2023 RUSH INTO GI:

AN UPDATE IN GASTROENTEROLOGY AND HEPATOLOGY

Liver Cancer Screening in Average and High-Risk Populations

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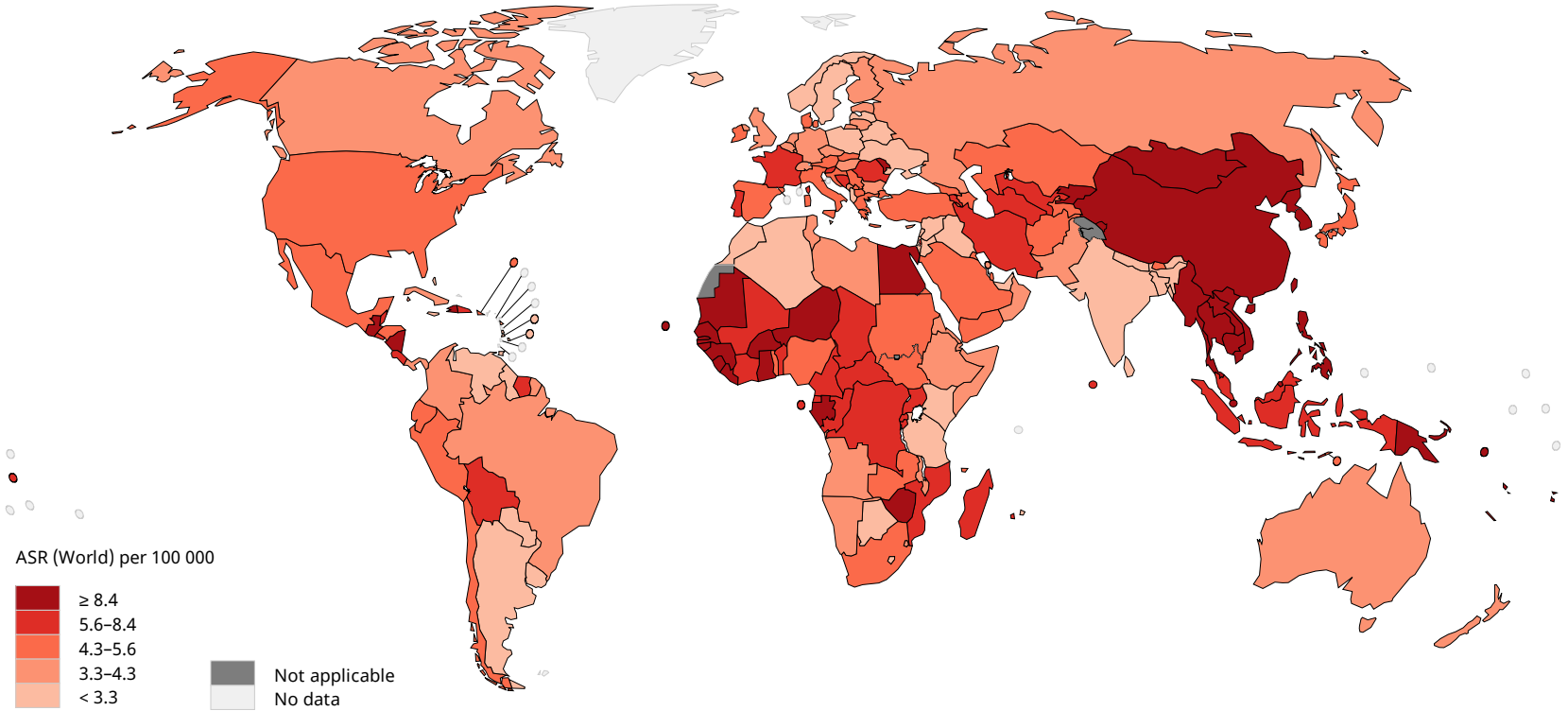
Disclosures

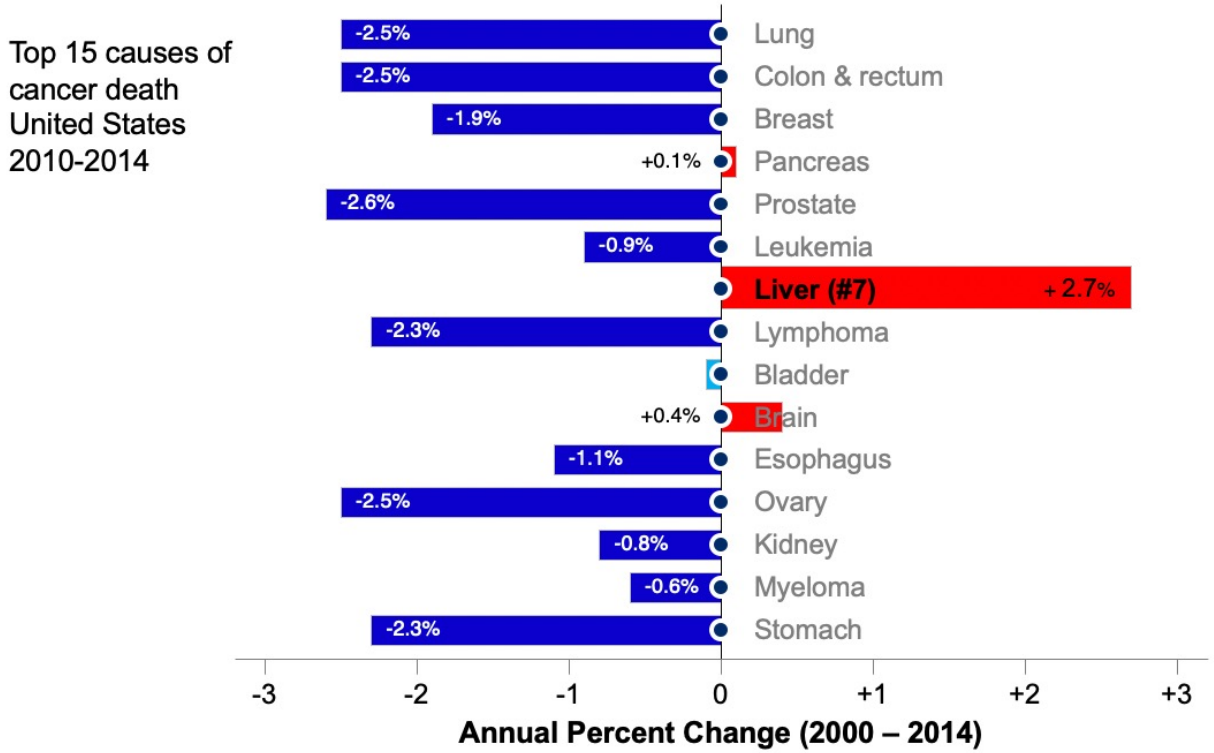
- Nothing pertinent to disclosure

Hepatocellular Carcinoma Is 4th Leading Cause of Cancer-Related Death Worldwide



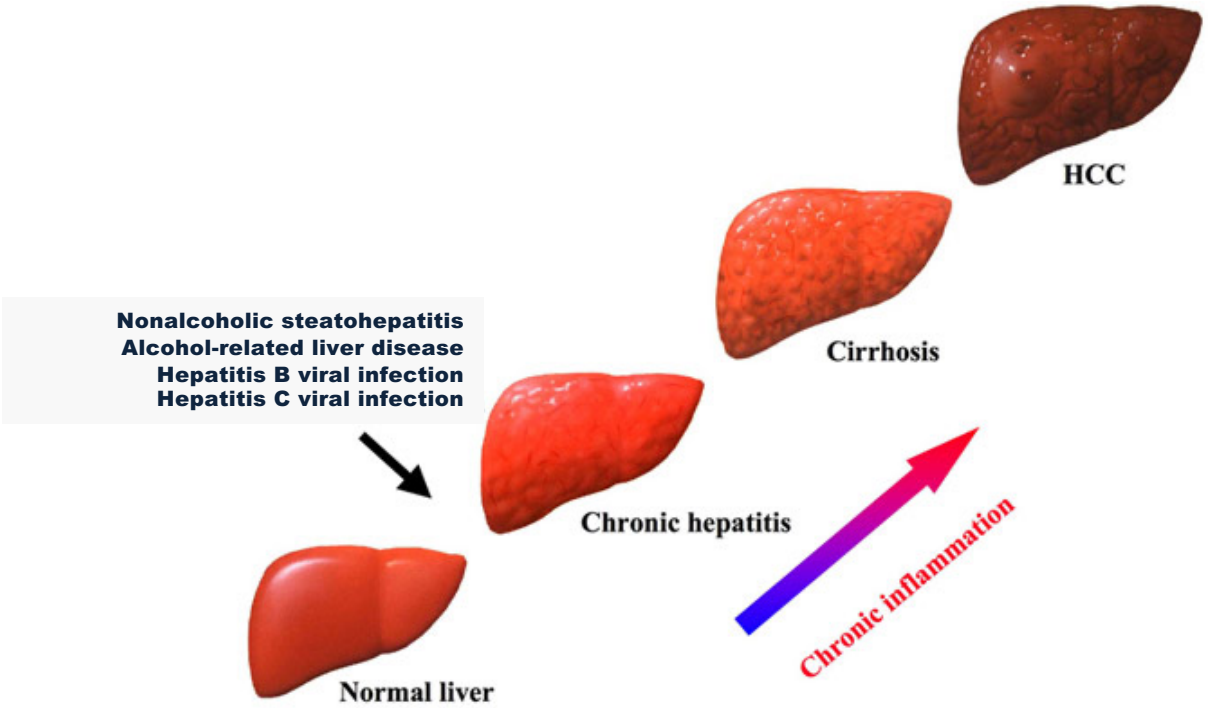
GLOBOCAN. 2020.

HCC-Related Morality Is Increasing in the United States



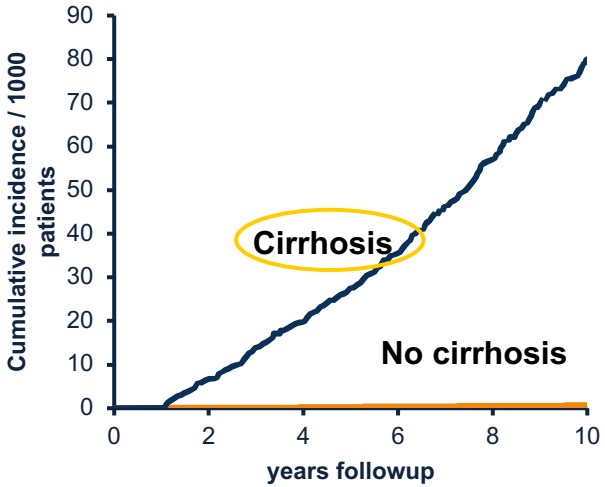
Data from http://seer.cancer.gov.

Most HCC in the United States Occur in the Setting of Cirrhosis

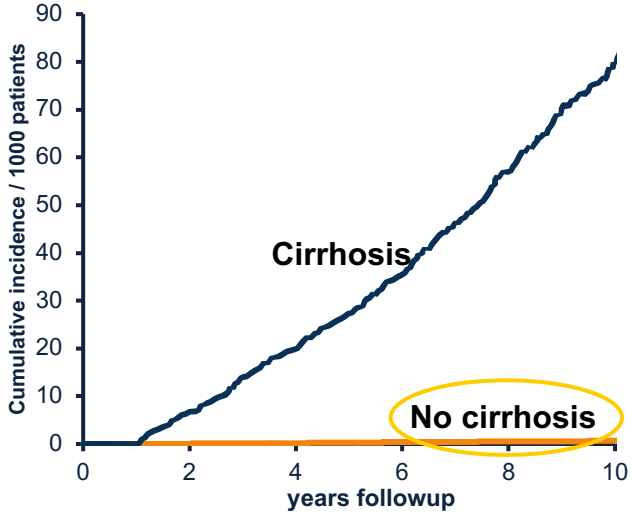


HCC Risk in Patients With NASH in Those With Cirrhosis

N= 4235 cirrhosis; 292,366 no cirrhosis



1.06 per 100 patient-years



0.008 per 100 patient-years

Kanwal et al. *Gastroenterology*. 2018.

Major Guidelines Recognize the Importance of Routine Surveillance in High-Risk Populations

Society/Institution	Guidelines
AASLD[1] American Association for the Study of Liver Diseases	US every 6 months with or without AFP
EASL[2] European Association for the Study of the Liver	US every 6 months
APASL[3] Asian-Pacific Association for the Study of the Liver	AFP + US every 6 months
NCCN[4] National Comprehensive Cancer Network	AFP + US every 6-12 months
VA[5] United States Department of Veterans Affairs	AFP + US every 6-12 months
JSH-HCC[6] Japan Society of Hepatology	High-risk: US every 6 months + AFP/DCP/AFP-L3 every 6 months Very High-risk: US every 6 months + AFP/DCP/AFP-L3 every 6 months + CT/MRI (optional) every 6-12 months

AFP=alpha-fetoprotein; AFP-L3=*Lens culinaris* agglutinin-reactive fraction of AFP; CT=computerized tomography; DCP=des-γ-carboxyprothrombin; MRI=magnetic resonance imaging; US=ultrasound.

1. Marrero J et al. *Hepatology*. 2018:68 (2);723-750: 2. EASL, EORTC. *J Hepatol.* 2012;56(4):908-943; 3. Omata M et al. *Hepatol Int*. 2010;4(2):439-474; 4. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hepatobiliary Cancers v1.2016.
 5. US Dept of Veterans Affairs. Available at: http://www.hepatitis.va.gov/pdf/2009HCC-guidelines.pdf. Accessed September 23, 2015; 6. Kokudo N et al. *Hepatol Res.* 2015;45.

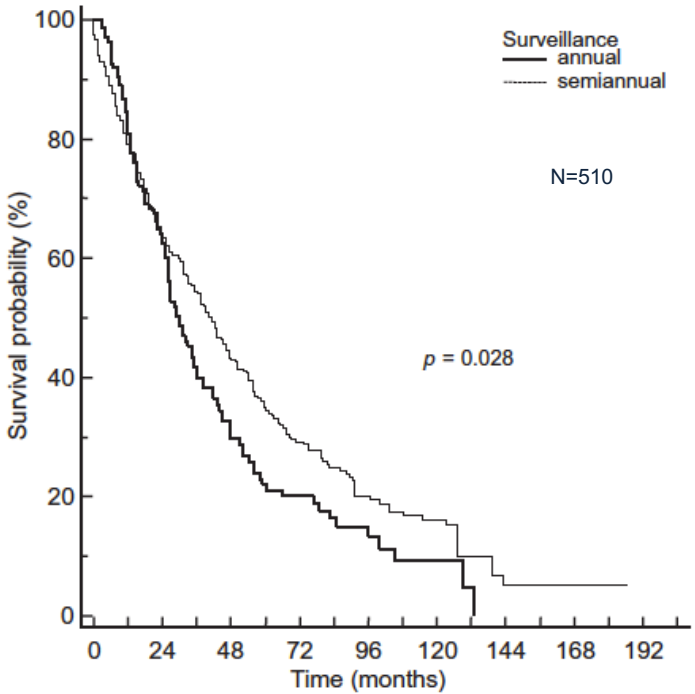
Professional Society Guidelines Recommend HCC Surveillance in High-Risk Individuals Including Those With Cirrhosis

Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases

Population Group	Threshold Incidence for Efficacy of Surveillance (>0.25 LYG; % per year)	Incidence of HCC
Surveillance benefit		
Asian male hepatitis B carriers over age 40	0.2	0.4%-0.6% per year
Asian female hepatitis B carriers over age 50	0.2	0.3%-0.6% per year
Hepatitis B carrier with family history of HCC	0.2	Incidence higher than without family history
African and/or North American blacks with hepatitis B	0.2	HCC occurs at a younger age
Hepatitis B carriers with cirrhosis	0.2-1.5	3%-8% per year
Hepatitis C cirrhosis	1.5	3%-5% per year
Stage 4 PBC	1.5	3%-5% per year
Genetic hemochromatosis and cirrhosis	1.5	Unknown, but probably >1.5% per year
Alpha-1 antitrypsin deficiency and cirrhosis	1.5	Unknown, but probably >1.5% per year
Other cirrhosis	1.5	Unknown
Surveillance benefit uncertain		
Hepatitis B carriers younger than 40 (males) or 50 (females)	0.2	<0.2 per year
Hepatitis C and stage 3 fibrosis	1.5	<1.5% per year
NAFLD without cirrhosis	1.5	<1.5% per year

Marrero et al. *Hepatology*. 2018.

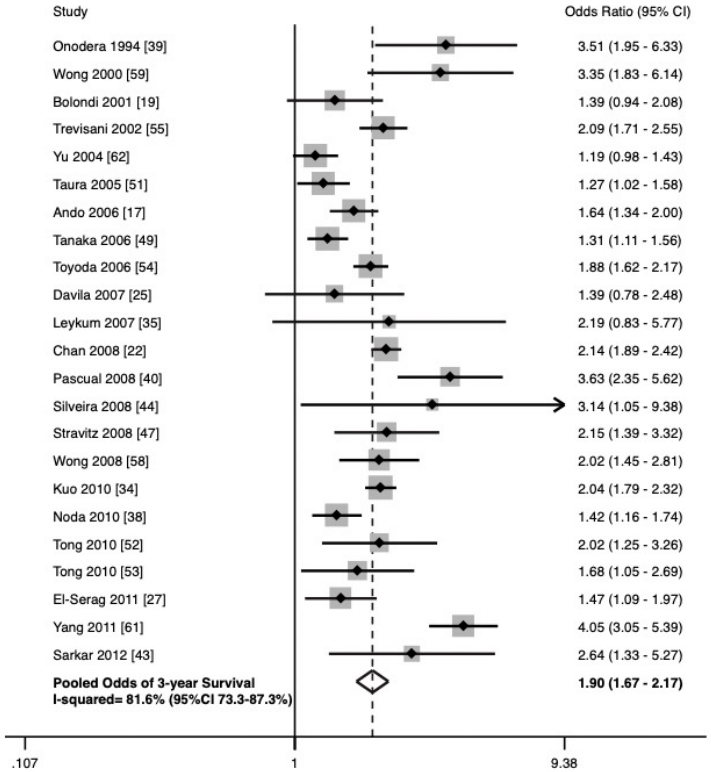
Surveillance Should Be Performed at Semi-Annual Intervals



Variable	3-month Surveillance (n=640)	6-month Surveillance (n=638)
Focal lesion <1 cm	73 (41%)	43 (28%)
Focal lesion 1-2 cm	71 (40%)	78 (50%)
HCC development **Less than 2 cm** **Within Milan**	53 (28%) 20 (38%) 42 (79%)	70 (42%) 29 (41%) 50 (71%)

Santi et al. *Hepatology*. 2010; Trinchet et al. *Hepatology*. 2011.

HCC Surveillance Associated With Early Detection and Improved Survival in Patients With Cirrhosis



Identified 47 studies with 15,158 patients – 6284 (41.4%) detected by surveillance

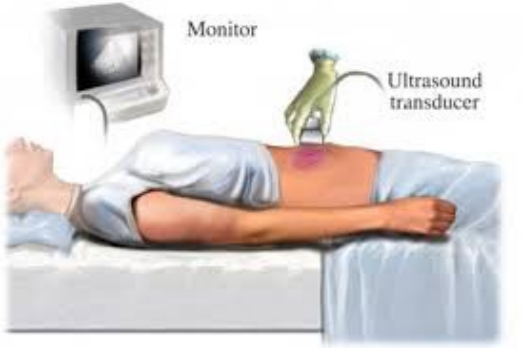
Surveillance associated with:

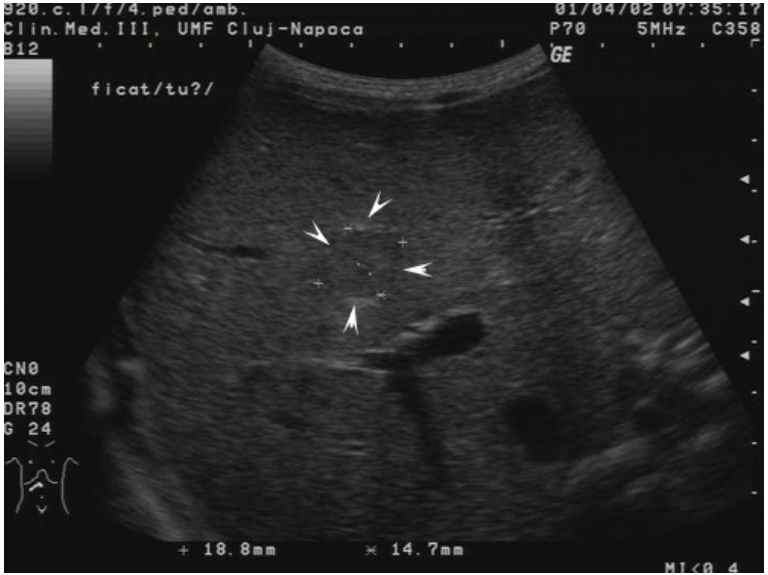
- Early detection OR 2.8, 95% CI 1.80 – 2.37
- Curative treatment: OR 2.24, 95%CI 1.99 – 2.52
- Improved survival OR 1.90, 95%CI 1.67 – 2.17

Survival benefit persisted in studies adjusting for lead time bias

Signal et al. *PLOS Medicine*. 2014.

Abdominal Ultrasound +/- Serum Biomarker, Alpha Fetoprotein, Are Recommended Surveillance Tests



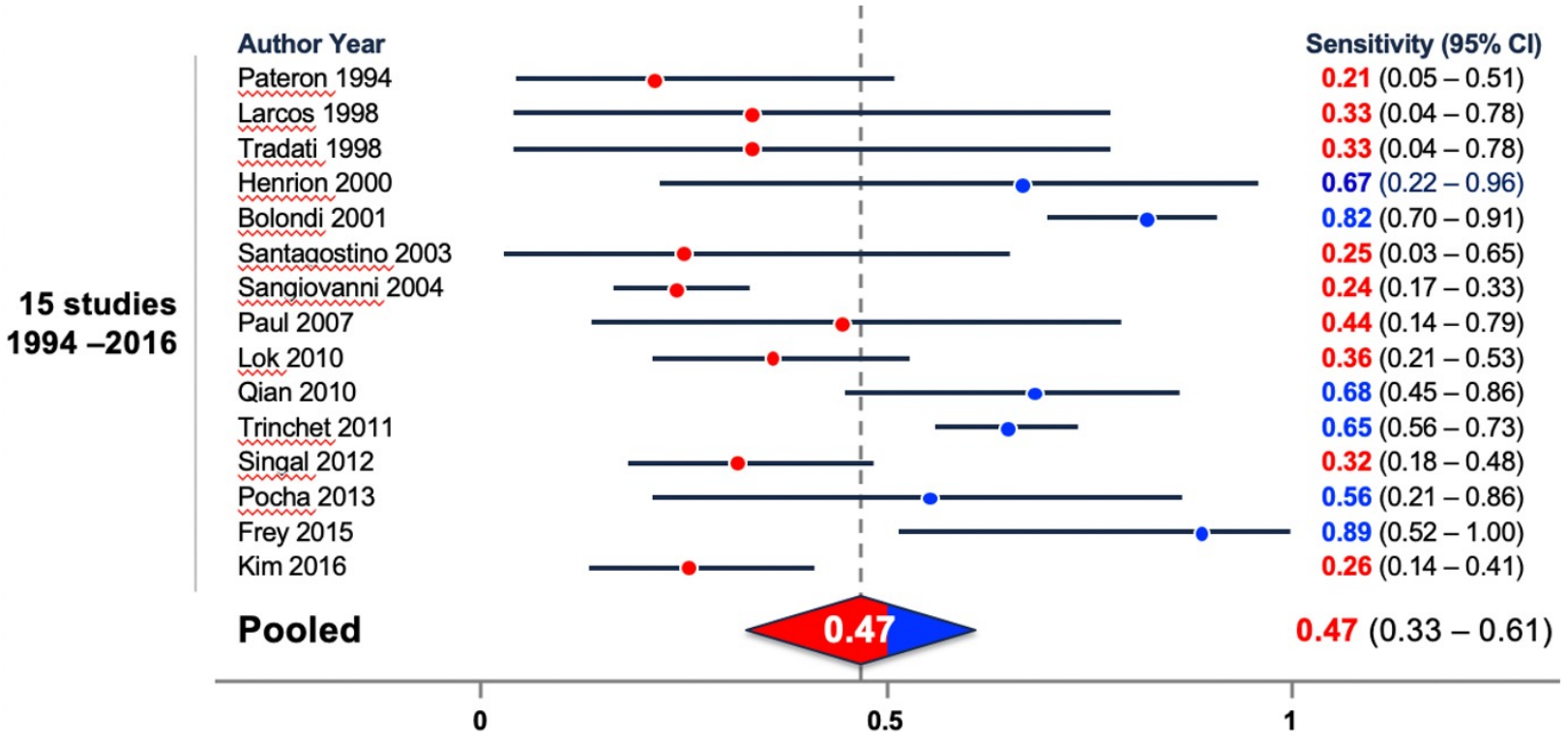


Ultrasound (US) in Surveillance

- Excellent specificity (>90%), but low sensitivity – a meta-analysis indicates US sensitivity in detecting early stage HCC may be as low as 63%
- Multiple limitations
  - Does not detect infiltrative disease
  - Sensitivity decreased in difficult patients
    - Cirrhotic nodular livers
    - Obesity
    - Abdominal gas
    - Noncompliant with breath-hold
    - Ascites
    - NASH
  - Highly operator dependent, time
- Real-life US sensitivity likely much lower than that of studies

Del Poggio P et al. *Clin Gastroenterol Hepatol*. 2014;12(11):1927-1933.e2.

Ultrasound Alone Has Poor Sensitivity for Early HCC Detection

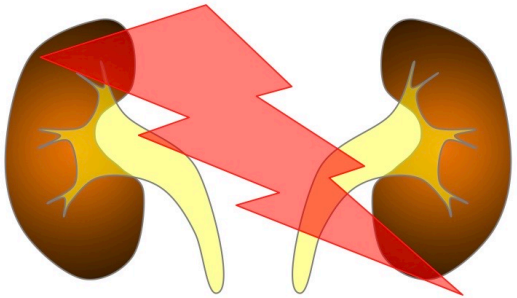


Tzartzeva et al. *Gastroenterology*. 2018.

CT Is Not Viable Routine Option for HCC Screening Given Potential Harms

More expensive

Ionizing radiation



Nephrotoxicity?

Slide courtesy of Claude Sirlin.

MRI Is More Sensitive for Early Tumor Detection but May Be Limited by Cost Effectiveness

- Prospective study with 407 Child A-B patients (majority HBV-infected)
  - 1112 surveillance round over 1.5 years
  - Semi-annual ultrasound and MRI done in all patients
- 43 patients diagnosed with HCC
  - 32 very early stage and 10 early stage HCC

Cohort	MRI	US	P-value
Sensitivity	86%	28%	P<0.001
Sensitivity for BCLC 0	86%	26%	P<0.001
Specificity	97%	94%	P=0.004

Kim et al. *JAMA Oncology*. 2016.

CT/MRI

- Implemented if ultrasound is unclear
- Implemented if there is high suspicion clinically
- Implemented diagnostically
  - Elevated AFP
  - A known lesion

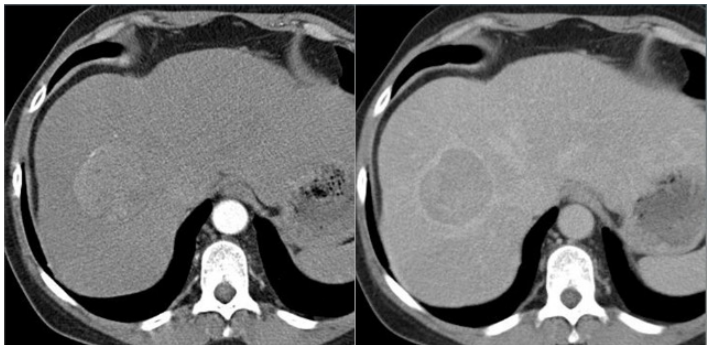
CT vs MRI

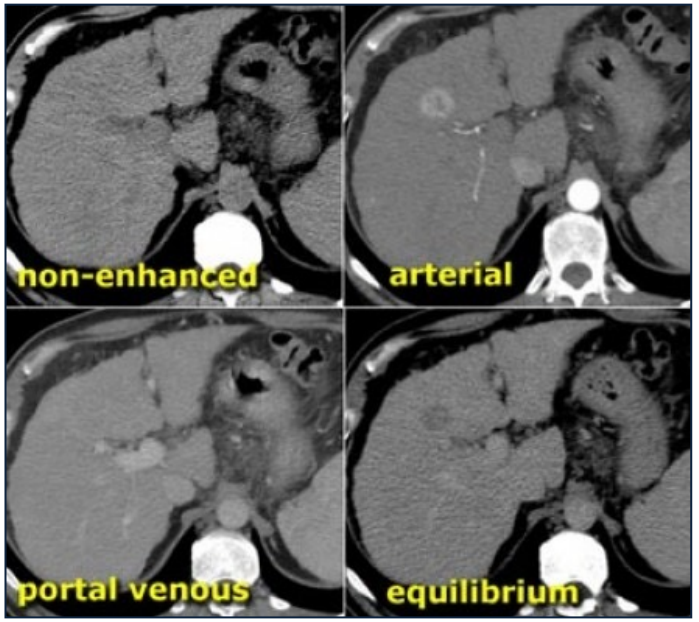
- Meta-analysis of 40 studies on CT or MRI imaging, total of 1135 patients with CT and 2489 patients with MRI

	CT	MRI (all)	MRI with Eovist
Per-patient sensitivity	83%	88%	
Per patient specificity	81%	94%	
Per lesion sensitivity	72%	79%	87%

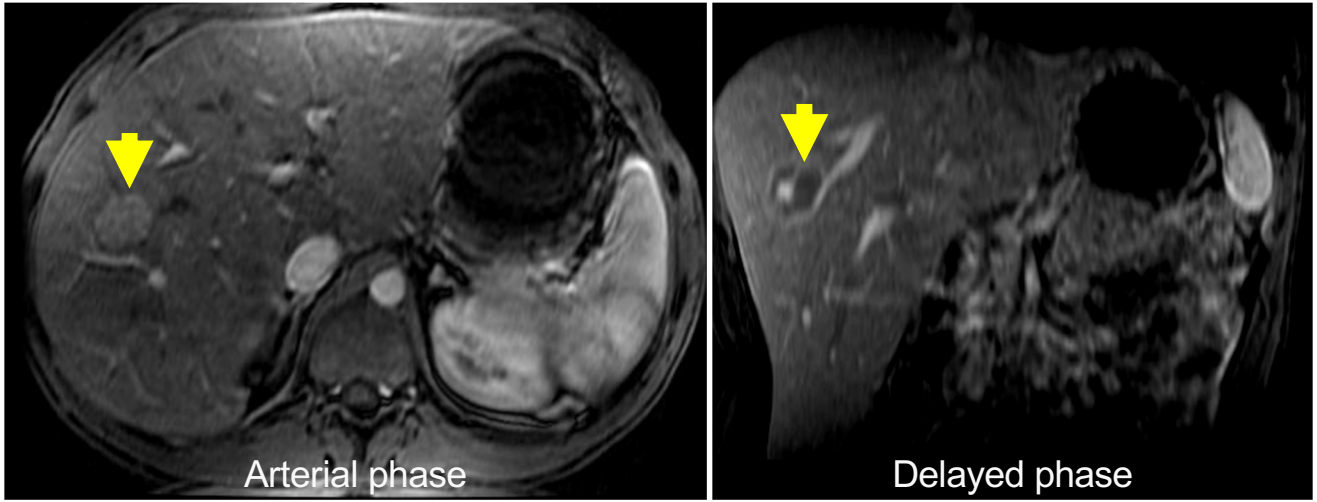
Lee et al. *Radiology*. 2015.

Cross-Sectional (Triple Phase) Imaging



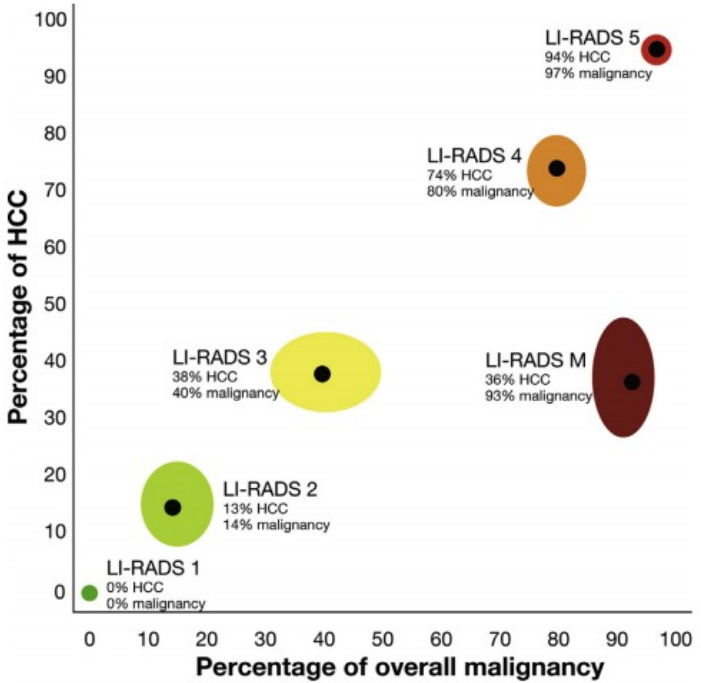


HCC Diagnosis Can Be Established Non-Invasively Based on Imaging Alone

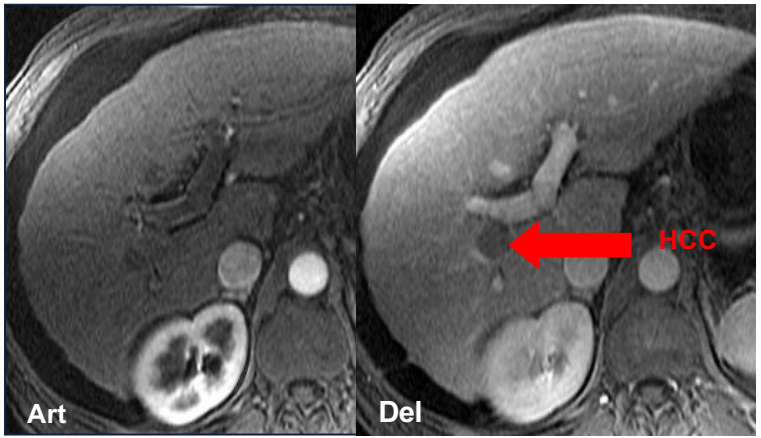


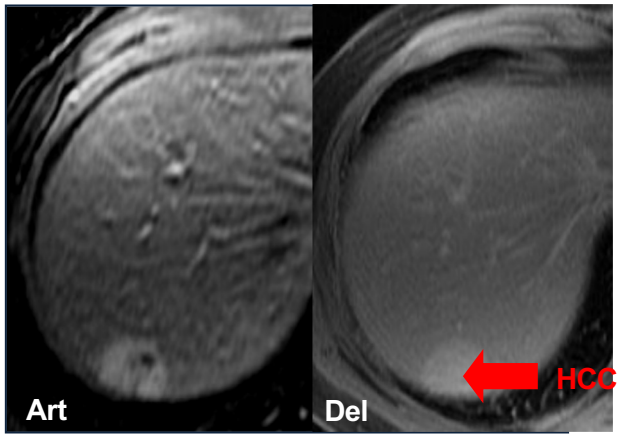
LI-RADS Criteria for HCC Diagnosis

LI-RADS Category	Concept and Definition
LR-1 **Definitely Benign**	**Concept:** 100% certainty observation is benign. **Definition:** Observation with imaging features diagnostic of a benign entity, or definite disappearance at follow up in absence of treatment.
LR-2 **Probably Benign**	**Concept:** High probability observation is benign. **Definition:** Observation with imaging features suggestive but not diagnostic of a benign entity.
LR-3 **Intermediate probability for HCC**	**Concept:** Both HCC and benign entity have moderate probability. **Definition:** Observation that does not meet criteria for other LI-RADS categories.
LR-4 **Probably HCC**	**Concept:** High probability observation is HCC but there is not 100% certainty. **Definition:** Observation with imaging features suggestive but not diagnostic of HCC.
LR-5 **Definitely HCC**	**Concept:** 100% certainty observation is HCC. **Definition:** Observation with imaging features diagnostic of HCC or proven to be HCC at histology.
LR-5V **Definitely HCC with Tumor in Vein**	**Concept:** 100% certainty that observation is HCC invading vein. **Definition:** Observation with imaging features diagnostic of HCC invading vein.
LR-M **Probable malignancy, not specific for HCC**	**Concept:** High probability that observation is a malignancy, but imaging features are not specific for HCC. **Definition:** Observation with one or more imaging features that favor non-HCC malignancy.
LR-Treated **Treated Observation**	**Concept:** Loco-regionally treated observation. **Definition:** Observation that has undergone loco-regional treatment



Biopsy Only Occasionally Plays a Role in HCC Diagnosis





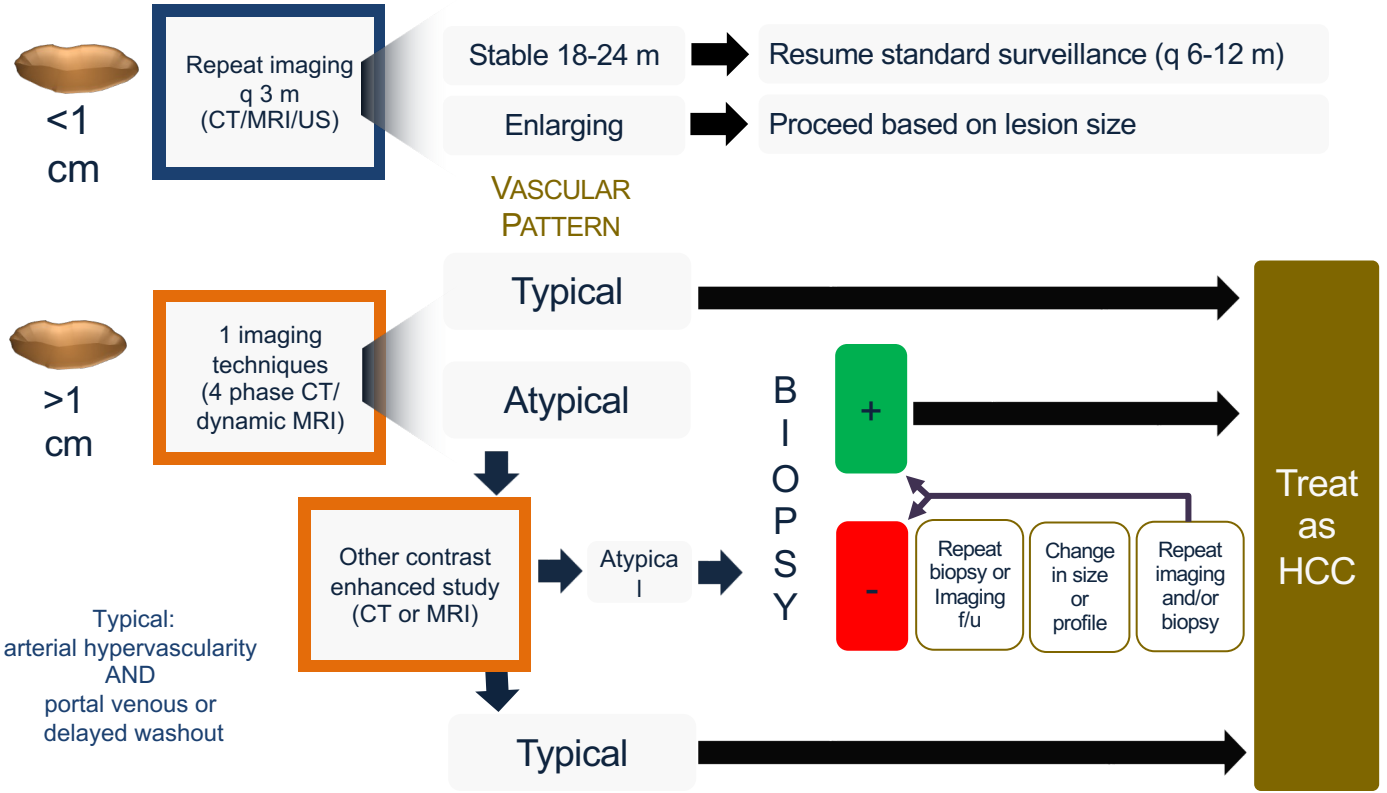
When to Biopsy

- When to biopsy and when NOT to biopsy
  - CT/MRI is excellent and often diagnostic
    - 95% specific for HCC: biopsy NOT needed in most patients
  - Only focal hepatic mass with atypical imaging findings or focal hepatic mass detected in a non-cirrhotic liver should undergo biopsy[1]
  - Normal AFP
- Why not?
  - Bleeding
  - Tumor seeding
  - False -

1. Bruix J et al. *Hepatology*. 2011;53(3):1020-1022.

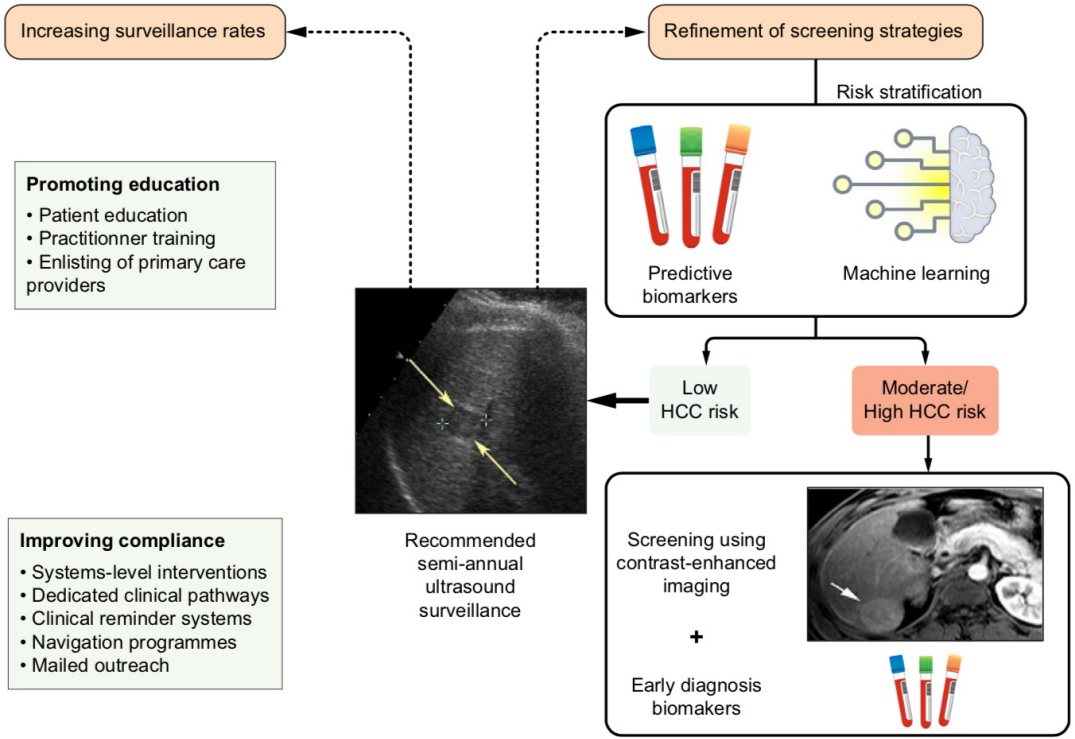
HCC Diagnosis

Following Detection of Mass in Cirrhotic Liver



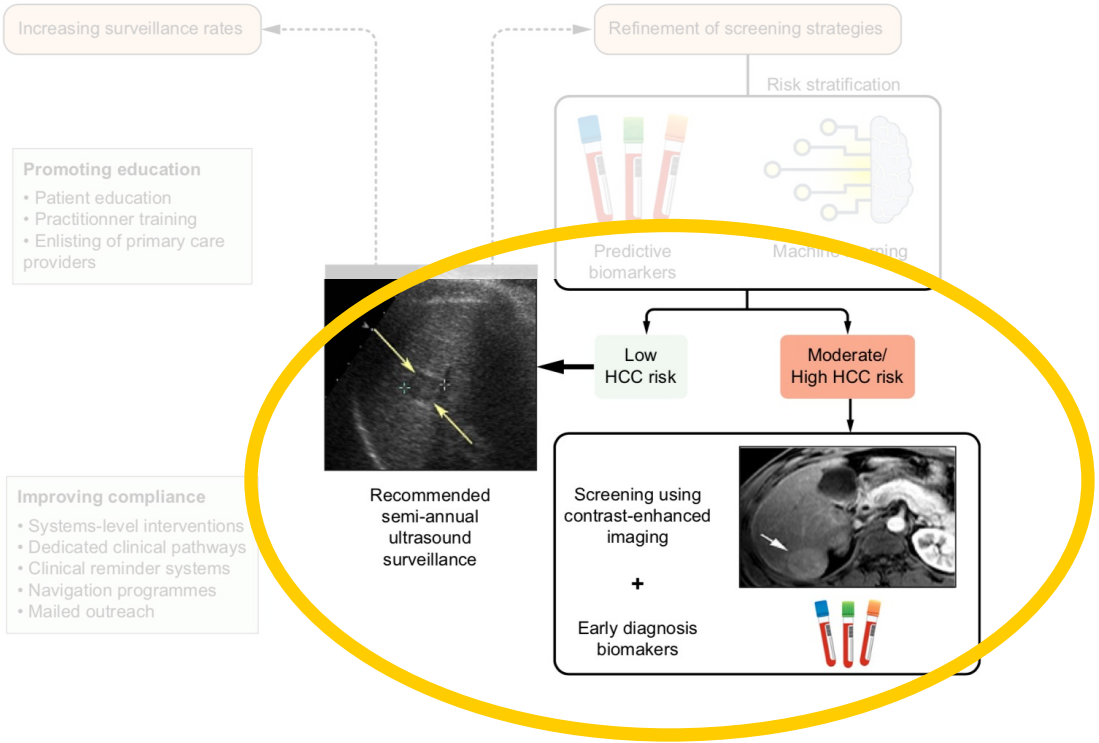
Bruix and Sherman. AASLD guidelines. 2010.

Potential Interventions to Improving Surveillance Effectiveness and Reducing HCC Morality



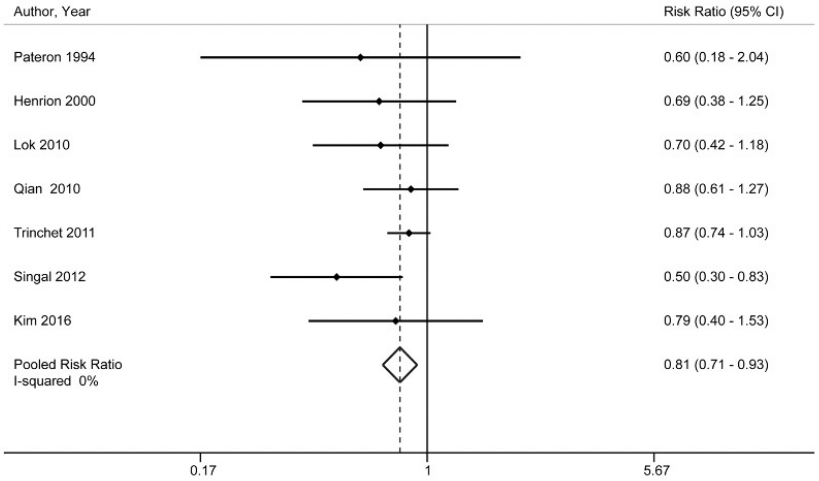
Signal et al. *J Hepatology*. 2019.

Potential Interventions to Improving Surveillance Effectiveness and Reducing HCC Morality

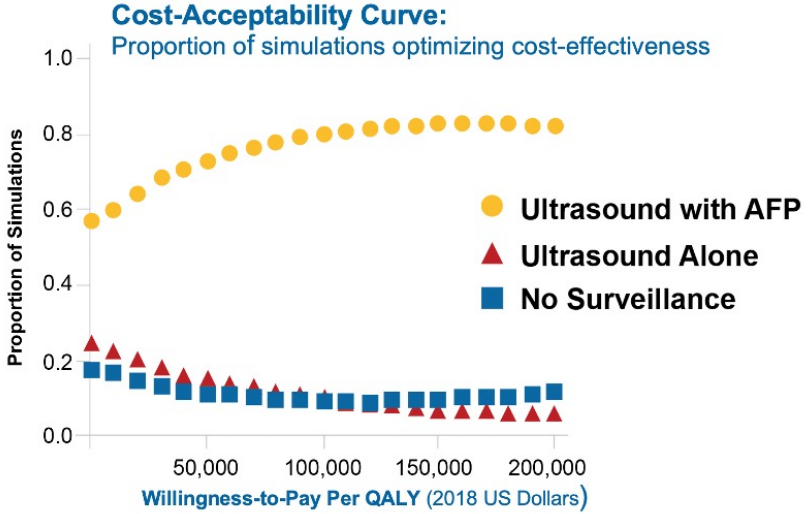


Signal et al. *J Hepatology*. 2019.

AFP Appears to Be of Benefit for Early HCC Detection



Sensitivity of US with vs without AFP for early-stage HCC:
63% vs. 45% (*p*=.002)



Tzartzeva et al. *Gastroenterology*. 2018; Parikh et al. *Am J Gastro (in press).*

Several Other Biomarkers Are Currently Undergoing Phase II-III Biomarker Evaluation

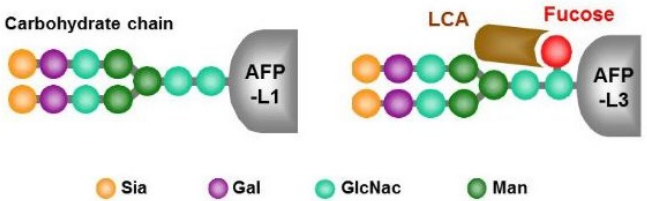
- AFP-L3 and DCP
- Golgi protein 73 (GP73)
- Glypican 3 (GPC3)
- Osteopontin
- miR-21 (circulating miRNA)
- Serum and urinary metabolites
- Fucosylated kininogen (Fc-Kin)
- Circulating tumor cells/methylated DNA markers

HCC Surveillance Biomarker: 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).
- Relevance of AFP-L3 to HCC:
  - AFP-L3 has been shown to be elevated in patients with HCC. Elevation of L3 occurs early in HCC
  - AFP-L3 (%) is highly specific for HCC

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

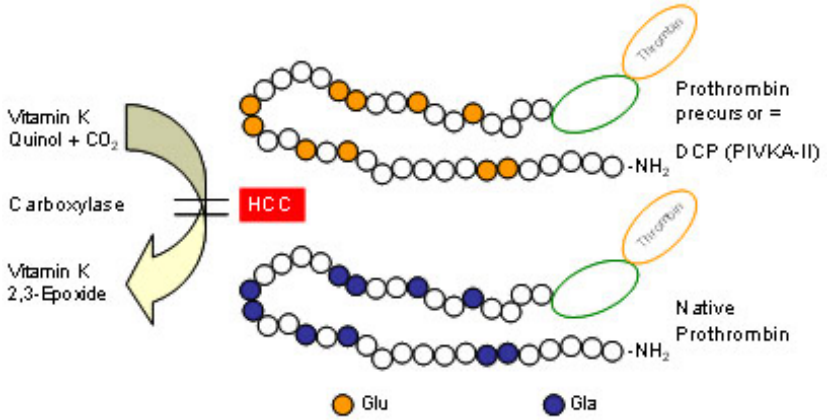
Cut-off Point: 10% (Intended Use)



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: Des-gamma-Carboxy Prothrombin (DCP)

- Normal hepatocytes post-translationally carboxylate prothrombin precursors before secretion.
- DCP is a secreted non-carboxylated immature form of prothrombin.
- Unconverted glutamic acid residues are due to an absence in many HCC of vit. K dependent carboxylase.
- aka PIVKA-II (proteins induced by vitamin K absence or antagonist-II).
  - *The carboxylation defect is also in vitamin K deficiency (also warfarin use)*



Cut-off Point: 7.5 ng/mL

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

GALAD Is a Promising Novel Biomarker Panel for Early Detection

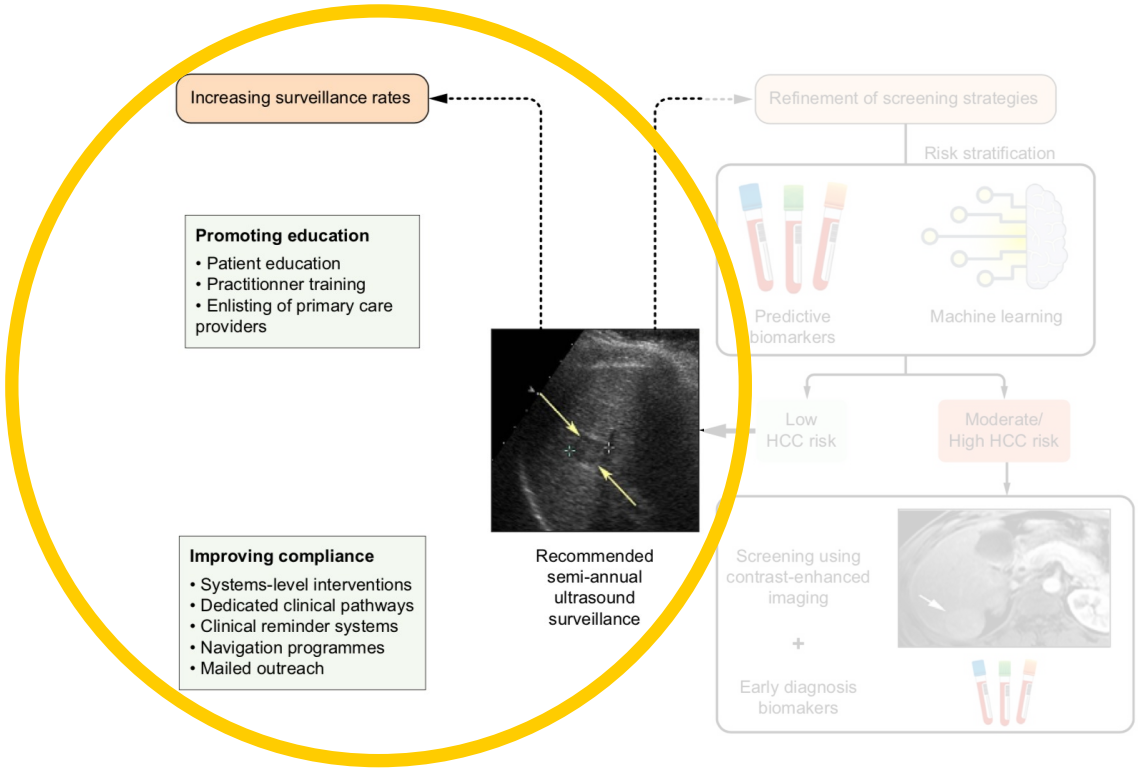
- GALAD: **G**ender, **A**ge, AFP-**L**3, **A**FP, and **D**CP
- Multi-national nested case control with 6834 patients (2430 HCC, 4404 CLD)

Variable	Sensitivity	Specificity	Correctly classified
UK cohort (all)	91.6%	89.7%	90.6%
UK cohort (Milan)	80.2%	89.7%	87.9%
Japan cohort (all)	70.5%	95.8%	87.2%
Japan cohort (Milan)	60.6%	95.8%	87.7%
Germany cohort (all)	87.6%	88.6%	88.3%
Germany cohort (unifocal <5cm)	67.4%	88.6%	87.5%

No difference in GALAD performance by cirrhosis etiology, SVR, or HBV treatment

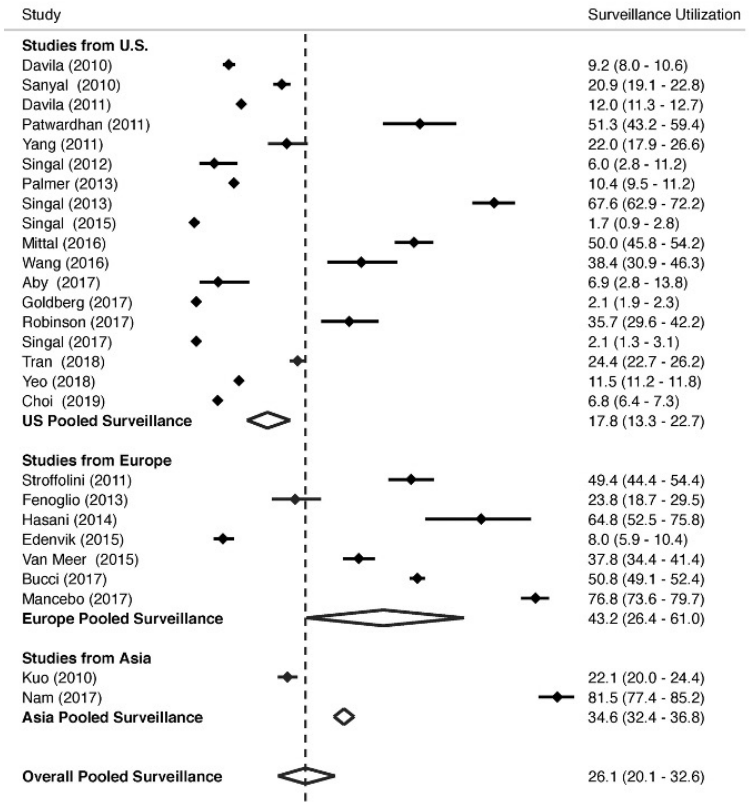
Berhane et al. *Clin Gastro Hep*. 2016.

Potential Interventions to Improving Surveillance Effectiveness and Reducing HCC Morality



Singal et al. *J Hepatology*. 2019.

HCC Surveillance Is Underused in Clinical Practice



Identified 29 studies between Jan 2010 – Aug 2018

Pooled surveillance estimate was only 26.1%

- Lower surveillance in US studies vs. Europe and Asia (17.8% vs. 43.2% and 34.6%)
- Higher surveillance in GI/Hepatology clinics vs. academic primary care clinics and population-based cohorts (73.7% vs. 29.5% and 8.8%)

Consistent correlates included higher surveillance with GI/Hepatology subspecialty care and increased number of clinic visits and lower surveillance in patients with NASH or alcohol-related cirrhosis.

Wolf et al. *Hepatology*. 2020.

Summary

- HCC surveillance supported by RCT in patients with chronic HBV and several cohort studies in those with cirrhosis
- Test accuracy and surveillance utilization are key factors for effectiveness
- Ultrasound has suboptimal sensitivity, particularly in contemporary cohorts
  - Novel blood- and imaging-based modalities are being evaluated
- Surveillance is underused in clinical practice due to patient- and provider-barriers