y90 was recommended

Still compensated. Platelet 119, Albumin 4.5, ALT 34, AST 27, T Bili 1.2 Cr 1.0

Q3. What is the next best step?

1. Surgical resection
2. Locoregional therapy by IR
3. Systemic therapy
4. Combination of LRT and Systemic therapy



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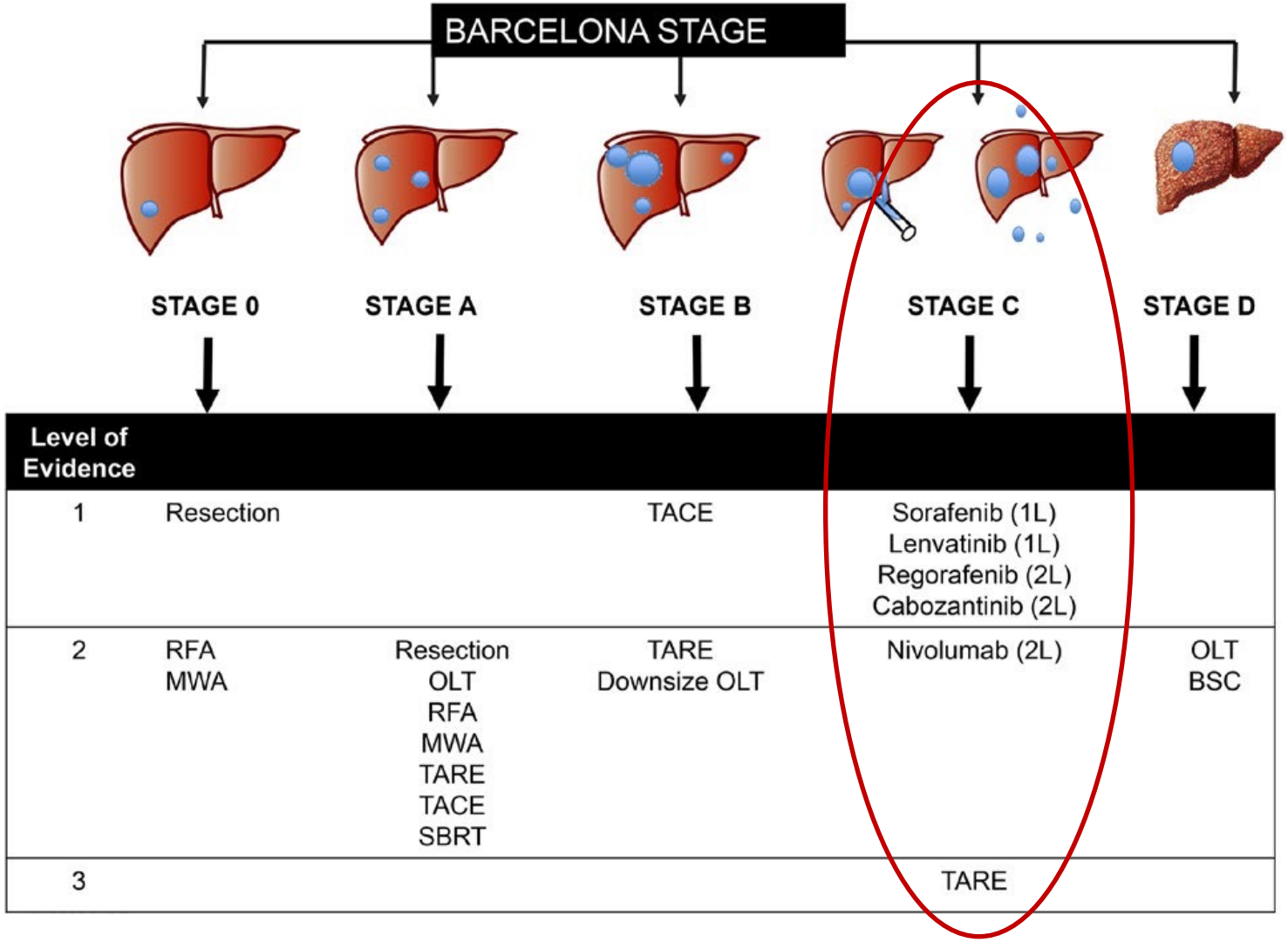
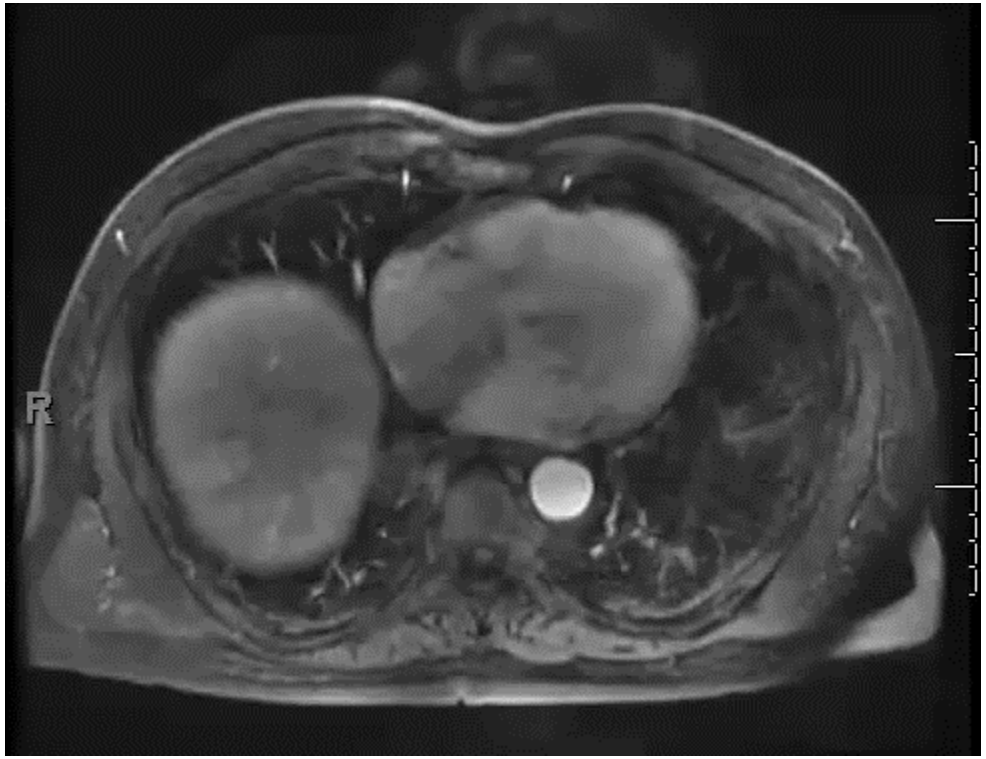
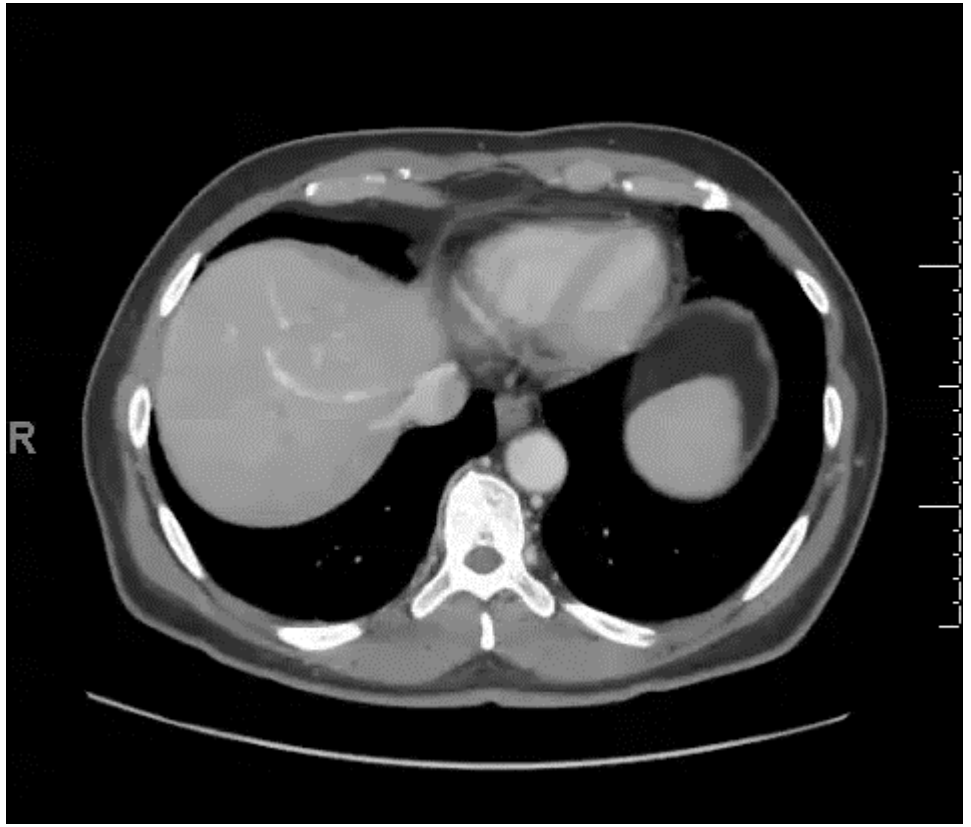


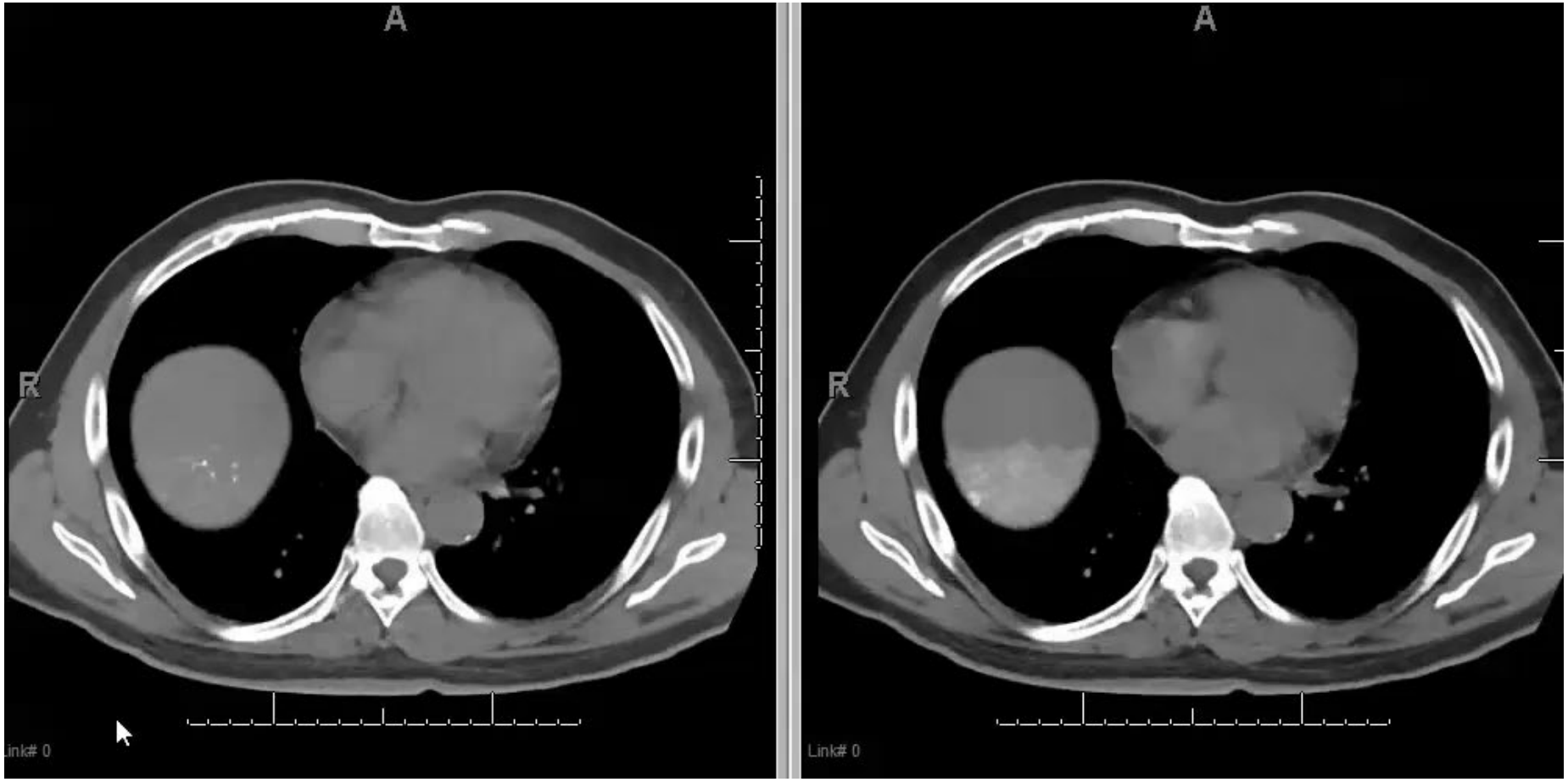
Level of Evidence					
1	Resection		TACE	Sorafenib (1L) Lenvatinib (1L) Regorafenib (2L) Cabozantinib (2L)	
2	RFA MWA	Resection OLT RFA MWA TARE TACE SBRT	TARE Downsize OLT	Nivolumab (2L)	OLT BSC
3				TARE	

Pre-Procedure Imaging

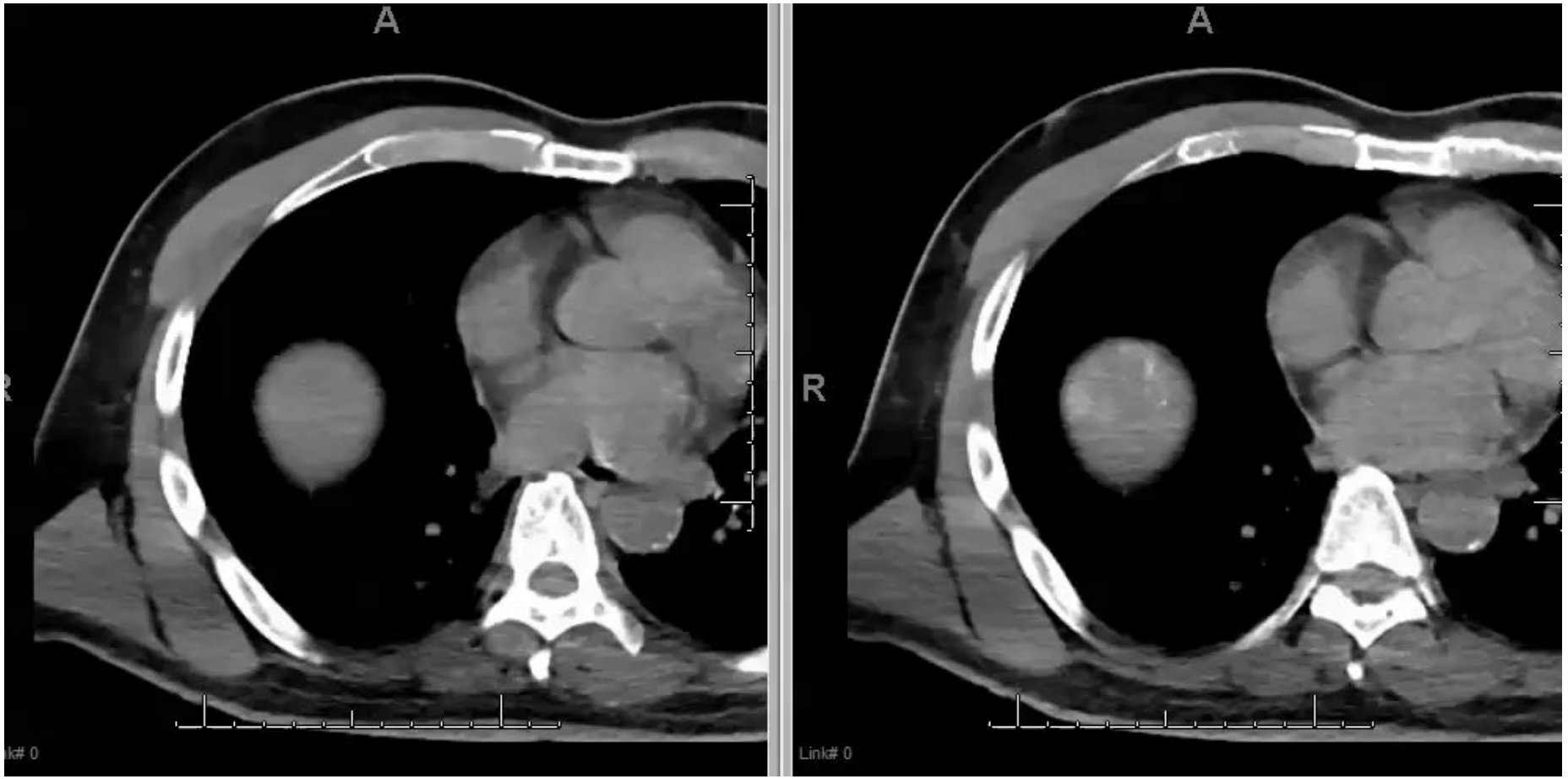




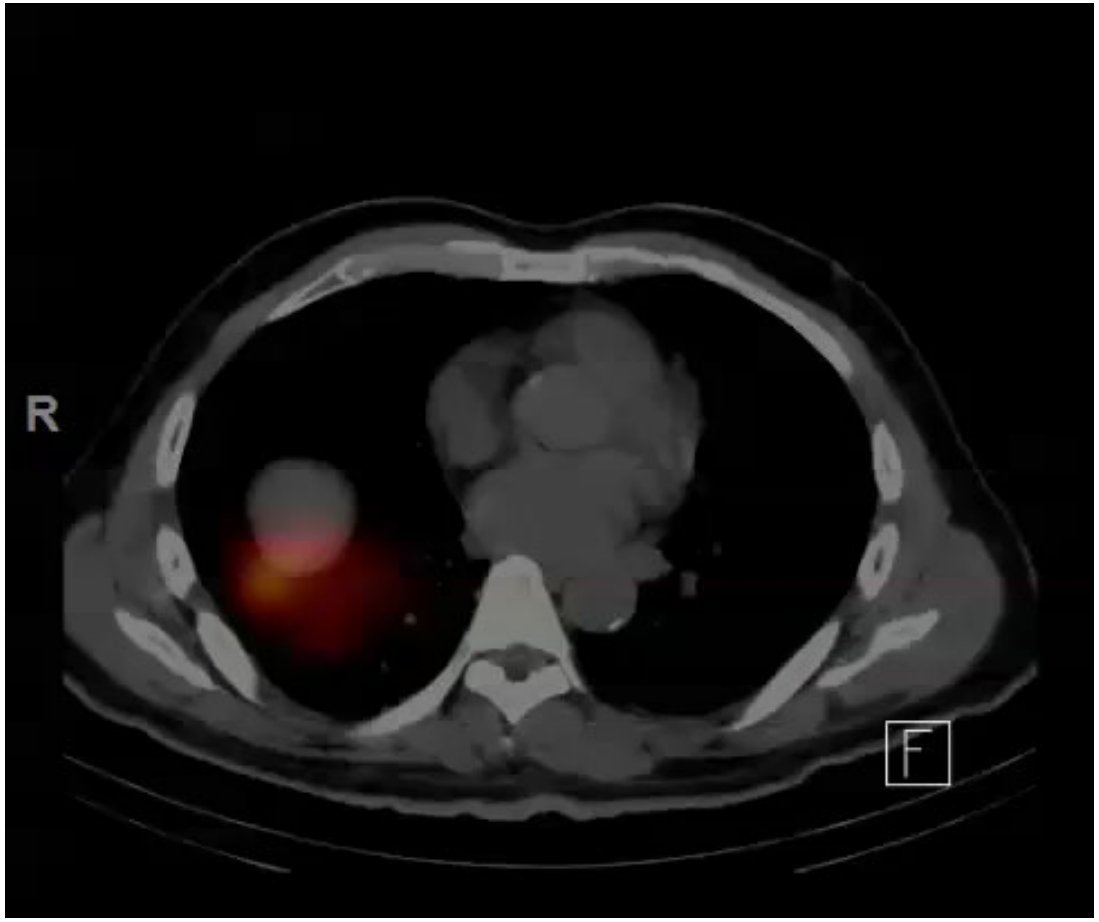
In Room Angio CT Early and Late Arterial



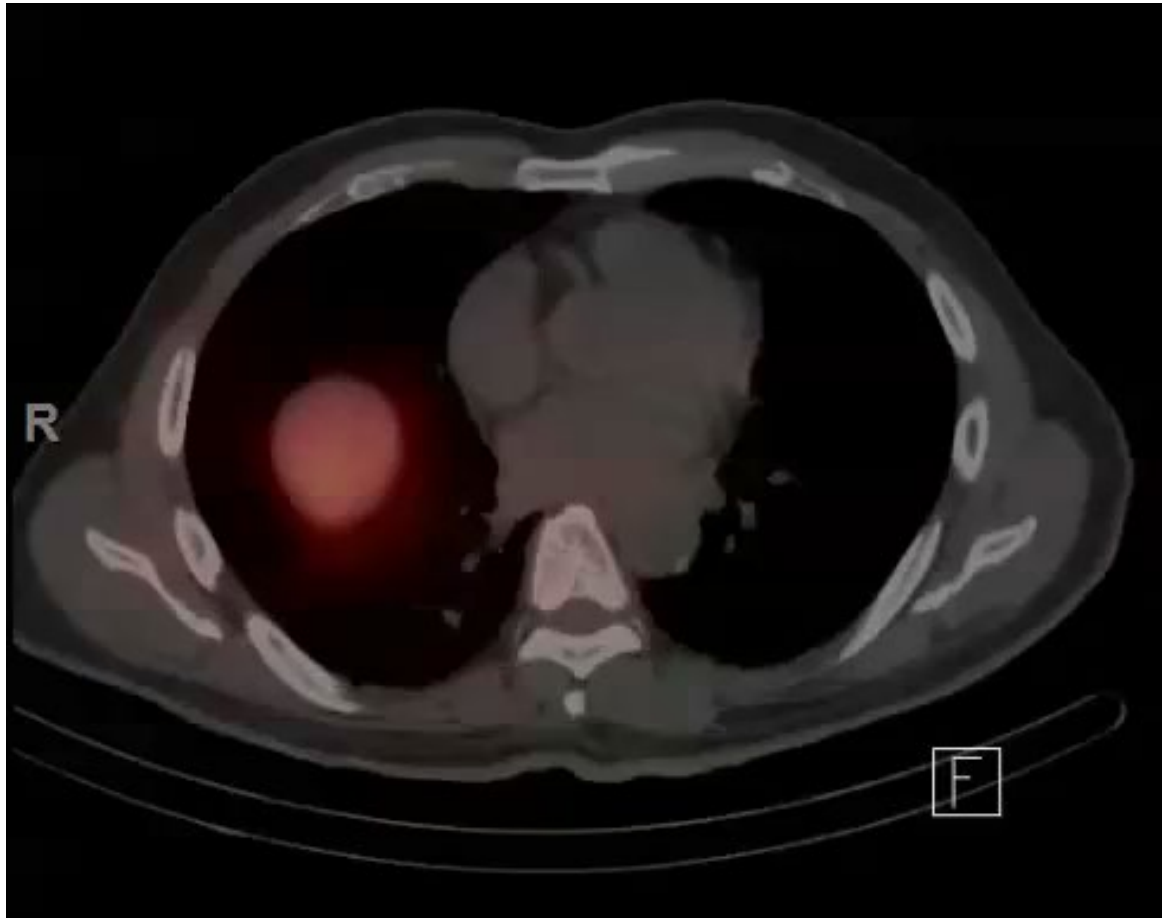
Left Lobe Angio CT



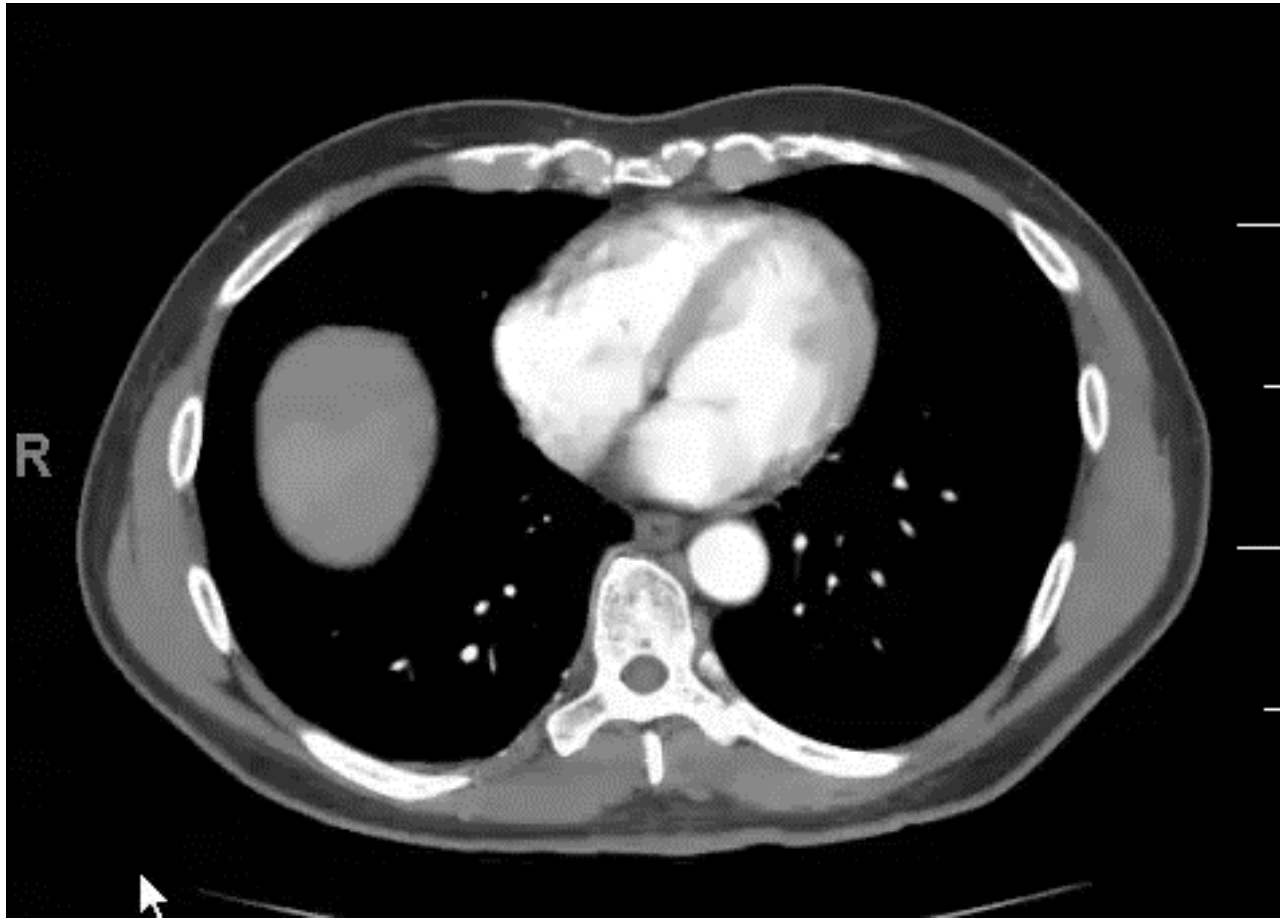
SPECT CT T99MAA



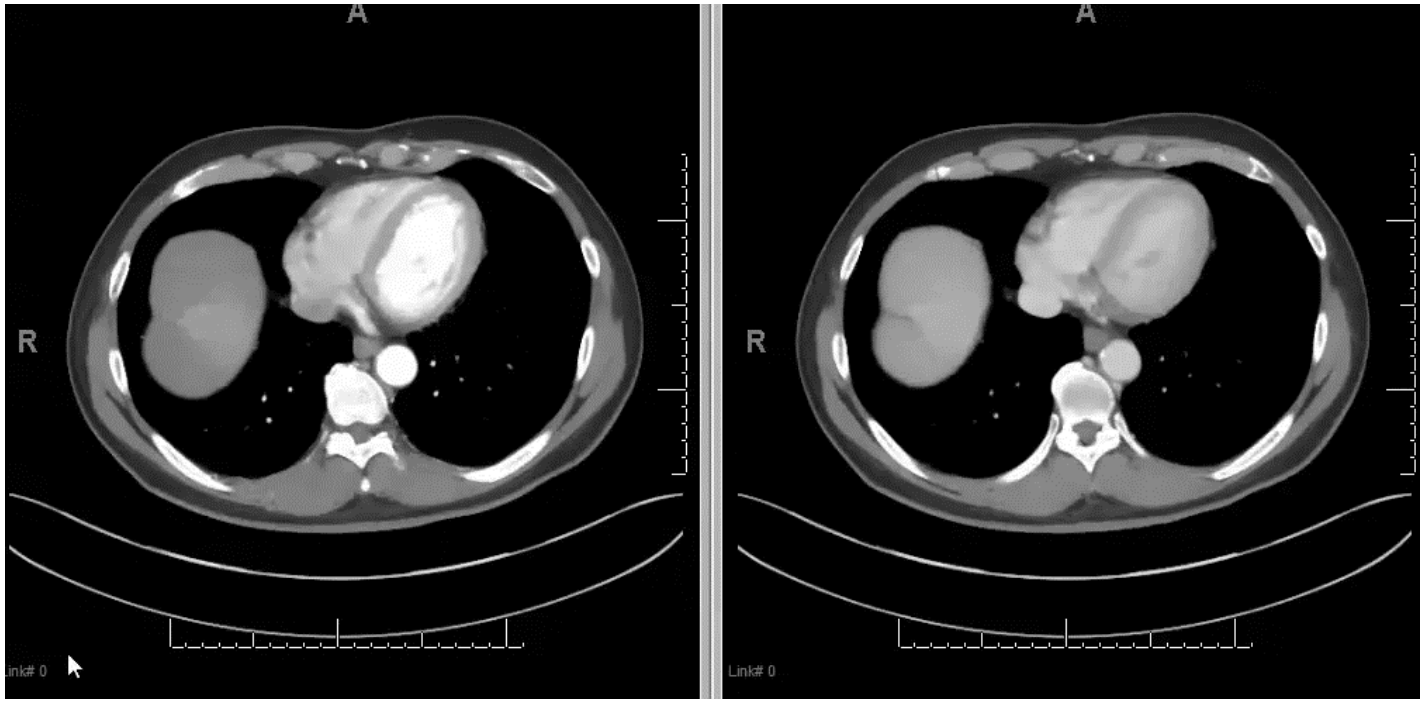
Post Y90 SPECT CT



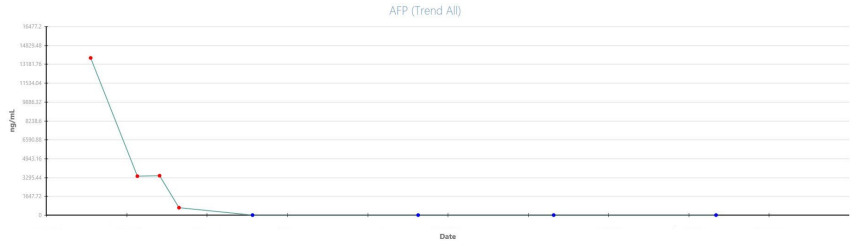
First Follow Up at 2 months



Follow up at 1 Year:



AFP Normalized



Intervention vs comparison	Design	Studies (n)	Child–Pugh	Outcome	Patients (n)	ES (95% CI)	GRADE
Macrovascular invasion:							
Sorafenib vs placebo	RCTs	2	Class A (96.6%) Class B (0.4%)	Overall Survival	311	HR 0.66 (0.51-0.87), $I^2 = 0\%$	⊕⊕⊕◯ MODERATE †
**Sorafenib-cryoRx vs sorafenib	RCT	1	Class A (80.9%) Class B (0.19%)	1-year survival rate	104	RR 1.7 (0.99-2.78)	⊕⊕⊕◯ MODERATE †
**Percutaneous RFA vs control	Observational study	1	Class A (78.9%) Class B (21.1%)	Mortality	57	RR 0.81 (0.67-0.97)	⊕◯◯◯ VERY LOW *†
**TACE vs Y 90	Observational study	1	NR	Median Survival	323	OR 2.1 (1.04-4.2)	⊕◯◯◯ VERY LOW *†
**131 I-lipiodol vs TACE/TAE	Observational study	1	Class A (59.7%) Class B (33.9%) Class C (6.4%)	1-year survival rate	20	RR 2.6 (0.39-16.9)	⊕◯◯◯ VERY LOW *†
Cytotoxic chemotherapy vs sorafenib	Observational study	1	Class A (76.1%) Class B (23.9%)	Overall Survival	49	HR 0.5 (0.1-1.7)	⊕◯◯◯ VERY LOW *†
**Transhepatic arterial chemotherapy vs control	Observational study	1	Intervention (7.0 ± 2.10) Control (8.5 ± 2.20)	6-month survival rate	23	RR 11.5 (0.69 – 190.8)	⊕◯◯◯ VERY LOW *†
**Chemoembolization with or without RT vs sorafenib	Observational study	1	Class A (64.4%) Class B (35.6%)	Overall survival	262	HR 0.28 (0.20-0.40)	⊕◯◯◯ VERY LOW *†
**Chemoembolization with or without RT vs sorafenib	Observational study	1	Class A (100%)	Overall survival	413	HR 0.34 (0.24-0.48)	⊕◯◯◯ VERY LOW *†
**Chemoembolization with or without RT vs sorafenib	Observational study	1	Class B (100%)	Overall survival	144	HR 0.26 (0.16-0.43)	⊕◯◯◯ VERY LOW *†
**Chemoembolization vs sorafenib	Observational study	1	Class A (79.8%) Class B (20.2%)	Overall survival	361	HR 0.67(0.47–0.95)	⊕◯◯◯ VERY LOW *†
**Chemoembolization and RT vs chemoembolization	Observational study	1	Class A (75.4%) Class B (24.6%)	Overall survival	491	HR 0.56 (0.45–0.71)	⊕◯◯◯ VERY LOW *†

Any role of systemic therapy?

The AASLD recommends the use of systemic therapy over no therapy for patients with Child-Pugh class A cirrhosis or well-selected patients with Child- Pugh class B cirrhosis plus advanced HCC with macrovascular invasion and/or metastatic disease

Case 1:

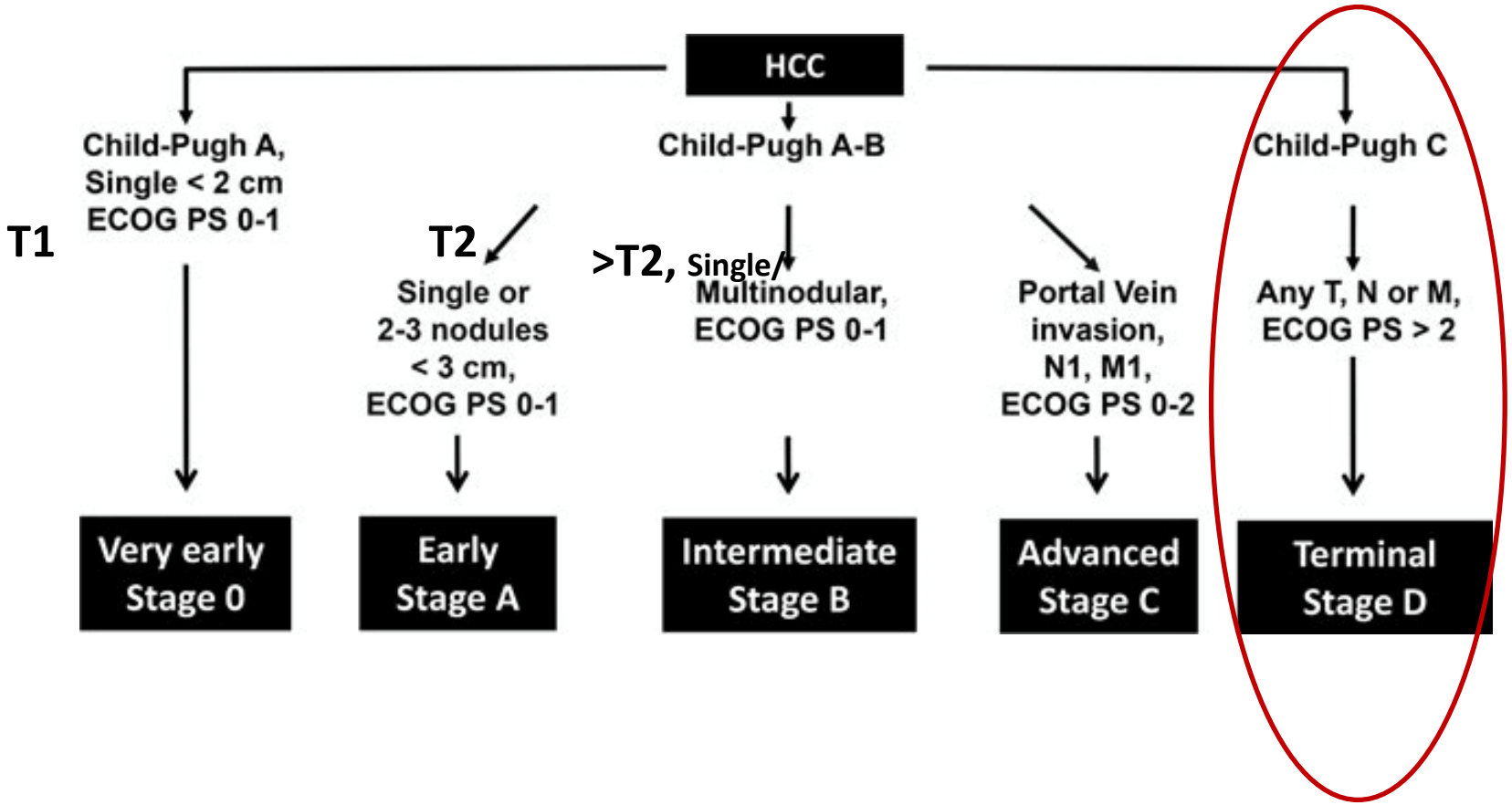
65 yrs/F Hispanic
2015: Metabolic syndrome: Type 2 DM, Hypertension, Hyperlipidemia, BMI 35
Family history of cirrhosis-Father, Uncle with history of alcohol
She does not drink alcohol
Labs: AST 65, ALT 45, Platelet 200, Albumin 3.7
Fibroscan: CAP score 320 dB/m(S3), Fibrosis score 10 kPa (F3)
US liver: Steatosis, no evidence of cirrhosis/portal hypertension

2019: Presented with upper abdominal discomfort
Contrast imaging showed **6.5 cm HCC**
Cirrhosis, Well compensated, Bili 1.2, Platelet 150, AFP 200
Treated with Y-90

2020: Admitted with encephalopathy and ascites. Bilirubin 4, MELD score 20

Q4. What is the next best step?

1. Systemic therapy
2. Combination of LRT and Systemic therapy
3. Palliative care
4. Listing for transplant

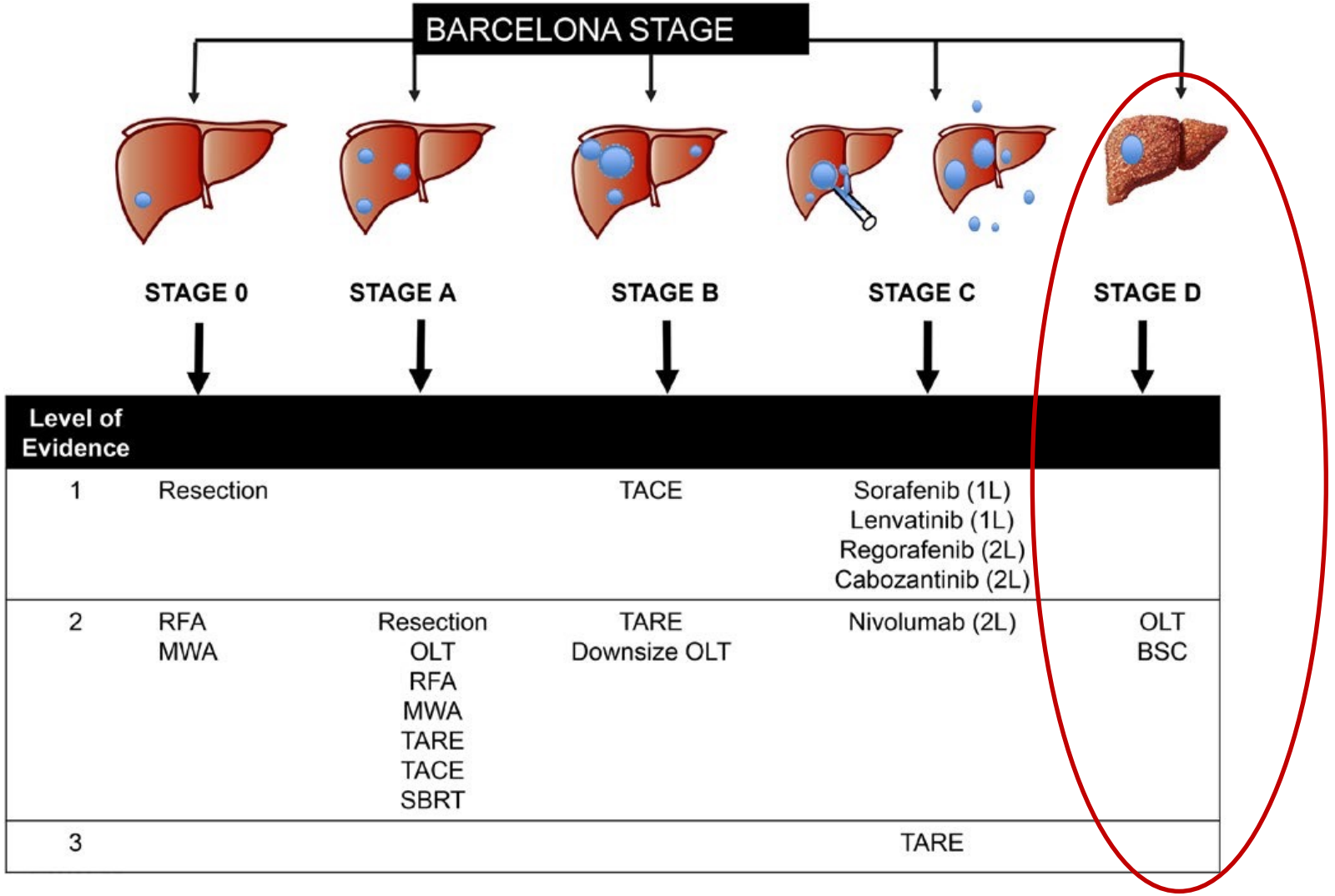


BCLC HCC staging system. Abbreviations: N, nodal metastasis; M, extrahepatic metastasis.

Hepatology, Vol. 68, No. 2, 2018

Treatment recommendations according to BCLC Stage.

Abbreviations: MWA, microwave ablation; BSC, best supportive care; 1L, first-line therapy; 2L, second-line therapy.



Level of Evidence					
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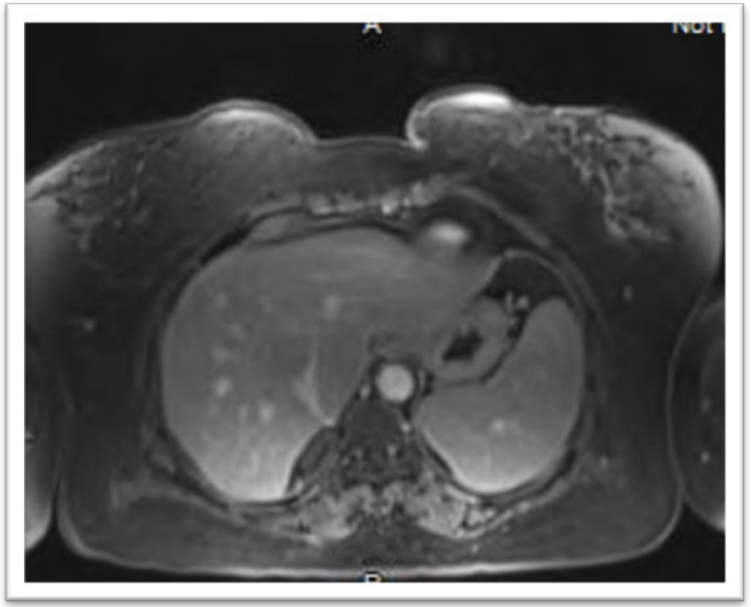
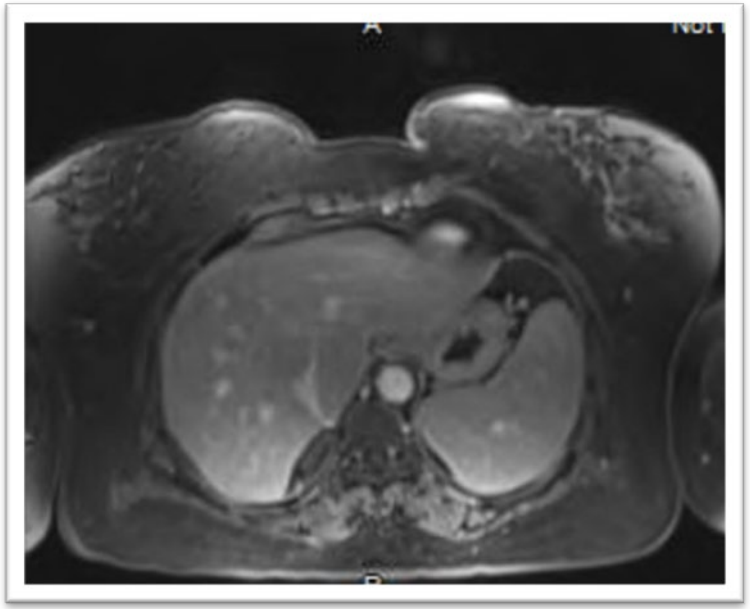
Case 2 N.G.



- 63 y/o female from Pakistan, seen by Baylor
- Hepatology in 2015 for positive HCV
- PMH: HTN, Obesity , BMI 35, HCV (Dx 2012)
- SH: No ETOH/Drugs/Tobacco
- Sx: none
- HCV treatment given in 5/2016 >> SVR (RNA not detected)
- MRI abdomen 4/2016 : Splenomegaly
- MRI Abd 12/2016: Cirrhosis and mild splenomegaly. No suspicious liver mass identified.
- Labs: BMP normal, LFT normal, PT 15.2 (nl 14.7) , INR 1.2, AFP 8.7, WBC 3.8, Hb 13.4 , platelets 87, MCV 84
- CT abdomen 10/2019 In Pakistan: Liver cirrhosis and a single 6 cm lesion c/w HCC
- Sorafenib 400 mg BID started in Pakistan in 10/2019

Case 2 N.G.



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- CT abdomen 10/2019 In Pakistan: Liver cirrhosis and a single 6 cm lesion c/w HCC
- Sorafenib 400 mg BID started in Pakistan in 10/2019

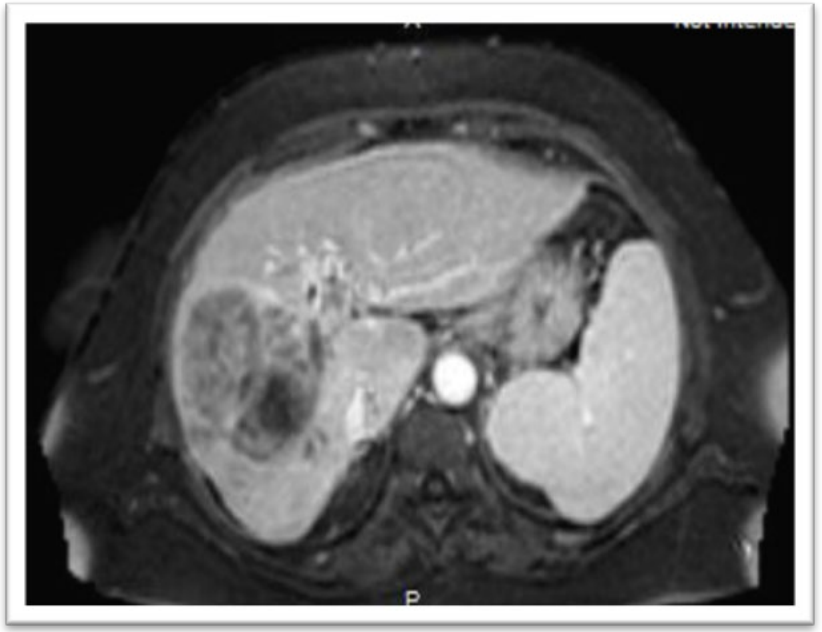
Case 2 N.G. Continued…

- 2/2020 Back in USA and visited Baylor hepatology with 3 months of intermittent RUQ pain and hematochezia
- Exam: BP 160/85, RUQ pain
- Meds: HCTZ and Metoprolol

- Labs: HCV SVR, HEPC Ab reactive, AFP 6950, T, bili 1.4, AST/ALT/AP normal, PLT 68, wbc 3.3, Hb 12.1, cr 0.6, Na 136, INR 16.3

- **MRI 2/2020 :** cirrhotic liver, a large complex mass is seen in the segment 6, 7, 8 of the liver measuring 6.7 x 8 3 x 9.4 cm. LIRADS 5, main R/L/main portal vein tumor Thrombus seen

- CT chest w contrast and Bone scan: NED



Case 2 N.G:
Question 1
What is the next best step?

- 1) Liver biopsy
- 2) Y-90
- 3) TACE
- 4) Hepatectomy
- 5) Liver transplant
- 6) Systemic therapy
- 7) Sorafenib followed by TACE or Y-90
- 8) TACE followed by Sorafenib


HCC MDTB
1-Hepatology
Cirrhosis
Non cirrhotic
Labs
AFP
LFT/CBC/CMP
Transplant or not
2- Radiology
Abd CT-Triple phase
Abd MRI- Triple phase
LIRADS assignment
staging
CT chest
Bone scan
3- Hepatectomy eval
Post resection remaining liver reserve
How many lesions
Tumor thrombus
PVT
AFP level
Co-morbidity/Age
4- Transplant evaluation
MELD score
MELD-NA score
ETOH, drug abuse
MILAN criteria
Extebded MILAN
Cardiac and lung function
portal HTN workup
Varices
Ascites
encephalopathy
AFP level
> 500?
Adequate Social suport
5-Interventional Radiology
Bridge to curative Tx
TACE
Ablation
Y-90
Combo
Non curative - Tumor Control
TACE
Ablation
Y-90
Combo
Liver or met Biopsy
Paracenthesis
Peritoneal catheter
6- Medical Oncology
Liver biopsy ?
Systemic Therapy
Locoregional theapy
7- Systemic therapy
Sorafenib
Lenvatinib
Atezolimzumab + Bevacizumab
Cabozantinib
Regorafenib
opdivo
Pembrolizumab
8- Palliative care
Child pugh C
BARCELONA D

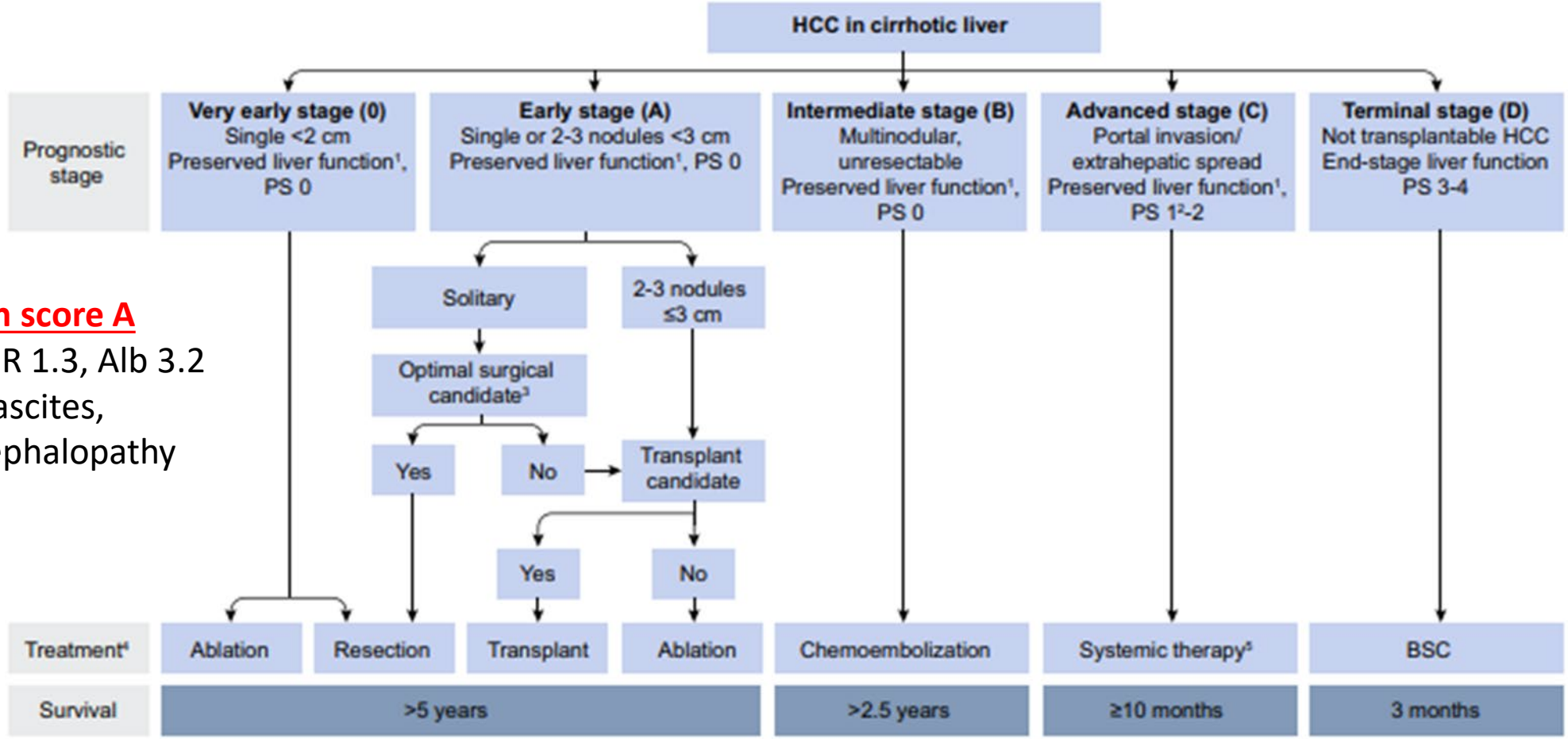
Barcelona staging system

Child Pugh score A

Bili 1.4, INR 1.3, Alb 3.2

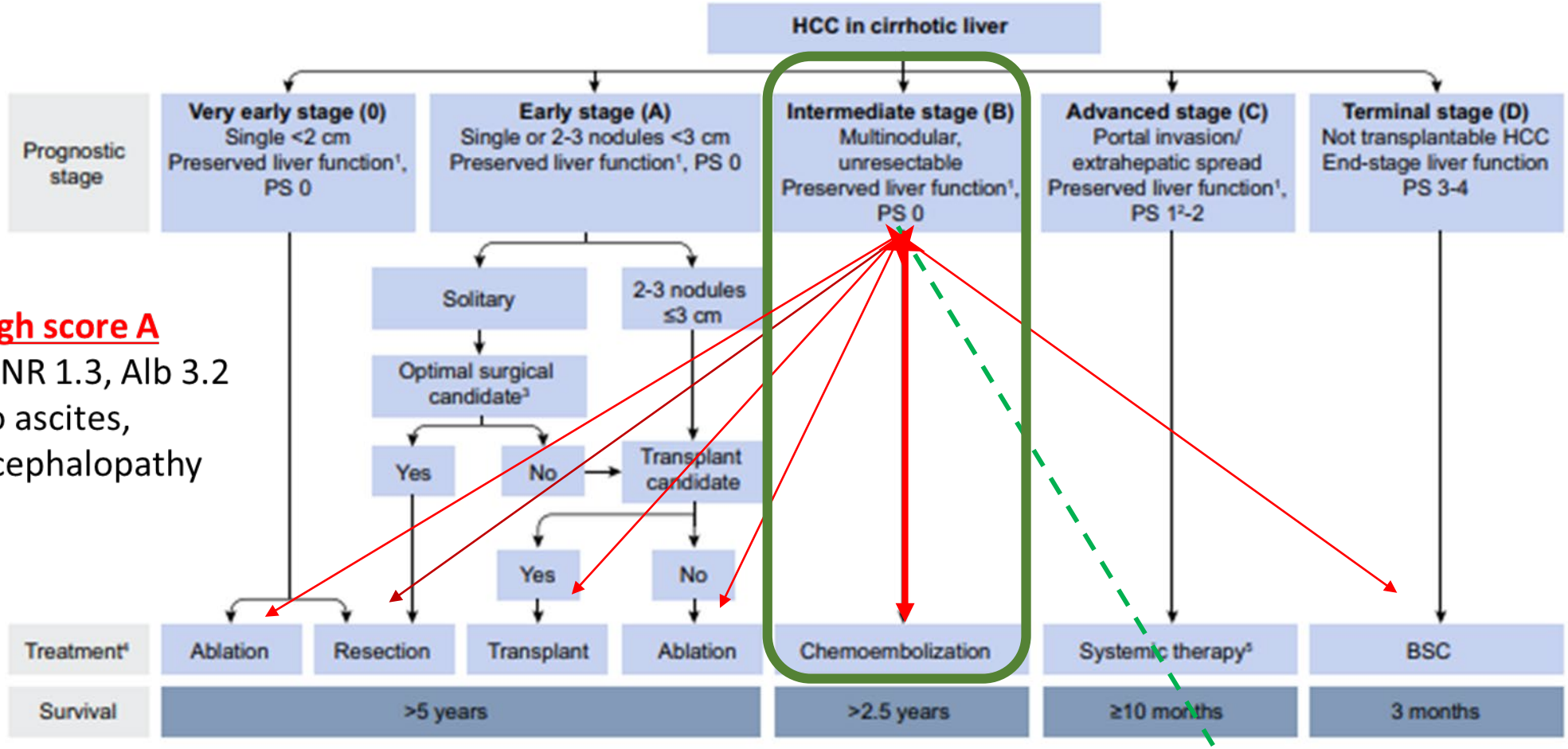
No ascites,

No encephalopathy



EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma, J, Hepatol.2012;56(4): 908-943

Updated Barcelona staging system (BCLC 2018)



Child Pugh score A

Bili 1.4, INR 1.3, Alb 3.2

No ascites,

No encephalopathy

Stage Migration (L>R or R>L)

Systemic therapy
8 options

EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma, J, Hepatol.2018

Case 2 N.G.

- Liver MDTB: systemic therapy advised
- GI: EGD for esophageal varices evaluation and banding if needed: :Grade I esophageal varices
- Lisinopril added to better control the BP
- BARCELONA C , Child Pugh score A (6) , ECOG 1

Case 2 N.G.

Question 2

Which systemic therapy option would you chose?

- 1) Nivolumab
- 2) Sorafenib
- 3) Lenvatinib/Pembrolizumab combo
- 4) Ramucirumab
- 5) Pembrolizumab
- 6) Atezolizumab/Bevacizumab Combo
- 7) Cabozantinib

Case 2 N.G.

- She was started on Q3W Atezolizumab and Bevacizumab combination
- 3/2020 - 9/2020:
- Restaging scans followed 3 , 6 months

Case 2 N.G:
Re-evaluation at 3 months on A + B

- Abdominal pain is better , BP normal, Urine Protein normal
- Oral mucositis
- AFP 308 (started at 6950 in 2/2020) , WBC 2.9, platelets 68, Hb 10.5, Bili 1.4, LFT normal, CPS A

-MRI 6/2020 : **unchanged mass** and tumor thrombus

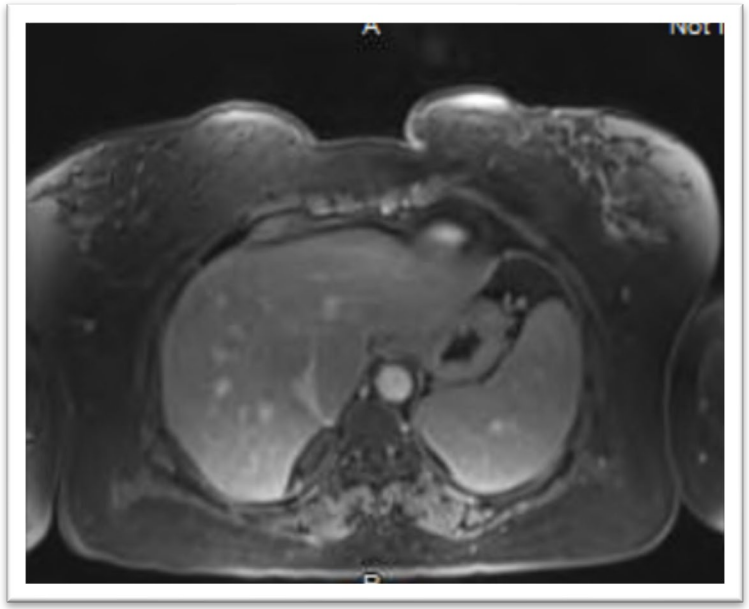
-CT chest and Bone scan 6/2020 NED

Case 2 N.G:
Re-evaluation at 6 months on A + B

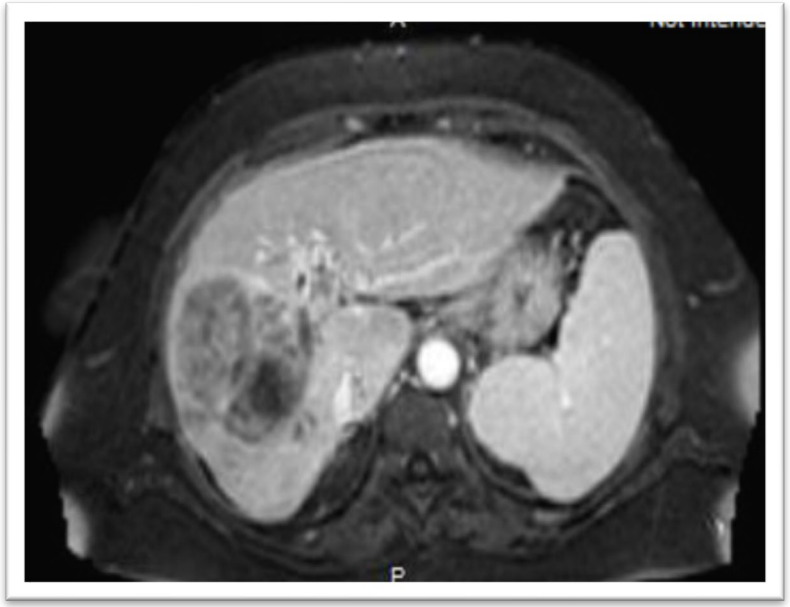
- No longer has abdominal pain
- BP normal , urine protein normal
- WBC 2.5, platelets 48, Hb 9.8 Bili 1.4, LFT normal, CPS A, AFP not checked
- **MRI 9/2020:** Good response: HCC lesion is smaller at 3 x 4.2 cm.
- Right portal vein thrombosis, but the previously seen thrombus in the left and main portal vein is mostly resolved
- CT chest and Bone scan 6/2020 NED

Case 2 N.G. Images

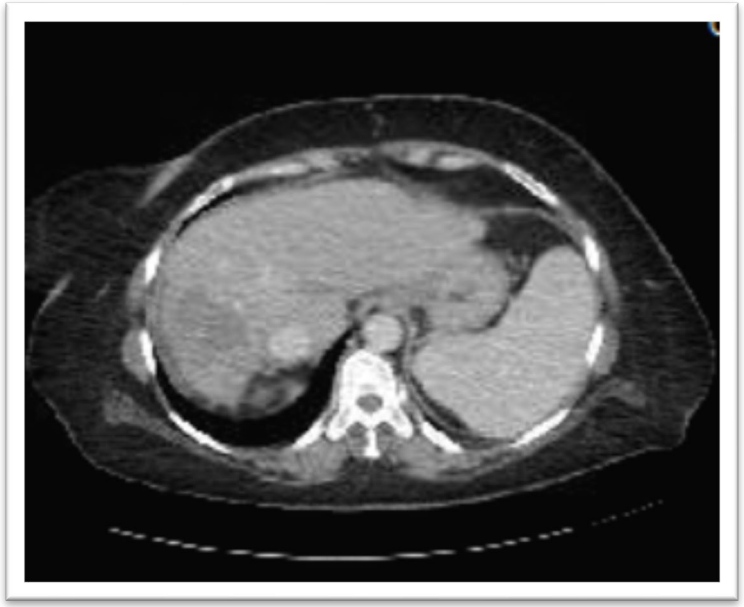
2016 (MRI)



3/2020 baseline (MRI)



9/2020, 6 mon CT post Atezo+Bev



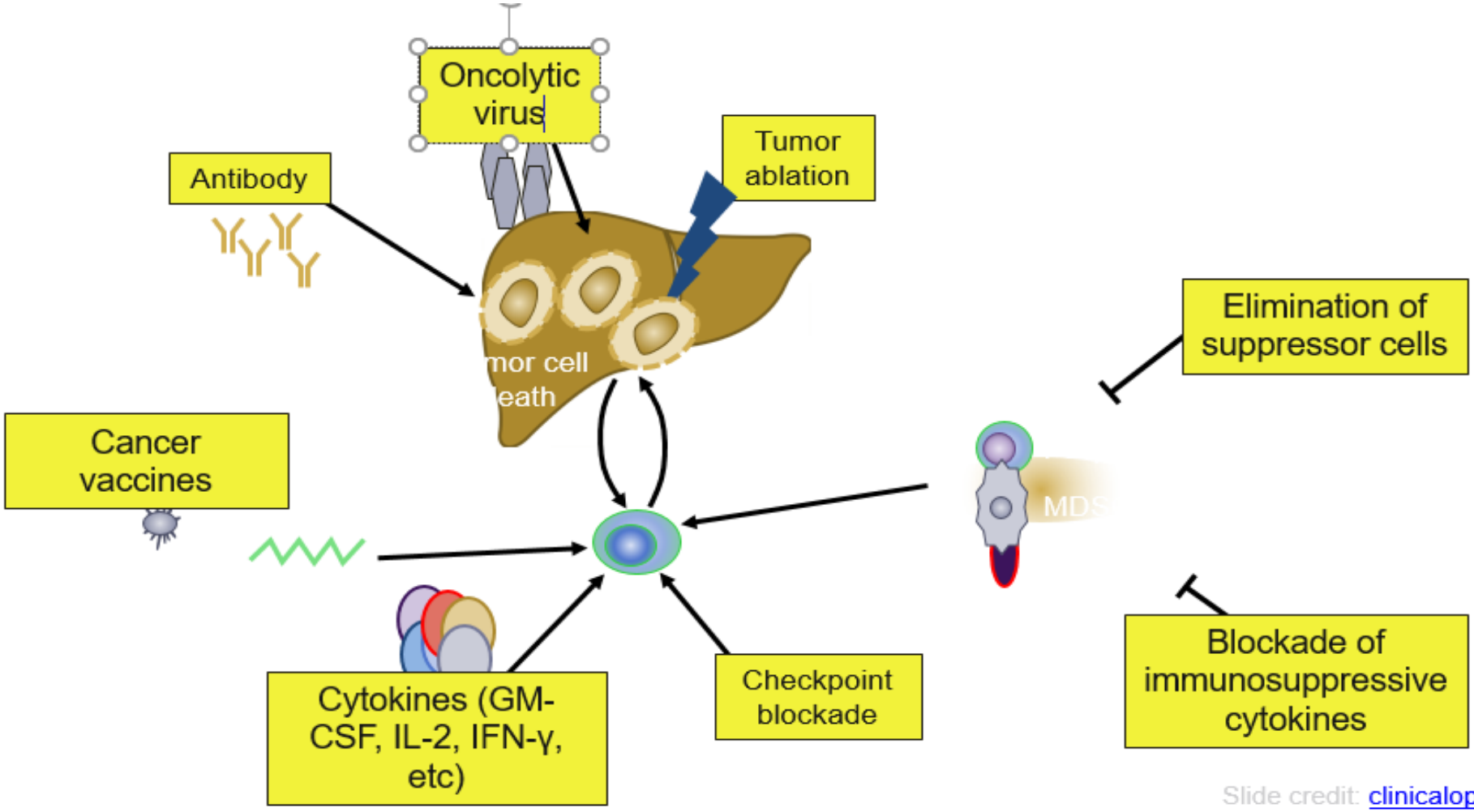
First line systemic therapies

- **Doublet Atezo + Bev (2020)** : It demonstrated statistically significant and clinically meaningful improvement in OS per RECIST , PFS and better QOL

- **Sorafenib (2018)**

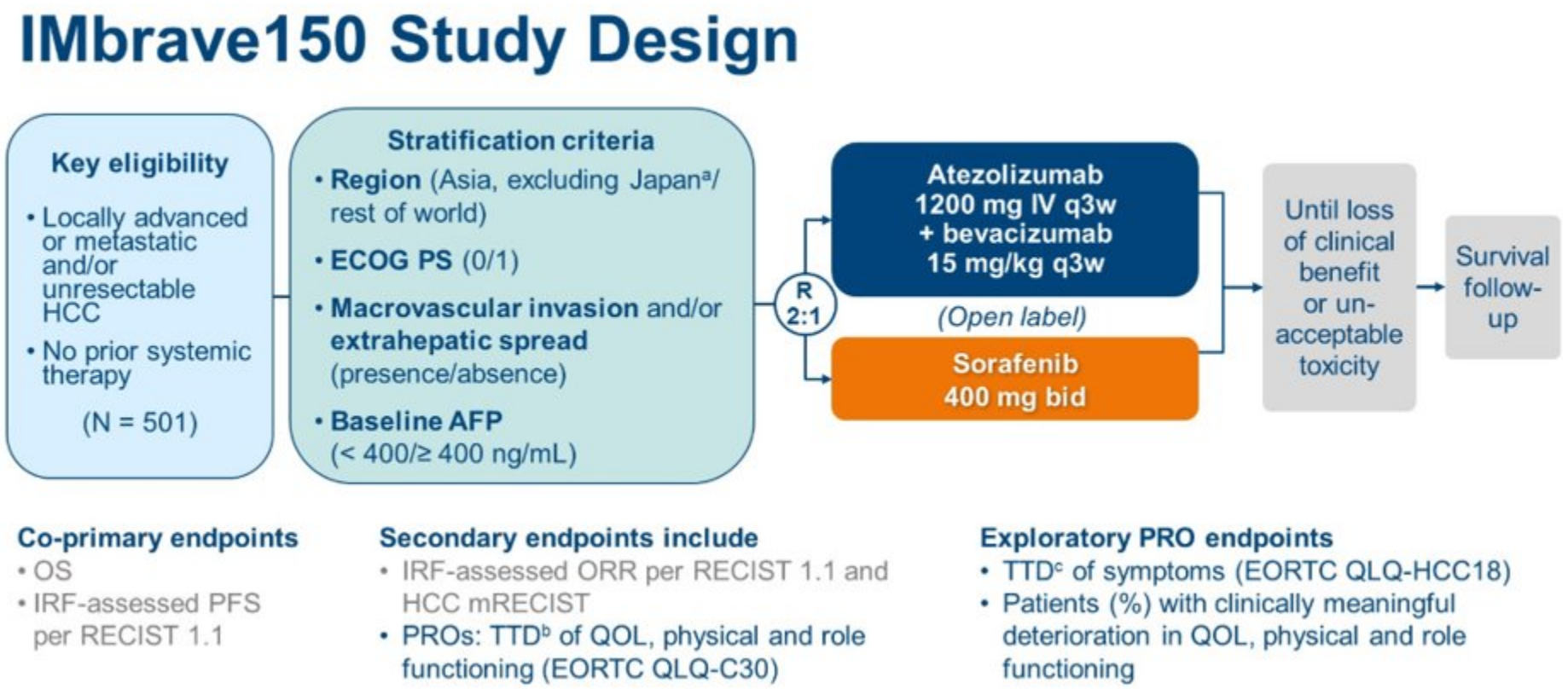
- **Lenvatinib (2018)**

Immune-based approaches in HCC



Slide credit: clinicaloptions.com

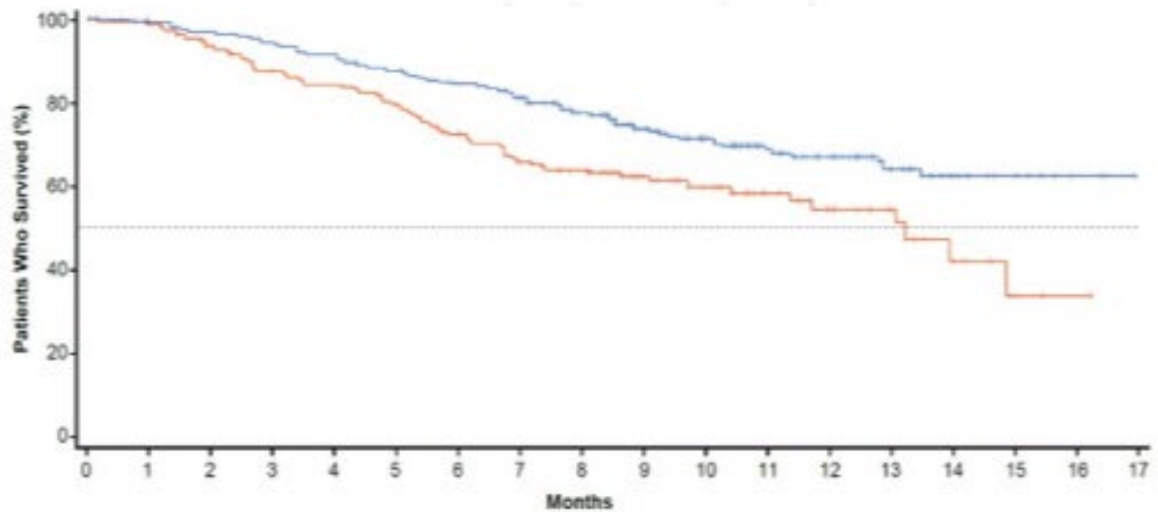
IMbrave 150
Hepatocellular carcinoma



Finn et al 5/2020

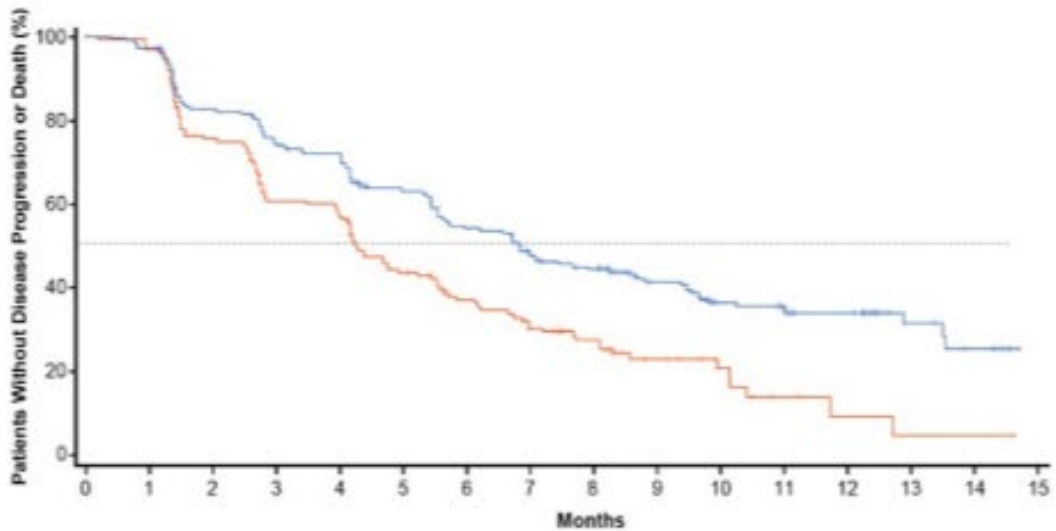
IMbrave150 Co-Primary Endpoints: OS and PFS[1]

OS	Atezo + Bev	Sorafenib
Median (95% CI), mo	NE	13.2 (10.4, NE)
HR	0.58 (95% CI: 0.42, 0.79)[a]	
P value	0.0006[b]	



No. at risk																		
Atezo + Bev	336	329	320	312	302	288	275	255	222	165	118	87	64	40	20	11	3	NE
Sorafenib	165	157	143	132	127	118	105	94	86	60	45	33	24	16	7	3	1	NE

PFS (IRF assessed RECIST 1.1)	Atezo + Bev	Sorafenib
Median (95% CI), mo	6.8 (5.7, 8.3)	4.3 (4.0, 5.6)
HR	0.59 (95% CI: 0.47, 0.76)[a]	
P value	< 0.0001[c]	



No. at risk																
Atezo + Bev	336	322	270	243	232	201	169	137	120	74	50	46	34	11	7	NE
Sorafenib	165	148	109	84	80	57	44	34	27	15	9	4	2	1	1	NE

Finn et al 5/2020

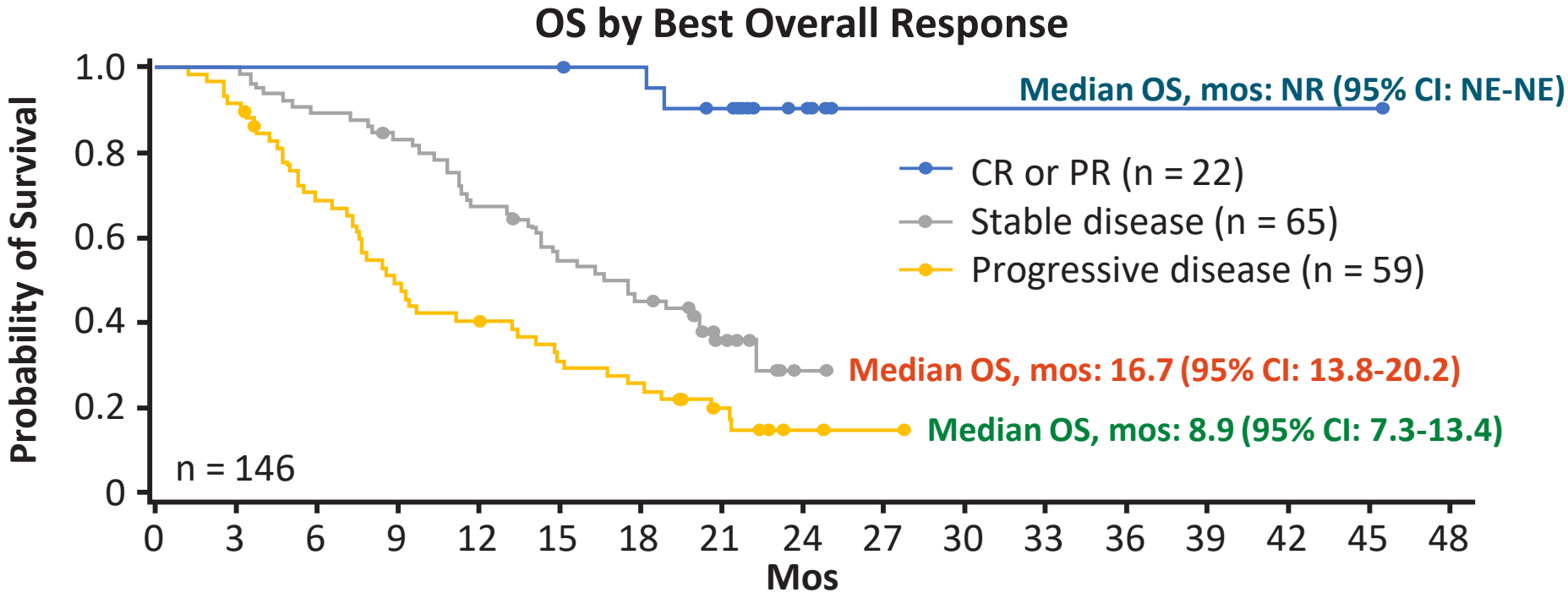
Advanced HCC systemic Treatments

Landmark Trial	Drug	Effect	mOS	mPFS months	FDA
SHARP (1st line) Randomized , Double blinded Advanced HCC, Tx, n=602 CP A,BCLC ≤ C, ECOG ≤ 2,	**Sorafenib** vs placebo	Multi-specific TKI Activity against CRAF, BRAF, KIT, FLT-3, RET/PTC, VEGFR-1,2,3, PDGFR-b	10.7 vs 7.9		2008
REFLECT (1st line) Randomized, open label,Non-inferiority trial n=954 CP A, BCLC B or C, ECOG 0/1	**Lenvatinib** vs sorafenib	Multi-targeted TKI VEGFR1,2,3,4, PDGFR-a, RET, KIT	13.6 vs 12.3	7.4 vs 3.7	2018
RESORCE (2nd line) Phase , Rand, III, DB, Progressed on Sorafenib ECOG <2. CP A. N=572	**Regorafenib** vs placebo		10.6 vs 7.8	3.1 vs 1.5	2017
CELESTIAL Phase III, Double blinded, Randomized CP A, ECOG 0/1, Up to 2 systemic prior TXs, N=707	**Cabozantinib** vs Placebo	Multi-targeted TKI VEGFR1,2,3,4, PDGFR-a, RET, KIT, MET, AXL, ROS-1, TYRO3, MER, TRKB, FLT-3, TIE-2	10.2 vs 8.0	5.2 vs 1.9	3/2019
REACH-2 AFP ≥ 400, BCLC stage B/C, CP A, ECOG 0/1, prior sorafenib	**Ramucurimab** vs placebo	Anti-VGFR monoclonal antibody	8.5 vs 7.3	2.8 vs 1.6	3/2019

Nivolumab: PD-1 inhibitor
Pembrolizumab: PDL-1 inhibitor

- CheckMate 459: Nivolumab vs sorafenib first line (negative)
- CheckMate 040: Nivolumab after sorafenib (Phase I/II), Phase III ongoing
- Keynote 240: Pemborlizumab after sorafenib: Did not reach dual endpoint

Checkmate 040: OS Analyzed by Best Overall Response or Change in Target Lesion Size



OS (95% CI), %	CR/PR (n = 22)	SD (n = 65)	PD (n = 59)
12 mos	100 (100-100)	67 (55-77)	41 (28-53)
18 mos	100 (100-100)	45 (33-57)	26 (15-38)

- Median OS: 15.1 mos (95% CI: 13.2-18.8) in overall analysis population (N = 154)

El-Khoueiry. ASCO GI 2018.

Slide credit: clinicaloptions.com

MERK Announcement (2/2019)
Pembrolizumab did not reach its dual endpoint for OS and PFS for Advanced HCC

Closer look:

- Effect of dual primary end point (Both PFS and OS had to be met)
- Pre-designed PFS Pv was 0.0001 and OS was 0.017
- High statistical bar to be called a positive study
- PFS: 3.8 to 4.2 months (P-value: 0.02)
- OS: 10.6 to 13.9 months (P-Value: 0.02)
- But 16% did not progress (Flat on curve)

Case 2: N.G
Question 3
Now that the mass is smaller which option would you chose next?

- 1) TACE
- 2) Y-90
- 3) Hepatectomy
- 5) Liver transplant
- 6) Continue current Systemic therapy until progression
- 7) TACE or Y-90 followed by current systemic therapy
- 8) Treatment holiday

Case 2: NG continued …

- The patient was evaluated for Y-90
- Angiogram was unable to visualize the mass well and Y-90 was not carried out
- Atezo and Bev is now being continued as of 10/2020

- At progression what would be your next plan?

Case 2: N.G

Question 4

Which option would you chose at progression?

- 1) Clinical trial
- 2) Sorafenib
- 3) Lenvatinib
- 4) Ramucirumab
- 5) Pembrolizumab
- 6) Cabozantinib
- 7) Nivolumab

Ongoing trials Future directions

1) Immunotherapy +/- targeted therapy upfront

Awaiting CheckMate 459 (nivo vs sorafenib)

Imbrave 150: atezolizumab + bevacizumab

Durvalumab + tremelimumab vs sorafenib (HIMALAYA)

Lenvatinib/pembro vs lenvatinib alone (LEAP-002)

2) Vaccine therapy:

- JX-594, an oncolytic pox virus vaccine. phase III clinical trial in combination with sorafenib compared to sorafenib alone (PHOCUS trial)
- phase-I/II JX-594 and nivolumab (NCT03071094). In addition,
- HEPAVAC-101 phase I/II first in-human planned to evaluate the role of IMA970A,
- a therapeutic cancer vaccine targeting tumor-associated peptides (TUMAPs)

3) Combining local therapy with systemic therapy

4) Predictive markers

Tumor

Host (?different treatment based on etiology of HCC)

Clinical Trials at Baylor

- Glypican 3-specific Chimeric Antigen Receptor Expressing T Cells for Hepatocellular Carcinoma (GLYCAR) : NCT02905188

- Meclizine for Hepatocellular Carcinoma (OPTIM): NCT03253289

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