Hepatocellular Carcinoma

27th Annual
WVU Fall Cancer Conference

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Longest Living Transplant Survivor
LT #33

Case Report:

- **4 y/o girl uncorrectable biliary atresia**
- **Ascites, variceal bleed, elevated AFP**
- **OLT January 22, 1970**
  University of Colorado
- **Path: 3 cm HCC**
- **Follow-up: Alive 47 years post-OLT, disease-free**

VanWyk J, Halgrimson CG, Giles G, Lilly J, Martineau G, Starzl TE
Liver transplantation in biliary atresia with concomitant hepatoma
***S Afr Med J* 1972**

LTx for biliary atresia w/HCC: 47 year survivor

Description and Overall Incidence of HCC

Hepatocellular carcinoma (HCC) has been categorized as two diseases in one—a virulent malignancy that develops in the setting of chronic liver disease

Incidence—500,000 to 1,000,000 new cases annually—making this one of the most common malignancies worldwide.

Hepatocellular Carcinoma (HCC)

- HCC is a major public health problem
- 3rd cause of cancer-related deaths
- 16th absolute (cancer and non-cancer) cause of death globally

- 62% increase in HCC-related annual death rate during the past 20 years (463,000 to 752,000)

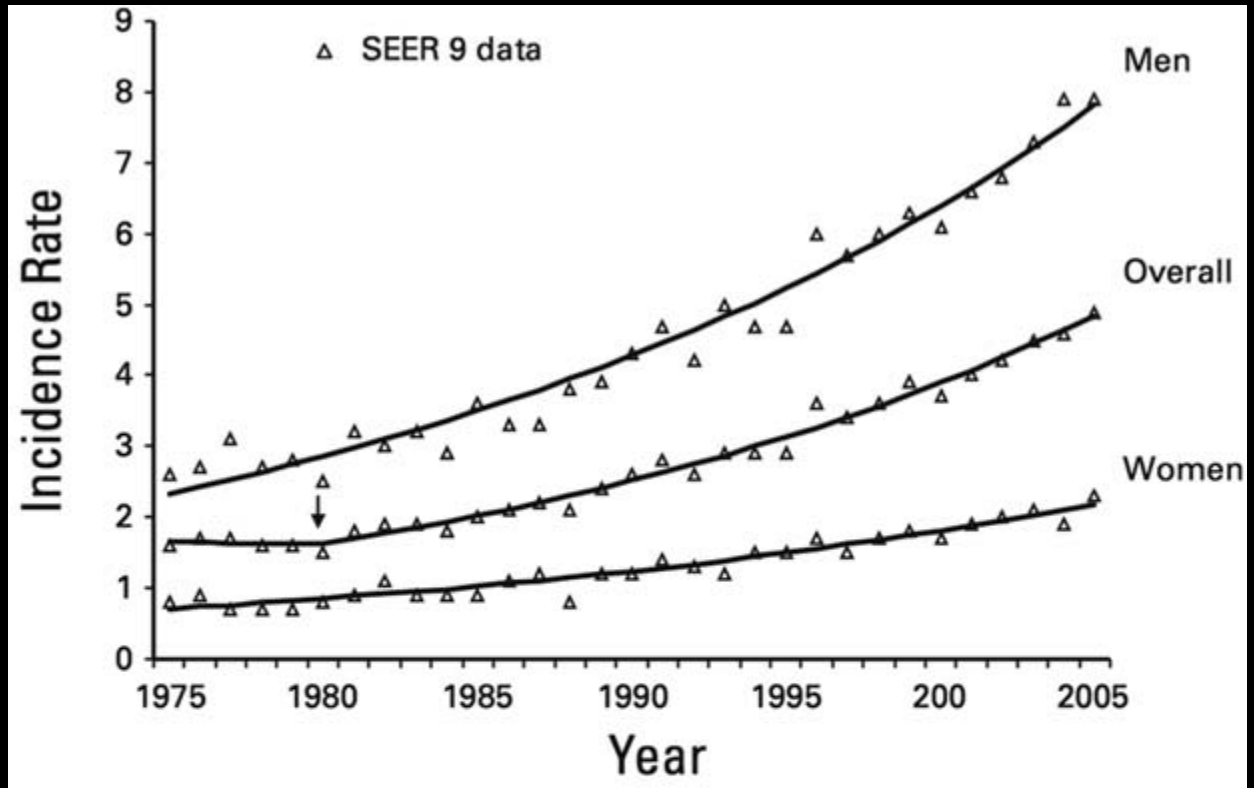
- HCC is the most rapidly escalating cause of cancer mortality in the US with 24,000 new cases annually

Llovet JM, Hernandez-Gea V. Hepatocellular Carcinoma: Reasons for Phase III Failure and Novel Perspectives on Trial Design. Clin Cancer Res; 2014: 20(8); 2072–9

HCC

- ~90% of HCCs are associated with cirrhosis
- HCC usually arises in a damaged liver with extensive inflammation and fibrosis responsible for the complex pathogenesis with deregulation of several signaling pathways and accumulation of genetic alterations
- Only ~30% diagnosed at a stage amenable for ablation, resection, or transplantation
- Median survival—60 months
- 70% recur at 5 years after resection or ablation (not transplant)
- No significant adjuvant therapies available

Llovet JM, Hernandez-Gea V. Hepatocellular Carcinoma: Reasons for Phase III Failure and Novel Perspectives on Trial Design. Clin Cancer Res; 2014: 20(8); 2072–9



	Joinpoint		Incidence		Annual Percent	
Sex	Segments	Years	Start	End	Change (APC)	Comments
Men	1	1975-2005	2.6	7.9	4.1*	
Overall	2	1975-1980	1.6	1.5	-.04	Jointpoint at arrow
		1975-2005	1.5	4.9	4.5*	(1980)
Women	1	1980-2005	0.8	2.3	3.8*	

Adapted from: Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. J Clin Oncol. 2009;27:1485-1491.

Fong ZV and Tanabe KK. The Clinical Management of Hepatocellular Carcinoma in the United States, Europe, and Asia: A Comprehensive and Evidence-Based Comparison and Review.

Worldwide Distribution of HCC

- Very high incidence (> 20)
- High incidence (11-20)
- Intermediate incidence (5-10)
- Low incidence (< 5)
- Unknown incidence

Etiology

The risk of developing HCC in patients with cirrhosis varies with the underlying etiology, but EVERY etiology is associated with increased risk.

The highest 5-year cumulative risk:

- Hemochromatosis (21%)
- HCV cirrhosis (17% in the West and 30% in Japan)
- HBV cirrhosis (10% in the West and 15% in Asia)
- Alcoholic cirrhosis (8%-12%)
- Biliary cirrhosis (4%)

El-Serag HB, Kanwal F. Epidemiology of Hepatocellular Carcinoma in the United States: Where Are We? Hepatology 2014: 60(5); 1767-75.

Etiology

HBV—Increased risk of developing HCC associated with:

- Male sex, older age, Asian or African ancestry
- Family history of HCC
- Viral subtype, load and co-infection (higher levels of HBV replication, HBV genotype, longer duration of infection, co-infection with HCV, HIV, or hepatitis D virus)
- Environmental factors (exposure to aflatoxin and heavy intake of alcohol or tobacco)

El-Serag HB, Kanwal F. Epidemiology of Hepatocellular Carcinoma in the United States: Where Are We? Hepatology 2014: 60(5); 1767-75.

Etiology

HBV viral load—important determinant of HCC risk

- Incidence of cirrhosis and HCC increase in proportion to HBV DNA

HBV genotypes—affect clinical outcomes

- Genotype D has a higher incidence of HCC than those with genotype A
- Some data associate genotype B with the development of HCC in young carriers without cirrhosis
- Mutations in the region of the HBV genome that encode the basal core promoter16 have been associated with increased HCC risk

El-Serag HB, Kanwal F. Epidemiology of Hepatocellular Carcinoma in the United States: Where Are We? Hepatology 2014: 60(5); 1767-75.

Etiology

HCV—Associated with a 15 to 20 fold increase in risk for HCC

- Rate of HCC ranges 1-3% over 30 years of chronic infection
- Once cirrhotic, HCC develops at an annual rate of 1-8% (average, 3.5%)

Risk factors include:

- Male sex
- Co-infection with HBV or HIV
- Diabetes
- Obesity
- High level of alcohol consumption

El-Serag HB, Kanwal F. Epidemiology of Hepatocellular Carcinoma in the United States: Where Are We? Hepatology 2014: 60(5); 1767-75.

Etiology

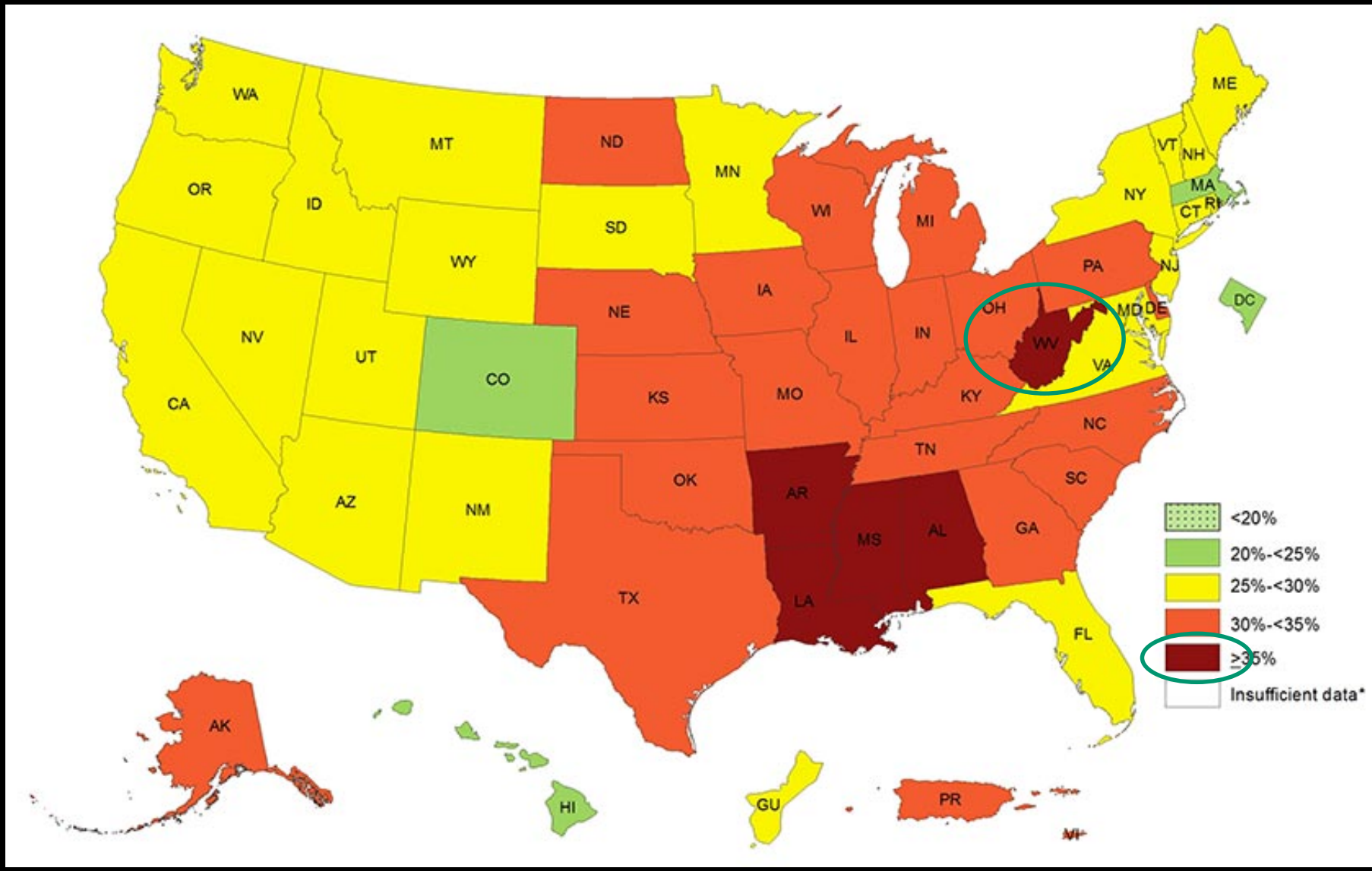
Metabolic Syndrome (MetS)—the syndrome or its various components (e.g., diabetes or obesity) have higher incidence of HCC

- There are emerging reports of HCC in the setting of MetS arising in the absence of cirrhosis (true extent of this condition or its risk factors are unclear)

- NAFLD is the hepatic manifestation of MetS
- Affects ~1/3 of the U.S. adult population
- Epidemiologic studies support at least a modest association between NAFLD /NASH and HCC

El-Serag HB, Kanwal F. Epidemiology of Hepatocellular Carcinoma in the United States: Where Are We? Hepatology 2014: 60(5); 1767-75.

Obesity Rates



Etiology

Alcohol—heavy intake (>50 - 70 g/day for prolonged periods) is a well-established risk factor for HCC

- Even moderate alcohol consumption may increase the risk of HCC in women

- There is evidence for a synergistic effect between heavy ingestion of alcohol and HCV infection and, to a lesser extent, HBV infection; similar synergism may be present with diabetes. These factors presumably operate together to promote cirrhosis and further increase the risk of HCC

El-Serag HB, Kanwal F. Epidemiology of Hepatocellular Carcinoma in the United States: Where Are We? Hepatology 2014: 60(5); 1767-75.

BIOLOGY

HCV-related mutations:
- p53
- Disintegrin and metalloproteinase domain–containing protein 22 (ADAM22)
- Janus kinase/signal transducer and activator of transcription (JAK) pathway
- Beta-catenin gene CTNNB1
- Transport protein particle (TRAPP)
- Never in mitosis A–related kinase 8 (NEK8) gene
- AT-rich interactive domain 2 (ARID2) gene

HBV-related mutations:
- p53
- ATPase family AAA domain–containing 2 (ATAD2)
- Interferon regulatory factor 2 (IRF2) genes

ETOH-related mutations:
- Chromatin remodelers

Aflatoxin-induced mutations:
- Genetically described by specific base substitutions

HBV and HCV self-inhibit viral clearance from infected liver cells

Page AJ, Cosgrove DC, Philosophe B, Pawlik TM. Hepatocellular Carcinoma: Diagnosis, Management, and Prognosis. Surg Oncol Clin N Am 2014; 289-311.

Diagnosis

Diagnosis

- Not usually difficult as it has specific imaging characteristics and happens most frequently in the setting of cirrhosis with a marked male predominance

- Most often made on either a surveillance scan (recommendation is every 6 months in patients with established cirrhosis) or on an initial scan in a patient with a new diagnosis of cirrhosis

Diagnosis

Notable recent change—decreased use of AFP and increased reliance on surveillance imaging (every 6 months)

Hallmark radiologic signs of HCC include:

- Intense arterial uptake followed by washout of contrast (the scan **MUST** include an arterial phase)

- If the lesion does not have these characteristics, a biopsy should be considered

- If lesion is < 1 cm, definitive diagnosis more difficult

- At a minimum, follow with surveillance imaging every 3 to 6 months

Page AJ, Cosgrove DC, Philosophe B, Pawlik TM. Hepatocellular Carcinoma: Diagnosis, Management, and Prognosis. Surg Oncol Clin N Am 2014; 289-311.

Blood work

1. Viral hepatitis panel
2. AFP
3. CBC with platelet count
4. Clotting studies
5. Liver Function tests—as the vast majority of patients with HCC have concomitant cirrhosis, therapy will be dictated by patient's performance status and liver function.
   NOTE: Bilirubin >2.5-3.0 severely limits **ANY** treatment
6. Other lab tests (eg, autoimmune markers, iron studies, copper, etc) will be dictated by history and other findings

Imaging

While ultrasound is a good screening tool and can be used for follow-up once a new liver tumor is discovered, CT or MRI imaging is indicated as these modalities can often distinguish between various liver masses (benign and malignant) and also survey for metastatic disease.

- While some single-center comparative studies have shown slightly better performance of dynamic MR imaging than multiphasic CT, the differences are small.

- The per-lesion sensitivity of MR imaging for nodular HCC of all sizes is 77%–100%, while that of CT is 68%–91%.

Per-lesion sensitivities, stratified by size:

- 2 cm—100% for both modalities for nodular HCCs
- 1-2 cm—44%–47% (MR) and 40%– 44% (CT)
- < 1 cm—29%–43% (MR) and 10%– 33% (CT)

Choi JY, Lee JM, Sirlin CB. CT and MR imaging, diagnosis and staging of hepatocellular carcinoma. Radiology 2014: 273(1): 30-50.

Imaging

Advantages of CT:
- Widely available
- Rapid and robust
- Requires less expertise to perform and interpret images compared with MR

Disadvantages of CT:
- Radiation exposure
- Relatively low soft tissue contrast

Advantages of MR:
- Higher soft-tissue contrast
- Permits assessment of a greater number of tissue properties (lesion detection and characterization)

Disadvantages of MR:
- More time consuming
- Less robust
- More prone to artifacts
- Requires greater expertise to perform and interpret
- Less availability

Thus, while MR imaging may be preferred over CT at many academic centers, there is insufficient data to recommend MR imaging over CT in community or less-specialized locations.

Choi JY, Lee JM, Sirlin CB. CT and MR imaging, diagnosis and staging of hepatocellular carcinoma. Radiology 2014: 273(1): 30-50.

Major imaging features of HCC

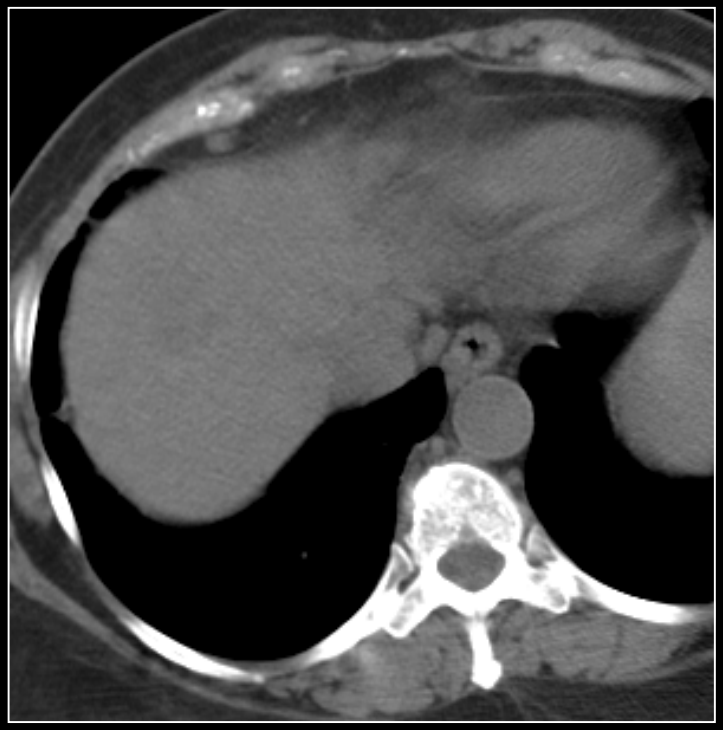
- Arterial phase hyper-enhancement
- Washout
- Capsule
- Threshold growth

Arterial phase hyperenhancement

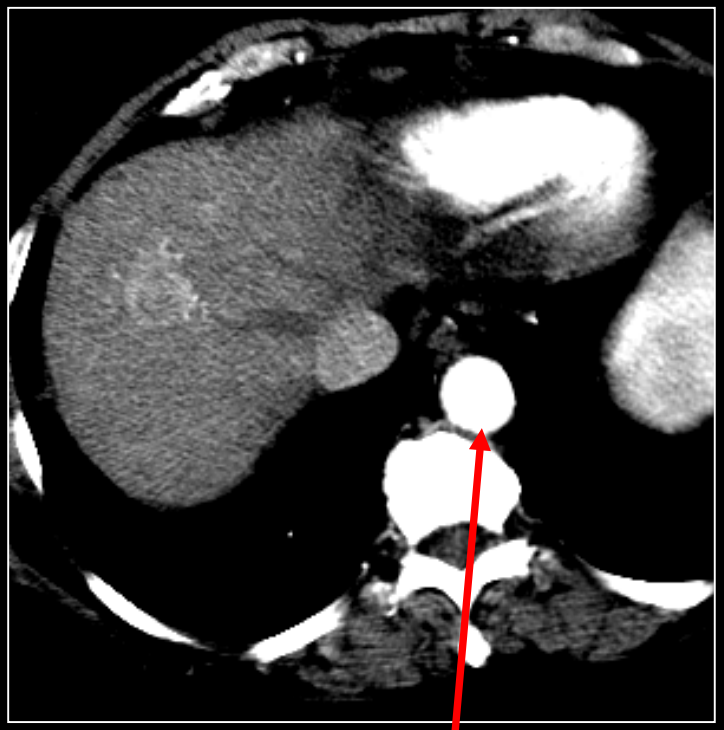
- Enhancement in the arterial phase that unequivocally is greater than that of the surrounding liver.

- In whole or in part unequivocally enhances in the arterial phase more than liver and are higher in attenuation or intensity than liver.

Arterial phase hyperenhancement



Non-contrast

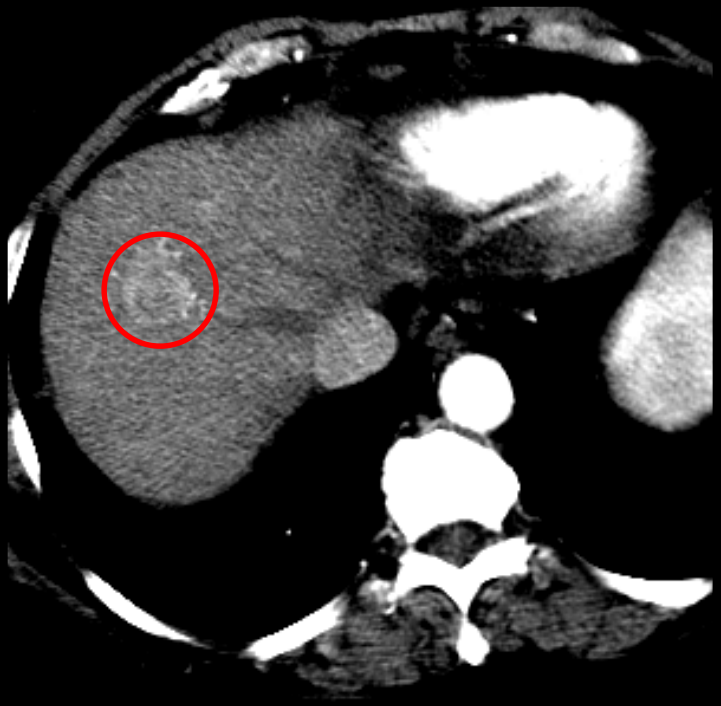


Arterial phase

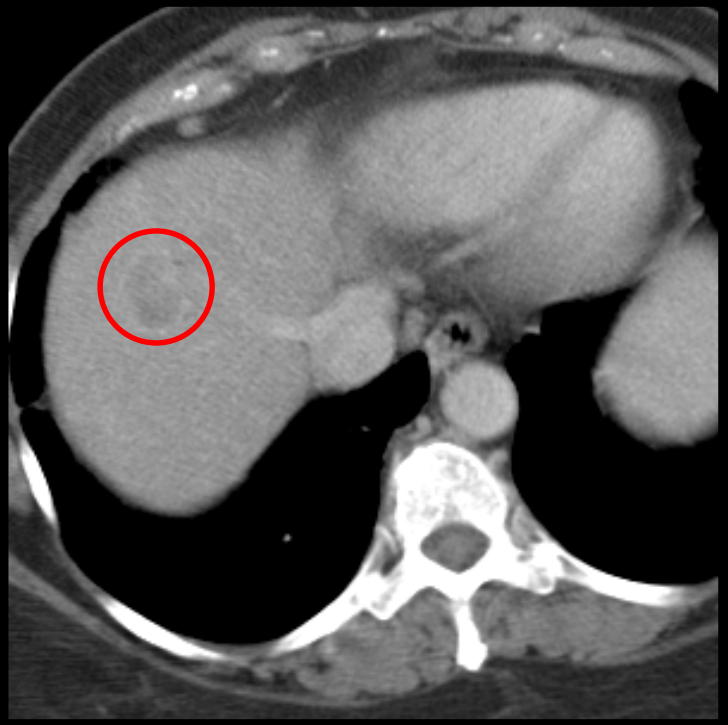
Washout appearance

- Visually assessed temporal reduction in enhancement relative to liver from an earlier to a later phase resulting in portal venous hypo-enhancement or delayed phase hypo-enhancement
- The enhancement should be compared to that of the adjacent liver parenchyma
- In the arterial phase the area in question may be hyper-enhancing OR hypo- or iso-enhancing but still washes out

Washout appearance



Arterial phase

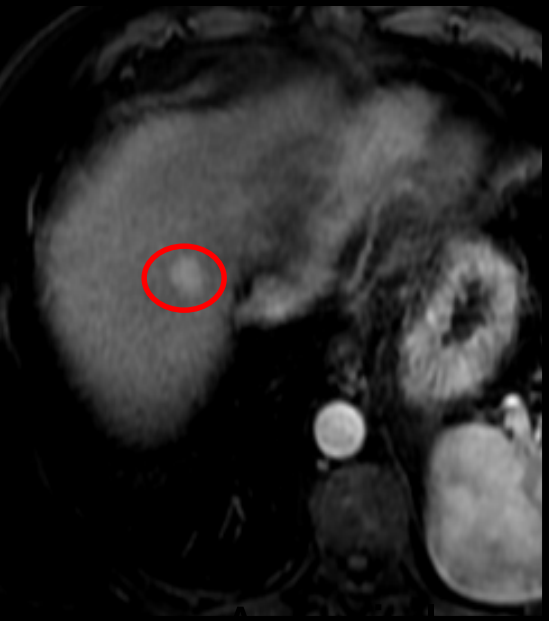


Portal venous phase

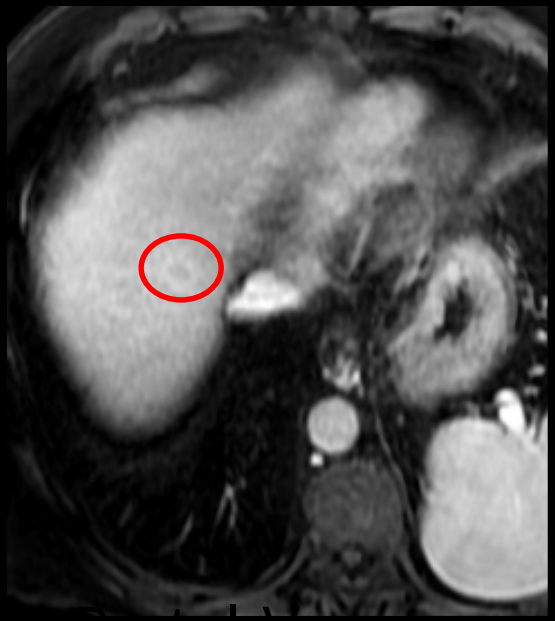
Capsule appearance

- Peripheral rim of smooth hyper-enhancement in the portal venous or delayed phase that unequivocally is thicker or more conspicuous than the rims surrounding background nodules
- The delayed phase may be superior to the portal venous phase for depicting this feature
- The distinction between true tumor capsule and pseudocapsule can only be made at pathology

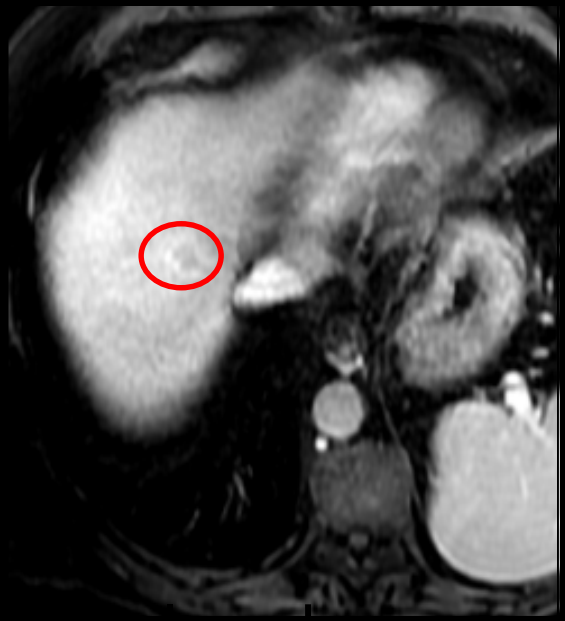
Capsule appearance



Arterial phase



Portal phase

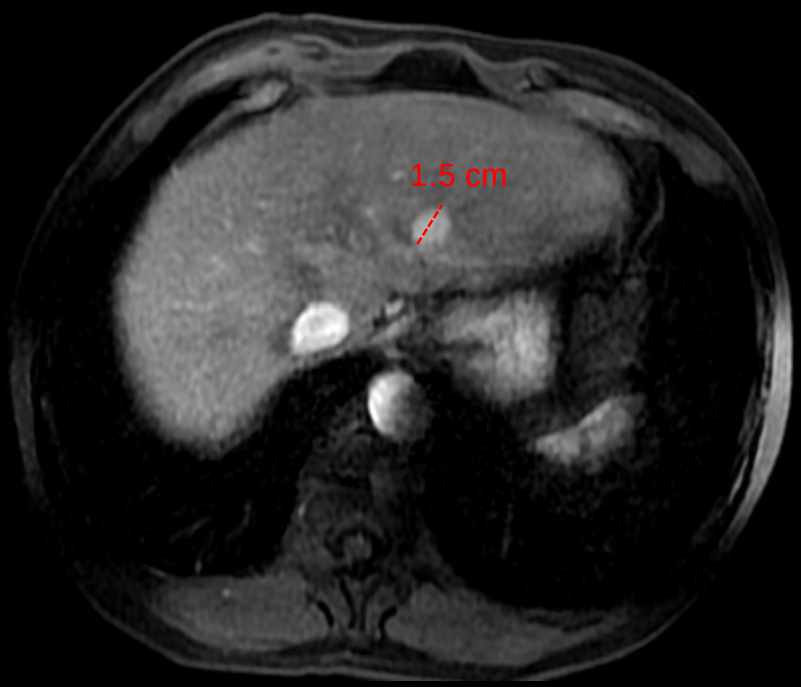


Delayed phase

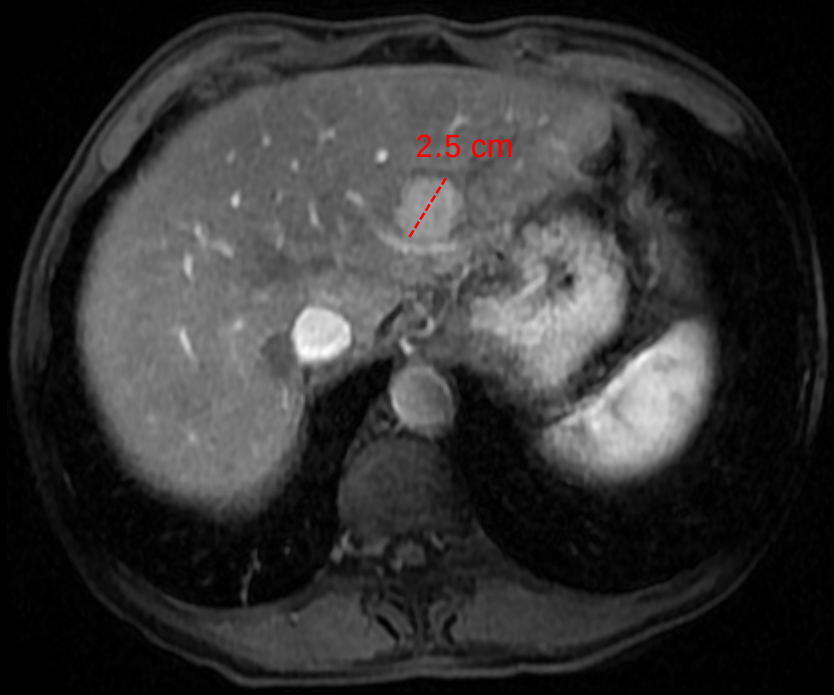
Threshold growth

- Diameter increase by a minimum of 5 mm AND ≥ 50% if time interval is ≤ 6 months, or ≥ 100% if the time interval is > 6 months
- Should be assessed in the same phase / sequence

Threshold growth



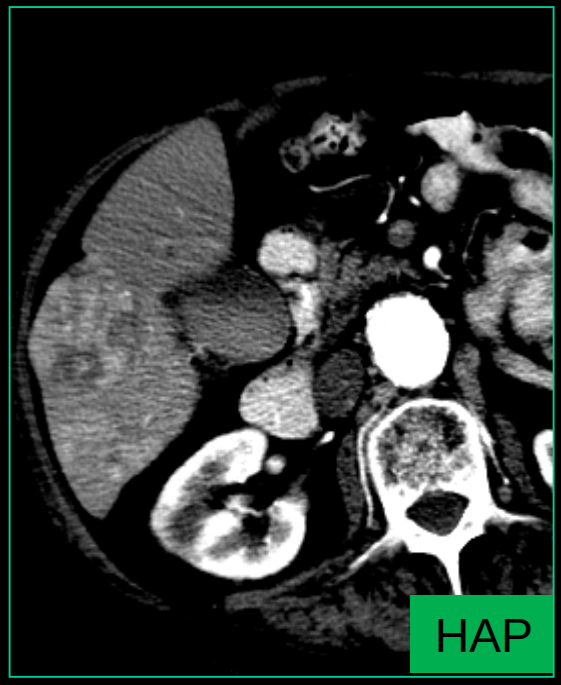
9/2010

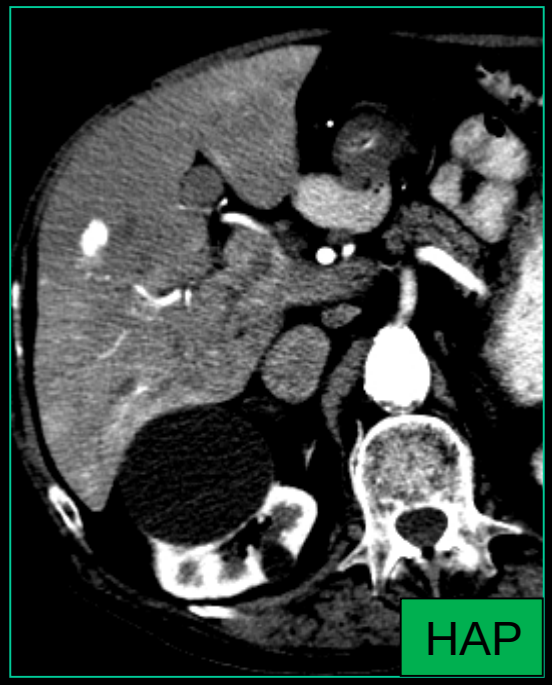


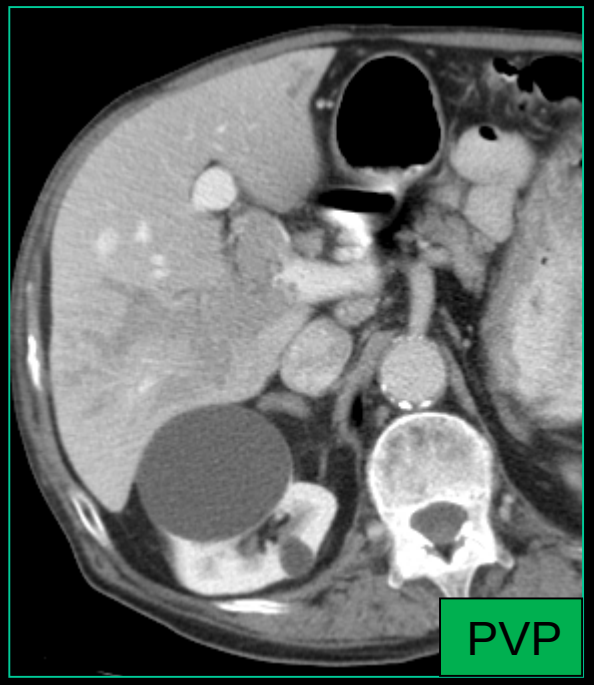
4/2011

Imaging

Portal Vein Tumor Invasion



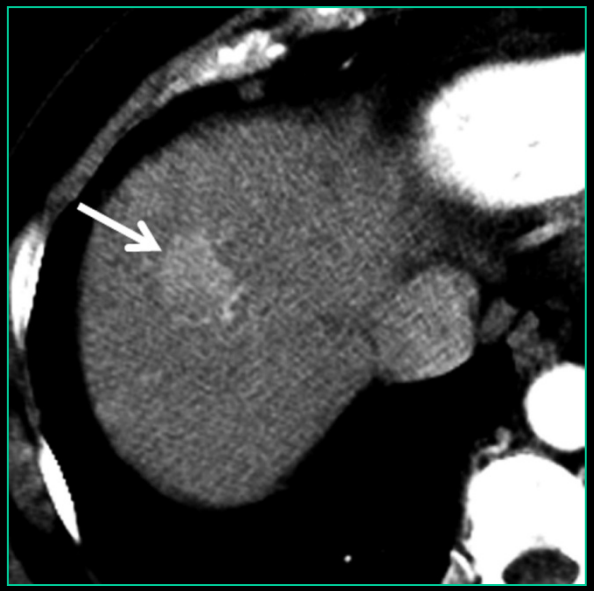




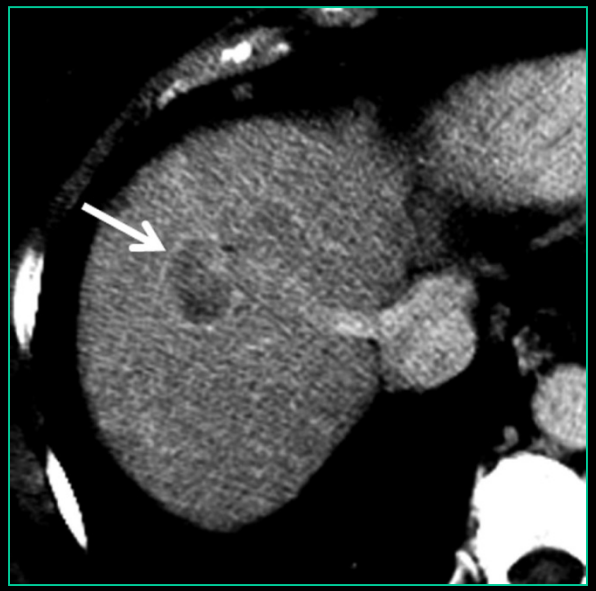
- Contiguous with the tumor
- Expansion of the vessel
- Hypervascular component to the thrombus (as opposed to bland thrombus)

Imaging

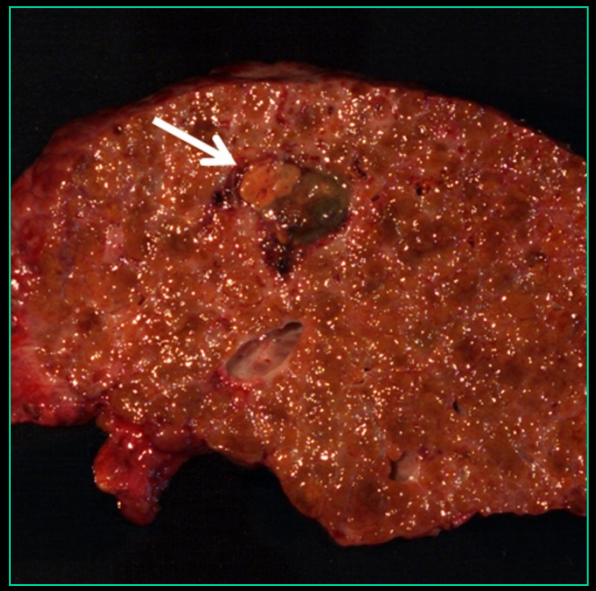
Typical CT Appearance



Late arterial phase



Venous phase

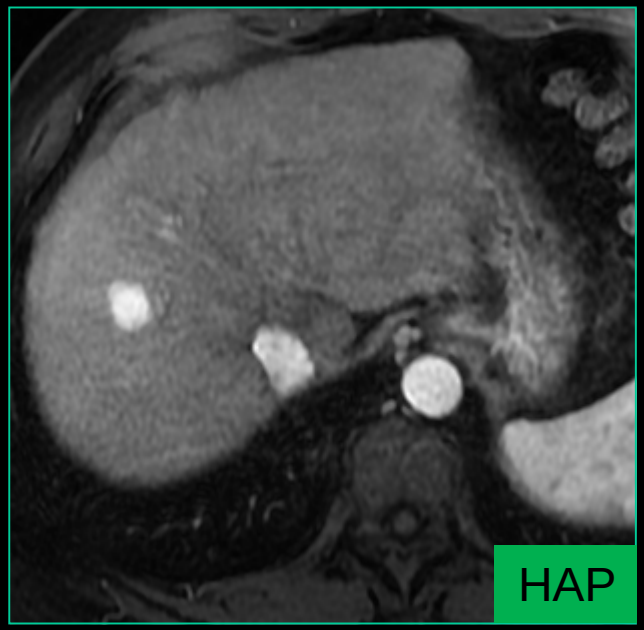


Path

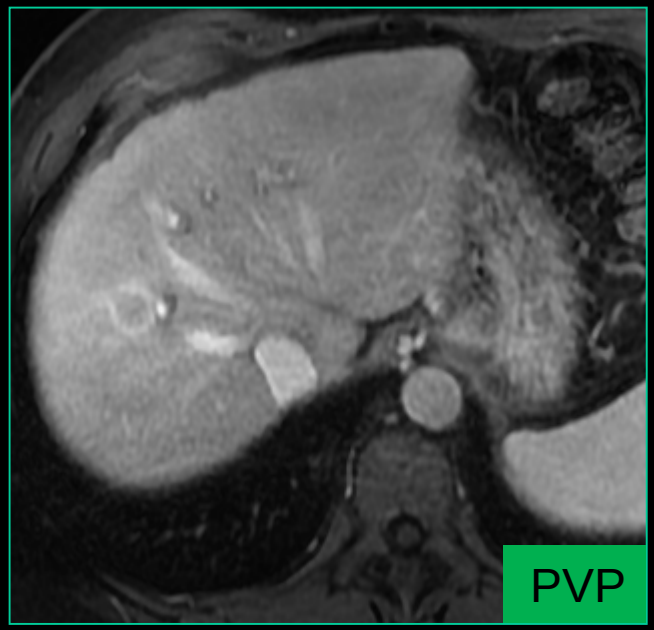
- PRE: iso-to-hypodense
- HAP: hyperenhancement
- PVP/DP: hypoenhancement (“washout”) + (pseudo)capsule enhancement

Imaging

Typical MRI Appearance

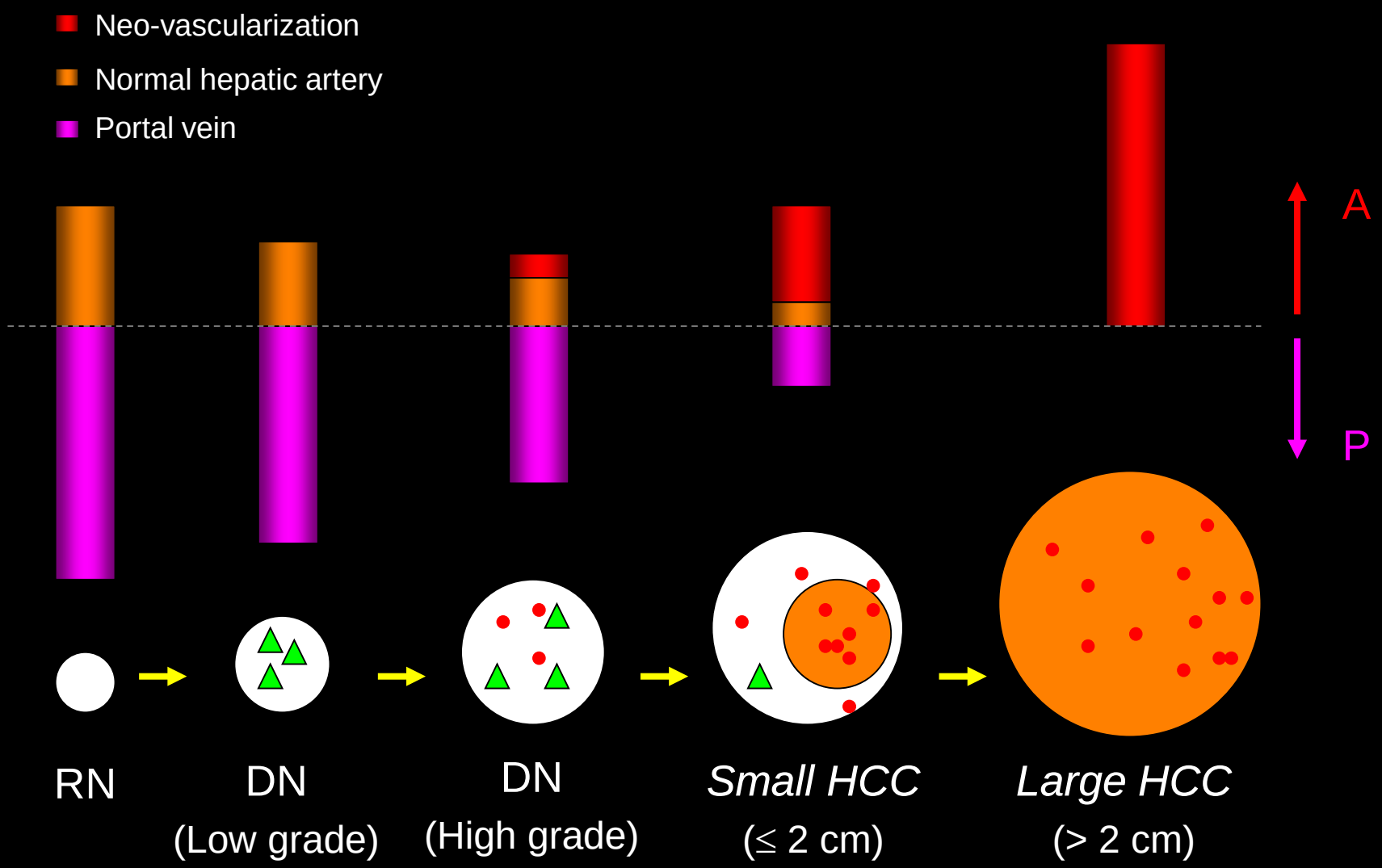


Hyperenhancement



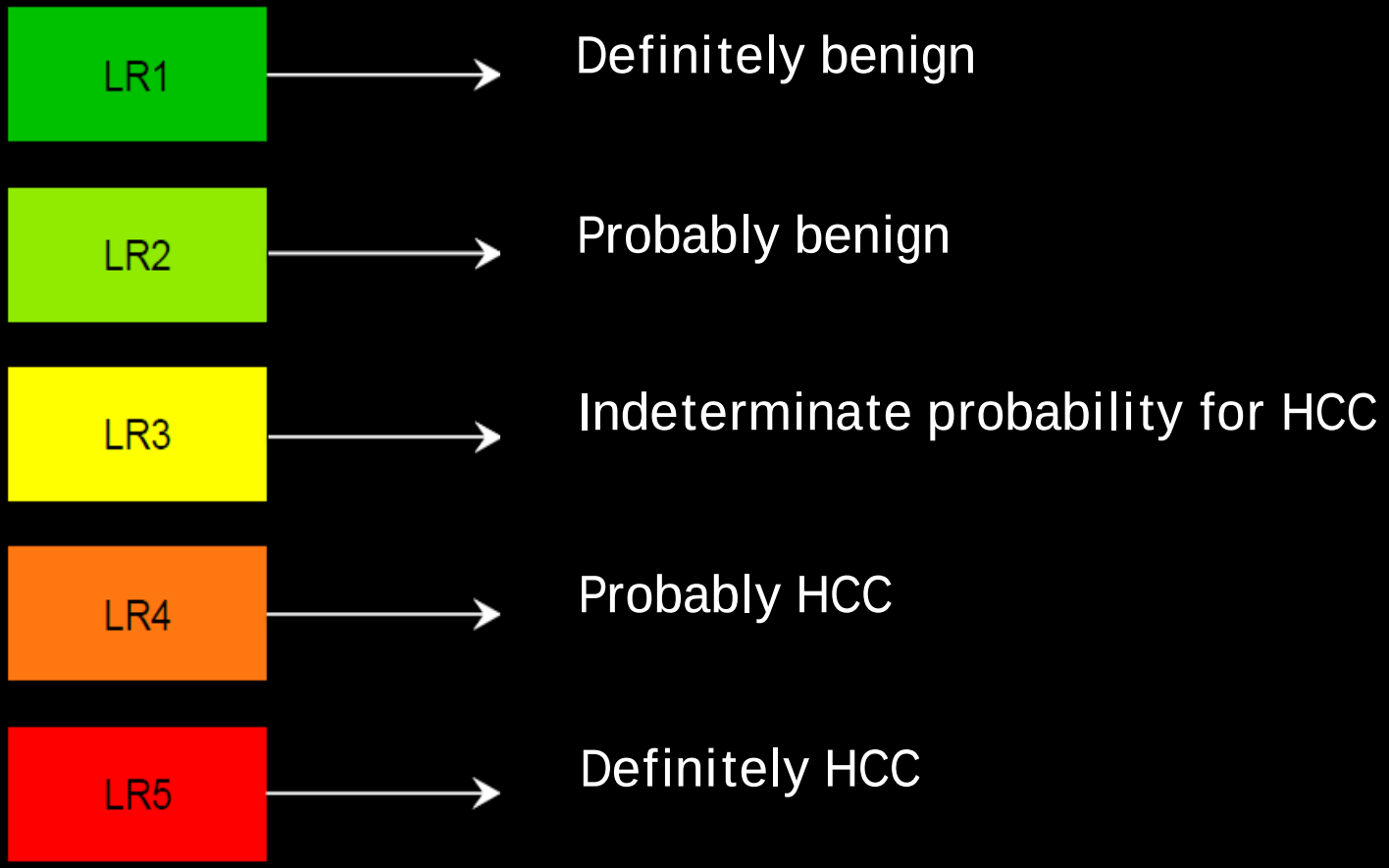
“washout”
“caspule”

Carcinogenesis

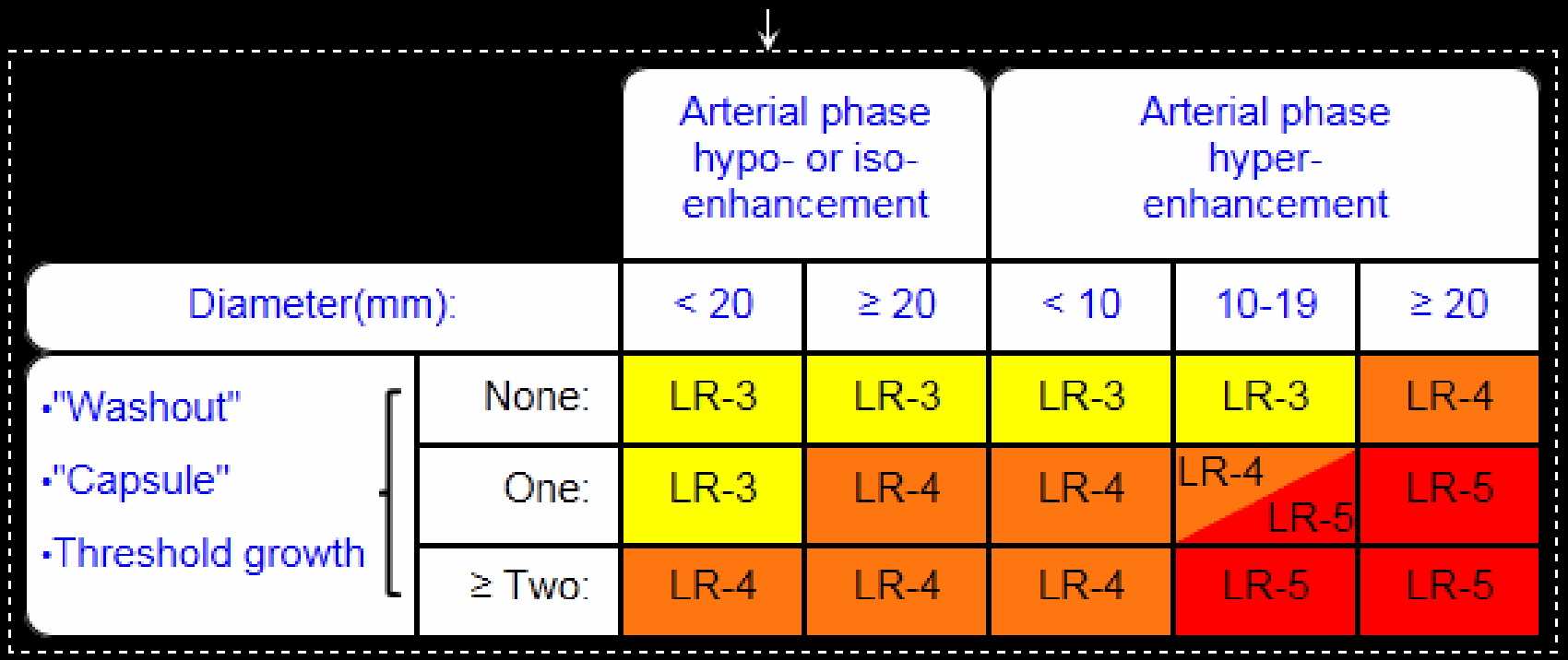


(Efremidis SC, et al. Eur Radiol 2007)

Li-RADS—Liver Imaging Reporting and Data System



Li-RADS—Liver Imaging Reporting and Data System



		Arterial phase hypo- or iso-enhancement		Arterial phase hyper-enhancement		
Diameter(mm):		< 20	≥ 20	< 10	10-19	≥ 20
•"Washout" •"Capsule" •Threshold growth	None:	LR-3	LR-3	LR-3	LR-3	LR-4
	One:	LR-3	LR-4	LR-4	LR-4 LR-5	LR-5
	≥ Two:	LR-4	LR-4	LR-4	LR-5	LR-5

Treatment options

Treatment options

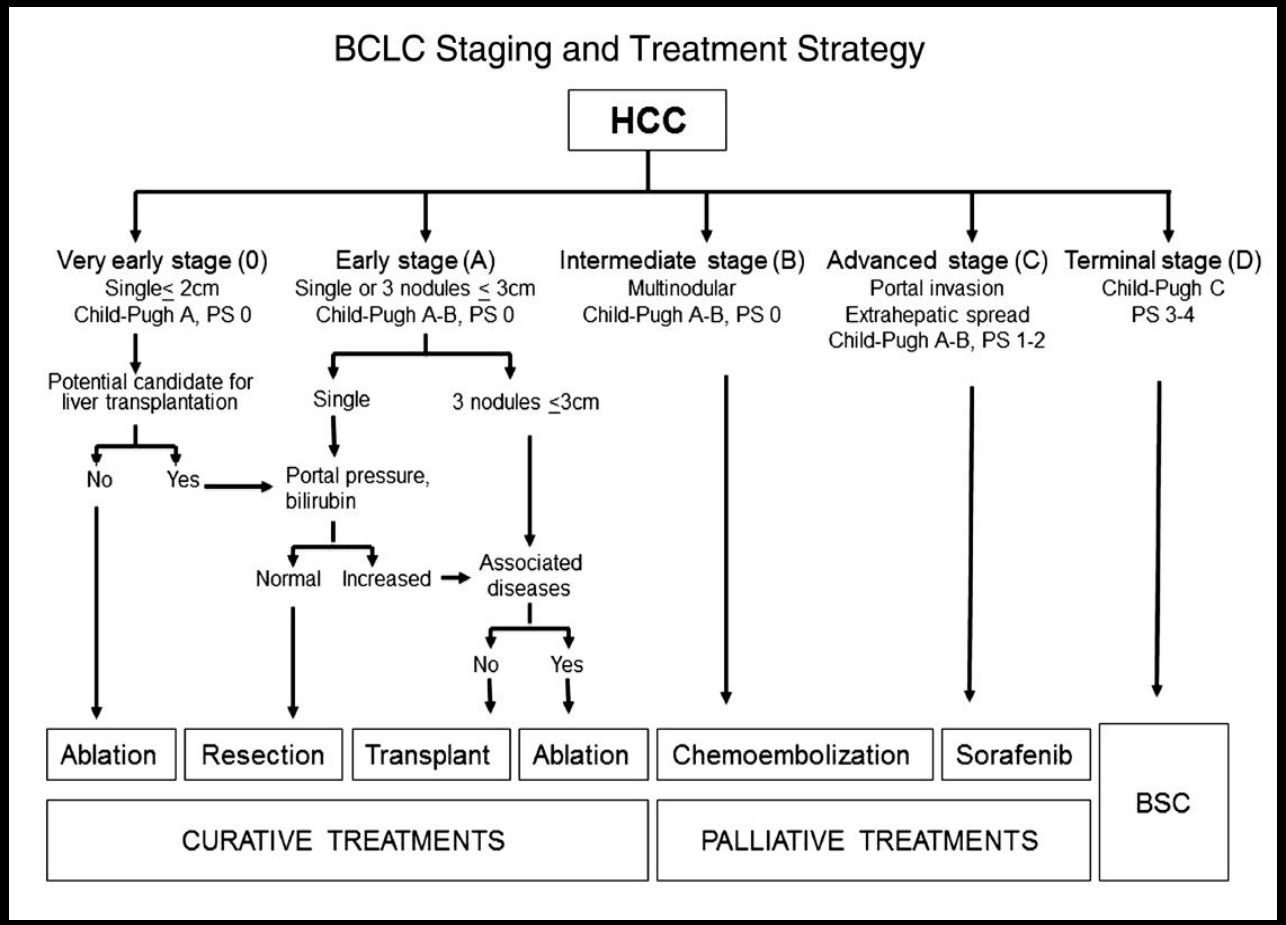
None for most 2º to late presentation

- Liver transplantation (deceased or living donor)
- Surgical resection
- Locoregional therapies which include ablation (burn, freeze, alcohol) and transarterial chemoembolization (TACE)
- Systemic chemotherapy

Factors that determine which treatment plan is most appropriate:

- tumor burden
- liver function
- performance status
- presence of extra hepatic disease

Treatment



Barcelona Clinic Liver Cancer Strategy

Bruix J, Gores GJ, Mazzaferro V. Hepatocellular carcinoma: clinical frontiers and perspectives. Gut 2014; 63:844-855

Liver Resection Candidates—evaluate functional liver reserve (FLR)

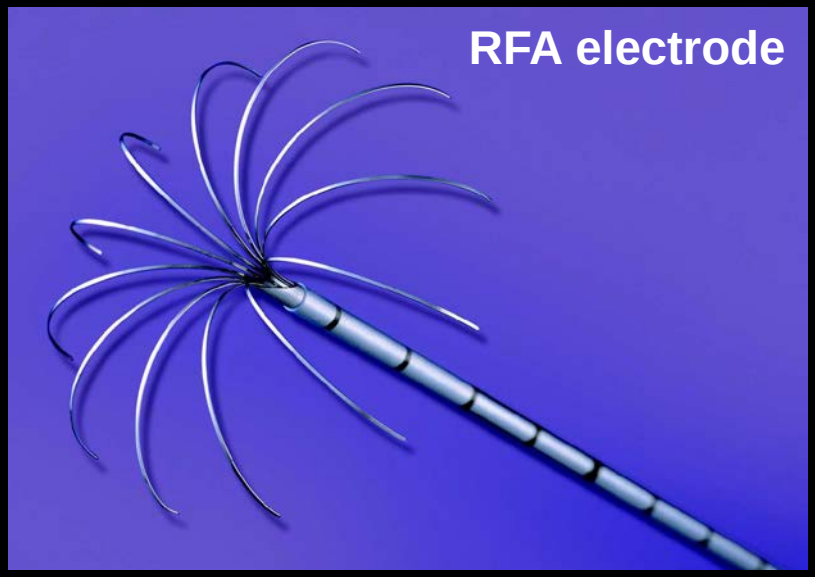
Both function and the volume of the liver need to be evaluated (CT or MR)

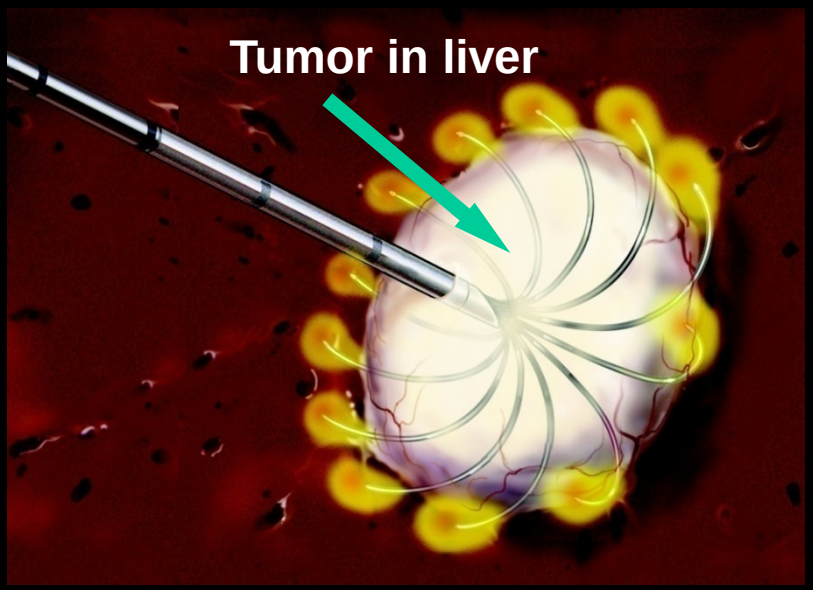
Hepatectomy is generally considered safe with a remnant of:

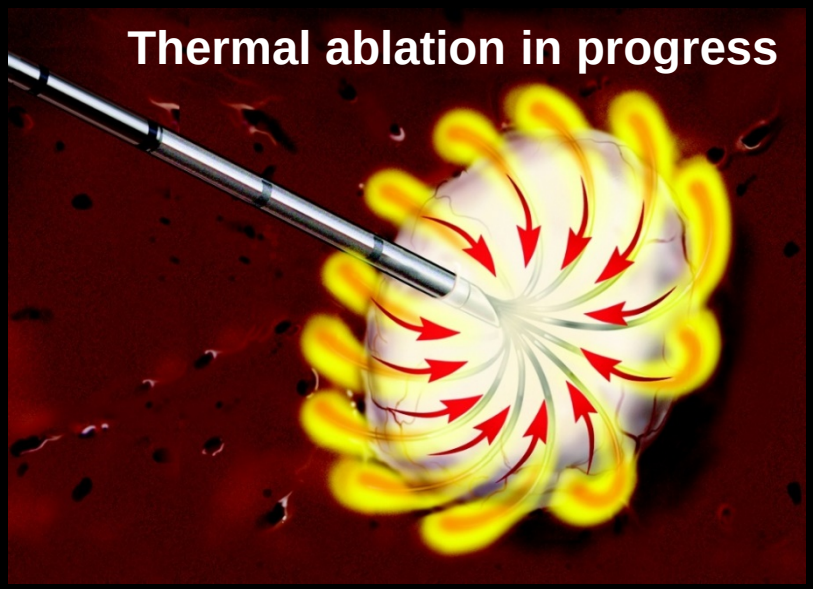
- 20-30% for patients with normal liver
- 30-40% for patients with chronic hepatitis
- 40-50% for patients with cirrhosis

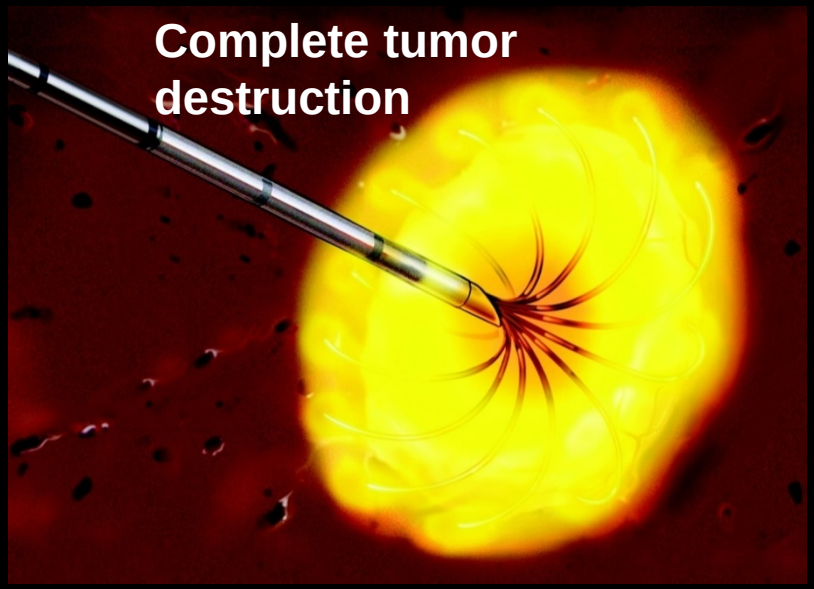
Kubota K, Makuuchi M, Kusaka K, et al. Measurement of liver volume and hepatic functional reserve as a guide to decision-making in resectional surgery for hepatic tumors. Hepatology 1997;26(5):1176–81.

Ablation


RFA electrode

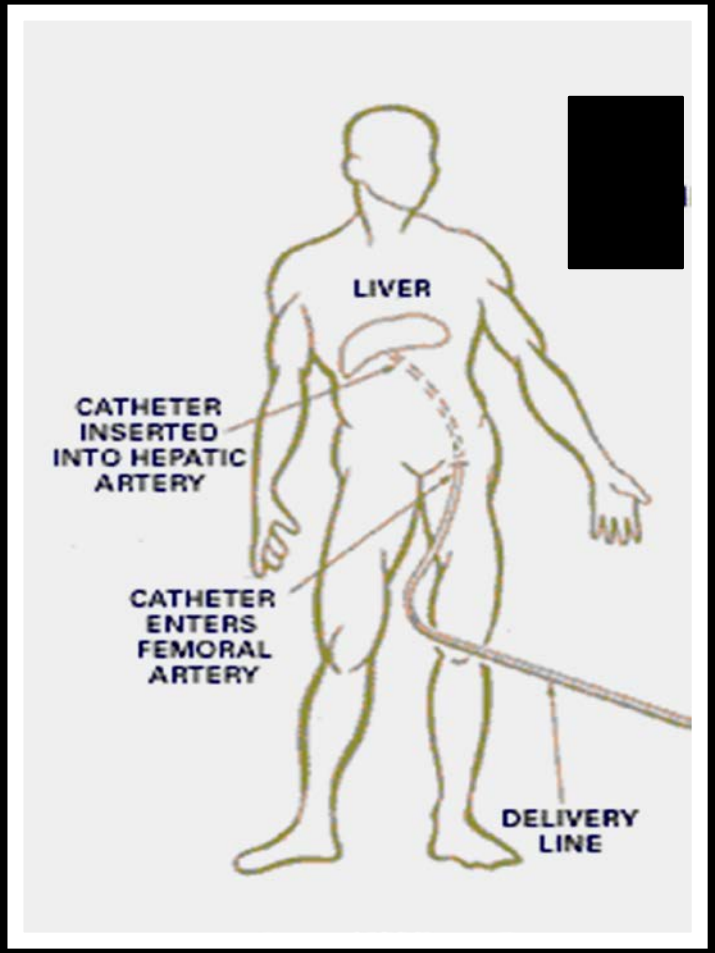

Tumor in liver


Thermal ablation in progress


Complete tumor destruction

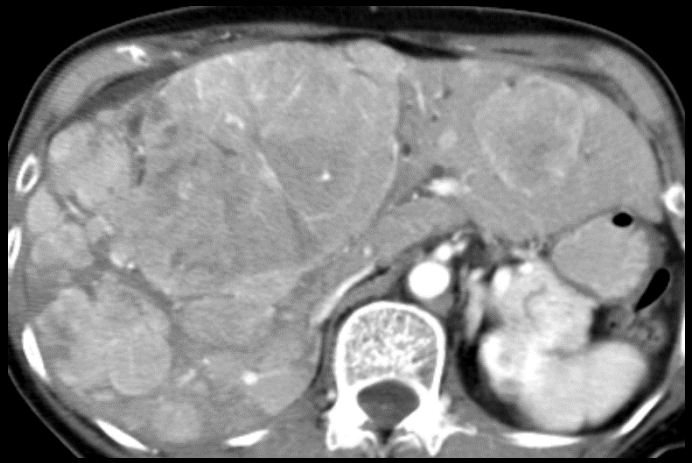
Hepatic Direct Chemotherapy

- Transcatheter Arterial Chemoembolization (TACE)
  - Used as a primary and complementary measure for inoperable HCC
  - Hepatic artery supplies 90% of the tumor blood flow and provides access for treatment
  - Targets chemotherapy and provides selective ischemia to the tumors
  - Leverages dual blood supply of the liver

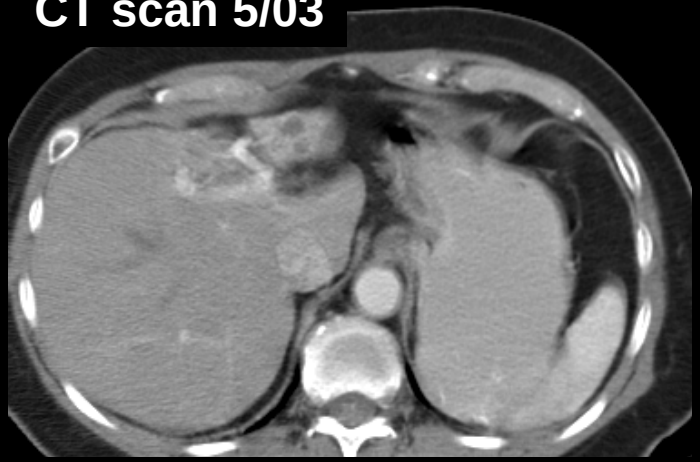


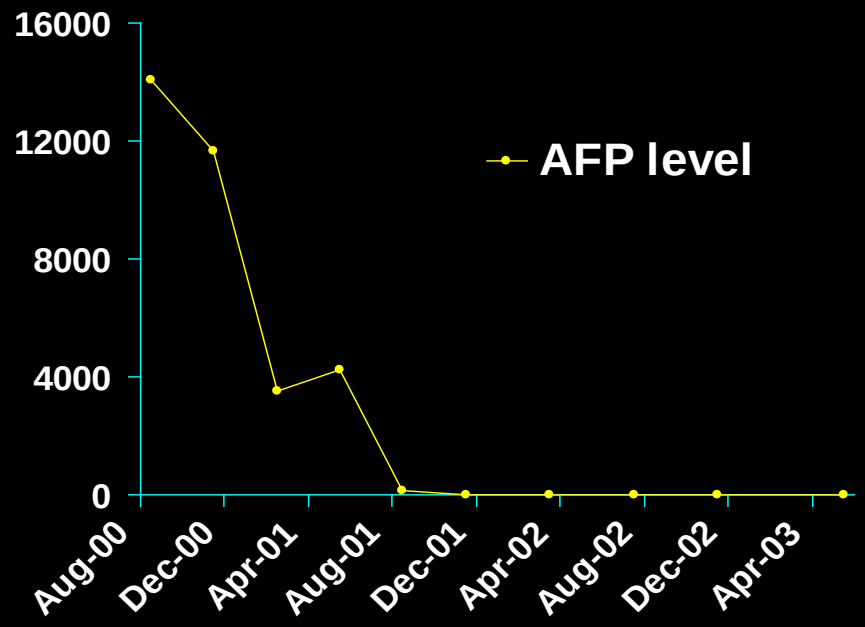
73 yo Asian F - unresectable HCC; Treatment: TACE x 12

Initial CT scan 4/00



CT scan 5/03

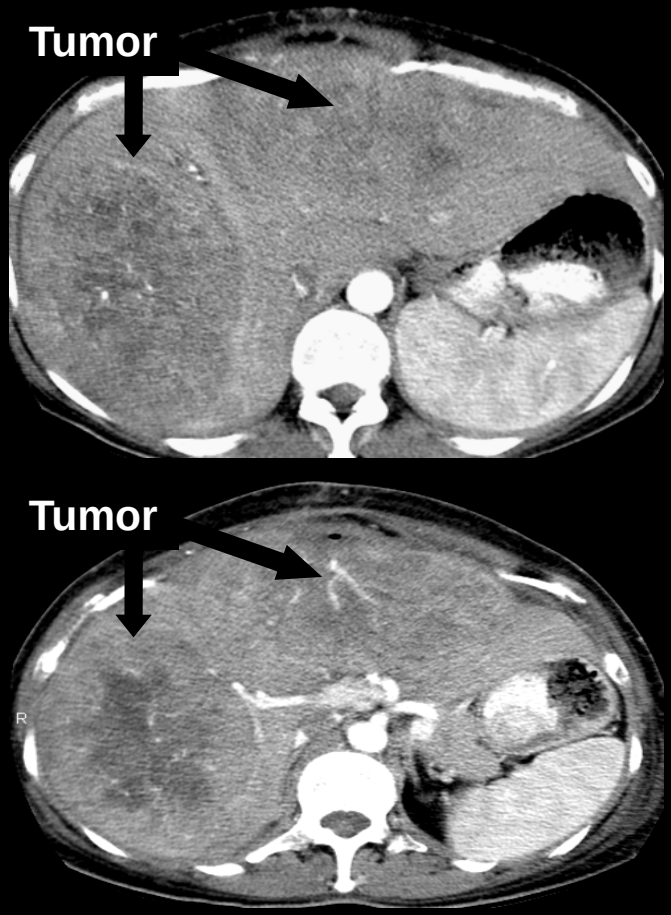




Complete response (5 year) of giant hepatocellular carcinoma (HCC) after 20 cycles of intra-hepatic chemoembolization (TACE)

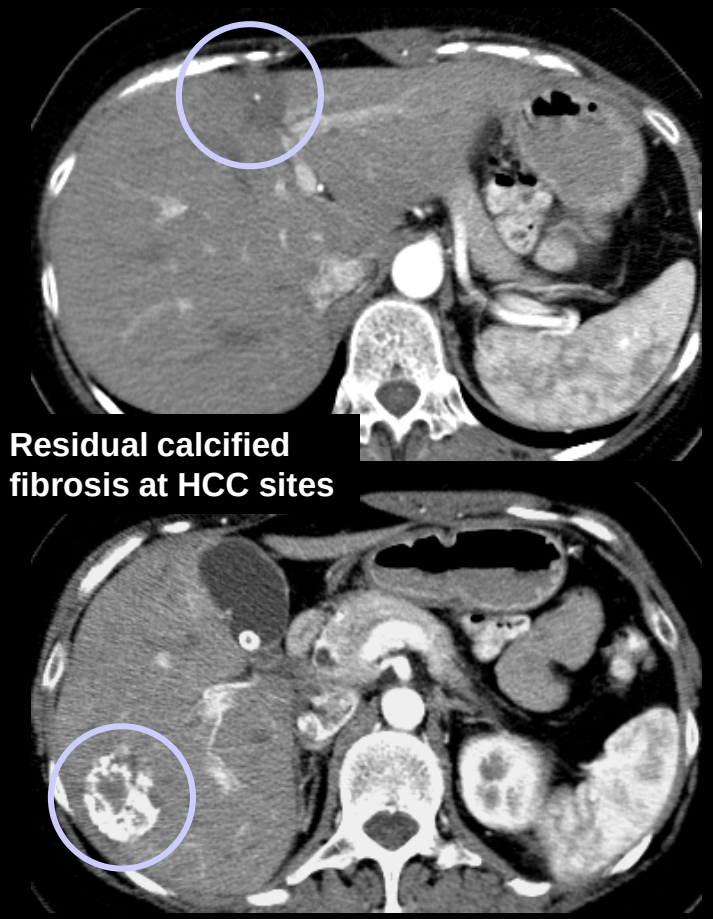
Initial CT scan: March, 1998

AFP 1,596



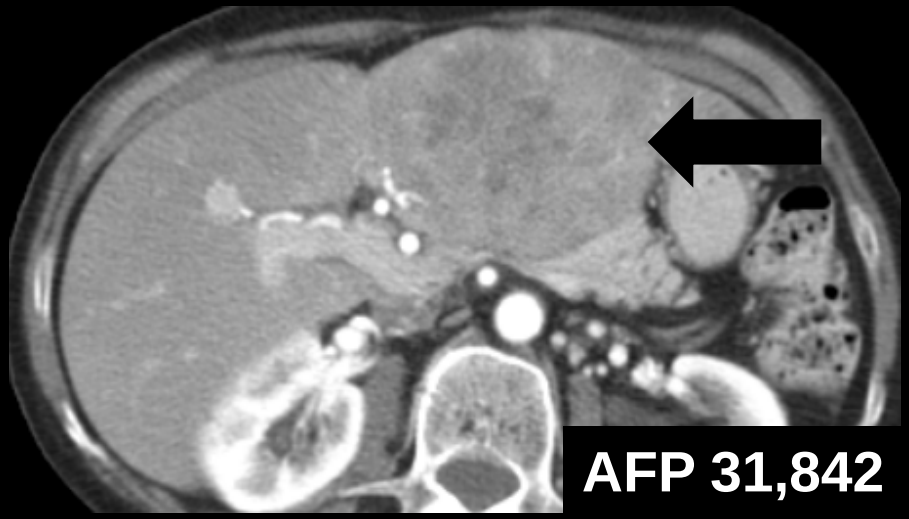
Follow-up CT: March, 2003

AFP 3

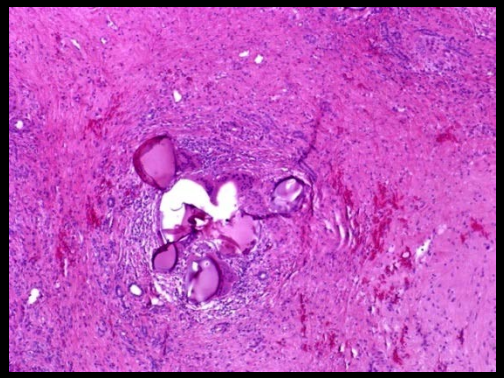


Patient - 74 yo WF, cirrhosis, large 10 cm left lobe HCC
Treatment: TACE x 4, then Lap. liver resection

Initial CT scan

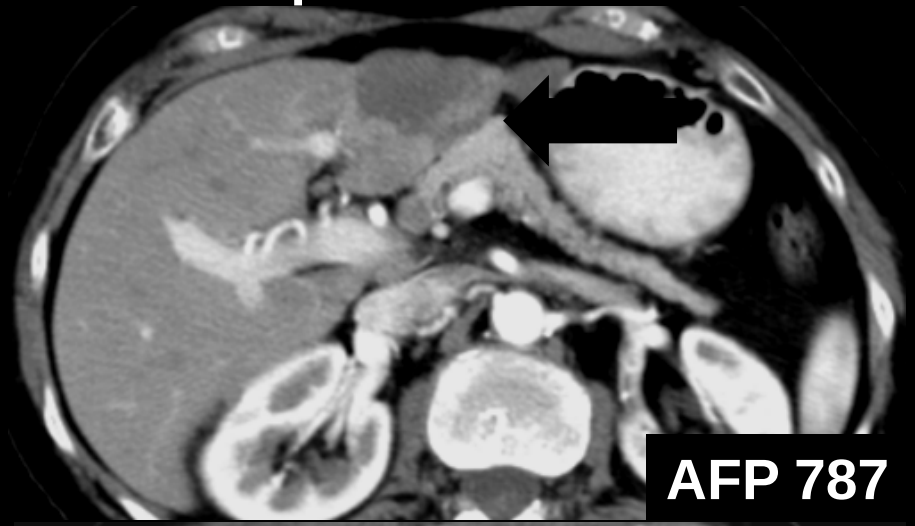


AFP 31,842

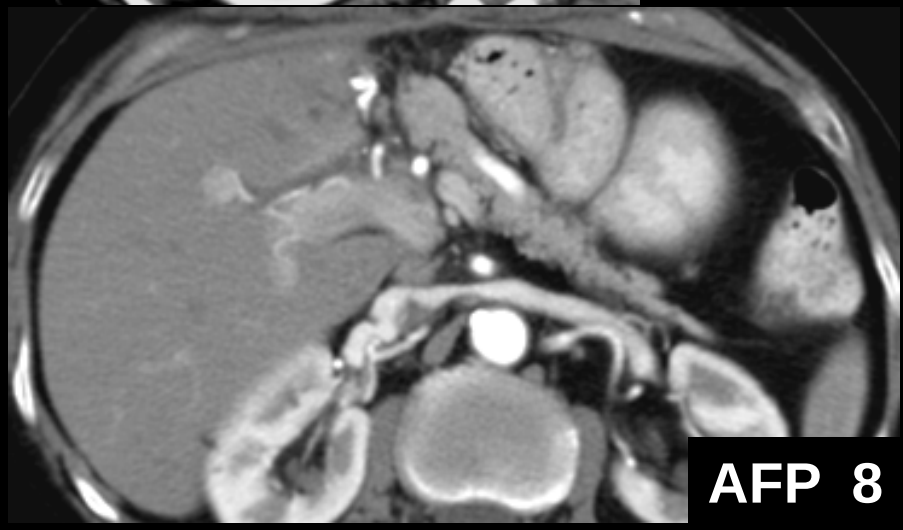


No tumor recurrence 12 mos post-op; normal AFP

Pre-Op CT 8 months later



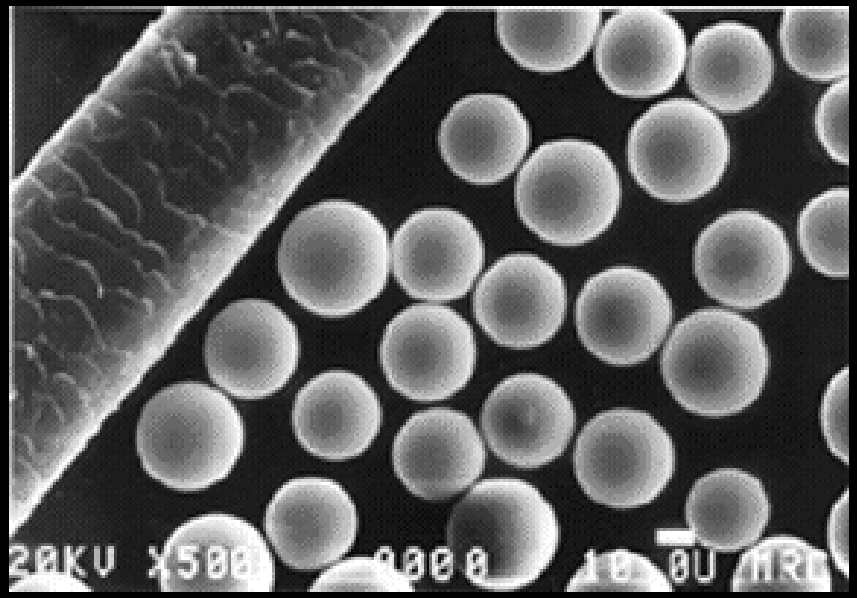
AFP 787



AFP 8

TheraSphere- Y^{90} Radioisotope (Internal XRT)

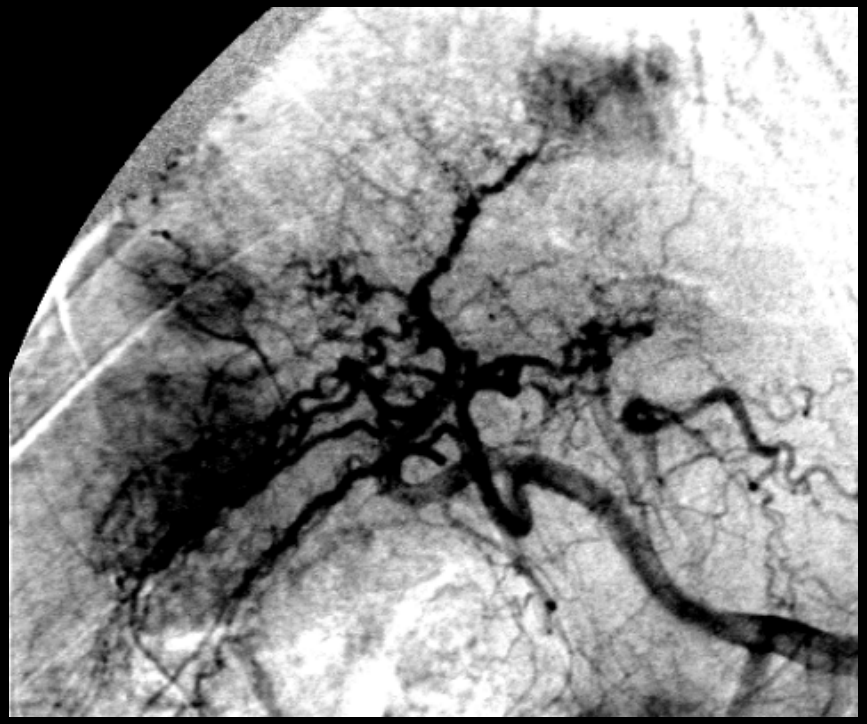
- **Pure beta emitter, half-life of 64.2 h**
- **Irradiates tissue average range of 2.5 mm**
- **Maximum penetration of approx. 1.0 cm**
- **Microsphere diameter 25μ - 35μ**



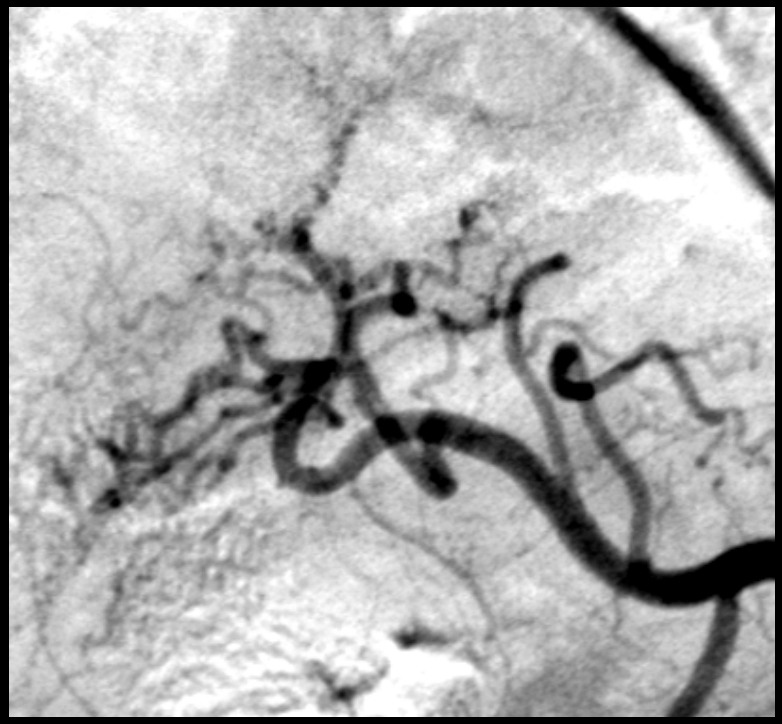
Patient - 69 yo WM, cirrhosis, multi-focal HCC

Treatment: Theraspheres (^{90}Y radiolabeled microspheres)

Angio, 3 hypervasc. masses



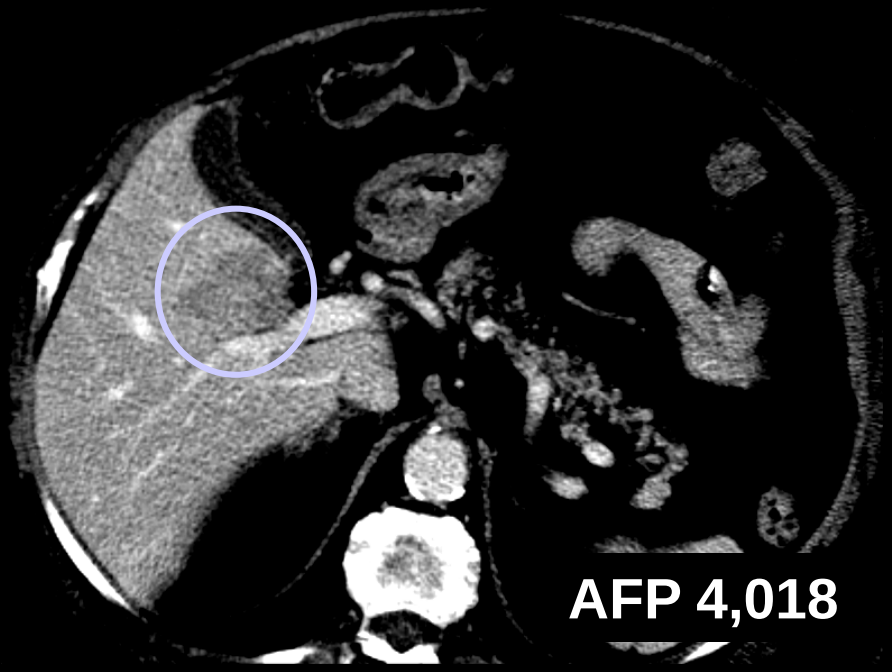
Post Therasphere



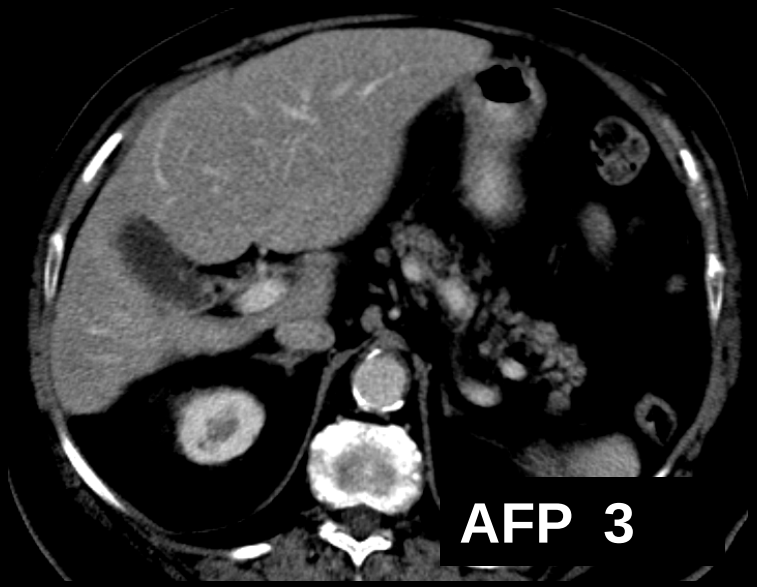
Patient – 87 yo, HCC – Complete response

Treatment: Therasphere x 1 (yttrium^{90})

Initial CT Scan



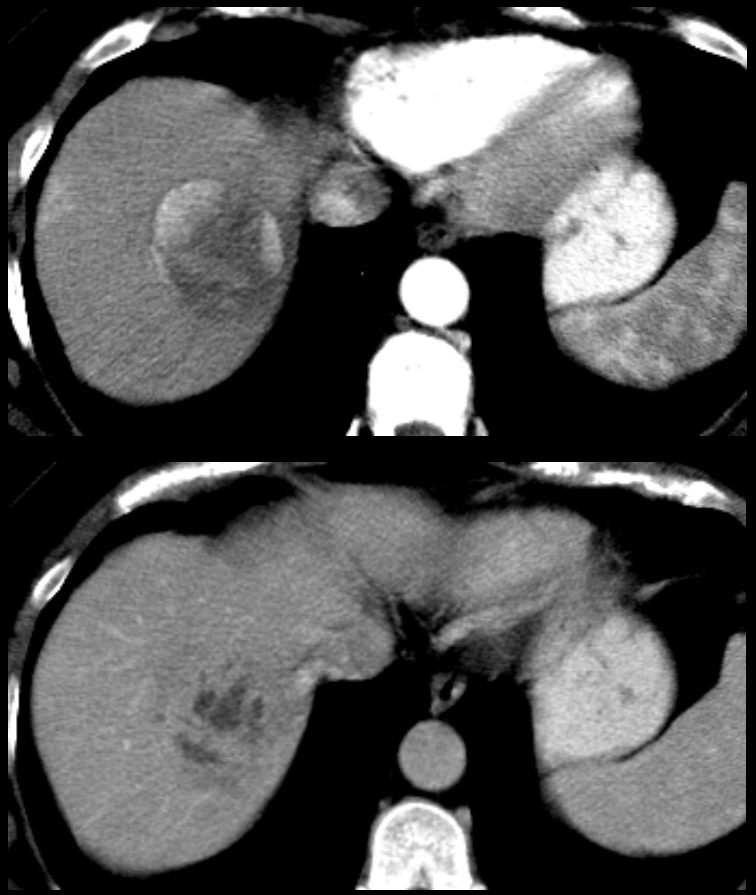
2 Year f/u CT



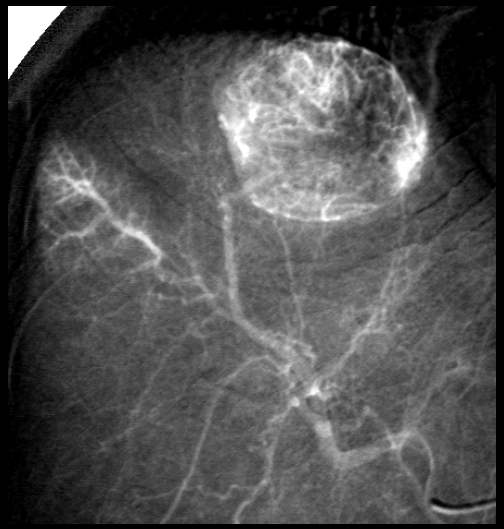
No Tumor, R lobe atrophied

53 yo WF, bx-proven 5.8 cm HCC
Treatment: ^{90}Yttrium-Theraspheres + embolization,

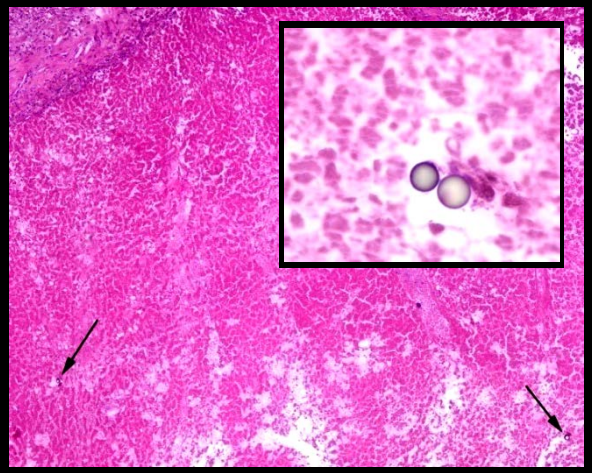
CT scan



Angiogram



Explanted path



Live donor
OLTx

Moderately differentiated HCC, 4.5 cm, extensive tumor necrosis, T1N0M0

LIVER TRANSPLANTATION

MELD Score

The MELD score determines, in large part, the time patients must wait to receive a liver transplant:

The Model for End-stage Liver Disease (MELD), which incorporates only bilirubin, INR and creatinine, is a continuous disease severity scale that is predictive of the risk of dying from liver disease for patients waiting on the transplant list. Its ability to predict death is NOT improved by including subjective parameters like variceal bleeding, ascites and encephalopathy.

MELD Score = $(0.957 \times \text{Log}_e(\text{creatinine mg/dL}) + 0.378 \times \text{Log}_e(\text{bilirubin mg/dL}) + 1.120 \times \text{Log}_e(\text{INR}) + 0.643) * 10$

MELD Score

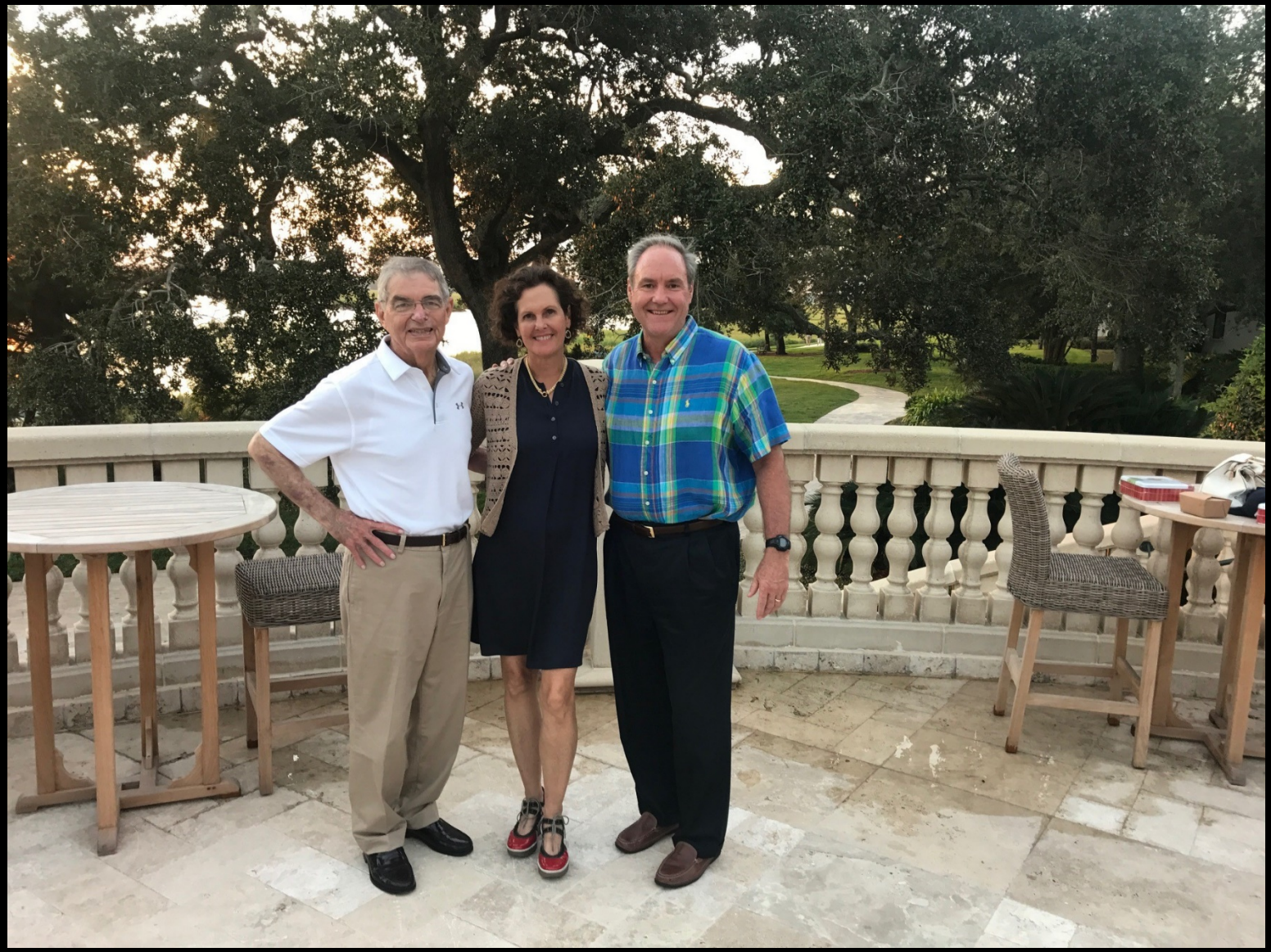
SPECIAL CASES

- HCC (hepatocellular carcinoma)
- HPS (hepatopulmonary syndrome)
- Familial amyloidosis
- Other cases not specified

Patients with hepatocellular carcinoma within the very restrictive Milan/UNOS criteria are given extra listing points on the UNOS waiting list.

American Liver Tumor Study Group Modified Tumor-Node-Metastasis (TNM) Staging Classification

Classification	Definition
TX, NX, MX	Not assessed
TO, NO, MO	not found
T1	One nodule <=1.9 cm
T2	One nodule 2.0-5.0 cm; two or three nodules, all <3.0 cm
T3	One nodule >5.0 cm; two or three nodules, at least one >3.0 cm
T4a	Four or more nodules, any size
T4b	T2, T3, or T4a plus gross intrahepatic portal or hepatic vein involvement as indicated by CT, MRI, or ultrasound
N1	Regional (portal hepatis) nodes, involved
M1	Metastatic disease, including extrahepatic portal or hepatic vein involvement
Stage I	T1
Stage II	T2
Stage III	T3
Stage IVA1	T4a
Stage IVA2	T4b
Stage IVB	Any N1, any M1



Thank you--Questions