HEPATOCELLULAR CARCINOMA (HCC) IN ALASKA NATIVE PEOPLE: EPIDEMIOLOGY, SURVEILLANCE AND MANAGEMENT

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CONFLICTS OF INTEREST

- Brian McMahon: None
- Our Program has 2 research grants from Gilead Sciences neither of which funds any of our salaries

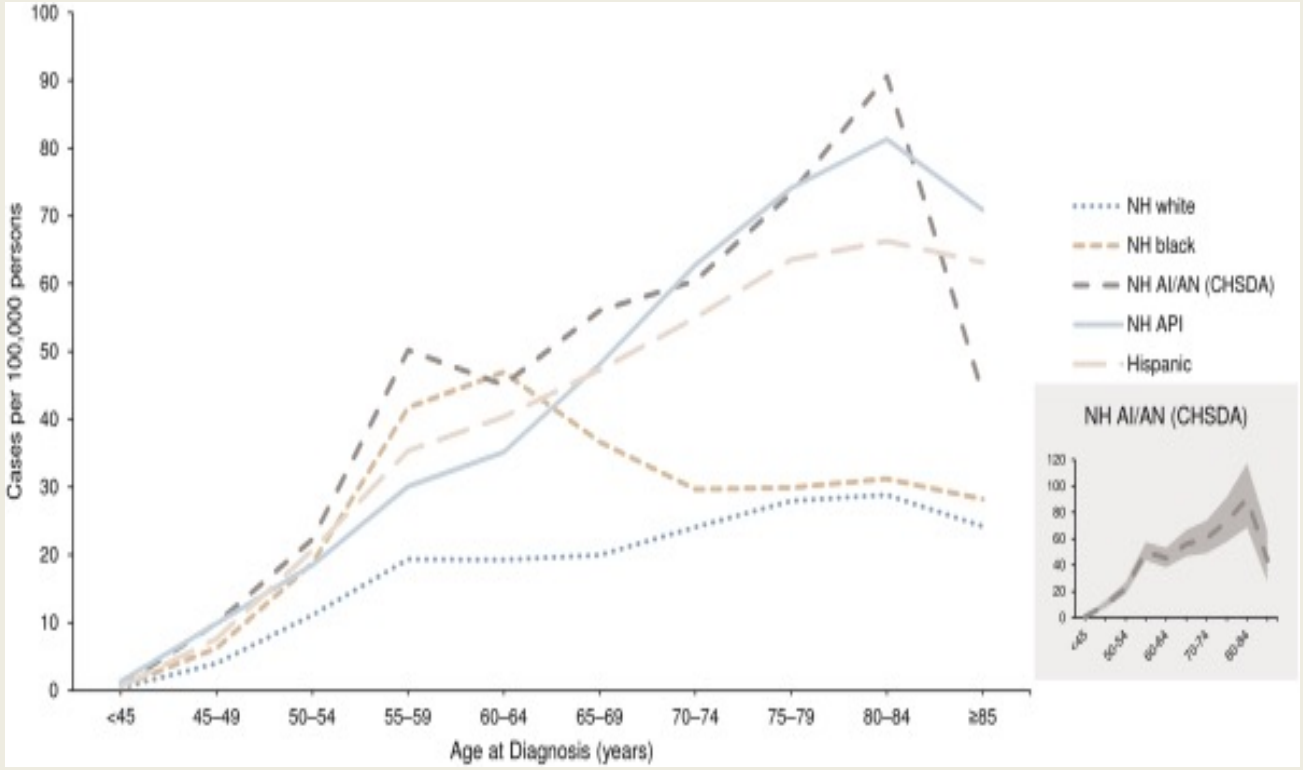
QUIZ: CHOSE THE BEST ANSWER(S)

1. In the past 20 years, the survival rate for HCC has improved by >50%
2. Overall 5-year survival after diagnosis of HCC is <20% nationally
3. Major advances in chemo and immunotherapy have given new hope for improved survival for large tumors
4. The best chances to cure HCC is to find the tumors when they are small and can be removed or ablated.
5. HCC is the number three cancer killer in men worldwide

GOALS OF PRESENTATION

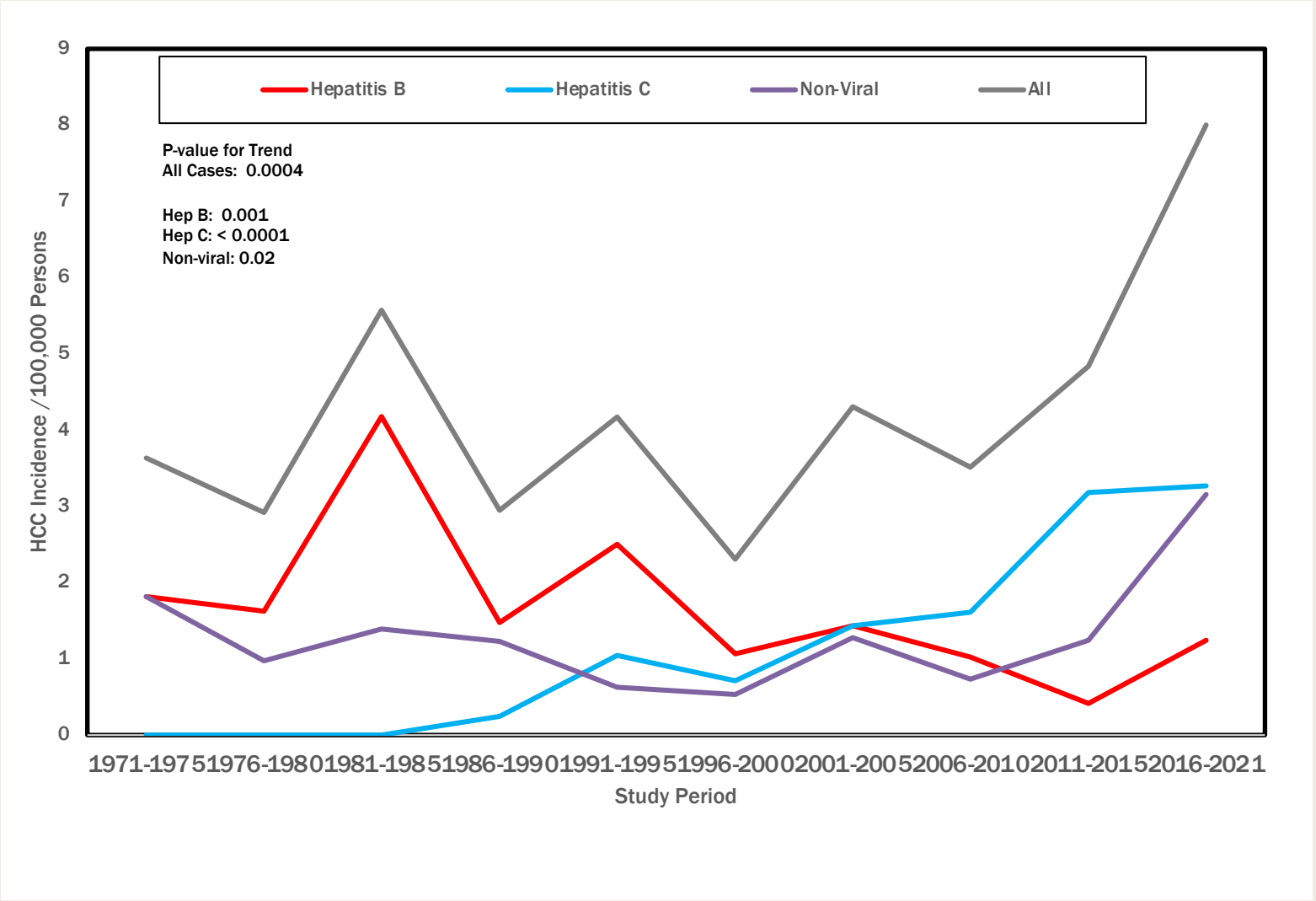
- Discuss incidence of hepatocellular carcinoma (HCC) in American Indian and Alaska Native Populations:
- Changes in the incidence and etiology in the last couple of decades
- Discuss major etiologies of cirrhosis and HCC
- Discuss risk factors for developing HCC in associated etiologies:
  - Hepatitis B virus (HBV)
  - Hepatitis C virus (HCV)
  - Non-alcoholic fatty liver disease (NAFLD)
  - Alcoholic cirrhosis
  - Other etiologies of cirrhosis and HCC
- Reducing the incidence of HCC: What must be done

ANNUAL REPORT TO THE NATION ON THE STATUS OF CANCER, 1975-2012, FEATURING THE INCREASING INCIDENCE OF LIVER CANCER



Cancer
9 MAR 2016 DOI: 10.1002/cncr.29936
http://onlinelibrary.wiley.com/doi/10.1002/cncr.29936/full#cncr29936-fig-0002

Incidence of Hepatocellular Carcinoma (HCC) in the Alaska Native Population:1971 through 2022



HOW TO DECREASE MORBIDITY AND MORTALITY IN AMERICAN INDIAN/ALASKA NATIVE AI/AN PEOPLE DUE TO HEPATOCELLULAR CARCINOMA (HCC) AND CIRRHOSIS

- Identify AI/AN Persons with underlying liver diseases early
- Determine the cause (etiology) of the underlying liver condition
  - Linkage to care
  - Prevent progression of this condition
    - Life style changes
    - Medication or other modalities
  - Cure condition if curative treatment is available
- Identify those with underlying liver condition at risk for HCC and initiate surveillance to detect HCC at an early and curable stage
    - Anyone with advanced fibrosis (F3) or cirrhosis (F4)
    - Persons with hepatitis B without cirrhosis at risk of HCC
- Apply most effective treatments for those who develop HCC
- Promote research, both scientific and community-based, to prevent and treat HCC

UNDERLYING CAUSES OF LIVER CANCER IN ALASKA NATIVE PEOPLE (ALL BUT HEP B FOR AI)

- Hepatitis B: in men 40 years and older, women 50 years and older, those who have family members who had liver cancer and those who have a cancer cause type (F)
- Hepatitis C: Those persons with cirrhosis, even if they have been cured
- MAFLD
- Alcoholic Liver Disease
- Other: Autoimmune Hepatitis/PBC?
- What to do
  - Identify these persons early
  - Treat their underlying condition
  - Asses the level of fibrosis
  - If they have F3 or F4 fibrosis, initiate surveillance

FINDING PERSONS AT RISK FOR HCC AND BY IDENTIFYING THOSE AT RISK FOR LIVER DISEASE

- Annual risk for those at highest risk ranges between 1 and 3/1,000
- HCV: CDC and USPSTF recommends all adults be tested once and high risk persons regularly
  - Baby boomers: Baby Boomers are at highest risk, 40% may have acquired HCV without using drugs
  - Evaluate HCV infected persons for advanced fibrosis and cirrhosis as they need surveillance:
  - For recently infected young persons the risk is low as incubation 20-40 years
- NAFLD: Identify those with NASH: Risk is high for those with F3/F4 fibrosis
  - Important to note that NAFLD frequently is co-present in persons with HCV and HBV
- Alcoholic Liver Disease: Annual risk in those with cirrhosis is lower ~1%/year
  - Reason may be that persons with ALD who continue to drink may die of liver failure
    - Once a person with cirrhosis quits alcohol the risk of HCC drops dramatically

Risk of Developing HCC in Alaska Native Persons with HCV from Time of Liver Biopsy by Fibrosis Stage: Pre DAA

Outcome	Time Period	None/Mild (Metavir 0-1) (n = 150)	Moderate (Metavir 2) (n = 131)	Severe (Metavir 3) (n = 88)	Cirrhosis (Metavir 4) (n = 38)
HCC	3-Year	0.0% (0.0, 3.2) (n = 118)	0.0% (0.0, 3.4) (n = 103)	1.1% (0.2, 7.7) (n = 65)	3.3% (0.5, 21.4) (n = 25)
	5-Year	1.0% (0.1, 6.9) (n = 95)	1.0% (0.1, 6.6) (n = 87)	1.1% (0.2, 7.7) (n = 54)	13.4% (4.4, 36.7) (n = 16)
	7-Year	1.0% (0.1, 6.9) (n = 81)	2.3% (0.6, 9.1) (n = 72)	6.0% (1.9, 18.2) (n = 42)	35.0% (16.5, 64.4) (n = 11)
	10-Year	1.0% (0.1, 6.9) (n = 52)	4.6% (1.4, 4.8) (n = 44)	8.4% (3.1, 21.6) (n = 27)	
	# of Cases	2	4	7	9

Bruden D et al. Hepatology 2017;66:37-45

NAFLD

- Incidence is not well described
- Some studies suggest increase risk in persons without cirrhosis independent of fibrosis
- Once cirrhosis is well established, life style changes of weight loss and exercise even if successful might not reduce subsequent risk of HCC

WHAT MEASURES MIGHT REDUCE RISK OF HCC

- HCV:
  - Diagnosis and treatment (cure) in persons with HCV
  - Programs to reduce acquisition of HCV, including opioid addiction treatment, clean needles
- NAFLD:
  - Progress in reducing obesity including diet, exercise, drugs such as appetite suppresses, obesity surgery, drugs that block hepatic steatosis and hepatic fibrosis
  - Other conditions including hemochromatosis, AIH, PBC etc.: early diagnosis and treatment

ASSESSING LEVEL OF FIBROSIS IN PERSONS WITH LIVER DISEASE

- Non-invasive serologic markers of fibrosis
  - APRI
  - FIB4
  - NAFLD Fibrosis Score
  - Commercial markers: Expensive, not that much better than above free markers
    - Fibrosure, FibroSpect2, and others
- Vibration Controlled Transient Elastography (VCTE or FibroScan®)
- Other sonographic techniques
- Magnetic resonance elastography (MRE)
- Liver Biopsy

‘Simple Scores’ for Predicting Presence of Advanced (F3/4) Fibrosis

NAFLD Fibrosis Score

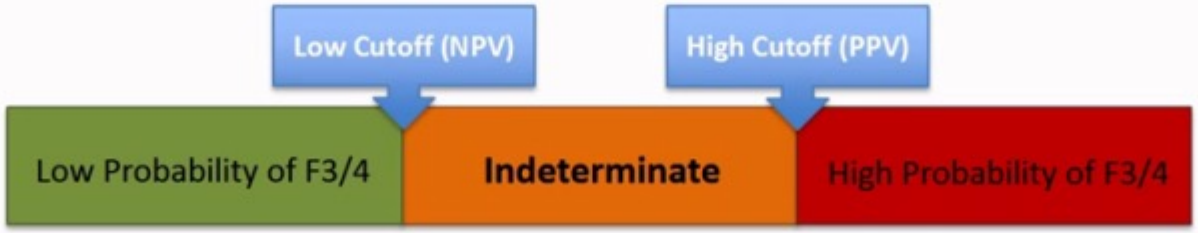
= -1.675 + 0.037 x **Age** + 0.094 x **BMI** + 1.13 x **IFG/diabetes** + 0.99 x **AST/ALT ratio** - 0.013 x **Platelets** - 0.66 x **Albumin**.

- A score of less than -1.455 excludes fibrosis (NPV 88-93%).
- A score of greater than 0.676 predicts fibrosis (PPV 82-90%). AOC 0.85

FIB-4 Score

= (**Age** * **AST**) / (**Platelets** * Sqrt (**ALT**))

- A score of less than 1.3 excludes fibrosis (NPV 95%)
- A score greater than 3.25 predicts fibrosis (PPV ~70%)



www.qxmd.com

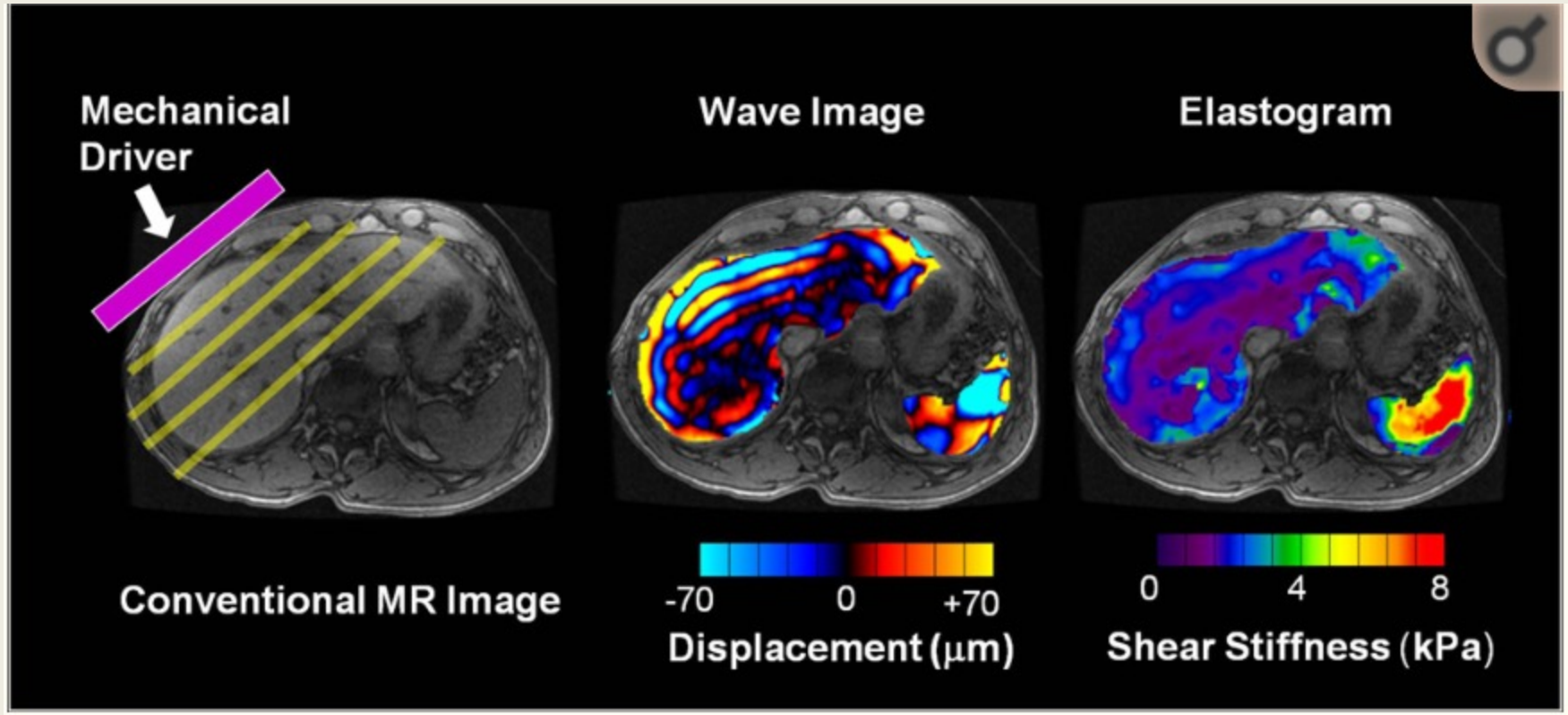
ngulo et al, Hepatology 2007: 45(4) 846

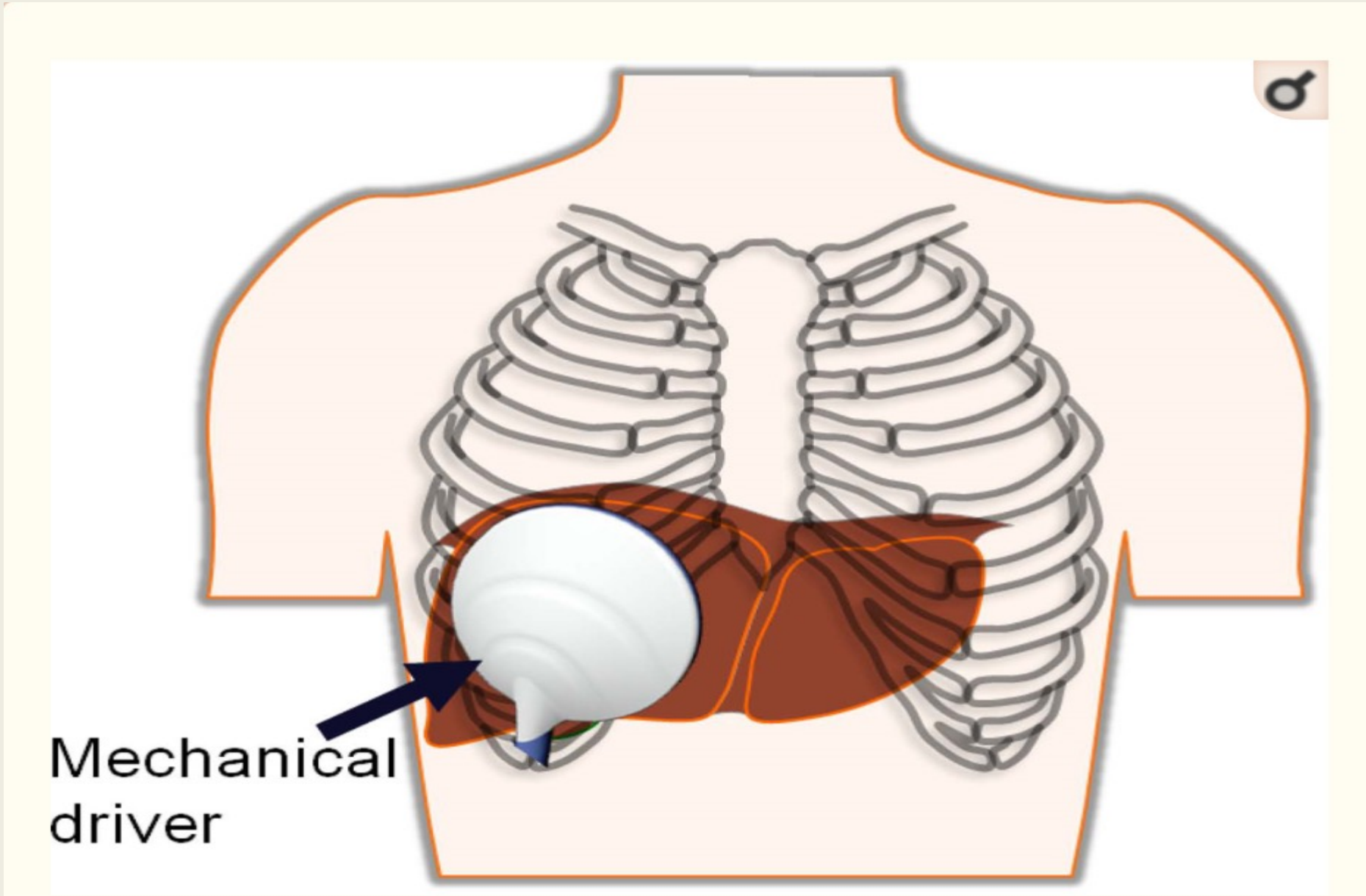
Sterling et al, Hepatology 2006: 43, 1317; McPherson et al, Gut 2010: 59(9), 1265

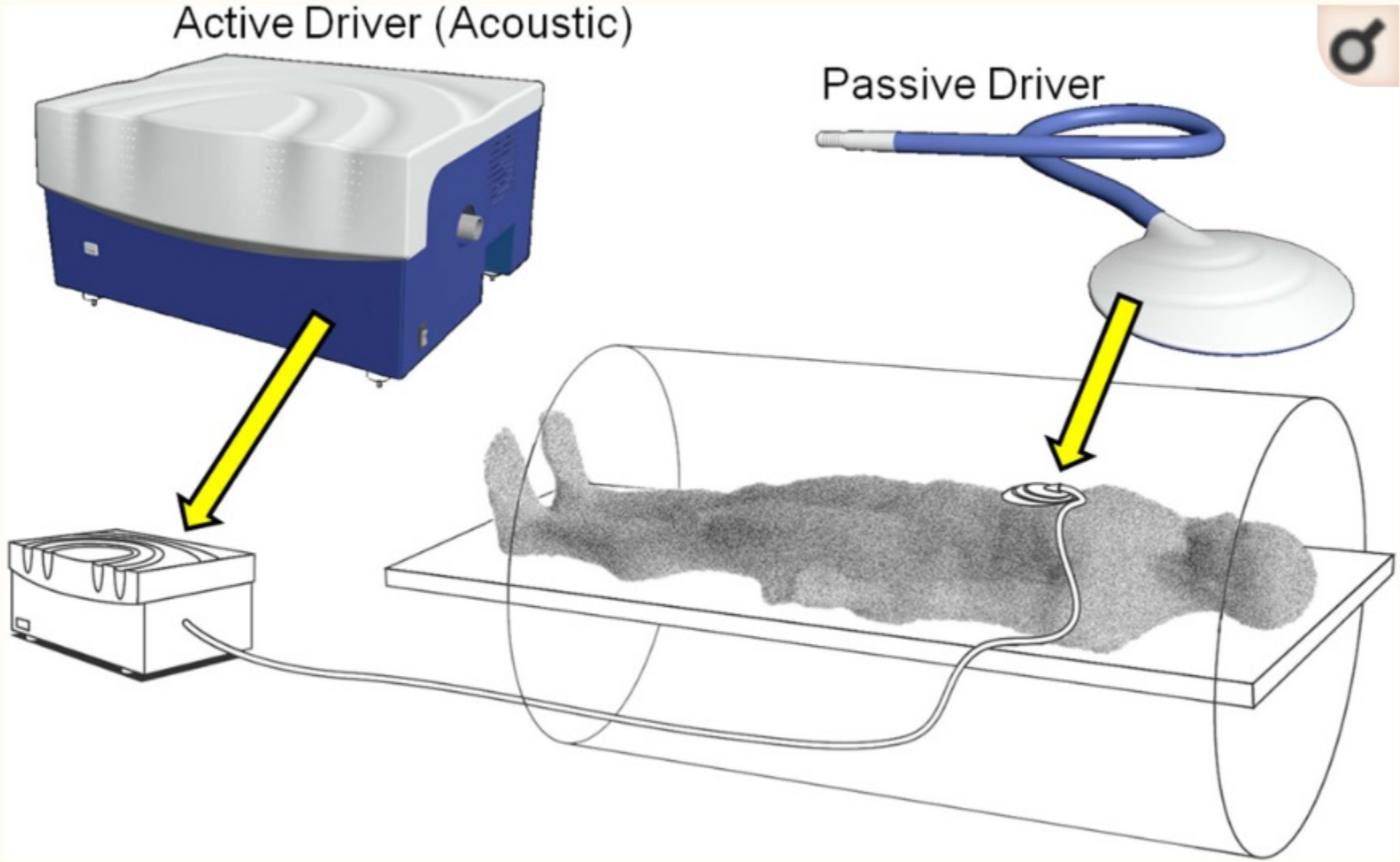
TRANSIENT ELASTOGRAPHY

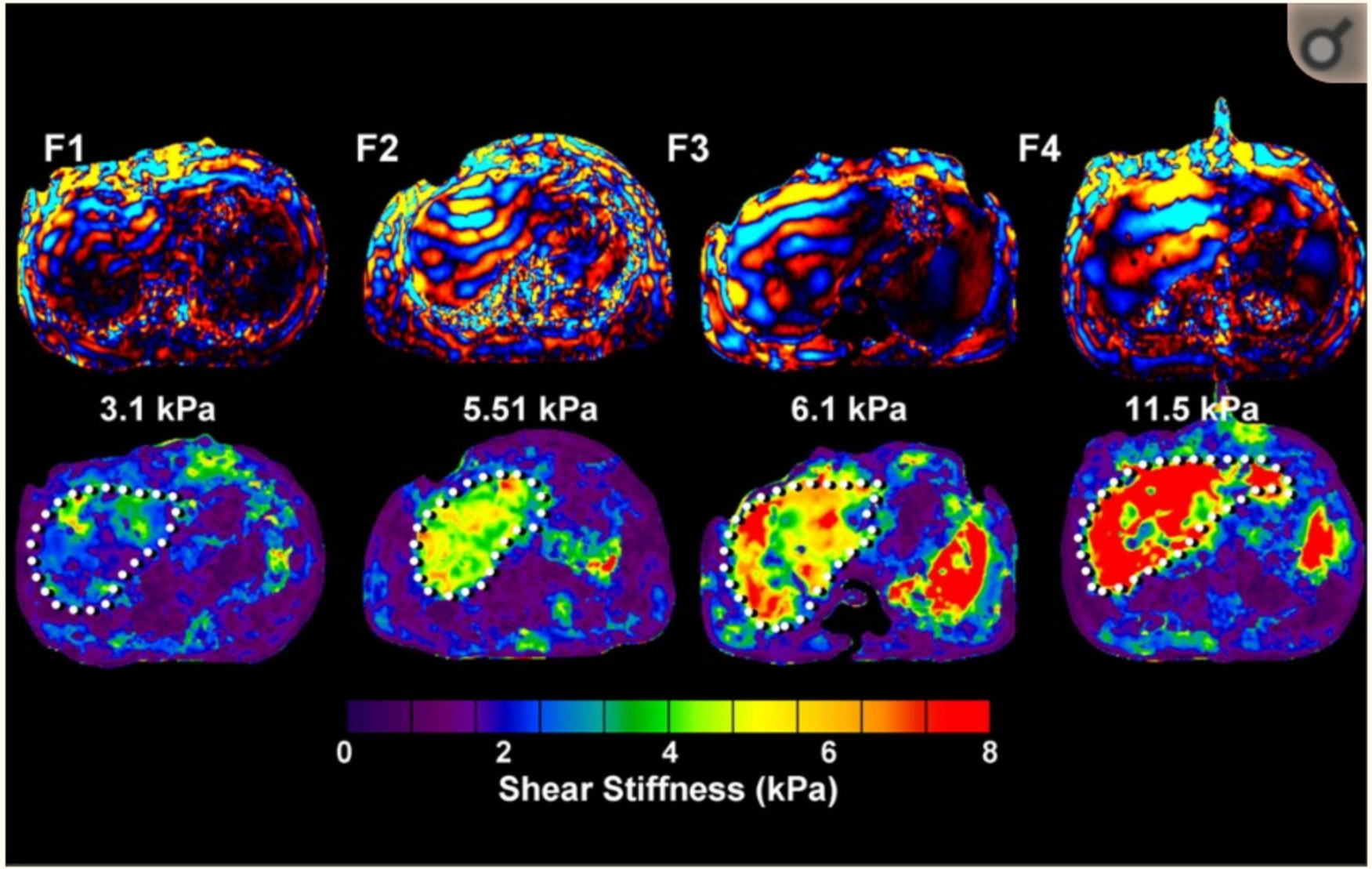
- Allows painless and simultaneous measurement of two quantitative parameters:
- Liver stiffness expressed in kPa
  - Correlated to liver fibrosis [1]
- Controlled Attenuation Parameter (CAP™) expressed in dB/meter
  - Correlated to liver steatosis [2]
- Both quantitative parameters are assessed on the same volume of liver tissue
- 100 times bigger than liver biopsy

1. Friedrich Rust, et al. *Gastroenterology*. 2008; 2. Sasso, et al. *Journal of Viral Hepatitis*. 2011.

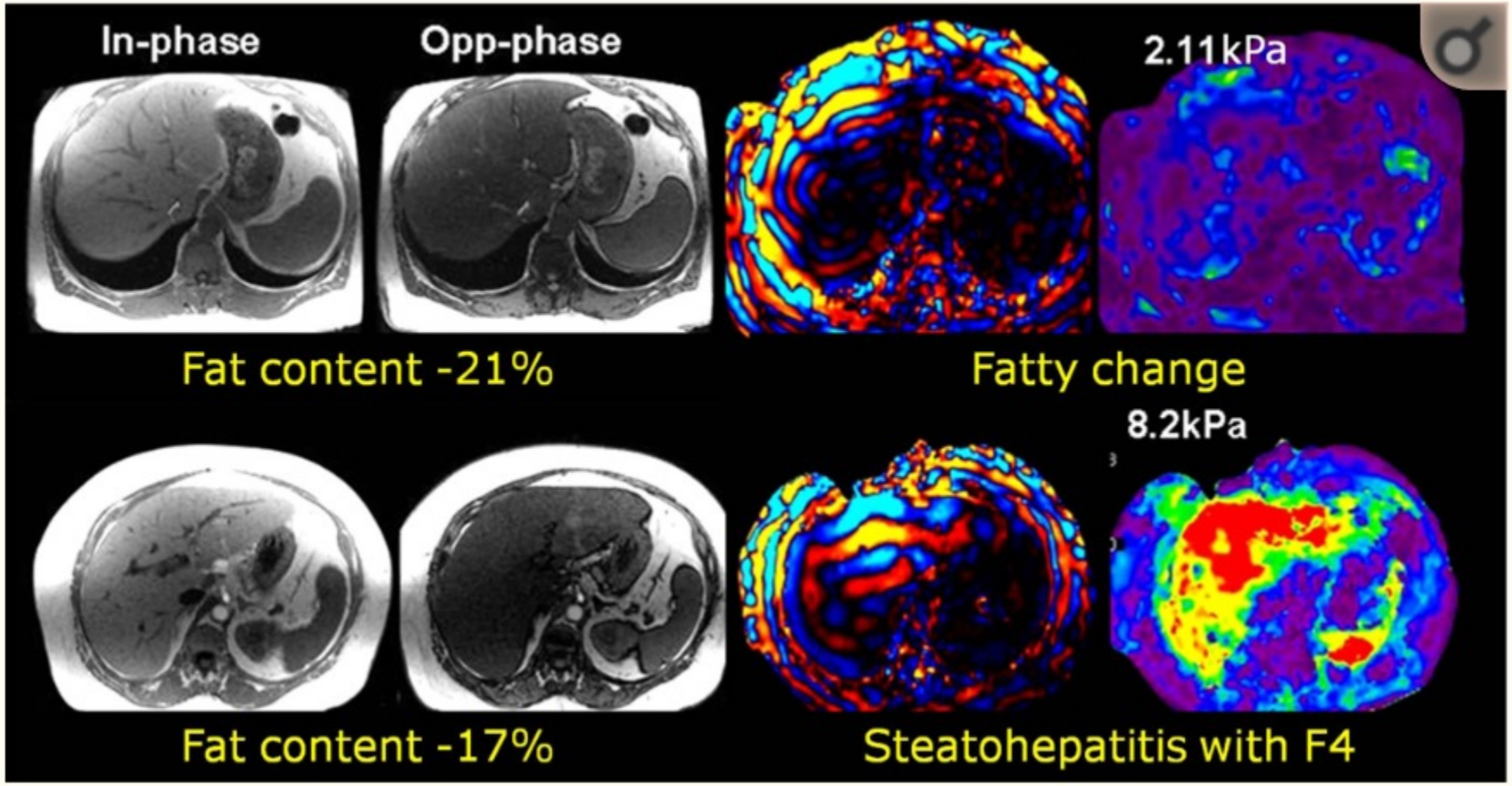

Mechanical
Driver
Wave Image
Elastogram
Conventional MR Image
-70
0
+70
Displacement (μm)
0
4
8
Shear Stiffness (kPa)


♂
Mechanical
driver


Active Driver (Acoustic)
Passive Driver


F1
F2
F3
F4
3.1 kPa
5.51 kPa
6.1 kPa
11.5 kPa
0
2
4
6
8
Shear Stiffness (kPa)

Upper Panel: NAFL with no Fibrosis; Lower Panel: Steatosis with Cirrhosis



WHAT SCREENING METHODOLOGIES TO USE AND HOW FREQUENTLY

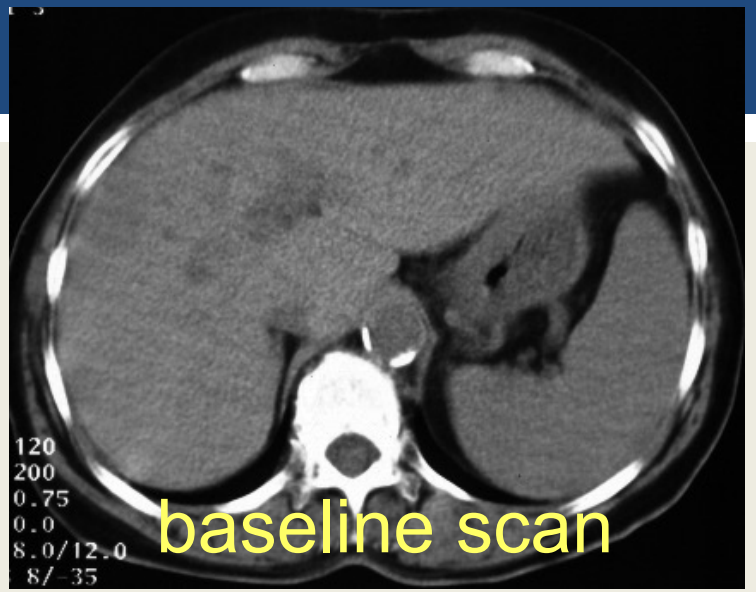
- Ultrasound of the liver and AFP every 6 months. Insurers will cover this in patients with cirrhosis

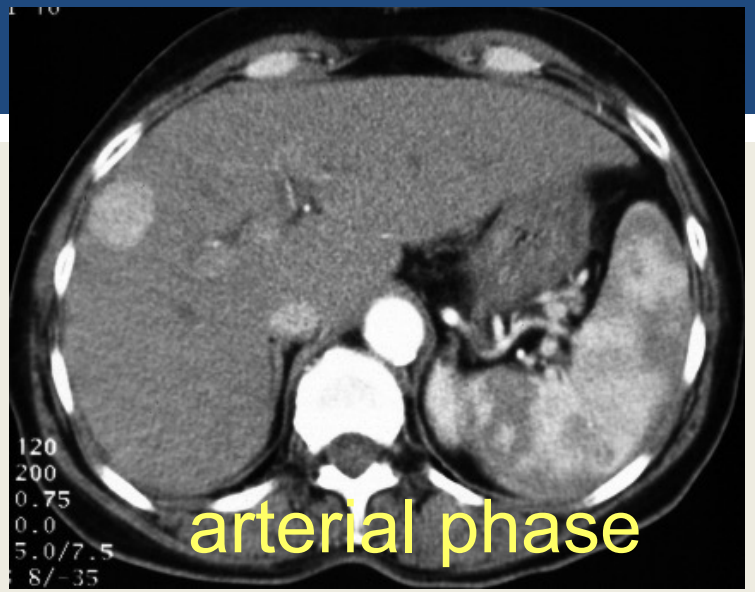
AASLD Guideline for HCC Hepatology 2018;67:358-380
Download for free at AASLD.org under practice guidelines

IMAGING MODALITIES FOR HCC SURVEILLANCE

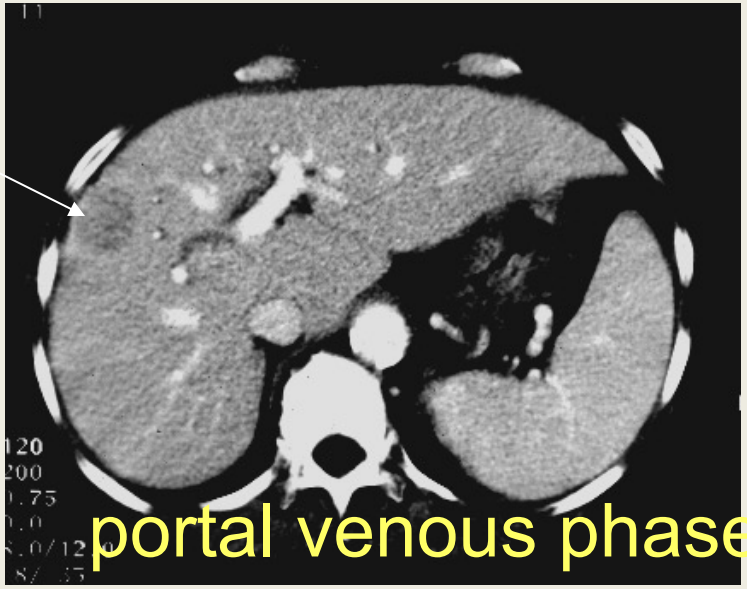
Imaging	Advantages	Disadvantages
Ultrasound	• Non-Invasive • Availability is ubiquitous • Low cost	• Highly operator & technique dependent -directly proportional to operator experience & skill • Low Sensitivity in Obesity • Soft tissue assessment • Low sensitivity in other Disease states
CT 4 Phase	• High sensitivity	• Risk of high radiation • High cost
MRI	• High sensitivity • High resolution	• Limited availability • Extremely high cost • GAD accumulation

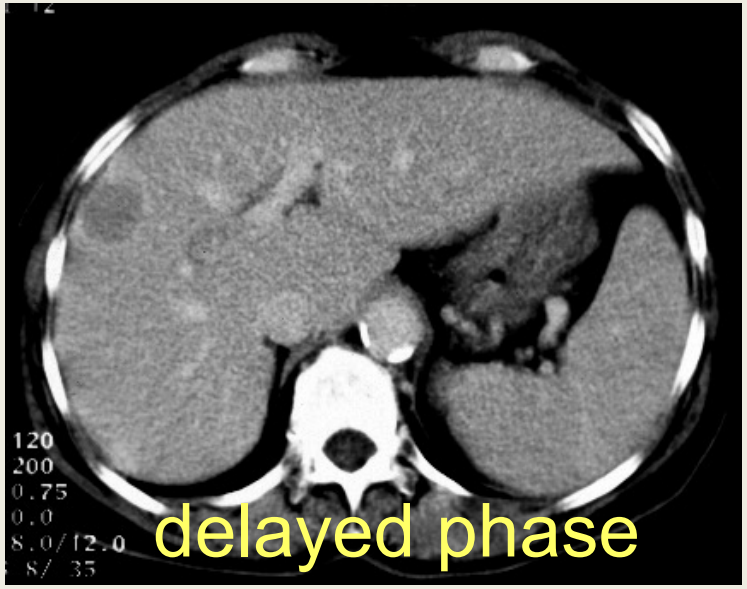
MULTIPHASIC CT FOR HEPATOCELLULAR CARCINOMA





Washout Phase





SENSITIVITY OF HCC DETECTION

Size	US	CT	MRI
Per-nodule	92/200 (46%)	126/194 (65%)	126/175 (72%)
<2cm	20/96 (21%)	35/88 (40%)	33/70 (47%)
2-4cm	44/71 (62%)	59/74 (80%)	66/77 (86%)
≥4cm	28/33 (85%)	32/32 (100%)	27/28 (96%)
Per-patient	88/138 (64%)	113/149 (76%)	99/117 (85%)

638 Liver transplant 225 (35%) HCC,
23 excluded *(infiltrative, multifocal)*

Yu NC. et al Clin Gastroenterol Hepatol 2011;9:161-167

WHY IS HCC SURVEILLANCE BENEFICIAL?
HCC TREATMENT OPTIONS: EARLIER IS BETTER

Tumor Diameter at diagnosis

Japan Surveillance

USA Surveillance

USA referred base no surveillance

2-4+cm

>5cm

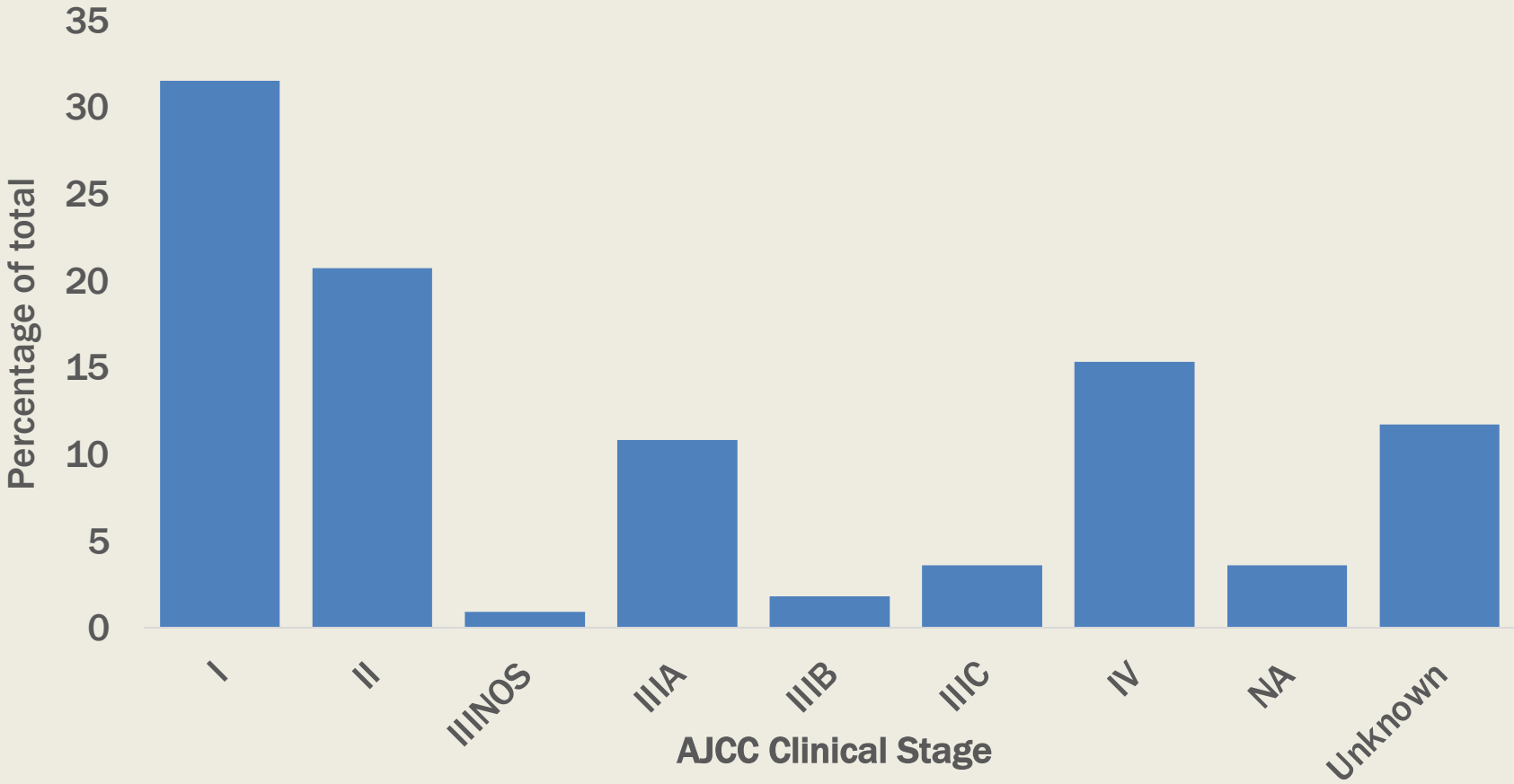
Curative treatment
Resection, Transplantation, Microwave/RFA

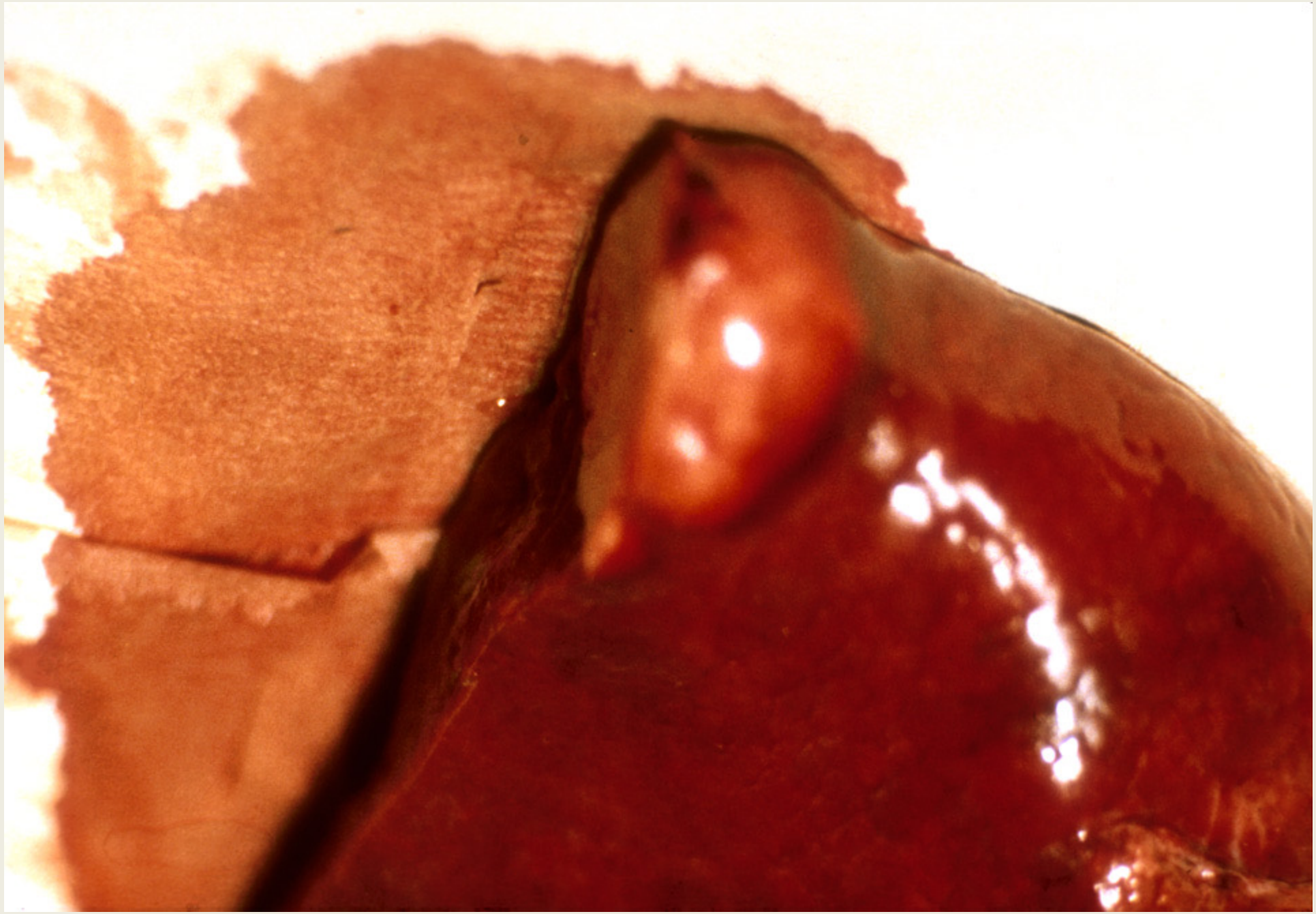
DEB TACE, TARE, cTACE,
Chemo/Immuno Therapy

Palliative treatment

4/1/2014

STAGE DISTRIBUTION OF LIVER CANCERS AMONG AN PEOPLE, 2004-2016





TREATMENT OF EARLY HCC

- Ablative therapies, Radiofrequency and Microwave can be curative HCC tumors 3cm or less.
  - If tumor is reachable in right lobe or in medial segments of the left lobe, procedure can be done in radiology suite using percutaneous US or CT guidance with conscious sedation
    - Patient will be out the door in 2-3 hours and back to full activity in 3 days
  - If tumor is deep in left lobe or near diaphragm or major vessel, ablation via laparoscopic approach is necessary and patient hospitalized overnight and back to full activities in 1 week
- Surgical resection of single lesions usually under 5 cm
- Liver Transplantation
  - 3 or less lesions,
  - All in one lobe,
  - Total diameter <7cm,
  - Largest <5cm

Survival data of Sorafenib, and other oral multikinase inhibitor, positive phase III trials in hepatocellular carcinoma

Study	Drug	Setting	Median OS (months)	HR (95% CI)
SHARP20	Sorafenib vs placebo	1st-line	10.7 vs 7.9	0.69 (0.55-0.87)
Asia-Pacific21	Sorafenib vs placebo	1st-line	6.5 vs 4.2	0.68 (0.50-0.93)
REFLECT49	Lenvatinib vs sorafenib[a]	1st-line	13.6 vs 12.3	0.92 (0.79-1.06)
RESORCE46	Regorafenib vs placebo	2nd-line	10.6 vs 7.8	0.63 (0.50-0.79)
CELESTIAL50	Cabozantinib vs placebo	2nd-/3rd-line	10.2 vs 8.0	0.76 (0.63-0.92)
REACH-262	Ramucirumab vs placebo	2nd-line	8.5 vs 7.3	0.71 (0.53-0.95)

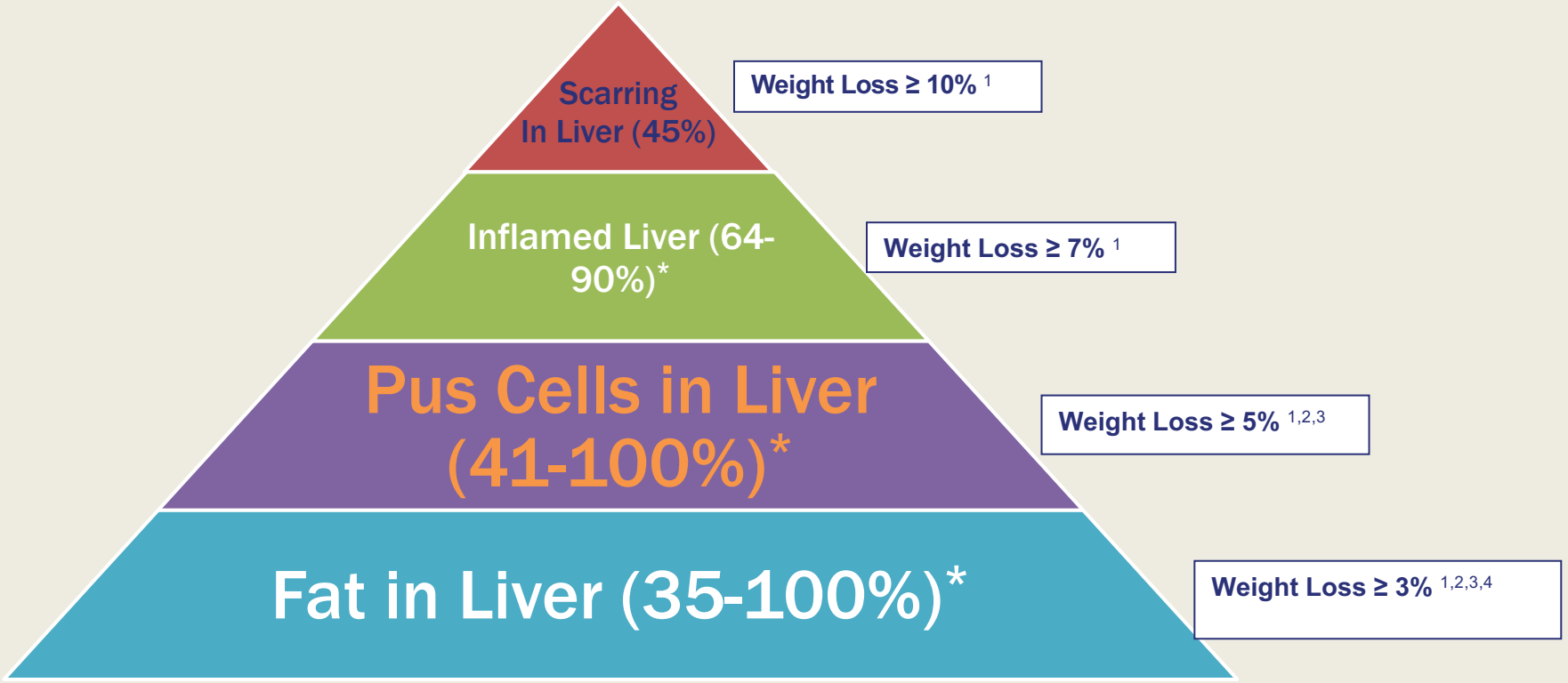
Should we subject patients to these drugs and the sometimes severe side effects?

COFFEE IS GOOD FOR YOUR LIVER

- Many studies have shown this.
  - Recent large study in England about one million people with cirrhosis followed for 10 years.
    - Persons didn't drink coffee had twice the death and liver cancer risk compared to those who drank any kind of coffee: decaf, drip, espresso or instant
- All coffee: instant, espresso, drip, decaf works
  - Reduces risk of liver cancer and liver related death
  - Benefit is not in the caffeine, it is in the bean

WEIGHT LOSS PYRAMID: LIFE STYLE MODIFICATION REDUCES NASH SEVERITY

With Weight Loss How Fast Does the Liver Improve



1. Vilar-Gomez. *Gastroenterology* 2015; 2. Promrat. *Hepatology* 2010; 3. Harrison. *Hepatology* 2009; 4. Wong. *J Hepatol* 2013
*Depending on degree of weight loss

CONCLUSION

- Identify patients at risk for liver disease and screen for diagnosis
- Ascertain the stage of liver fibrosis
- Initiate every 6 month surveillance with liver US and AFP for those at highest risk of HCC including all persons with advanced fibrosis or cirrhosis
- Remember that there are significant limitations to our screening modalities and to keep a high level of suspicion
- Detecting HCC tumors early can lead to long-term survival
- HCC that is to advanced to ablate, resect or transplant is ultimately fatal as unlike other cancers, no chemotherapy for cure is available

CONCLUSIONS

- Overall survival for HCC is poor due to under identification of persons at risk and inadequate surveillance.
- Surveillance for HCC to detect tumors early is beneficial and can greatly prolong survival
- Need for better radiographic and biomarker tools to detect HCC earlier and reduce false positive lesions
- Can we combine risk factors (age, genotype, viral load etc.) to come up with better algorithms for frequency of surveillance
- We need better treatment modalities for treating non-curable HCC
- Globally to reduce HCC due to hepatitis B, Vaccinate all newborns and reduce aflatoxin exposure
- Treatment of active viral replication to reduce incidence in both HBV and cure HCV

QUIZ: CHOSE THE BEST ANSWER(S)

1. In the past 20 years, the survival rate for HCC has improved by >50%
2. Overall 5-year survival after diagnosis of HCC is <20% nationally: Correct
3. Major advances in chemo and immunotherapy have given new hope for improved survival for large tumors
4. The best chances to cure HCC is to find the tumors when they are small, asymptomatic, and can be removed or ablated. Correct
5. HCC is the number three cancer killer in men worldwide: Correct