HEPATOCELLULAR CARCINOMA SURVEILLANCE IN PERSONS WITH CHRONIC HEPATITIS B INFECTION

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CONFLICTS OF INTEREST

- Brian McMahon: None

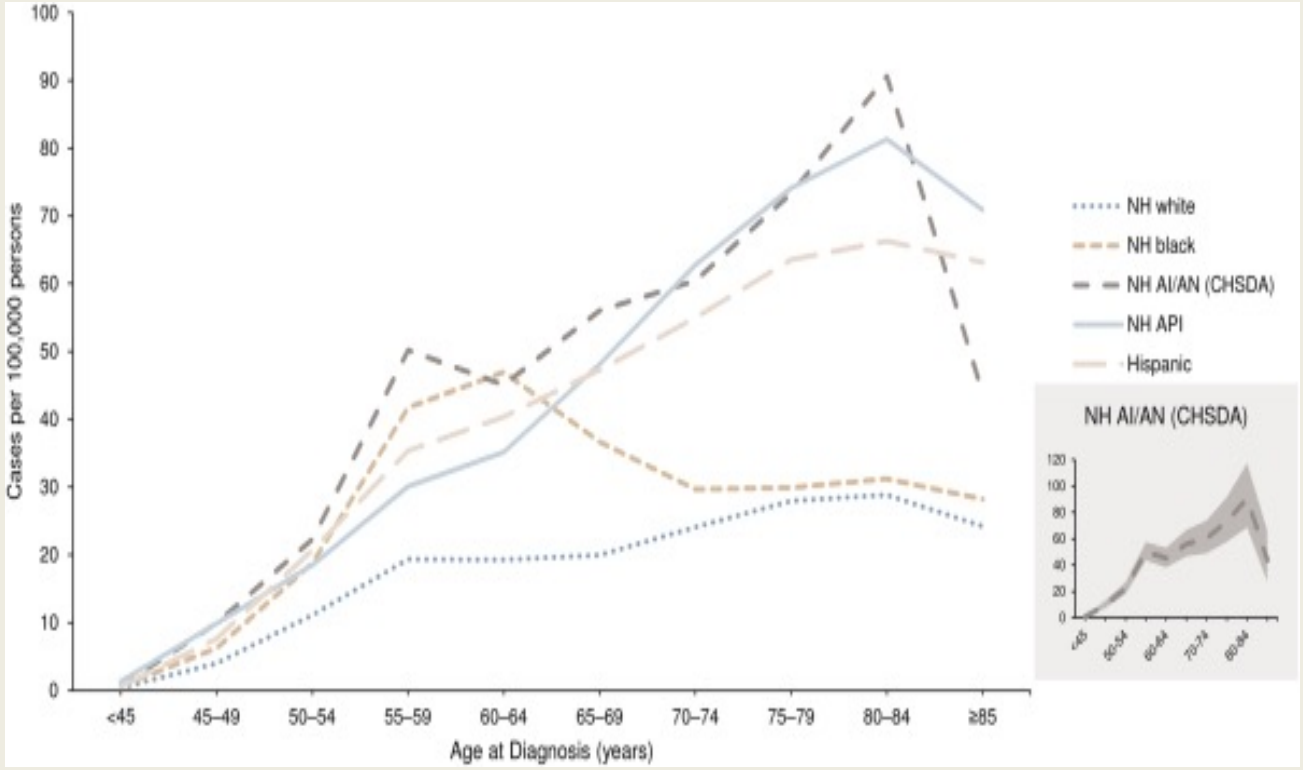
GOALS OF PRESENTATION

- Discuss risk factors for developing HCC in persons with Hepatitis B virus (HBV)
- Reducing the incidence of HCC: What must be done
- Detect HCC early in patients with chronic HBV: How we do this in Alaska and how can it be done elsewhere

THE ALASKA EXPERIENCE

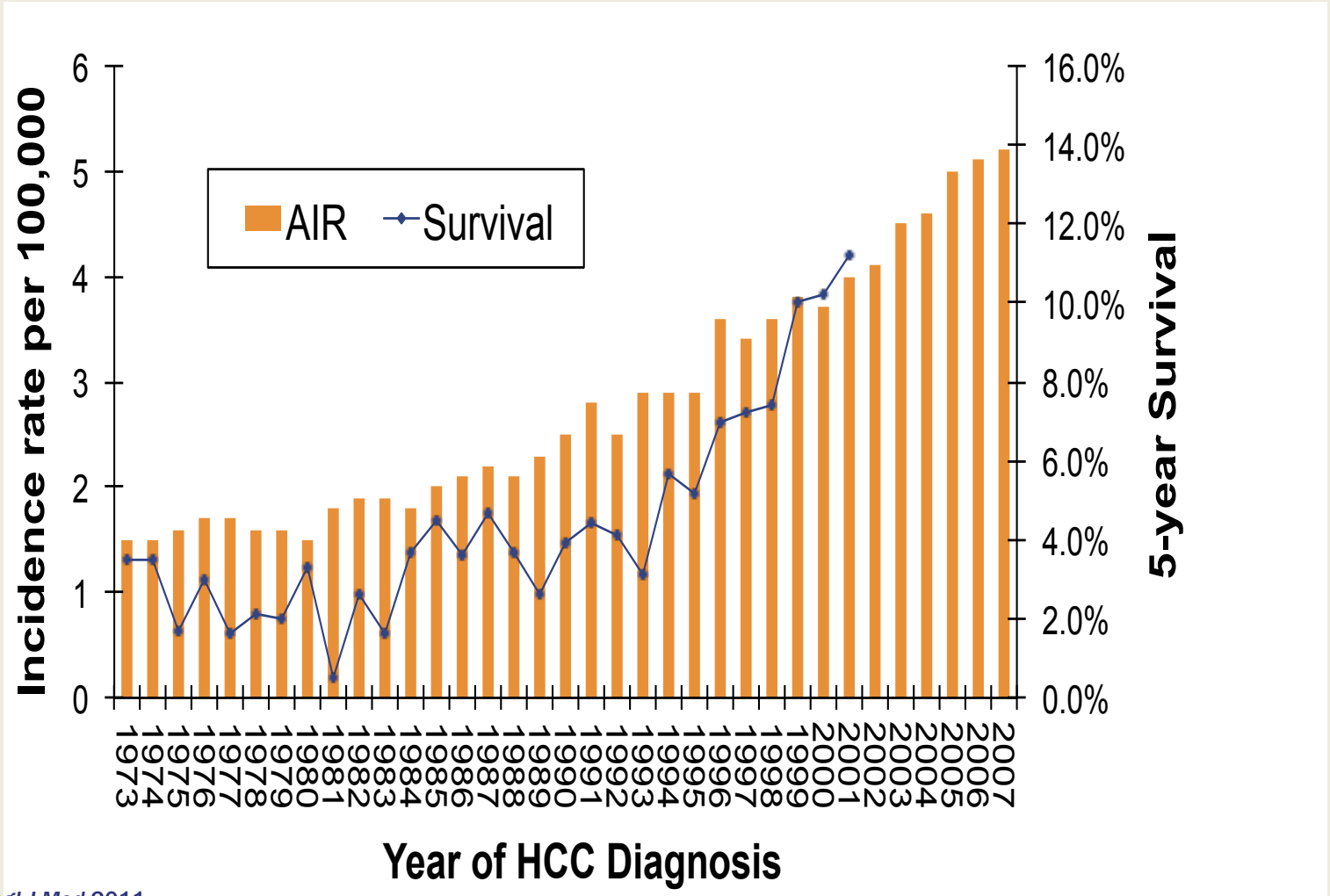
- In the 1970's, Alaska Native People living along the Bering Sea Coast were found to have high rates of chronic HBV similar to those found in SE Asia and sub-Saharan Africa
  - The prevalence of HBsAg ranged from 4% to 8%
  - Massive screening and vaccination campaign coupled with newborn immunization in the 1980's has resulted in halting transmission and no persons < 20 years with chronic HBV
  - Five of the Eight HBV genotypes have been found in this population: A2, B6, C2, D2,3, F1b
  - The HCC surveillance system in Alaska will be discussed later

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

THE INCIDENCE AND 5-YEAR SURVIVAL OF HCC IN UNITED STATES



El-Serag HB. *N Engl J Med* 2011

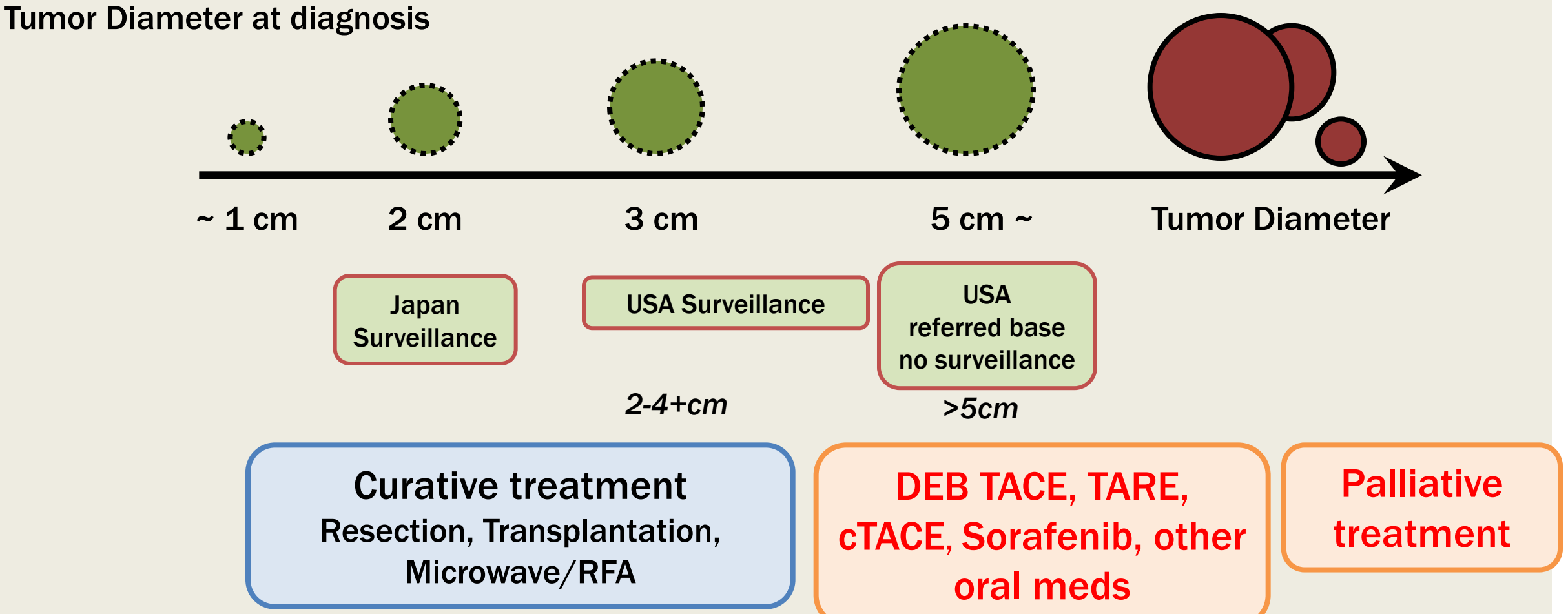
HCC IN THE USA

- The incidence of HCC has more than doubled in the US in the past 3 decades
- HCC is the only cancer where mortality has increased; for all other cancers in the US mortality has decreased
- Chemotherapy will not cure HCC
- Early detection followed by tumor destruction or removal are the only pathways to cure

HOW TO DECREASE MORBIDITY AND MORTALITY IN PEOPLE WITH HBV DUE TO HEPATOCELLULAR CARCINOMA (HCC) AND CIRRHOSIS

- Identify Persons with chronic HBV infection
  - Linkage to care
  - Prevent progression of this condition by following HBV practice guidelines/guidance at aasld.org
- Identify those with underlying liver condition at risk for HCC and initiate surveillance to detect HCC at an early and curable stage
  - Asian men 40 and over, women 50 and over: age to implement screening in other racial/ethnic groups are not well established
    - Anyone with advanced fibrosis (F3) or cirrhosis (F4)
    - Persons with HBV and a family history of HCC
- Apply most effective treatments for those who develop HCC depending on the stage
- Promote research, both scientific and community-based, to prevent and treat HCC

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



4/1/2014

CAN WE STRATIFY FREQUENCY OF SURVEILLANCE BY CAN CAN WE USE UNDERLYING RISK FACTORS SUCH AS HBV GENOTYPE, ETHNICITY AND FAMILY HISTORY

- A previous analysis in HBV suggested surveillance became cost effective once the an annual risk of HCC exceeded 0.2/100
- Population-based data found that these rates did exceed that threshold for Asian and Alaskan Native, males ≥40, females ≥50, persons with a family history of HCC and those with cirrhosis
  - African and North Americans Black persons are also recommended to screen above age 20 but data is mainly anecdotal or based on case series. Aflatoxin exposure may be a reason that HCC rates are higher

BIG FOUR RISK FACTORS FOR HCC IN PERSONS WITH HBV

- Viral load
- Genotype
- Family History: the strongest risk factor according to the REVEAL study in Taiwan
- Cirrhosis
- Race and Ethnicity regarding age: (HCC appears at an earlier age in persons who have emigrated from sub-Saharan Africa

DETERMINING FIBROSIS STAGE IN HBV

- Persons at any age with F3 or F4 fibrosis need surveillance
  - FIB4 and APRI are good first steps
  - Serologic Fibrosis scores such as FibroSure, FibroTest and FibroSpect2 are expensive but a little better than FIB4
    - Important to note that these test have good specificity at the low and high ends but in between suggest flipping a coin for less expensive accuracy
  - Liver Ultrasound with portal vein flow study
  - FibroScan
  - MRI elastography (MRE)
  - Liver biopsy

WHAT SCREENING METHODOLOGIES TO USE AND HOW FREQUENTLY

- Ultrasound of the liver and AFP every 6 months for men starting age 40, women starting age 50 years. Insurers will cover this also in patients with cirrhosis

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

HOW WE DO SURVEILLANCE FOR HCC IN ALASKA FOR PERSONS WITH CHRONIC HBV INFECTION

- 75% of those with chronic HCV (~1,000 persons) live outside of Anchorage
- 50% live in remote villages with no licensed provider but with a clinic run by an Indigenous Community Health Aide/Provider (CHAP) who completes a 16 week training program and is certified by the State of Alaska to provide care in his/her community (they learn to draw blood and have centrifuges to separate sera)
- A reminder letter is sent to each person with chronic HBV every 6 months to get blood drawn for AFP, HBV DNA, LFTs and to attempt to go to the nearest regional facility that has ultrasound for screening
- Hepatology providers review all this data on the EHR and make recommendations if further studies are needed
- We get on average one or more liver US on about 60% of persons at least yearly

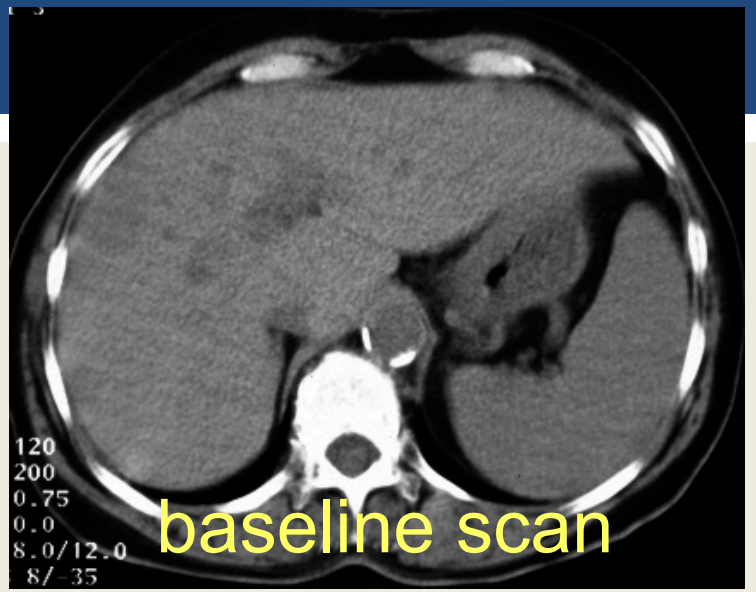
IMAGING MODALITIES FOR HCC SURVEILLANCE

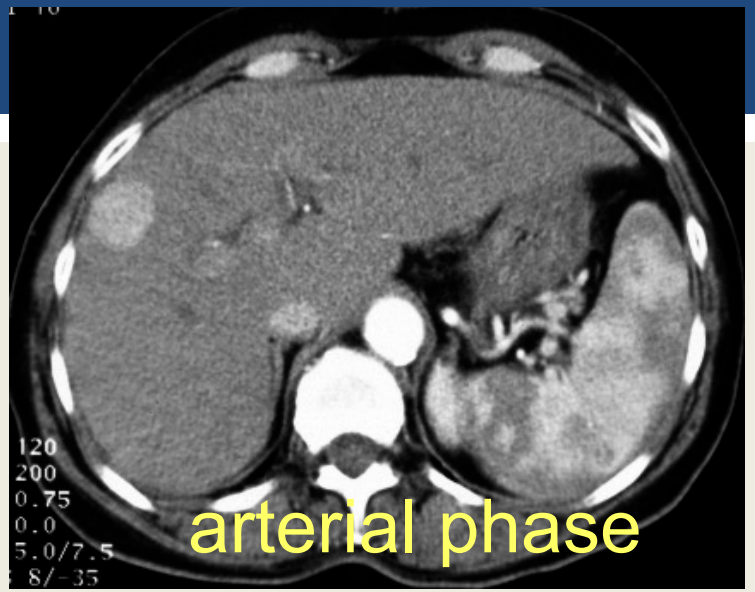
Imaging	Advantages	Disadvantages
Ultrasound	• Non-Invasive • Availability is ubiquitous • Low cost	• Highly operator & technique dependent -directly proportional to operator experience & skill • Low Sensitivity in Obesity • Soft tissue assessment • Low sensitivity in other Disease states
CT 4 Phase	•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

HARMFUL EFFECTS OF IMAGING

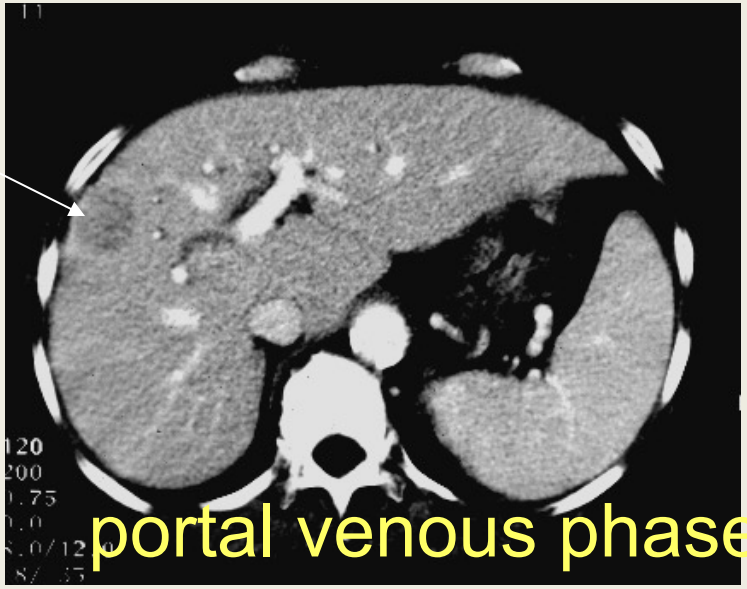
- 999 patients with cirrhosis followed 2.2 years
- Ultrasound followed by CT or MRI if indeterminate lesion found
- 26% had a lesion found
  - 27% of those had HCC
    - 78% met Milan Criteria
  - 73% indeterminate lesion requiring further imaging and 11 had diagnostic liver biopsy of lesion
    - 6 HCC, 5 benign
- One in four patients undergoing surveillance had abnormal lesion, ¾th of them were indeterminate requiring further imaging and potential harm
- Better markers for HCC are needed
  - Liver Transplant 2019;25:369-379

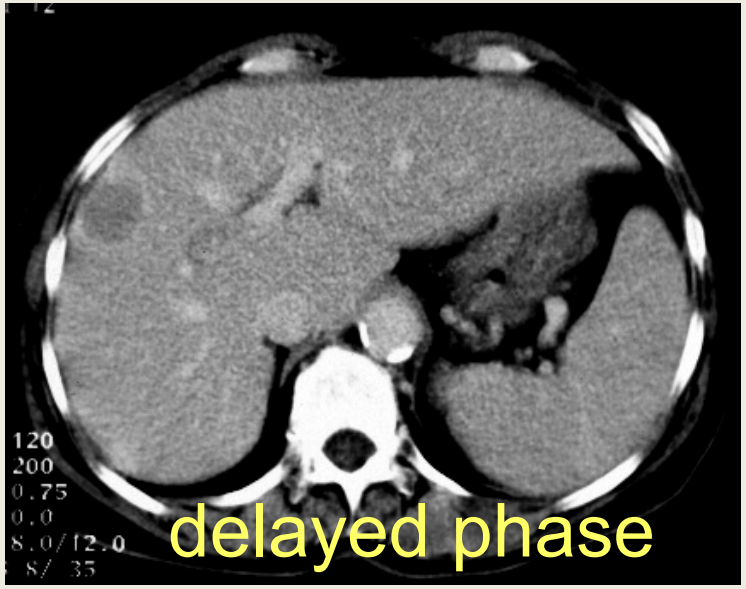
CT FOR HEPATOCELLULAR CARCINOMA





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

ABBREVIATED MRI

- New Technique using contrast but taking only 10-15 minutes
  - Multiphase with contrast: Non-contrast, arterial phase, venous phase, late phase
  - Can be done on any MRI machine
  - However, not yet studied enough to recommend
  - Since MRI is twice as sensitive as US in picking up small HCC lesions between 1 and 3 cm., could substantially improve early detection of easily curable lesions
  - We have put in a P 20 NIH grant to study abbreviated MRI compared to US with four other centers, UW, Fred Hutchinson both in Seattle and SW Texas Medical School in Dallas

TREATMENT OF HCC IN HBV

- Potential cure can be obtained by:
  - Ablation (Radiofrequency or microwave)
  - Surgical Resection
  - Transplantation
- Prolonged survival supported by randomized trials
  - Transarterial Chemoembolization (TACE)
  - Transarterial Radioembolization (TARE); ytrium 90
  - Sorafenib and it’s cousins (yes but barely)

CURE IN HCC WITH HBV VS. OTHER LIVER DISEASES

- Ablative and surgical cures may be higher in HBV due to 30% of patients do not have cirrhosis at diagnosis
- However, long-term reappearance of HCC rates may be higher due to ongoing viral replication and integration of HBV genome into hepatocyte DNA
  - Recurrence rate may far less common after transplantation due to antiviral suppression of HBV DNA in recipient's donated liver
- We have patients with HCC with HBV whose tumors were ablated or surgically removed who are alive and healthy without recurrence 5 to 35 years later

ABLATION DEMO

rita animation.mpg

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

CONCLUSION

- Identify patients at risk for HBV and screen for diagnosis
- If HBV+ 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 too 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 if treatment criteria is met