# Hepatocellular Carcinoma

**Lanla F. Conteh, MD, MPH, MBA**
*Associate Professor of Medicine*
*Division of Gastroenterology, Hepatology, and Nutrition*
*Department of Internal Medicine*
*The Ohio State University Wexner Medical Center*

MedNet21
Center for Continuing Medical Education

The Ohio State University
Wexner Medical Center

## Disclosure

- No financial or potential conflicts of interest to disclose

# Outline

- Epidemiology of Hepatocellular Carcinoma (HCC)
- Prevention and Screening for HCC
- Treatment of HCC

# Hepatocellular Carcinoma

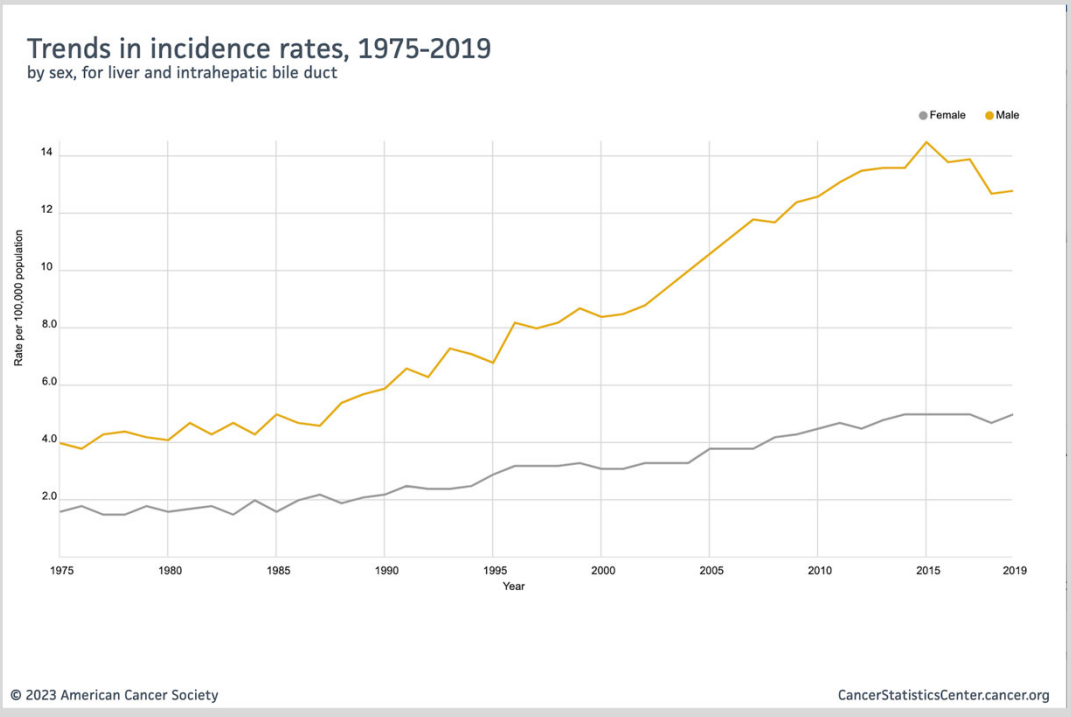
- Hepatocellular carcinoma (HCC) is the 6th most common malignancy worldwide
- It is the 3rd most common cause of cancer related mortality
- Responsible for 1 million deaths each year
- In the US, over the past 20 years, the incidence of HCC has increased
- In the US, rate of death from HCC increased by 43% between 2000 to 2016

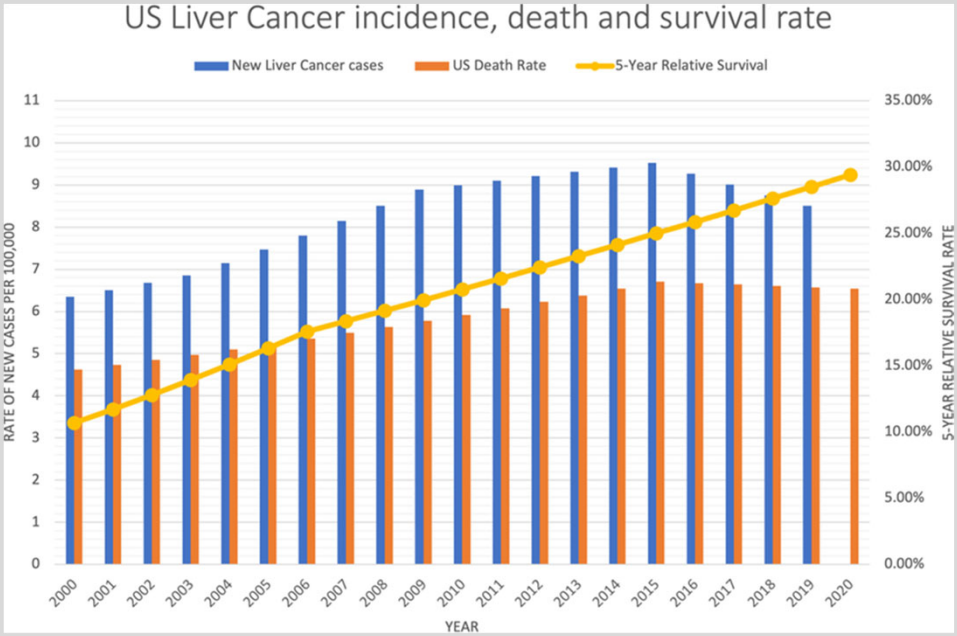
Forner et al., Lancet, 2012
CDC National Center for Health Statistics, 2018

# HCC

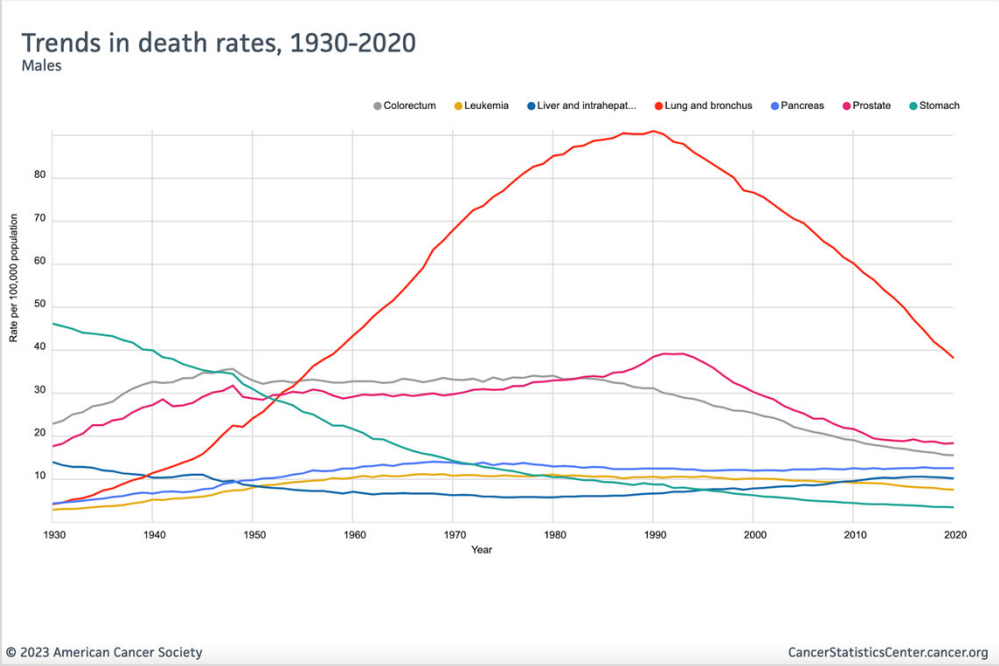
- Despite advances in screening and early detection, HCC still has a poor overall 5-year survival rate of 18-20%
- HCC is the second most lethal cancer, after pancreatic cancer
- Liver cancer incidence has tripled since 1980
- Liver cancer death rates have been increasing by an average of 3% a year over the last 10 years

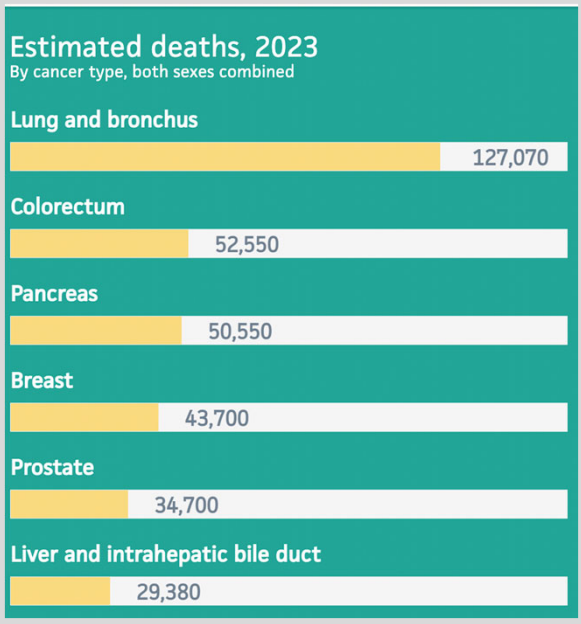
Jemal et al., J Natl Cancer Inst, 2017






SEER Database






American Cancer Society

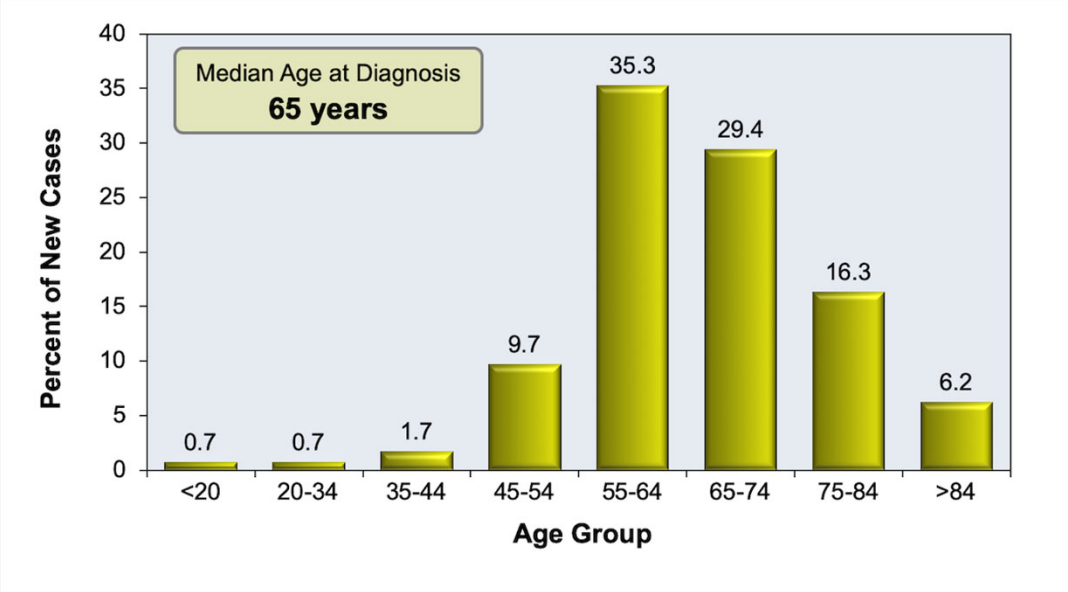
# Liver and intrahepatic bile duct

AT A GLANCE

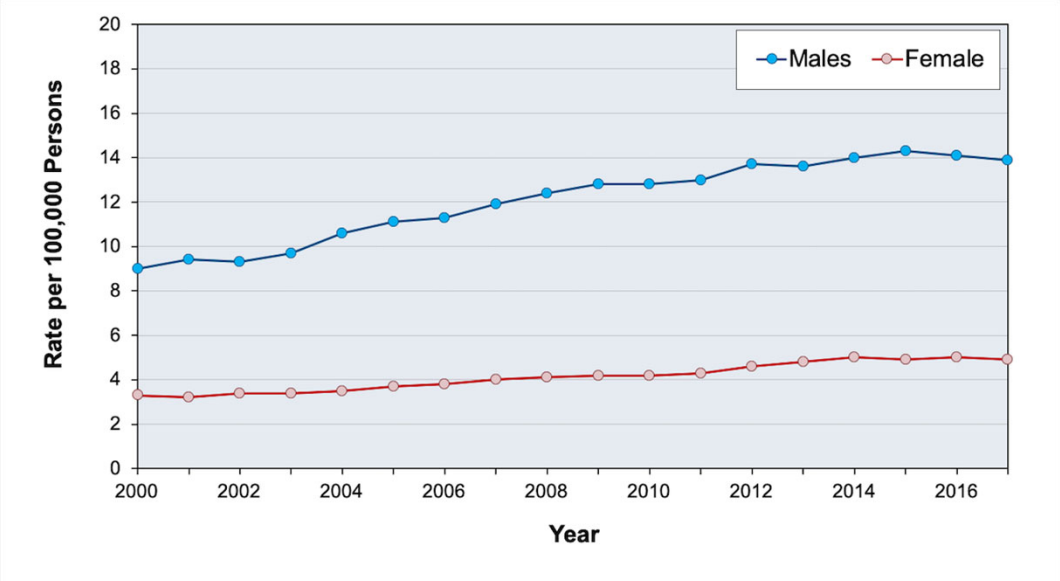
| Estimated new cases, 2023 | Estimated deaths, 2023 | Incidence rates, 2015-2019 | Death rates, 2016-2020 |
|---|---|---|---|
| 41,210 | 29,380 | 8.6 | 6.6 |
| | | Average annual rate per 100,000, age adjusted to the 2000 US standard population. | Average annual rate per 100,000, age adjusted to the 2000 US standard population |

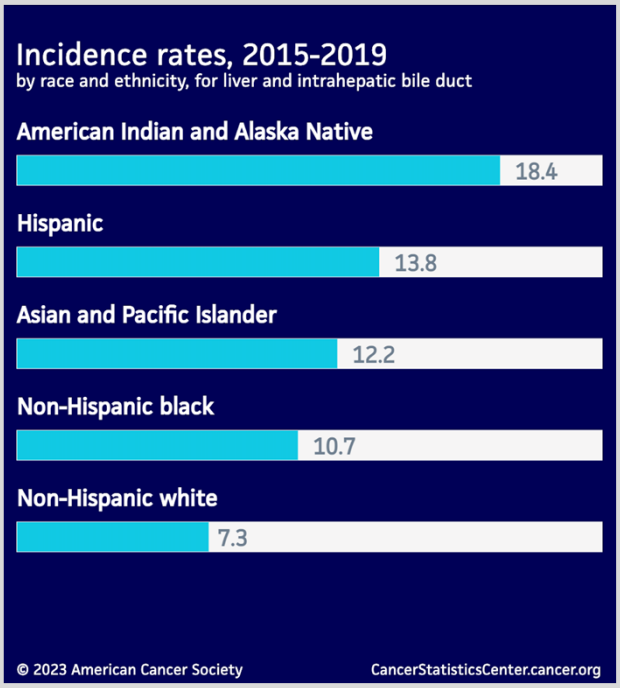
American Cancer Society

# Demographics




# Demographics




Incidence rates, 2015-2019
by race and ethnicity, for liver and intrahepatic bile duct
American Indian and Alaska Native
18.4
Hispanic
13.8
Asian and Pacific Islander
12.2
Non-Hispanic black
10.7
Non-Hispanic white
7.3
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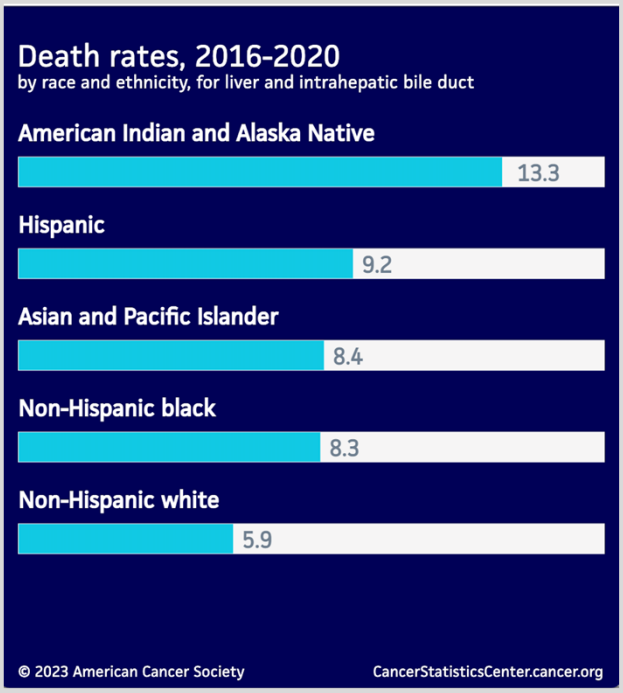
CancerStatisticsCenter.cancer.org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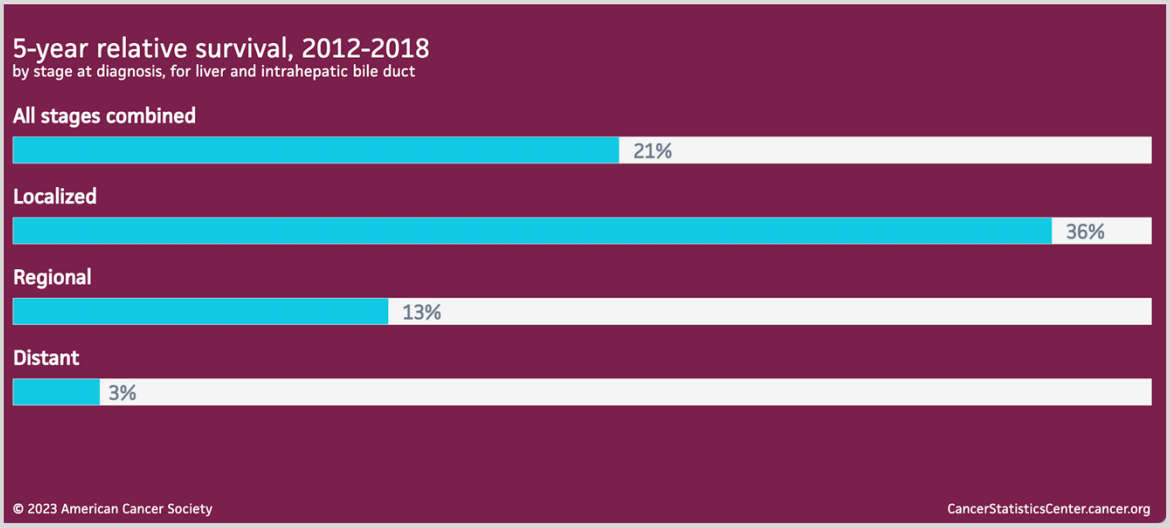
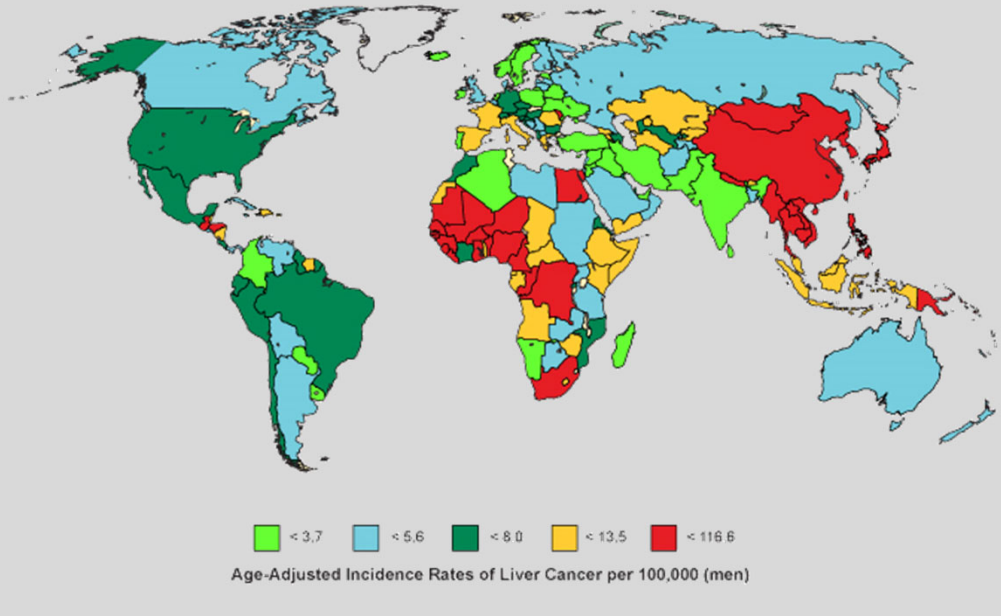
8.4
Non-Hispanic black
8.3
Non-Hispanic white
5.9
© 2023 American Cancer Society
CancerStatisticsCenter.cancer.org

# Survival




# HCC is a Global Problem



# Prevention

- Focus on preventing progression of chronic liver disease to cirrhosis
  - Hepatitis B vaccination *
  - Hepatitis C screening *
  - Non-Alcoholic Fatty Liver Disease (NAFLD)
  - Alcohol
  - Autoimmune Hepatitis (AIH)
  - Primary Biliary Cirrhosis (PBC)
  - Primary Sclerosing Cholangitis (PSC)

-Smoking and HIV also contribute to HCC development

# NAFLD

- Incidence is increasing worldwide
- In the US, HCC incidence due to NAFLD is expected to increase by 122% between 2016 and 2030

Estes et al., J Hepatol, 2018

# SCREENING

19

## AASLD: Screening Guidelines

- The recommended imaging screening interval is 6 months with ultrasound +/- AFP
- Screen patients with cirrhosis and those with chronic hepatitis B with or without cirrhosis
- AFP alone should not be used for screening

Heimbach, Hepatology 2017
Kim DK, Hepatology. 2007
Bruix H, Hepatology 2005

## Clinical Presentation

- Usually no additional symptoms other than those related to chronic liver disease
- High index of suspicion in patients with previously compensated cirrhosis who suddenly decompensate
- Alpha-fetoprotein (AFP) lacks adequate sensitivity and specificity for effective surveillance and for diagnosis
- Not all tumors secrete AFP

Lok et al, Gastroenterology 2010;138:493-502
Forner et al, Hepatology 2008;47:97-104

# Is Surveillance Effective?

- Repeated application of a screening test to an at-risk population
- Detect disease at an earlier stage when potential curative options are available and thus reducing disease-related mortality
- HCC readily lends itself to surveillance
- Randomized control trial in China
  - 18,816 patients with chronic HBV infections randomized to biannual surveillance with ultrasonography + serum α-fetoprotein (AFP) or no surveillance

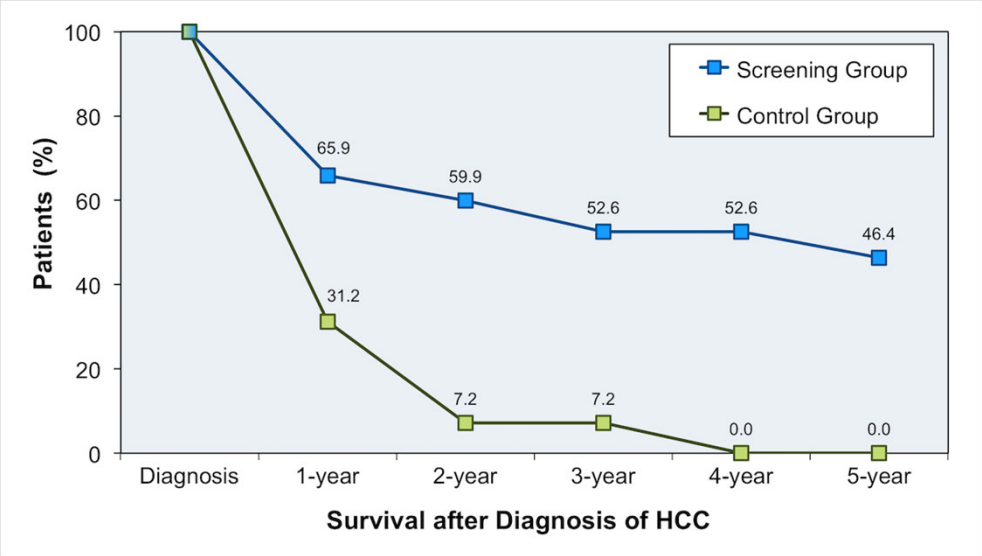
Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. *J Cancer Res Clin Oncol* 2004;**130**:417–422.
Trevisani F, Santi V, Gramenzi A, Di Nolfo MA, Del Poggio P, Benvegnù L, et al.;for Italian Liver Cancer Group. Surveillance for early diagnosis of hepatocellular carcinoma: is it effective in intermediate/advanced cirrhosis?*Am J Gastroenterol* 2007;**102**:2448–2457.

# Why Screen?

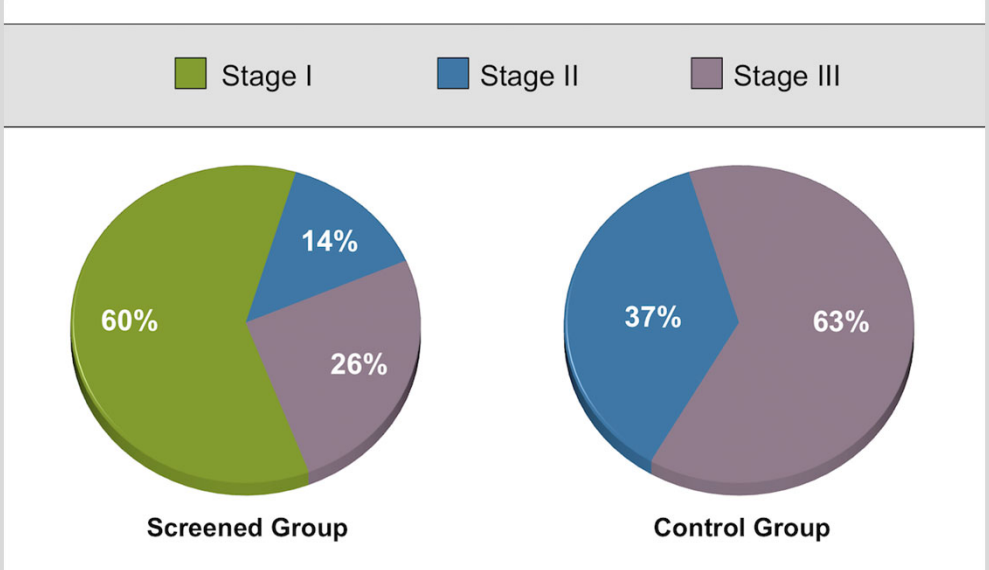
- Symptomatic advanced-stage HCC has dismal outcomes
  - 5-year life expectancy < 10%
- In comparison, HCC identified before the onset of symptoms is more amenable to treatment
  - 5-year survival rates greater than 50% for both resection and liver transplantation

Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology* 2011;**53**:1020–1022

# Screening Decreases Mortality




Zhang et al., J Cancer Res Clin Oncol. 2004




Zhang et al., J Cancer Res Clin Oncol. 2004

## Who to Screen?

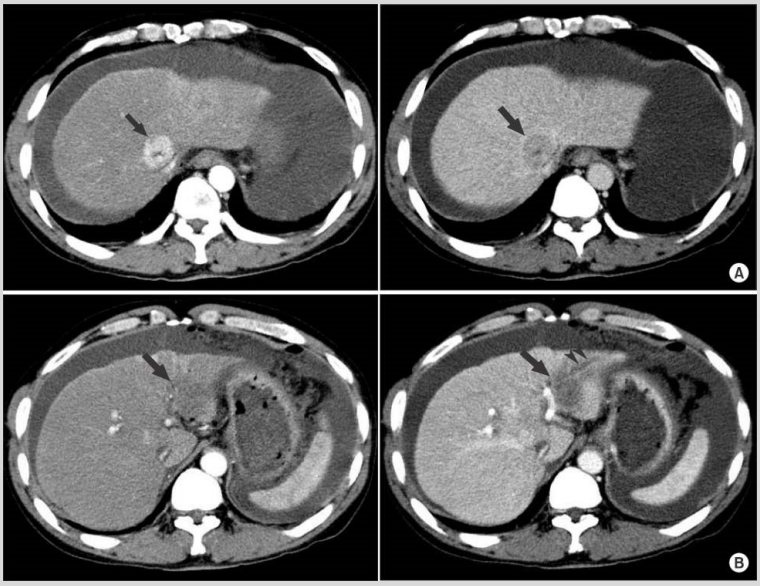
- Asian men hepatitis B carriers > 40 years
- Asian women hepatitis B carriers > 50 years
- Hepatitis B carrier with family history of HCC
- Patients with HBV and cirrhosis
- Africans and North American Blacks with hepatitis B
- All patients with cirrhosis

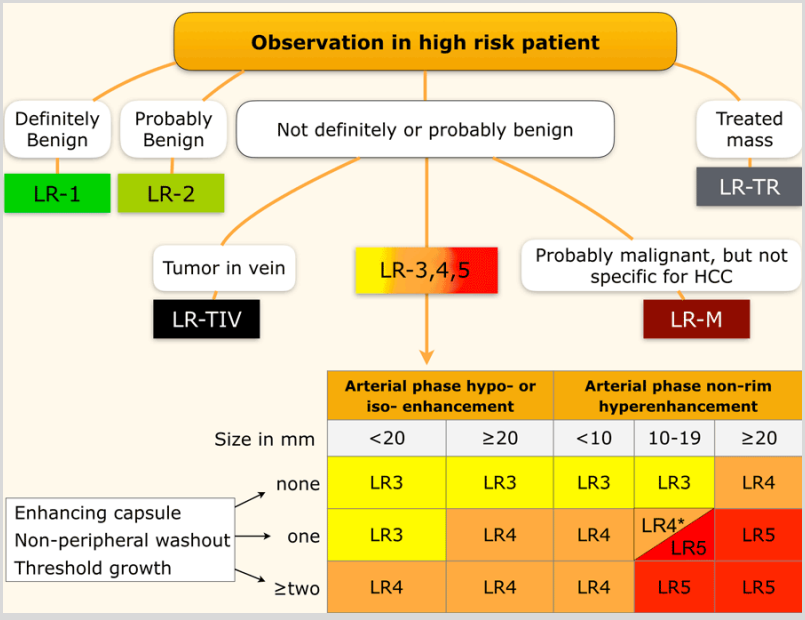
## DIAGNOSIS

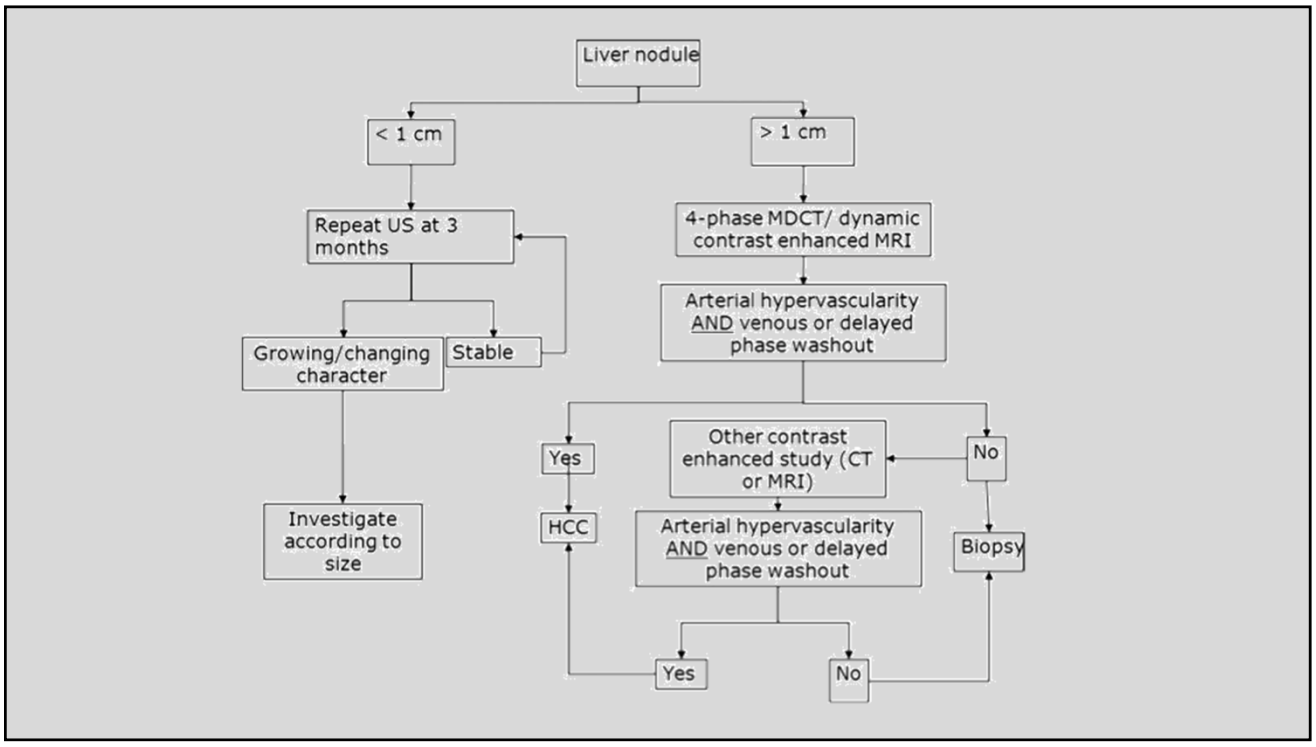
# Diagnosis

- Diagnosis should be based on imaging techniques and/or biopsy
- Multiphase Imaging: intense arterial uptake followed by "washout" of contrast in the venous-delayed phases

- Size > 1 cm
- Features:
  - Arterial enhancement
  - Less bright in venous and delayed phases
  - Pseudocapsule
- Biopsy rarely indicated


A
B


Observation in high risk patient
Definitely Benign
Probably Benign
Not definitely or probably benign
Treated mass
LR-1
LR-2
LR-TR
Tumor in vein
LR-3,4,5
Probably malignant, but not specific for HCC
LR-TIV
LR-M
Arterial phase hypo- or iso- enhancement
Arterial phase non-rim hyperenhancement
Size in mm
<20
≥20
<10
10-19
≥20
Enhancing capsule
Non-peripheral washout
Threshold growth
none
one
≥two
LR3
LR3
LR3
LR3
LR4
LR3
LR4
LR4
LR4* LR5
LR5
LR4
LR4
LR4
LR5
LR5


Liver nodule
< 1 cm
> 1 cm
Repeat US at 3 months
4-phase MDCT/ dynamic contrast enhanced MRI
Growing/changing character
Stable
Arterial hypervascularity AND venous or delayed phase washout
Investigate according to size
Yes
Other contrast enhanced study (CT or MRI)
No
HCC
Arterial hypervascularity AND venous or delayed phase washout
Biopsy
Yes
No

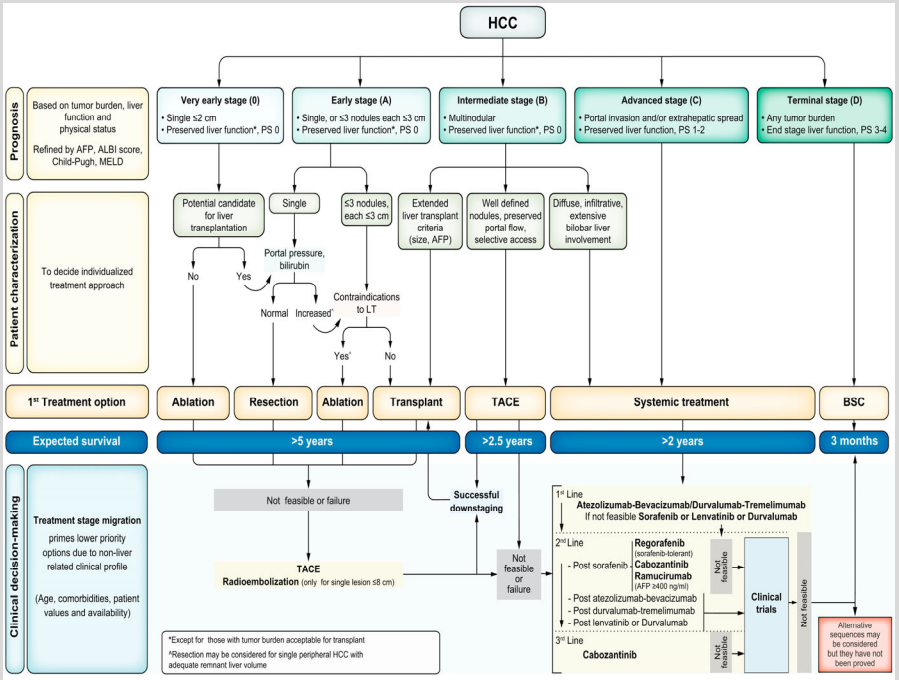
# TREATMENT

# Barcelona Clinic Liver Cancer (BCLC)

- Most widely used algorithm endorsed in clinical practice guidelines since 1999
- Used as the acceptable benchmark in clinical trial design
- Classifies patients into 5 stages
- Treatment recommends per stage
- Tumor burden quantified by number and size of nodules, presence or vascular invasion, extrahepatic spread
- Uses Child-Turcotte-Pugh for assessment of hepatic synthetic dysfunction

Llovet et al, Semin Liver Dis, 1999
EASL, J Hepatol, 2018
Marrero et al, Hepatology, 2018

## BCLC strategy for prognosis prediction and treatment recommendation The 2022 update




*Journal of Hepatology* 2022 76681-693DOI: (10.1016/j.jhep.2021.11.018)

## Liver Directed Therapy

- Liver Transplantation
- Resection/Hepatectomy
- Percutaneous Ablation (RFA)
- Transarterial Chemoembolization (TACE)
- Radioembolization: $Yttrium_{90}$ (TARE)
- Stereotactic Body Radiation Therapy (SBRT)

## Determining Best Therapy

- Underlying liver dysfunction/hepatic reserve
  - MELD Score/Child-Turcotte-Pugh score
- Stage of disease at presentation
  - Tumor burden, size, location
- Extrahepatic spread, portal vein invasion
- Co-morbid conditions

# Surgical Resection

- Potentially curative in patients with adequate liver functional reserve

- Ideal patient
  - Solitary HCC confined to the liver
  - No radiographic evidence of invasion of the hepatic vasculature
  - No evidence of portal hypertension
  - Well-preserved hepatic function
  - Platelets > 100-150
  - No cirrhosis or Child-Pugh class A cirrhosis

# Assessing Surgical Risk with Cirrhosis

- CPT useful in assessing global liver function, however, significant heterogeneity among Child-Pugh class A patients
- MELD can help select ideal candidates
- Patients with a preoperative MELD >10 have 90-day mortality rates approaching 15% to 20%
- Noninvasive, indirect measures of portal hypertension
  - Platelet count of ≤100 used as surrogate for significant portal hypertension
- Tumor-specific factors in determining the suitability of hepatectomy for HCC include tumor size, tumor number, and presence of vascular invasion

Maithel SK, Kneuertz PJ, Kooby DA, Scoggins CR, Weber SM, Martin RC 2nd, et al. Importance of low preoperative platelet count in selecting patients for resection of hepatocellular carcinoma: a multi-institutional analysis. *J Am Coll Surg* 2011;**212**:638-648;
Pawlik TM, Poon RT, Abdalla EK, Zorzi D, Ikai I, Curley SA, et al. Critical appraisal of the clinical and pathologic predictors of survival after resection of large hepatocellular carcinoma. *Arch Surg* 2005;**140**:450-457; discussion 457–458.

## Goals of Locoregional Therapy

- Prolong survival by inducing tumor cell death and necrosis
- Slow the progression of tumors to reduce pre-transplantation dropout rates
  - Keep Milan within Milan
- Downstage tumors to meet transplantability criteria

## Percutaneous Ablation

- Destruction of tumor cells achieved by injection of chemical substances (ethanol, acetic acid, or boiling saline) or by modifying the temperature (radiofrequency, microwave, laser, cryotherapy)
- Usually performed under ultrasound guidance

# Radiofrequency Ablation (RFA)

- Needle conducts a high-energy electrical current into the tumor
- Best outcomes are in patients with a single tumor <4 cm in diameter
- Well validated and utilized by many centers
- Efficacy assessed by multiphase imaging 1 month after therapy

Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, Christensen E, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol 2001;35:421-430.

# Transarterial Chemoembolization (TACE)

- HCC gets majority blood supply from hepatic artery
- Used most often for the treatment of large unresectable HCCs
- Also used commonly as "bridging therapy" prior to transplant
- Agents: Doxorubicin, Mitomycin C, Cisplatin

## TACE: Contraindications

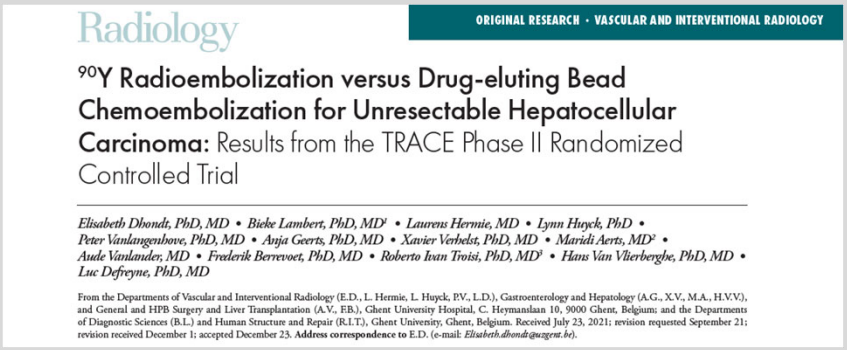
- Absolute contraindications
  - Absence of hepatopetal blood flow (portal vein thrombosis), biliary obstruction
- Relative contraindications:
  - Serum bilirubin >3 mg/dL
  - Tumor burden involving >50% of the liver
  - Cardiac or renal insufficiency

## Radioembolization: Y90/TARE

- Intra-arterial injection of small microspheres loaded with the radionuclide yttrium-90 ($Y_{90}$)
- Delivery of the microspheres into the feeding vessels of the tumor leads to their settling in the tumor itself without affecting the vasculature
- Beta-emitting particle that has a localized radius of radiation delivery (2.5–11.0 mm)
- 1/2-life 60 hours

# $Y_{90}$

- Advantages:
  - Low toxicity
  - Potential to treat patients with significant tumor burden
  - Relatively limited side effects
  - Has been used with PVT
- Disadvantages:
  - High cost
  - The costs approached $17,000 for TACE versus $31,000 or $48,000 for unilobar or bilobar radioembolization
  - Requires at least two abdominal angiographies
  - Certain anatomical constraints (eg, pass-through of the radioactive material to the lung in some patients with shunting)



Radiology

ORIGINAL RESEARCH • VASCULAR AND INTERVENTIONAL RADIOLOGY

**$^{90}$Y Radioembolization versus Drug-eluting Bead Chemoembolization for Unresectable Hepatocellular Carcinoma:** Results from the TRACE Phase II Randomized Controlled Trial

*Elisabeth Dhondt, PhD, MD • Bieke Lambert, PhD, MD[1] • Laurens Hermie, MD • Lynn Huyck, PhD • Peter Vanlangenhove, PhD, MD • Anja Geerts, PhD, MD • Xavier Verhelst, PhD, MD • Maridi Aerts, MD[2] • Aude Vanlander, MD • Frederik Berrevoet, PhD, MD • Roberto Ivan Troisi, PhD, MD[3] • Hans Van Vlierberghe, PhD, MD • Luc Defreyne, PhD, MD*

From the Departments of Vascular and Interventional Radiology (E.D., L. Hermie, L. Huyck, P.V., L.D.), Gastroenterology and Hepatology (A.G., X.V., M.A., H.V.V.), and General and HPB Surgery and Liver Transplantation (A.V., F.B.), Ghent University Hospital, C. Heymanslaan 10, 9000 Ghent, Belgium; and the Departments of Diagnostic Sciences (B.L.) and Human Structure and Repair (R.I.T.), Ghent University, Ghent, Belgium. Received July 23, 2021; revision requested September 21; revision received December 1; accepted December 23. **Address correspondence to** E.D. (e-mail: *Elisabeth.dhondt@uzgent.be*).

-single center prospective randomized controlled trial: TARE vs TACE

-BCLC stage B (intermediate) and stage A (early) not eligible for resection, ablation, or transplant HCC

-70 participants received treatment and followed

Radiology, Volume: 303, Pages: 699-710, 2022

# TACE vs. TARE (Y90)

- Time to tumor progression
  - 17.1 months (TARE) vs 9.5 months (DEB-TACE); P = .002
- Overall survival
  - 30.2 months (TARE) vs 15.6 months (DEB-TACE); P = .006

Radiology, Volume: 303, Pages: 699-710, 2022

# Locoregional Therapy Summary

**Table 1.** Summary of Locoregional Therapy Options for Hepatocellular Carcinoma.

| Modality | Techniques | Clinical Utility | Risks | Benefits |
|---|---|---|---|---|
| TAE | Particulate or liquid embolic agents | Disease control (BCLC B) and bridging/downstaging to transplant (BCLC A, B). | PES, liver failure, liver abscess/biloma | Improves OS vs. best supportive care. Avoids chemotherapy toxicity. Less expensive than TACE. |
| TACE | Conventional emulsified chemotherapeutic agent (c-TACE) or drug-eluting beads (DEB-TACE) | Same as TAE. Can combine with portal vein embolization before resection. | PES, liver failure, liver abscess/biloma | Improves OS vs. best supportive care. Simultaneous embolic and chemotherapeutic effects. |
| TARE | Yttrium-90 radioisotope loaded onto microspheres | Same as TAE/TACE. RS for nonsurgical early stage patients (BCLC 0, A). Can also be used in portal vein thrombosis. | RILD, radiation-induced pneumonitis, PES, liver failure, liver abscess/biloma | Higher quality of life/TTP vs. TACE. RS outcomes comparable to curative-intent treatments (e.g., resection and ablation) at 5 years |
| Ablation | Microwaves, radiofrequency alternating current, laser, cooling | Early stage HCC < 2–3 cm in non-surgical candidates (BCLC 0, A). Improved outcomes for tumors 3–5 cm when combined with TACE. | PAS, bleeding, adjacent organ injury | Similar outcomes as resection for tumors < 3 cm. |

PES—postembolization syndrome. PAS—postablation syndrome. OS—overall survival. RILD—radiation-induced liver disease. CP—Childs-Pugh class. RS—radiation segmentectomy. TTP—time to progression.

Cancers, Volume: 12, July 2020

ORIGINAL ARTICLE

Liver Transplantation for the Treatment of Small Hepatocellular Carcinomas in Patients with Cirrhosis

Vincenzo Mazzaferro, M.D., Enrico Regalia, M.D., Roberto Doci, M.D., Salvatore Andreola, M.D., Andrea Pulvirenti, M.D., Federico Bozzetti, M.D., Fabrizio Montalto, M.D., Mario Ammatuna, M.D., Alberto Morabito, Ph.D., and Leandro Gennari, M.D., Ph.D.

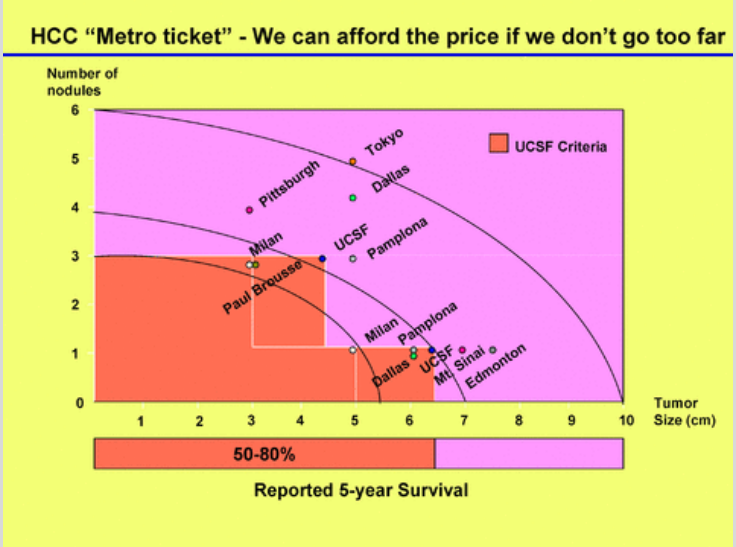
- Inclusion criteria: single lesion ≤ 5 cm, 2-3 lesions each ≤ 3 cm, no evidence of extra-hepatic disease
- Diagnosis: biopsy or AFP > 300 ng/ml
- 48 transplants during study period

## Total Hepatectomy with Liver Transplantation for Early-Stage HCC

- Following liver transplantation
  - Actuarial survival at 4 yrs: 75%
  - Recurrence-free survival at 4 years: 83%

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

Liver Transplantation for Hepatocellular Carcinoma: Beyond the Milan Criteria




American Journal of Transplantation, Volume: 8, Issue: 10, Pages: 1982-1989, First published: 16 September 2008

# MELD Exception Points

- To give patients with Stage II HCC equal opportunity for transplantation
- Initially given additional points aimed at matching the risk of death in endstage cirrhosis
- Too high a priority was given to HCC patients - unfair to patients without cancer
- Has undergone several iterations
- Most recent: Can only start accumulating exception points after being on the waitlist for 6 months. Awarded additional points at 6 months based on regional median MELD score
- Allows time to assess tumor biology

Bruix and Sherman, Hepatology, July 2010
Freeman RB, Wiesner RH, Edwards E, Harper A, Merion R, Wolfe R. Results of the first year of the new liver allocation plan. Liver Transpl 2004;10:7–15

## MELD Exception Points

- US => Milan Criteria
- T2 Lesions to qualify for MELD exception points:
  - AFP ≤ 1000 ng/ml
  - One lesion 2-5 cm
  - Two or three lesions each 1-3 cm
  - NO vascular or extrahepatic invasion

## Liver Transplantation

- Liver Transplantation is now accepted as the best curative therapy for Stage II HCC
- Provides complete oncologic resection and correction of the underlying liver disease

# Liver Transplantation

- Advantages
  - Definitive management of not only HCC but also underlying liver disease
- Disadvantages
  - Long waiting time for donor organs
  - Lifelong immunosuppression

# Liver Transplantation

- Use of marginal grafts and living donation have increased organ pool
- Significant gap remains between available donor and patient awaiting transplant

## Systemic Therapy

- Advanced, unresectable HCC
- NOT amenable to curative or locoregional therapy
- Adequate performance status

## Systemic Therapy

- HCC considered to be a relatively chemotherapy-refractory tumor
- High rate of expression of drug resistance genes
- Challenging to gauge benefit from chemotherapy in patients with advanced HCC
- Survival is most often determined by degree of hepatic dysfunction
- Systemic chemotherapy is usually not well tolerated by patients with significant underlying hepatic dysfunction

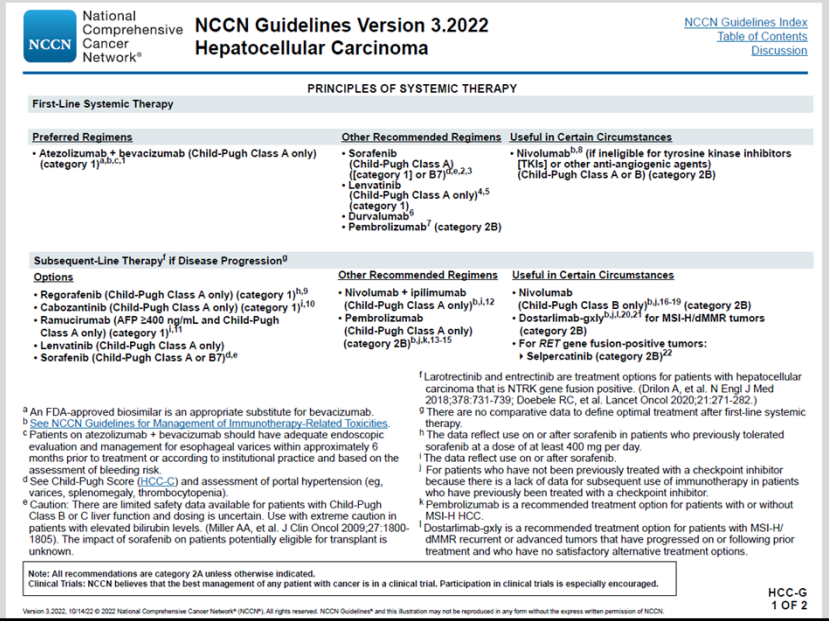
# SHARP TRIAL

- Placebo-controlled, phase III trial
- Patients with Child-Pugh A and HCC compatible with stage C disease by the BCLC system
- Median survival nearly 3 months compared to placebo 10.7 months vs. 7.9 ($p<0.001$)
- Largely stabilized the tumor by delaying tumor progression → mainly acts as a cytostatic agent
- Led to approval by regulatory agencies in 2007 (USA and EU)

Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;**359**:378–390

# Hepatocellular Carcinoma

## Systemic Therapy



National Comprehensive Cancer Network®

**NCCN Guidelines Version 3.2022**
**Hepatocellular Carcinoma**

NCCN Guidelines Index
Table of Contents
Discussion

**PRINCIPLES OF SYSTEMIC THERAPY**

**First-Line Systemic Therapy**

| Preferred Regimens | Other Recommended Regimens | Useful in Certain Circumstances |
|---|---|---|
| • Atezolizumab + bevacizumab (Child-Pugh Class A only) (category 1)[a,b,c,1] | • Sorafenib (Child-Pugh Class A) ([category 1] or B7)[d,e,2,3]<br>• Lenvatinib (Child-Pugh Class A only)[4,5] (category 1)<br>• Durvalumab[6]<br>• Pembrolizumab[7] (category 2B) | • Nivolumab[b,8] (if ineligible for tyrosine kinase inhibitors [TKIs] or other anti-angiogenic agents) (Child-Pugh Class A or B) (category 2B) |

**Subsequent-Line Therapy[f] if Disease Progression[g]**

| Options | Other Recommended Regimens | Useful in Certain Circumstances |
|---|---|---|
| • Regorafenib (Child-Pugh Class A only) (category 1)[h,9]<br>• Cabozantinib (Child-Pugh Class A only) (category 1)[i,10]<br>• Ramucirumab (AFP ≥400 ng/mL and Child-Pugh Class A only) (category 1)[i,11]<br>• Lenvatinib (Child-Pugh Class A only)<br>• Sorafenib (Child-Pugh Class A or B7)[d,e] | • Nivolumab + ipilimumab (Child-Pugh Class A only)[b,j,12]<br>• Pembrolizumab (Child-Pugh Class A only) (category 2B)[b,j,k,13-15] | • Nivolumab (Child-Pugh Class B only)[b,j,16-19] (category 2B)<br>• Dostarlimab-gxly[b,j,l,20,21] for MSI-H/dMMR tumors (category 2B)<br>• For *RET* gene fusion-positive tumors:<br>‣ Selpercatinib (category 2B)[22] |

[a] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[b] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[c] Patients on atezolizumab + bevacizumab should have adequate endoscopic evaluation and management for esophageal varices within approximately 6 months prior to treatment or according to institutional practice and based on the assessment of bleeding risk.
[d] See Child-Pugh Score (HCC-C) and assessment of portal hypertension (eg, varices, splenomegaly, thrombocytopenia).
[e] Caution: There are limited safety data available for patients with Child-Pugh Class B or C liver function and dosing is uncertain. Use with extreme caution in patients with elevated bilirubin levels. (Miller AA, et al. J Clin Oncol 2009;27:1800-1805). The impact of sorafenib on patients potentially eligible for transplant is unknown.
[f] Larotrectinib and entrectinib are treatment options for patients with hepatocellular carcinoma that is NTRK gene fusion positive. (Drilon A, et al. N Engl J Med 2018;378:731-739; Doebele RC, et al. Lancet Oncol 2020;21:271-282.)
[g] There are no comparative data to define optimal treatment after first-line systemic therapy.
[h] The data reflect use on or after sorafenib in patients who previously tolerated sorafenib at a dose of at least 400 mg per day.
[i] The data reflect use on or after sorafenib.
[j] For patients who have not been previously treated with a checkpoint inhibitor because there is a lack of data for subsequent use of immunotherapy in patients who have previously been treated with a checkpoint inhibitor.
[k] Pembrolizumab is a recommended treatment option for patients with or without MSI-H HCC.
[l] Dostarlimab-gxly is a recommended treatment option for patients with MSI-H/dMMR recurrent or advanced tumors that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.

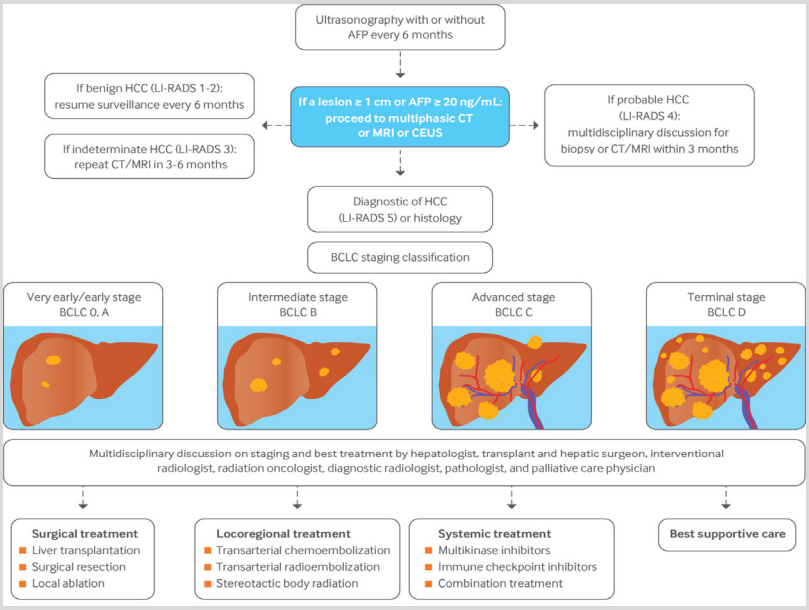
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

HCC-G
1 OF 2

# Systemic Therapy

- Atezolizumab + bevacizumab **OR** Tremelimumab + durvalumab
  - Child A, no anticoagulation, no recurrence after liver transplant
- Tyrosine-Kinase inhibitors: Lenvatinib or sorafenib
  - Child A or B, post-transplant
- Immunotherapy: immune checkpoint inhibitors
  - Contraindicated post-transplant

## Summary

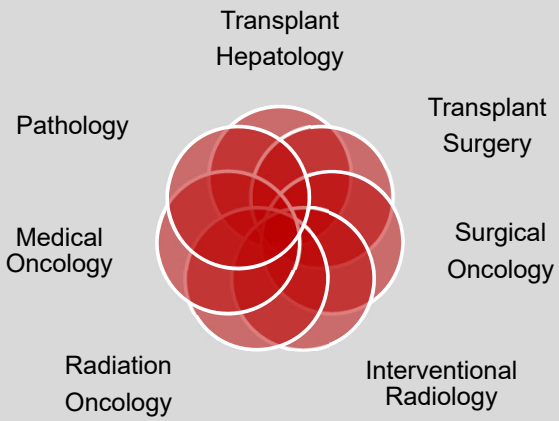



Dr. Keith Siau

# Conclusion

- Incidence and death rate of HCC is increasing
- Screening is vital
- HCC is a complex disease for which multidisciplinary care is warranted
- For patients with cirrhosis and portal hypertension, mainstay of therapy should be transplant if appropriate
- LRT can be used to bridge patients to transplant

# Multidisciplinary Team




THANK YOU
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The Ohio State University
Wexner Medical Center