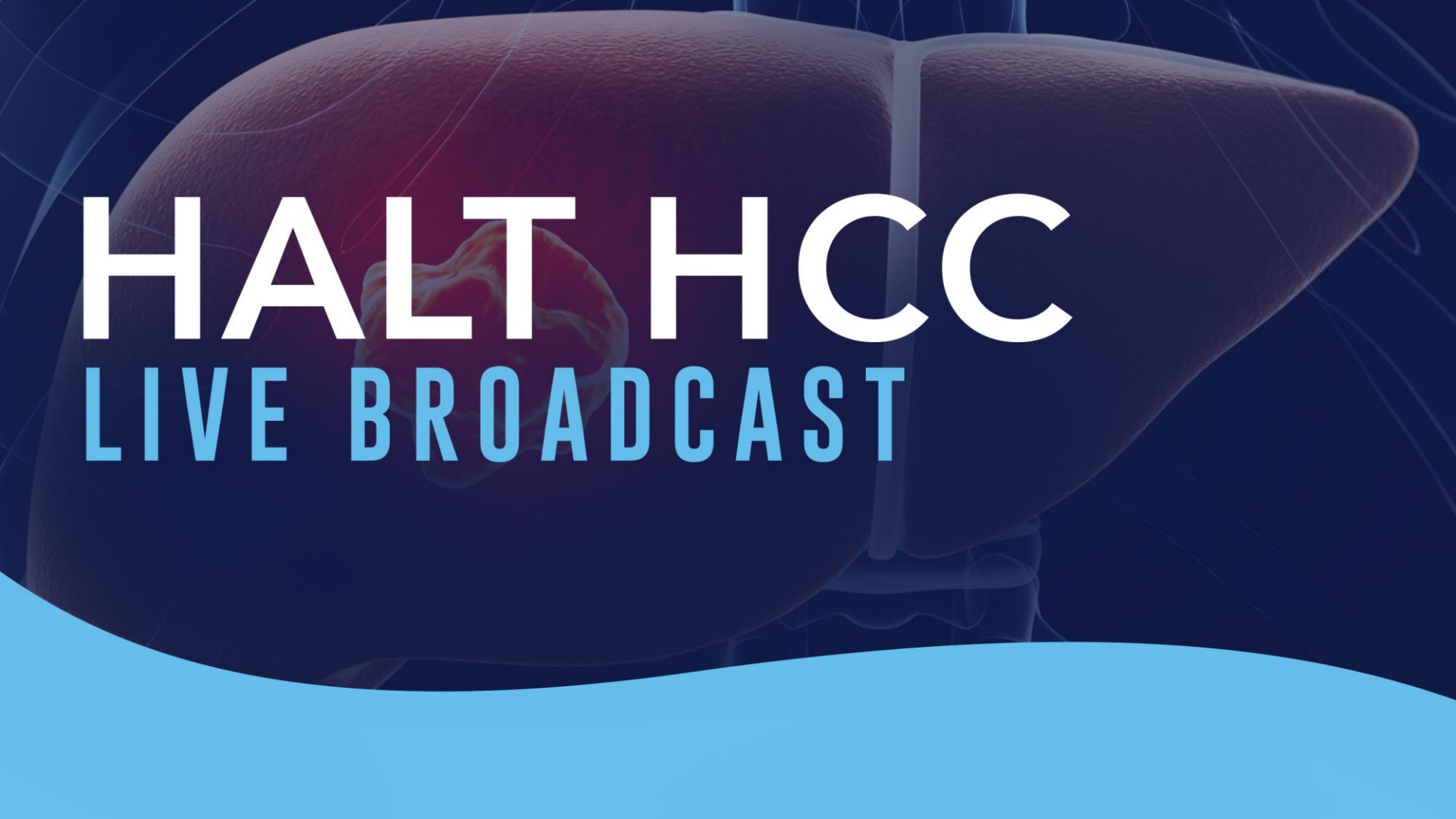
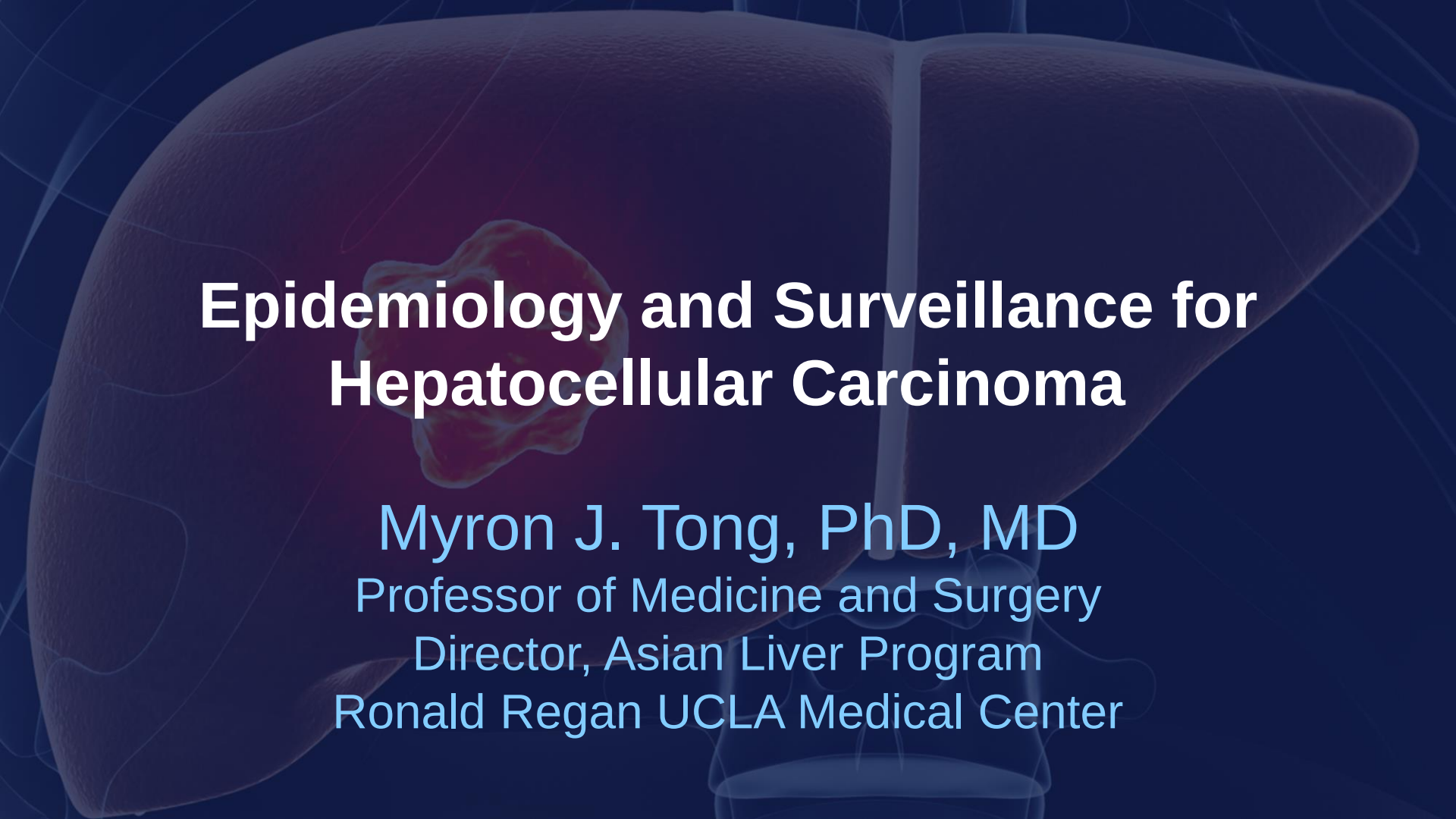

HALT HCC
LIVE BROADCAST



Epidemiology and Surveillance for Hepatocellular Carcinoma

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Disclosures

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Faculty:

- **Myron J. Tong, Ph.D., M.D.**
  - No relevant disclosures.

Hepatocellular Carcinoma

- HCC accounts for > 80% of primary liver cancers
- HCC is the 4th leading cause of cancer-related deaths worldwide
- 2005-2015, HCC was the 2nd leading cause of “years of life lost from cancer” (4.6% increase in absolute lives lost)
- In most regions of the world, the prognosis is poor so the HCC incidence and mortality rates are similar (2015: 854,000 liver cancer cases and 810,000 deaths)

Yang 2019, Global Burden of Disease Study 2015)

Epidemiology of HCC

- 90% of HCC cases arise in the setting of cirrhosis
- An estimated 1/3 of cirrhosis patients will develop HCC during their lifetime
- Main Risk Factors for HCC in cirrhosis patients:
  - Hepatitis C
  - Alcoholic Liver Disease
  - Hepatitis B
  - NAFLD
  - Other causes of cirrhosis
- HCC in non-cirrhotic patients: (HBV,HCV, NAFLD, other)

Other Contributing Risk Factors for HCC (independent or additive)

- Metabolic Syndrome
  - Diabetes
  - Obesity
- Environmental
  - Smoking (OR 1.55 in smokers and OR 1.39 in former smokers)
  - Aflatoxin B1 exposure

HBV alone	11-fold ↑
AFB 1 alone	6-fold ↑
HBV + AFB 1	54-fold ↑

- Genetic susceptibility (familial clustering of HCC in HBsAg+ families)

McGlynn 2021

Hepatocellular Carcinoma in the USA

- Between 2000 and 2012, there was an increase of 115% in the number of HCC cases
- 54% occur in adults ages 50-69 years old
  - Birth cohort effect: highest rates in baby boomers
- Patients who present with advanced HCC:
  - Median survival of ***<12 months***
- At present, only ***11%*** of HCC patients receive potentially "curative" treatments (OLT, resection, ablative therapies)

El Serag HB. *Gastroenterol*. 2012; Valery PC. *Hepatol*. 2018.

Causes of HCC Deaths Varies Among Ethnicities

(12,000 HCC cases in the USA 2017)

	NAFLD (%)	Hepatitis C (%)	Hepatitis B (%)	ALD (%)
White	***40.4***	***50.1***	0.7	5.3
Black	20.0	***72.5***	2.8	3.0
Hispanic	***42.4***	***45.5***	0.8	9.2
Asian	9.1	12.7	***74.8***	2.1
AIAN	34.7	***52.0***	0.7	9.5

Paik 2020

HCC in Alcohol-Related Liver Disease

- Alcohol-related liver disease is the most prevalent type of chronic liver disease worldwide, it accounts for ~30% (range: 20%-60%) of HCC cases
- Annual incidence of HCC: 0.5 to 2.9%

RR	
2.4	alcohol
9.9	alcohol + Diabetes
53.9	alcohol + HCV

- Because of impaired surveillance and poor patient compliance, prognosis is poor in ALD patients

Gunne-Carrie 2019

HCC and Alcoholic-related Liver Disease

- Alcohol consumption associated with an increased risk of general malignancies
- 3%-10% of ALD patients with cirrhosis will develop HCC
- HCC risk starts at doses as low as: 12g/day (RR 1.08) and rises by increments to 125g/day (RR 5.2)
- In patients consuming > 80g/day of alcohol for >10 years, the risk for HCC increases 5-fold
- Carcinogenesis due to acetaldehyde toxicity

Gunne-Carrie 2019, Chuang 2015

NAFLD-related HCC

- Global prevalence of NAFLD > 25%
- USA ~85 million people with NAFLD
- 1 in 4 NAFLD patients will progress to NASH-cirrhosis
- Annual incidence for progression from cirrhosis to HCC is 0.5 to 2.6%
- Rates of NAFLD HCC increases in parallel with the obesity epidemic (Obese USA population 2012: 35%; 2030: 48.9%)
- NAFLD is the most rapidly emerging risk factor for HCC

Loomba 2020, Huang 2020

NAFLD-related HCC

- Occurs in older patients (mean age 73 years)
- HCC diagnosed at late clinical stages (no surveillance) so poor survival compared to viral-related HCC
- HCC may develop in up to 38% of non-cirrhotic NAFLD patients (presence of diabetes associated with highest risk for HCC)
- NAFLD leading cause of HCC in the United Kingdom (UK)

NAFLD-related HCC in the USA

- SEER (2004-2019)
- Younossi (2002–2017)
- Estes Markov Model (2018)

➢ 14.1% of HCC patients had NAFLD

(annual increase 9%)

➢ Patients transplanted or on waiting list

2002 - 2.17%
2016 - 16.2% (increase of 8.5 fold)

➢ Prevalence 2015 – 2030

NASH ↑ 63%
NAFLD- related HCC ↑ 146%

Risk Factors for NALFD-related HCC

- Older age
- Male
- Latinos (vs Caucasians and African-Americans)
- Cirrhosis
- Diabetes (prevalence of NAFLD 56%; fibrosis 17%)
- Body habitus - Overweight (BMI 25.0 to <30) ↑ risk 48%
  - Obesity (BMI >30) ↑ risk by 83%
- Smoking (OR 1.55)
- Genetic susceptibility PNPL3 SNP mutation

Hepatitis C and HCC

- HCV is the leading viral related cause of HCC in North America, Europe, Japan and Egypt
- 57 million persons have chronic HCV worldwide and 10-20% will develop decompensated cirrhosis and HCC
- 90% of HCV-related HCC cases are preceded by cirrhosis
- In patients with HCV cirrhosis, annual incidence of HCC ranges from 0.5% to 10%

Kulik 2019, Global Burden of Disease 2017

Hepatitis C and HCC

- In the USA, HCV-related HCC cases increased by 130% between 1990-1999 and 2000-2009 (peak expected 2020)

- Cofactors for HCC development in persons with active Hepatitis C:

Male	Longer duration of infection
HCV Genotype 3	Obesity
Co-infection with HBV or HIV	Diabetes
Hispanic	Alcohol

- Tumorigenesis is through repetitive damage, regeneration and fibrosis

McGlynn 2021

Decreased Risk of HCV-related HCC After SVR

- Risk of HCC after sustained virologic response to anti-viral therapies reduced by 50-80%, but risk is not eliminated
- Similar risk reductions in DAA and Interferon-based therapies
- After SVR, annual incidence: 0.9%
  - Highest in cirrhosis: 1.22%
  - Cumulative 1, 2, 3 years HCC risk: 1.1%, 1.9% and 2.8%
- Risk for HCC after SVR:

Cirrhosis (Fib 4 > 9), i.e. F3, F4	Male
Diabetes	Older age
Obesity	Lack of SVR
Alcohol	

McGlynn 2021

Hepatitis B and HCC

- Hepatitis B is the leading etiology of HCC worldwide, especially in East Asian countries and most African countries
- There is an estimated 257 million individuals with chronic HBV infections
  - Between 2015 and 2030, there will be ~5 million deaths from HCC
- Most HBV-HCC cases (70%-90%) arise in the setting of cirrhosis
- In endemic countries, HCC may arise in 30-50% of non-cirrhosis patients
- Lifetime risk of developing HCC among HBV patients ranges from 10-25%

Kim 2019

Risk Factors for HCC in Chronic Hepatitis B Patients

- Male, Older Age, Asian or African Ancestry, Family History of HCC
- High levels of HBV replication
- Longer duration of infection
- Co-infection with HCV, HIV, or HDV
- Cirrhosis
- Environmental co-factors: aflatoxin exposure, ETOH, Tobacco
- Metabolic co-factors: Obesity, Diabetes

Kulik 2019

Hepatitis B in the USA

- Annual incidence in the USA 0.42% (>50% Asian Americans)
- VA data base (2001-2013) annual incidence
  - Asians/PI 0.65%
  - Whites 0.57%
  - Blacks 0.40%
  - Age adjusted HR
    - 40-49 1.97
    - 50-59 3.0
    - >60 4.02
  - Cirrhosis 3.69

Kulik 2019

Reduction of chronic Hepatitis B Infection Decreases HCC Development

In the 1980's:

- HBV vaccination programs in Asia
  - Taiwan - in cohorts born after vaccination programs began: HCC incidence declined 80% and morbidity declined 92%
- Use of anti-viral agents (nucleoside/nucleotide analogs) can achieve sustained reductions in HBV DNA, improve liver function and histology
  - Antiviral treatment can reduce but not eliminate risk of HCC
- HCC can arise in any clinical stage of HBV:
  - Immune tolerant
  - Chronic hepatitis
  - Cirrhosis
  - Inactive carriers
  - After HBsAg loss

Surveillance for HCC

- Cancer Surveillance
  - Detect tumors at early stage
  - Amenable to “curative treatments”
  - Improve patient survival
- Tests must be inexpensive, readily available, safe, accurate
- When HCC surveillance implemented, patient survival is *prolonged*
- Challenges:
  - Initiate HCC surveillance in high-risk patients
  - Encourage patient compliance

Surveillance Tests for HCC

- Ultrasound (US) - sensitivity of early-stage detection 47%, operator dependent, less accurate in obese patients, fatty liver, cirrhosis, alcoholic steatohepatitis
- CT or MRI:
  - More accurate, expensive, CT radiation, MRI contrast exposure
- Alpha-fetoprotein (AFP) - inexpensive, sensitivity under 50%, elevated in liver inflammation, other GI and testicular cancers
- Sensitivity for detecting early-stage HCC:
  - US : 45%
  - AFP : 32-49%
  - US + AFP : 63%
- Other available tests: AFP L3, des-gamma carboxyprothrombin (DCP) but inadequate information for use as surveillance tests for HCC

Ultrasound Detection of a 3 cm HCC

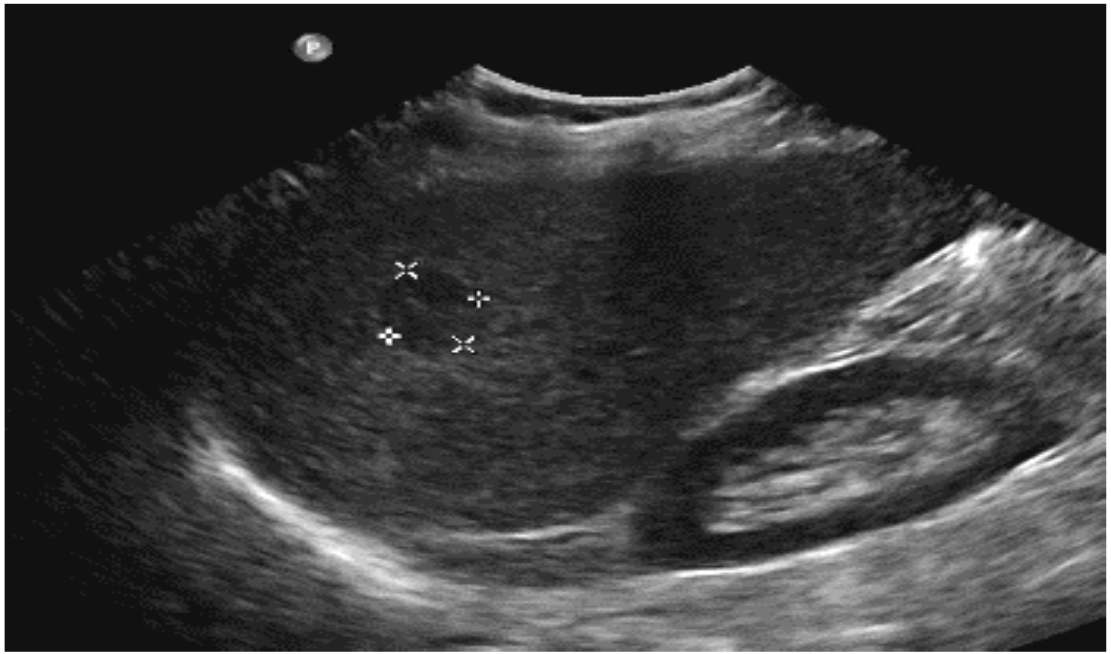


Figure 3

Surveillance for HCC in Alcoholic Cirrhosis

- Alcohol cirrhosis patients have poor survival compared to other cirrhosis patients:

	Overall survival (median months)		
	other	Alcohol	P
ITALY	33.6	27.4	0.02
FRANCE	9.7	5.7	≤ 0.001

- Main reasons for reduced survival: poor liver function and worse tumor characteristics (multi-focal, infiltrating/massive, PVT) and usually no surveillance
- Initiate surveillance for HCC in all patients with alcohol related cirrhosis

Gunne-Carrie 2019

AGA update on Surveillance for HCC in NAFLD:
Expert Review (2020)

1. Screen for HCC (high risk) q 6 months in NAFLD patients:
    1. Clinically established cirrhosis
    2. Non-invasive markers showing advanced fibrosis and cirrhosis (NAFLD fibrosis score, FIB-4, FibroScan©, MR elastography)
2. If abdominal ultrasound suboptimal (i.e. cirrhosis, obesity) use CT or MRI +/- AFP every 6 months
3. Non-cirrhotic NASH patients with other co-morbidites: diabetes, obesity but no evidenced based recommendations on surveillance

Loomba 2020

Surveillance for HCC in HCV patients

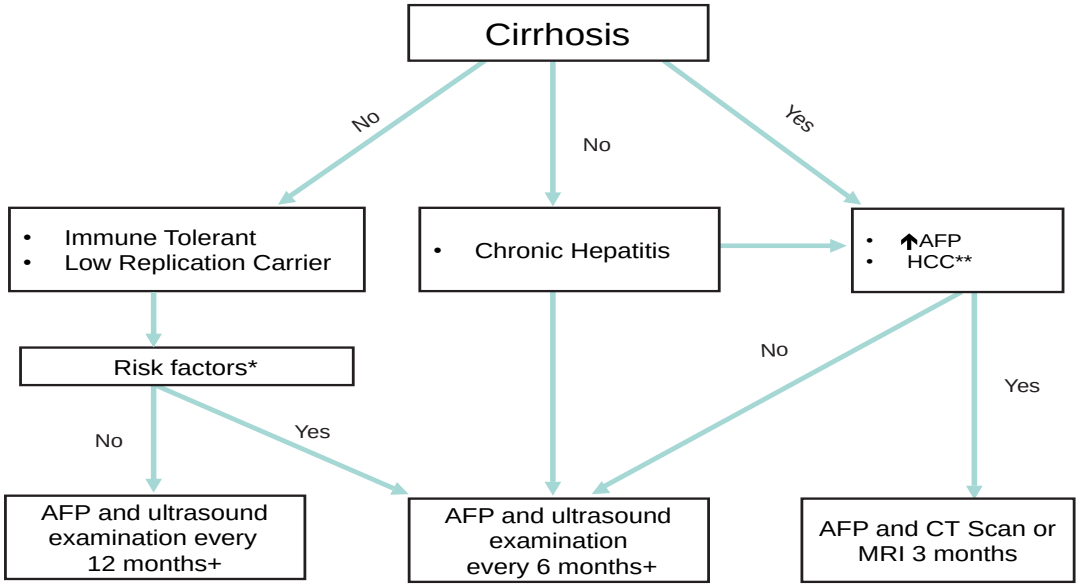
- Most HCC patients now post-treatment with DAAs and achieved SVR
  - SVR reduces HCC risk by 70%
- Annual risk continues to be >2% for up to 10 years after SVR in patients with cirrhosis and FIB-4 of ≥ 3.25**
- Annual risk >1% after SVR in patients without cirrhosis and FIB-4 ≥ 3.25**
- Surveillance for HCC every six months in F3 and F4 patients

* Ioannou 2021, ** FIB-4: age, AST, ALT, platelet count

HCC Surveillance in Hepatitis B Patients *(treated and untreated)*

- Cirrhosis hepatitis B
- Without cirrhosis
  - Asian Male ≥ age 40 years old
  - Asian Female ≥ 50 years old
  - Family history of HCC
  - African persons ≥ 20 years old

HCC Surveillance Intervals in Asian Patients with Hepatitis B



*Risk Factors; Family History of HCC, Basal Core Promoter Mutant, Diabetes, NASH, HCV or HIV Coinfection
**Ongoing HCC Treatment
+ If ultrasound examination suboptimal, proceed with contrast CT scan or MRI

AFP: alpha-fetoprotein
HCC: Hepatocellular carinoma
CT: computerized tornography
MRI: Magnetic Resonance Imaging

Tong et al 2018

HCC Surveillance

- Abdominal ultrasound and AFP every 6 months
- If US suboptimal, consider CT or MRI in high-risk patients
- Align with multidisciplinary Liver Cancer Center


Thank you!