Hepatocellular Carcinoma: Before During and After

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"Your liver has issues."

Objectives

- Identify risk factors associated with HCC
- Understand approach to HCC surveillance
- Become familiar with uncertainties surrounding HCC diagnosis surveillance and management
- Understand currently available treatment options for HCC
- Understand the importance of multidisciplinary approach for management of patients with HCC

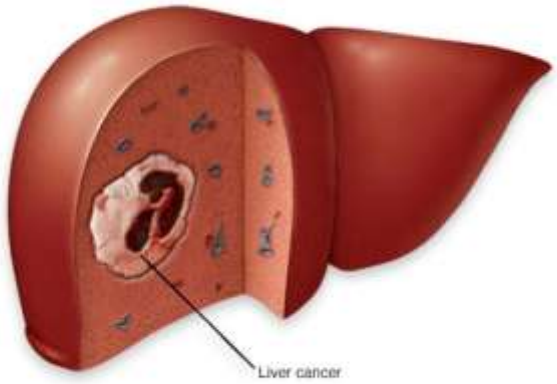
What do these patients h common?

- 38 man with chronic verticall Hepatiti ate ar therapy
- 67 man tabolic syndrome and earl

- 58 woman cured from chr is C 12 years ago with interfe regimen

What is HCC?

- Primary cancer arising from the liver cells (hepatocytes)
- The most common type of primary liver cancer
- Minimal symptoms until advanced stages



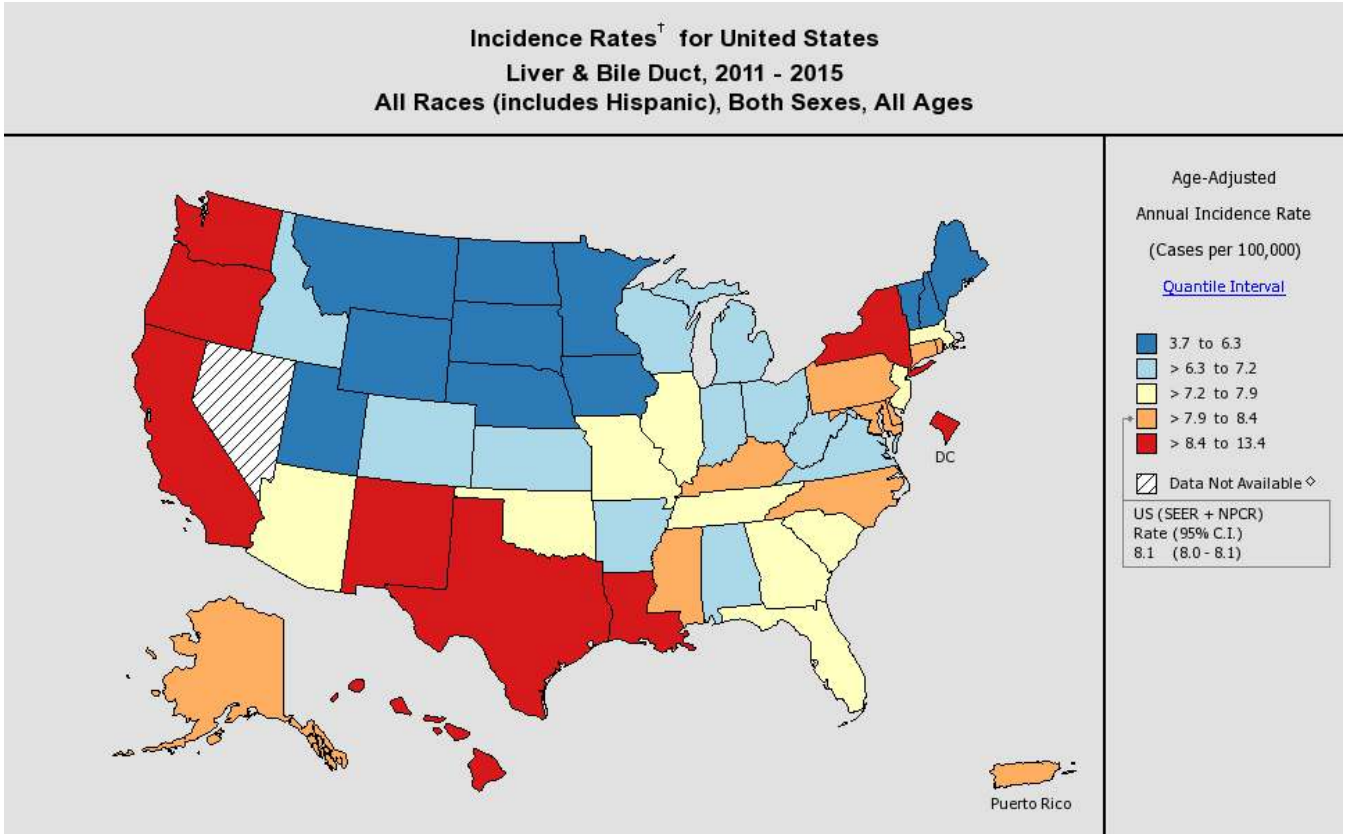
HCC: How Big of a Problem is it?

- 5th most common cancer in the world
- 3rd cause of cancer related mortality
- Highest rates in east Asia and Sub-Saharan Africa (>15 cases/100,00 inhabitants)
- Incidence rapidly rising in US
  - 7.8 cases/100,00
  - 39,230 cases; 27,170 death in 2016,
  - Highest increases in Hispanics
  - Continuous rise predicted until 2030

WHO globacan.iarc.fr
Petrick J. Jclin Oncol 2016;34:1787-1974

Incidence of Liver Cancer in US

#1 DC 13.2
#2 HI 11.3
#3 TX 11.1
#4 CA 9.7
#5 NM 9.3
#8 WA 8.6
#18 AZ 7.7



Who is at Risk for HCC?

- Cirrhosis
  - Of all etiologies
- Non-cirrhotic patients with:
  - NASH
  - Hepatitis B

Case of Mr. X

55 year-old man with alcoholic cirrhosis, found on screening ultrasound to have a 3 cm lesion in the right lobe. Triple-phase CT of the abdomen confirmed the presence of a 3.5 cm lesion in the right lobe along with mild ascites. Examination showed no spider nevi. Spleen tip palpable.

Labs: bilirubin 1.7, ALT 28, AST 42, albumin 3.5, INR 1.3, platelets 85,000, AFP 36.

Questions:

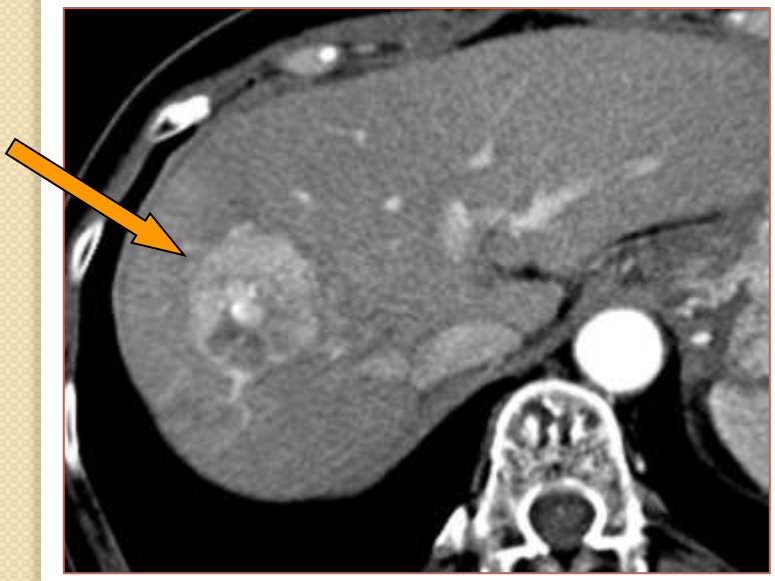
1. What are the typical characteristics of HCC on triple-phase CT?
2. Would you biopsy the lesion and why?

Liver Imaging Reporting and Data System: LI-RAD

- **Major diagnostic criteria:**
  - Arterial phase hyper-enhancement
  - Delayed phase "washout"
  - Pseudo-capsule
  - Interval growth ≥ 50% diameter within 6 months

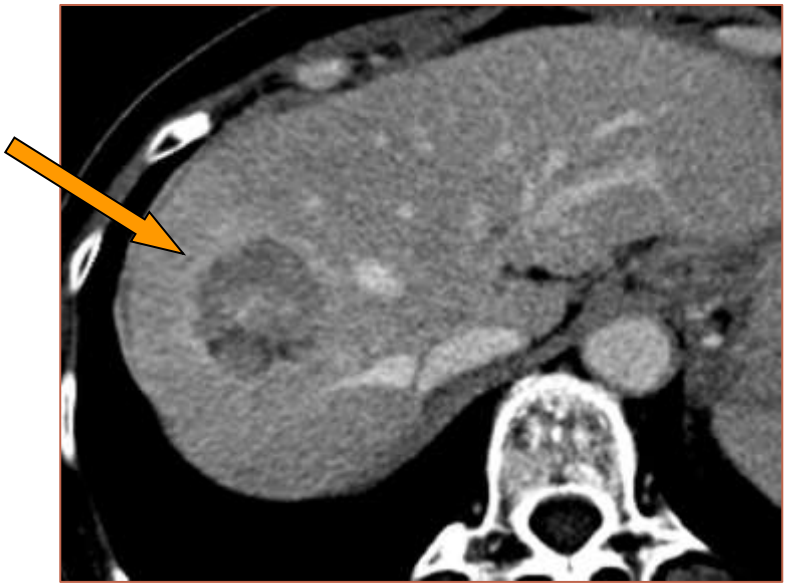
HCC – radiologic diagnosis

Arterial Phase



Hyper-enhancement

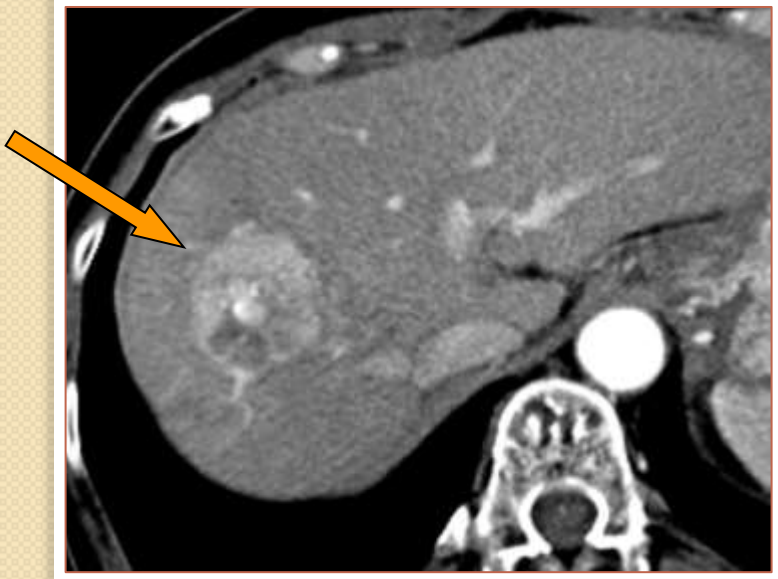
Portal Venous phase



"Washout"

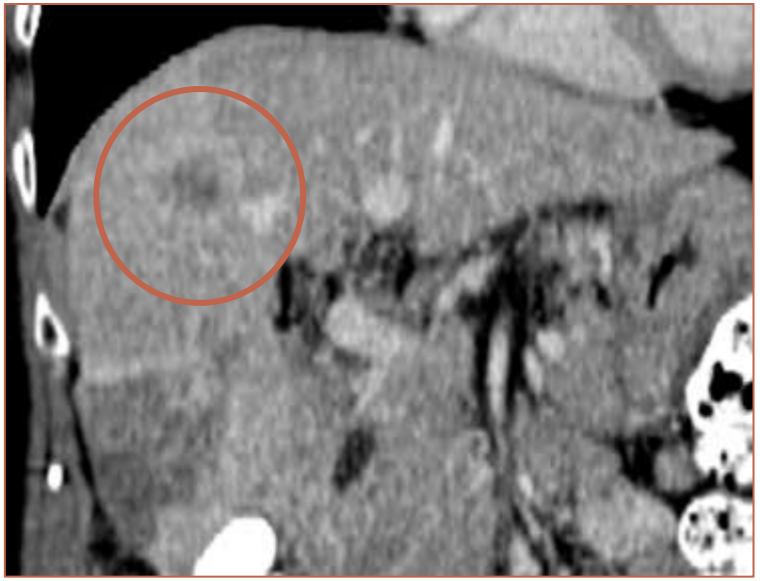
HCC – Radiologic Diagnosis

Arterial Phase



Hyper-enhancement

Portal Venous phase



"Pseudo-capsule"

Liver Imaging Reporting and Data System: LI-RAD

American College of Radiology:

Li-RAD 1:	Definite benign
Li-RAD 2:	Probable benign
Li-RAD 3:	Indeterminate
Li-RAD 4:	Probable HCC
Li-RAD 5:	Definite HCC

Liver Imaging Reporting and Data System: LI-RAD

Count major diagnostic criteria		LIVER MASS				
		Arterial phase hypo- or iso-enhancement		Arterial phase hyper-enhancement		
		< 2 cm	≥ 2 cm	< 1 cm	1-1.9 cm	≥ 2 cm
"Washout" "Capsule" Threshold growth	None	LIRAD 3	LIRAD 3	LIRAD 3	LIRAD 3	LIRAD 4
	One	LIRAD 3	LIRAD 4	LIRAD 4	LIRAD 4	LIRAD 5
	≥ Two	LIRAD 4	LIRAD 4	LIRAD 4	LIRAD 5	LIRAD 5

HCC – Is biopsy necessary?

- Biopsy is not necessary to confirm HCC diagnosis if the lesion meets radiologic criteria in the appropriate clinical setting
- False negative biopsy common in clinical practice and may lead to delay in diagnosis and treatment
- Tumor seeding along the biopsy tract in <1-2%
- Biopsy in selected cases if atypical radiologic appearance or lack of strong risk factor for HCC

Case of Mr. X

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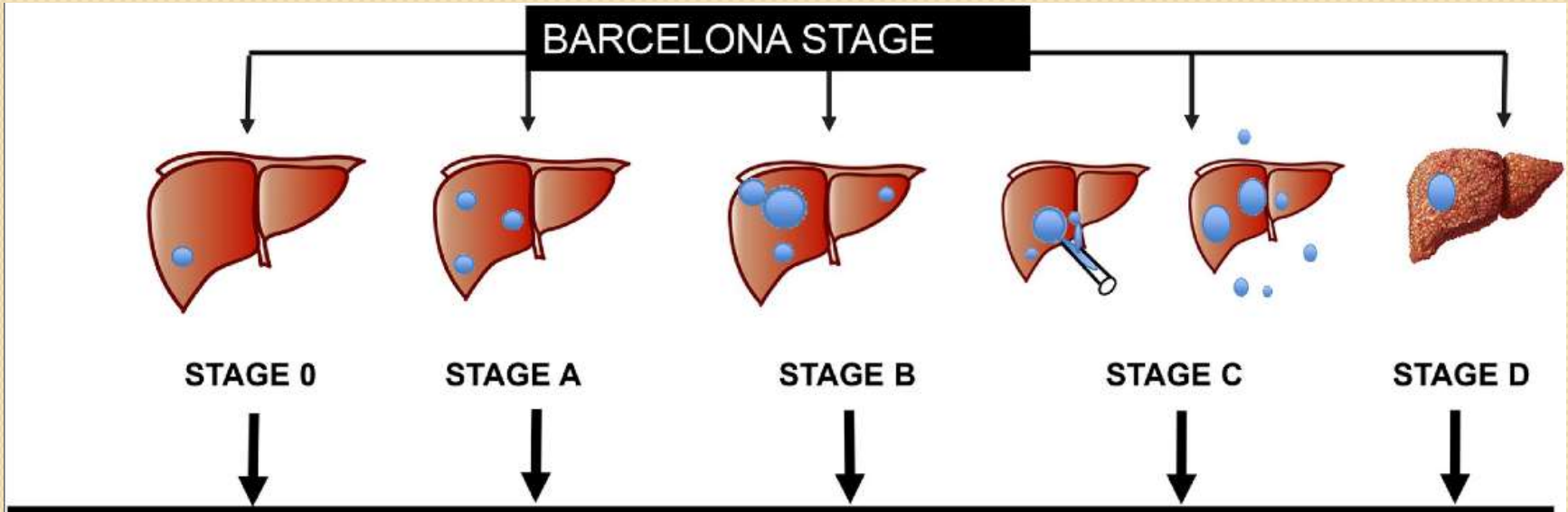
Labs: bilirubin 1.7, ALT 28, AST 42, albumin 2.8, INR 1.7, platelets 52,000, AFP 36.

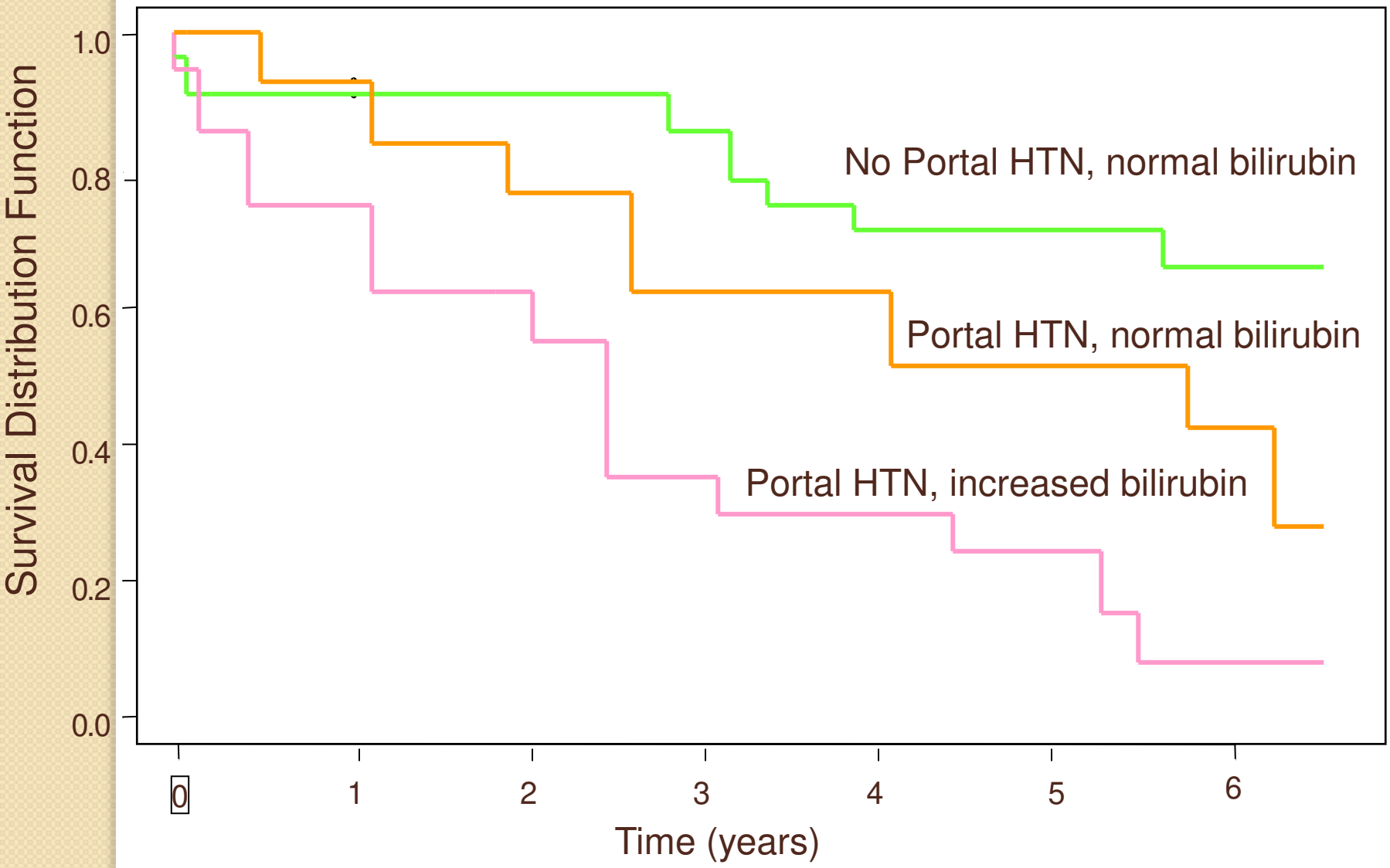
What treatment would you recommend?

1. Resection
2. Liver transplantation
3. Percutaneous radiofrequency ablation (RFA)
4. TACE



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	

Survival following resection: Impact of portal hypertension

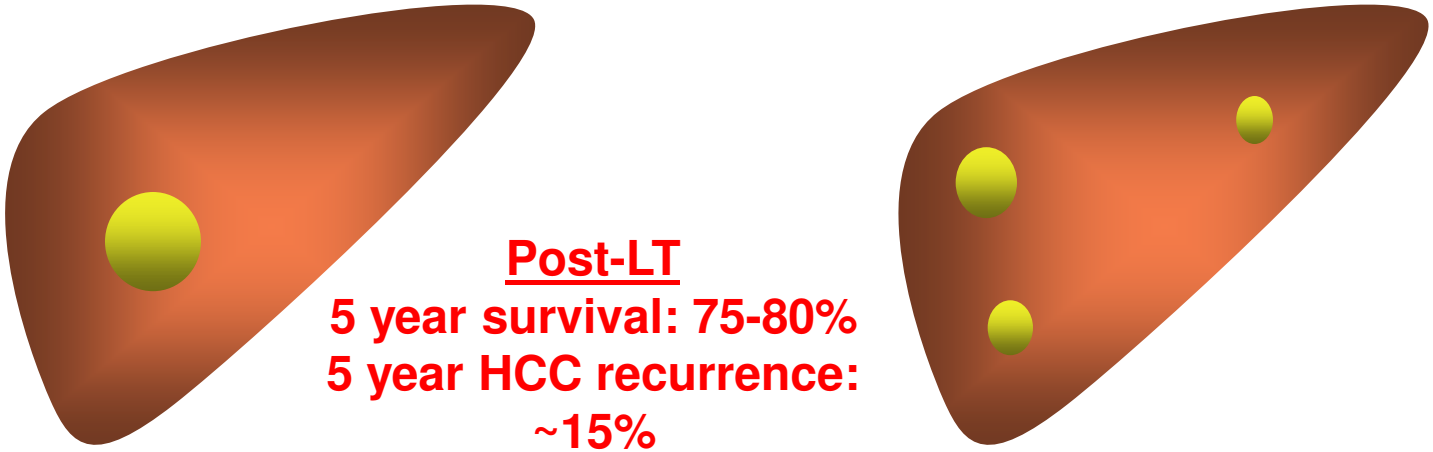


Llovet et al. Hepatology 1999; 30:1434

Liver transplantation for HCC: Milan Criteria

1 lesion ≤ 5 cm

2 to 3, none > 3 cm



Post-LT
5 year survival: 75-80%
5 year HCC recurrence: ~15%

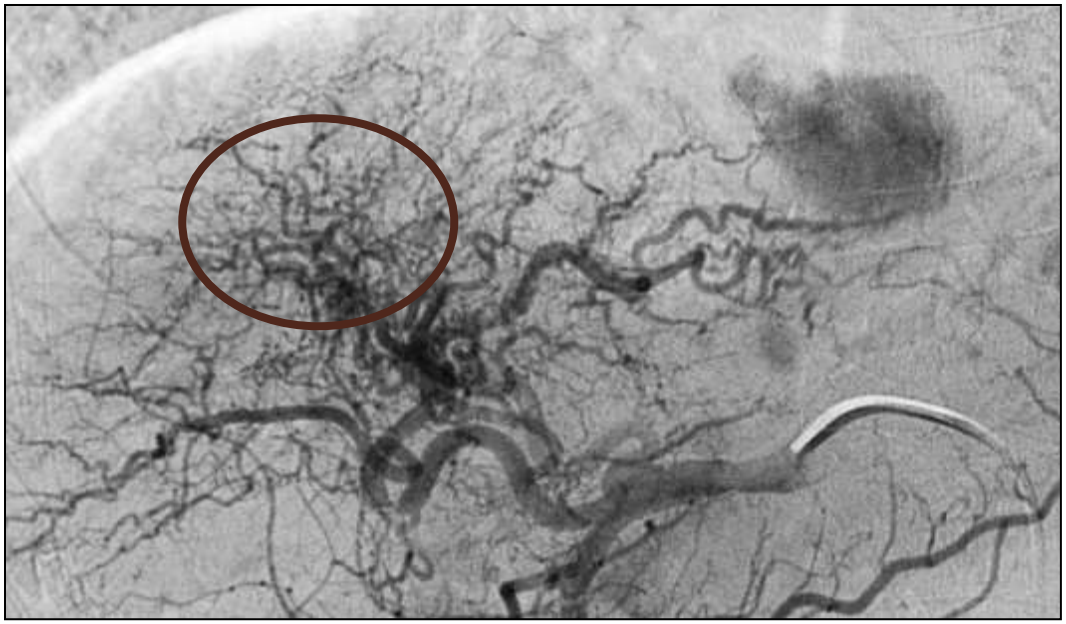
+
Absence of Macroscopic Vascular Invasion
Absence of Extra-hepatic Spread

Mazzaferro, et al. N Engl J Med 1996;334:693-699

Local regional treatments for HCC

- Thansarterial chemoembolization: TACE
- Ablation
  - Chemical: percutaneous ethanol injection (PEI)
  - Thermal: Radiofrequency ablation: RFA
  - Microwave/cryo- ablation
- Radioembolization: Y-90
- External beam radiation: SBRT

TACE

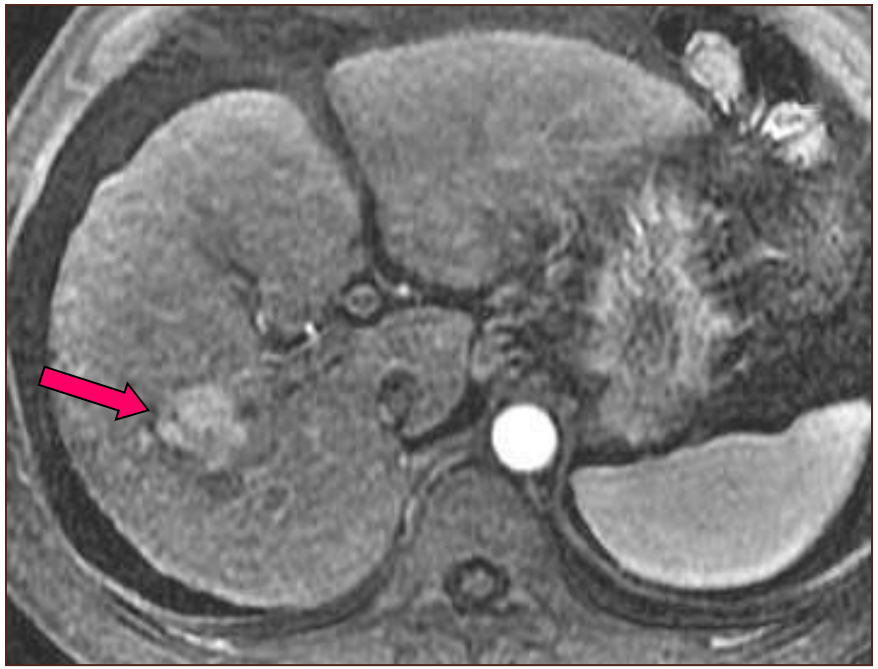


- Selective embolization of the hepatic arterial supply to tumor via the common femoral artery.
- Cytotoxic agent (Cis-platinum, Doxorubicin, Mitomycin-C, 5-FU) mixed with drug eluding beads.
- Ischemic + cytotoxic effect

RFA

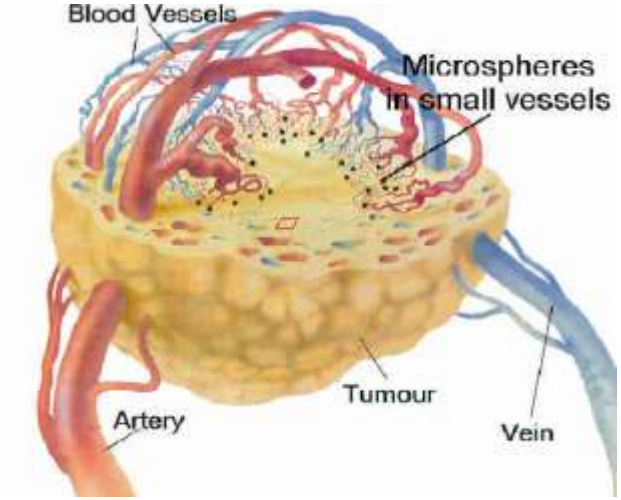
Choice of treatment based on location and size

- <3 cm
- Least hepatic toxicity expected
- Combination therapy for lesions >3 cm



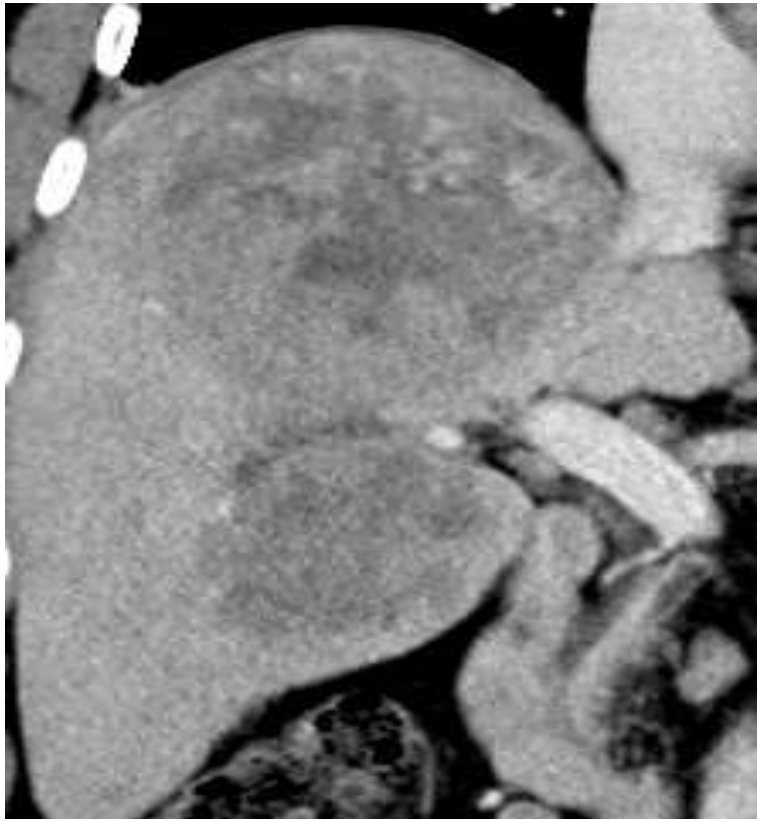
Y-90 Radioembolization

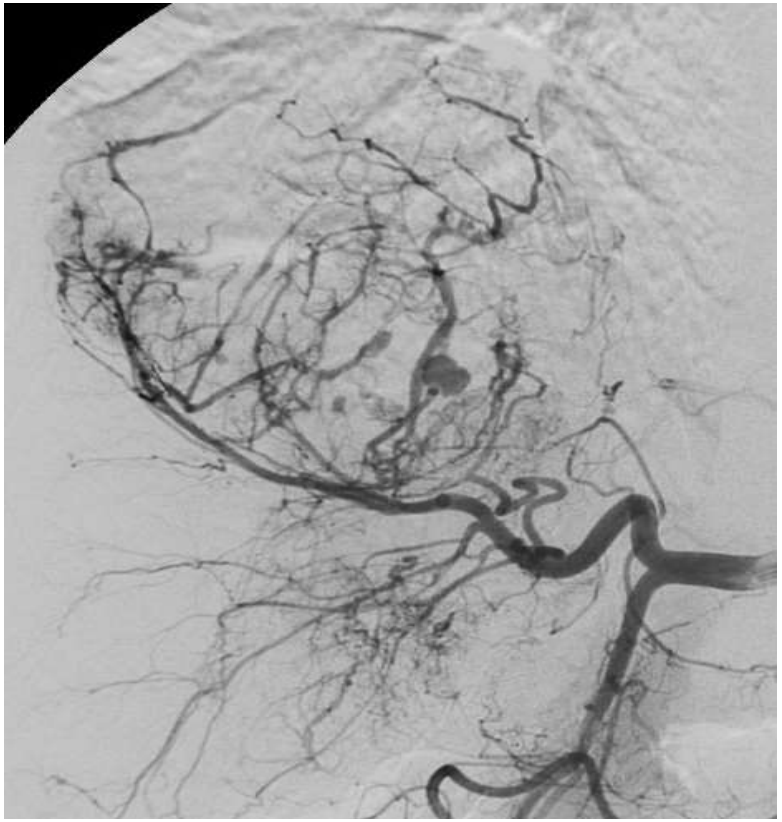
- TheraSphere (glass microspheres)
- SIR-Spheres (resin microspheres)
- Radiographic response up to 90%
- Survival benefit unknown
- Risks of radiation damage
- Advanced tumor stage and preserved liver function (bilirubin < 2mg/dl)
- Primarily cytotoxic effect, less ischemic



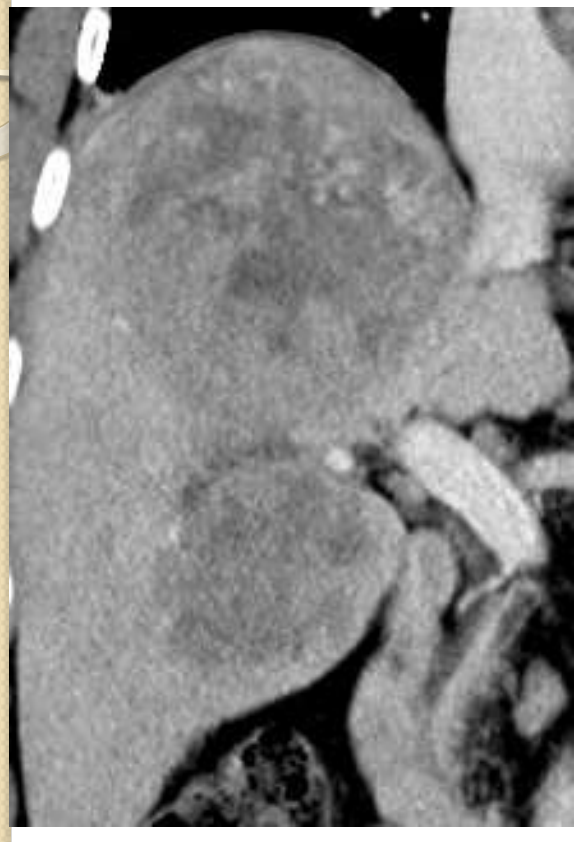
56M with HCV and large HCC

Radioembolization with TheraSphere/Y-90

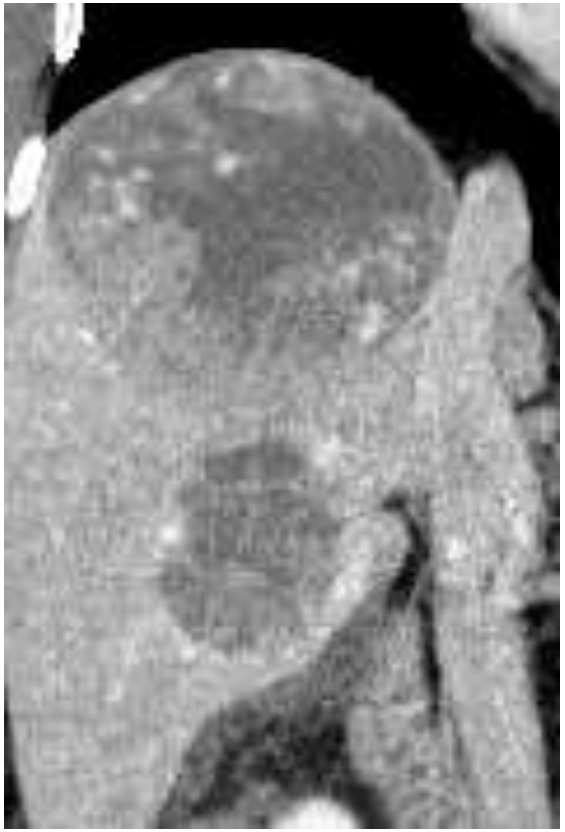




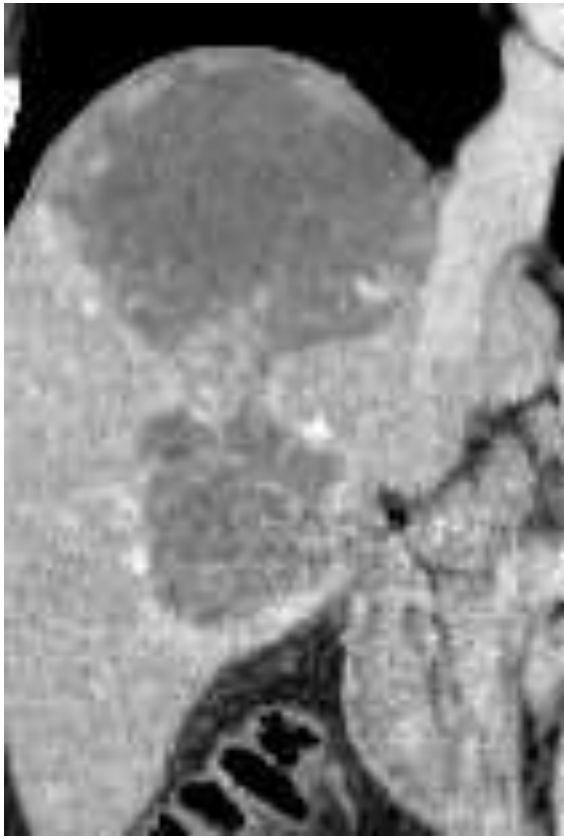
56 y/o man with HCV and large HCC



Pre-treatment



1 mo after Y-90 #1



1 mo after Y-90 #2
4 mo after Y-90 #1

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TABLE 1. PATIENTS AT THE HIGHEST RISK FOR HCC

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

Abbreviation: LYG, life-years gained.

Guidelines: whom to screen: HCV

- Screen all patients for HCC with imaging and AFP prior to initiating HCV therapy
- Evaluate all patients (non-invasively) for the degree of fibrosis
- AASLD: continue every 6 months surveillance AFTER cure ONLY in cirrhotic patients 
- EASL: continue every 6 months surveillance AFTER cure in patients with advanced fibrosis: F3-4 

Guidelines: whom to screen HBV

- Asian men > 40
- Asian women > 50
- Africans >20
- HBV cirrhosis regardless of age
- 1st degree relative with HCC
- Co-infection with HDV
- NAFLD?
- Metabolic syndrome?
- Alcohol?
- HIV?

My practice: at least once a year surveillance in patients that to not clearly fit into high risk groups

Guidelines: whom to screen NAFLD or MAFLD

- AASLD: not recommended
  - Japan: 25-fold increase of HCC in patients with NAFLD and advanced fibrosis 
- EASL: the role of surveillance in patients without cirrhosis is unclear
  - May be considered in all subjects with F3 fibrosis regardless of etiology
- My practice:
  - F0-2 imaging and AFP every 12 months
  - F3-4 imaging and AFP every 6 months

Kawamura Y et al. Large-scale long-term follow-up study of Japanese patients with non-alcoholic Fatty liver disease for the onset of hepatocellular carcinoma. Am J Gastroenterol 2012;107:253-261.

Guidelines: HCC treatment

- AASLD 2018: delay HCV treatment for 3-6 months
- EASL: ?

- Hepatology 2020: Cure With Interferon-Free Direct-Acting Antiviral Is Associated With Increased Survival in Patients With Hepatitis C Virus-Related Hepatocellular Carcinoma
  - 60-70% improvement in 5 year survival!

- My practice: HCV promotes carcinogenesis: treat HCV and HCC simultaneously

Cure With Interferon-Free Direct-Acting Antiviral Is Associated With Increased Survival in Patients With Hepatitis C Virus-Related Hepatocellular Carcinoma From Both East and West Hansen Dang et al. Hepatology, Vol. 71, No. 6, 2020

How to screen: imaging

- AASLD: CT and MRI not recommended for routine surveillance
- 407 patients with cirrhosis compared US to MRI for the surveillance of HCC
  - 43 patients developed HCC
  - One detected by US only
  - 26 by MRI alone
  - 11 by both
  - 5 missed by both modalities
- My practice: alternate US and cross-sectional imaging especially in obese or high risk patients

Kim SY et al. MRI with liver-specific contrast for surveillance of patients with cirrhosis at high risk of hepatocellular carcinoma. JAMA Oncol 2017;3:456.

How to screen: tumor markers

- AASLD and EASL: AFP in combination with imaging
- GALAD score: promising in phase II studies
- My practice: I agree with guidelines

Sex:

Female

Male

Age:

years

Alpha-fetoprotein (AFP):

ng/mL

Alpha-fetoprotein-L3% (AFP-L3):

%

Des-gamma-carboxy prothrombin (DCP):

ng/mL

Calculate

Johnson PJ et al. The detection of hepatocellular carcinoma using a prospectively developed and validated model based on serological biomarkers. Cancer Epidemiol Biomarkers Prev 2013;23:144-153.

In summary…

- Our understanding of HCC risk factors is evolving
- Guidelines may lag behind the published literature
- Be your patient's advocate

"...and that's how you handle liver!"