

HCC: SURVEILLANCE AND MANAGEMENT

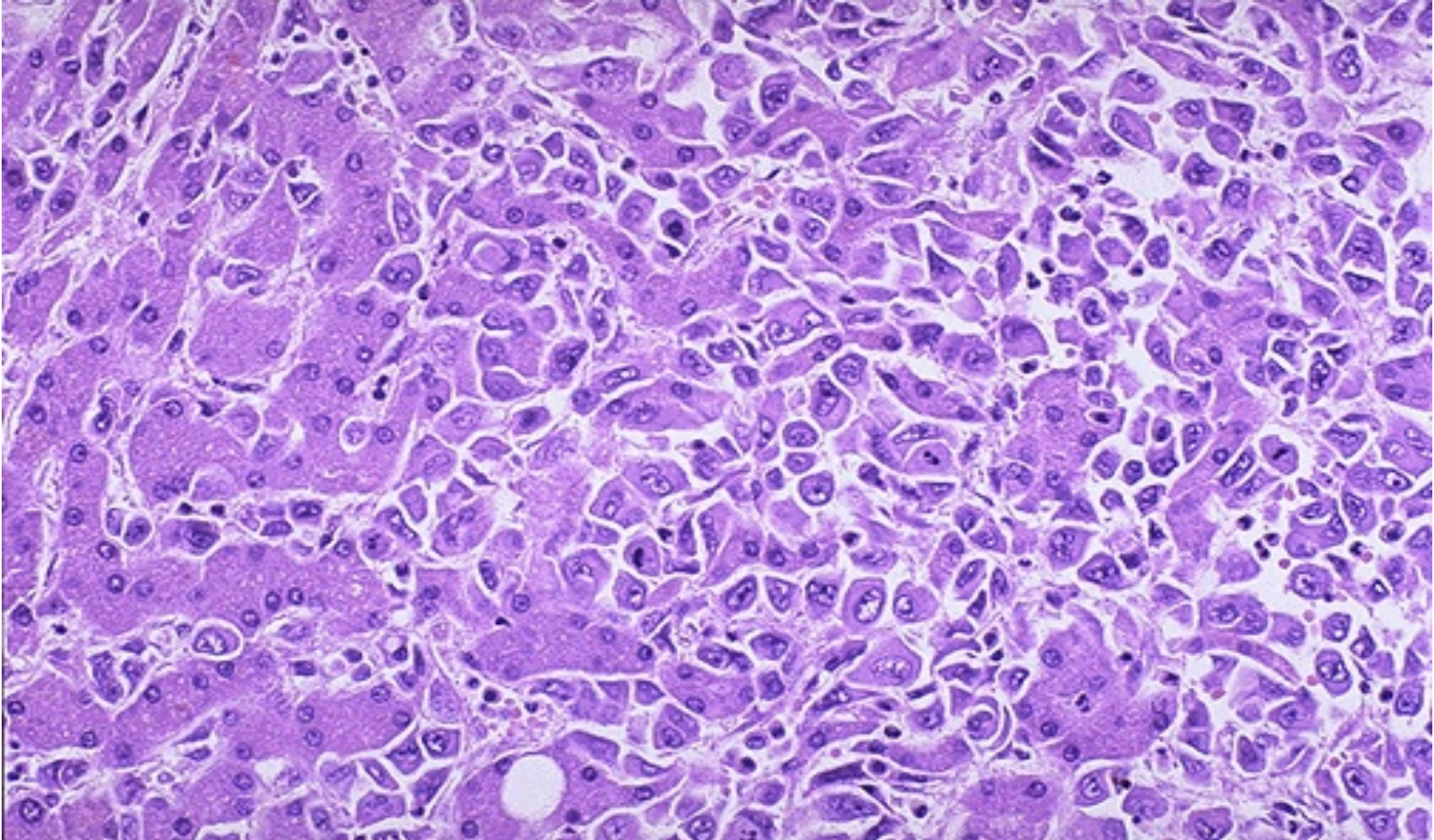
Hillel Tobias, MD PhD

Professor of Medicine and Surgery

Medical Director, Liver Transplant Service

New York University Langone Medical Center

Normal hepatocytes -----HCC



Emerging Trends in HCC

Incidence and Mortality (in U.S.)

- HCC is 2nd or 3rd most common cause of cancer related deaths worldwide
- Historically more common in developing world
- Recently incidence in developed world has doubled (secondary to increase in cirrhosis)
- Tumor size (>5cm) and vascular invasion increase risk of death
- Hepatology 61:191-200 Njei et al

Risk Factors for HCC

- Chronic Hepatitis B accounts for 52% of all HCC (350 million world wide have HBV)
- Followed by chronic hepatitis C and Alcohol related liver disease
- Obesity/diabetes/NASH
- Hemochromatosis
- PBC, AIH
- Aflatoxin

Reduction of Incidence: Prevention of Risk Factors

- Cirrhosis due to hepatitis B
- Cirrhosis due to hepatitis C
- Reduction in Alcohol Consumption & Cirrhosis
- Epidemic of obesity, metabolic syndrome, and non alcoholic fatty liver disease
- Plus: higher rate of early detection
- And: Effective treatment options

Cirrhosis vs. HCC

- Most cases of HCC arise in patients with cirrhosis especially in HCV and ARLD
- However chronic hepatitis B can give rise to HCC in the absence of cirrhosis
- Now reported NAFLD can also give rise to HCC in absence of cirrhosis

HCC Screening/Surveillance

- The only valid screening process for HCC is regular *six month* imaging of the liver in susceptible individuals
- MRI is the most sensitive imaging
- 3 Phase contrast CT is next most sensitive
- Ultrasound is next most sensitive --being the least expensive it is the “recommended” test- sensitivity 65-80%, specificity 90%
- Use of serologic tumor markers is not recommended in screening guidelines

HCC Diagnosis Is Established by Imaging Criteria

- Intense contrast uptake in the arterial phase followed by contrast washout in the venous phase is considered specific for HCC on MRI and CT
- Nodules 1 cm or less can not be validated as tumor
- Such nodules should be followed with serial studies
- PET scans are not useful due to low sensitivity of pick up

HCC-Arterial Phase Enhancement



Liver Biopsy in the Diagnosis of HCC

- Biopsy of small nodules within a cirrhotic liver seen on imaging studies is not reliable
- Sampling errors occur
- Distinguishing HCC from Dysplastic Nodule is often erroneous
- A “negative” biopsy can not rule out malignancy
- 30% of HCC patients can have a ‘non diagnostic” biopsy or tumor is inaccessible

Future Use of Serologic HCC Markers

- Lens culinaris agglutinin-reactive fraction of AFP
AFP L3
- AFP protein normally produced by yolk sac and liver in fetal development
- AFP L3 is fucosylated isoform of AFP
- The biomarker is ratio of AFP L3 to AFP
- Level of 10% or greater suggests HCC
- DCP (Pivka II): HCC secretes non carboxylated prothrombin because HCC cells have a carboxylation defect.

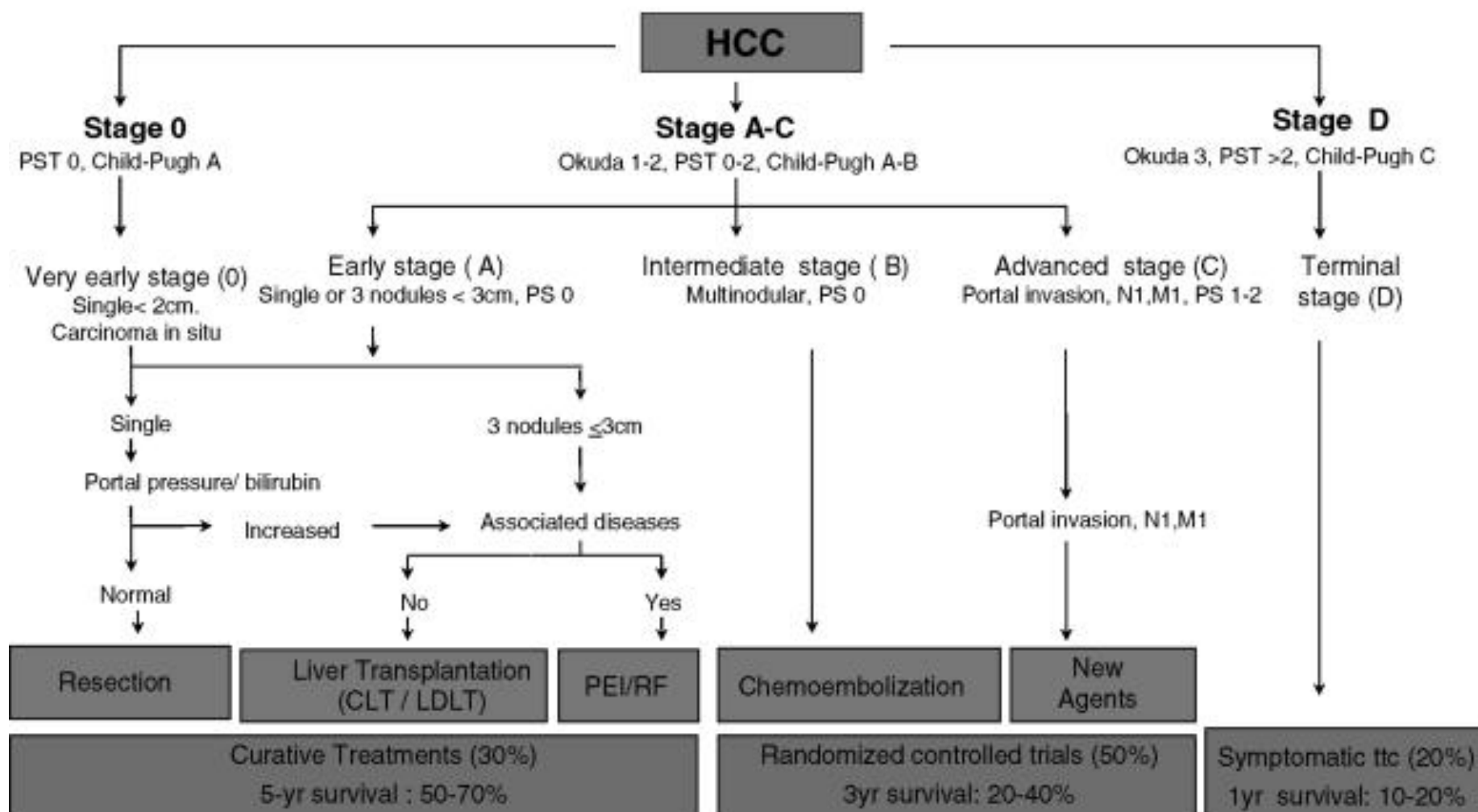
Management of HCC

- Resection vs. Transplantation vs. Ablation
- If patient presents with hepatic decompensation expected outcome offered by transplantation (within the Milan Criteria) clearly superior
- Compensated liver disease survival (within Milan Criteria) is >70% vs 40-50% for resection and/or ablation
- Large tumors are not well served by ablations and may require TARE in cirrhosis and resection in non cirrhotics

Barcelona Clinic Liver Cancer Algorithm

- Stratifies HCC patients into five stages with links to treatment
- **BCLC '0'** : single HCC <2cm - low probability of microscopic dissemination (?resection)
- **BCLC 'A'** : single nodule, or up to 3 nodules <3cmC (? resection,?ablation? Transplantation)
- **BCLC 'B'**: large/or multifocal HCC without extrahepatic spread (TACE recommended)
- **BCLC 'C'**: extrahepatic spread /constitutional symptoms (Sorafenib)
- **BCLC 'D'**: heavily impaired liver function/major physical deterioration. (Symptomatic Rx)

BCLC Staging and treatment schedule



Surgical Resection

- Recommended in the BCLC: benefit of segmental resection may only be apparent in tumors between 1 and 2 cm
- Recurrence after resection occurs in up to 80% in 5 yrs
- Presence of portal hypertension negatively impacts results of resection.
- In tumors <2cm resection and RFA have similar results
- This is generally not followed in centers with Transplant Teams
- Barcelona '0' and 'A' as well as 'B' are considered candidates for transplantation under the Milan Criteria

Survival Benefit of Liver Resection for HCC Across Different BCLC Stages

Vitale, A & Italian Liver Cancer Group J.Hepatology 2015 62:617-24

- Cohort: 2090 BCLC A, B, C^v HCC patients studied 200-2012
- Resection: 550, 1040 loco-regional therapy (LRT), 494 best supportive care (BSC)
- Median Net Survival Benefit of resection over LRT was BCLC-0 = 62%, BCLC-A = 45%, BCLC -C = -16%
- CHILDS A patients always had a large positive net survival benefit of resection over LRT independent of BCLC stage.
- Use of resection negates the use of the Transplant Pathway

Locoregional Approaches

- RF-ablation, TACE, TACE-DEB, TARE-radioembolization, Hepatic Artery Infusion Chemotherapy(HAIC)
- TACE clearly improves survival of HCC
- TACE Effective in HCC patients with compensated liver disease without vascular invasion of extrahepatic spread
- TACE induces major tumor necrosis
- TACE may be repeated upon disease progression
- Combining TACE with Sorafanib
- Median survival of TACE treated patients should exceed 3years

Transarterial Chemoembolization

(EASL Indications and Patient Selection)

- TACE is the BCLC recommended treatment modality for asymptomatic large or multifocal HCC without macrovascular invasion or extrahepatic metastasis (“Intermediate HCC”, BCLC stage B)
- In U.S. liver centers with transplant capabilities it is the recommended modality for earliest HCC as well.

Results of TACE

- Results of treatment are better in lesions <5cm than those >5cm
- Best in lesions around 2 cm
- Overall significant rate of retreatment to attain 100% necrosis
- And to deal with recurrence. “radiologic progression”
- Generally judged on repeat MRI 2-3 months after treatment

Contraindications to TACE

- **Absolute contraindications**

Factors related to cirrhosis: Decompensated cirrhosis – jaundice, HE, refractory ascites, hepatorenal syndrome, portal vein thrombosis, hepatofugal flow

- *Factors related to HCC:* extensive tumor involving entirety of both liver lobes, malignant portal vein thrombosis

- *Impaired renal function:* GFR <30

- **Relative contraindications:**

- *Factors related to cirrhosis:* esophageal varices at high risk of bleeding

- *Factors related to HCC:* large tumor >10 cm

Percutaneous Cryoablation vs RFA for HCC

Wang, C etal Hepatology 2015 61:1579-1590

- Cohort: 360 patients-Childs-Pugh A or B cirrhosis
- HCC: 1 or 2 lesions <4 cm
- Treatment naïve, no metastases
- Endpoint: **local tumor progression** @ 1,2,3 yrs
- Cryo: 3%, 7%, 7% RFA: 9%,11%,11% (p=.04)
- Lesions >3cm cryo 7.7% vs RFA 18.2%
- **Survival Rate:** 1 yr:97%, 3yr:67%, 5yr:40% Cryo
- RFA: 97%, 66% 38% RFA

RFA vs Surgical Resection for Small HCC

- 168 patients with nodules less than 4 cm and up to 2 nodules
- Three year follow up
- Resection: 1yr 96%, 2yr 87.6%, 3yr 74.8%
- RFA: 1yr 93.1, 2yr 83.1%, 3yr 67.2%
- *No statistical differences in overall survival or recurrence free survival rate*
- Feng et al. J. Hepatology 2012;57:794-802

Tranarterial Radio Embolization(TARE)

- Arterial delivery of glass or resin spheres loaded with radiation agent such as Yttrium 90
- Useful in large tumors unsuitable for TACE
- And Patients with portal vein thrombosis

BCLC Strategy

- “From an oncological point of view liver transplantation is preferable to surgical resection as it can remove all the intrahepatic tumor foci and the oncogenic cirrhotic liver”
- The 5 year transplant survival exceeds 70%
- Recurrence after resection occurs in up to 80% of patients in 5 years

The Milan Criteria

- No single tumor greater than 5 cm in diameter
- Multiple tumors: none greater than 3 cm in diameter
- Maximum of three tumors, none greater than 3 cm in diameter, adding up to maximum of 9 cm

The NYU Approach to HCC-1

- **Careful and regular Q 6 months screening of all patients at risk for HCC:**

All patients with cirrhosis even if they have cleared their HCV or HBV

All patients with HBV even if they don't have cirrhosis

All patients with NASH/NAFLD even if they don't have cirrhosis

All patients with PBC, Autoimmune Cirrhosis, Hemochromatosis

- All at risk patients from time of diagnosis, irrespective of age

NYU Approach to HCC-2

- **Approach to lesions picked up in screening**
- Lesions less than 1 cm-2 cm with arterial enhancement are screened Q 3months until they get to 2 cm
- At 2 cm they are listed for transplant under the Milan Criteria Program
- After documenting the 2 cm lesion they are treated with TACE and monitored Q 3 months thereafter while on the transplant waiting list
- If tumor recurs or progresses patient receives repeat TACE treatment as necessary

NYU Approach to HCC - 3

- **Lesions outside Milan Criteria:**

Lesions beyond the Milan Criteria in HBV patients without cirrhosis can be resected with radical resections

Large lesions in patients with cirrhosis are treated with radio active embolization (Yttrium 90)

Attempts are made to shrink the lesions down to Milan Criteria

Systemic Chemotherapy

- Novel agent that targets specific molecular mechanisms related to cancer growth and progression
- Multi kinase inhibitor
- Inhibits specifically serine-threonine kinases (Raf-1, B-Raf) and tyrosine kinase activity of VEGF receptors
- 30% improvement in survival
- Targeted therapy is aimed at specific targets which need to be identified by biomarkers and molecular profile

Coffee Intake Reduces Incidence of Liver Cancer and Liver Disease Death

- US Multiethnic Cohort Study (162,022 individuals) – Hawaii & California
- 18 year follow up
- Coffee drinkers vs. non drinkers
- 2-3 cups/day : 38% reduction in risk of HCC
- >4 cups/day : 41% reduction in risk of HCC
- 2-3 cups/day : 46% reduction in CLD death
- >4 cups /day : 71% reduction in CLD death
- Irrespective of ethnicity, sex, BMI, smoking status, alcohol intake, or diabetes
- Setiawan etal. Gasroenterology 2015, 148: 118-125