AASLD Guidelines and HCC: a US based commentary

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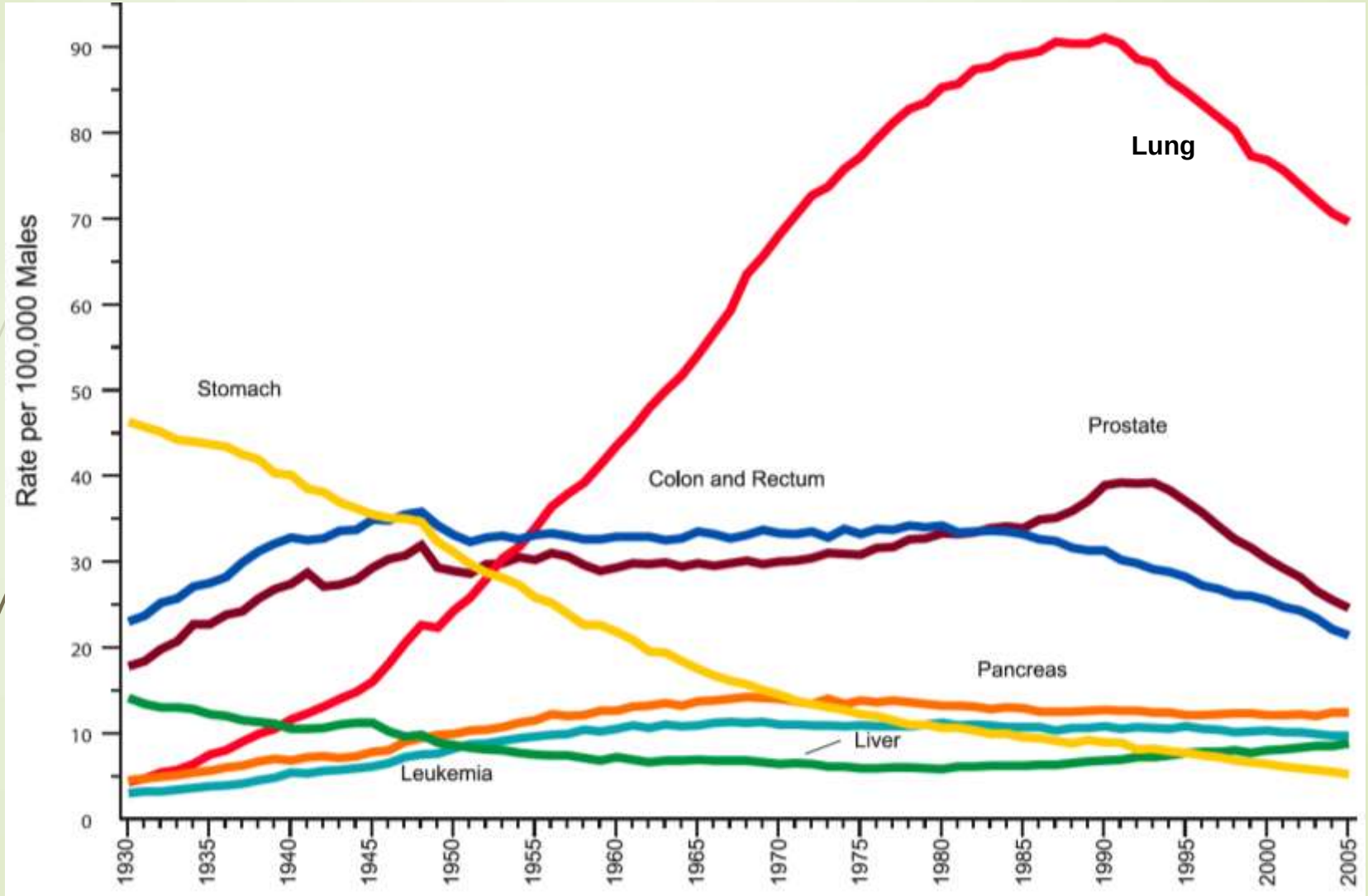
Mortality from Common Malignancies in US



Jemal A et al. CA Cancer J Clin 2009;59:225-229.

Estimated Deaths from Cancer Worldwide by Rank

Men		Women	
Cancer ranking	No.	Cancer ranking	No.
2. Liver	**478,300**	**7. Liver**	**217,600**

695,900 liver cancer deaths

GLOBCAN 2008

New AASLD HCC Guidelines are in process of being written:

- Proposal
- We are the world
- Need to look at HCC as a global disease and recognized the diversity of disease and resources throughout the world

Table 2. Definitions

- Screening–application of diagnostic tests in patients at risk for HCC, but in whom there is no a priori reason to suspect that HCC is present.
- Surveillance–the repeated application of screening tests.
- Enhanced follow-up–the series of investigations required to confirm of refute a diagnosis of HCC in patients in whom a surveillance test result is abnormal. In addition to the use of additional diagnostic tests the interval between assessments is shorter than for surveillance since there is a concern that a cancer already exists.
- Lead-time bias–This is the apparent improved survival that comes from the diagnosis being made earlier in the course of a disease than when the disease is diagnosed because of the development of symptoms. Unless properly controlled, studies of surveillance will show enhanced survival simply because the cancer is diagnosed at an earlier stage.
- Length bias–This is the apparent improvement in survival that occurs because surveillance preferentially detects slow growing cancers. More rapidly growing cancers may grow too large to be treated between screening visits

AASLD Recommendations for HCC Surveillance

HBV carriers

(Cost effective if risk >0.2%/y)

- Asian M≥40y, F≥50y
- Africans/Af Am >20yo
- Family history of HCC
- Cirrhosis

Non HBV-cirrhosis

- HCV

(Cost effective if risk >1.5%/y)

- Alcoholic cirrhosis
- Genetic hemochromatosis
- Primary biliary cirrhosis

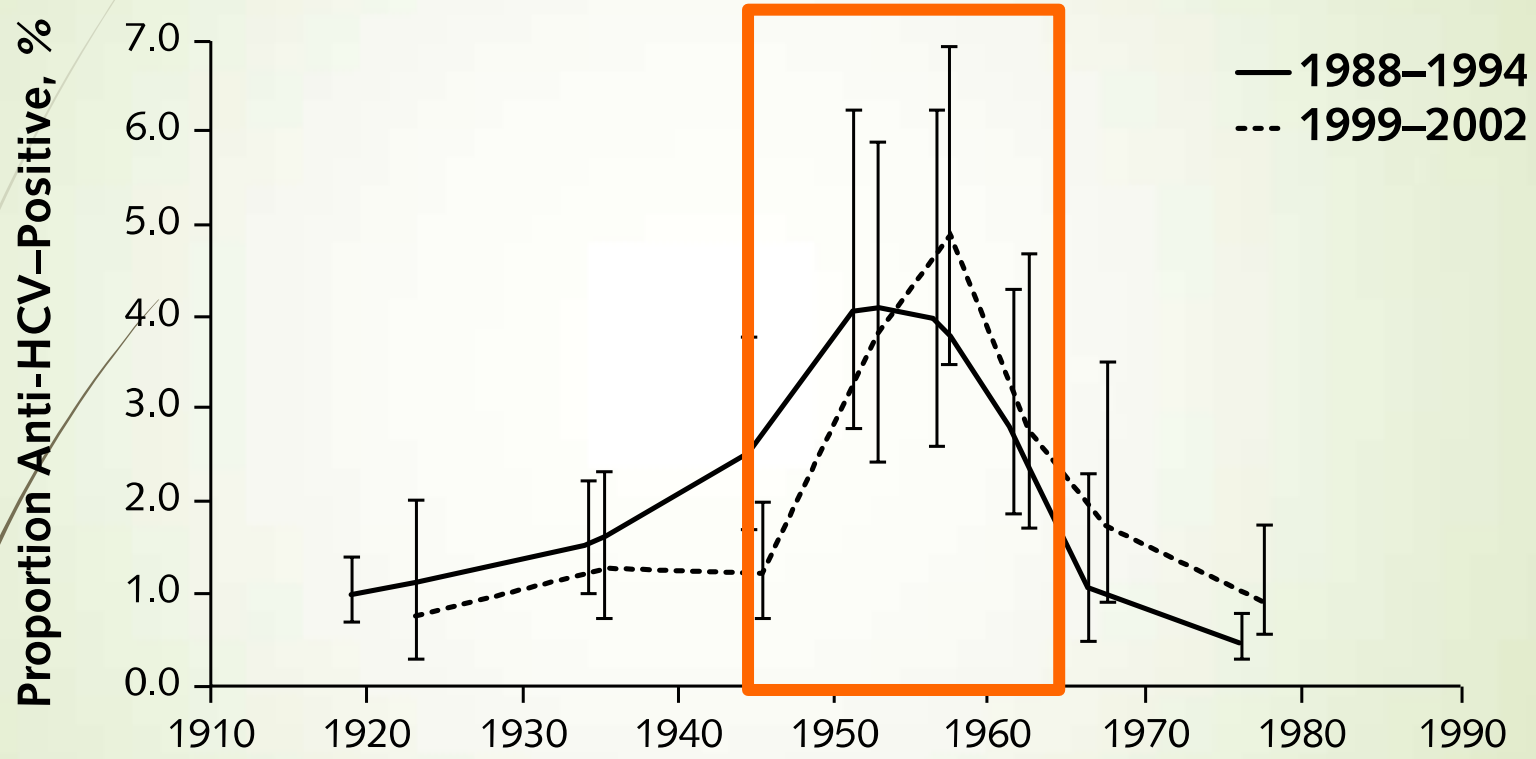
Increased risk but insufficient data to recommend surveillance

- Alpha1-antitrypsin
- Non-alcoholic steatohepatitis
- Autoimmune hepatitis

Bruix J & Sherman M. Hepatology 2005;42:1208-36. Bruix J & Sherman M. Hepatology 2011;53:1020-22 Bruix and Sherman, Hepatology 2010, 1-35.

‘Birth Cohort’ Screening for HCV

- HCV Prevalence in US General Population (National Health and Nutrition Examination Surveys)



The USPSTF recommends screening for HCV infection in persons at high risk for infection. The USPSTF also recommends offering 1-time screening for HCV infection to adults born between 1945 and 1965.

Armstrong GL et al. Ann Intern Med. 2006;144:705-14. Moyer. Ann Intern Med. 2013;159:I-32.

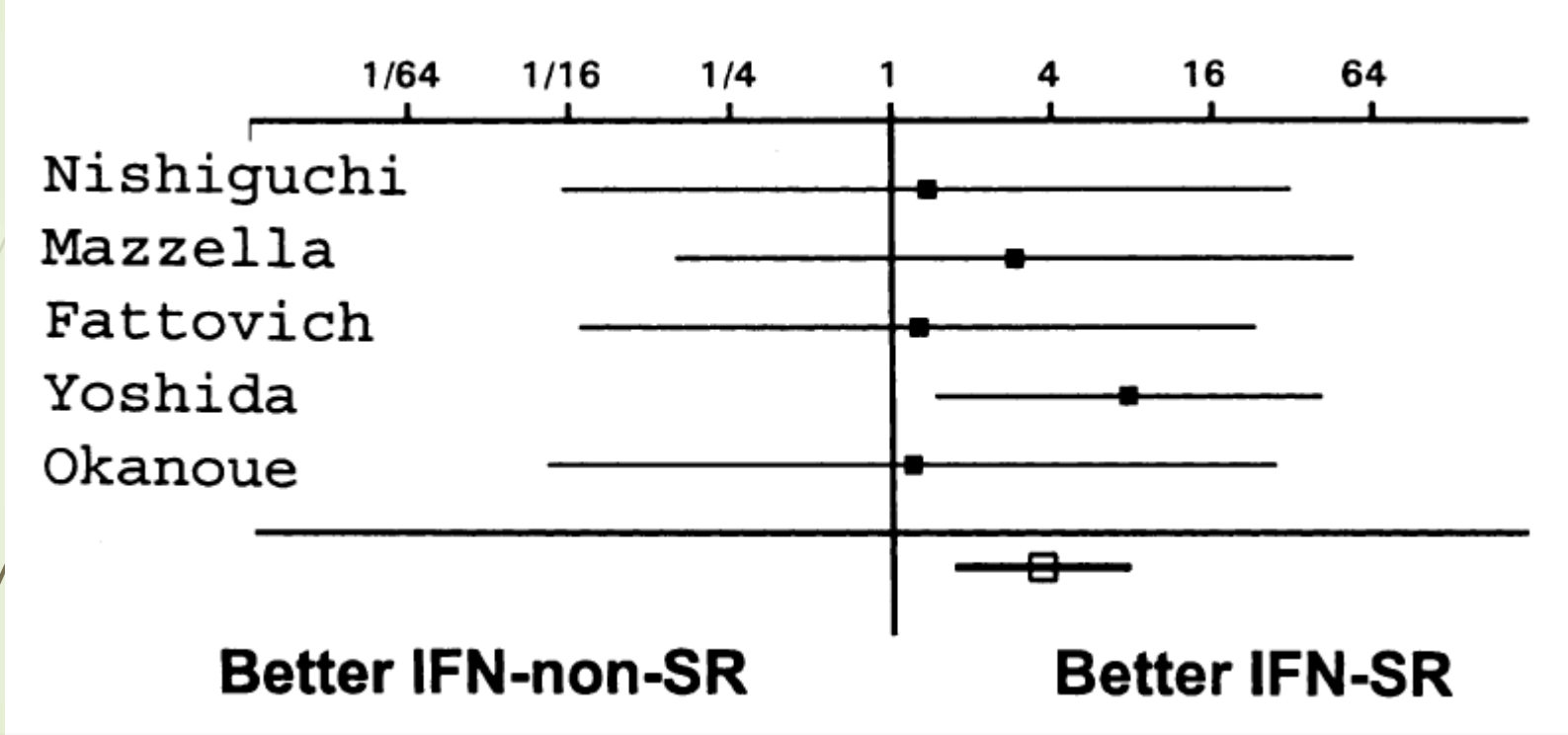
Benefits of Birth Cohort Screening

- Projected reduction in Incidence among Americans born 1946-1970

McGarry LJ et al. Hepatology 2012;55:1344-55.

Reduction of HCC with IFN for HCV

- Meta-analysis in cirrhotics



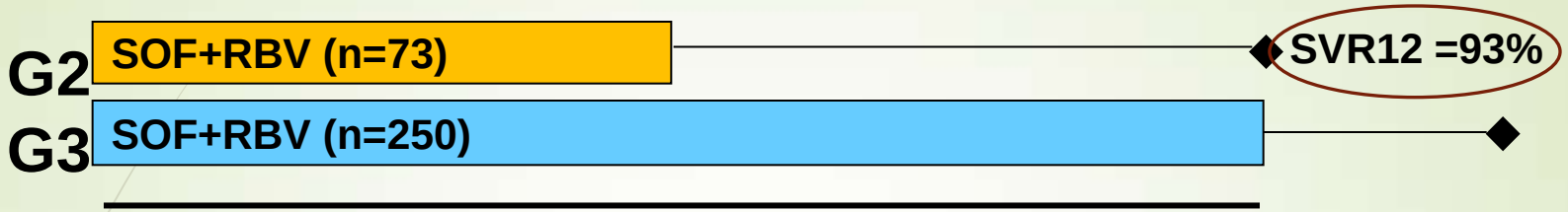
Hepatitis C patients achieving SVR was 3.7* times less likely to develop HCC than non-SVR patients.

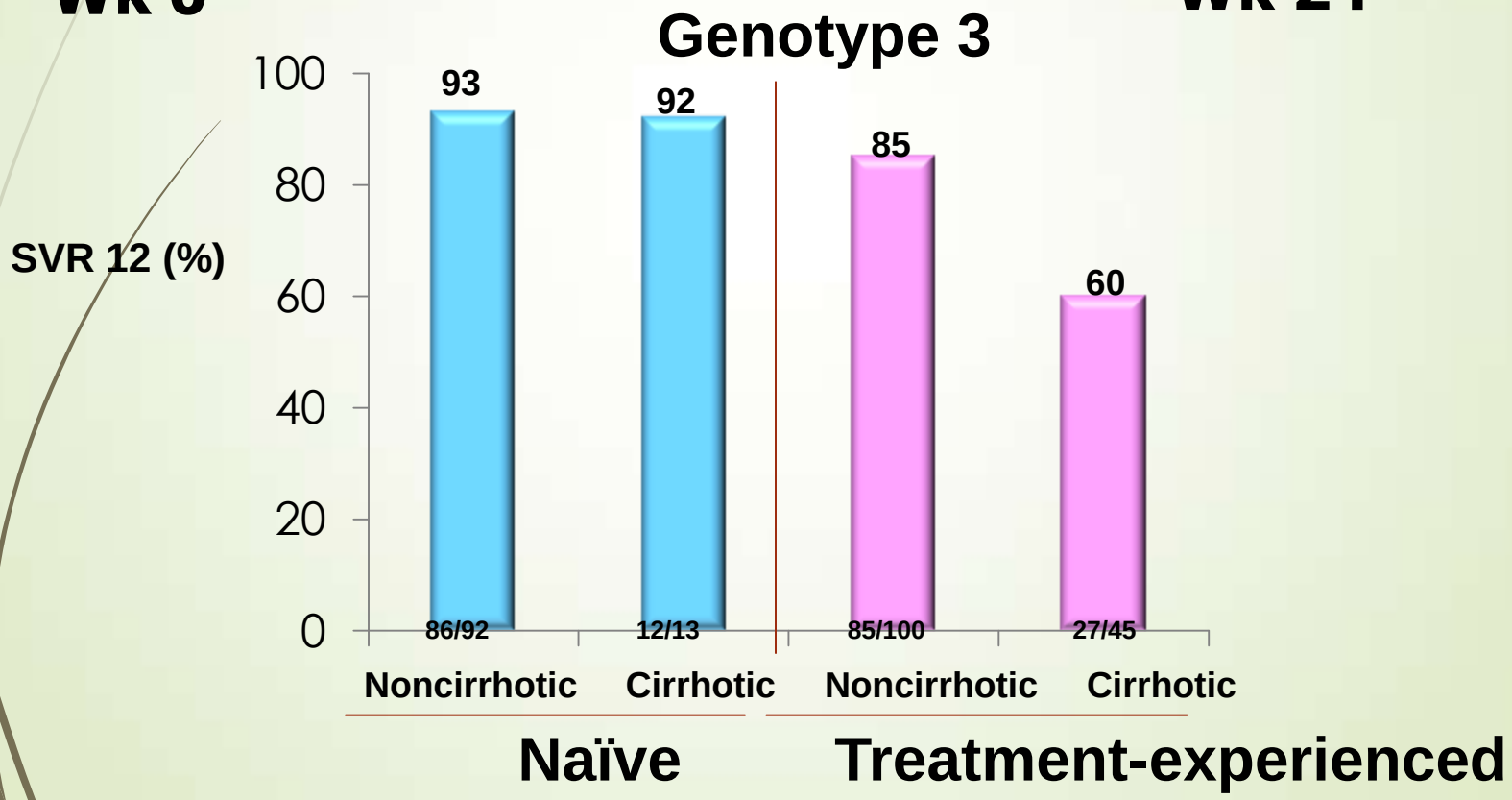
*95% confidence interval 1.7-7.8

Papatheodoridis GV et al. AP&T 2001;15:689-98.

Sofosbuvir + RBV

VALENCE: Genotype 2,3 IFN naïve, ineligible or treatment failures





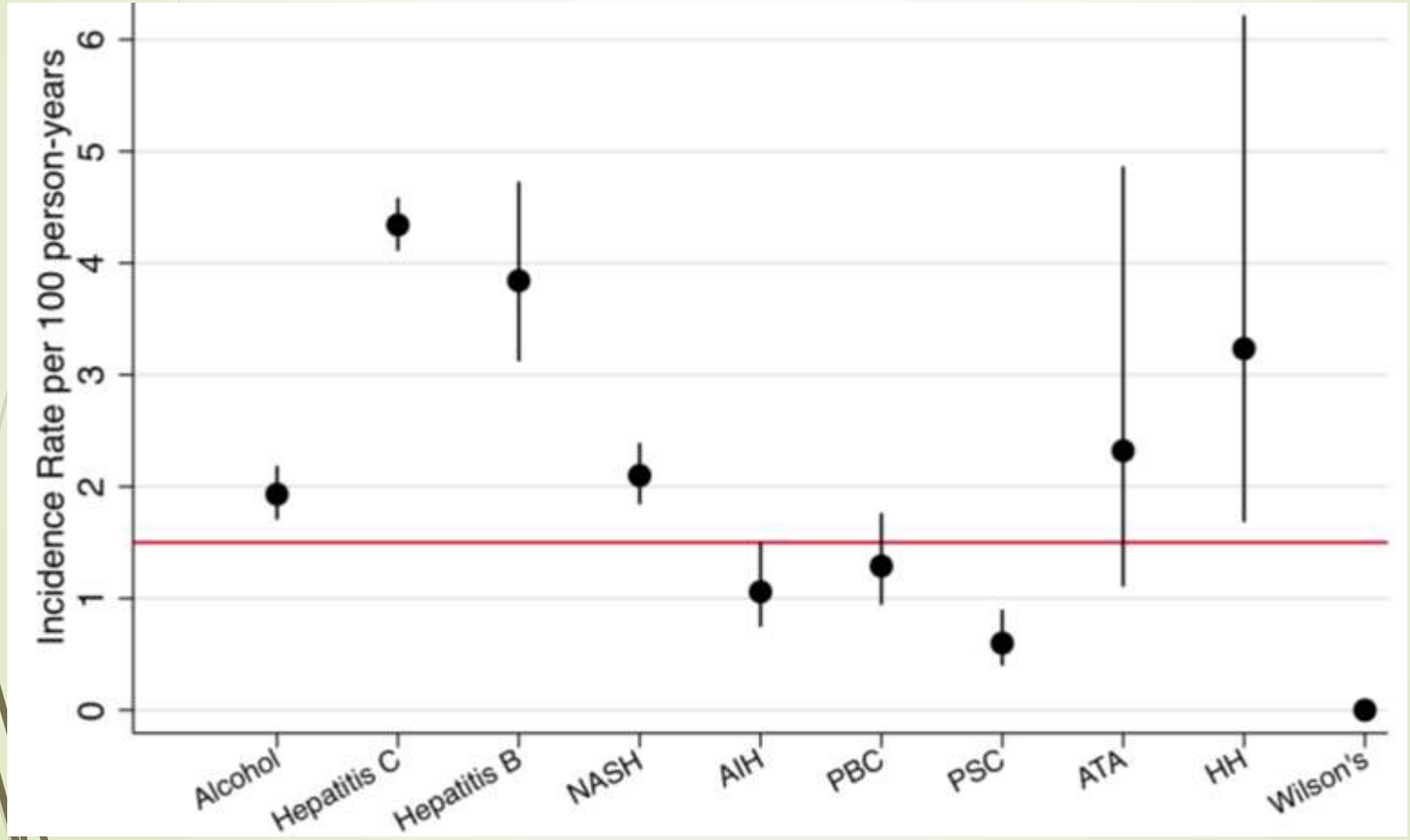
FDA Advisory Committee Meeting, Oct 25, 2013; Zeuzem S et al, AASLD 2013, #1085

Need to update who needs surveillance and when

- NASH is the next HCV/HBV

Estimating Risk of HCC

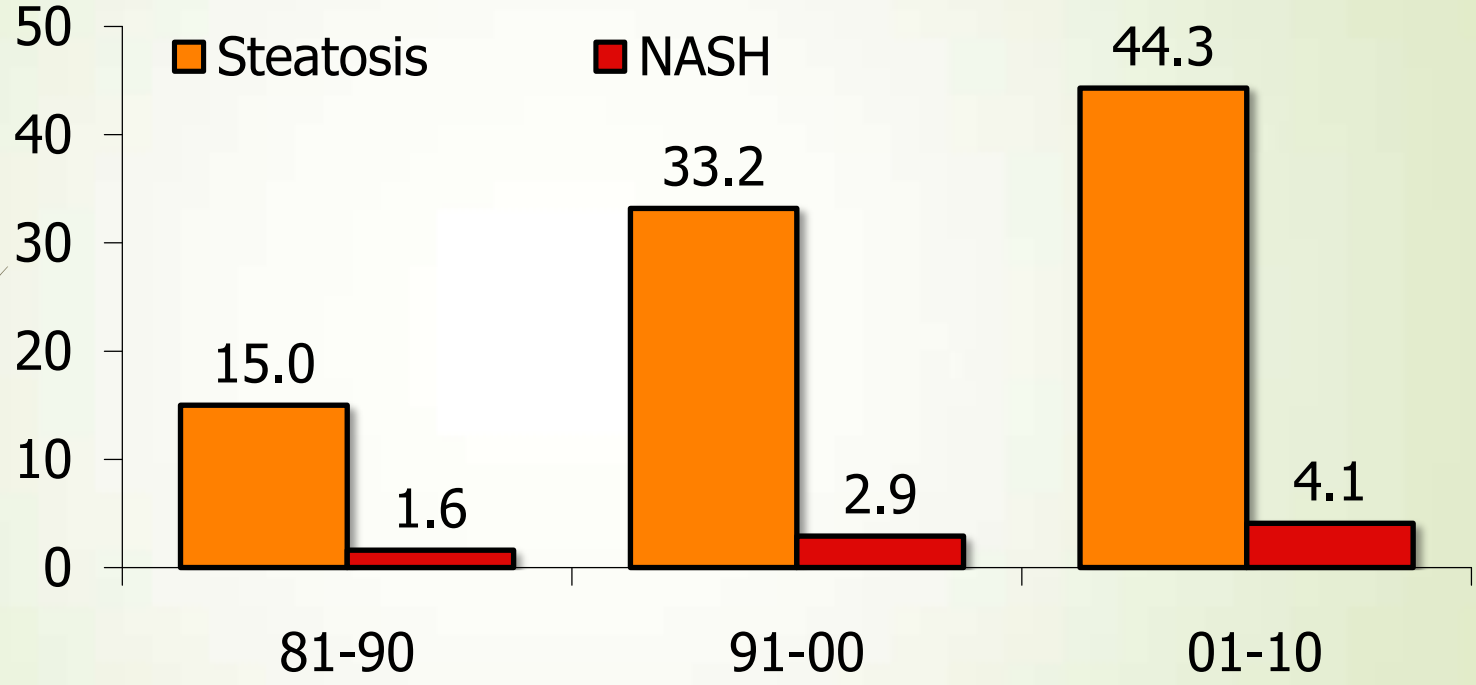
- UNOS data (2002-2011):
- Incidence of de novo HCC on waitlist



Flemming JA et al. AASLD 2012. Abstract 1931.

Prevalence of NAFLD

- Liver histology in autopsies of descendants from non-natural causes (n=465, 1981-2010)

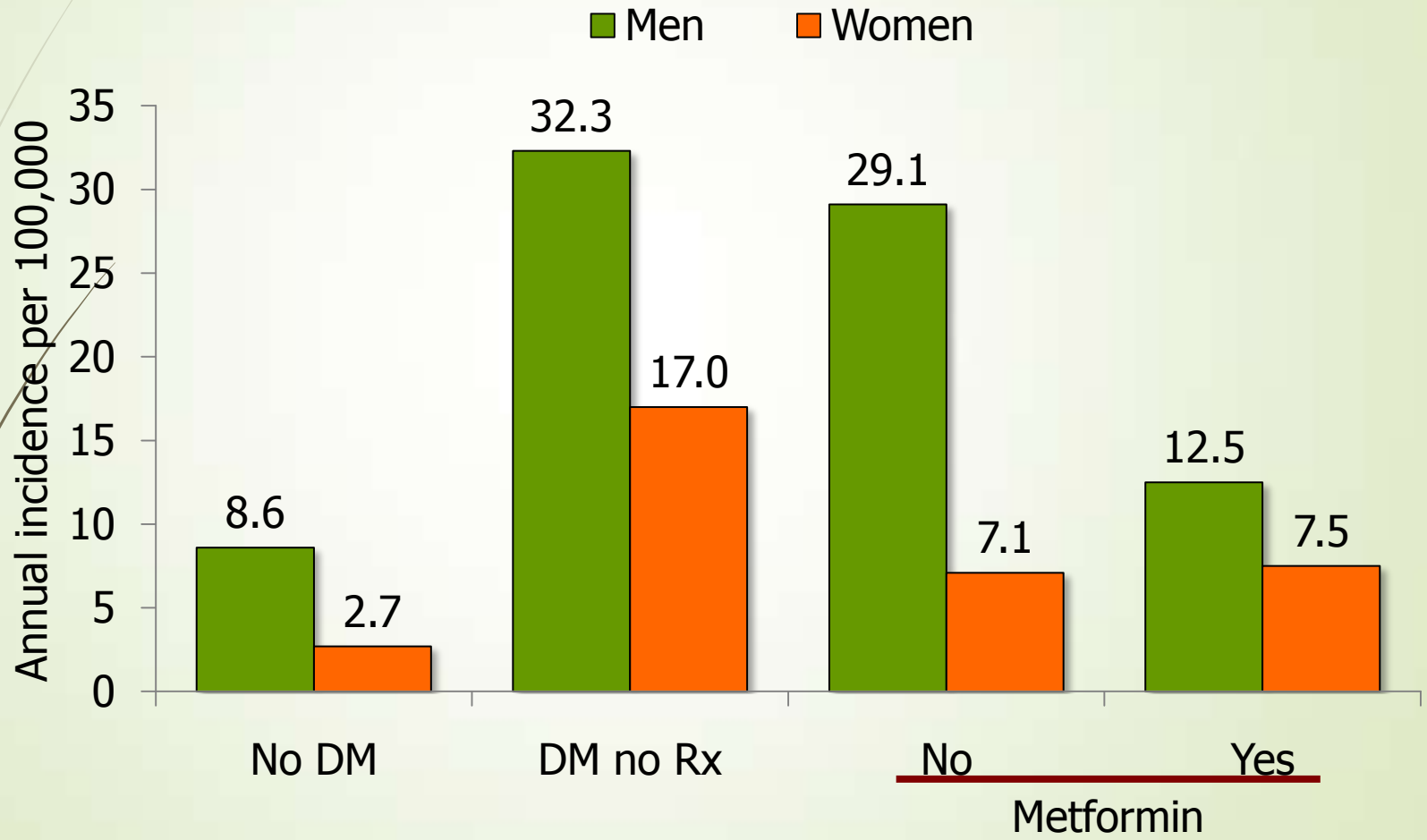


Mean BMI	23.9	26.5	27.8
Obesity	11%	26%	29%

Lee YS et al. DDW 2012; abstract 1054.

Effect of Metformin on HCC

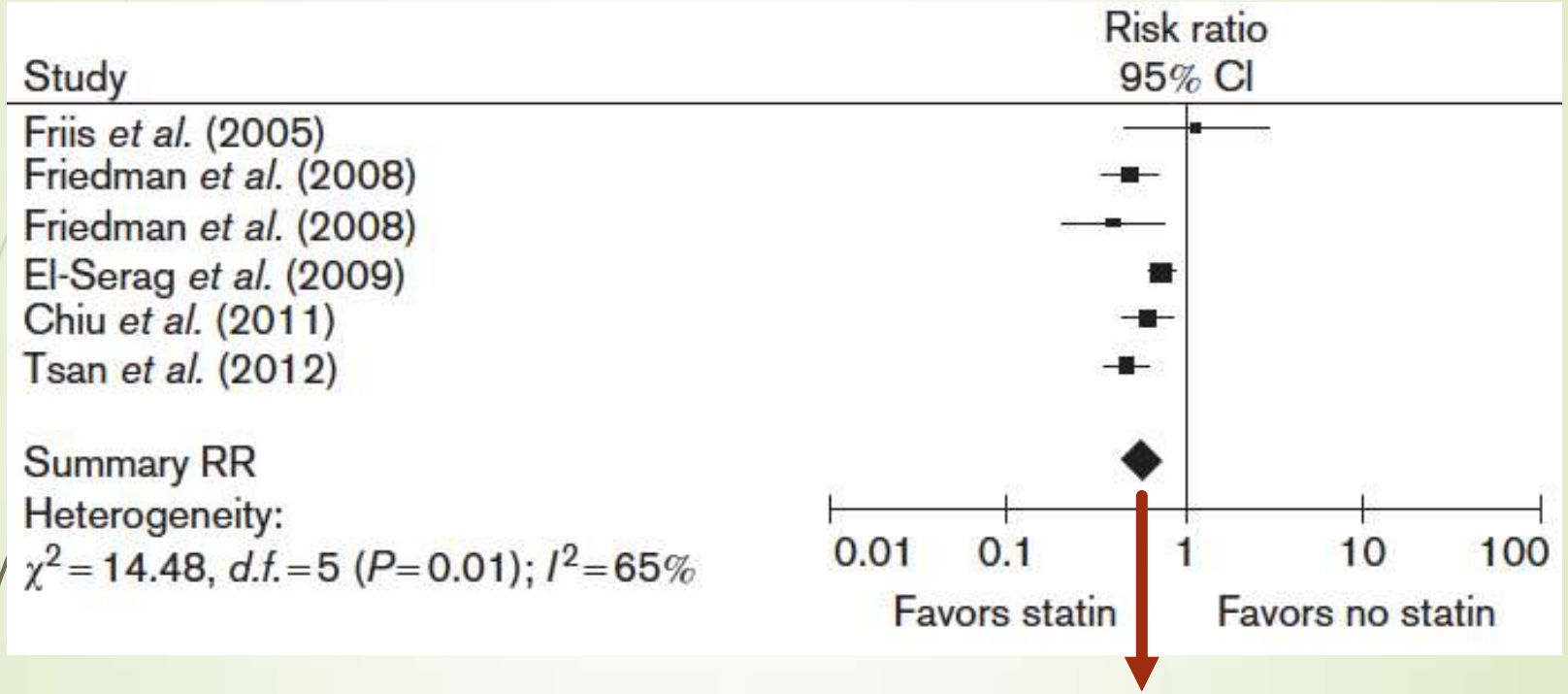
- Taiwanese cohort study: National Health Insurance data (n=480,984)



Lee M-S et al. BMC Cancer 2011;11:20 (doi:10.1186/1471-2407-11-20).

Effect of Statins on HCC

- Meta-analysis of 6 observational studies 'all comers': with and without liver disease 3 Case-control and 3 Cohort studies



RR= 0.58 (95% CI 0.46–0.74).
42% Risk Reduction

Pradelli. Eur J Ca Prev 2013;22:229.

ADRESS-HCC Model

- Scoring system to predict HCC incidence > 1.5% per year

Variable	Score
Age (per year)	1
Diabetes	4
Non-Caucasian **R**ace	4
Etiology - Alcohol/Metabolic* - Viral	7 23
Male **S**ex	10
Severity (CTP Score)	2
Cut-off	88

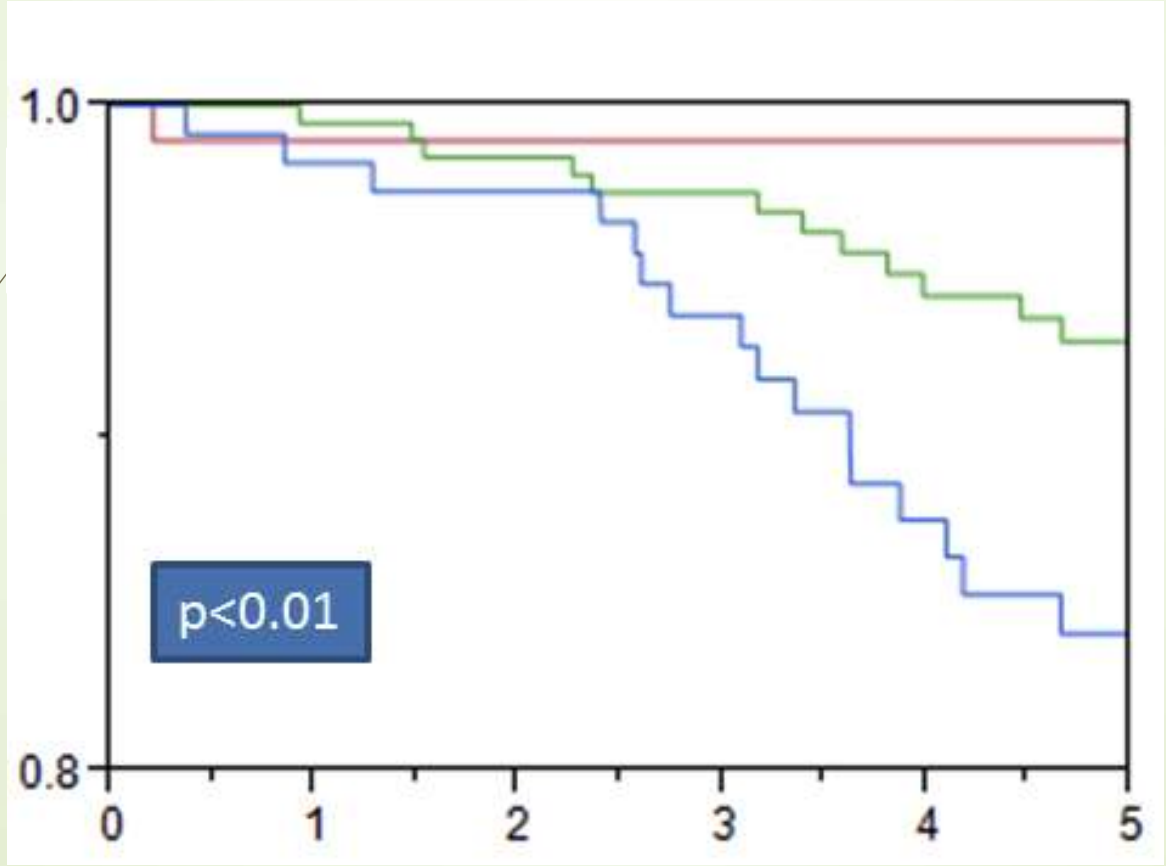
Example	Case 1	Case 2
Age	50	60
Diabetes	0	4
Non-Caucasian	4	4
Etiology - Alcohol - HBV	7 -	- 23
Male	0	10
CTP Score	10	14
Score	71	115

*Metabolic: NASH, HH, A1ATD, Cryptogenic

Flemming JA et al. AASLD 2013

Validation of ADRESS-HCC

- HALT-C Data
- Threshold for Screening: Sensitivity = 96%



Yang JD et al. AASLD 2013

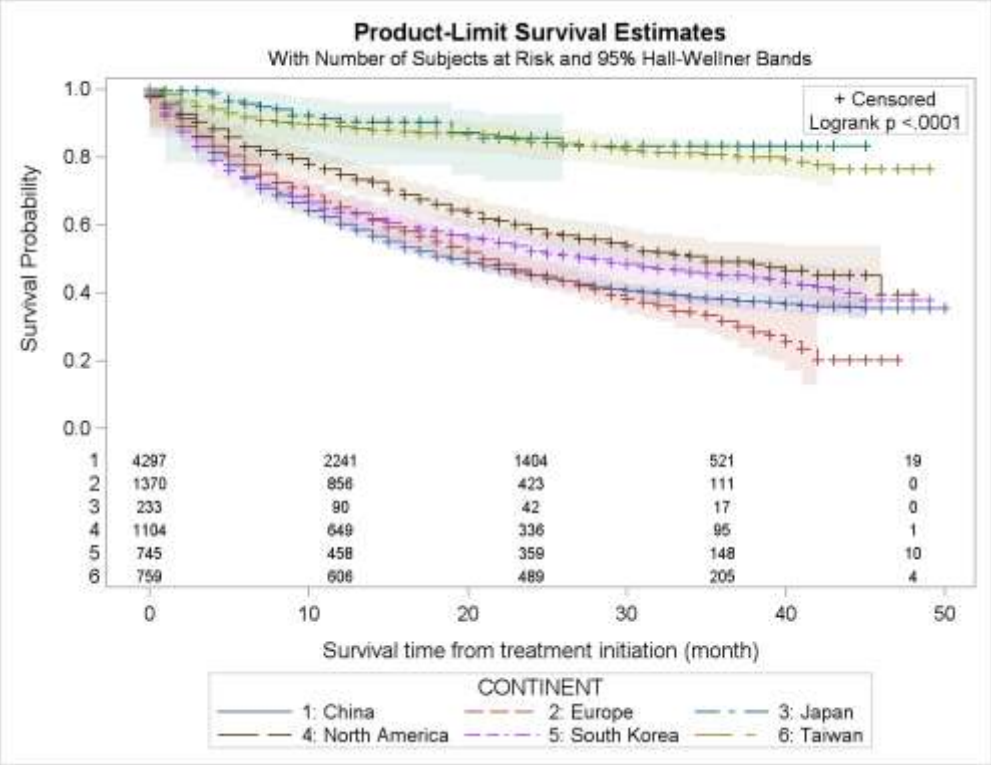
BRIDGE Study

- The global HCC BRIDGE study ("Bridge to Better Outcomes in HCC") is the first multiregional, large-scale, observational study to document real-world HCC patient experience from diagnosis to death[1]
  - Designed to provide additional understanding of global patterns of HCC therapy and associated outcomes across real-world clinical practice, as recorded in patient charts
  - Aims to include all patients who have received treatment for HCC, regardless of treatment type
  - Includes patients treated for HCC in 3 major regions: Asia, Europe, and North America
- Interim analysis examining the Asian cohort compared with the European and North American cohorts, based on available data as of March 2012

Kudo et al., APPLE 2012

1. Sherman M, et al. Presented at the 5th Annual Conference of the International Liver Cancer Association (ILCA), September 2-4, 2011; Hong Kong, China. Abstract P-202.

Median Survival from First Treatment



- **Median follow-up time was approximately 24 months for this cohort**
- **Median OS was not reached for Taiwan and Japan**
- **Median OS was 35 mo for North America, 28 mo for South Korea, 21 mo for Europe, and 19 mo for China**

What's changed since 2005 > 2010 in the AASLD Guidelines?

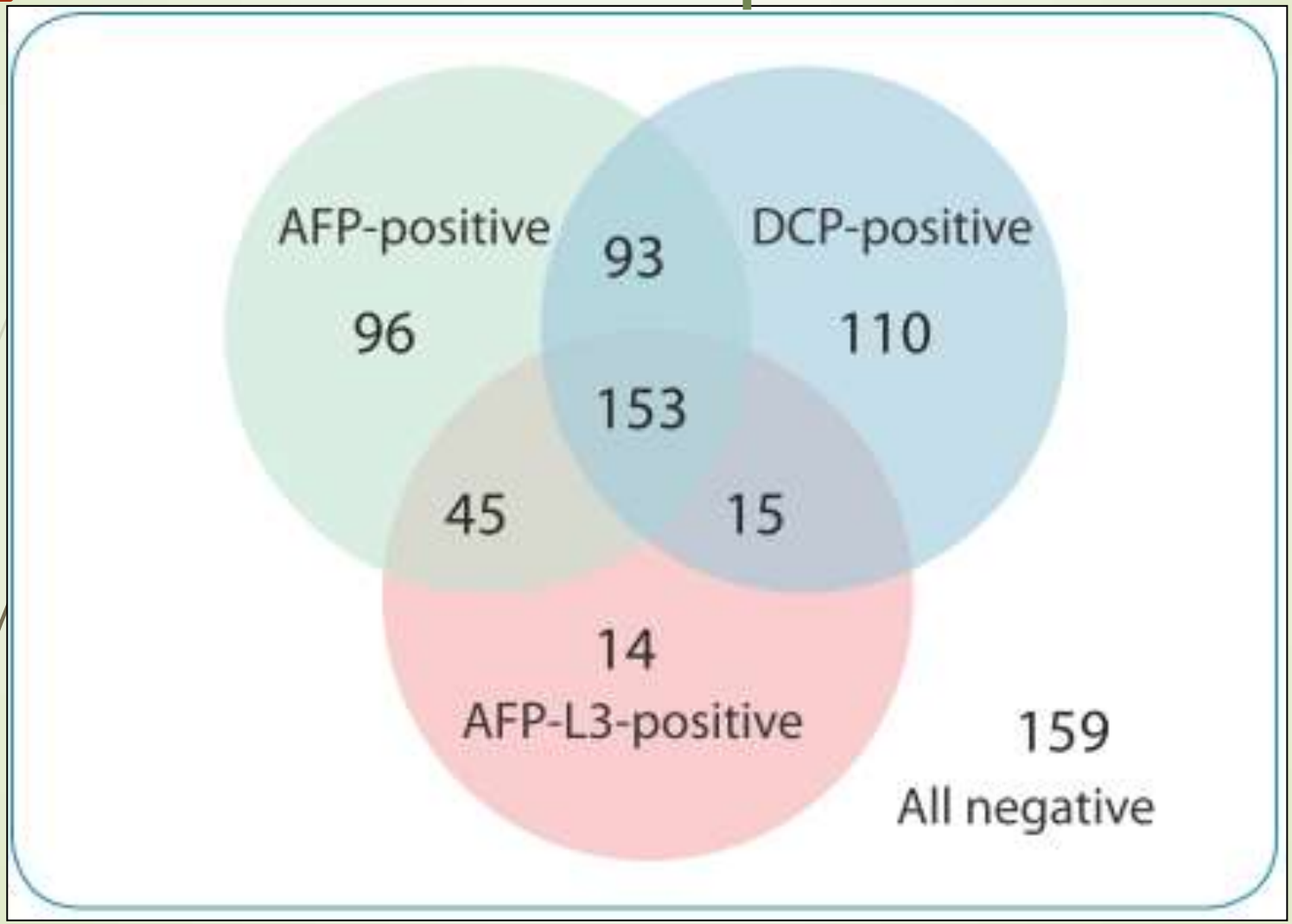
- HCC surveillance in at risk patients is recommended every 6 months instead of every 6-12 months
  - AFP has been removed as a first line test for surveillance
- Sorafenib is recommended as first line option in patients who can not benefit from resection, transplantation, ablation or transarterial chemoembolization, and still have preserved liver function. (level 1)
- Radioembolization with Yttrium90-labeled glass beads has been shown to induce extensive tumor necrosis with acceptable safety profile. However, there are no studies demonstrating an impact on survival … it cannot be recommended as standard therapy for HCC (level 2)

Proposal for changes 2013

- Add back laboratory tests such as AFP as a biomarker
- Consider AFPL3% and DCP which are both FDA approved as "risk markers" and not intended for diagnsosis

Surveillance for Hepatocellular Carcinoma Biomarkers: AFP, AFP-L3 and DCP

Pattern of biomarkers in patients with HCC



Toyoda H, et al. Clin Gastroenterol Hepatol. 2006;4:111-7.

HCC Biomarker Panel

- ALPL3% and DCP: FDA approved as risk markers
  - Near term predictor of developing HCC if no tumor is present on imaging
- Uses and Utilization
  - Higher levels associated with
    - Vascular invasion
    - More poorly differentiated tumors
    - Higher risk of recurrence after surgery and transplant

Guidelines For HCC Surveillance

	USA AASLD	Europe EASL	Japan JSH
Updated	2010	2012	2009 (updating in 2013)
Interval	6 months	6 months	3-4 months for very high risk 6 months for high risk (3-4 months after treatment, 2013)
Test	Ultrasound	Ultrasound	Ultrasound AFP AFP-L3 DCP

More than one biomarker is recommended for HCC surveillance in Japan.

Approval/Clearance And Reimbursement

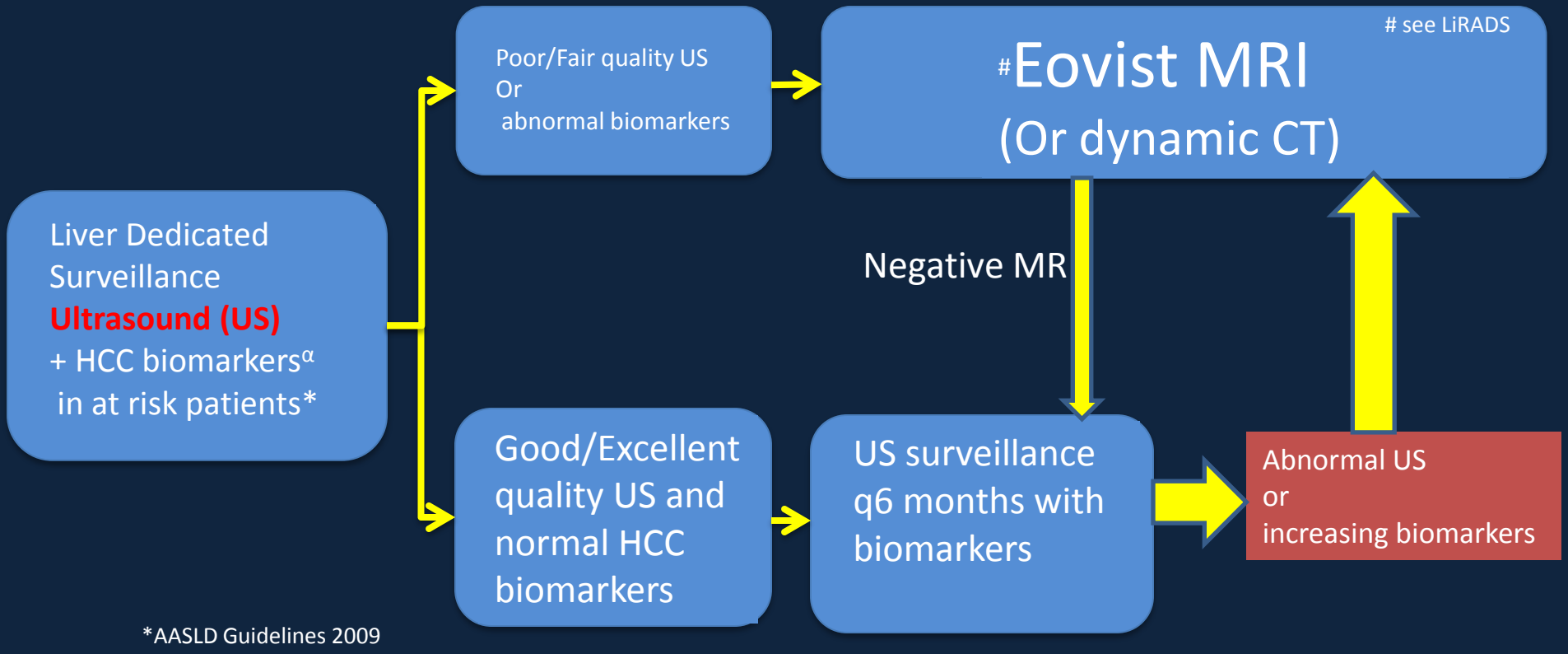
	USA FDA	Canada Health Canada	Europe CE Mark	Japan MHLW
AFP	Not cleared for HCC	Yes	Yes	Yes Reimbursed
AFP-L3	Yes Reimbursed	Yes	Yes	Yes Reimbursed
DCP	Yes Reimbursed	Yes	Yes	Yes Reimbursed

The biomarkers have been already approved in almost every regions.

Embrace and advised ultrasound protocols

- Protocol on how Ultrasounds are to be performed
- Requirements on who is trained and authorized to perform US studies
- Reporting /Synoptic guidelines

Proposed Liver Ultrasound Algorithm

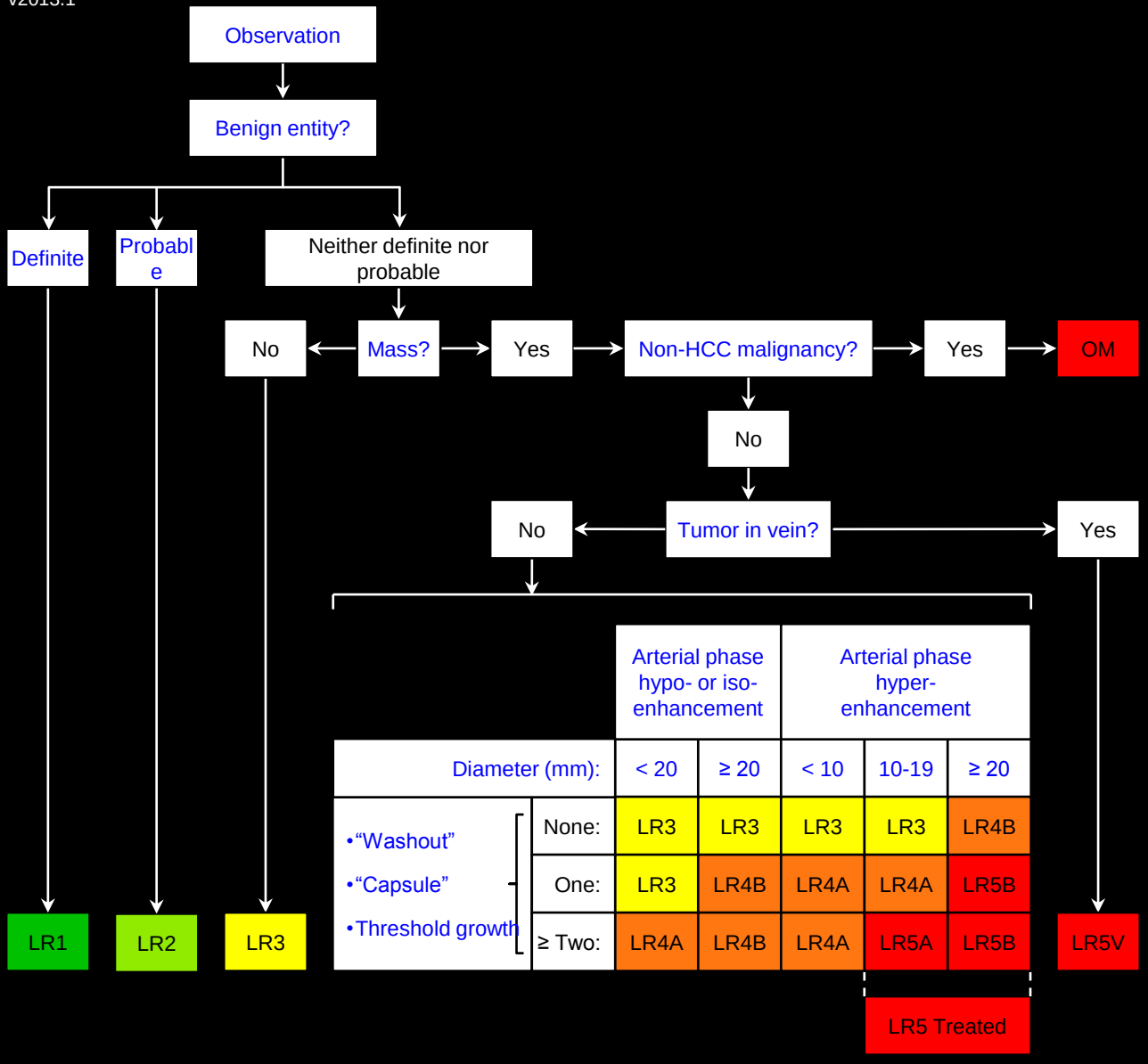


*AASLD Guidelines 2009

αblood tests AFPL3%/DCP (HCC serum biomarkers)

LI-RADS

v2013.1



Overview:

LI-RADS categorizes observations reflecting likelihood of benignity or HCC in at-risk patients, as shown in algorithm.

Definitely or probably benign observations are categorized LR1 and LR2, respectively.

Remaining observations that are not masses then are categorized LR3.

Masses with features suggestive of non-HCC malignancy are categorized Other Malignancy (OM).

Remaining masses with definite tumor in vein are categorized LR5V.

Masses without definite tumor in vein are categorized LR3, LR4, or LR5 as shown in Table based on major features.

LR4 observations are designated A (diameter < 20mm) or B (diameter ≥ 20mm).

LR5 observations are designated A (diameter 10-19mm) or B (diameter ≥ 20mm).

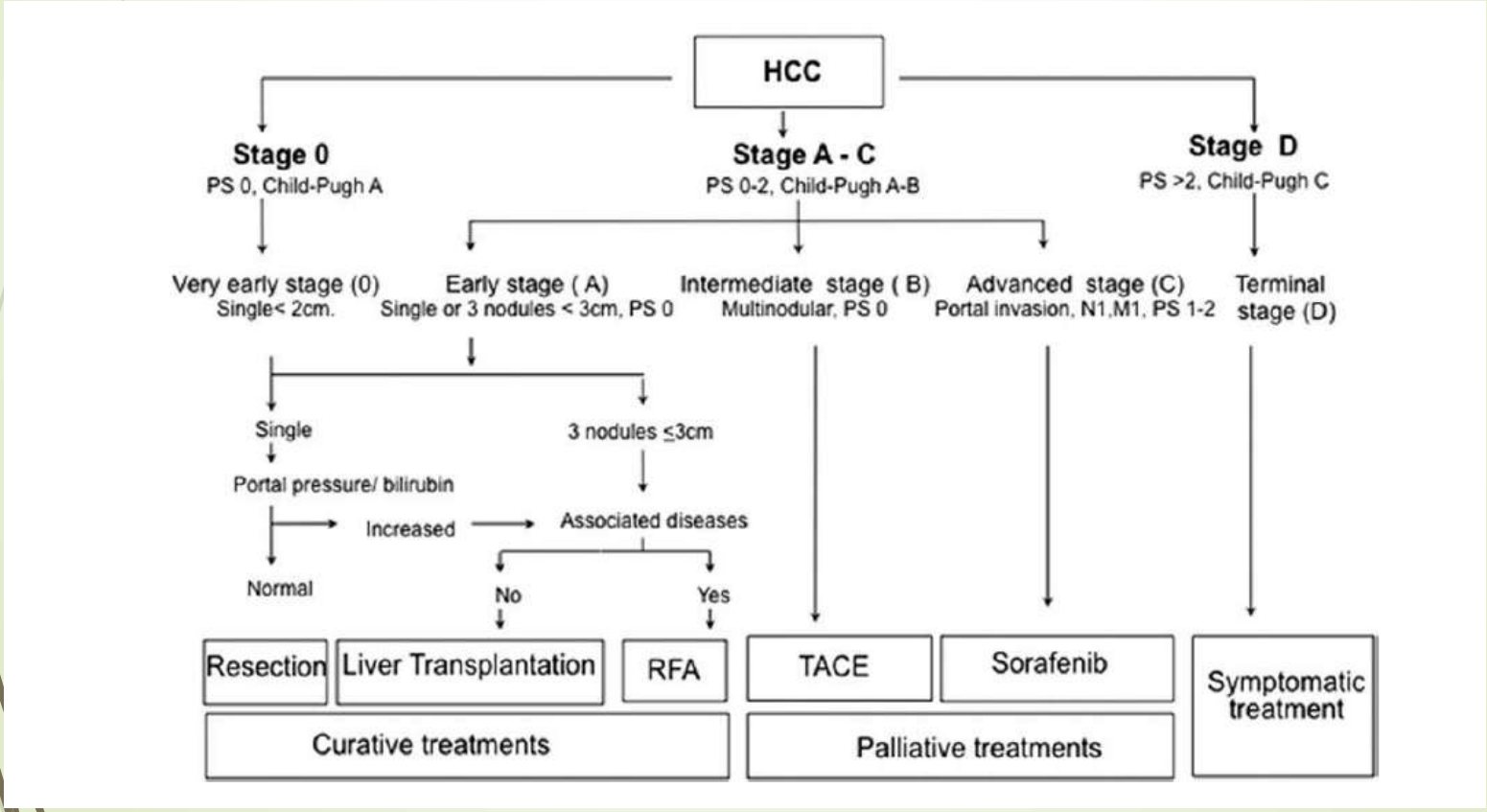
Smaller observations must satisfy stricter criteria to be assigned an equivalent LR category.

The final category may be adjusted using ancillary features and then tie-breaking rules.

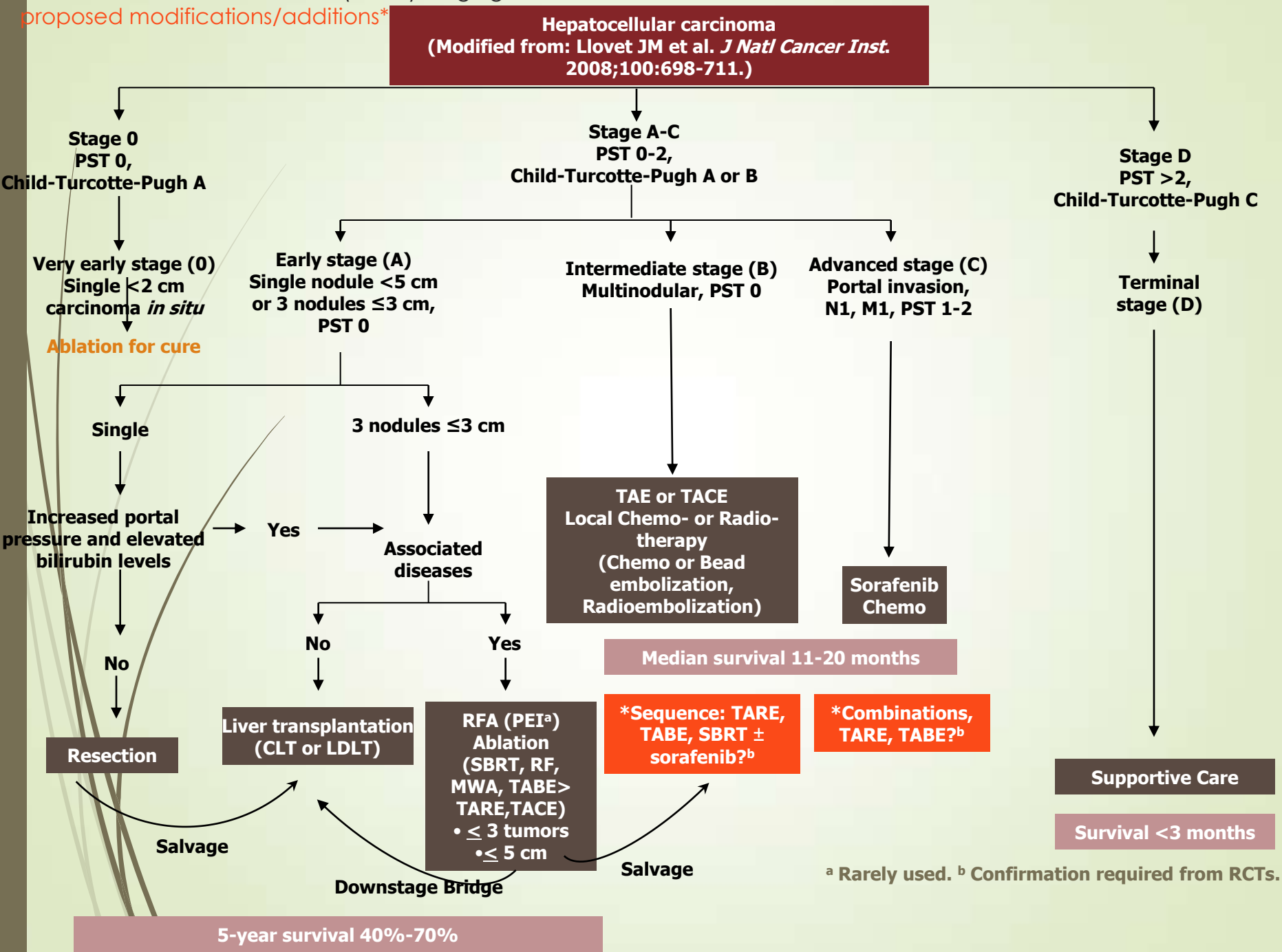
LR5A or 5B observations or biopsy-proven HCC lesions that have undergone loco-regional treatment are categorized LR5 Treated.

Click on the following links for details on LI-RADS: Reporting, Management, Technical Requirements.

LiRADS 5 lesion: what is next?



Barcelona Clinic Liver Cancer (BCLC) Staging Classification and Treatment Schedule: proposed modifications/additions*

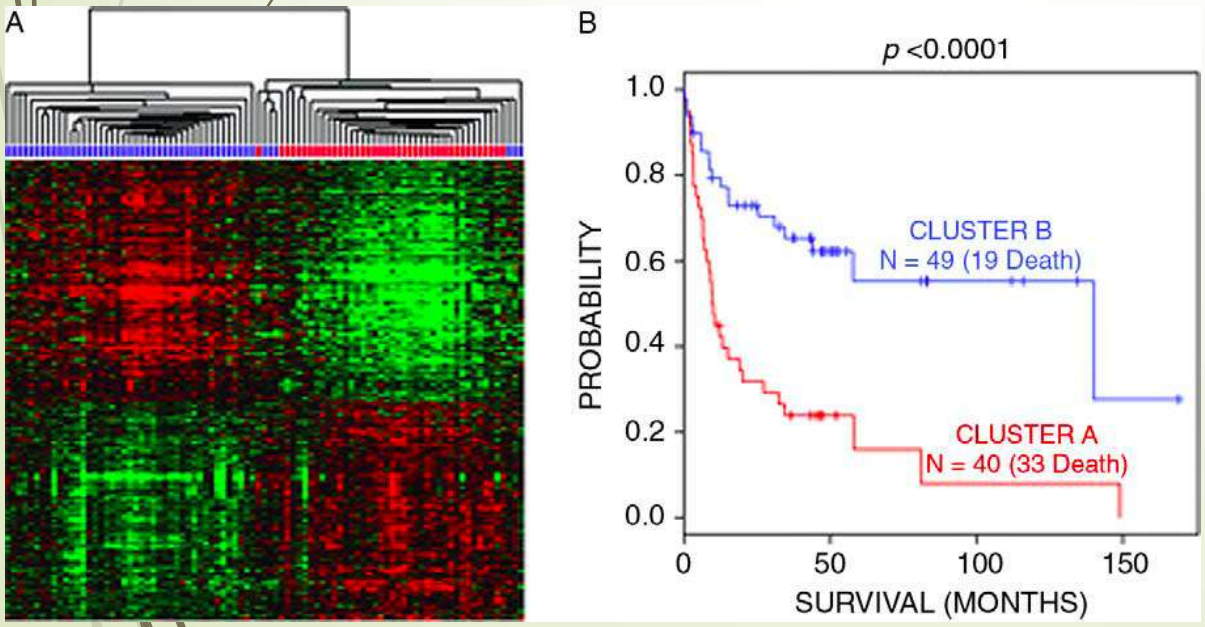


[a] Rarely used. [b] Confirmation required from RCTs.

Add tumor biopsy to the guidelines?

New Role for Biopsy

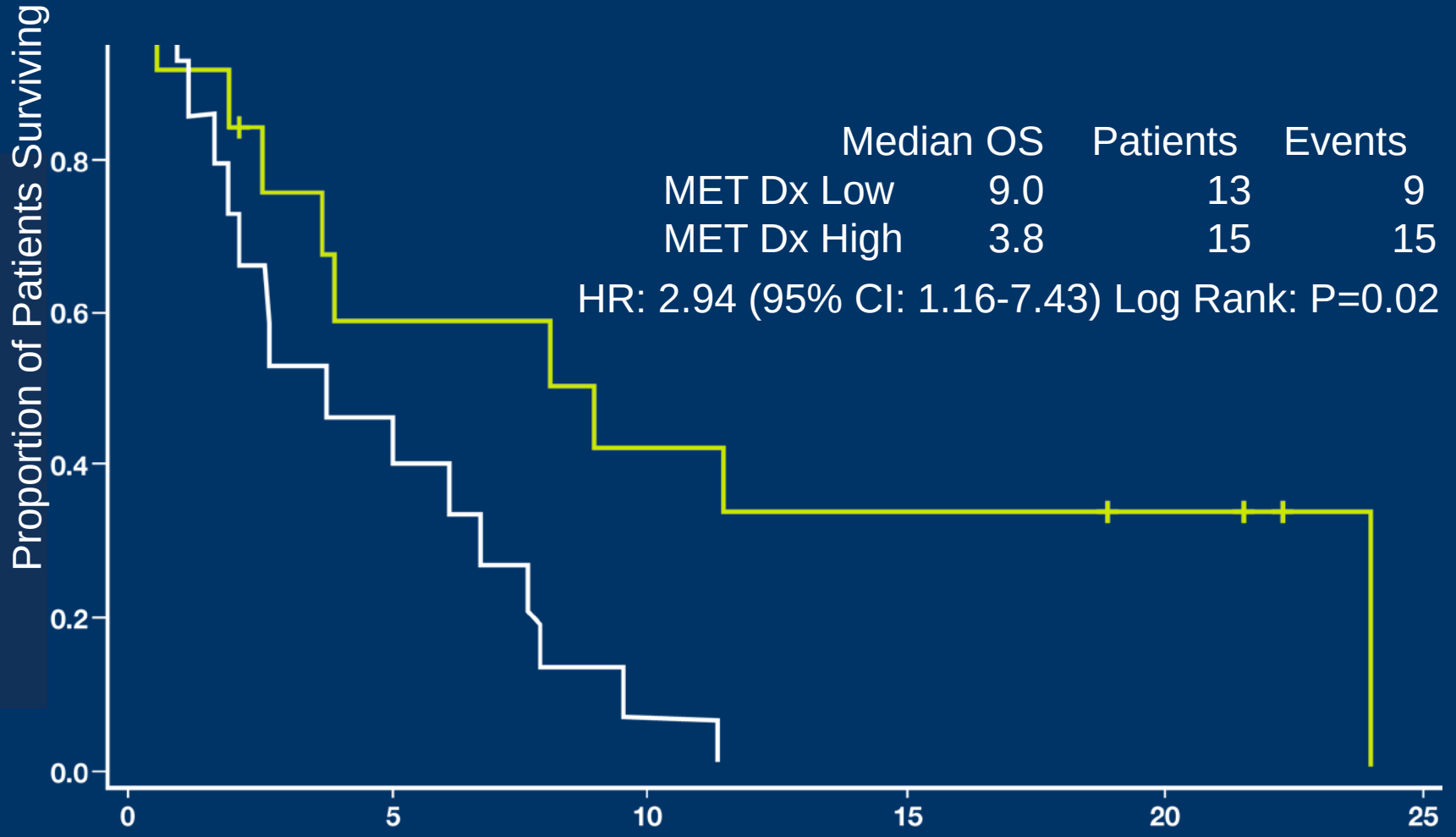
- Molecular profiling for prognosis and therapeutic decision making in HCC patients
  - DNA Microarray technique
  - miRNA profiling



"survival genes"

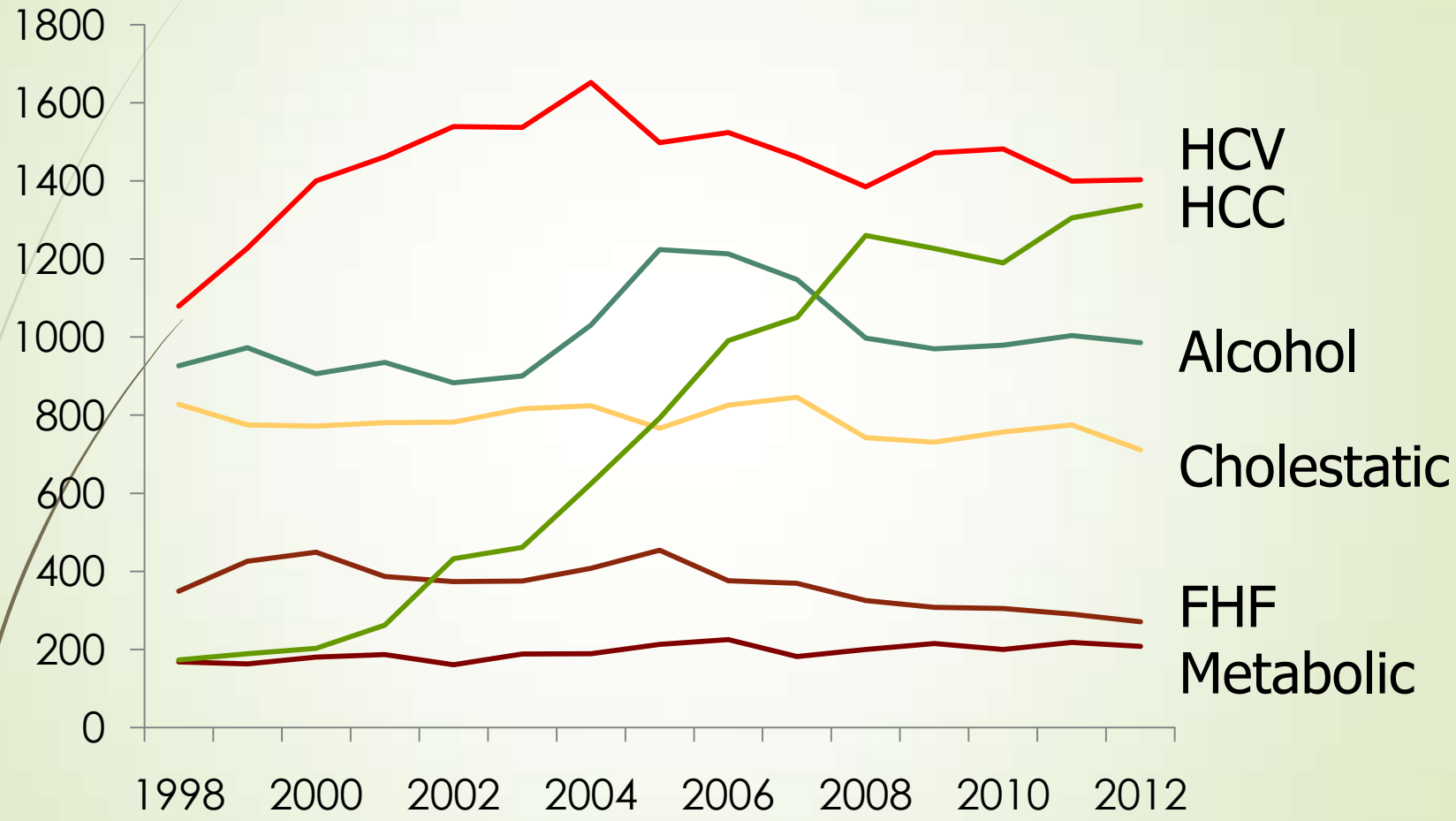
Lee JS, et al. Classification and prediction of survival in hepatocellular carcinoma by gene expression profiling. Hepatology 2004;40:667–676.

Tissue MET as a Prognostic Factor



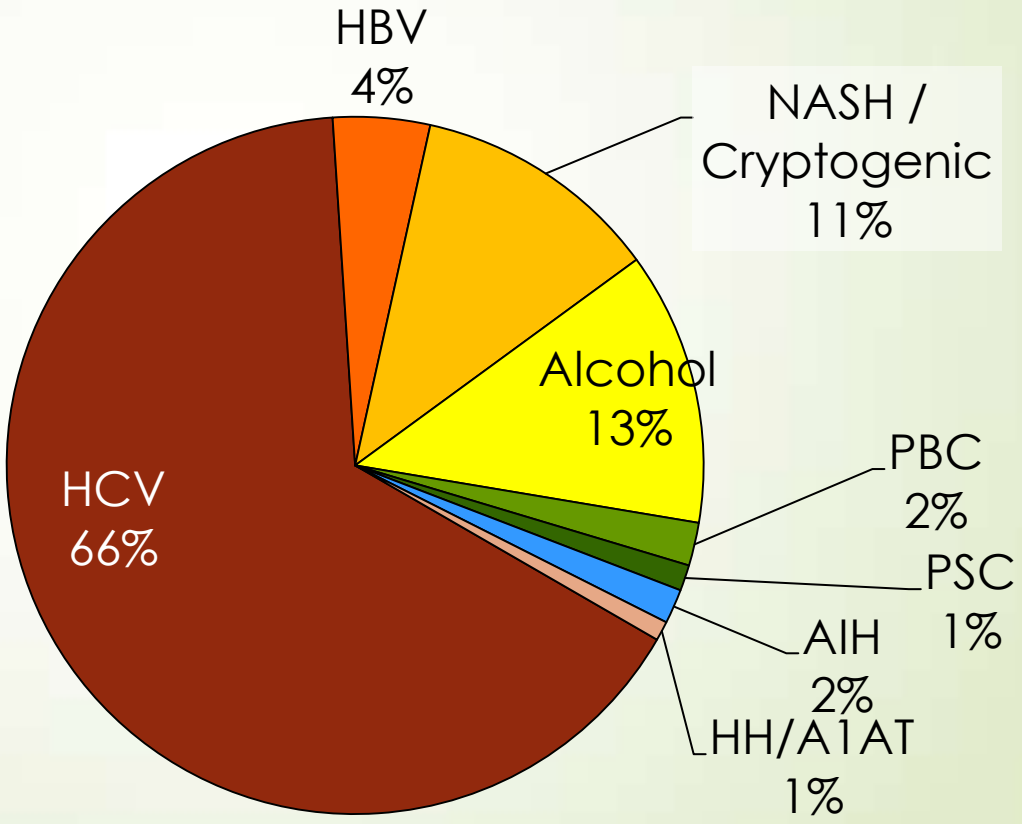
Rimassa, L, et al. Abstract 4006. ASCO 2012

Trends in Liver Transplants in US



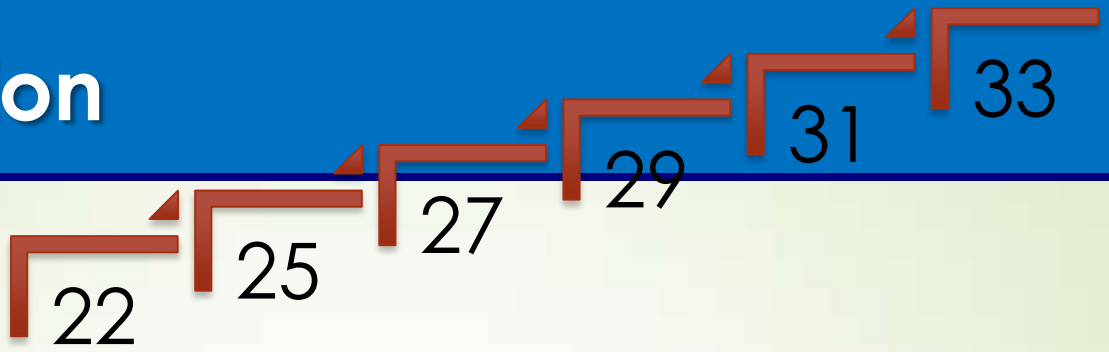
Incident HCC on Transplant Waitlist

- UNOS data (2002-2011)
  - Incidence of de novo HCC on UNOS waitlist
  - 1,960 new HCCs in 34,932 waitlist registrants



Flemming JA et al. AASLD 2013.

MELD Inflation



- **Patients with HCC exceptions**
  - Start at 22 MELD points independent of your biologic MELD
  - Every three months additional points are added
  - Window of opportunity for successful transplant is wide

- **Patients without MELD exceptions**
  - MELD score based solely on your lab work
  - Patients with high MELD scores are often unstable
  - Window of opportunity to successfully undergo transplant is very narrow

	Bilirubin	INR	Creatinine	Biologic MELD	MELD exception
Patient A	2.5	2.7	1.1	22	none
Patient B	8	2.7	2.3	**33**	none
Patient C	1.0	0.9	0.8	6	**33 (HCC)**

AASLD Recommendations for HCC Surveillance are expected to change

HBV carriers

(Cost effective if risk >0.2%/y)

- Asian M≥40y, F≥50y
- Africans/Af Am >20yo
- Family history of HCC
- Cirrhosis

Non HBV-cirrhosis

- HCV

(Cost effective if risk >1.5%/y)

- Alcoholic cirrhosis
- Genetic hemochromatosis
- Primary biliary cirrhosis

Increased risk but insufficient data to recommend surveillance

- Alpha1-antitrypsin with cirrhosis ?
- Non-alcoholic steatohepatitis with cirrhosis
- Autoimmune hepatitis with cirrhosis?
- **F3 disease ?**

Bruix J & Sherman M. Hepatology 2005;42:1208-36. Bruix J & Sherman M. Hepatology 2011;53:1020-22 Bruix and Sherman, Hepatology 2010, 1-35.

American Perspectives for HCC Management, Control and Prevention

Prevention

- Continued prevention of acute viral hepatitis infection
- Screen (Birth Cohort) for chronic HCV and HBV and link to treatment
- Improve treatment outcome/ SVR rates
- Obesity epidemic? Behaviour modification
- Chemoprevention: Metformin? Statins?
- HBV Vaccine

Control

HCC surveillance strategies and linkage to care

Treatment

Thank you to

- APASL and the HSP for hosting this meeting

- Ray Kim for his HCC insights, leadership and slides
- Lewis Roberts for his research and teaching in biomarkers and genomics

- My North American Colleagues who have help shape HCC on our continent
  - Morris Sherman
  - Heshem El-Serag
  - Richard Finn
  - Ghassan Abou-Alfa
  - Adrian Di Besceglie