Improved Liver Cancer Surveillance with Serum Biomarkers AFP-L3 & DCP

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This webinar will:

- Review the epidemiology of HCC
- Summarize staging and curative treatment options
- Describe in detail the available biomarkers for early detection of HCC and their application

Learning Objectives

- Identify patients at risk for HCC
- Understand the importance of early detection of HCC
- Be able to describe and apply the available serum biomarkers for HCC

Pre-Questions

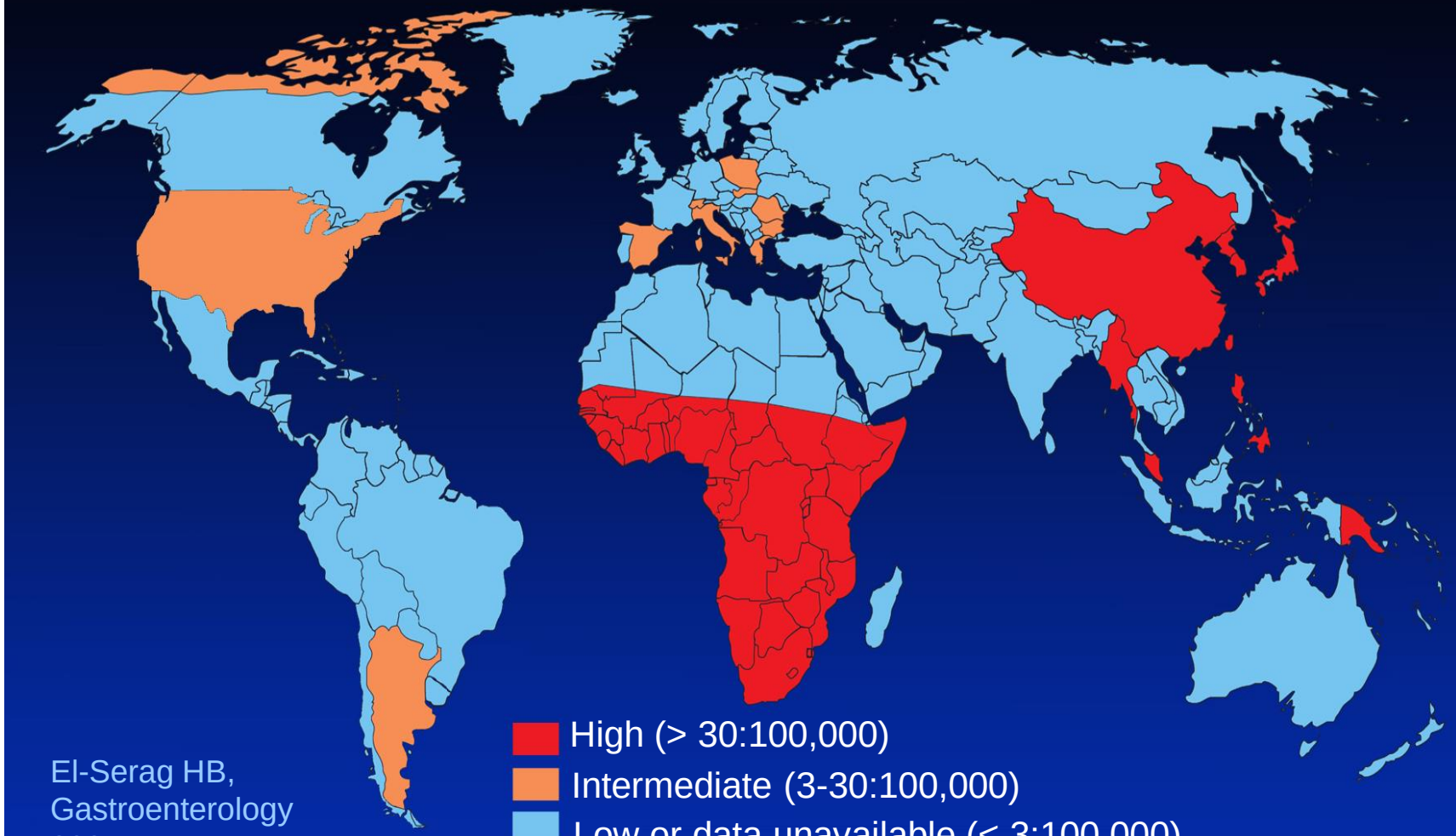
- How does efficacy vs effectiveness apply to HCC screening?
- What processes could laboratories implement to aid early diagnosis of HCC?
- What role do biomarkers play in determining response to treatment and/or recurrence of HCC?

HCC Epidemiology

- 3rd leading cause of cancer mortality worldwide
- 10th leading in US
- Almost exclusively presents in patients with chronic liver disease

HCC Epidemiology

Worldwide Incidence of Hepatocellular Carcinoma



El-Serag HB, Gastroenterology 2004

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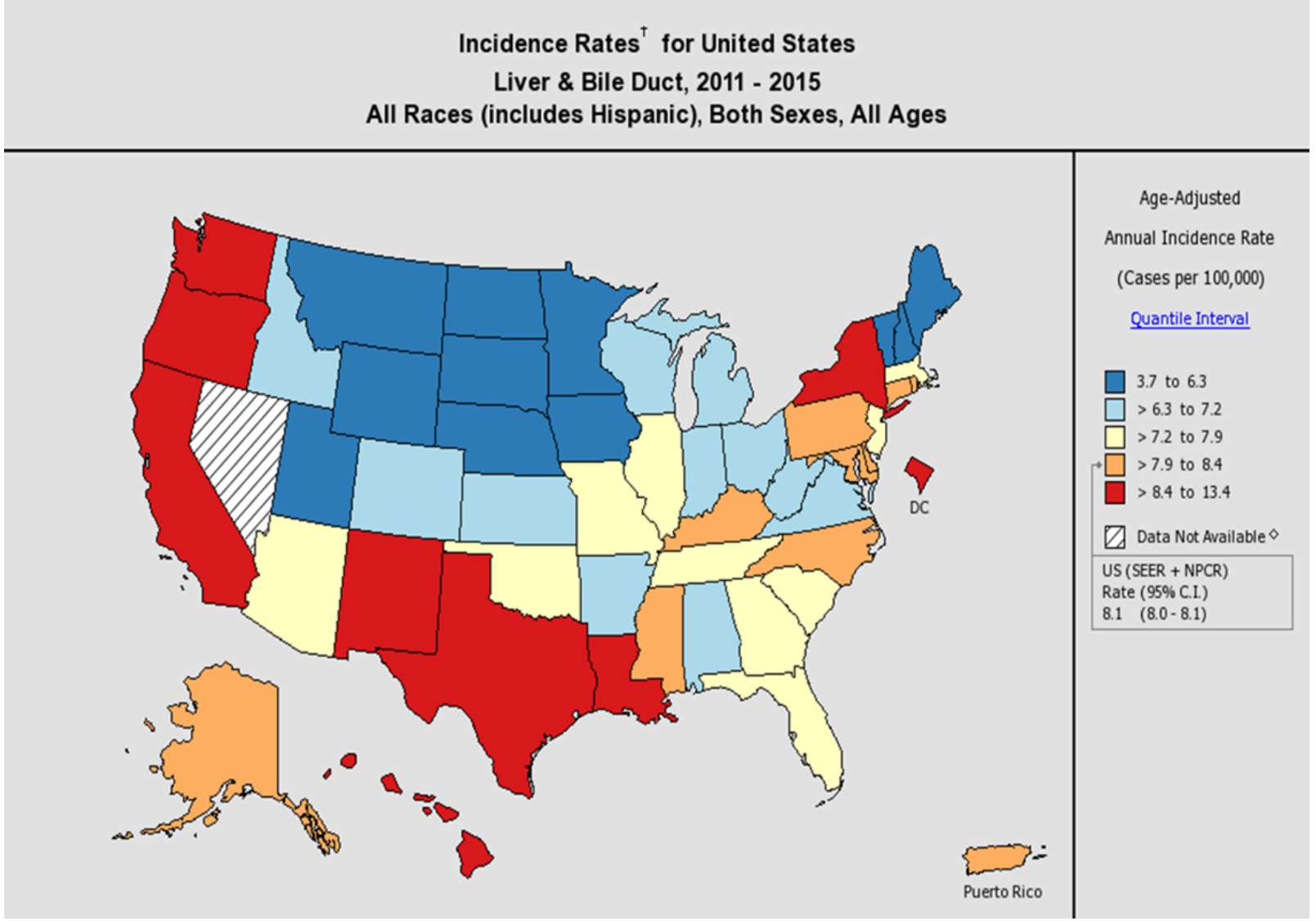
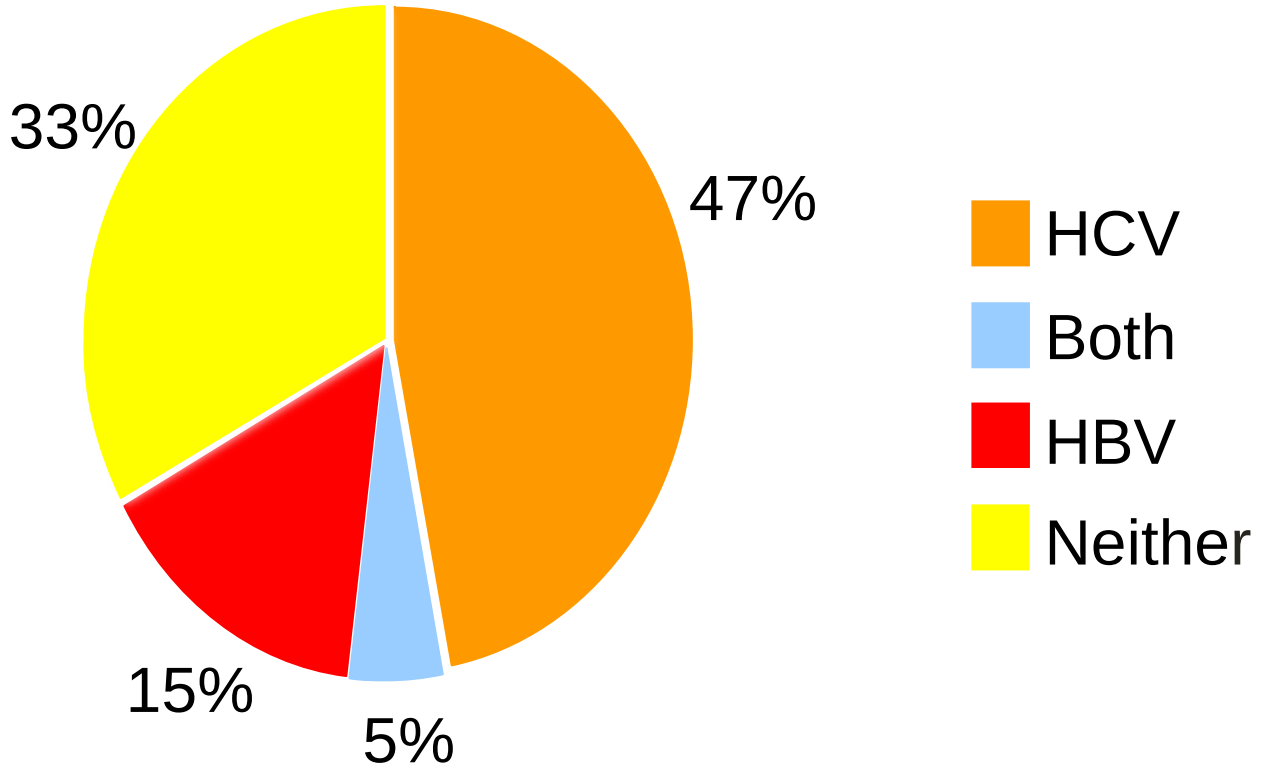
Incidence by State



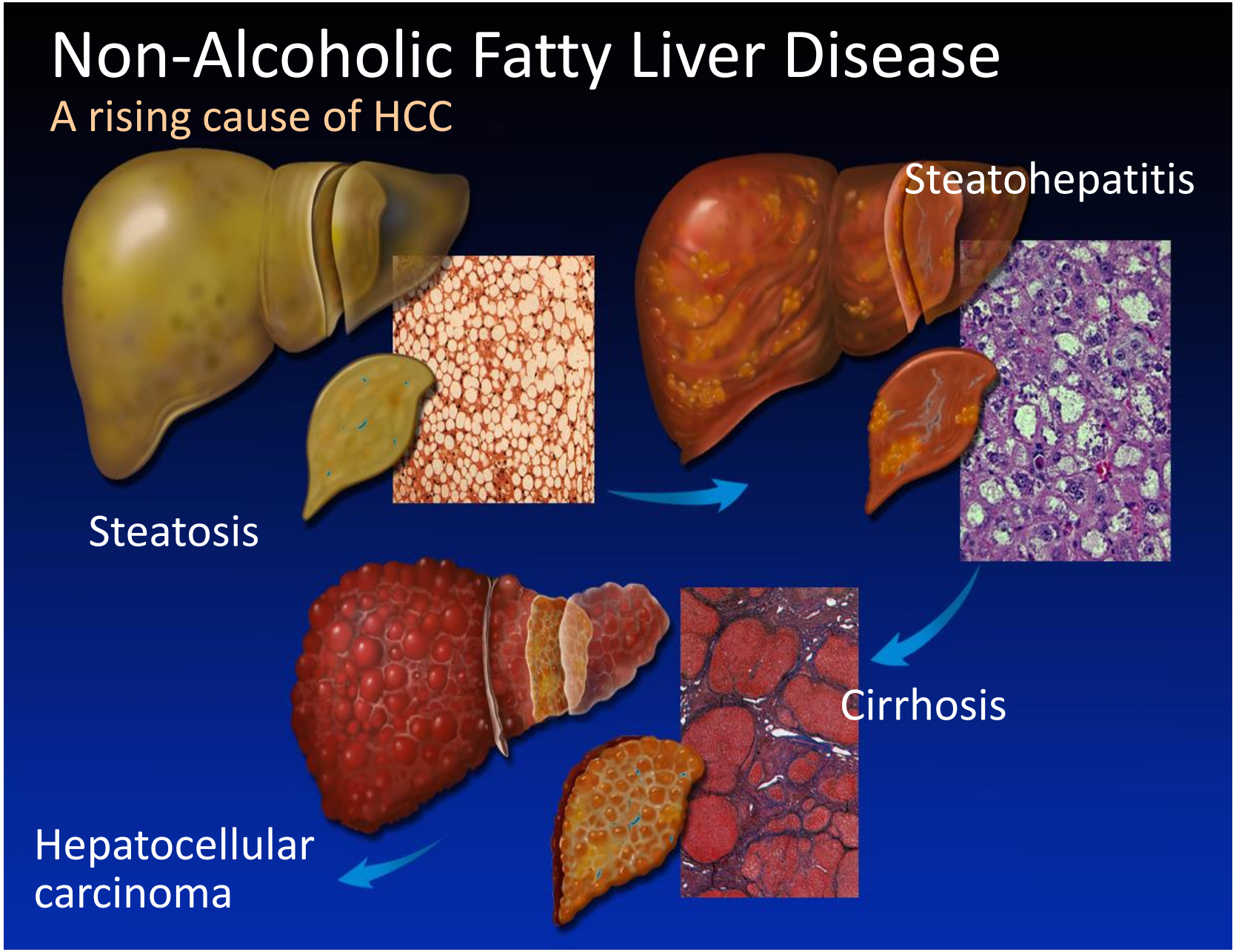
HCC Epidemiology

Viral Hepatitis causes most HCC in the United States



Non-Alcoholic Fatty Liver Disease

A rising cause of HCC



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Epidemiology Summary

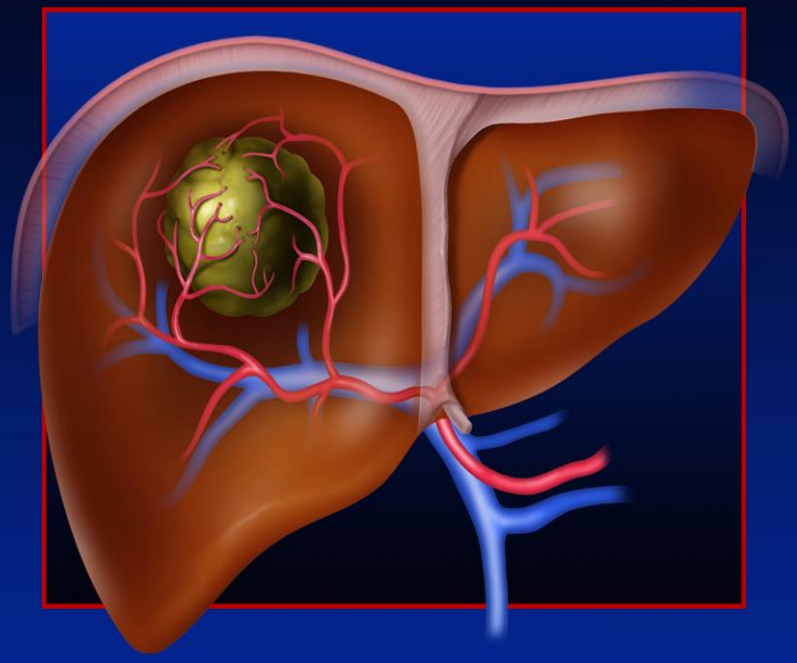
- HCC is more common than people realize
- Most HCC occurs in patients with underlying liver disease

Diagnosis and Management Overview

HCC Diagnosis

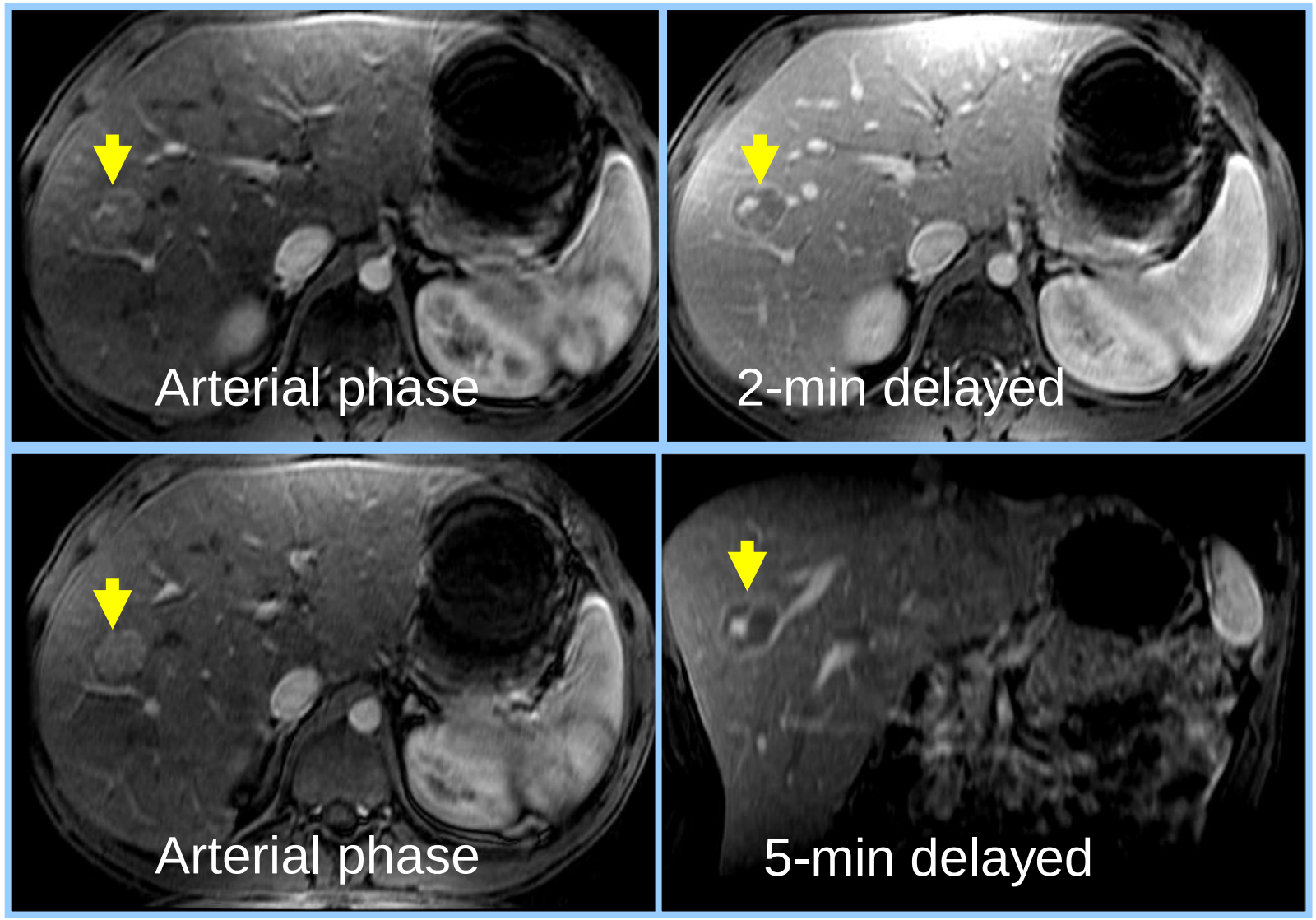
Dual Blood Supply of Liver

- Vascular supply of HCC arises from the hepatic artery through neovascularization.
- Triple phase contrast imaging is key



Yu JS, et al, Am J Roentgenol 1999

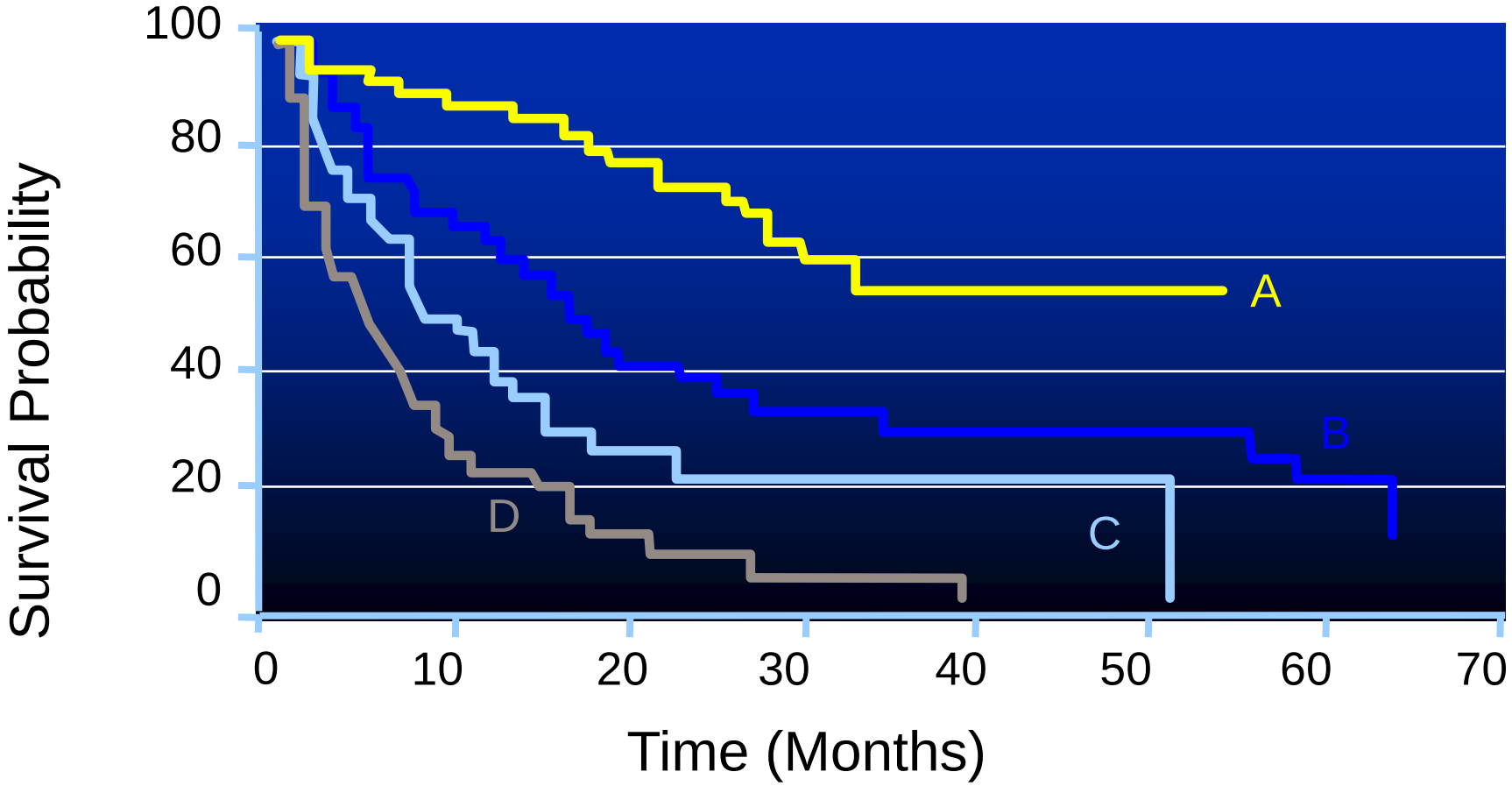
Triple Phase Imaging in HCC



LI-RADS

- Classification system for imaging diagnosis of HCC:
  - 1,2: not HCC
  - 3: indeterminate
  - 4: suspicious
  - 5: diagnostic

Prognosis by BCLC Stage



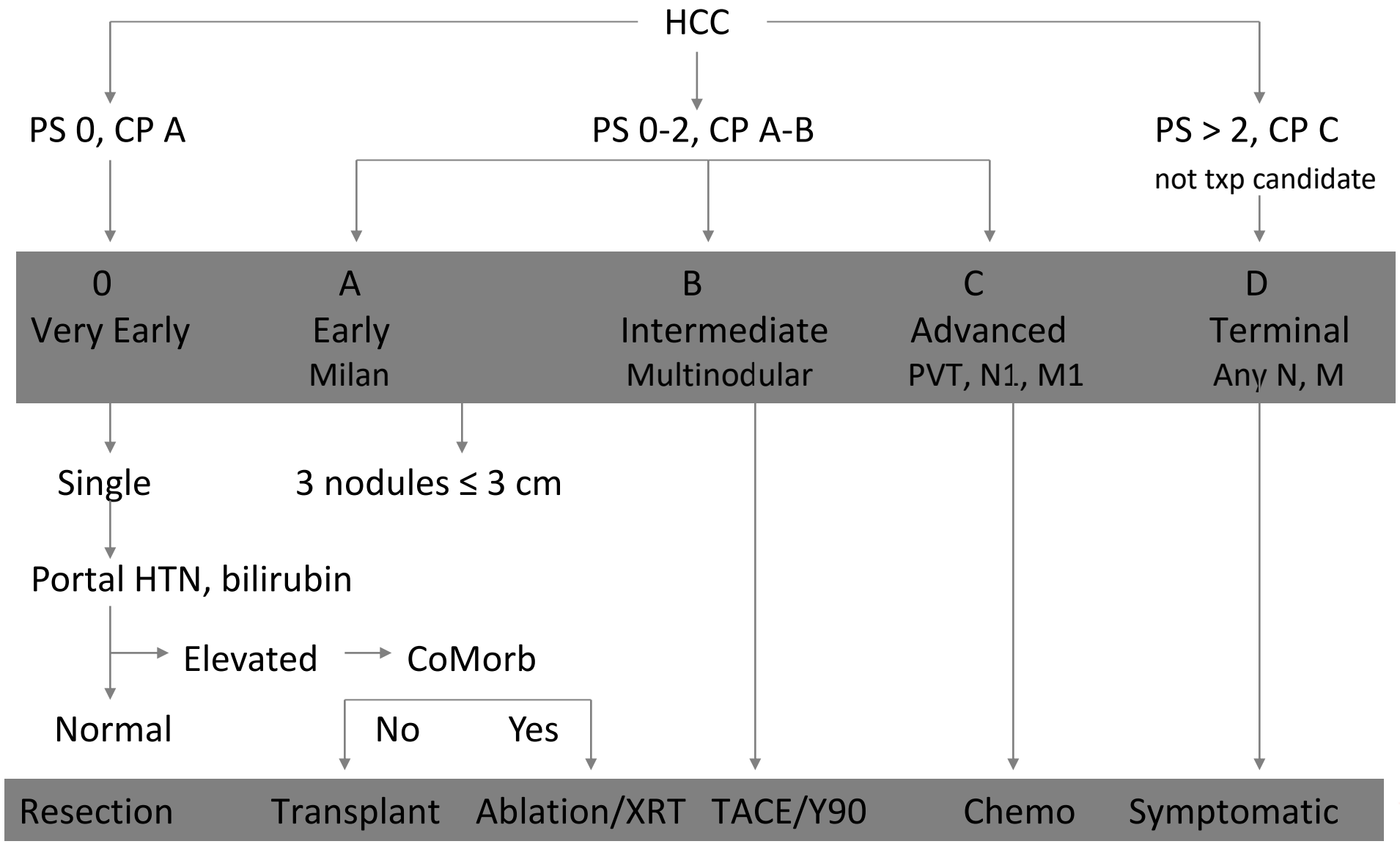
Marrero JA, et al, Hepatology 2005

BCLC Stage A

Early HCC (potential cure)

- Resection
  - 1 tumor <5 cm, no portal hypertension
- Ablation
  - 1 tumor <3 cm
- Transplant
  - Milan criteria: 1 tumor 2-5 cm, 3 <3 cm, no macrovascular invasion

Barcelona Management Strategy



Diagnosis and Management Summary

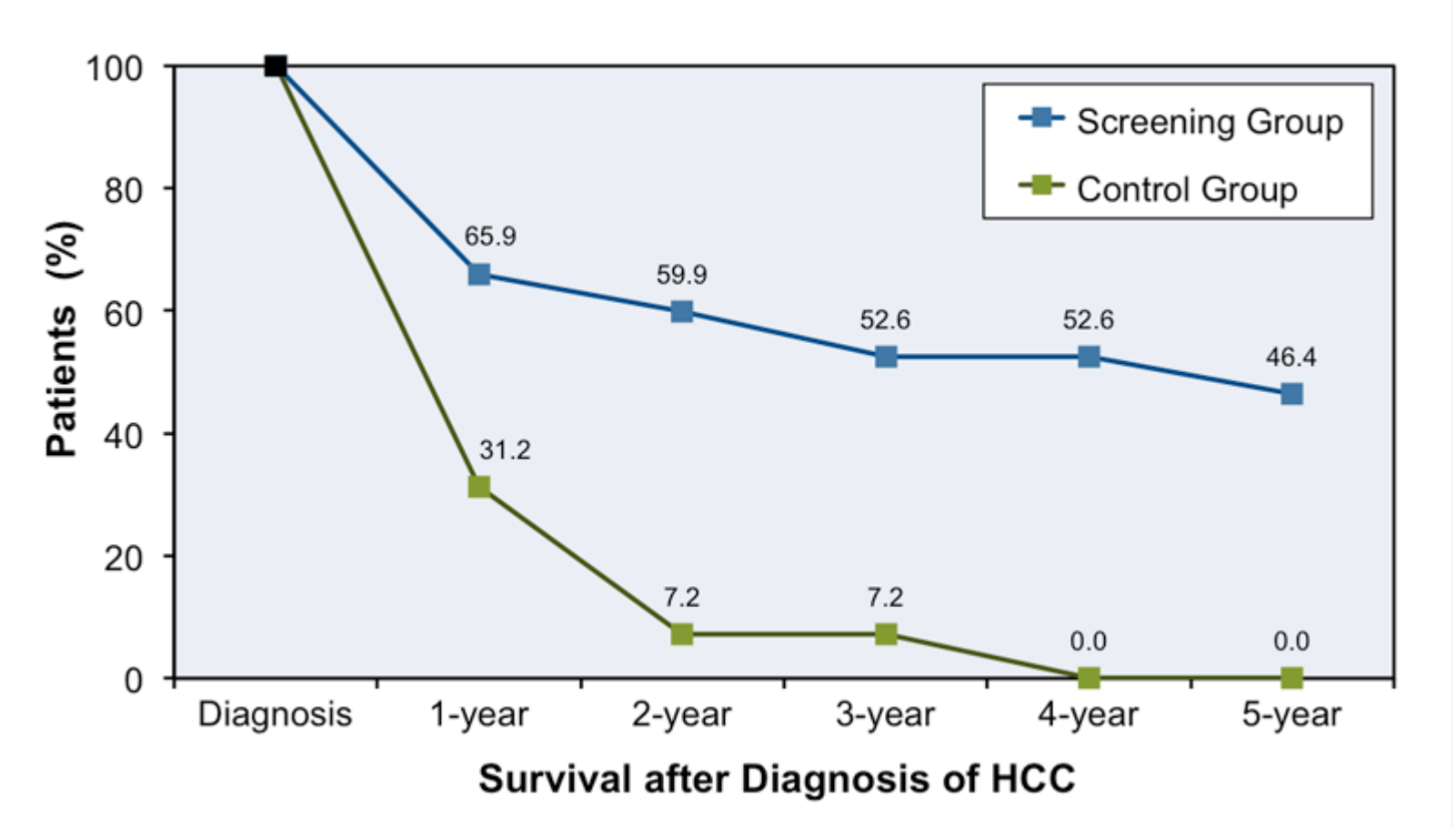
- Diagnosis of HCC is usually by triple-phase CT/MRI
  - Biopsy needed <10% of time
- Management is guided by stage
- Curative treatment depends on early diagnosis!

Screening and Surveillance

- **Screening:** Application of diagnostic tests, imaging or procedures in apparently healthy patients
- **Surveillance:** Serial application of blood-based tests, imaging or procedures in an at-risk patient population

Surveillance for HCC Reduces Mortality:

A Randomized Controlled Trial



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

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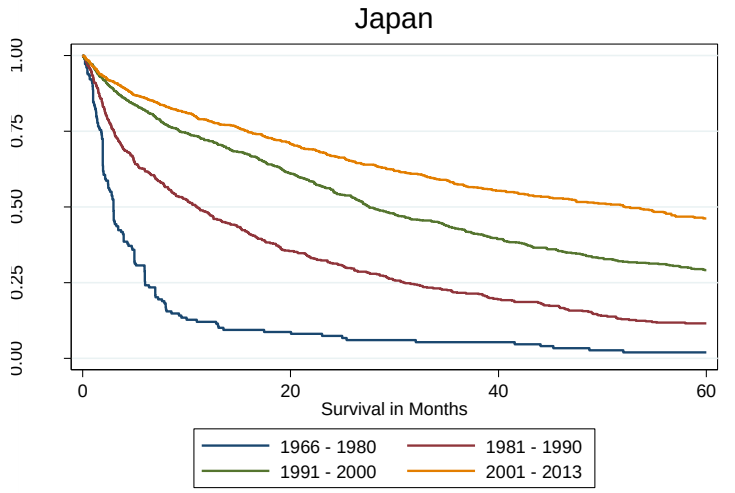
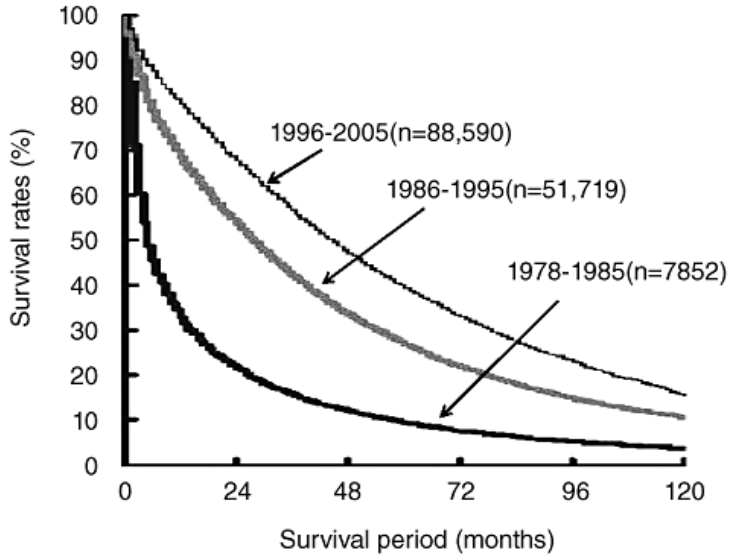
Changes in Survival in Japan Since Inception of Surveillance





Ikai I et al, Hepatol Res. (2010)

Pre-surveillance →

Period	N	Median survival in months	% screened	Median age (IQR)
1966 – 1980	178	2.96 (2.4 – 3.4)	15.23 (n=151)	60 (54 – 67)
1981 – 1990	509	10.99 (8.8 – 13.2)	55.26 (n=418)	61 (55 – 68)
1991 – 2000	812	27.5 (25.8 – 31.1)	72.41 (n=812)	64 (59 – 70)
2001 – 2013	1105	52.2 (44.1 – 59.7)	76.80 (n=1103)	70 (63 – 76)

Courtesy of Dr. P. Johnson, UK

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Guidelines for HCC Surveillance

Institutions	Guidelines
AASLD American Association for the Study of Liver Diseases	US, every 6 months +/- AFP
NCCN National Comprehensive Cancer Network	AFP + US every 6-12 months
EASL European Association for the Study of the Liver	US, every 6 months
APASL Asian-Pacific Association for the Study of the Liver	AFP + US, every 6 months
JSH Japan Society of Hepatology	AFP + AFP-L3 + DCP + US, 3-4 months for very high risk 6 months for high risk (3-4 months after treatment, 2013)

NOTE: Jan 2019 AASLD HCC surveillance guidance mentions AFP-L3% , DCP and GALAD as potential enhancements

Efficacy vs Effectiveness

- Variable completion rate
- Operator dependent: > half of the patients enrolled in surveillance programs receive a suboptimal quality ultrasound
  - Excellent 13/154 (8.4%)
  - Good 44/154 (28.6%)
  - Fair 44/154 (28.6%)
  - Poor 53/154 (34.4%)

1. Bruix J et al. Hepatology. 2005;42:1208-36
2. Bruix J et al. Hepatology. 2011;53:1020-2
3. Bennett GL et al. AJR 2002;179:75–80.
4. Joshi et al. Dig Dis Sci 2014 JUL 16, In Print

HCC Surveillance Biomarker:

Alpha-fetoprotein (AFP)

- AFP is a glycoprotein produced by:
  - Normal fetal hepatocytes
  - Normal regenerating hepatocytes
  - Most (not all HCCs)
  - Inflammation
- Low overall sensitivity and specificity for HCC
- Better performance when levels are exponentially rising (trending up) or fluctuating

Sherman M. Clin Liver Dis. 2011; 15: 323-334, Lee…Volk, et al. J Clin Gastro 2013;11:437

Alpha-fetoprotein-L3

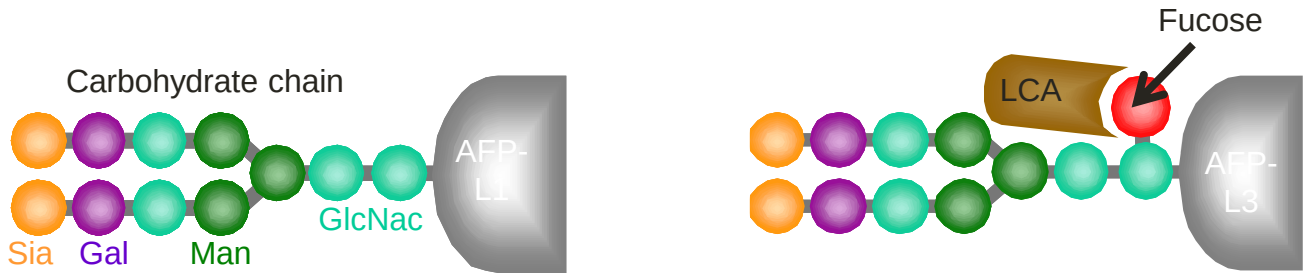
AFP-L3%

- **AFP-L3** is a fucosylated isoform of AFP.
- **AFP-L3** binds to lectin Lens culinaris (lentil) agglutinin (LCA) which interacts with AFP-L3 but not AFP-L1 (majority of AFP).
- **AFP-L3%** is FDA cleared for HCC risk assessment.
- Measured as percentage of the overall AFP, not linked to absolute amount **AFP-L3**.

Sato Y, et al. N Engl J Med. 1993;328:1802-6.
Makuuchi M, et al. Hepatol Res. 2008;38:37-51.

HCC Surveillance Biomarker

AFP-L3 Alpha-fetoprotein L3



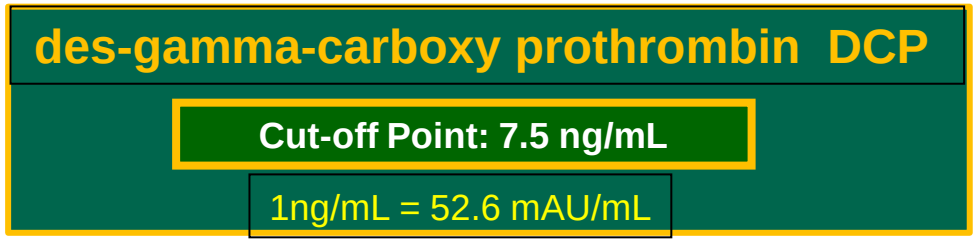
AFP-L3%: expressed as a % of the ratio of AFP-L3 to total AFP

$$\text{AFP- L3 (\%)} = \frac{\text{AFP- L3 (ng/mL)}}{\text{Total AFP (ng/mL)}} - \text{X 100}$$

Threshold: 10% (Intended Use)

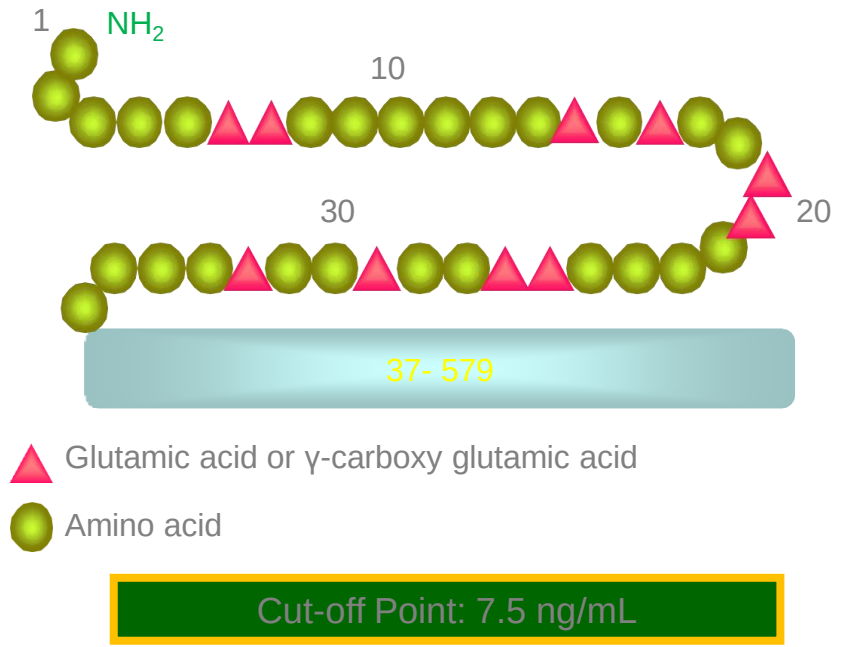
des-gamma-carboxy prothrombin: DCP

- Normal hepatocytes post-translationally carboxylate prothrombin precursors before secretion.
- **DCP** is a secreted non-carboxylated immature form of prothrombin.
  - aka PIVKA-II (proteins induced by vitamin K absence or antagonist-II)
- Unconverted glutamic acid residues are due to an absence in many HCC cells of vit. K dependent carboxylase.
- **DCP** is FDA cleared for HCC risk assessment.



Liebman HA, et al. N Engl J Med. 1984;310:1427-31.

des-gamma-carboxy prothrombin: DCP



1ng/mL = 52.6 mAU/mL

A Statistical Model (GALAD):

A Combination of AFP, AFP-L3 & DCP with Age and Gender

The model predicts HCC presence in patients with chronic liver disease:

$$Z = -10.32 + 0.10 \times [Age] + 1.39 \times [Gender] + 2.43 \times \log[AFP] + 0.040 \times [AFP\text{-}L3] + 1.45 \times \log[DCP]$$

From the calculated value of Z, the probability of HCC in a patient with chronic liver disease (ranging from 0 to 1) is calculated by:

$$GPr(HCC) = \exp(Z)/(1+\exp(Z))$$

Johnson et al, Cancer Epi Biom and Prev 2014

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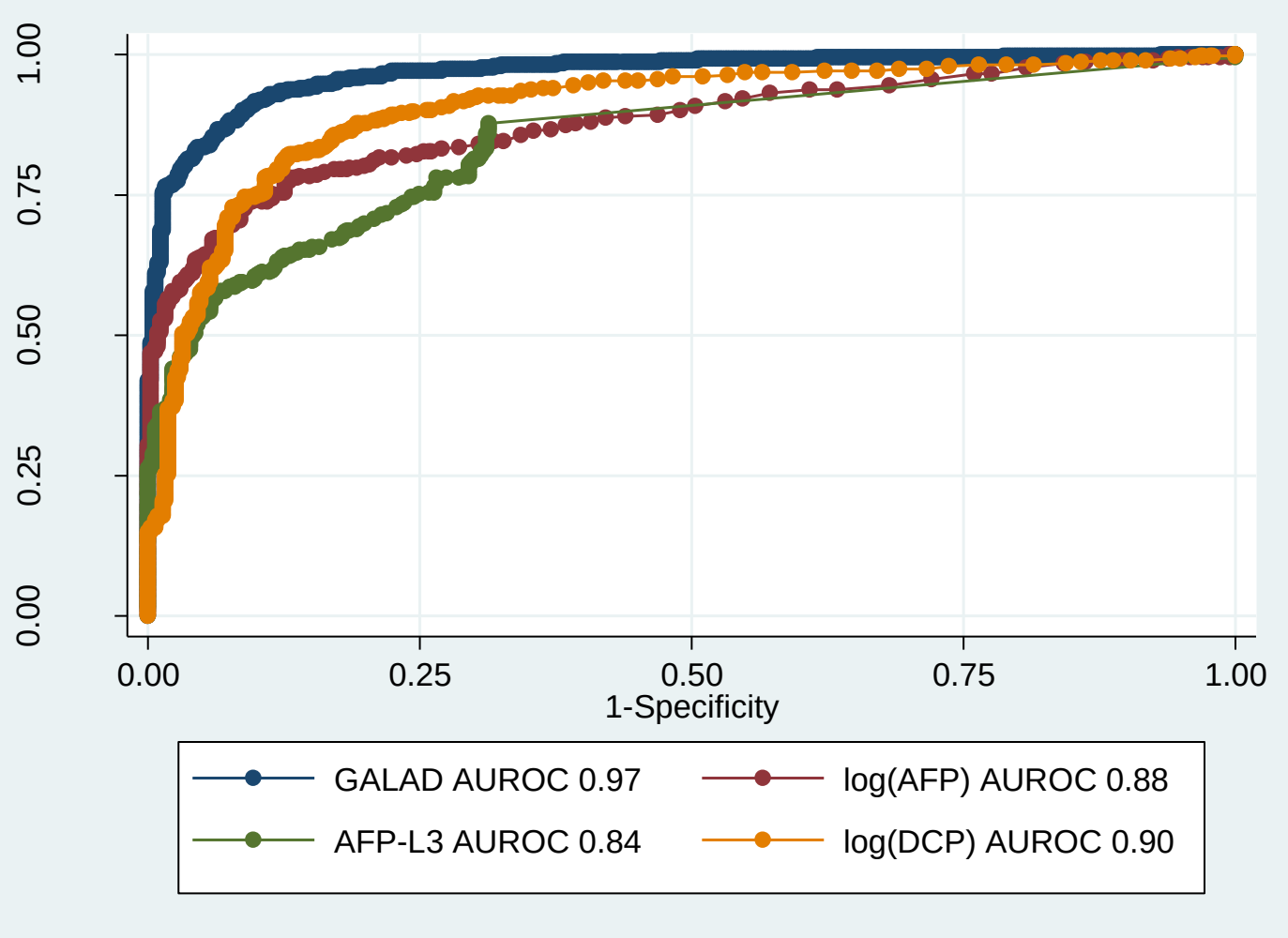
Added Value of The GALAD Model



Roles for Biomarkers

- Early detection (screening/surveillance)
- Prognosis
- Evaluate for recurrence

What role does the lab play?

- Implement the GALAD model
- Flag rising values
- Linkage to care

Questions?