# Solid Liver Lesions

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# Disclosures

- I have no relationships to disclose.

# Outline

## Disease overview

- Background
- Characteristics of common liver lesions
- Basic management of a ‘liver nodule’

## Guidelines

- Hepatic hemangiomas*
- Focal nodular hyperplasia (FNH)*
- Hepatocellular adenoma (HCA)*
- Patients with multiple lesions*
- Screening for HCC

*Guidelines for each nodule category cover: epidemiology, clinical characteristics, imaging and diagnosis, clinical management and key recommendations. EASL CPG benign liver tumours. *J Hepatol*. 2016;65:386–98

# Benign Solid Tumors – Background

- Heterogenous group of liver lesions
- Frequently found incidentally – due to widespread imaging use
- Often have a benign course
- Some are of greater clinical relevance than others

- Clinical Practice Guidelines for benign tumors:*
  - Hepatic hemangiomas
  - Focal nodular hyperplasia (FNH)
  - Hepatocellular adenoma (HCA)

*Nodular regenerative hyperplasia, although its histology is 'benign', has a clinical course and management distinct from other benign lesions considered in this guideline and is not reviewed here.

EASL CPG benign liver tumours. *J Hepatol*. 2016;65:386–98.

# Characteristics of Common Benign Solid Liver Lesions

| | Hemangioma | FNH | HCA |
|---|---|---|---|
| Estimated prevalence | Common<br>~5%* | Less common<br>0.03% | Rare<br>≤0.004% |
| Age | 30–50 years | 20–40 years | All ages |
| Gender | F > M | F ~ M | F >> M |
| US | Hyperechoic | Varied | Varied |
| CT | Centripetal enhancement | Central scar | Varied |
| MRI | Centripetal enhancement<br>Hyperintense T2-w | Central scar | Varied |
| Calcification | Yes | No | No |
| Rupture | Rare | No | Yes |

*Estimated prevalence in imaging series; has been reported to be as high as 20% in autopsy series.

Bahirwani R, Reddy KR. *Aliment Pharmacol Ther*. 2008;28:953–65; EASL CPG benign liver tumours. *J Hepatol.* 2016;65:386–98.

# Basic Management of a ‘Liver Nodule’

**Examination and baseline investigations**

- Associated symptoms:
  - Abdominal pain
  - Weight loss
  - Hepatomegaly
  - Abnormal liver function tests
- Medical history
  - Conditions associated with liver lesions (e.g. cancer, anorexia, asthenia)
  - History of foreign travel or dysentery
  - Medication history, particularly OCPs
- Exclude primary tumor distant to liver
- Risk factors
  - History of/current viral hepatitis/cirrhosis
  - History of transfusion, tattoos, IV drug abuse
  - Family history of liver disease/tumours
  - Alcohol excess, smoking
  - Features of metabolic syndrome (obesity, T2DM, HTN, CV disease)
  - Drug history (methotrexate, tamoxifen, androgens)

Following examination and baseline investigations

**Contrast-enhanced imaging (CEUS, CT, MRI) for tumor characterization**

- Imaging and baseline investigations should be sufficient to diagnose benign liver tumours
- In cases of significant doubt, a biopsy or resection may be appropriate
- Invasive procedures should only be pursued after consideration by an experienced MDT

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# Hepatic Hemangiomas: Epidemiology/Clinical Characteristics

- Most common primary liver tumors
  - Prevalence on imaging series: ~5%[1]
  - Prevalence on autopsy series: up to 20%[2,3]
  - Most common in women aged 30–50 years[3]
    - Female to male ratio ranges from 1.2–6:1
    - Can occur in all age groups
- Rarely of clinical significance
  - Often solitary and small (<4 cm), although can reach 20 cm in diameter[2,3]
  - Most patients are asymptomatic even with large hemangiomas[2,3]
  - Larger tumors (>10 cm) may be symptomatic – associated with pain and features of KMS (inflammatory reaction syndrome and coagulopathy)[4,5]

1. Horta G et al. *Rev Med Chil.* 2015;143:197–202; 2. Bahirwani R, Reddy KR. *Aliment Pharmacol Ther.* 2008;28:953–65;
3. Gandolfi L et al. *Gut.* 1991;32:677–80; 4. Hall GW. *Br J Haematol.* 2001;112:851–62; 5. O'Rafferty C et al. *Br J Haematol.* 2015;171:38–51;
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# Hepatic Hemangiomas: Key Diagnostic Recommendations

- Classic appearance on US is a homogenous hyperechoic mass

| Recommendations | Grade of evidence | Grade of recommendation |
|---|---|---|
| In patients with a normal/healthy liver, a hyperechoic lesion is very likely to be a liver haemangioma<br><br>US is sufficient for diagnosis in cases of typical radiology (homogeneous hyperechoic, sharp margin, posterior enhancement, absence of halo sign) in lesions <3 cm | II-2 | 1 |
| Contrast enhanced imaging (CEUS, CT or MRI) is required in oncology patients and patients with underlying liver disease | II-2 | 1 |
| Diagnosis by contrast-enhanced imaging is based on a typical vascular profile, characterized by peripheral and globular enhancement on arterial phase followed by a central enhancement on delayed phases<br><br>MRI provides additional findings: e.g lesion signal on T1-, T2-weighted sequences; diffusion imaging | II-2 | 1 |

EASL CPG benign liver tumours. *J Hepatol.* 2016;65:386–98.

# Hepatic Hemangiomas: Key Management Recommendations

- Hemangiomas are mostly asymptomatic incidental discoveries
  - May change in size during long-term follow-up
  - No relationship between size and complications
  - Little relationship between symptoms and characteristics
  - Benefit of surgery debatable

| Recommendations | Grade of evidence | Grade of recommendation |
|---|---|---|
| Due to its benign course, imaging follow-up is not required for typical hemangioma | II-2 | 1 |
| Pregnancy and OCPs are not contraindicated | III | 2 |
| Conservative management is appropriate for typical cases | II-2 | 1 |
| Refer to benign liver tumor MDT in the presence of KMS, growing lesions or lesions that are symptomatic by compression | III | 1 |

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# FNH: Epidemiology/Clinical Characteristics

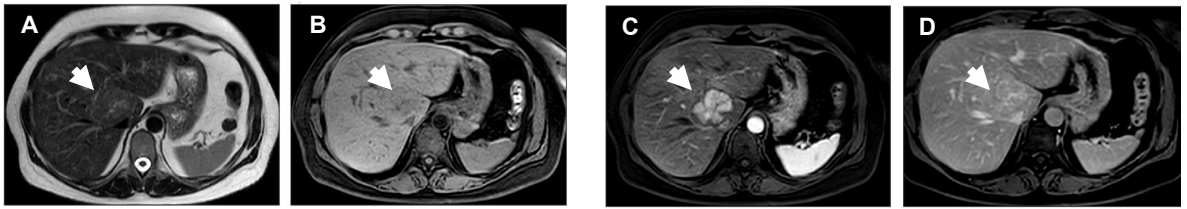
- Epidemiology
  - Clinically relevant prevalence: 0.03% (autopsy series: 0.4–3%)[1,2]
  - Up to 90% of patients are female
  - Average age at presentation: 35–50 years
- Clinical characteristics
  - Most cases are solitary and <5 cm; multiple FNH in 20–30% of cases[3,4]
  - Hyperplastic hepatocellular lesions resulting from arterial malformation
  - Size is stable over time in most cases[5]
  - Most cases are asymptomatic and complications are extremely rare[5]
- Genetics
  - Upregulation of ECM genes associated with TGF-β signaling[6]
  - Overexpression of Wnt/β-catenin target genes, e.g. *GLUL*[6]

1. Rubin RA, Mitchell DG. *Med Clin North Am.* 1996;80:907–28; 2. Marrero JA et al. *Am J Gastroenterol.* 2014;109:1328-47; 3. Nguyen BN et al. *Am J Surg Pathol.* 1999;23:1441–54; 4. Vilgrain V et al. *Radiology.* 2003;229:75–9; 5. D'Halluin V et al. *Gastroenterol Clin Biol.* 2001;25:1008–10; 6. Rebouissou S et al. *J Hepatol.* 2008;49:61–71; EASL CPG benign liver tumours. *J Hepatol.* 2016;65:386–98.

# FNH: Imaging

- Diagnosis is based on a combination of five imaging features:
  1. Lesion homogeneity, excluding the central scar
  2. Slight difference from adjacent liver tissue on pre-contrast US, CT and MRI (**A & B**)
  3. Strong, homogeneous enhancement on arterial phase CEUS, CT or MRI with a central vascular supply (**C**); becomes isointense to liver tissue on portal venous and delayed phases (**D**)
  4. Central scar best seen on MRI
  5. Lack of capsule with often lobulated contours

**T2- and T1-weighted images** | **Contrast-enhanced images**




Lesion barely visible | Lesion easily visible

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# FNH: Key Diagnostic Recommendations

- MRI sensitivity
  - Lesion >3 cm – very good
  - Lesion <3 cm – second imaging modality advised, such as CEUS
- Refer to a specialist center if in doubt with two imaging modalities

| Recommendations | Grade of evidence | Grade of recommendation |
|---|---|---|
| CEUS, CT, MRI: nearly 100% specificity with a combination of typical imaging features | II-2 | 1 |
| MRI has the highest diagnostic performance overall<br>Highest diagnostic accuracy by CEUS is achieved in FNH <3 cm | II-2 | 1 |

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# FNH: Key Management Recommendations

- In the absence of symptoms a conservative management approach is recommended
- No indication for discontinuing OCPs
- Follow-up during pregnancy is not necessary

| Recommendations | Grade of evidence | Grade of recommendation |
|---|---|---|
| For a typical FNH lesion, follow-up is not necessary unless there is underlying vascular liver disease | III | 2 |
| Treatment is not recommended | II-3 | 2 |
| If imaging is atypical, or the patient is symptomatic, refer to a benign liver tumor MDT | III | 1 |

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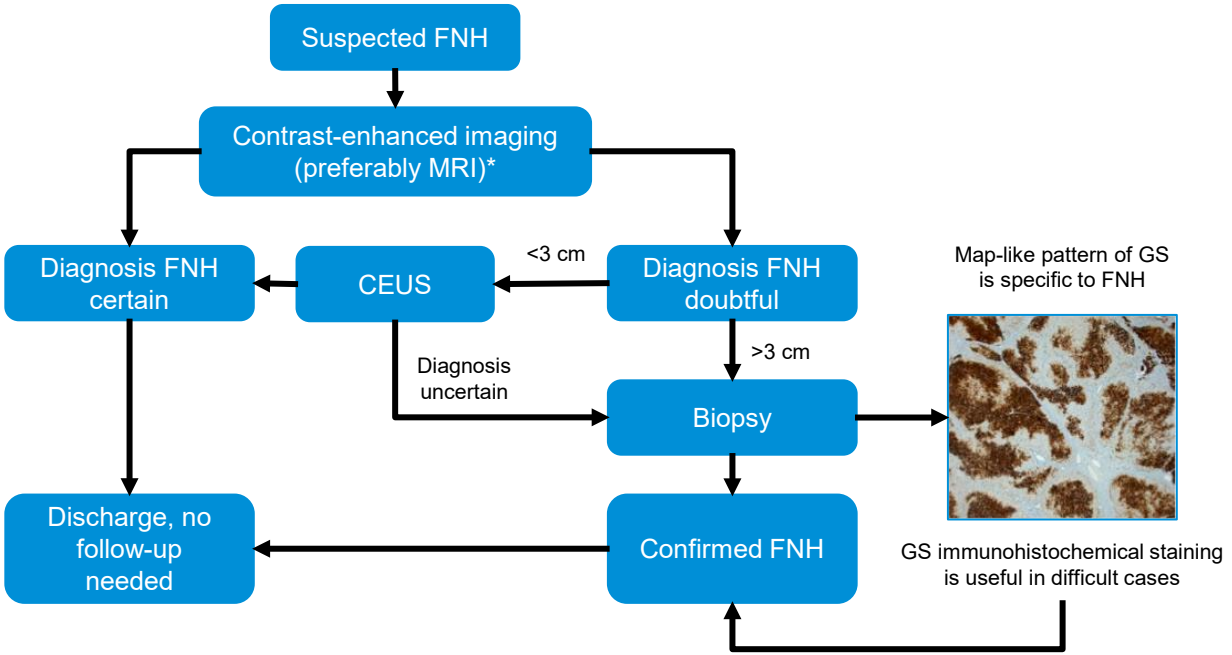
# FNH: Management Algorithm




*Imaging modalities may include US, CEUS, CE-CT and CE-MRI.

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# Adenoma: Epidemiology/Clinical Characteristics

- Epidemiology[1–3]
  - Reported prevalence: 0.001–0.004%
  - ~10x less common than FNH
  - Most common in women (10:1 female to male), especially aged 35–40 years
- Potential role of sex hormones
  - 30–40-fold increase in incidence with long-term OCP use[4]
  - Incidence among males is associated with androgenic steroids[5,6]
- Recent increase in prevalence associated with rising obesity and metabolic syndrome[7–9]
- Significant risk of haemorrhage and malignant transformation
  - Especially with lesions ≥5 cm

HCAs need to be followed more closely than other benign tumours

1. Bonder A, Afdhal N. *Clin Liver Dis.* 2012;16:271–83; 2. Karhunen PJ. *J Clin Pathol.* 1986;39:183–8; 3. Cherqui D et al. *Gastroenterol Clin Biol*. 1997;21:929–35; 4. Giannitrapani L et al. Ann NY *Acad Sci.* 2006;1089:228–36; 5. Socas L et al. *Br J Sports Med.* 2005;39:e27; 6. Nakao A et al. *J Gastroenterol.* 2000;35:557–62; 7. Bunchorntavakul C et al. *Aliment Pharmacol Ther.* 2011;34:664–74; 8. Bioulac-Sage P et al. *Liver Int.* 2012;32:1217–21; 9. Chang CY et al. *Int J Hepatol.* 2013;2013:604860; EASL CPG benign liver tumours. *J Hepatol.* 2016;65:386–98.

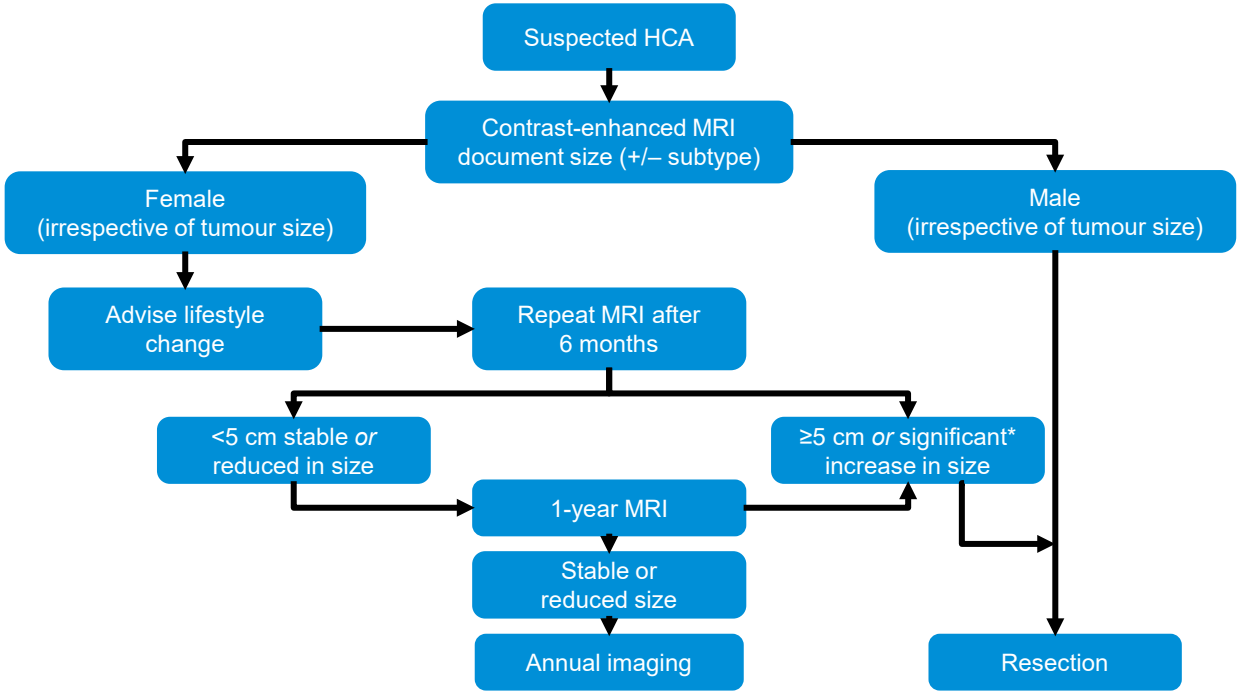
# Adenoma: Key Management Recommendations

- Adenomas have the potential for hemorrhage or malignant transformation
  - Management should involve a benign liver tumor MDT

| Recommendations | Grade of evidence | Grade of recommendation |
|---|---|---|
| Base treatment decisions on sex, size and pattern of progression | III | 2 |
| Discontinuation of OCPs and weight loss should be advised | II-2 | 1 |
| **Resection irrespective of size is recommended in men** and in all cases of proven β-catenin mutation | II-3 | 2 |
| **Observe women for 6 months after lifestyle change**.<br>• Resection is indicated with lesions ≥5 cm and those continuing to grow<br>• Reassess lesions <5 cm at 1 year with annual imaging thereafter | II-3<br>II-3<br>III | 2<br>2<br>2 |
| Bleeding HCAs with haemodynamic instability should be embolized and a residual viable lesion on follow-up imaging is an indication for resection | III | 2 |

EASL CPG benign liver tumours. *J Hepatol*. 2016;65:386–98.

# Adenoma: Management Algorithm




*≥20% diameter.

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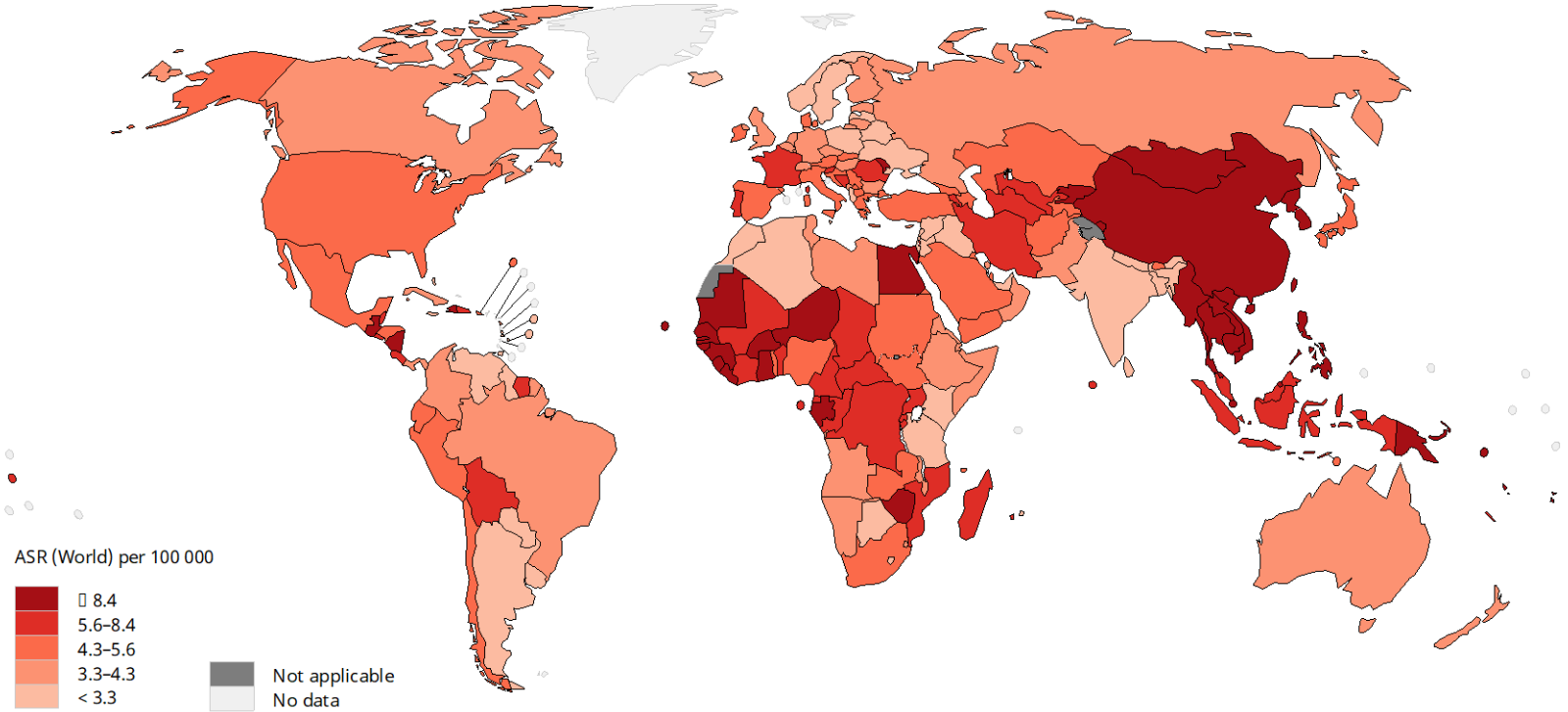
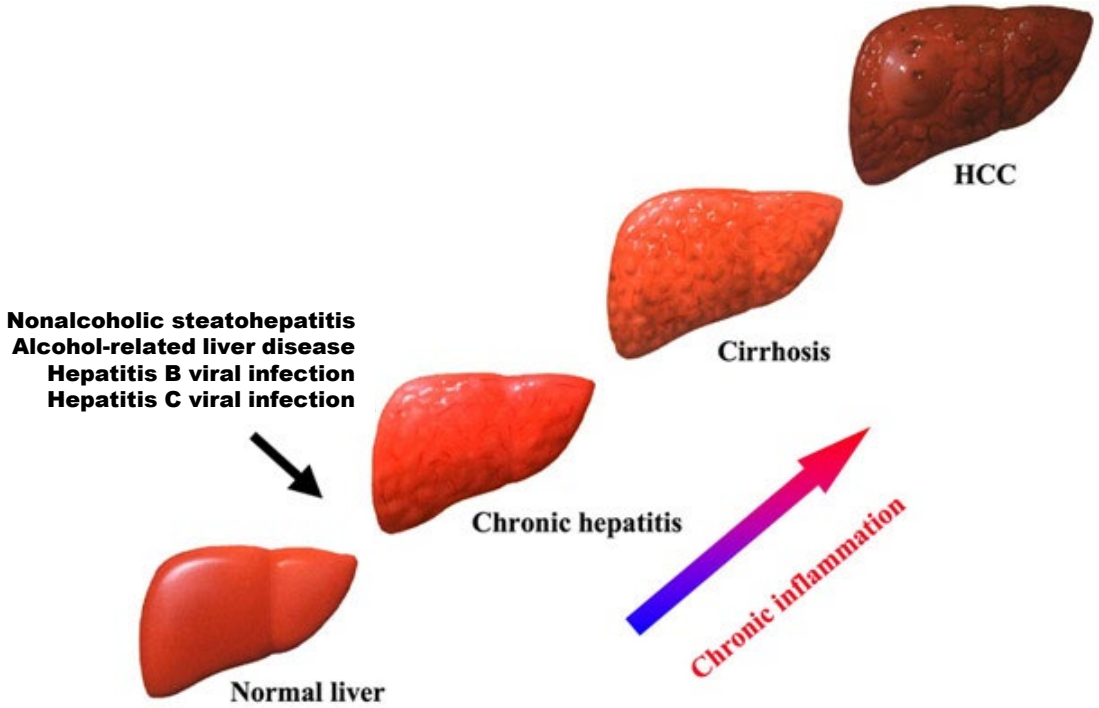
# Hepatocellular Carcinoma Is 4th Leading Cause of Cancer-Related Death Worldwide




*GLOBOCAN*. 2020.

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



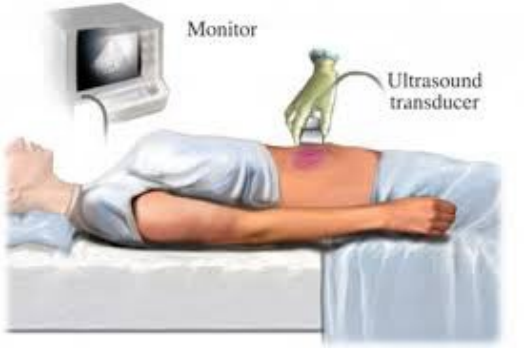
# Major Guidelines Recognize the Importance of Routine Surveillance in High-risk Populations

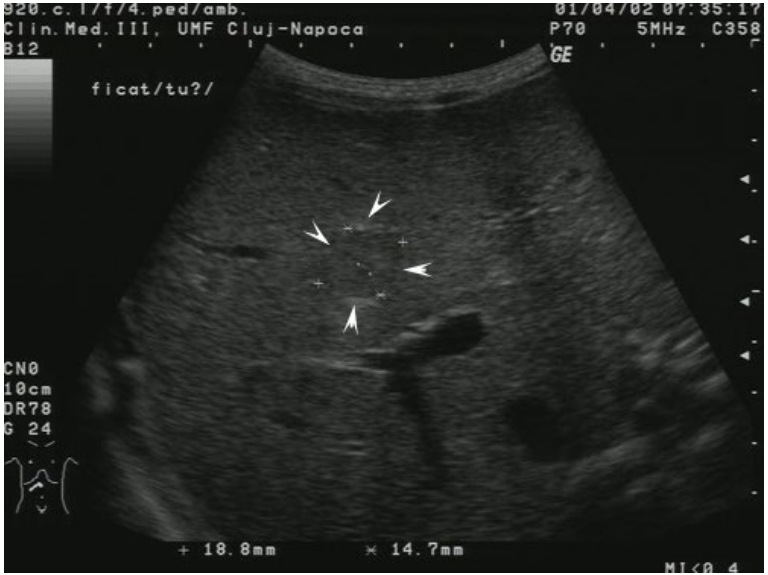
| Society/Institution | Guidelines |
|---|---|
| AASLD[1]<br>American Association for the Study of Liver Diseases | US every 6 months |
| EASL[2]<br>European Association for the Study of the Liver | US every 6 months |
| APASL[3]<br>Asian-Pacific Association for the Study of the Liver | AFP + US every 6 months |
| NCCN[4]<br>National Comprehensive Cancer Network | AFP + US every 6-12 months |
| VA[5]<br>United States Department of Veterans Affairs | AFP + US every 6-12 months |
| JSH-HCC[6]<br>Japan Society of Hepatology | High-risk: US every 6 months + AFP/DCP/AFP-L3 every 6 months<br>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.

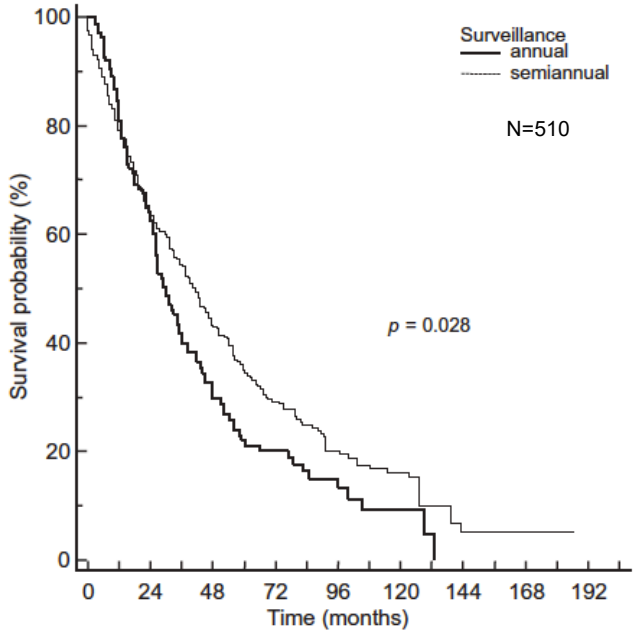
1. Bruix J et al. *Hepatology*. 2011;53:1020-1022; 2. EASL, EORTC. *J Hepatol.* 2012;56(4):908-943; 3. Omata M et al. *Hepatol Int*. 2010;4(2):439-474; 4. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hepatobiliary Cancers v1.2016. © National Comprehensive Cancer Network, Inc. 2016. All rights reserved. Accessed February 10, 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.

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



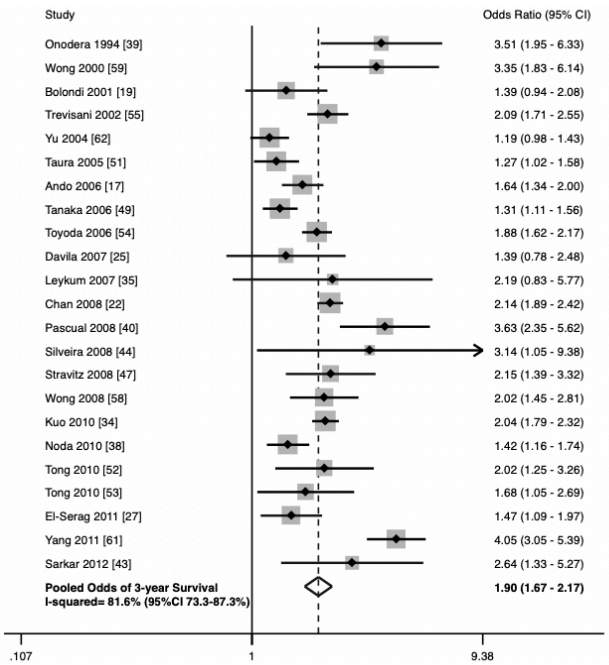
# Surveillance Should Be Performed at Semi-Annual Intervals




| 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**<br>**Less than 2 cm**<br>**Within Milan** | 53 (28%)<br>20 (38%)<br>42 (79%) | 70 (42%)<br>29 (41%)<br>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

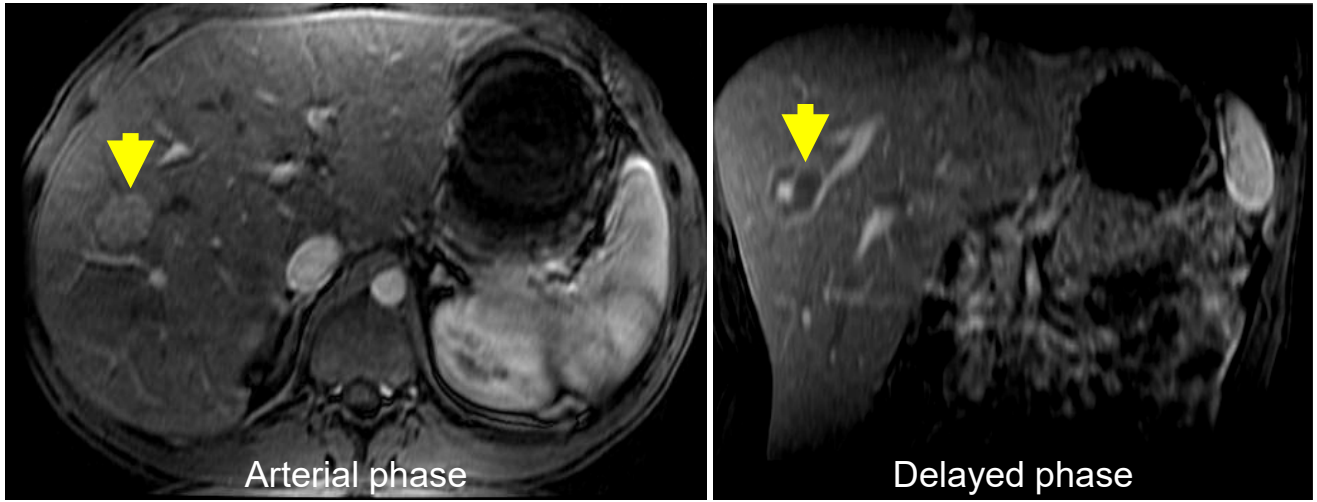
Signal et al. *PLOS Medicine*. 2014.

# Ultrasound (US) in Surveillance

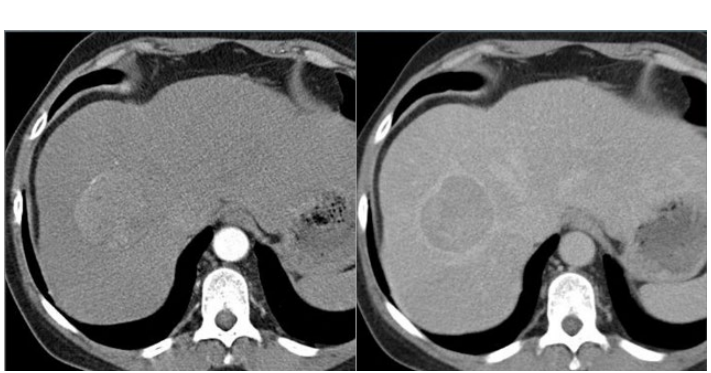
- Excellent specificity (>90%), but low sensitivity – a meta-analysis indicates US sensitivity in detecting early stage HCC may be as low as 63%
- Multiple limitations
  - Does not detect infiltrative disease
  - Sensitivity decreased in difficult patients
    - Cirrhotic nodular livers
    - Obesity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

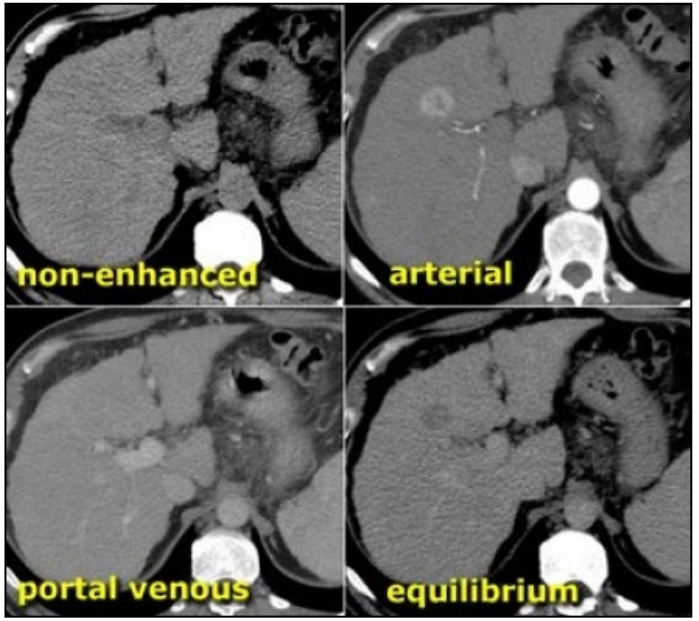
Del Poggio P et al. *Clin Gastroenterol Hepatol*. 2014;12(11):1927-1933.e2.

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



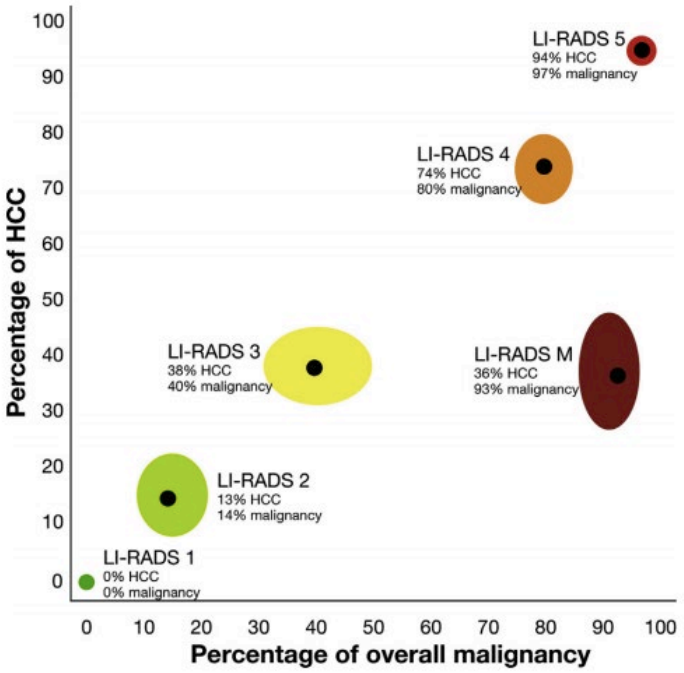
# Triple Phase Imaging



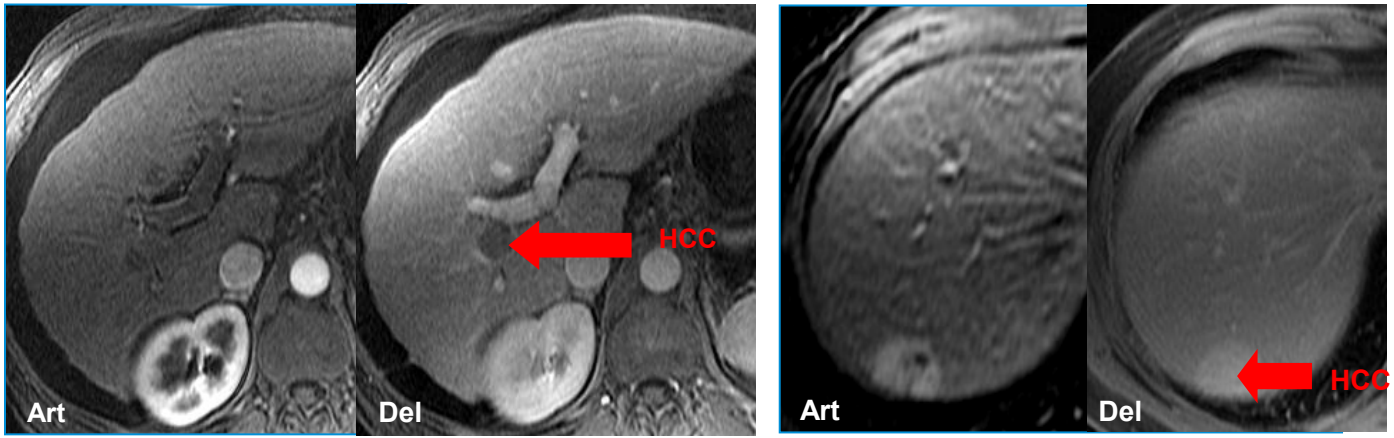


# LI-RADS Criteria for HCC Diagnosis

| 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 |



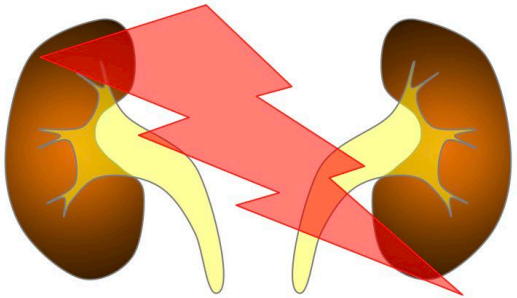
# Biopsy Only Occasionally Plays a Role in HCC Diagnosis



# CT Is Not Viable 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 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.

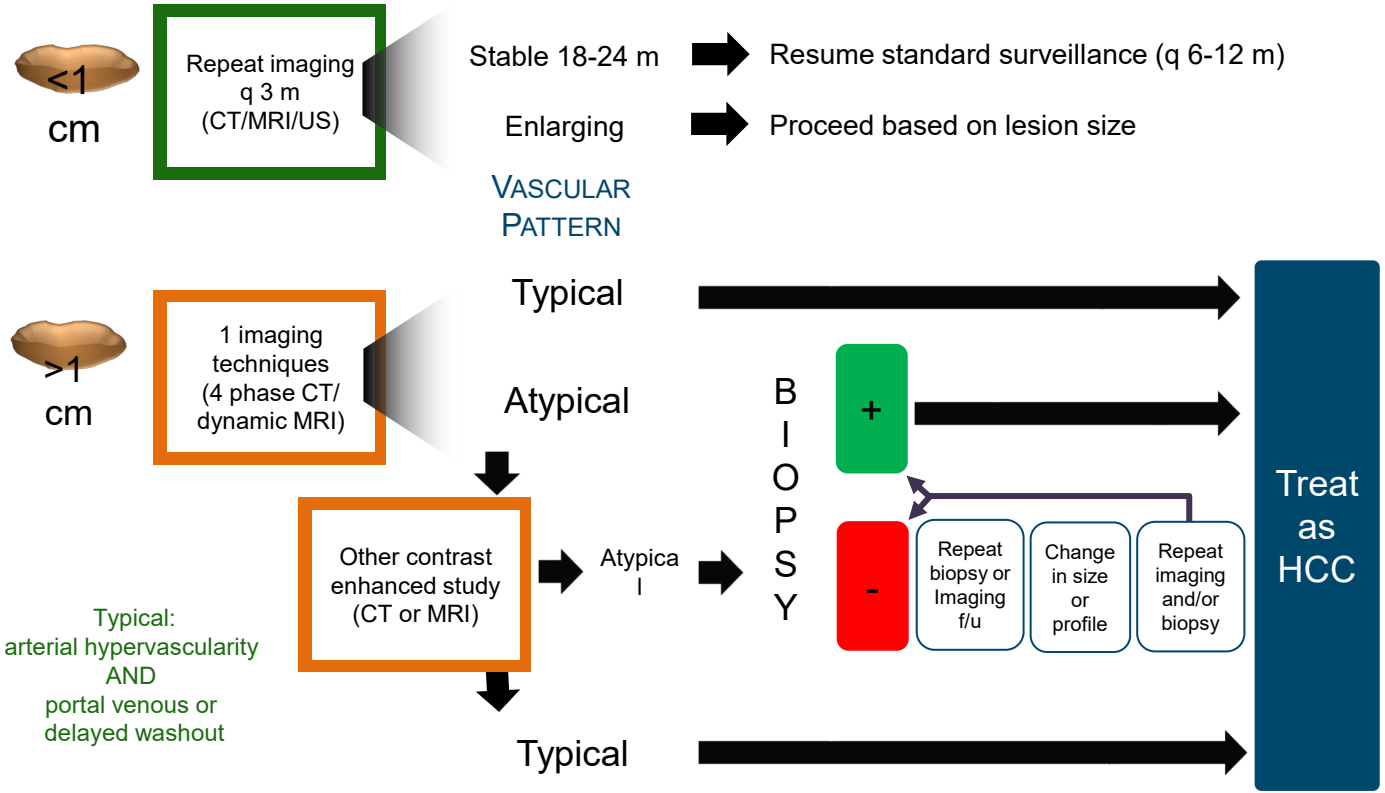
# Scans and Biopsies

- Scans: ***Which ones?***
  - US is used for ease and cost, but sensitivity is low[1]
  - Triple-phase helical CT or triple-phase dynamic contrast enhanced MRI is more sensitive[2]
    - Presence of arterial enhancement followed by washout has sensitivity (90%) and specificity (95%)[3]
  - When to biopsy and when NOT to biopsy
    - **95% specific for HCC: biopsy NOT needed in most patients[3]**
    - Only focal hepatic mass with atypical imaging findings or focal hepatic mass detected in a non-cirrhotic liver should undergo biopsy[3]

1. Del Poggio P et al. *Clin Gastroenterol Hepatol*. 2014;12(11):1927-1933.e2; 2. Digumarthy S et al. *Cancer Imaging*. 2005;5(1):20-24;
3. Bruix J et al. *Hepatology*. 2011;53(3):1020-1022.

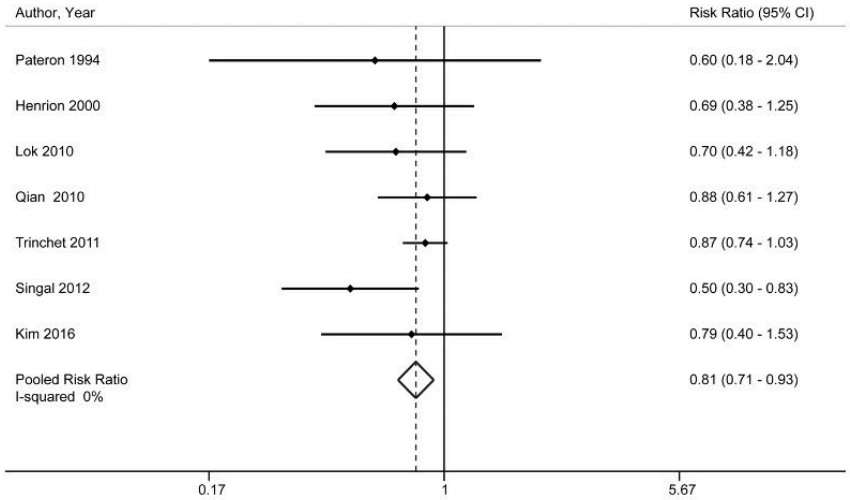
# HCC Diagnosis

## Following Detection of Mass in Cirrhotic Liver

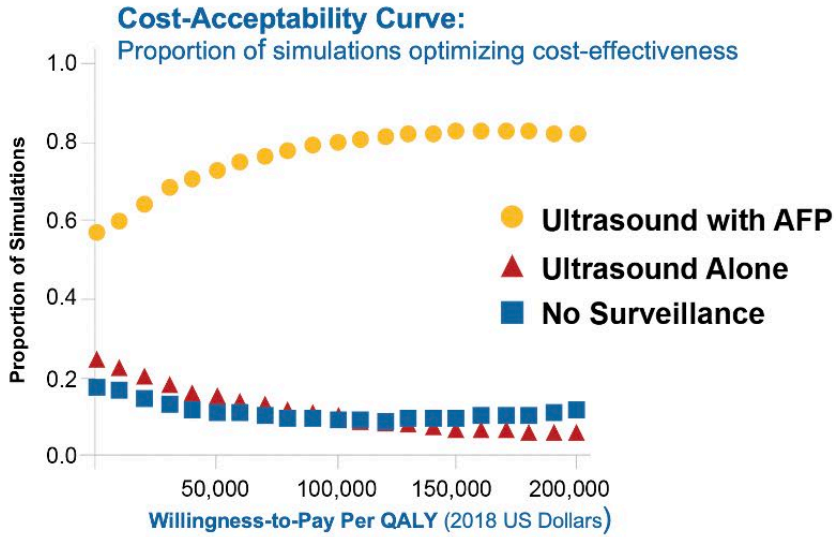



Bruix and Sherman. AASLD guidelines. 2010.

# 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

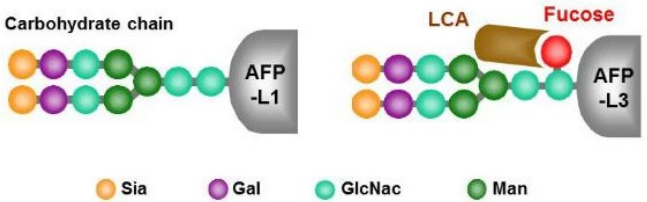
- AFP-L3 and DCP
- Golgi protein 73 (GP73)
- Glypican 3 (GPC3)
- Osteopontin
- miR-21 (circulating miRNA)
- Serum and urinary metabolites
- Fucosylated kininogen (Fc-Kin)
- Circulating tumor cells/methylated DNA markers

# 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

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

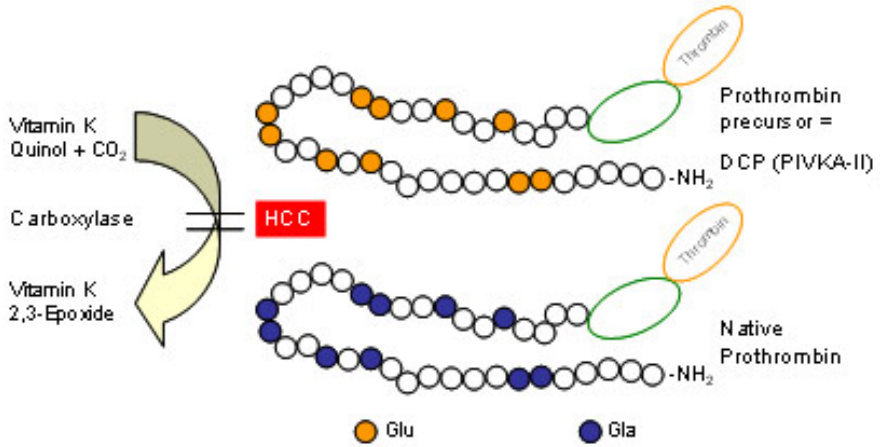
***Cut-off Point: 10% (Intended Use)***




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*

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

# GALAD Is a Promising Novel Biomarker Panel for Early Detection

*COI

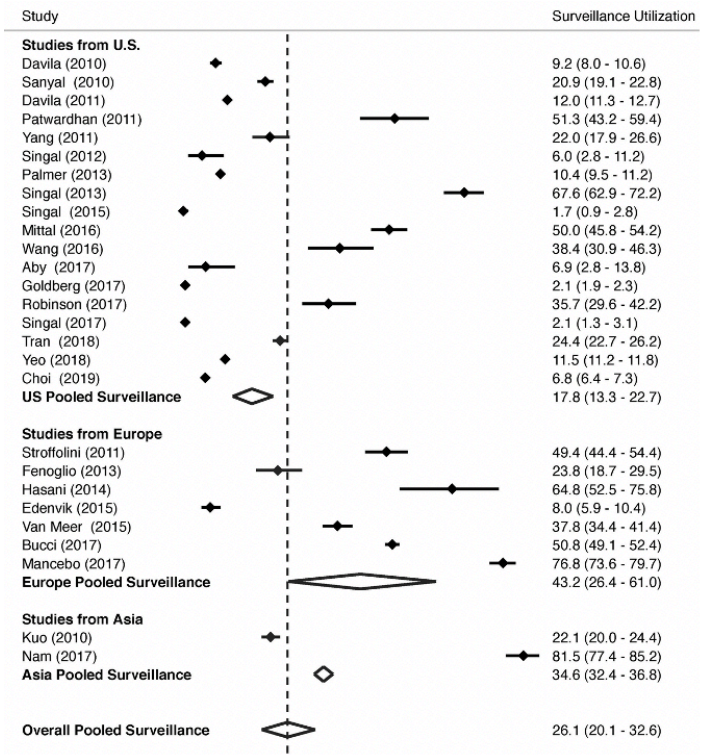
- GALAD: **G**ender, **A**ge, AFP-**L**3, **A**FP, and **D**CP
- Multi-national nested case control with 6834 patients (2430 HCC, 4404 CLD)

| 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.

# 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 1

- Benign solid liver tumors are common
  - Hemangiomas
  - Focal nodular hyperplasia
  - Adenomas

# Summary 2

- HCC surveillance supported by RCT in patients with chronic HBV and several cohort studies in those with cirrhosis
- 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