Hepatocellular Carcinoma and Y-90 Radioembolization

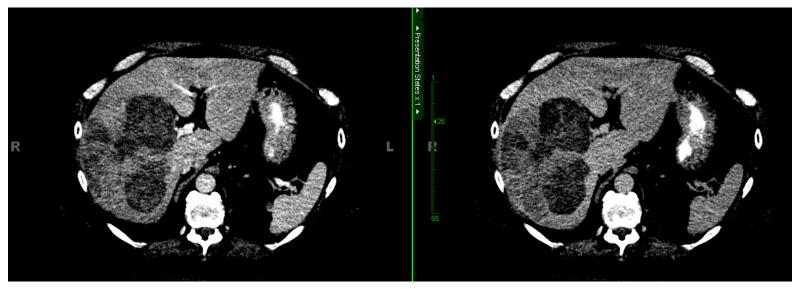
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Case: Initial Presentation

- 53-year-old man with new onset hematuria
 Abdominal ultrasound: demonstrated a 7.3 x 8.6 cm mass in the liver
- 3-phase liver protocol CT: Tumor replacing the entire right lobe of the liver with areas of enhancement and areas of necrosis; no lesions in the left lobe



Arterial Phase: Enhancement

Venous Phase: subtle washout



Case

Labs (normal range)

AFP: $137 \mu g/L (< 10)$

AST: 68 IU/L (14-20)

ALT: 54 IU/L (10-40)

Tbili: 0.7 mg/dL (< 0.3)

Alk Phos: 95 IU/L (53-128)

- Unresectable due to tumor location and bulk
- Referred for consideration of radiation therapy



HCC - Epidemiology

Worldwide:

- 5th most common cancer in men, 2nd leading cause of cancer-related mortality
- 7th most common cancer in women and 6th leading cause of cancer-related mortality

• Rising incidence in the US:

- Increase in hepatitis B (HCV B) and C (HCV C) from 1960s 1990s
- Metabolic syndrome associated non-alcoholic steatohepatitis (NASH)

Risk Factors:

- Infectious: hepatitis B, chronic hepatitis C,
- Genetic: hematochromatosis, alpha-1 antitrypsin deficiency
- Demographic: older age, black race, aflatoxin
- Medical History: diabetes mellitus type 2, metabolic syndrome, cirrhosis of any cause
- Social History: heavy alcohol use, smoking



Screening with AFP and Liver US

- Recommended every 6-12 months for the following patients:
 - With cirrhosis:
 - Hep B, C
 - Alcohol
 - Genetic hemochromotosis
 - Non-alcoholic fatty liver disease (NAFLD)
 - Stage 4 primary biliary cirrhosis
 - Alpha 1-antitrypsin deficiency
 - Other causes of cirrhosis
 - Without cirrhosis
 - Hep B carriers



Workup

- A rising AFP or nodule on US should prompt liver imaging studies
 - At least a 3-phase liver protocol CT or MRI
- Labs: hepatitis panel, CMP, CBC, PT or INR, albumin, AFP
- Chest CT
- Bone scan if clinically indicated



Work-up: Imaging

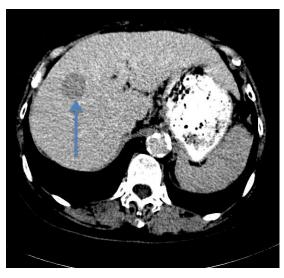
- 3-phase liver protocol CT
- Imaging Characteristics: arterial hyper-enhancement and venous phase washout



Arterial Phase: Contrast Enhancement



Venous Phase: Washout

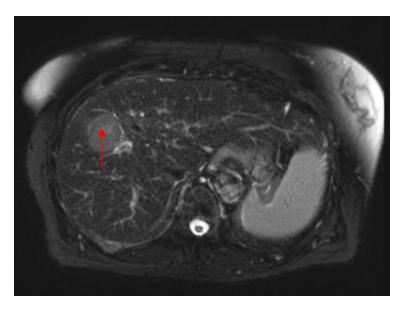


Time Delay: Washout

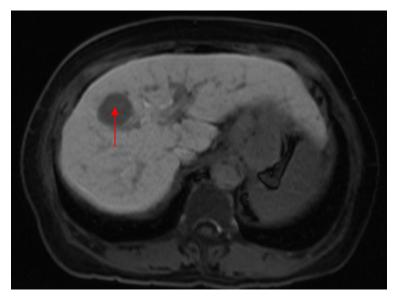


Work-Up: Imaging

3-phase liver protocol MRI



T2 hyperintensity



Eovist delayed phase: nonenhancement of lesion compared to background liver

 Biopsy: not required in select patients with cirrhosis; recommended in patients without cirrhosis (see NCCN guidelines)



Prognostic factors

- Milan Criteria: to determine eligibility for transplant
 - solitary lesion < 5 cm</p>
 - up to 3 lesions smaller than 3 cm
 - no extrahepatic manifestations
 - no vascular invasion
- Alpha fetoprotein level
- Portal vein thrombosis
- MELD Score: used to quantify end-stage liver disease for purposes of transplant
 - Factors: Tbili, Creatinine, INR
- Child Pugh Score: to quantify degree of liver disease (next slides)



Prognostic Factors

Child-Pugh Score

Points	1	2	3
Bilirubin	< 2 mg/dL	2-3	> 3
Albumin	> 3.5	2.8-3.5	<2.8
PT (secs)	1-4	4-6	> 6
Hepatic Encephalopathy	None	1-2	3-4
Ascites	None	Mild (detectable)	Severe (tense)

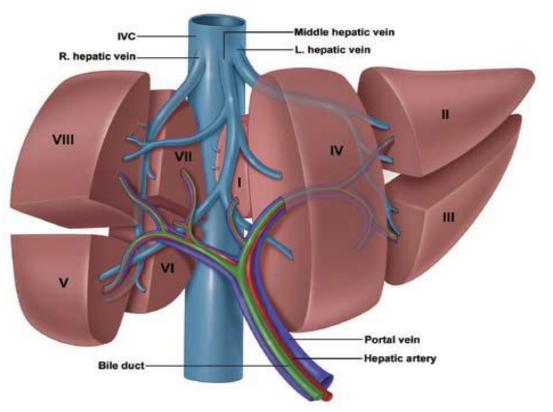
Prognostic Factors

Child-Pugh Designation

Class	Points	1-year survival
Α	5-6	100%
В	7-9	81%
С	10-15	45%



Anatomy



- Middle hepatic vein: divides liver into left and right lobes
- Right hepatic vein: divides R lobe in anterior/posterior segments
- Left hepatic vein: divides L lobe into medial/lateral segments
- Portal vein: divides liver into upper and lower segments



Patterns of Spread

- Regional LN
 - 1/3 have regional disease at diagnosis
 - Hilar, hepatoduodenal ligament, inferior phrenic, caval LNs
- Metastases
 - 1/3 have distant disease at diagnosis
 - Distant metastases: lungs and bones most common
 - Adjacent organs: adrenals, diaphragm, and colon



HCC Staging – AJCC 7th edition

Primary Tumor Staging		
Tx	Primary Tumor cannot be assessed	
T0	No evidence of primary tumor	
T1	Solitary tumor without vascular invasion	
T2	Solitary tumor with vascular invasion or multiple tumors, none greater than 5 cm	
T3a	Multiple tumors, greater than 5 cm	
T3b	Tumor involving a major branch of the portal vein or hepatic vein	
T4	Tumor with direct invasion of adjacent organs other than the gall bladder, or perforation of visceral pleura	

Nodal Staging		
Nx	Regional nodes cannot be assessed	
N0	No evidence of regional nodal metastasis	
N1	Evidence of regional nodal metastases	

Metastatic Staging		
M0	None	
M1	Yes	



HCC Staging - AJCC 7th Edition

Stage I	T1	NO	MO
Stage II	T2	NO	MO
Stage IIIA	T3a	NO	MO
Stage IIIB	T3b	NO	MO
Stage IIIC	T4	NO	MO
Stage IVA	Any T	N1	MO
Stage IVB	Any T	Any N	M1

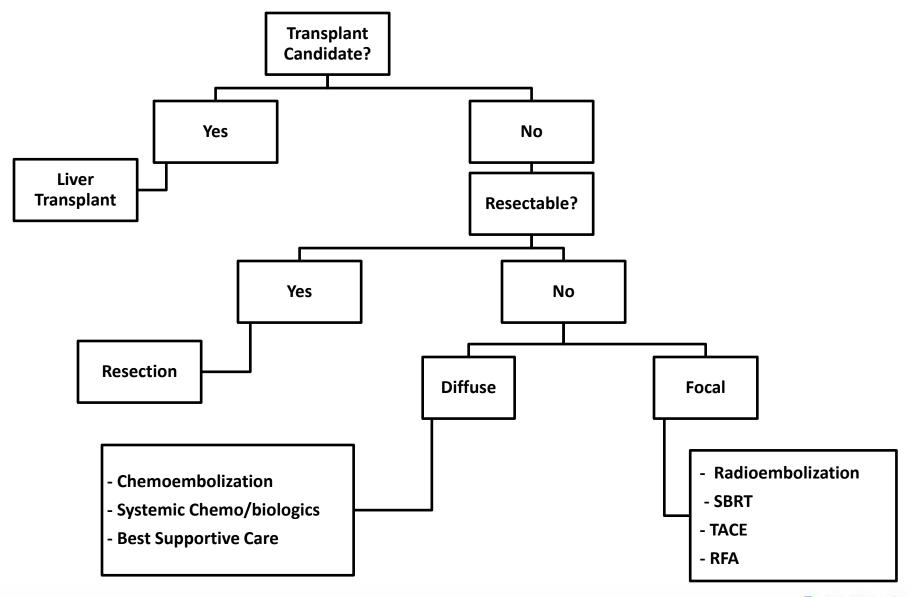
BCLC (Barcelona Clinic Liver Cancer) Staging

More commonly used than AJCC

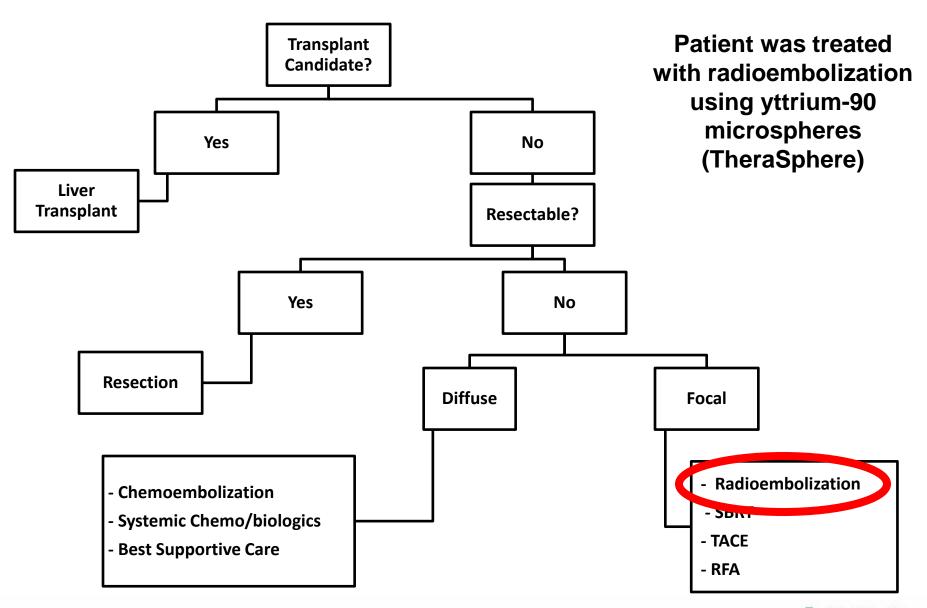
Stage	ECOG PS	Child Pugh Score	Other Criteria
0: Very early stage	0	Α	Single HCC < 2 cm
A: Early Stage	0	A-B	Single HCC or up to 3 nodules < 3 cm
B: Intermediate Stage	0	A-B	Multinodular
C: Advanced Stage	1-2	A-B	Portal invasion, Stage IV disease
D: Terminal Stage	> 2	С	



Treatment Algorithm - HCC



Case



Principals of Radioembolization

 Microspheres are delivered to the liver and intrahepatic tumor through a catheter placed into the hepatic artery, the primary blood supply to liver tumors.

 Since microspheres are unable to pass through the vasculature of the liver and liver tumor due to arteriolar capillary blockade, they are trapped and exert a local radiotherapeutic effect



TheraSphere

- TheraSphere consists of yttrium-90 (Y-90) as an integral constituent of insoluble glass microspheres.
- Mean sphere diameter 20-30 μm
- Y-90
 - Pure beta emitter
 - Decays to stable zirconium-90
 - Physical half life of 64.2 hours (2.68 days)
 - Average energy of beta emissions is 0.94 MeV
 - Average range of 2.5mm in tissue, with max range1cm



SIR-Spheres

- SIR-Spheres are also microspheres that contain yttrium-90
- They are made of a polymer resin (rather than glass)
- Mean sphere diameter 20 60 μm.



Radioembolization Criteria

Inclusion criteria:

- Unresectable hepatocellular carcinoma
- Age > 18 years
- ECOG Performance Status < 2
- Laboratory criteria: WBC >
 1.5, Plt > 50, Cr < 2.0, Tbili <3 mg/dL</p>
- Ability to undergo angiography

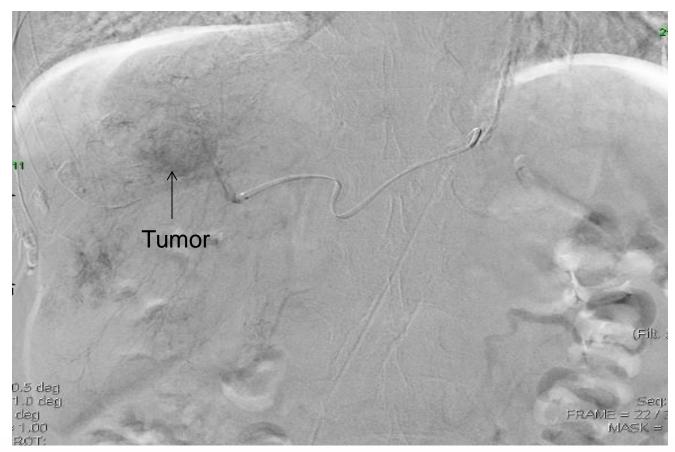
Exclusion criteria:

- Uncorrectable flow to the GI tract
- Significant extrahepatic disease
- Lung dose > 30 Gy in a single fraction
- Lung dose > 50 Gy in multiple administrations



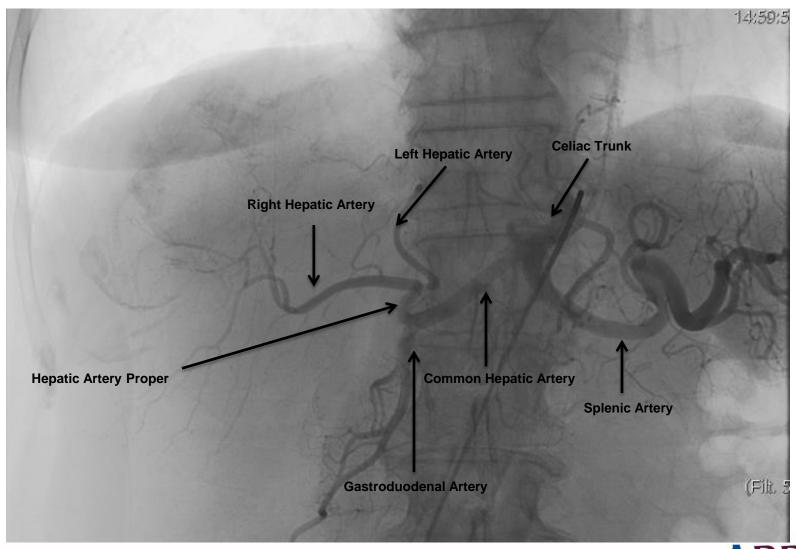
Pre-Embolization Evaluation

Angiography

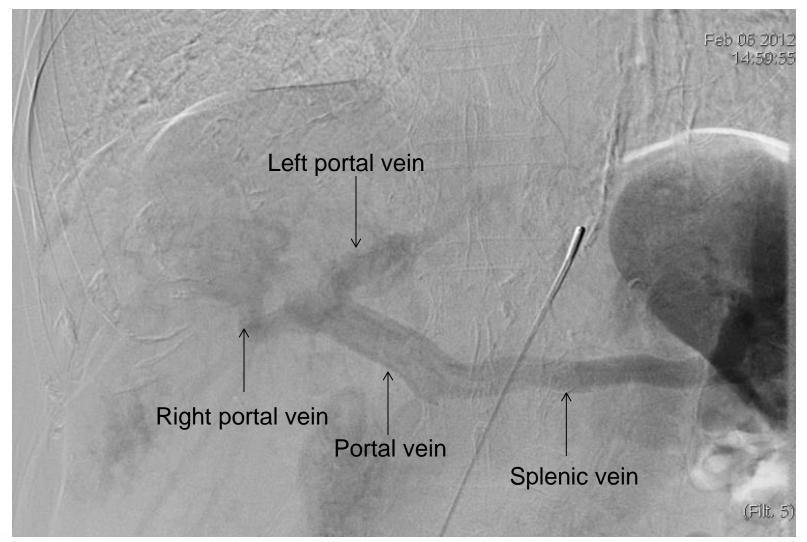




Hepatic Vascular Anatomy



Hepatic Vascular Anatomy



Lung Shunt Fraction

- Assessed during the pre-embolization evaluation to determine extra hepatic flow to the lungs and GI tract
- Technetium-99 macro-aggregated albumin administered through a catheter in the hepatic artery and images obtained via gamma camera
- Lungs can tolerate up to 30 Gy per treatment and 50 Gy cumulatively over multiple treatment



Treatment Planning

Based on pretreatment angiography and 3-dimensional reconstruction of the liver

- $D = A \times 50 \times (1 LSF) \times (1-R) / m$
- $A = D \times m / 50$

D = dose in gray

A = activity in GigaBequerels

m = mass of the liver in kilograms

R = percent of residual activity in the vial after treatment

LSF = lung shunt fraction



Toxicities and Management

- Acute side effects: fatigue, nausea/vomiting, flu-like symptoms, abdominal / chest wall pain
 - Managed with NSAIDs, anti-emetics, and pain medication
- Radioembolization-induced liver disease (REILD):
 - Presentation: increased LFTs, edema on CT and pain
 - Monitor if asymptomatic and slow steroid taper if symptomatic
- Radiation pneumonitis
 - Presentation: persistent nonproductive cough, shortness of breath and low grade fever
 - Slow steroid taper
- Gastrointestinal complications: Rare
 - Carafate for GI ulcers, Argon plasma coagulation for symptomatic bleeding



Follow-up

 6 week follow-up with CBC, CMP, AFP, PT/PTT and CT 3 Phase Liver

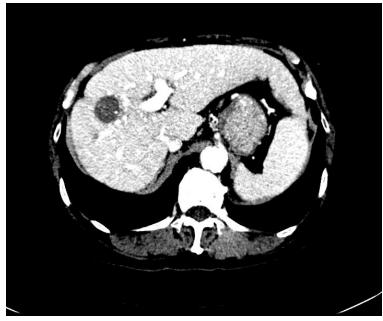
 Q 3 - 4 month follow-up for the first 2 years with CBC, CMP, AFP, PT/PTT and 3-phase liver protocol CT



Post-embolization CT



Arterial Phase: No enhancement



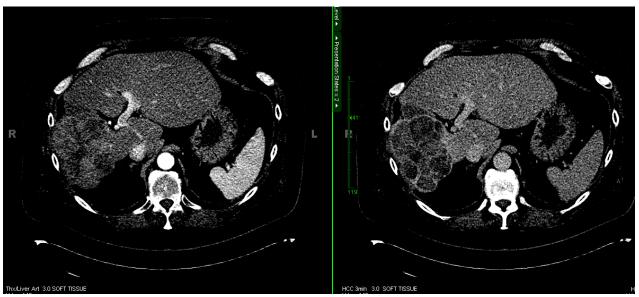
Venous Phase: No enhancement

- Arterial perfusion on the pre vs. post CT scan measures viable tumor and is associated with 1 year overall survival
- Size of the lesion is not associated with progression or survival



Case: Follow-up

- Improvement in AFP and Interval response in tumor enhancement
- At 2 years, increase in tumor enhancement on 3 Phase Liver CT in the setting of a rising AFP



Arterial Phase: New enhancement Venous Phase: Washout



Case: Follow-up

- Referred for Angiography
 - Retreatment found not to exceed normal tissue tolerance
- Patient underwent successful repeat radioembolization without acute adverse events



References

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- NCCN guidelines version 2.2014
- Image (slide 12): http://www.cpmc.org/advanced/liver/patients/topics/liver-cancer-profile.html

